Valentine Nenajdenko *Editor*

Fluorine in Heterocyclic Chemistry Volume 1

5-Membered Heterocycles and Macrocycles

Springer

Fluorine in Heterocyclic Chemistry
Volume 1

Valentine Nenajdenko
Editor

Fluorine in Heterocyclic Chemistry Volume 1

5-Membered Heterocycles and Macrocycles

Springer

Editor
Valentine Nenajdenko
Department of Chemistry
Moscow State University
Moscow, Russia

Volume 1: ISBN 978-3-319-04345-6 ISBN 978-3-319-04346-3 (eBook)
Volume 2: ISBN 978-3-319-04434-7 ISBN 978-3-319-04435-4 (eBook)
Set ISBN 978-3-319-06036-1
DOI 10.1007/978-3-319-04346-3
DOI 10.1007/978-3-319-04435-4
Springer Cham Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014942653

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

Why Fluorine in Heterocyclic Chemistry?

Organofluorine chemistry is almost as old as organic chemistry. First organofluorine compound synthesized ever was a very simple compound. In 1835, Dumas prepared fluoromethane by the reaction of potassium fluoride with dimethyl sulfate. Therefore, organofluorine chemistry is only 7 years younger than organic chemistry, which started its history from urea synthesis by Wöler in 1828. For more than one century the development of organofluorine chemistry has been not very active. Maybe the most important impulse was done by weapon chemists mainly in USA, USSR and UK before and after the Second World War. After that new fluorinated reagents appeared to intensify the development in the field of fluorinated organic compounds. As a result this part of organic chemistry started its enormous growth.

Another milestone in this field was the synthesis of 5-fluorouracil by Heidelberger in 1957. It was demonstrated that 5-fluorouracil works as antineoplastic agent being antimetabolite of natural uracil. It was the first fluorinated synthetic drug. Nowadays fluorine substitution is a commonly used tool in medicinal chemistry and agrochemistry. The presence of fluorine can result in substantial functional changes in the biological as well as physicochemical properties of organic compounds. Incorporation of fluorine into drug molecules can greatly affect their physicochemical properties, such as bond strength, lipophilicity, bioavailability, conformation, electrostatic potential, dipole moment, pKa etc. as well as pharmacokinetic properties, such as tissue distribution, rate of metabolism and pharmacological properties, such as pharmacodynamics and toxicology.

The main part of modern marketed drugs are heterocyclic compounds of various types. Fluorinated heterocycles are becoming increasingly important in many areas including the pharmaceutical industry, materials science and agriculture. To reflect the importance of this topic, two excellent books (Petrov V.A. (ed.) *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*. 2009, Wiley; and Gakh A., Kirk K.L. (eds.) *Fluorinated Heterocycles*. 2009, ACS) and a number of nice reviews have been published recently.

The present work combines comprehensive information on the chemistry of the fluorinated heterocycles of interest to synthetic organic chemists in general, and particularly for those colleagues working in the fields of heterocyclic-compound chemistry, materials chemistry, medicinal chemistry, and fluorine chemistry. All information is presented and classified clearly to be effective source for broad auditory of chemists. The main feature of this book is classification based on the type of heterocycle. I believe that separate presentation of each type of heterocycles makes clear reading, operation and search through this book to be helpful for readers. I hope that this book will be also interesting for scientists working in the field of inorganic and coordination chemistry as well as materials science.

It is a great honor and pleasure for me to be the editor of this book. I would like to thank all the contributors for their excellent chapters. These outstanding scientists are known experts in this field. Thank you very much for your efforts and your time! This book is a result of worldwide cooperation of contributors from many countries. I would like also to thank all my collaborators at Springer for help to realize this project.

I wish to dedicate this book to my wife Svetlana and our daughters Liza and Zhenya. Their support is really invaluable for me.

Contents of Volume 1

Contents of Volume 2

Tactical Applications of Fluorine in Drug Design and Development

Nicholas A. Meanwell, Kyle J. Eastman, and Eric P. Gillis

Contents

Abstract The increasing utilization of fluorine in drug design parallels advances in understanding the physicochemical attributes of this element and an enhanced appreciation of how these unique properties can be exploited to address the numerous challenges encountered in pharmaceutical candidate optimization. Judicious placement of fluorine in a candidate compound can markedly affect potency, increase metabolic stability and enhance membrane permeability. The powerful electron-withdrawing nature of fluorine serves to modulate the pK_a of proximal functionality, particularly basic amines, and can be an important tool for controlling physical properties. Fluorine also exerts a conformation bias that is significant and can be utilized strategically. The ^{18}F isotope is of particular importance in positron

N.A. Meanwell (✉) • K.J. Eastman • E.P. Gillis
Department of Medicinal Chemistry, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492, USA
e-mail: Nicholas.Meanwell@bms.com; Kyle.Eastman@bms.com; Eric.Gillis@bms.com

V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_1,

emitting tomography (PET), an imaging technique of increasing importance for assessing drug-target engagement in both preclinical and clinical settings. This chapter provides a synopsis of some of the prominent and emerging applications of fluorine in the design and optimization of biologically active molecules.

Keywords *Gauche* interaction • Fluorine and basicity • Fluorine and conformation • Fluorine and hydrogen-bonding • Fluorine and membrane permeability • Fluorine and metabolic stability • Positron emitting tomography imaging

1 Introduction

Fluorine is a remarkable and unique atom capable of imparting a myriad of advantageous properties to small molecules, particularly in the context of medicinal chemistry. Over the last five decades the knowledge and understanding of this almost "magical" substituent has been enhanced substantially. Ever improving technologies for the installation of fluorine into novel small molecules facilitate attempts to utilize fluorine to address numerous challenges encountered in drug design: conformational control; modulating pK_a; improving metabolic stability, solubility, permeability and potency; or tracking the distribution of a compound *in vivo* using positron emission tomography (PET) imaging. Recently, fluorine has found utility in fragment-based drug design by taking advantage of the ^{19}F NMR signal to both identify fragments that bind to targeted sites and to probe the presence of fluorophilic environments in proteins [1–3]. The applications of fluorine in medicinal chemistry continue to increase and its strategic deployment is considerably less empirical than it once was. However, there remains much to be understood regarding this privileged atom and its ability to aid in the fine tuning of pharmacodynamic (PD) and pharmacokinetic (PK) properties.

Fluorine is the most abundant halogen in the earth's crust (and ranks 13th in abundance of all elements), but this has not translated into a proportional prevalence among naturally occurring organic compounds. There are only a handful of natural products known to contain fluorine, attributed to the fact that fluorine is found naturally in insoluble forms that are not readily available [4].

For example, seawater concentrations of fluoride have been measured at 1.3 ppm compared to ubiquitous chloride concentrations which are 1,900 ppm. Another factor contributing to the dearth of fluorine in organic molecules is the extremely high heat of hydration of fluoride [5]. Fluoride is heavily hydrated in water rendering it weakly nucleophilic and thus limiting its role in direct displacement chemistry. The high heat of hydration of fluoride relative to other halides is principally responsible for the inordinately high energy needed to generate F^+ from aqueous F^-[6]. This key difference from other halides precludes incorporation of fluorine into natural products *via* the haloperoxidase reaction that is a common pathway for the incorporation of chlorine, bromine and iodine [7, 8].

Despite the low concentrations of fluorine available on land and in the sea, some marine and terrestrial organisms can accumulate significant quantities of inorganic fluorine. However, the presence of organo-bound fluorine has only been identified in a

handful of tropical and sub-tropical terrestrial plants and in only two microorganisms. A great deal of effort has gone into the elucidation of the biosynthesis of fluorine-containing natural products [8–11]. The most prominent example is the synthesis of highly toxic fluoroacetic acid by the bacterium *Streptomyces cattleya* from *S*-adenosyl-L-methionine and fluoride mediated by the enzyme 5′-fluoro-5′-deoxy adenosine synthetase [9–11]. However, to date there is no evidence to support the *de novo* synthesis of the C-F bond in the animal or insect kingdoms [4]. Indeed, caterpillars of the moth *Sindus albimaculatus* acquire trifluoroacetate from their host plant, *Dichapetalum cymosum*, in concentrations that render them toxic to predators [12]. It is interesting that despite the scarcity of fluorine-containing compounds found in the natural world, fluorine plays a prominent and ever increasing role in contemporary drug design.

One of the earliest synthetic fluorinated drugs is 5-fluorouracil, an antimetabolite synthesized for the first time in 1957 (Fig. 1) [13]. Since that discovery, the

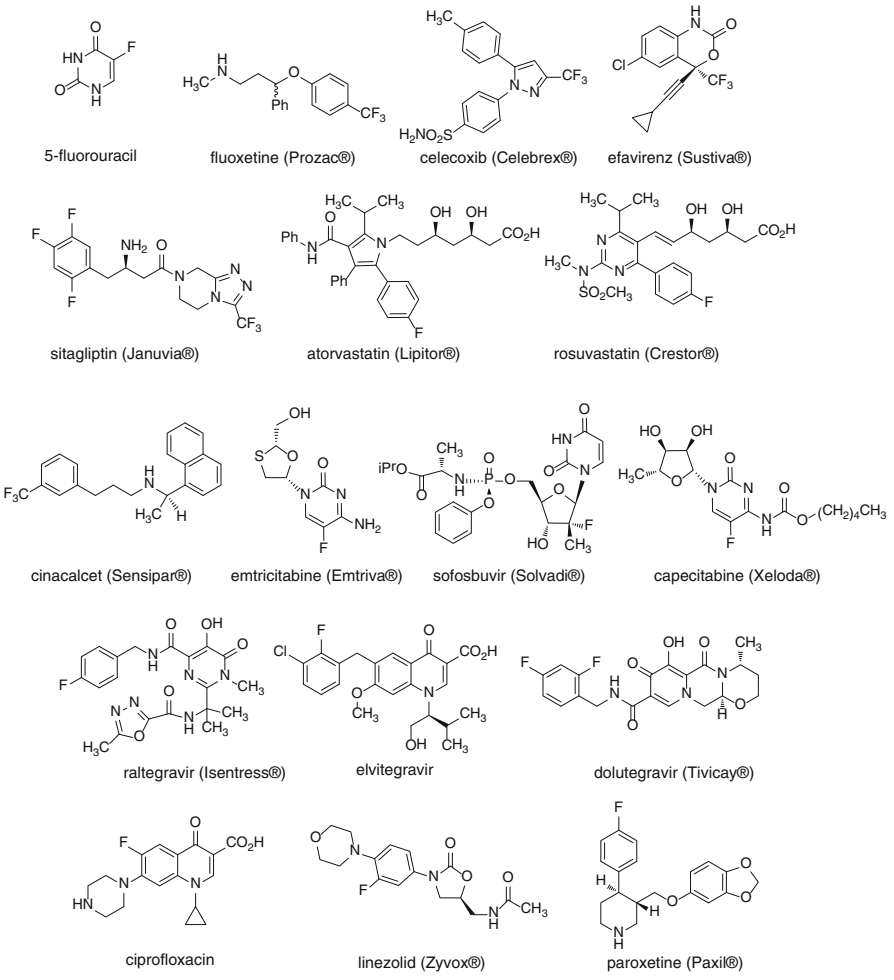


Fig. 1 (**a**, **b**) Examples of fluorine-containing drugs

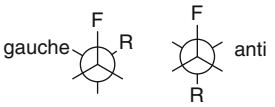
deployment of fluorine in small molecule drug candidates has grown, as have the technologies to install this atom. Today, 20–25 % of marketed drugs contain fluorine, including blockbusters such as fluoxetine (Prozac®, depression), celecoxib (Celebrex®, arthritis), efavirenz (Sustiva®, human immunodeficiency virus (HIV)), sitagliptin (Januvia®, diabetes), atorvastatin (Lipitor®, dyslipidemia), rosuvastatin (Crestor®, dyslipidemia), cinacalcet (Sensipar®, hyperparathyroidism) and the nucleosides emtricitabine (Emtriva®, HIV). Other prominent fluorinated drugs include sofosbuvir (Solvadi®), capecitabine (Xeloda®, breast and colorectal cancer), the HIV integrase inhibitors raltegravir (Isentress®, HIV), elvitegravir (HIV) and dolutergavir (Tivicay®), ciprofloxacin, the prototypical fluoroquinolone antibiotic, linezolid (Zyvox®, antibiotic) and paroxetine (Paxil®, antidepressant). The objective of this chapter is to provide an overview of the impactful nature of fluorine on drug discovery as it is currently understood.

2 Fluorine and Conformation in Drug Design

The high electronegativity of fluorine is responsible for the strong polarization of the C-F bond, manifested as the highest measured dipole in organic molecules at 1.85 D for CH_3F. This phenomenon can strongly influence the interaction of C-F with a range of proximal functionality [14–22].

Depending on the nature of the functionality, these effects can be of sufficient magnitude to significantly affect conformational preferences, and can be exploited in the design of both drugs and organocatalysts [21, 22]. The basis for these intramolecular effects include dipole-dipole interactions, attractive electrostatic effects, repulsive effects between F and another electronegative atom, p-orbital repulsion, and a hyperconjugative effect in which the C-H bond of an adjacent atom interacts with the low lying σ* orbital of the C-F bond [21–23]. An understanding of the interactive relationship between F and a range of organic functional groups has been developed using density functional theory (DFT) calculations that provide some instruction on potential utility and applications [23]. Table 1 captures the predicted energy of an individual interaction and offers a possible explanation for the preferred conformation based on the underlying physical chemistry [23]. Whilst several of these specific structural elements are of limited interest in drug design and the inherent energy of some interactions are too low to be of significance in the absence of additional reinforcing effects, the underlying physical organic chemistry principles offer considerable insight into the role that fluorine plays in influencing conformation. The most prominent functionality for which the energy of interaction with fluorine is such that the effect might be gainfully exploited in drug design are the amine, alcohol and amide moieties [21, 22].

Table 1 Calculated energy differences between the *gauche* and *anti* conformers of substituted fluoroethanes



R	Δ energy *gauche-anti* (kcal mol^{-1}) B3LYP	Δ energy *gauche-anti* (kcal mol^{-1}) M05-2X	Preferred conformer	Difference in dipole between the *gauche* and *anti* conformers (D)	Interaction underlying the predicted effect
-NH_3^+	−6.65	−7.37	Strongly gauche	NA	Electrostatic Fδ$^-$ and NH_3^+ δ$^+$
-NO_2	−1.22	−1.12	Strongly gauche	4.42	Anti-parallel δ$^-$FC-H and N δ$^+$-O δ$^-$; Fδ$^-$ and N
-NCHO	−1.00	−1.12	Strongly gauche	4.53	Electrostatic C-F δ$^-$ and N-H δ$^+$
-F	−0.82	−0.66	Strongly gauche	3.02	σC(F)-H to σ*C-F
-N_3	−0.76	−1.21	Strongly gauche	3.42	Electrostatic C-F δ$^-$ and central N δ$^+$
-N=C=O	−0.74	−1.06	Strongly gauche	3.97	Electrostatic C-F δ$^-$ and C=O C δ$^+$
-CH=NH	−0.25	−0.65	Strongly gauche	3.62	
-CH_3	−0.18	−0.35	Weakly gauche	2.11	
-$CH{=}CH_2$	−0.01	−0.17	Weakly gauche	1.95	
-C≡N	0.64	−0.64	Strongly anti	4.68	p orbital repulsion
-CHO	0.84	−1.20	Strongly anti	3.82	p orbital repulsion and anti-parallel dipole: C=Oδ$^-$···δ$^+$HCF δ$^-$
-C≡CH	0.98	−1.03	Strongly anti	2.18	p orbital repulsion

2.1 Fluorine-Fluorine Interactions

The conformation of fluoroalkane derivatives is of considerable contemporary interest. The influence of fluorine on the conformation of vicinally substituted compounds is based on a stabilizing *gauche* interaction that relies upon hyperconjugation between a C-H bond and the low lying σ* orbital of the C-F bond. The energy of this interaction is estimated to be 0.8 kcal mol^{-1}, modest but

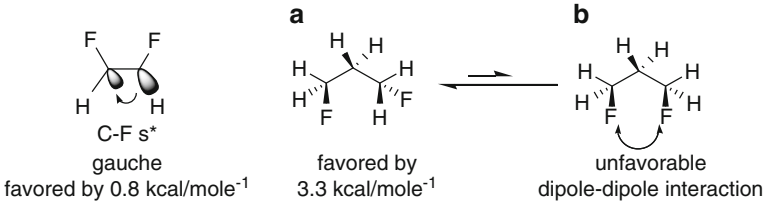


Fig. 2 (**a**) Conformation of 1,2-difluoroalkane, (**b**) conformational preference of 1,3-difluoropropane

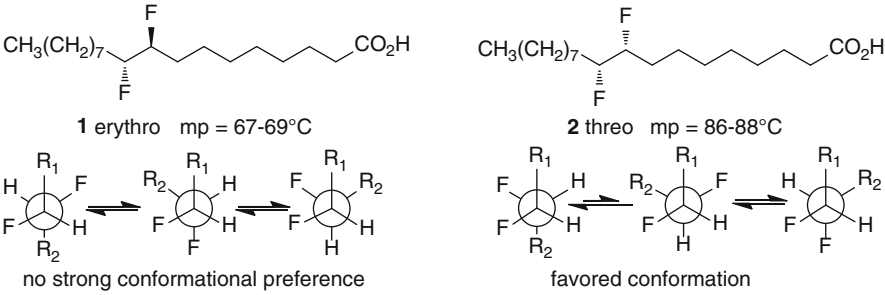


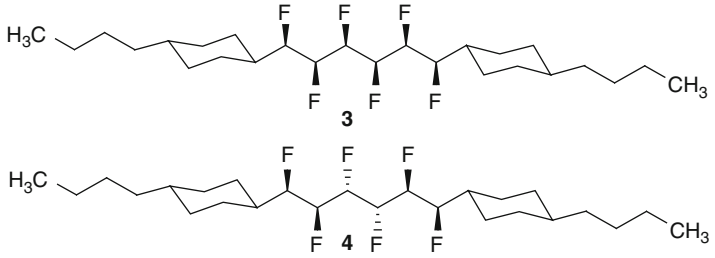
Fig. 3 *erythro*- and *threo*-9,10-difluorostearic acid **1** and **2** and Newman projections capturing their preferred conformations

nevertheless sufficient to exert an influence on conformation [21, 24] (Fig. 2a). In addition, there is a destabilizing repulsion between fluorine atoms in a 1,3-relationship that is of higher energy and which minimizes unfavorable dipole-dipole interactions [21, 24, 25]. The preferred conformation of 1,3-difluoropropane shown in Fig. 2b is estimated to be 3.3 kcal/mol^{-1} more stable than the alternative [21, 24, 25].

An interesting example of the effect of the preference for a *gauche* arrangement of vicinal fluorine atoms on physical properties is provided by the two diastereomers of 9,10-difluorostearic acid, **1** (*erythro*) and **2** (*threo*), which were carefully synthesized in a fashion that ensured stereochemical integrity (Fig. 3) [24, 26]. These molecules differ only by the stereogenicity of the fluorine atom at C-10 yet their melting points differ by 20 °C, with the *erythro* isomer **1** melting at 67–69 °C while for *threo* isomer **2**, the melting point is 86–88 °C. The *threo* isomer **2** was anticipated to be the more stable isomer, with the fully extended form favored by the conformational preference exerted by the *gauche* interaction between the two F atoms, a conformation similar to that adopted by the native fatty acid. Langmuir isotherm measurements confirmed the similarity between **2** and stearic acid whilst the *erythro* isomer **1** displayed significant disorder, consistent with the lower melting point [24, 26]. In the Newman projections about the C9-C10 bond of **1**, the stabilizing effect of the *gauche*-disposed F atoms is offset by unfavorable

interactions between the two carbon chains such that none of the conformations are preferred although all are accessible.

Derivatives in which the vicinal difluoromethylene motif is extended to include 3, 4, 5 and 6 fluorine atoms have been examined to determine conformational preferences [24]. The most sophisticated study focused on the hexafluoromethylene motif, carefully assembled in the diastereomers **3** and **4**, that extended earlier studies on tetra- and pentafluoro alkanes [24, 27]. The conformation of these compounds, both in the solid state and in solution, indicates that in order to avoid unfavorable 1,3-dipolar interactions between F atoms, **3** adopts a helical topography that simultaneously allows the vicinal fluorine atoms to adopt the preferred *gauche* arrangement. The same effect favors an extended *anti* conformation for **4** that presents no unfavorable 1,3-dipolar interactions and facilitates 3 out 5 possible *gauche* arrangements of the vicinal fluorine atoms [24, 27].



2.2 *Fluorine-Amide Interactions*

The conformation of α-fluoro-substituted amides is dominated by dipole-dipole interactions between the C-F and C=O bonds, with additional support from a productive electrostatic interaction between the fluorine atom and the amide NH if the molecule is configured appropriately [20, 28–33]. The synthesis and analysis of the enantiomers of α-fluoro capsaicin (**6**) as vanilloid receptor agonists is illustrative of the potential to take advantage of this kind of effect in drug design. *Ab initio* calculations of the rotational energy profile of 2-fluoro-*N*-methylpropanamide indicated that the *trans* conformer was the most stable with a 6 kcal mol^{-1} advantage over the *gauche* conformer which was 2 kcal mol^{-1} more stable than the *cis* conformer (Fig. 4) [28, 29, 33]. The stability of the *trans* conformation is attributed to a favorable alignment of the C-F and C=O bond dipoles supported by a productive electrostatic interaction between the F and amide H atoms. In the case of **6**, the (*R*) and (*S*)-enantiomers would be expected to adopt conformations that stereo-differentiated the side chain projection vectors, potentially providing insight into the bound conformation of the natural **5** [33].

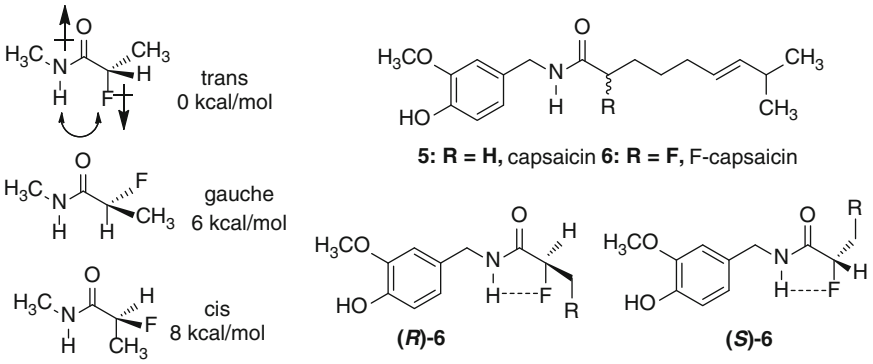
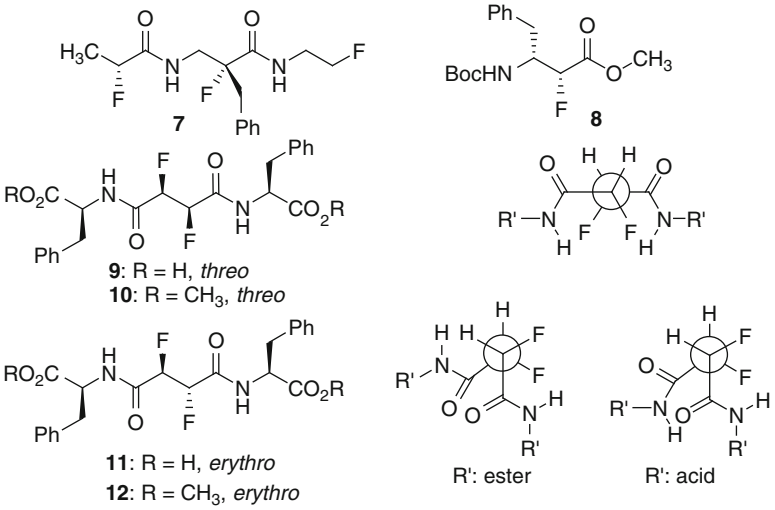


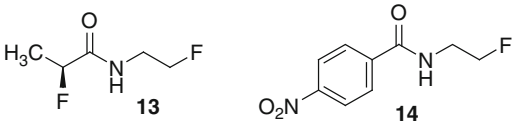
Fig. 4 *Ab initio* energies of conformers of *N*-methyl-2-fluoropropanamide. Potential conformation of (*R*) and (*S*)-α-fluoro capsaicin (**6**) at the TRPV1 receptor explored by these molecules

However, both the (*R*) and (*S*)-enantiomers of **6** performed similarly as TRPVI receptor agonists, leading to the conclusion that the conformation captured by **5** in Fig. 4 in which the alkyl side chains project in vectors parallel to each other and in the plane defined by the amide moiety represents that of the natural product rather than that in which the alkyl chains project orthogonally to the plane of the amide, as depicted in (*R*)-**6** and (*S*)-**6** in Fig. 4 [33].

A study examining the effect of fluorination on the conformational preferences of β-peptide derivatives installed the fluorine atom α- to the amide carbonyl, a topology that simultaneously placed the F β- to the amine moiety. This structural arrangement allowed an analysis of the roles of the dipole-dipole effect between F and C=O and the *gauche* interaction between vicinally-deployed F and amide moieties [34]. X-ray crystallographic structures of the synthesized compounds revealed that the C-F and C=O bonds aligned in an *anti*-periplanar conformation to satisfy the dipole interactions whilst the F and amide moieties adopted the anticipated *gauche* arrangement [34, 35]. In the representative compound **7**, the torsion angle associated with the fluoropropionamide moiety in the solid state was −172.46° whilst that for the other α-fluoroamide was −179.7°. For the internal F-CH_2-CH_2-NHCO element, a torsion angle of −73.7° satisfied a *gauche* arrangement; however, in this particular example the F atom of the terminal NH-CH_2-CH_2-F moiety was disordered, interpreted as an effect of packing forces overcoming a *gauche* preference calculated to be 1.8 kcal mol^{-1} [34, 35]. In the ester **8**, the torsion angle between the F atom and the ester C=O moiety was 154.5°, reflecting a reduced preference that is based on the weaker dipole associated with an ester that manifests as a calculated stabilization energy for the *anti*-periplanar form of 4.5 kcal mol^{-1}, which compares to 7.5 kcal mol^{-1} for an α-fluoro amide and 2.2 kcal mol^{-1} for an α-fluoro ketone [20, 28, 29, 35, 36].



The difluoro succinamide esters **9** (*threo*) and **11** (*erythro*) and the corresponding acids **10** (*threo*) and **12** (*erythro*) were prepared and the solid state structures determined which revealed conformational differences that were reflected in the preservation of a vicinal F-F *gauche* interaction in all 4 molecules [31, 32]. In the case of **11**, one of the fluorine-carbonyl pairs adopted a higher energy conformation that sacrificed the dipole-preferred *anti*-periplanar arrangement whilst in **9**, **10**, and **12** all arrangements between F and the C=O moieties were in, or very close, to the preferred *anti*-periplanar topography [31, 32]. NMR studies that analyzed $^{3}J_{HF}$ and $^{3}J_{HH}$ coupling constants revealed that these conformations were also prevalent in solution, underscoring the influence of the F-*gauche* effect.



The preference for a *gauche* relationship between fluorine and the N-CO moiety observed in **7** and **8** is of broader significance as a conformational tool. In the solid state, the conformation of 2-fluoro-*N*-(2-fluoroethyl)-propionamide (**13**) reflects a *gauche* relationship between the fluorine and NH-CO moieties, torsion angle = −69.9°, whilst the F atom α- to the amide carbonyl is aligned in a fashion consistent with the preferred dipole interactions in which the two are *anti*-periplanar, torsion angle = 2° [29]. A similar phenomenon is observed with **14** [35].

A particularly striking example of the *gauche* effect in β-fluoroamides is provided by the two 4-F proline diastereomers **15** and **16**. Here the fluorine atom exerts a significant influence on the conformational mobility of this unique amino acid, providing insight into the stabilizing influences of 4-hydroxyproline (**17**, Hyp), prevalent in the natural protein collagen [22]. Collagen is comprised of repeat units of Xaa-Yaa-Gly in which Xaa and Yaa are frequently proline or 4-(*R*)-Hyp. The polypeptide associates into a tightly-wound triple helix fibril, the thermal stability of which is enhanced by the presence of the hydroxyl substituent [37–42]. Although this phenomenon was initially attributed to the H-bonding properties of the hydroxyl moiety, a triple helix assembled from $(\text{Pro-4-}(R)\text{-F-Pro-Gly})_{10}$ exhibits a CD spectrum identical to $(\text{Pro-Hyp-Gly})_{10}$ or $(\text{Pro-Pro-Gly})_{10}$ with all spectral data consistent with triple helix formation [37]. These observations support the conclusion that the stabilizing effect of Hyp (**17**) is based on an inductive effect rather than H-bonding. Following this observation, additional studies have evaluated the consequence of substituting the Xaa and Yaa positions with **15** and **16** rather than proline and Hyp (**17**), with the results leading to a deeper understanding of collagen conformation [38–43]. Proline has an inherent preference for the C^{γ}-endo conformation, calculated as 0.41 kcal mol^{-1}, which favors this conformer by 2:1 at room temperature (Fig. 5) [44]. The introduction of a 4-(*S*)-F substituent (**16**) augments this preference, increasing the stability to a difference of 0.61 kcal mol^{-1}, stabilized by the *gauche* effect between the F and amide moieties that facilitates a conformation in which the F atom adopts an axial disposition (Fig. 5) [43, 44]. This effect is manifested in the single crystal X-ray of Boc-4-(*S*)-fluoroproline [43]. However, in 4-(*R*)-fluoroproline (**15**) the C^{γ}-exo conformation is favored by 0.85 kcal mol^{-1}, stabilized by the *gauche* effect between the F and amide moieties that also disposes the F atom axially [44]. This phenomenon is mimicked by Hyp (**17**) where the C^{γ}-exo conformer is calculated to be 0.48 kcal mol^{-1} more stable than the C^{γ}-endo conformer [45]. These insights provide an explanation for the structural similarity of $(\text{Pro-4-}(R)\text{-F-Pro-Gly})_{10}$, $(\text{Pro-Hyp-Gly})_{10}$ and $(\text{Pro-Pro-Gly})_{10}$. Additionally, in **15**–**17** the E_{trans} isomer of the peptide bond is calculated to be more stable than the E_{cis} isomer regardless of the ring pucker, with the energy differences providing a stability hierarchy of 4-(*R*)-Pro > Pro > 4-(*S*)-Pro (Fig. 5) [38, 44]. The preference for an E_{trans} geometry has been attributed to this conformation allowing a favorable n-π* interaction between the O atom of the C=O moiety bound to the ring N atom and the C=O carbon of the exocyclic amide, as depicted in Fig. 5 [38, 46–48].

Molecular modeling studies have suggested that when proline is in the Xaa position of a $(\text{Pro-Pro-Gly})_{10}$ helical strand, it adopts a C^{γ}-endo pucker but when in the Yaa position a C^{γ}-exo conformation is preferred, consistent with the observations noted above that $(\text{Pro-4-}(R)\text{-F-Pro-Gly})_{10}$, $(\text{Pro-Hyp-Gly})_{10}$ and $(\text{Pro-Pro-Gly})_{10}$ form stable helical complexes [39, 49]. When a substituted proline is installed at the Xaa position, the conformational preference for the C^{γ}-endo conformation would suggest that 4-(*S*)-F-Pro would function to form a collagen-like helix structure but the 4-(*R*)-F-Pro diastereomer would not based on their conformational bias [39, 43]. This has been observed experimentally with both

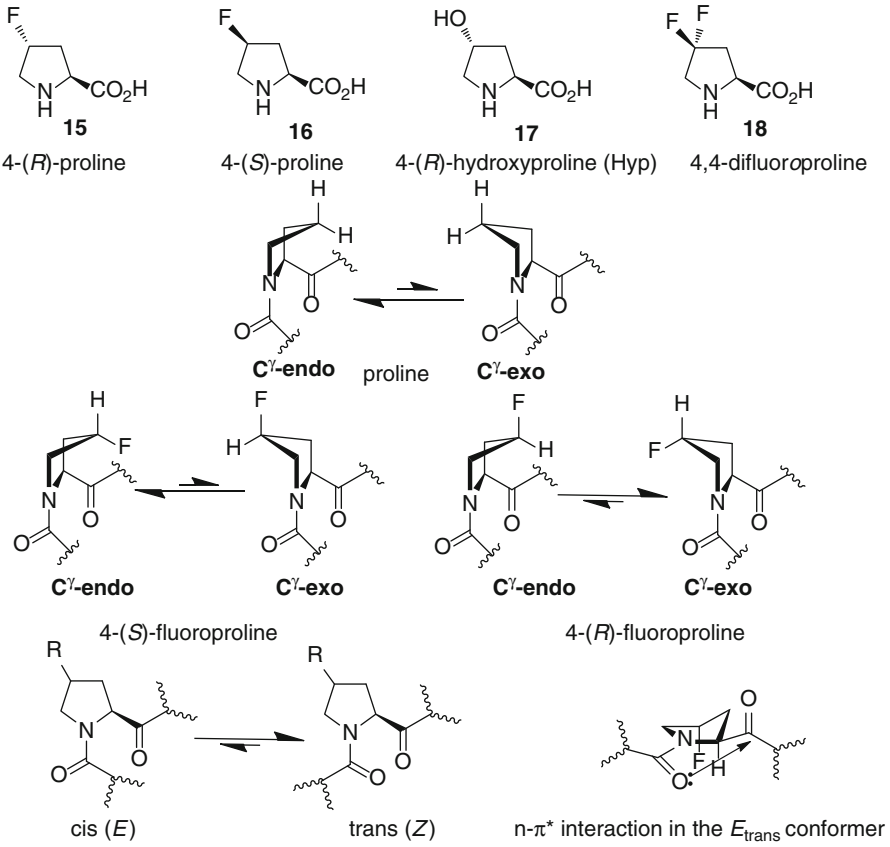
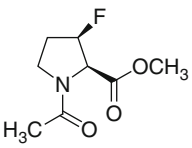


Fig. 5 Conformational preferences for proline, 4-(*S*)- and 4-(*R*)-fluoroproline. Preferred equilibrium for *cis-trans* amide isomerism in proline derivatives and stabilization of the *trans* isomer by a n to π* interaction

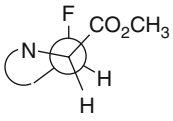
(4-(*S*)-F-Pro-Pro-Gly)$_{10}$ and 4-(*S*)-F-Pro-Pro-Gly)$_7$ forming stable triple helices while (4-(*R*)-F-Pro-Pro-Gly)$_{10}$ and (4-(*R*)-F-Pro-Pro-Gly)$_7$ do not [39, 43]. Similarly, 4,4-difluoroproline (**18**), which offers no conformational bias, does not substitute effectively for Hyp (**17**) to form stable triple helices in collagen-related peptides [42].

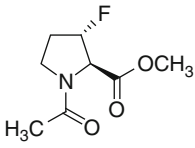
Incorporation of fluorine at the 3-postion of proline also introduces a conformational bias, a phenomenon initially explored with the diastereomeric esters **19** and **20** [50]. These molecules crystallized with the *trans* configuration between the amide and ester moieties, as depicted in **19** and **20**, but the conformation of the proline rings differed, each stabilized by a *gauche* interaction between the F and amide moieties that deployed the halogen in an axial orientation. In **19**, the pyrrolidine ring adopted the Cγ-exo conformation, which contrasts with **20** where the Cγ-endo

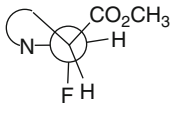
arrangement prevailed [50]. The stereoelectronic effects of the 3-F-prolines **19** and **20** are complementary to those of the 4-F isomers **15** and **16**. Thus, an *anti* orientation of the fluorine atom with respect to the ester moiety results in the C^{γ}-endo conformation for **20** but a C^{γ}-exo for **15** with the opposite effect for the *syn* epimers [50]. The C^{γ}-endo conformation of **20** was found to be present in solution as assessed by the coupling constant between the α- and β-protons in the ^{1}H NMR spectrum. This coupling constant was ≤1 Hz and the calculated thermodynamic parameters suggested that this would be populated to the extent of 97 %. In contrast, the C^{γ}-exo conformation of **19** was predicted to amount to 69 % of the population, attributed to repulsion between the F atom and adjacent ester moiety as a consequence of unfavorable steric and electronic interactions [41, 50]. The conformational preferences of **19** and **20** were preserved when these proline derivatives were incorporated into short peptide sequences [41, 50, 51].



19: 3-(*R*)







20: 3-(*S*)

2.3 Fluorine-Amine Interactions

Protonated β-amino fluoroalkanes show a strong preference to adopt a *gauche* conformation based on a favorable electrostatic interaction between the ammonium moiety and the electronegative F atom, the energetics of which are estimated to be 5.8 kcal/mol [20, 23, 52]. In the unprotonated form, 2-fluoroethylamine experiences only a weakly stabilizing intramolecular interaction between the NH_2 and F that has been viewed as a bridging H-bond estimated at ~1 kcal mol^{-1} in favor of the *gauche* conformation, although the precise nature of fluorine-hydrogen interactions is controversial (*vide infra*).

In cyclic amines, such as the protonated form of 3-fluoro-*N*-methyl-piperidine (**21**), these interactions provide significant conformational bias [53–55]. In **21**, the ring F atom strongly prefers an axial disposition despite experiencing steric compression, with the calculated conformer populations provided in Fig. 6 [55]. As the global minimum, conformer A dominates to the extent of 95–96 %, stabilized by an electrostatic interaction between the F and NH^{+} moieties, whilst conformer D contributes 4–5 % at equilibrium with the unfavorable diaxial interactions compensated by a productive electrostatic effect.

Trans-4-fluoro-L-proline (**15**) and its *cis*- isomer **16** both adopt a defined conformation in aqueous solution in which the favored conformations project the F atom in an axial orientation that is *gauche* with respect to the amino moiety [56].

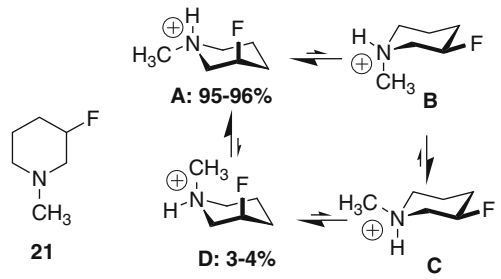


Fig. 6 Conformational preference of **21** in its protonated form

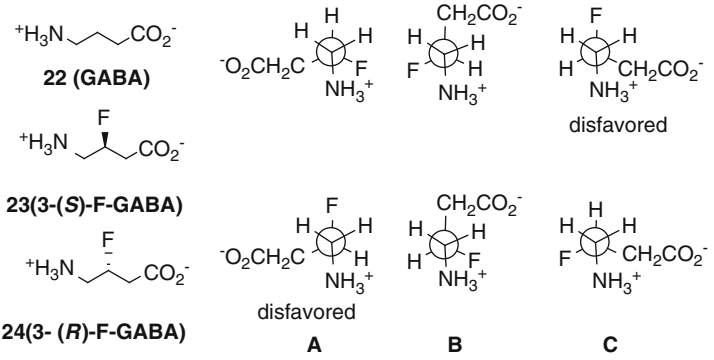


Fig. 7 GABA (**22**), the enantiomeric fluorinated derivatives **23** and **24** and their preferred conformations

The two fluorinated enantiomers **23** and **24** of the neurotransmitter γ-aminobutyric acid (GABA, **22**) represent an interesting example where the preferred *gauche* disposition between a protonated amine and a fluorine atom was used to glean insight into aspects of biologically-relevant conformations (Fig. 7) [57, 58]. The introduction of fluorine to GABA (**22**) reduces the basicity and increases the acidity of the natural amino acid in a fashion that preserves the zwitterionic nature at neutral pH. In solution, an extended conformation was observed for all molecules based on NMR analysis, stabilized in the case of **23** and **24** by the *gauche* interaction between the F and NH_3^+ moieties [57]. The range of conformations for each enantiomer are captured in Fig. 7 which also notes those that would be disfavored based on the absence of a *gauche* effect [57]. Both **23** and **24** were found to activate the cloned human $GABA_A$ receptor with similar potency but were markedly less potent than GABA (**22**) itself [57, 58].

This observation suggested that the bound form of the neurotransmitter was the extended form accessible to both **23** and **24** in a fashion that preserves the *gauche* relationship between F and NH_3^+, represented by conformation B in Fig. 7 [57, 58]. However, GABA aminotransferase caused elimination of HF from the (*R*)-isomer

24 with 20-fold higher efficiency than for the (*S*)-isomer **23**. This suggested that the conformation recognized by the enzyme placed the NH_3^+ and $CH_2CO_2^-$ moieties in a *gauche* arrangement that would be destabilized, consistent with conformation C being preferred [57, 58] (Fig. 7). This conformation was also deduced to be that preferably recognized by the $GABA_C$ receptor [59]. Both **23** and **24** were found to act as agonists rather than antagonists at ρ1 and ρ2 $GABA_C$ receptors, with the (*R*)-isomer **24** the more potent but still ten-fold weaker than GABA (**22**), whilst the (*S*)-isomer **23** was 20-fold weaker than the natural ligand, attributed to weaker electrostatic interactions as a consequence of the reduced basicity. These observations suggested that GABA (**22**) adopted a folded binding orientation represented by conformation C at the $GABA_C$ receptor [59].

An analogous strategy was adopted to probe the bound conformation of *N*-methyl-D-aspartate (**26**), an agonist of the neurotransmitter glutamic acid (**25**), at recombinant GluN2A and GluN2B receptors expressed in *Xenopus laevis* oocytes (Fig. 8) [60]. (2*S*,3*S*)-3F-NMDA (**27**) was prepared in an enantiospecific fashion whilst (2*S*,3*R*)-3F-NMDA (**28**) was obtained along with the (2*R*,3*S*)- stereoisomer after separation of diastereomeric α-methylbenzylamine precursors. Analysis of ^{1}H- and ^{19}F NMR spectra indicated distinct chemical shifts and coupling constants for the individual compounds that were consistent with (2*S*,3*S*)-3F-NMDA (**27**) in solution adopting conformation A, shown in Fig. 8, whilst (2*S*,3*R*)-3F-NMDA (**28**) avoided conformer C and was concluded based on DFT calculations to prefer conformer B, the conformer observed in the single crystal X-ray structure. In the biological assays, (2*S*,3*S*)-3F-NMDA (**27**) evoked currents in oocytes expressing either GluN2A or GluN2B receptors, although the responses were less than that observed with NMDA (**26**), whilst (2*S*,3*R*)-3F-NMDA (**28**) and its enantiomer were essentially inactive [60]. These results suggested that only (2*S*,3*S*)-3F-NMDA (**27**) was able to adopt a conformation similar to that of bound NMDA (**26**), designated as A in Fig. 8. This result is consistent with X-ray crystallographic data of NMDA (**26**) bound to the GluN2D receptor which is highly homologous to the GluN2A and GluN2B receptors.

The effect of a fluorine atom β- to a protonated amine on conformational preference and its potential impact on biological recognition has further been documented in 8-membered rings and in fluorinated pyrrolidine elements incorporated to replace the peripheral pyrrolidines of G-quadruplex binding ligands based on an acridine scaffold [61, 62].

2.4 Fluorine-Hydroxyl and Fluorine-Alkoxy Interactions

The *gauche* conformation of β-fluoroethanol derivatives has been estimated to be favored by ~2 kcal mol^{-1} when the F and OH moieties can engage in an intramolecular H-bonding-like interaction [52, 63, 64]. In the absence of this interaction, the preference for the *gauche* relationship is essentially absent, with an energy

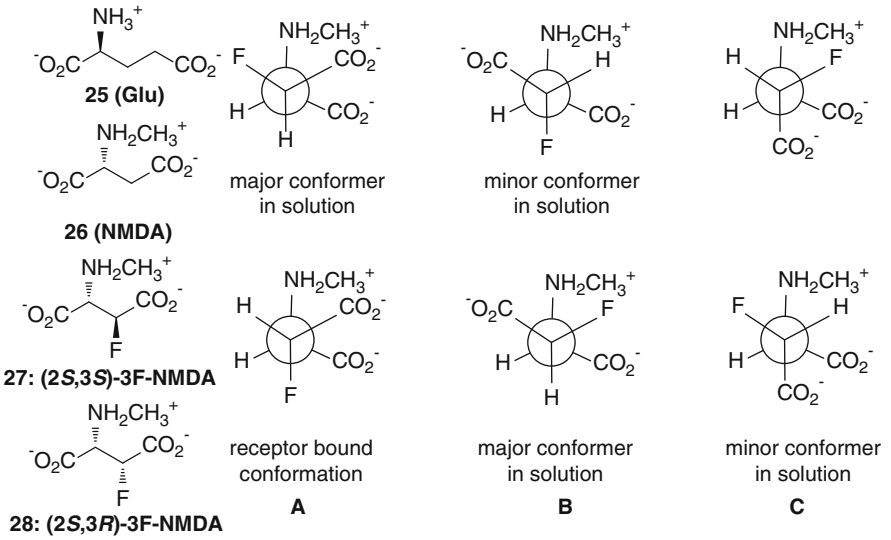
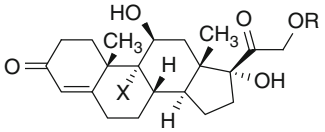


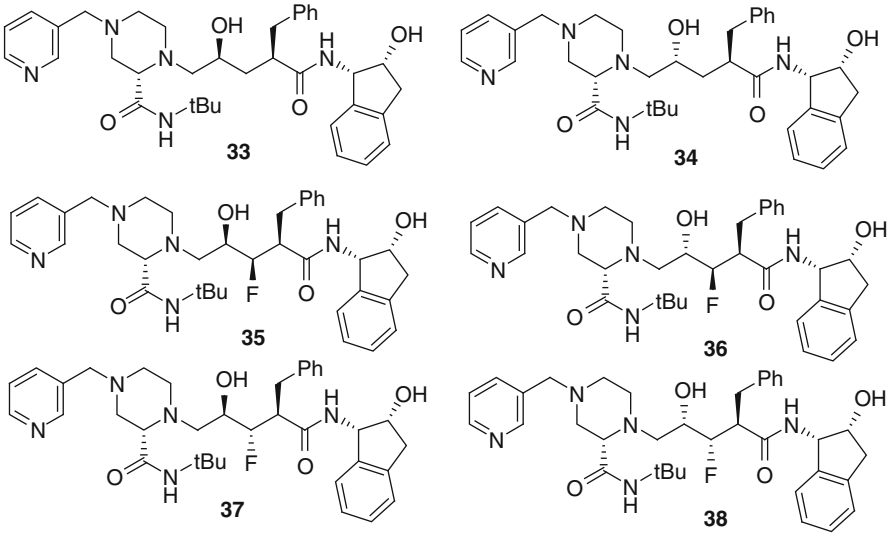
Fig. 8 Structures of glutamic acid (**25**) NMDA (**26**), the enantiomeric fluorinated derivatives **27** and **28** and their preferred conformations

estimated at only 0.1–0.2 kcal mol^{-1}. However, protonation of the alcohol significantly enhances the stability of the *gauche* conformer, estimated at ~7 kcal mol^{-1} and attributed to a combination of both a stereoelectronic effect and an intramolecular HO-F interaction [52, 63, 64]. Several drug design studies have attempted to exploit the effects of deploying F and OH moieties in a vicinal arrangement that either take advantage of the *gauche* conformational preference or the effect of F on the H-bonding potential of the hydroxyl. An early example explored the effect of replacing the C-9 α-H atom of hydrocortisone acetate (**29**) with F to afford **30**, which demonstrated ten-fold greater glucocorticoid activity in restoring liver glycogen deposition in the adrenalectomized rat and four- to nine-fold higher activity at increasing the survival time of adrenalectomized dogs with a concomitant reduction in sodium retention [65, 66]. Fludrocortisone (**32**) is an anti-inflammatory agent that improved on the therapeutic index of the progenitor hydrocortisone (**31**) and was the first marketed fluorinated pharmaceutical product [67]. The origin of the improved biological properties of fluorinated steroids remains enigmatic and may be a function of the combination of several effects that includes the increased acidity of the 11β-hydroxyl moiety, a distortion of the A ring due to non-bonded interactions between the F atom and proximal axial substituents and reduced metabolism *in vivo* [14, 68–70].



29: X = H, R = $COCH_3$
30: X = F, R = $COCH_3$
31: X = H, R = H
32: X = F, R = H

The judicious introduction of a fluorine atom into the HIV-1 protease inhibitor indinavir (**33**) and epi-indinavir (**34**) provided an opportunity to assess the effect of F-OH interactions on biological properties related to conformational disposition [71]. The four fluorinated derivatives **35**–**38** were prepared with the anticipation of complex effects due to the F atom which was expected to affect the acidity of the OH and influence the population of conformers in addition to affecting steric interactions and solvation. The K_i data for the inhibition of HIV-1 protease are summarized in Table 2 and reveal interesting profiles.



The syn, syn fluorinated derivative **35** fully retained the activity of the parent drug **33** while the anti,anti isomer **37** was an order of magnitude weaker. For the epi-indinavir derivatives **36** and **38**, the syn,anti analogue **38** improved potency by eight-fold over **34** whilst the anti,syn diastereomer exhibited a 36-fold weaker Ki [71]. An analysis of the ^{1}H-^{1}H and ^{1}H-^{19}F coupling constants indicated that the syn,syn (**35**) and syn,anti (**38**) diastereomers adopted the fully extended conformation that characterizes indinavir (**33**) when bound to HIV-1 protease, attributed to

Table 2 K_i data of **33**–**38** for the inhibition of HIV-1 protease

Compound	Ki (nM)	Log *P*	Compound	Ki (nM)	Log *P*
33	1.9	3.03	**36**	5,900	3.31
34	160	3.02	**37**	27	3.01
35	2.0	3.23	**38**	20	3.12

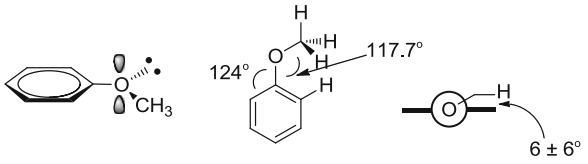
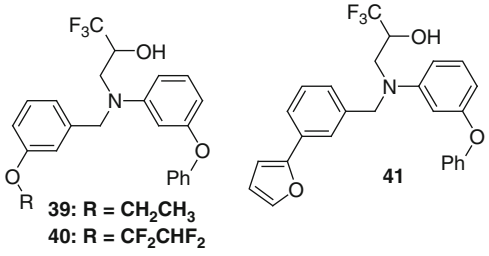


Fig. 9 Conformation of arylmethyl ethers

the preference of F and OH to adopt a gauche relationship. In contrast, the other 2 diastereomers **36** and **37** populated additional conformers to a significant extent, providing an explanation for the observed reductions in potency. The lipophilicity of each of the diastereomers was determined from the measured 1-octanol/water partition coefficient and all were marginally increased compared to indinavir (**33**), with the exception of the anti,anti analogue **37**.

Fluorination also impinges on the conformation of ethers, most prominently in anisoles [15, 72–74]. Arylmethyl ethers without *ortho* substituents adopt a conformation in which the methoxy moiety is close to coplanar with the aryl ring, a consequence of rehybridization of the substituent that maximizes electronic overlap of the oxygen atom with the π system and overcomes the inherent allylic 1,3-strain, with bond angles summarized in Fig. 9 [75–79]. In contrast, the trifluoromethoxy substituent is typically orthogonal to the plane of the benzene ring, favored by 0.5 kcal mol^{-1}, inverting the calculated 3 kcal mol^{-1} preference for planarity observed with anisole [15, 80]. Difluoralkoxyaryl moieties behave similarly, indicating that these structural elements should not be considered as simple isosteres of alkoxy substituents but as moieties capable of exploring a broader range of conformational space [15, 74].

The arylethyl ether **39** is an inhibitor of cholesterol ester transfer protein, $IC_{50} = 1.6$ μM, but the fluorinated homologue **40** is eight-fold more potent, $IC_{50} = 0.2$ μM, attributed to a combination of steric effects and drug-protein interactions that are more favorable in **40** [73].



Ab initio calculations indicated that while the ethoxy moiety preferred a conformation coplanar with the aryl ring, the fluorinated ether projected in a vector that was more perpendicular. Interestingly, a 2-furyl substituent provided the optimal OCF_2CHF_2 mimetic, $IC_{50} = 0.48$ μM, attributed to the preferred conformation of the furan ring also being orthogonal to the plane of the phenyl moiety [73].

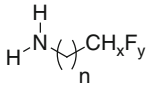
3 Modulation of pK_a with Fluorine

Fluorine is the most electronegative element (Pauling electronegativity of 3.98) [84]. Due to the significant electron-withdrawing influence that fluorine exerts inductively through σ-bonds, fluorine substituents typically lower the pK_a of neighboring functionality (although exceptions exist [81]): protic groups become more acidic as measured by a decrease in the pK_a of the functional group itself, and basic groups become less basic as measured by a decrease in the pK_a of the conjugate acid. The ionization state of basic and acidic functionality not only affects potency and the absorption, distribution, metabolism, and excretion (ADME) properties of a molecule, but may also play a role in reducing the potential for a compound to exhibit toxicity [82]. Specifically, molecules incorporating basic nitrogen atoms are known to be more promiscuous and may show increased potential for cardiovascular toxicity *via* promoting interference with the hERG potassium ion channel and may increase the occurrence of phospholipidosis [83–86]. The significant influence of fluorine on the pK_a of adjacent functionality, in combination with other desirable properties including a small steric volume (similar in volume to oxygen) and high metabolic stability of the C-F bond, provides a powerful tool by which to modulate pK_a during drug candidate optimization [14].

3.1 pK_a Trends with Fluorine Substitution

An understanding of the correlation between fluorine substitution and pK_a enables a rational approach to drug candidate optimization. For acyclic aliphatic amines, the observed pK_a often represents the contribution of a conformational average of substituents and, as a consequence, the decrease in pK_a due to fluorine substitution is generally additive [87]. As shown in Fig. 10, the shift in pK_a of aliphatic amines due to fluorine substitution can be accurately predicted based on this additive property. The significance of the effect decreases with increased σ-transmission distance: each fluorine substituent at the β-carbon reduces the pK_a by 1.7 units, at the γ-carbon by 0.7, and at the δ-carbon by 0.3. As a point of reference for the calculation, the pK_a of alkyl amines can be generally approximated as primary amine = 10.7; secondary amine = 11.1; and tertiary amine = 10.9 [87, 88]. The chain length of the alkyl groups does not generally shift the pK_a of the amine; however, *N*-methyl substitution is an exception (Fig. 11) [87].

For unstrained cyclic amines in saturated systems the change in pK_a upon substitution can be approximated by summing the contribution of both σ-transmission pathways [87, 88]. Figure 12 demonstrates the application of this approach towards a series of substituted piperidines. For example, in 3-fluoropiperidine there are two σ-transmission pathways from the fluorine atom to the nitrogen atom: “path



	Prediction	Experimental pK_a			
n	ΔpK_a	*y*=0	*y*=1	*y*=2	*y*=3
1	-1.7	10.7	9.0	7.3	5.7
2	-0.7		9.9		8.7
3	-0.3	10.7			9.7
4	-0.1				

Fig. 10 For aliphatic amines, the change in pK_a due to fluorine substitution is generally additive in nature [88]

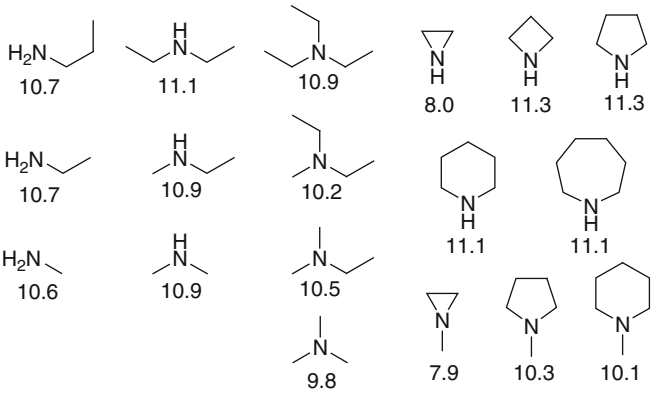
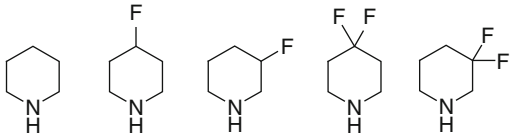


Fig. 11 pK_a values of acyclic and cyclic alkyl amines [88, 89]



predicted	σ-path 1		γ = -0.7	δ = -0.3	γ = -1.4	δ = -0.6
	σ-path 2		γ = -0.7	β = -1.7	γ = -1.4	β = -3.4
	ΔpK_a		-1.4	-2.0	-2.8	-4.0
observed	pK_a	11.1	9.4	9.3	8.5	7.4
	ΔpK_a		-1.7	-1.8	-2.6	-3.7

Fig. 12 Predicted and observed pK_a of fluoro-substituted piperidines [88]

1"=F-C-C-C-C-NH and "path 2"=F-C-C-NH. The pK_a of 3-fluoropiperidine can therefore be predicted using the values of the linear system provided in Fig. 10: pK_a = 11.1 (piperidine) – 0.3 ("path 1") – 1.7 ("path 2") = 9.1. This predicted value is in close agreement with the experimental pK_a of 9.3.

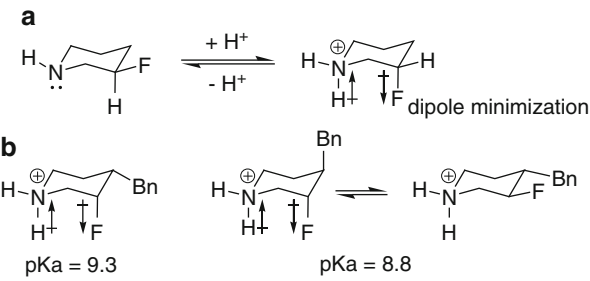


Fig. 13 Dipole minimization of the N^+–H and C-F bond leads to stabilization of the protonated amine

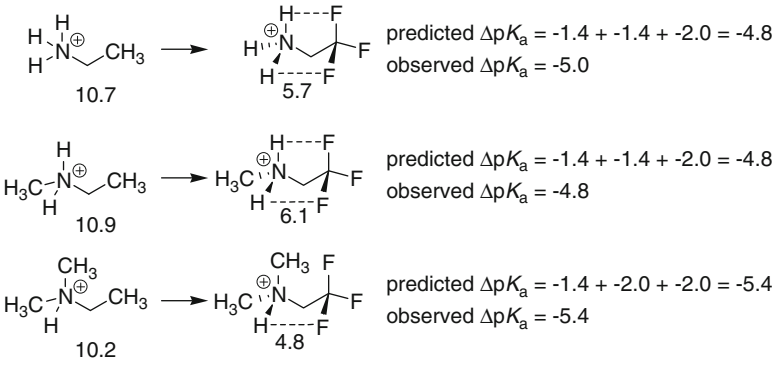
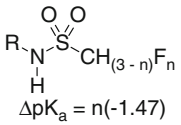


Fig. 14 The *syn*-β-fluoro effect can be used to refine pK_a predictions for amines containing β-fluoro substitution [88]

That the observed pK_a of 3-fluoropiperidine is slightly less acidic than predicted may be explained by stabilization of the ammonium species *via* dipole minimization, as depicted in Fig. 13a [88]. In fact, NMR studies with 3-fluoropiperidine have revealed that the 3-fluoro substituent inverts from a completely equatorial orientation to a completely axial orientation upon protonation of the amine [53]. Similarly, the fluoro substituent of *cis*-3-fluoro-4-benzylpiperidine adopts a completely axial orientation in the protonated species leading to stabilization and a pK_a of 9.3 (Fig. 13b). Upon protonation of *trans*-3-fluoro-4-benzylpiperidine, the 3-fluoro substituent occupies both the axial and equatorial orientation equally, leading to reduced stabilization and a pK_a of 8.8 [88].

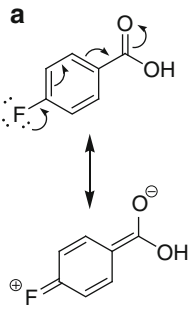
The stabilization of ammonium species *via* *syn*-β-fluoro substituents appears to be a general phenomenon. The ΔpK_a shift due to β-fluoro substitution can be refined to accommodate for this influence: $\Delta pK_a = -1.4$ for a full 1,3-*syn* CF-$^+$NH interaction and $\Delta pK_a = -2.0$ in the complete absence of a 1,3-*syn* CF-$^+$NH interaction [88]. This refinement enables the accurate prediction of pK_a values for primary, secondary and tertiary amines with β-fluoro substituents (Fig. 14).

Table 3 Experimental pK_a measurements from a series of methanesulfonamides demonstrate an additive change in pK_a upon fluorine substitution [90]



n	R=H	R=Ph	R=3-C_6H_4COPh
0	10.8	8.85	8.19[a]
1	9.32[a]	7.57[a]	6.77[a]
2	8.06[a]	6.19[a]	5.44[a]
3	6.33	4.45	3.70[a]

[a]aqueous pK_a values were calculated from experimental measurements obtained with solvent = 67% DMF-H_2O



b

Substituent	$\sigma_{inductive}$	$\sigma_{resonance}$
F	0.45	-0.39
Cl	0.42	-0.19
Br	0.45	-0.22
CF_3	0.38	0.16
CF_3O	0.39	-0.04
CH_3	0.01	-0.15
CH_3O	0.26	-0.56
NO_2	0.65	0.13
CN	0.51	0.15

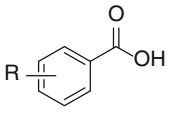
Fig. 15 (**a**) Fluorine is inductively electron-withdrawing but is electron-donating through resonance. (**b**) The discrete inductive contribution and resonance contribution to Hammet's σ_{para} constants [14]

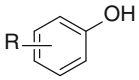
Additionally, the *syn*-β-fluoro effect may, in part, account for the difficulty in predicting the pK_a of imperfectly staggered heterocycles such as fluoro-substituted pyrrolidines [88].

Fluorine substitution of methanesulfonamides also leads to an additive decrease in the pK_a of the NH proton. As shown in Table 3, the decrease in pK_a is approximately 1.47 units per fluorine substituent and is independent of the R-group bound to nitrogen [90]. The linearity observed in this trend is postulated to be due to the small steric changes associated with replacing hydrogen by fluorine and the fact that fluorine substitution is somewhat remote (two atoms away from the acidic site) [90]. In the case of fluoroacetic acids, the decrease in pK_a due to fluorine substitution is not additive: the pK_a of acetic acid = 4.76; fluoroacetic acid = 2.59; difluoroacetic acid = 1.33; and trifluoroacetic acid = 0.50 [91].

Although fluorine exerts a strong electron-withdrawing influence through σ-bonds, fluorine is electron-donating through resonance (Fig. 15a). Due to the excellent 2p orbital overlap between fluorine and carbon, this influence can be quite strong and the significance of this effect is not matched by the other halogens (Fig. 15b) [14, 92]. Due to these opposing forces, the effect of fluorine on pK_a in

Table 4 pK_a values of benzoic acids and phenols [91, 94]





Substituent	pK_a^{ortho}	pK_a^{meta}	pK_a^{para}	pK_a^{ortho}	pK_a^{meta}	pK_a^{para}
H	4.02	4.02	4.02	9.99	9.99	9.99
F	3.27	3.87	4.14	8.73	9.29	9.89
Cl	2.88	3.83	3.99	8.55	9.10	9.43
Br	2.85	3.81	3.99	8.45	9.03	9.34
F_3C	4.0	3.6	3.6	8.3	9.0	8.7
H_3C	3.90	4.27	4.36	10.3	10.0	10.3
H_3CO	4.09	4.08	4.49	9.99	9.65	10.2
NO_2	2.18	3.46	3.44	7.22	8.35	7.15

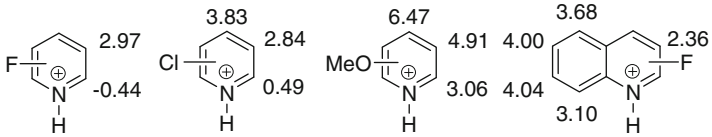


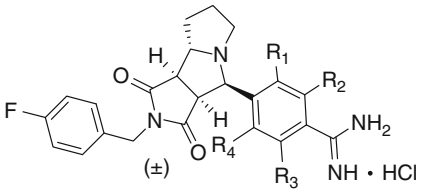
Fig. 16 pK_a values of mono-substituted fluoro pyridines and quinolines (pK_a pyridine = 5.17; pK_a quinoline = 4.85). pK_a values of analogous chloro and methoxy pyridines are provided for comparison [17]

aromatic systems is strongly dependent on the through-resonance relationship of the fluorine substituent and the functional group of interest. Fluorine acts as an electron-withdrawing group in positions *ortho*- or *meta*- to functionality. Fluorine in a *para*-relationship to a functional group behaves as a neutral substituent because the through-resonance electron-donating character of fluorine essentially cancels out its inductive electron-withdrawing influence [92]. As shown in Table 4, this trend is observed with benzoic acids and phenols, archetypical systems of cross-conjugated and directly-bound functionality, respectively. Similarly, the changes in pK_a of aniline (pK_a = 4.62) upon fluorine substitution is: 2-fluoroaniline = −1.40, 3-fluoroaniline = −1.04 and 4-fluoroaniline = +0.03 [17]. Basic heterocycles such as pyridine also follow this trend (Fig. 16). Although the aqueous pK_a of 4-fluoropyridine has not been reported, gas phase measurements indicate that 4-fluoro substitution leads to a small decrease in the pK_a in the gas phase and a predicted aqueous pK_a similar to that of pyridine [93]. It should be noted that the CF_3 group is electron-withdrawing both inductively and through-resonance, and thus always reduces the pK_a of adjacent functionality [93, 94].

4 The Effect of Fluorine Atoms on Drug Potency

Appropriate modulation of pK_a, conformational preference, hydrophobic interaction, hydrogen bonding, lipophilicity, solubility or a combination of these properties exerted by the deployment of fluorine atoms can improve potency/binding affinity and sometimes even selectivity of drug molecules. This phenomenon is manifested in many examples taken from a wide range of areas of medicinal chemistry.

In keeping with the theme from the previous section, the influence of fluorine on the pK_a of basic functionality was systematically studied in the context of optimizing the pharmaceutical properties of a thrombin inhibitor [95]. All permutations of single and double fluorine substitution of the amidinium-bearing arene were synthesized and the pK_a of the amino group of the tricyclic skeleton (pK_{a1}) and the pK_a of the amidinium residue (pK_{a2}) were experimentally determined (Fig. 17). The change in pK_a upon introduction of fluorine followed the expected trends, with the exception of double fluorine substitution *meta*- to the amidinium group, compound **45**. In this case, the pK_a unexpectedly increased to 4.21 from 4.10 measured for the monofluoro analog **44** and insight into this phenomenon was sought through DFT calculations (RB3LYP, 6-31G**). For the mono-fluorinated arene, the *exo*-conformer, which minimizes allylic-1,3-like strain between the nitrogen lone pair and fluorine, is calculated to be 3.4 kcal mol^{-1} more stable than the *endo*-conformer (Fig. 18a). In the difluorinated arene, unfavorable allylic strain is unavoidable, as illustrated in Fig. 18b. Upon protonation, both the mono- and di-fluorinated arenes adopt conformations in which there is a favorable C-F···H-N$^+$ interaction. However, because this favorable interaction is present in both analogs, the increased basicity of the difluoro analog is best explained by the differences observed in the unprotonated state,



	R_1	R_2	R_3	R_4	pK_{a1}	pK_{a2}	log D	K_i (μM)	Selectivity
42	H	H	H	H	4.47	11.14	-1.16	0.057	67
43	H	**F**	H	H	4.21	10.69	-1.08	0.63	22
44	**F**	H	H	H	4.10	10.83		0.61	11
45	**F**	H	H	**F**	4.21	10.36		1.7	7.6
46	**F**	**F**	H	H	3.73	10.28		5.0	4.6
47	H	**F**	**F**	H	3.73	10.06	-0.35	9.0	7.6

Fig. 17 Properties of a series of thrombin inhibitors: the pK_a of the amino group of the tricyclic skeleton (pK_{a1}), the pK_a of the amidinium residue (pK_{a2}), log D, binding affinity (K_i), and selectivity for thrombin compared to trypsin as a function of fluorine substitution [95]

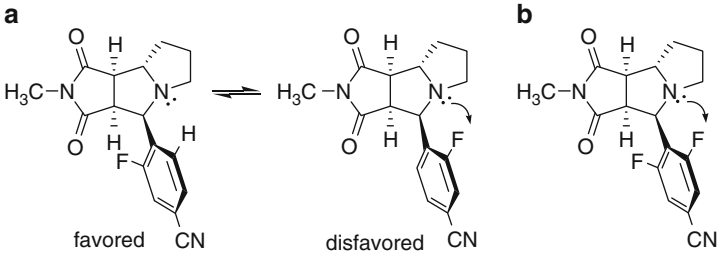
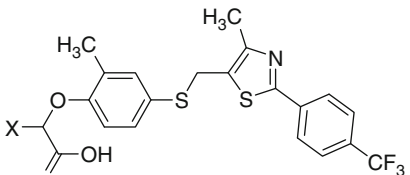


Fig. 18 (**a**) Allylic 1,3-like strain between the fluorine and the nitrogen lone pair disfavors the *endo*-conformation of the mono-fluorinated arene. (**b**) For the di-fluorinated arene, proximation of the nitrogen and fluorine atoms is unavoidable

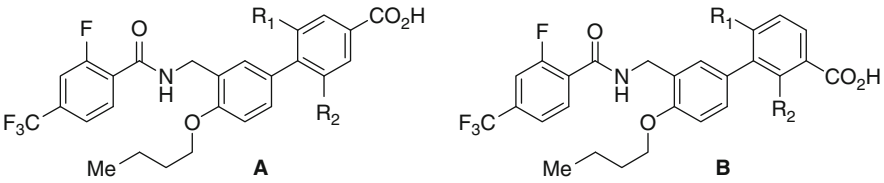


Compound	EC_{50} (nM)	PPARα EC_{50} (nM)	PPARγ EC_{50} (nM)	PPARδ EC_{50} (nM)
48	0.03	>1000	912	2.9
49	3.7	560	>1000	55

Fig. 19 Activation of oleic acid oxidation (EC_{50}) and agonism of individual PPAR subtypes by acids **48** and **49** [97]

i.e., the electrostatic interaction between the C-F dipole and the nitrogen lone pair [91]. In all cases the decrease in pK_a corresponded to a decrease in binding affinity (K_i). Although the change in binding affinity is likely complex in origin, linear free energy relationships correlating pK_a and binding free enthalpies ($-\Delta G$) calculated for inhibition of thrombin and trypsin demonstrated a relationship between affinity and pK_a. Specifically, this analysis found that inhibition of thrombin is 2.5 times more sensitive to the pK_a of the amidine functionality than is inhibition of trypsin, providing a possible means towards increasing thrombin selectivity [95].

Peroxisome proliferator-activated receptors α, δ and γ (PPARα, PPARδ and PPARγ) are implicated in regulating transcription of genes responsible for lipid and carbohydrate metabolism [96]. A series of fluorine-substituted analogs of the PPARδ modulator GW-501516 (**48**) was synthesized and studied based on the hypothesis that fluorine substitution at the α-carbon (**49**) would reduce the pK_a of the adjacent carboxylic acid moiety and lead to stronger binding affinity (Fig. 19) [97]. In practice, the fluoro-substituted analog **49** was a less potent activator of oleic acid oxidation than the progenitor GW-501516 (**48**). However, when the affinity of



Parent	R_1	R_2	solubility (mg/mL)[a]	calculated dihedral angle (deg)	PPARδ EC_{50} (nM)
A	H	H	0.375	43.5	170
A	Me	H	0.985	52.5	11
A	F	H	3.22	36.9	53
B	H	H	1.35	36.9	29
B	Me	H	9.95	57.5	1.6
B	F	F	10.4	46.2	5.7

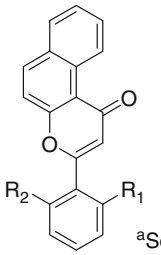
[a]Solubility in equal volumes of EtOH and aq. 1/15 M phosphate buffer (pH 7.4)

Fig. 20 The solubility, calculated dihedral angle, and EC_{50} values for a series of PPARδ agonists [98]

each compound towards the PPAR subtypes was assayed, it was found that the fluoro-analog demonstrated a modestly positive effect on PPARα activation, essentially behaving as a modest dual PPARα/δ agonist. Computational modeling predicted that both enantiomers of the fluoro-analog bound similarly, and that the dual agonism is due to interactions remote from the fluorine atom.

Judicious fluorine substitution can provide a means of improving the solubility of drug molecules. The solubility of several classes of pharmaceutical compounds can be improved by disrupting molecular planarity and, in turn, potentially reduce crystal packing density [98]. Although this argument explains, in part, the observed improvements in solubility, fluorine substitution leading to increased solubility is explained "not only by disrupting molecular planarity but also *via* other mechanism(s)" [98]. In these cases, the trends observed in Fig. 20 can be understood as a manifestation of the inductively withdrawing/resonance-donating electronic effects of fluorine that underlie its influence on pK_a. For example, fluorine substitution *ortho* and *meta* to a carboxylic acids leads to an increase in acidity which can consequently increase solubility. Fluorine is a strong through-resonance donor (*vide supra*) which can impart partial π-bond character to biphenyl systems, leading to a decrease in dihedral angle, but this effect is reduced if there is a strong resonance-accepting group such as a carboxylic acid *ortho* or *para* to a fluorine atom.

This through-resonance effect of a fluorine atom is also manifested in the properties observed with the series of fluorine-substituted aryl hydrocarbon receptor (AhR) agonists depicted in Fig. 21 [98]. The decrease in dihedral angle is most dramatic for the mono-fluoro analog **51** where solubility is increased. Both of these changes are likely due to an increase in polarization resulting from strong through-resonance communication between the fluorine substituent and the ketone



	R_1	R_2	solubility (mg/mL)[a]	calculated dihedral angle (deg)	EROD EC_{50} (μM)[b]
50	H	H	84.6	17.8	1.4
51	F	H	153	9.1	0.33
52	F	F	248	40.5	0.20
53	H	Me	262	37.9	>10
54	Me	Me	1270	70.0	>10

[a]Solubility in equal volumes of EtOH and aq. 1/15M phosphate buffer (pH 7.4).

[b]7-ethoxyresorufin *O*-deethylase (EROD) activity in MCF-7 breast cancer cells.

Fig. 21 The solubility, calculated dihedral angle, and EC_{50} values for a series of AhR agonists [98]

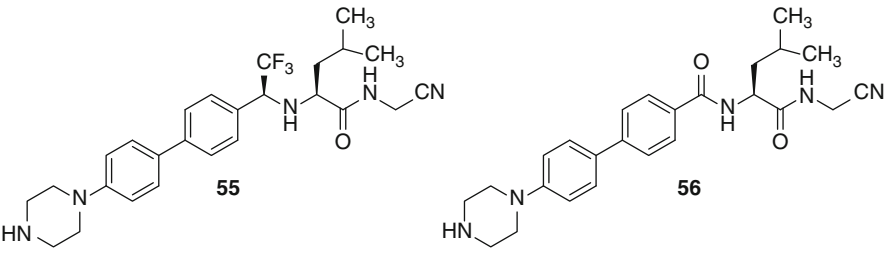


Fig. 22 Cathepsin K inhibitors

functionality. In the case of the difluoro derivative **52**, both the dihedral angle and solubility are similar to the mono-methyl substituted compound **53**, suggesting that disrupting planarity may be the underlying influence. Fortuitously, fluorine substitution also led to an increase in potency as well as solubility.

An example of fluorine substitution in the context of the cysteine protease cathepsin K highlights not only the advantageous impact of fluorine on potency but also the isosteric relationship between a trifluoroethylamine moiety and an amide [99]. The replacement of amide bonds with isosteric functionality has been extensively explored within the field of medicinal chemistry and there are many well-established isosteres of the amide moiety. However, there are only a few isosteres that conserve the hydrogen-bond donating properties of the amide. Reduction of an amide to the corresponding amine not only removes a hydrogen-bond acceptor but also introduces a basic amine, typically providing poor mimetic properties. Addressing this deficiency, the strategic introduction of a trifluoromethyl moiety led to reduced basicity whilst preserving the near 120° backbone angle and conferring isopolarity with the carbonyl moiety, as illustrated by **55** in Fig. 22 [99, 100]. In addition to providing an acceptable isostere for the bis-amide **56**, trifluoroethylamine **55** also exhibited improved potency and selectivity compared to **56**. The trifluoroethylamine derivative **55** was the most potent compound identified, demonstrating an IC_{50} of less than 0.005 nM toward inhibition of cathepsin K. Modeling

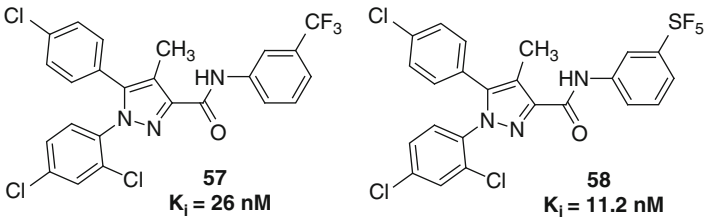


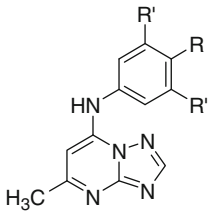
Fig. 23 Cannabinoid CB_1 receptor ligands

and SAR were used to rationalize the stark difference in potency between **55** and **56** [99]. Specifically, in **55** the sp^2 nature of the amide leads to an interaction with the adjacent aromatic ring which enforces a suboptimal geometry for both the aromatic ring and for the hydrogen-bonding interaction to the protease. In the case of **55**, the newly introduced sp^3 center allows for a perpendicular arrangement of the aromatic ring thus stabilizing it in what is presumed to be the active conformation while simultaneously allowing for a more optimal hydrogen bond interaction with a residue in the active site. In addition to improved potency and selectivity with **55**, the metabolic stability was also increased significantly: **55** demonstrated no susceptibility toward hydrolysis, a significant liability observed with dipeptide compounds.

The SF_5 substituent has not been extensively exploited in drug design despite that this group has been referred to as a "super trifluoromethyl group" due to the fact that these two functionalities share many features (although this designation is probably imprecise) [101–104]. The shared features between SF_5 and CF_3 include high electronegativity, good thermal and chemical stability and high lipophilicity, with the SF_5 group exhibiting each of these features to a greater extent than the CF_3 group. Both of these substituents are xenobiotic and have remarkable stability under physiological conditions, lending to their usefulness in drug discovery. While there is some consensus on CF_3 being similar in size (van der Waals volume) to the ethyl group, comparative comments on the relative size of an SF_5 moiety are more speculative [16]. However, it has been suggested that the volume of the SF_5 group is slightly less than that of a *tert*-butyl group but larger than the CF_3 group [102]. In addition to differences in size, the geometries of these two groups are quite different. The SF_5 group displays a pyramid of electron density whereas the CF_3 group is associated with a cone shape of electron density [103]. The subtle differences in properties between these two groups provides opportunity for deployment of the SF_5 group in a fashion that allows optimization of many of the PK and PD properties discussed in this chapter, including potency. An interesting example where an SF_5 moiety provided an advantageous impact on potency is in the context of cannabinoid CB_1 receptor ligands [104]. In two different pyrazole series illustrated by the prototype *meta*-CF_3-aniline **57** and its SF_5 analogue **58** (Fig. 23), the SF_5 compounds consistently exhibited a lower K_i for the CB_1 receptor than the CF_3-analogs. The increased potency was attributed to a potential "better fit" of the SF_5 group in a pocket of the CB_1 receptor relative to the CF_3 group, indicating that in this setting the two groups are not biologically equivalent.

Table 5 SAR associated with a series of *Pf*DHODH inhibitors

			IC_{50} (uM)	
	R	**R'**	**P*f*DHODH**	***Pb*DHODH**
59	SF_5	H	0.13	0.38
60	CF_3	H	0.28	0.28
61	CF_3	F	0.19	0.11



Another example where SF_5 and CF_3 substitution has been examined in a matched pairs-type of analysis was disclosed in the context of a *P. falciparum* dihydroorotate dehydrogenase (*Pf*DHODH) inhibitor program [105]. The C-4 SF_5 analogue **59** (Table 5) provided a two- to three-fold potency improvement over the CF_3 analogue **60** as an inhibitor of *Pf*DHODH. It was suggested that the enhanced potency may be due to the increased hydrophobicity of the SF_5 substituent. In addition to increased potency, the SF_5 analogue **59** exhibited good metabolic stability, promising PK parameters *in vivo* and no apparent liabilities. The 3,5-di-F-analog **61** also provided an interesting illustration of the effect of fluorine substitution. This compound compared well with **60** in many respects but showed significantly improved efficacy *in vivo*. These data illustrate again that the SF_5 group can be a suitable substitute for CF_3 with advantage in an optimization effort.

5 Effects of Fluorine on Metabolic Stability

Metabolic stability is a perpetual concern in drug discovery and there are many factors that govern the metabolism of a given compound. Perturbation of properties such as lipophilicity, polarity, sterics, and conformation can often reduce metabolic liabilities. When modifying a compound, changes must be carefully balanced such that the solution to one problem does not introduce another. One strategy to solving a metabolic stability issue is to identify the metabolic "soft spot", i.e. the site of oxidation, and then block that site with a substituent resistant to metabolism. One way to accomplish this is to replace a labile/susceptible carbon-bound hydrogen with a fluorine atom. This type of substitution infrequently impairs drug-target interactions and is a strategy that has been employed successfully in many contexts [106–110].

One notable example is the discovery of ezetimibe (**63**) (Fig. 24), a marketed β-lactam derivative that lowers systemic cholesterol levels by blocking intestinal absorption of cholesterol [108, 109]. A key experiment led to the identification of active metabolites of the prototype compound **62** after dosing to rats [108], which in turn led to the discovery that metabolites were more efficiently localized to the putative site of action of the drug than **62** itself. Additional studies elucidated the

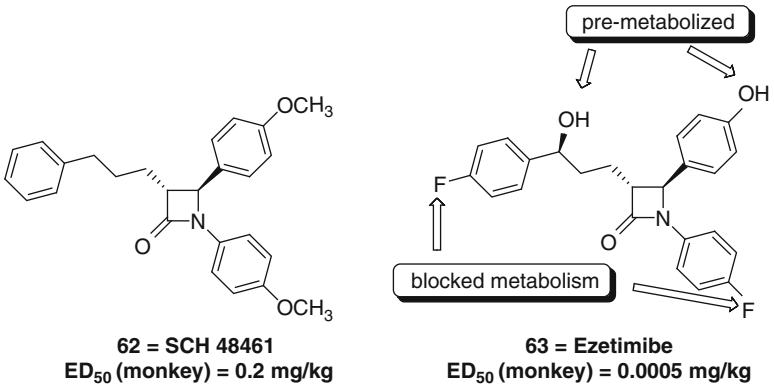
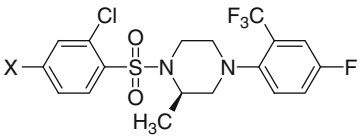


Fig. 24 The structure of ezetimibe (**63**) and its progenitor **62**

structure of several metabolites, some of which offered advantageous localization to the intestine while others did not [111]. Armed with this knowledge, a second generation compound was designed in which sites of detrimental metabolism were blocked via strategic incorporation of substituents. The result was ezetimibe (**63**), a compound which contains hydroxyl functionality crucial to activity and selectivity, as well as fluorine atoms in two key locations which serve to blocked detrimental metabolic pathways without adversely affecting cholesterol absorption inhibitory activity significantly.

The metabolism of heterocycles which leads to reduced potency, poor PK properties or bioactivation into chemically reactive species is a particular concern in drug design, and strategies to mitigate these pathways have been reviewed and summarized [112]. As demonstrated by the discovery of ezetimibe (**63**), if the site of metabolism is known or even presumed, a useful and common strategy is to simply block that position with a fluorine atom. In a thorough effort towards improving metabolic stability in a series of piperidine-based 11β-hydroxysteroid dehydrogenase type I (11β-HSD1) inhibitors, it was discovered that introducing fluorine or polar substituents led to an increase in metabolic stability [113]. It can be reasoned that polar groups lowered the lipophilicity and log *D*, likely contributing to the increase in metabolic stability. Moreover, in a modification that presumably blocked a metabolic soft spot present in **64** (Fig. 25), installation of a *para*-fluoro substituent (**65**) had a positive effect on metabolic stability in mouse liver microsomes (MLM); a MLM $T_{1/2}$ of >30 min was demonstrated which compared favorably with the unsubstituted piperidine analogue **64**, which exhibited a $T_{1/2}$ of just 6 min.

As suggested above, high lipophilicity can have an adverse impact on metabolic stability. In an effort to improve the metabolic stability of the lead histamine 3 receptor (H_3R) inverse agonist **66** (Fig. 26), ring contraction of the azepine ring coupled with the introduction of fluorine substitution was explored [114]. While there was some confidence that this strategy would lead to increased metabolic



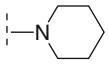
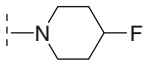
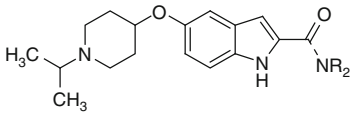
compound	X	MLM $t_{1/2}$ (min)
64		6
65		> 30

Fig. 25 Mouse liver microsome (MLM) half-life data for piperidine-based 11β-hydroxysteroid dehydrogenase type I (11β-HSD1) inhibitors



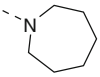
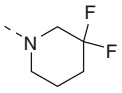
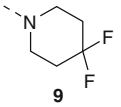
	66	67	68	69
clearance RLM = (μL/min/mg)	 55	 17	 9	 12

Fig. 26 Rat liver microsome (RLM) clearance values for several histamine 3 receptor (H_3R) inverse agonists

stability, there was concern that the structural changes would adversely affect solubility. In the event, the smaller ring size associated with piperidines **67** and **68** resulted in more stable molecules with rat liver microsome (RLM) clearance values of 17 and 9 μL/min/mg, respectively, as compared to an RLM clearance of 55 μL/min/mg for **66**. However, the structural changes were accompanied by some adverse affects, with **68** inhibiting the hERG channel by 73 % at a concentration of 10 μM. Attention was thus shifted toward the morpholine analogue **69** which had reasonable metabolic stability and did not share the hERG liability.

While these examples demonstrate the beneficial effect of blocking metabolism by taking advantage of the inherent strength of a carbon-fluorine bond, in extreme cases this property may be disadvantageous. An example of such a situation was observed in the discovery of SC-58635 (**70**), a cyclooxygenase 2 (COX 2) inhibitor known generically as celecoxib (Fig. 27). The early lead molecule **71** possessed a 4-fluorophenyl moiety that rendered the molecule extremely metabolically stable *in vivo*, represented by the greater than 220 h half life measured in rats [115]. Interestingly, a similar high level of metabolic stability was observed with the chloro analog **72** which had a measured half life of 117 h in rats. In an effort to bring this value into a more acceptable range, the introduction of functionality with greater

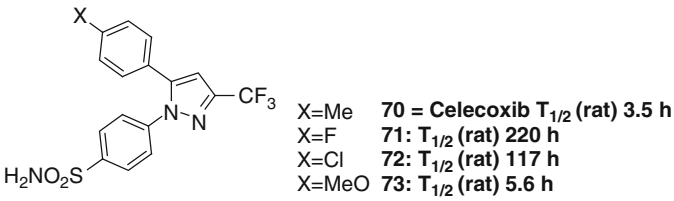


Fig. 27 Rat *in vivo* half life data for celecoxib and related analogues

susceptibility to metabolism was examined. As such, the methoxy analog **73** and the methyl derivative **70** were prepared with both compounds exhibiting a shorter half life in the rat: 5.6 and 3.5 h, respectively.

There are several interesting cases where the introduction of a fluorine atom does not prevent metabolic oxidation at the site of deployment [15]. A specific example is observed in phenyl rings that incorporate a nitrogen substituent *para* to the fluorine atom. In this arrangement, P450-catalyzed oxidation can facilitate fluorine rearrangement to the adjacent carbon atom resulting in a hydroxyl moiety being installed on the carbon atom vacated by the fluorine [116–118].

6 The Effect of Fluorine Substitution on Membrane Permeability

Absorption of an orally administered drug is governed primarily by one of two processes: passive transport, or active transport which requires energy that is typically supplied by ATP. The majority of drugs permeate membranes passively, the ease of which depends on the properties of both the membrane and the diffusing molecule. Membranes are a highly organized, anisotropic system with sufficient fluidity to allow translational and rotational movements of the constituent lipid and protein molecules; the packing density of the constituent elements influences binding to and permeation of drugs [119–121]. Lipophilicity and the cross sectional area of a drug are the two most influential properties governing membrane binding [121]. While the ability of fluorine to influence permeability may diminish with the size of a molecule, it is well suited for use in modulating lipophilicity in the context of small molecule drug discovery.

Lipophilicity is often expressed as log *P*, the logarithm of the partition coefficient of a compound between octanol and water. A distribution coefficient (log *D*) is also used to quantify lipophilicity in the event that charge states need to be taken into consideration. A log *D* value is the logarithm of the coefficient of the distribution of a molecule between water and octanol at a particular pH, typically 7.4 because of physiological relevance. Based on an analysis of the physical properties of orally bioavailable drugs, the optimal log *P* for an orally administered drug is between 1 and 5 [122].

It is a misconception to assume that fluorination of a molecule always increases lipophilicity. Monofluorination or trifluorination of saturated alkyl groups often

Table 6 log *P* (octanol-H_2O) measurements for fluoroalkanes and fluoroalcohols

Fluoroalkane	log *P*	Fluoroalcohol	log *P*	Fluoroalcohol	log *P*
CH_3CH_3	1.81	CH_3CH_2OH	–0.32	$CF_3(CH_2)_3OH$	0.90
CH_3CHF_2	0.75	CF_3CH_2OH	0.36	$CF_3(CF_2)_2CH_2OH$	1.94
$CH_3(CH_2)_3CH_3$	3.11	$CH_3(CH_2)_2OH$	0.34	$CH_3(CH_2)_4OH$	1.19
$CH_3(CH_2)_3CH_2F$	2.33	$CF_3(CH_2)_2OH$	0.39	$CF_3(CH_2)_4OH$	1.15
		$CH_3(CH_2)_3OH$	0.88		

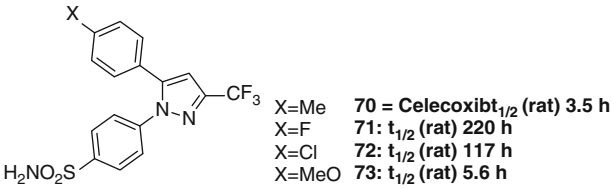


Fig. 28 *In vivo* efficacy and log *P* of leukotriene receptor antagonists

decreases lipophilicity due to the relatively polar character of the monfluoro- and trifluoro-methyl alkanes which possess highly polar C-F and C-CF_3 bonds. The same is true for difluorination when fluorine is introduced at the terminal carbon atom of an alkane (Table 6) [123]. In contrast to the data shown in Table 6, lipophilicity is typically increased upon aromatic fluorination, perfluorination, and fluorination adjacent to atoms with π-bonds, with the notable exception of some α-fluorinated carbonyl compounds [123]. Presumably, in these cases the lipophilicity is increased due to the excellent overlap between the F-C 2p orbitals which results in significant resonance electron-donation from fluorine to carbon that offsets the inductive electron-withdrawing influence of fluorine.

The situation becomes far less predictable when a heteroatom is proximal to the site of fluorine substitution. As indicated in Table 6, fluorination has little effect on lipophilicity when the site of fluorination is less than 3C-C bonds away, at least in the case in the case of terminal trifluoromethylated alcohols [123].

The impact of fluorine substitution on lipophilicity (as measured by log *P*) has been studied in the context of leukotriene (LT) receptor antagonists [124]. Leukotrienes are signalling molecules responsible for triggering constriction of smooth muscle, and the overproduction of leukotrienes is implicated in contributing to asthma in humans. The development of LT receptor antagonists is one approach towards moderating the bronchoconstrictive properties of leukotrienes. For a series of indole carboxamide-based LT antagonists represented by **74** (Fig. 28), an increase in lipophilicity *via* the careful installation of a trifluoromethyl group led to an increase in efficacy and oral availability. Extending the length of the alkyl chain of the indole amide led to increased lipophilicity but was also associated with a loss in affinity for the LT receptor. Fluorine substitution increased lipophilicity and, in comparison to non-fluorinated analogs, increased *in vivo* potency ten-fold. In a head-to-head comparison, the fluorinated analogs consistently exhibited greater lipophilicity than the non-fluorinated analog as measured by log *P* (Fig. 28).

	R	R'	Caco-2 permeability
75	CH_3	H	1.20 x 10^{-6} cm/s
76	CH_3	F	3.14 x 10^{-6} cm/s
77	CF_3	H	3.38 x 10^{-6} cm/s
78	CF_3	F	4.86 x 10^{-6} cm/s

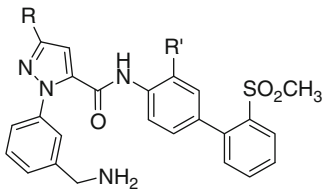


Fig. 29 Caco-2 permeability for a series of pyrazole-based factor Xa inhibitors

	R	R'	IKKβ IC_{50}	Log *D*	PAMPA P_e
79	H	H	55 nM	1.8	0.84 x 10^{-6} cm/s
80	F	H	64 nM	1.8	19 x 10^{-6} cm/s
81	F	F	27 nM	3.1	> 50 x 10^{-6} cm/s

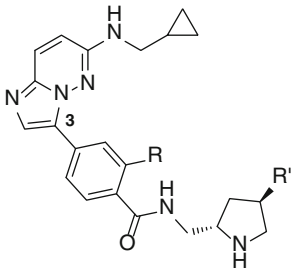


Fig. 30 *In vitro* potency, log *D* and permeability of a series of imidazolo[1,2-*b*]pyridazine-based IKKβ inhibitors

The influence of fluorine substitution on permeability, as measured across a Caco-2 bilayer, has been studied in a series of factor Xa (fXa) inhibitors [125, 126]. It was observed during the optimization of the series of pyrazole-based fXa inhibitors **75**–**78** shown in Fig. 29 that the substitution of the aromatic ring with fluorine afforded a greater than two-fold increase in Caco-2 permeability (**75** vs. **76**). Similarly, the exhaustive introduction of fluoro to the methyl substituent bound to the aromatic ring (CH_3 to CF_3) resulted in a similar improvement in Caco-2 permeability (**77** vs **75**). Further, when both the aromatic ring and the methyl substituent were substituted with fluorine (**78**) the Caco-2 measured permeability increased to 4.86×10^{-6} cm/s, a >four-fold improvement over that non-fluoro analog **75**. Furthermore, the increased permeability of **78** was complemented by the best *in vivo* potency within the series and **78** also exhibited a high selectivity ratio for fXa versus thrombin (1,000-fold) and fXa versus trypsin (300-fold).

The advantageous impact of fluorine on permeability has been explored in the discovery of a family of imidazolo[1,2-*b*]pyridazine-based IKKβ inhibitors where it was assumed that the central benzamide played a key role in pharmacokinetic properties [127]. As shown in Fig. 30, modifications to the benzamide region (C-3) of the imidazo[1,2-*b*]pyridazine had a dramatic affect on permeability: the measured PAMPA values for **79** and **80** were 0.84×10^{-6} cm/s and 19×10^{-6} cm/s, respectively [128]. Although **79** and **80** differ by only a single F-for-H substitution, the observed improvement in permeability is presumed to arise from a combination of factors. These factors include the enhancement of hydrophobicity and the formation of a weak interaction between the fluorine atom and the NH moiety, possibly a dipolar interaction.

While the inhibitory activity and log *D* of **79** and **80** remained essentially identical, the installation of a second fluorine on the pyrrolidine moiety (**81**) resulted in an increase in both the measured log *D* and PAMPA values. In the case of **81**, the added lipophilicity coupled with the small difference in size between H and F also afforded a two-fold increase in potency compared to **79** and **80**.

6.1 Inter- and Intra-molecular H-Bonding of Fluorine

Numerous X-ray crystallographic structures of fluorine-containing compounds demonstrate close inter- and intra-molecular C-F···H contacts and the strong hydrogen-bonding capacity of hydrofluoric acid has long been recognized [30, 129–132]. The intriguing possibility that optimization of C-F···H contacts might lead to an increase in the potency of pharmaceutical agents has, in part, contributed to a significant interest in determining the capacity of fluorine to act as a hydrogen-bond acceptor. Even though the nature of this interaction remains a topic of considerable debate, it is recognized that the C-F···H interaction is much weaker than that of O···H hydrogen-bonding, and that interpretation of possible C-F···H interactions requires care and attention to multiple factors [20, 129, 133–138].

Due to the strong electronegativity of fluorine, the three lone pairs of electrons are tightly held, resulting in fluorine being a poorly polarizable atom [16, 20]. However, the substantial ionic nature of the C-F bond gives rise to a large dipole moment (μ). For example, in fluoromethane the dipole moment is 1.85 D while in difluoromethane it is 1.97 D [20]. In systems such as 3-fluoropiperidinium, dipole minimization rather than C-F···H bonding has been suggested to best explain the observed conformational bias [55]. The C-F···H interaction is variously described as a hydrogen-bonding or a dipolar interaction. The distinction is that a hydrogen-bonding interaction has a covalent component which is anisotropic, while a dipolar interaction is entirely electrostatic and not dependent on directionality. A recent analysis of C-F···H contacts documented in the Cambridge Structural Database (CSD) supports the absence of an anisotropic component in the C-F···H interaction. Specifically, in a survey of 100 compounds with C-F···H bond distances between 1.85 Å and 2.35 Å, the C-F···H bond angle was found to vary significantly between 95° and 165°, while demonstrating no dependence on F···H distance [30]. The absence of a directional dependence of C-F···H interactions is in agreement with an earlier analysis of the Protein Data Bank (PDB) [129]. The C-F···H interaction is therefore best described as a dipolar interaction.

The presence of inter- and intra-molecular C-F···H contacts is mostly supported by crystallographic data. Often a F···H distance shorter than the sum of the F and H van der Waals radii (~2.65 Å) is used as evidence for a C-F···H interaction [129]. A review of the PDB in 2004 using this distance criterion as well as directional constraints found that "*…there is an 18% chance that a generic PDB entry with a co-crystallized fluorine-containing ligand presents a hydrogen-bond occurring at the fluorine*" and that "*10% of the overall amount of fluorine atoms from the PDB*

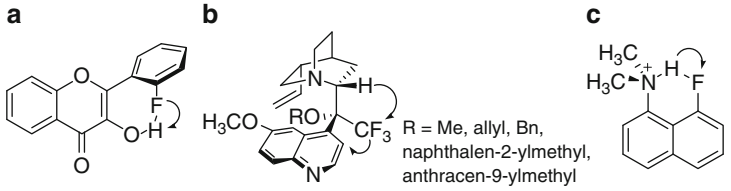


Fig. 31 C-F···H interaction in (**a**) 2′-fluoroflavonol; (**b**) O-alkyl 9-dehydro-9-trifluoromethyl-9-epiquinidines; (**c**) 8-fluoro-*N*,*N*-dimethylnaphthalen-1-amine

are involved in hydrogen bonding contacts" [129]. The mean F···H distances calculated for aliphatic, aromatic, and geminal fluorines (CF_2H, CF_3) are 2.113 Å, 2.698 Å, and 2.350 Å, respectively. When standard deviation values are considered, the differences between the three types of C-F bond are not statistically significant. Instead, a calculated mean F···H distance of 2.313 Å is more appropriate [129]. As a comparison, almost all H···O and H···N contacts observed crystallographically are less than 2.2 Å in length [138]. It is therefore suggested that a bond distance much shorter than 2.65 Å is often needed for a productive F···H interaction, and that this distance criterion is not a reliable indicator of F···H interactions [137].

Many studies have attempted to provide non-crystallographic evidence for a C-F···H interaction. For example, the magnitude of a $^{1h}J_{F,H(O)}$ NMR coupling constant has been used as evidence for a C-F···H interaction in 2′-fluoroflavonol (Fig. 31a) [139]. However, this analysis targets a minor conformer of 2′-fluoroflavonol and relies upon several assumptions regarding electronics. The same authors report that the $^{1h}J_{F,H(O)}$ coupling constants found for 2-fluorophenol and 4-bromo-2-fluorophenol arise from overlap of the electronic clouds surrounding both coupling nuclei (owing to their spatial proximity) rather than from transmission through a hydrogen bond [140].

In another study, the nature of intramolecular C-F···H-C bonding was interrogated using O-alkyl 9-dehydro-9-trifluoromethyl-9-epiquinidines as model systems (Fig. 31b) [134]. These compounds demonstrate many phenomena consistent with C-F···H-C bonding: X-ray crystal structures contain close F···H contacts, as low as 2.19 Å when R=Me; ^{19}F NMR spectra contain three distinct resonances with first order $^2J_{F\text{-}F}$ coupling indicating that the rotation of the CF_3 group is greatly restricted; and noticeable deshielding is observed in ^1H NMR for the proton most proximal to the CF_3 group. A combination of crystallographic and NMR observations with Erying analysis and extensive computational analysis were used to probe the nature of this C-F···H-C interaction [134]. Despite the strong appearance of a C-F···H-C bonding interaction, it was concluded that steric crowding is responsible for the short F···H distances and restricted rotation; even the strongest C-F···H-C bonding interactions in the system contribute minimally to the ground state geometry or hinder rotation [134].

In contrast to C-F···H-C bonding, the C-F···H-N^+R_3 interaction is considered one of the strongest C-F···H bonding interactions. As a tool to further study the C-F···H-N^+R_3 interaction, 8-fluoro-*N*,*N*-dimethylnapthalen-1-amine, the fluoro analog of 1,8-bis(dimethylamino)naphthalene ("Proton Sponge"), was prepared and studied (Fig. 31c) [133]. The basicity of this compound is slightly greater (<1 pK_a

unit) than that of the parent compound *N*,*N*-dimethylnaphthalen-1-amine. Crystal structures of the protonated molecule with either a TfO^- or $B(C_6F_5)_4^-$ counterion indicate an intramolecular C-F···H-N^+R_3 bonding interaction, with F···H distances of 2.131 Å and 2.027 Å, respectively. In both cases, hydrogen-bonding is observed between the proton and the counterion with significance equal to that of the C-F···H-N^+R_3 contact. Unlike Proton Sponge, the H-N^+R_3 proton is observed crystallographically to lie outside of the naphthalene plane, with deviations from planarity of 39.5° and 29.5° for TfO^- and $B(C_6F_5)_4^-$ counter ions, respectively. Observation in ^{19}F NMR of a large $J_{F,H}$ coupling constant is cited as further support of the C-F···H-N^+R_3 bonding interaction. Interestingly, the $J_{F,H}$ coupling observed with a $B(C_6F_5)_4^-$ counterion is suppressed if TfO^- or Cl^- are instead used as the counterion, or if the solvent for the $B(C_6F_5)_4^-$ counterion is switched from CH_2Cl_2 to acetonitrile. Taken together, the evidence points towards the existence of a weak C-F···H-N^+R_3 interaction which, in terms of significance, is of approximately equal in magnitude to that of the TfO^-···H interaction.

The large number of C-F···H contacts observed in crystallographic databases may mislead into an overly optimistic assessment of the importance of this interaction. Care must be taken in attributing the interaction to C-F···H bonding rather than to other conformational or intramolecular influences. Where the strongest isolated C-F···H interaction, C-F···H-N^+R_3, is in fact relatively weak, less significant C-F···H interactions become negligible. However, even weak interactions can play a supporting role in drug-target interactions and, as the prevalence of C-F···H contacts observed crystallographically suggests, the significance of the C-F···H interaction may be amplified in specific environments such as within the cavity of a protein. That the potency of a compound can be increased *via* fluorine substitution is clear, but the contributing factors are likely complex in origin.

7 Fluorine in Positron Emitting Tomography (PET) Imaging

PET imaging has emerged as a useful *in vivo* imaging technique that is non-invasive in nature and is useful in both a pre-clinical and clinical setting. Positrons are antimatter to electrons and encounters between the two particles lead to annihilation and the release of energy in the form of two photons of light. These photons are of high energy (511 keV), travel in opposing directions, and are readily detected simultaneously by PET cameras surrounding the subject [141, 142]. Of particular utility, the coupling of a PET camera with a computed tomography (CT) scanner allows both anatomy and metabolism data to be combined into a unique image [141, 142]. Molecules containing PET atoms are proving to be useful for probing biochemical aspects of disease *in vivo* and drug target engagement [141–146]. The utility of the ^{18}F isotope in PET imaging relies upon its 110 min decay half life, the longest of all of the short-lived positron-emitting radionuclides with applicability in small molecule imaging (Table 7), and the facility with which drug molecules will accommodate fluorine as a substitute for a hydrogen atom whilst preserving fundamental

Table 7 Half lives for decay and products of the most commonly used radionuclides in PET imaging

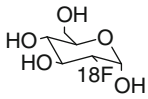
Radionuclide	$T_{1/2}$ (min)	Product
^{11}C	20.4	^{11}B
^{13}N	9.97	^{13}C
^{15}O	2.04	^{15}N
^{18}F	110	^{18}O

biological properties [141–146]. However, this aspect of biochemistry must be determined by careful experimentation, particularly in the context of allosteric modulators where structure-activity relationships can be subtle and small structural changes can invert pharmacological properties [147–150]. In addition, the energy of the positron emitted by ^{18}F is such that it travels only short distances before the annihilation event, effectively localizing the signal within a specific tissue. The utility of ^{18}F in PET imaging is further amplified by the frequency with which fluorine atoms are being incorporated into contemporary drug candidates and marketed drugs as medicinal chemists seek to take advantage of the unique and sometimes enigmatic properties that can be conferred by this atom [15–19, 67]. Recent estimates suggest that 20 % of the drugs in the current pharmacopeia and 9 of the 30 best selling small molecule drugs (*vida supra*) in 2009 contain fluorine, providing an opportunity to introduce the ^{18}F isotope in a fashion that would be expected to exert no demonstrable effect on the biological profile of a prototype molecule [17, 67].

Against this backdrop, ^{18}F derivatives have emerged as important tools in biomedical imaging, with broad application essentially limited only by the methodology to introduce this isotope into molecules in a convenient fashion at the very last stages of compound synthesis and under mild conditions that preserve molecular integrity [151–158]. Production of ^{18}F requires a cyclotron in which, most commonly, ^{18}O-enriched water is bombarded with accelerated protons to produce [^{18}F] fluoride ions ([^{18}F]F^-) which are trapped on an ion exchange resin for the purpose of separation and released by using a carbonate or bicarbonate solution containing the appropriate metal counter ion. However, fluoride ion is poorly nucleophilic but quite basic, a problem solved by elution with a solution of 2,2,2-cryptand and K_2CO_3 in CH_3CN which, after drying, provides a complex of [(crypt-222)K]$^{+18}F^-$ in which chelation of the potassium ion increases fluoride reactivity [141]. The highly electrophilic [^{18}F]-fluorine gas ([^{18}F]F_2) can also be prepared in a cyclotron by bombarding natural neon with high energy deuterons or, preferably, $^{18}O_2$ with protons to provide alternative reactivity pathways with which to introduce ^{18}F.

2-[^{18}F]-Fluoro-2-deoxy-D-glucose ([^{18}F]-FDG, **82**) has found widespread application for assessing the metabolic status of heart, lungs and brain and, particularly, for imaging tumor cells, which accumulate the molecule based on their high metabolic demands (Fig. 32) [159]. [^{18}F]-FDG (**82**) is recognized as glucose and taken up by cells *via* the glucose transporter and phosphorylated by hexokinase to [^{18}F]-FDG-6-phosphate, which cannot be metabolized further due to the presence of the 2-fluorine substituent [142, 143]. This maximizes the value of [^{18}F]-FDG (**82**) as a PET agent by localizing the molecule and preventing its metabolic conversion into a myriad of degradation products. Moreover, decomposition of [^{18}F]-FDG (**82**)

Fig. 32 2-[^{18}F]-Fluoro-2-deoxy-D-glucose ([^{18}F]-FDG)



82

ultimately affords 2-^{18}O glucose, a heavy atom analogue that is innocuously metabolized by normal pathways. ^{18}[F]-FDG (**82**) is used to diagnose a range of cancers including lung and intestinal cancer, lymphomas and melanomas and metastatic tumors but is not without its limitations as a diagnostic tool since its utility is dependent on tumor location and homogeneity [142].

The radiolabeling of ligands for specific receptors, transporters or enzymes with ^{18}F provides reagents of particular value for the development and assessment of central nervous system (CNS) function *in vivo* in a non-invasive fashion that has both preclinical and clinical utility [142]. In addition to providing insights into brain metabolism and neurotransmission, ^{18}F-labeled ligands can be used to provide evidence of brain distribution and target engagement by an exploratory drug candidate for which a homologue incorporating a positron emitting element has been identified. However, the development of PET ligands to label specific receptors in the brain is not always straightforward and success depends on several factors including the intrinsic affinity of a ligand for the protein target of interest, specific radioactivity of the probe molecule, susceptibility to metabolic degradation that leads to loss of the radiolabel, blood-brain barrier permeability of the compound which can be a function of P-glycoprotein-mediated efflux, and the extent of non-specific binding to tissues which can lead to poor signal contrast [143, 144]. The latter is often a function of molecules that are highly lipophilic and which are attracted with facility to fatty acid elements in cell membranes, providing high background signals that are manifested as noise. For optimal brain penetration, a log *P* value of between 1.5 and 3 is generally considered to be optimal although log *D* measurements that take into account the charge at the physiological pH of 7.4 are considered to be the more relevant index of lipophilicity [143]. However, there are exceptions to these guidelines and the development of ^{18}F-labeled PET ligands remains an experimental science.

Many useful PET ligands that demonstrate specificity for target receptors, transporters or enzymes have been developed, and these ligands have proven useful as probes for imaging receptor occupancy, monitoring changes in target density, and measuring *in vivo* drug distribution and kinetics after local administration, particularly to the CNS and the lung (Fig. 33) [144, 160–163]. A prominent example is [^{18}F]-fluoro-L-DOPA (**83**), the first agent developed to image the dopamine system. **83** is used as a metabolic tracer to characterize neuroendocrine tumors which take up [^{18}F]-FDG (**82**) only poorly and to monitor dopamine distribution and metabolism in the brain where it is converted to [^{18}F]-fluorodopamine (**84**) and additional metabolites useful in the study of Parkinson's disease [144, 164–167]. [^{18}F]-2β-carbomethoxy-3β-(4-chlorophenyl)-8-(2-fluoroethyl)-nortropane ([^{18}F]-FECNT) (**85**) is an analogue of cocaine used to assess the density of presynaptic dopamine transporters whilst [^{18}F]-fallypride (**86**) is a useful ligand for labeling the dopamine D2 receptor [144, 168–170].

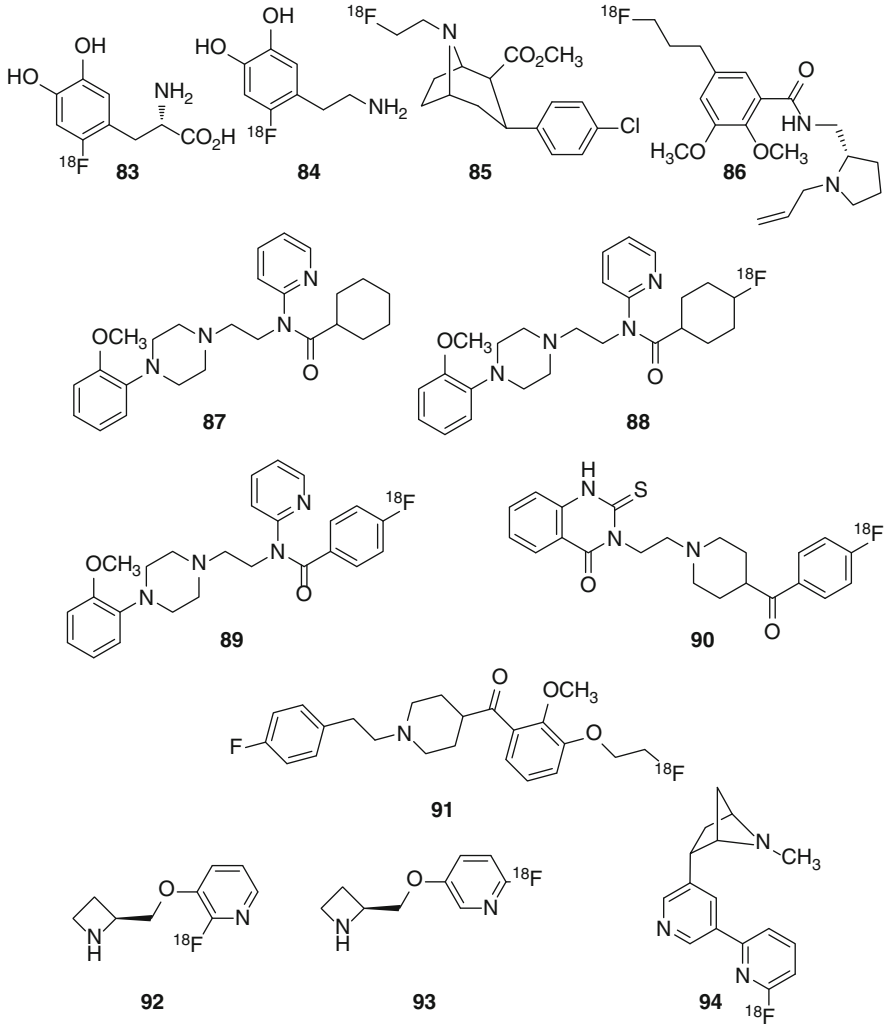


Fig. 33 PET ligands that have been used to target receptors, transporters or enzymes

WAY-100635 (**87**) was originally described as a potent and selective $5HT_{1A}$ receptor antagonist, $K_i = 2.2$ nM, prompting the development of labeled forms used to illuminate the pharmacology of these receptors *in vivo* [144, 171]. A ^{11}C label was readily introduced at the carbonyl carbon for PET imaging since the absence of fluorine in the molecule prevented simple replacement, necessitating the development and profiling of the analogues **88** and **89** in order to take advantage of the properties of ^{18}F [172]. However, more recent studies have revealed that **87** binds to dopamine $D_{4.2}$ receptors with a $K_i = 16.4$ nM where it acts as a full agonist, providing caution on the use of **87** and its analogues in imaging [171].

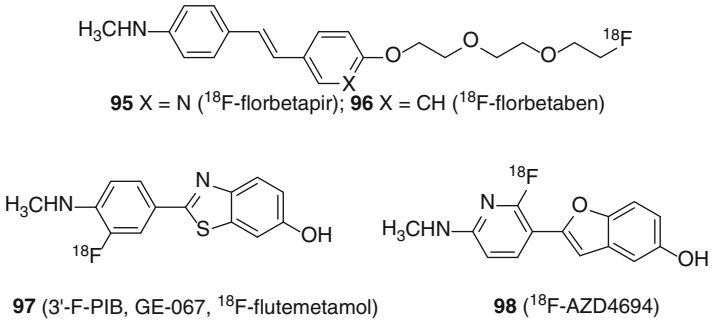


Fig. 34 PET tracers for the detection of Aβ amyloid plaques

^{18}F-Altanserine (**90**) is used to label $5HT_{2A}$ receptors while MA-1 (**91**) offers enhanced receptor selectivity and lipophilicity [144, 173, 174]. 2-[18F]-F-A85380 (**92**) and 6-[^{18}F]-F-A85380 (**93**) have been developed as useful PET ligands for labeling the nicotinic acetylcholine receptor but take several hours to reach steady state concentration in the brain and exhibit low binding potentials (B_{max}/K_d), prompting the development of **94** as a α2β4 antagonist, Ki = 240 pM, with improved brain kinetics [144, 175].

The ^{18}F-labelled styrylpyridine derivative florbetapir (**95**) was approved by the FDA on April 6th, 2012 for use as a PET ligand that labels Aβ amyloid plaques in the brain (Fig. 34) [176, 177]. ^{18}F-Florbetapir (**95**) derives from a series of stilbene derivatives that labeled amyloid plaques but were too lipophilic to be practically useful since they afforded high levels of non-specific binding in healthy brain [178–187]. The replacement of one of the phenyl rings with a pyridine heterocycle coupled with the introduction of a short polyethylene glycol moiety terminating with fluorine substitution provided **95**, a molecule with improved physical properties that bound to amyloid Aβ aggregates from post-mortem Alzheimer's disease brain tissue with a K_d of 3.72 nM and a B_{max} of 8,811 fmol/mg protein [185]. Licensing of ^{18}F-florbetapir (**95**) was based on the results of a Phase 3 clinical trial conducted in 29 patients dying of Alzheimer's disease in which the amyloid Aβ plaque levels estimated by the tracer were compared with post-mortem samples, an analysis that revealed excellent concordance [187]. Three additional amyloid plaque labeling agents in clinical trials are ^{18}F-florbetaben (**96**), a close analogue of ^{18}F-florbetapir (**95**), ^{18}F-flutemetamol (**97**) and ^{18}F-AZD4694 (**98**) [188–196].

The introduction of ^{18}F into potential PET ligands requires synthetic methodology that allows late stage installation of the radiolabel under conditions that are compatible with inherent and potentially labile functionality [141–145, 197]. The most common method of introducing ^{18}F into an alkyl chain relies upon ^{18}F fluoride displacement of a leaving group, typically a sulfonate, with cryptands used to sequester the counter ion and enhance the reactivity of the weakly nucleophilic anion [141–145, 197]. However, preparative procedures for a number of prosthetic moieties that incorporate alkyl fluorides have been developed that offer some advantage should this element be a part of the candidate molecule [144]. The application

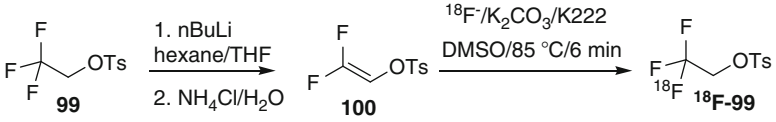


Fig. 35 Preparation of a ^{18}F-fluoroethyl reagent

of microwave heating techniques has markedly facilitated some of these procedures, improving both yields and speed of synthesis. The ^{18}F-fluoroethyl moiety is quite prominent in ^{18}F PET ligands, with the label readily introduced by treating the corresponding tosylate or trifluoromethyl sulfonate derivative with ^{18}F-fluoride [141–145, 168, 169, 197]. ^{18}F-Labeled 2,2,2-trifluoroethyl 4-methylbenzenesulfonate (^{18}F-**99**) is a prosthetic group that offers a useful approach to prepare potential PET ligands and is accessible from the unlabeled material which is sequentially subjected to nBuLi-mediated elimination of HF to afford the divinyl fluoride **100** which adds ^{18}F quickly and efficiently under mild and carefully optimized conditions (Fig. 35) [198]. ^{18}F-**99** was prepared with good specific radioactivity and readily alkylated 4-cyanophenol, diphenylmethanethiol, 4-chlorobenzoic acid and dibenzylamine rapidly under mild conditions mediated by Cs_2CO_3 as the base in DMF as solvent [198].

Aryl fluorides are a much more common structural motif, ubiquitously explored in lead optimization campaigns where a phenyl ring is part of the pharmacophore. Whilst these moieties offer the potential to prepare an ^{18}F-labeled analogue of a highly optimized ligand, the introduction of fluorine to these rings late in a synthetic scheme can present a considerable challenge and both nucleophilic and electrophilic processes have been developed [141–145, 197].

Aryl or heteroaryl ring fluorination can be accomplished using $^{18}F^-$ to displace a range of leaving groups, including F, Cl, Br, and I in addition to NO_2, NMe_3^+ and ArI^+, a reaction facilitated by the presence of an electron withdrawing moiety on the ring [151–158, 197, 199]. Electrophilic aromatic fluorination processes are more difficult and have typically relied upon the use of $^{18}F_2$ gas, which is highly reactive and must be used under controlled conditions, with regiochemistry influenced by using trialkyl tin or mercury substituents to direct incorporation [197]. A promising new approach to electrophilic fluorination that exhibits greater compatibility with the kind of functionality found in drug molecules takes advantage of palladium catalysis with the palladium fluoride complex **102** prepared efficiently from **101** by exposure to fluoride for 5 min (Fig. 36) [200]. The palladium fluoride complex **102** functions as an electrophilic fluorinating agent and reacts with Pd-aryl complexes to afford aryl fluorides in good yield when heated in acetone at 85 °C for 10 min [200]. In a representative example, Pd complex **105** afforded the aryl fluoride **106** in 72 % yield under these conditions. Practical considerations relating this chemistry to ^{18}F labeling applications include the stability of the Pd complexes **101** and **102**, with the former stable at room temperature and to brief air exposure, whilst the palladium fluoride complex **102** is stable at 100 °C for 24 h and in 10 % aqueous CH_3CN for

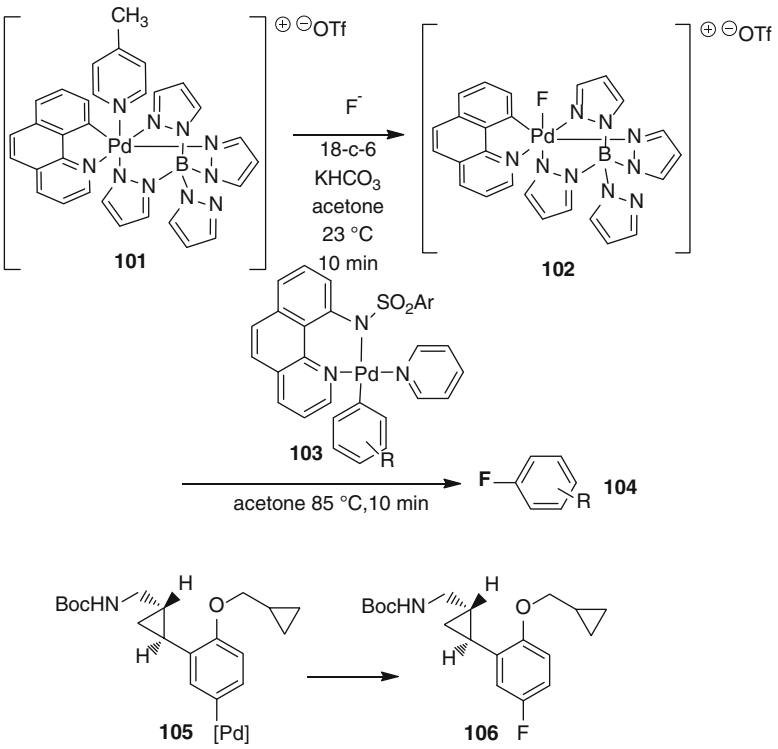


Fig. 36 ^{18}F-Pd complex **102** serves as a useful source of electrophilic ^{18}F

3 h at 23 °C. However, stoichiometric quantities of the catalyst **102** are required and care must be taken to purify the organic products to remove residual Pd. Complex **101** was shown to react with solutions of $^{18}F^-$prepared under conventional conditions to afford ^{18}F-labelled **102** which provided ^{18}F-labelled **106** in an average 18 % radiochemical yield in two steps from $^{18}F^-$ [200].

A particularly interesting fluorination process that relies upon fluoride ion as the source and is radical-based in nature takes advantage of the manganese porphyrin catalyst Mn(TMP)Cl (**107**) to promote an oxidative fluorination that is applicable to aliphatic C-H moieties, potentially offering wide substrate versatility (Fig. 37) [201]. The experimental protocol exposes substrate to three equivalents of AgF, 6–8 equivalents of iodosylbenzene, 0.3 equivalents of tetrabutylammonium fluoride trihydrate and 6–8 mole % of catalyst **107** in mixture of CH_3CN and CH_2Cl_2 at 50 °C under an inert atmosphere. The active catalyst in this process is believed to be *trans*-difluoroMn^{IV}(TMP) (**108**) which transfers a fluorine atom to a carbon radical generated by a Mn^V oxo species produced by iodosylbenzene oxidation, as depicted in the catalytic cycle shown in Fig. 37. The procedure provides products in modest yields, typically just below 50 %, and with generally poor stereoselectivity at sites that are electronically unactivated. Nevertheless, the procedure is compatible

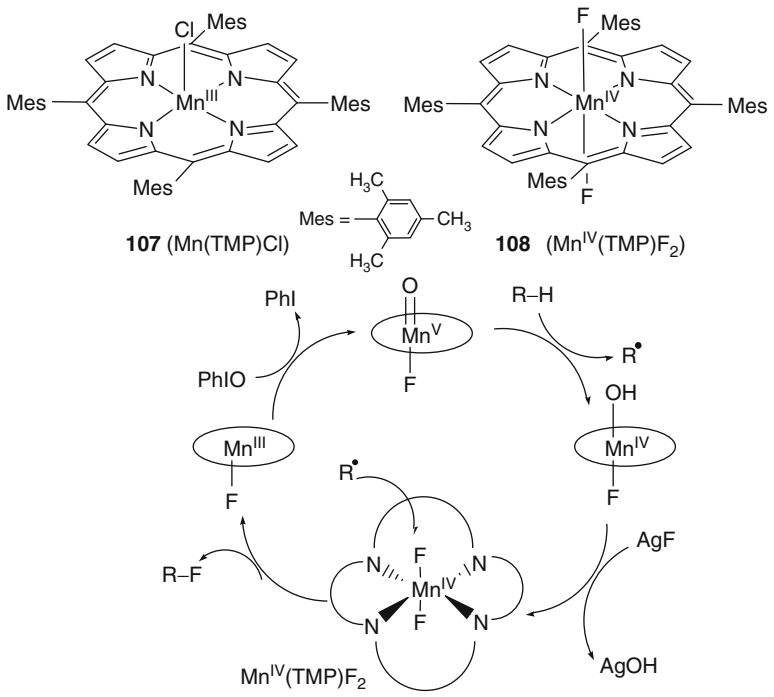


Fig. 37 Catalytic cycle for the fluorination of aliphatic substrates initiated by the manganese porphyrin derivative **107**

with a wide range of functional groups and provides access to compounds that would otherwise require significant synthetic manipulation to access by a *de novo* approach.

8 Conclusion

Fluorine is a unique atom that has found widespread application in drug design to address problems associated with controlling conformation, enhancing potency, interfering with metabolism, increasing membrane permeability and modulating the pK_a of proximal functionality. Although the physical chemistry underlying many of these effects is reasonably well understood, there remains much to learn about the influence of fluorine on drug properties and how fluorine can be exploited to full advantage. With continuing advances in the development of mild and efficient methods to introduce fluorine into organic molecules, it can be anticipated that applications of this remarkable element in drug discovery and development will grow in both sophistication and understanding. The promise of new and deeper insights into the properties and utility of fluorine should provide additional creative stimulus for improved synthetic methods, broadening and enhancing productive applications.

References

1. Vulpetti A, Hommel U, Landrum G, Lewis R, Dalvit C (2009) Design and NMR-based screening of LEF, a library of chemical fragments with different local environments of fluorine. J Am Chem Soc 131:12949–12959
2. Jordan JB, Poppe L, Xia X, Cheng AC, Sun Y, Michelsen K, Eastwood H, Schnier PD, Nixey T, Zhong W (2012) Fragment based drug discovery: practical implementation based on ^{19}F NMR spectroscopy. J Med Chem 55:678–687
3. Vulpetti A, Dalvit C (2012) Fluorine local environments: from screening to drug design. Drug Discov Today 17:890–897
4. Harper DB, O'Hagan D, Murphy CD (2003) The handbook of environmental chemistry, vol 3 Part P. Springer, Berlin/Heidelberg, pp 141–169
5. Bowen HJM (1966) Trace elements in biochemistry. Academic, London
6. Sharpe AG (1967) In: Gutmann V (ed) Halogen chemistry, vol 1. Academic, New York, p 12
7. Neidleman SL, Geigert J (1986) Biohalogenation: principles, basic roles and applications. Ellis Horwood Ltd, Chichester
8. Vaillancourt F, Yeh E, Vosburg DA, Garneau-Tsodikova S, Walsh CT (2006) Nature's inventory of halogen catalysts: oxidative strategies predominate. Chem Rev 106:3364–3378
9. O'Hagan D (2006) Recent developments on the fluorinase of streptomyces cattleya. J Fluor Chem 127:1479–1483
10. Zhu X, Robinson DA, McEwan AR, O'Hagan D, Naismith JH (2007) Mechanism of enzymatic fluorination in *Streptomyces cattleya*. J Am Chem Soc 139:14597–14604
11. Wagner C, El Omari M, König GM (2009) Biohalogenation: nature's way to synthesize halogenated metabolites. J Nat Prod 72:540–553
12. Meyer M, O'Hagan D (1992) Rare fluorinated natural products. Chem Br 28:785
13. Heidelberger C, Chaudhuri NK, Danneberg P, Mooren D, Griesbach L, Duschinsky R, Schnitzer RJ, Pleven E, Scheiner J (1957) Fluorinated pyrimidines, a new class of tumour-inhibitory compounds. Nature 179:663–666
14. Bégué J-P, Bonnet-Delpon D (2008) Bioorganic and medicinal chemistry of fluorine. Wiley, Hoboken
15. Böhm H-J, Banner D, Bendels S, Kansy M, Kuhn B, Müller K, Obst-Sander U, Stahl M (2004) Fluorine in medicinal chemistry. ChemBioChem 5:637–643
16. Müller K, Faeh C, Diederich F (2007) Fluorine in pharmaceuticals: looking beyond intuition. Science 317:1881–1886
17. Hagmann WK (2008) The many roles for fluorine in medicinal chemistry. J Med Chem 51:4359–4369
18. Purser S, Moore PR, Swallow S, Gouverneur V (2008) Fluorine in medicinal chemistry. Chem Soc Rev 37:320–330
19. Shah P, Westwell AD (2007) The role of fluorine in medicinal chemistry. J Enzym Inhib Med Chem 22:527–540
20. O'Hagan D (2008) Understanding organofluorine chemistry: an introduction to the C-F bond. Chem Soc Rev 37:308–319
21. Hunter L (2010) The C-F bond as a conformational tool in organic and biological chemistry. Belistein J Org Chem 6. doi:103762/bjoc.6.38
22. Zimmer LE, Sparr C, Gilmour R (2011) Fluorine conformational effects in organocatalysis: an emerging strategy for molecular design. Angew Chem Int Ed 50:11860–11871
23. Buissonneaud DY, van Mourik T, O'Hagan D (2010) A DFT study on the origin of the fluorine gauche effect in substituted fluoroethanes. Tetrahedron 66:2196–2202
24. O'Hagan D (2012) Organofluorine chemistry: synthesis and conformation of vicinal fluoromethylene motifs. J Org Chem 77:3689–3699
25. Wu D, Tian A, Sun H (1998) Conformational properties of 1,3-difluoropropane. J Chem Phys A 102:9901–9905

26. Tavasli M, O'Hagan D, Pearson C, Petty MC (2002) The fluorine *gauche* effect. Langmuir isotherms report the relative conformational stability of (±)-*erythro*- and (±)-*threo*-9,10-difluorostearic acids. Chem Commun 1226–1227
27. Hunter L, Kirsch P, Slawin AMZ, O'Hagan D (2009) Synthesis and structure of stereoisomeric multivicinal hexafluoroalkanes. Angew Chem Int Ed 48:5457–5460
28. Banks JW, Batsanov AS, Howard JAK, O'Hagan D, Rzepa H, Martin-Santamaria S (1999) The preferred conformation of α-fluoroamides. J Chem Soc Perkin 2:2409–2411
29. Briggs CRS, O'Hagan D, Howard JAK, Yulfi DS (2003) The C-F bond as a tool in the conformational control of amides. J Fluor Chem 119:9–13
30. Dalvit D, Vulpetti A (2012) Intermolecular and intramolecular hydrogen bonds involving fluorine atoms: implications for recognition, selectivity, and chemical properties. ChemMedChem 7:262–272
31. Schöler M, O'Hagan D, Slawin AMZ (2005) The vicinal F-C-C-F moiety as a tool for influencing peptide conformation. Chem Commun 4324–4326
32. O'Hagan D, Rzepa HS, Schöler M, Slawin AMZ (2006) The vicinal difluoro motif: the synthesis and conformation of *erythro*- and *threo*-diastereomers of 1,2-difluorodiphenylethanes, 2,3-difluorosuccinic acids and their derivatives. Beilstein J Org Chem. doi:10.1186/1860-5397-2-19
33. Winkler M, Moraux T, Khairy HA, Scott RH, Slawin AMZ, O'Hagan D (2009) Synthesis and vanilloid receptor (TRPV1) activity of the enantiomers of α-fluorinated capsaicin. ChemBioChem 10:823–828
34. Peddie V, Butcher RJ, Robinson WT, Wilce MCJ, Traore DAK, Abell AD (2012) Synthesis and conformation of fluorinated β-peptidic compounds. Chem Eur J 18:6655–6662
35. O'Hagan D, Bilton C, Howard JAK, Knight L, Tozer DJ (2001) The preferred conformation of N-β-fluoroethylamides: observation of the fluorine amide *gauche* effect. J Chem Soc Perkin Trans 2:605–607
36. O'Hagan D, Rzepa HS (1997) Some influences of fluorine in bioorganic chemistry. Chem Commun 645–652
37. Holmgren SK, Taylor KM, Bretscher LE, Raines RT (1998) Code for collagen's stability deciphered. Nature 392:666–667
38. Bretscher LE, Jenkins CL, Taylor KM, DeRider ML, Raines RT (2001) Conformational stability of collagen relies on a stereoelectronic effect. J Am Chem Soc 123:777–778
39. Hodges JA, Raines RT (2003) Stereoelectronic effects on collagen stability: the dichotomy of 4-fluoroproline diastereomers. J Am Chem Soc 125:9262–9263
40. Doi M, Nishi Y, Uchiyama S, Nisiuchi Y, Nakazawa T, Ohkubo T, Kobayasji Y (2003) Characterization of collagen model peptides containing 4-fluoroproline: (4(*S*)-fluoroproline-Pro-Gly)10 forms a triple helix, but (4(*R*)-fluoroproline-Pro-Gly)10 does not. J Am Chem Soc 125:9922–9923
41. Hodges JA, Raines RT (2005) Stereoelectronic and steric effects in the collagen triple helix: toward a code for strand association. J Am Chem Soc 127:15923–15932
42. Shoulders MD, Kamer KJ, Raines RT (2009) Origin of the stability conferred upon collagen by fluorination. Bioorg Med Chem Lett 19:3859–3862
43. Doi M, Nishi Y, Kiritoshi N, Iwata T, Nago M, Nakano H, Uchiyama S, Nakazawa T, Wakamiya T, Kbayashi Y (2002) Simple and efficient syntheses of Boc- and Fmoc-protected 4(*R*)- and 4(*S*)-fluoroproline solely from 4(*R*)-hydroxyproline. Tetrahedron 58:8453–8459
44. DeRider ML, Wilkins SJ, Waddell MJ, Bretscher LE, Weinhold F, Raines RT, Markley JL (2002) Collagen stability: insights from NMR spectroscopic and hybrid density functional computational investigations of the effect of electronegative substituents on prolyl ring conformations. J Am Chem Soc 124:2497–2505
45. Park S, Radmer RJ, Klein TE, Pande VS (2005) A new set of molecular mechanics parameters for hydroxyproline and its use in molecular dynamics simulations of collagen-like peptides. J Comput Chem 26:1612–1616

46. Hodges JA, Raines RT (2006) Energetics of an n → π* interaction that impacts protein structure. Org Lett 8:4695–4697
47. Hinderaker MP, Raines RT (2003) An electronic effect on protein structure. Protein Sci 12:1188–1194
48. Raines RT (2006) 2005 Emil Thomas Kaiser Award. Protein Sci 15:1219–1225
49. Improta R, Mele F, Crescenzi O, Benzi C, Barone V (2002) Understanding the role of stereoelectronic effects in determining collagen stability: a quantum mechanical/molecular mechanical study of (proline-proline-glycine)$_n$ polypeptides. J Am Chem Soc 124:7857–7865
50. Kim W, Hardcastle KL, Conticello VP (2006) Fluoroproline flip-flop: regiochemical reversal of a stereoelectronic effect on peptide and protein structures. Angew Chem Int Ed 45:8141–8814
51. Kitamoto T, Ozawa T, Abe M, Marubayashi S, Yamazaki T (2008) Incorporation of fluoroprolines to proctolin: study on the effect of a fluorine atom towards peptidic conformation. J Fluor Chem 129:286–293
52. Briggs CRS, Allen MJ, O'Hagan D, Tozer DJ, Slawin AMZ, Goeta AE, Howard JAK (2004) The observation of a large *gauche* preference when 2-fluoroethylamine and 2-fluoroethanol become protonated. Org Biomol Chem 2:732–740
53. Lankin DC, Chandrakumar NS, Rao SN, Spangler DP, Snyder JP (1993) Protonated 3-fluoropiperidines: an unusual fluoro directing effect and a test for quantitative theories of solvation. J Am Chem Soc 115:3356–3357
54. Snyder JP, Chandrakumar NS, Sato H, Lankin DC (2000) The unexpected diaxial orientation of cis-3,5-difluoropiperidine in water: a potent CF – NH charge-dipole effect. J Am Chem Soc 122:544–545
55. Sun A, Lankin DC, Hardcastle K, Snyder JP (2005) 3-Fluoropiperidines and N-methyl-3-fluoropiperidinium salts: the persistence of axial fluorine. Chem Eur J 11:1579–1591
56. Gerig JT, McLeod RS (1973) Conformation of *cis*- and *trans*-4-fluoro-L-proline in aqueous solution. J Am Chem Soc 95:5725–5729
57. Deniau G, Slawin AMZ, Lebl T, Chorki F, Issberner JP, van Mourik T, Heygate JM, Lambert JJ, Etherington L-A, Sillar KT, O'Hagan D (2007) Synthesis, conformation and biological evaluation of the enantiomers of 3-fluoro-γ-aminobutyric acid ((*R*)- and (*S*)-3F-GABA): an analogue of the neurotransmitter GABA. ChemBioChem 8:2265–2274
58. Clift MD, Ji H, Deniau GP, O'Hagan D, Silverman RB (2007) Enantiomers of 4-amino-3-fluorobutanoic acid as substrates for γ-aminobutyric acid aminotransferase: conformational probes for GABA binding. Biochemistry 46:13819–13828
59. Yamamoto I, Deniau GP, Gavande N, Chebib M, Johnston GAR, O'Hagan D (2011) Agonist responses of (*R*)- and (*S*)-3-fluoro-γ-aminobutyric acids suggest an enantiomeric fold for GABA binding to GABAC receptors. Chem Commun 47:7956–7958
60. Chia PW, Livesey MR, Slawin AMZ, van Mourik T, Wyllie DJA, O'Hagan D (2012) 3-Fluoro-*N*-methyl-D-asaprtic acid (3F-NMDA) stereoisomers as conformational probes for exploring agonist binding at NMDA receptors. Chem Eur J 18:8813–8819
61. Gooseman NEJ, O'Hagan D, Slawin AMZ, Teale AM, Tozer DJ, Young RJ (2006) The intramolecular β-fluorine···ammonium interaction in 4- and 8-membered rings. Chem Commun 3190–3192
62. Campbell NH, Smith DL, Reszka AP, Neidle S, O'hagan D (2011) Fluorine in medicinal chemistry: β-fluorination of peripheral pyrrolidine attached to acridine ligands affects their interactions with G-quadruplex DNA. Org Biomol Chem 9:1328–1331
63. Abraham RJ, Chambers EJ, Thomas AW (1994) Conformational analysis. Part 22. An NMR and theoretical investigation of the *gauche* effect in fluoroethanols. J Chem Soc Perkin Trans 2:949–955
64. Abraham RJ, Smith TAD, Thomas AW (1996) Conformational analysis. Part 28. OH-F hydrogen bonding and the conformation of trans-2-fluorocyclohexanol. J Chem Soc Perkin Trans 2:1949–1955

65. Fried J, Sabo EF (1954) 9α-Fluoro derivatives of cortisone and hydrocortisone. J Am Chem Soc 76:1455–1456
66. Fried J (1955) Biological effects of 9 α-fluorohydrocortisone and related halogenated steroids in animals. Ann N Y Acad Sci 61:573–581
67. O'Hagan D (2010) Fluorine in health care: organofluorine-containing blockbuster drugs. J Fluor Chem 131:1071–1081
68. Mock W, Zhang JZ (1990) Concerning the relative acidities of simple alcohols. Tetrahedron Lett 31:5687–5688
69. Weeks CM, Duax WL, Wolff ME (1973) A comparison of the structure of six corticosteroids. J Am Chem Soc 95:2865–2868
70. Wolff ME, Baxter JD, Kollman PA, Lee DL, Kuntz ID, Bloom E, Matulich DT, Morris J (1978) Nature of steroid-glucocorticoid receptor interactions: thermodynamic analysis of the binding reaction. Biochemistry 17:3201–3208
71. Myers AG, Barbay JK, Zhong B (2001) Asymmetric synthesis of chiral organofluorine compounds: use of nonracemic fluoroiodoacetic acid as a practical electrophile and its application to the synthesis of monofluoro hydroxyethylene dipeptide isosteres within a novel series of HIV protease inhibitors. J Am Chem Soc 123:7207–7219
72. Leroux F, Jeschke P, Schlosser M (2005) α-Fluorinated ethers, thioethers, and amines: anomerically biased species. Chem Rev 105:827–856
73. Massa MA, Spangler DP, Durley RC, Hickory BS, Connolly DT, Witherbee BJ, Smith ME, Sikorski JA (2001) Novel heteroaryl replacements of aromatic 3-tetrafluoroethoxy substituents in trifluoro-3-(tertiaryamino)-2-propanols as potent inhibitors of cholesterol ester transfer protein. Bioorg Med Chem Lett 11:1625–1628
74. Horne DB, Bartberger MD, Kaller MR, Monenschein H, Zhong W, Hitchcock SA (2009) Synthesis and conformational analysis of α, α-difluoroalkyl heteroaryl ethers. Tetrahedron Lett 50:5452–5455
75. Hehre WJ, Radom L, Pople JA (1972) Molecular orbital theory of the electronic structure of organic compounds. XII. Conformations, stabilities, and charge distributions in monosubstituted benzenes. J Am Chem Soc 94:1496–1504
76. Anderson GM III, Kollman PA, Domelsmith LN, Houk KN (1979) Methoxy group nonplanarity in *o*-dimethoxybenzenes. Simple predictive models for conformations and rotational barriers in alkoxyaromatics. J Am Chem Soc 101:2344–2352
77. Hummel W, Huml K, Bürgi H-B (1988) Conformational flexibility of the methoxyphenyl group studies by statistical analysis of crystal structure data. Helv Chim Acta 71:1291–1302
78. Brameld KA, Kuhn B, Reuter DC, Stahl M (2008) Small molecule conformational preferences derived from crystal structure data. A medicinal chemistry focused analysis. J Chem Inf Model 48:1–24
79. Johnson F (1968) Allylic strain in six-membered rings. Chem Rev 68:375–413
80. Klocker J, Karpfen A, Wolschann P (2003) On the structure and torsional potential of trifluoromethoxybenzene: an *ab initio* and density functional study. Chem Phys Lett 367:566–575
81. Graton J, Wang Z, Brossard A-M, Monteiro DG, Questel J-YL, Linclau B (2012) An unexpected and significantly lower hydrogen-bond-donating capacity of fluorohydrins compared to nonfluorinated alcohols. Angew Chem Int Ed 51:6176–6180
82. Meanwell N (2011) Improving drug candidates by design: a focus on physicochemical properties as a means of improving compound disposition and safety. Chem Res Toxicol 24:1420–1456
83. Peters JE, Schnider P, Mattei P, Kansy M (2009) Pharmacological promiscuity: dependence on compound properties and target specificity in a set of recent Roche compounds. ChemMedChem 4:680–686
84. Azzaoui K, Hamon J, Faller B, Whitebread S, Jacoby E, Bender A, Jenkins JL, Urban L (2007) Modeling promiscuity based on *in vitro* safety pharmacology profiling data. ChemMedChem 2:874–880

85. Jamieson C, Moir EM, Rankovic Z, Wishart G (2006) Medicinal chemistry of hERG optimizations: highlights and hang-ups. J Med Chem 49:5029–5046
86. Fischer H, Kansy M, Bur D (2000) CAFCA: a novel tool for the calculation of amphiphilic properties of charged drug molecules. Chimia 54:640–645
87. Clark J, Perrin DD (1964) Prediction of the strengths of organic bases. Q Rev Chem Soc 18:295–320
88. Morgenthaler M, Schweizer E, Hoffmann-Röder A, Benini F, Martin RE, Jaeschke G, Wagner B, Fischer H, Bendels S, Zimmerli D, Scheider J, Diederich F, Kansy M, Müller K (2007) Predicting and tuning physicochemical properties in lead optimization: amine basicities. ChemMedChem 2:1100–1115
89. Bruice PY (1984) Relative reactivity of amines and oxyanions toward proton abstraction from nitroethane. Electrostatic effects and the reactivity-selectivity principle. J Am Chem Soc 106:5959–5964
90. Trepka RD, Harrington JK, Belisle JW (1974) Acidities and partition coefficients of fluoromethanesulfonamides. J Org Chem 39:1094–1098
91. Dean JA (1999) Lange's handbook of chemistry, 15th edn. McGraw-Hill, New York
92. Hansch C, Leo A, Taft RW (1991) A survey of Hammett substituent constants and resonance field parameters. Chem Rev 91:165c–195c
93. Taagepera M, Summerhays KD, Hehre WJ, Topsom RD, Pross A, Radom L, Taft RW (1981) Analysis of the acidities of 3- and 4-substituted pyridinium and anilinium ions. J Org Chem 46:891–903
94. Schlosser M (1998) Parametrization of substituents: effects of fluorine and other heteroatoms on OH, NH, and CH acidities. Angew Chem Int Ed 110:1496–1513
95. Olsen J, Seiler P, Wagner B, Fischer H, Tschopp T, Obst-Sander U, Banner DW, Kansy M, Muller K, Diederich F (2004) A fluorine scan of the phenylamidinium needle of tricyclic thrombin inhibitors: effects of fluorine substitution on pKa and binding affinity and evidence for intermolecular C-F CN interactions. Org Biomol Chem 2:1339–1352
96. Michalik L, Auwerx J, Berger JP, Chatterjee VK, Glass CG, Gonzalez FJ, Grimaldi PA, Kadowaki T, Lazar MA, O'Rahilly S, Palmer CAN, Plutzky J, Reddy JK, Spiegelman BM, Staels B, Wahli W (2006) International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors. Pharmacol Rev 58:726–741
97. Ciocoiu CC, Ravna AW, Sylte I, Rustan AC, Hansen TV (2011) Synthesis, molecular modeling studies and biological evaluation of fluorine substituted analogs of GW 501516. Bioorg Med Chem 19:6982–6988
98. Ishikawa M, Hashimoto Y (2011) Improvement in aqueous solubility in small molecule drug discovery programs by disruption of molecular planarity and symmetry. J Med Chem 54:1539–1554
99. Black WC, Bayly CI, Davis DE, Desmarais S, Falgueyret J-P, Léger S, Li CS, Massé F, McKay DJ, Palmer JT, Percival MD, Robichaud J, Tsou N, Zamboni R (2005) Trifluoroethylamines as amide isosteres in inhibitors of cathepsin K. Bioorg Med Chem Lett 15:4741–4744
100. Herrero S, Suárez-Gea ML, Suárez-Gea ML, González-Muñiz R, García-López MT, Herranz R, Ballaz S, Barber A, Fortuño A, Del Río J (1997) Pseudopeptide CCK-4 analogues incorporating the Ψ[CH(CN)NH peptide bond surrogate. Bioorg Med Chem Lett 855–860
101. Kirsch P (2004) Modern fluoroorganic chemistry, synthesis, reactivity applications. Wiley-VCH, Weinheim
102. Wipf P, Mo T, Geib SJ, Caridha D, Dow GS, Gerena L, Roncal N, Milner EE (2009) Synthesis and biological evaluation of the first pentafluorosulfanyl analogs of mefloquine. Org Biomol Chem 7:4163–4165
103. Welch JT, Lim DS (2007) The synthesis and biological activity of pentafluorosulfanyl analogs of fluoxetine, fenfluramine, and norfenfluramine. Bioorg Med Chem 15:6659–6666
104. Altomonte S, Zanda M (2012) Synthetic chemistry and biological activity of pentafluorosulphanyl (SF5) organic molecules. J Fluor Chem 143:57–93

105. Gujjar R, El Mazouni F, White KL, White J, Creason S, Shackleford DM, Deng X, Charman WN, Bathurst I, Burrows J, Floyd DM, Matthews D, Buckner FS, Charman SA, Phillips MA, Rathod PK (2011) Lead optimization of aryl and aralkyl amine-based triazolopyrimidine inhibitors of plasmodium falciparum dihydroorotate dehydrogenase with antimalarial activity in mice. J Med Chem 54:3935–3949
106. Smith DH, Waterbeemd H, Walker DK (2001) Pharmacokinetics and metabolism in drug design, methods and principles in medicinal chemistry, vol 13. Wiley-VCH, Weinheim
107. Barnette WE (1984) The synthesis and biology of fluorinated prostacyclins. CRC Crit Rev Biochem 15:201–235
108. Heek M, France CF, Compton DS, McLeod RL, Yumibe NP, Alton KB, Sybertz EJ, Davies HR Jr (1997) In vivo metabolism-based discovery of a potent cholesterol absorption inhibitor, SCH58235, in the rat and rhesus monkey through the identification of the active metabolites of SCH48461. J Pharmacol Exp Ther 283:157–163
109. Clader JW (2004) The discovery of ezetimibe: a view from outside the receptor. J Med Chem 47:1–9
110. Penning TD, Talley JJ, Bertenshaw SR, Carter JS, Collins PW, Docter S, Graneto MJ, Lee LF, Malecha JW, Miyashiro JM, Rogers RS, Rogier DJ, Yu SS, Anderson GD, Burton EG, Cogburn EG, Gregory SA, Koboldt CM, Perkins WE, Seibert K, Veenhuizen AW, Zhang AW, Isaakson PC (1997) Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3- (trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (SC-58635, celecoxib). J Med Chem 40:1347–1365
111. Rosenblum SB, Huynh T, Afonso A, Davis HR Jr, Yumibe N, Clader JW, Burnett DA (1998) Discovery of 1-(4-fluorophenyl)-(3*R*)-[3-(4-fluorophenyl)-(3*S*)-hydroxypropyl]-(4*S*)-(4-hydroxyphenyl)-2-azetidinone (SCH 58235): a designed, potent, orally active inhibitor of cholesterol absorption. J Med Chem 41:973–980
112. St Jean Jr DJ, Fotsch C (2012) Mitigating heterocycle metabolism in drug discovery. J Med Chem 55:6002–6020
113. Wan Z-K, Chenail E, Xiang J, Li H-Q, Ipek M, Bard J, Svenson K, Mansour TS, Xu X, Suri V, Hahm S, Xing Y, Johnson CE, Li X, Qadri A, Panza D, Perreault M, Tobin JF, Saiah E (2009) Efficacious 11β-hydroxysteroid dehydrogenase type I inhibitors in the diet-induced obesity mouse model. J Med Chem 52:5449–5461
114. Pierson PD, Fettes A, Freichel C, Gatti-McArthur S, Hertel C, Huwyler J, Mohr P, Nakagawa T, Nettekoven M, Plancher JM, Raab S, Richter H, Roche O, Rodríguez Sarmiento RM, Schmitt M, Schuler F, Takahashi T, Taylor S, Ullmer C, Wiegand R (2009) 5-Hydroxyindole-2-carboxylic acid amides: novel histamine-3 receptor inverse agonists for the treatment of obesity. J Med Chem 52:3855–3868
115. Seibert K, Zhang Y, Leahy K, Hauser S, Masferrer J, Perkins W, Lee L, Isakson P (1994) Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. Proc Natl Acad Sci U S A 91:12013–12017
116. Park BK, Kitteringham NR, O'Neill PM (2001) Metabolism of fluorine-containing drugs. Annu Rev Pharmacol Toxicol 41:443–470
117. Koerts J, Soffers AE, Vervoort J, De Jager A, Rietjens IM (1998) Occurrence of the NIH shift upon the cytochrome P450-catalyzed in vivo and in vitro aromatic ring hydroxylation of fluorobenzenes. Chem Res Toxicol 11:503–512
118. Dear GJ, Ismail IM, Mutch PJ, Plumb RS, Davies LS (2000) Urinary metabolites of a novel quinoxaline non-nucleoside reverse transcriptase inhibitor in rabbit, mouse and human: identification of fluorine NIH shift metabolites using NMR and tandem MS. Xenobiotica 30:407–426
119. Boguslavsky V, Bebecchi M, Morris AJ, Jhon DY, Rhee SG, McLaughlin S (1994) Effect of monolayer surface pressure on the activities of phosphoinositide-specific phospholipase C-β.1, -γ.1, and δ1. Biochemistry 33:3032–3037
120. Hanakam F, Gerisch G, Lotz S, Alt T, Seelig A (1996) Binding of hisactophilin I and II to lipid membranes is controlled by a pH-dependent myristoyl–histidine switch. Biochemistry 35:11036–11044

121. Fischer H, Gottschlich R, Seelig A (1998) Blood-brain barrier permeation: molecular parameters governing passive diffusion. J Membr Biol 165:201–211
122. Lennarnas H, Abrahamsson B (2005) The use of biopharmaceutical classification of drugs in drug discovery and development: current status and future extensions. J Pharm Pharmacol 57:273–285
123. Smart B (2001) Fluorine substituent effects (on bioactivity). J Fluor Chem 109:3–11
124. Jacobs RT, Bernstein PR, Cronk LA, Vacek EP, Newcomb LF, Aharony D, Buckner CK, Kusner EJ (1994) Synthesis, structure-activity relationships, and pharmacological evaluation of a series of fluorinated 3-benzyl-5-indolecarboxamides: identification of 4-[[5-[((2*R*)-2-methyl-4,4,4-trifluorobutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3methoxy-N-[(2-methylphenyl)sulfonyl]benzamide, a potent, orally active antagonist of leukotrienes D4 and E4. J Med Chem 37:1282–1297
125. The Caco-2 cell line, derived from a human colorectal carcinoma, has become an established in vitro model for the prediction of drug absorption across the human intestine. When cultured on semi-permeable membranes, Caco-2 cells differentiate into a highly functionalized epithelial barrier with remarkable morphological and biochemical similarity to the small intestinal columnar epithelium. The membrane transport properties of novel compounds can thereby be assessed using these differentiated cell monolayers. The apparent permeability coefficients (Papp) obtained from Caco-2 cell transport studies have been shown to correlate to human intestinal absorption. Irvine JD, Takahashi L, Lockhart K, Cheong J, Tolan JW, Selick HE, Grove JR, (1999) MDCK (Madin–Darby canine kidney) cells: a tool for membrane permeability screening. J Pharm Sci 88:23–33
126. Pinto DJ, Orwat MJ, Wang S, Fevig JM, Quan ML, Amparo E, Cacciola J, Rossi KA, Alexander RS, Smallwood AM, Luettgen JM, Liang L, Aungst BJ, Wright MR, Knabb RM, Wong PC, Wexler RR, Lam PY (2001) Discovery of 1-[3-(aminomethyl)phenyl]-N-[3-fluoro-2′-(methylsulfonyl)-[1,1′-biphenyl]-4-yl]-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (DPC423), a highly potent, selective, and orally bioavailable inhibitor of blood coagulation factor Xa. J Med Chem 44:566–578
127. Shimizu H, Yamasaki T, Yoneda Y, Muro F, Hamada T, Yasukochi T, Tanaka S, Toki T, Yokoyama M, Morishita K, Iimura S (2011) Discovery of imidazo[1,2-*b*]pyridazines as IKKβ inhibitors. Part 3: Exploration of effective compounds in arthritis models. Bioorg Med Chem Lett 21:4550–4555 and refs therein
128. PAMPA: Parallel Artificial Membrane Permeability Assay is a method which determines the permeability of substances from a donor compartment, through a lipid-infused artificial membrane into an acceptor compartment. PAMPA models regularly exhibit a high degree of correlation with permeation across a variety of barriers including Caco-2 cultures, the GI tract, blood-brain barriers and skin
129. Carosati E, Sciabola S, Cruciani G (2004) Hydrogen-bonding interactions of covalently bonded fluorine atoms: from crystallographic data to a new angular function in the GRID force field. J Med Chem 47:5114–5125
130. Pfleiderer T, Waldner I, Bertagnolli H, Tödheide K, Fischer HE (2000) The structure of liquid and supercritical deuterium fluoride from neutron scattering and using high-pressure techniques. J Chem Phys 113:3690–3696
131. Barbarich TJ, Rithner CD, Miller SM, Anderson OP, Strauss SH (1999) Significant inter- and intra-molecular O-H···F-C hydrogen-bonding. J Am Chem Soc 121:4280–4281
132. Murray-Rust P, Stallings WC, Monti CT, Preston RK, Glusker JP (1983) Intermolecular interactions of the C-F Bond: the crystallographic environment of fluorinated carboxylic acids and related structures. J Am Chem Soc 105:3206–3214
133. Scerba MT, Leavitt CM, Diener ME, DeBlase AF, Guasco TL, Siegler MA, Bair N, Johnson MA, Lectka T (2011) NH+−F hydrogen-bonding in a fluorinated "Proton Sponge" derivative: integration of solution, solid-state, gas-phase, and computational studies. J Org Chem 76:7975–7984
134. Prakash GKS, Wang F, Rahm M, Shen J, Ni C, Haiges R, Olah GA (2011) On the nature of C-H···F-C interactions in hindered CF_3-C(sp^3) bond rotations. Angew Chem Int Ed 50:11761–11764

135. Chopra D (2012) Is organic fluorine really "not" polarizable? Cryst Growth Des 12:541–546
136. Dunitz JD (2004) Organic fluorine: odd man out. ChemBioChem 5:614–621
137. Cormanich RA, Freitas MP, Tormena CF, Rittner R (2012) The F···HO intramolecular hydrogen bond forming five-membered rings hardly appear in monocyclic organofluorine compounds. RSC Adv 2:4169–4174
138. Dunitz JD, Taylor R (1997) Organic fluorine hardly ever accepts hydrogen bonds. Chem Eur J 3:89–98
139. Fonseca TAO, Ramalho TC, Freitas MP (2012) F···HO intramolecular hydrogen bond as the main transmission mechanism for $^{1h}J_{F,\,H(O)}$ coupling constant in 2′-fluoroflavonol. Magn Reson Chem 50:551–556
140. Cormanich RA, Moreira MA, Freitas MP, Ramalho TC, Anconi CPA, Rittner R, Contreras RH, Tormena CF (2011) $^{1h}JF,_{H}$ coupling in 2-fluorophenol revisited: is intramolecular hydrogen bond responsible for this long-range coupling? Magn Reson Chem 49:763–767
141. Nolting DN, Nickels ML, Huo N, Pham W (2012) Molecular imaging probe development: a chemistry perspective. Am J Nucl Med Mol Imaging 2:273–306
142. Le Bars D (2006) Fluorine-18 and medical imaging: radiopharmaceuticals for positron emission tomography. J Fluor Chem 127:1488–1493
143. Miller PW, Long NJ, Vilar R, Gee AD (2008) Synthesis of ^{11}C, ^{18}F, ^{15}O and ^{13}N radiolabels for positron emission tomography. Angew Chem Int Ed 47:8998–9033
144. Ametamey SM, Honer M, Schubiger PA (2008) Molecular imaging with PET. Chem Rev 108:1501–1516
145. Pauwels EKJ, van der Klaauw AA, Corporaal T, Stokkel MPM (2002) Fluorine-18-radiolabeled pharmaceuticals for imaging with positron emission tomography, excluding [^{18}F]-fluorodeoxyglucose. Drugs Future 27:655–667
146. Daniels S, Farah M, Tohid S, Velanguparackel W, Westwel AD (2010) The role and future potential of fluorinated biomarkers in positron emission tomography. Expert Opin Drug Discov 5:291–304
147. Sharma S, Rodriguez AL, Conn PJ, Lindsley CW (2008) Synthesis and SAR of a mGluR5 allosteric partial antagonist lead: unexpected modulation of pharmacology with slight structural modifications to a 5-(phenylethynyl)pyrimidine scaffold. Bioorg Med Chem Lett 18:4098–4101
148. Sams AG, Mikkelsen AK, Brodbeck RMG, Pu X, Ritzén A (2011) Efficacy switching SAR of mGluR5 allosteric modulators: highly potent positive and negative modulators from one chemotype. Bioorg Med Chem Lett 21:3407–3410
149. Packiarajan M, Mazza Ferreira CG, Hong S-P, White AD, Chandrasena G, Pu X, Brodbeck RM, Robichaud AJ (2012) *N*-Aryl pyrrolidinonyl oxadiazoles as potent mGluR5 positive allosteric modulators. Bioorg Med Chem Lett 22:5658–5662
150. Packiarajan M, Mazza Ferreira CG, Hong S-P, White AD, Chandrasena G, Pu X, Brodbeck RM, Robichaud AJ (2012) Azetidinyl oxadiazoles as potent mGluR5 positive allosteric modulators. Bioorg Med Chem Lett 22:6469–6474
151. Schirrmacher R, Wängler C, Schirrmacher E (2007) Recent developments and trends in ^{18}F-radiochemistry: syntheses and applications. Mini Rev Org Chem 4:317–329
152. Cai L, Lu S, Pike VW (2008) Chemistry with [^{18}F]-fluoride ion. Eur J Org Chem 2853–2873
153. Littich R, Scott PJH (2012) Novel strategies for fluorine-18 radiochemistry. Angew Chem Int Ed 51:1106–1109
154. Hollingworth C, Gouverneur V (2012) Transition metal catalysis and nucleophilic fluorination. Chem Commun 48:2929–2942
155. Prakash GKS, Chacko S (2008) Novel nucleophilic and electrophilic fluoroalkylation methods. Curr Opin Drug Discov Dev 11:793–802
156. Shimizu M, Hiyama T (2004) Modern synthetic methods for fluorine-substituted target molecules. Angew Chem Int Ed 44:214–231
157. Kirk KL (2008) Fluorination in medicinal chemistry: methods, strategies, and recent developments. Org Proc Res Dev 12:305–321

158. Furuya T, Kuttruff CA, Ritter T (2008) Carbon-fluorine bond formation. Curr Opin Drug Discov Dev 11:803–819
159. Pauwels EKJ (2001) ^{18}F-Labeled fluorodeoxyglucose for PET imaging: the working mechanism and its clinical implication. Drugs Future 26:659–668
160. Gatley SJ, Volkow ND, Fowler JS, Ding Y-S, Logan J, Wang G-J, Gifford AN (2003) Positron emission tomography and its use to image the occupancy of drug binding sites. Drug Dev Res 59:194–207
161. Berridge MS, Heald DL, Lee Z (2003) Imaging studies of biodistribution and kinetics in drug development. Drug Dev Res 59:208–226
162. Hicks JW, Van Brocklin HF, Wilson AA, Houle S, Vasdev N (2010) Radiolabeled small molecule protein kinase inhibitors for imaging with PET or SPECT. Molecules 15:8260–8278
163. Badgaiyan RD (2011) Neurotransmitter imaging: basic concepts and future perspectives. Curr Med Imaging Rev 7:98–103
164. Jager PL, Chirakal R, Marriott CJ, Brouwers AH, Koopmans KP, Gulenchyn KY (2008) 6-L-^{18}F-fluorodihydroxyphenylalanine PET in neuroendocrine tumors: basic aspects and emerging clinical applications. J Nucl Med 49:573–586
165. Minn H, Kauhanen S, Seppanen M, Nuutila P (2009) ^{18}F-FDOPA: a multiple-target molecule. J Nucl Med 50:1915–1918
166. Garnett ES, Firnau G, Nahmias C (1983) Dopamine visualized in the basal ganglia of living man. Nature 305:137–138
167. DeJesus OT (2003) Positron-labeled DOPA analogs to image dopamine terminals. Drug Dev Res 59:249–260
168. Goodman MM, Kilts CD, Keil R, Shi B, Martarello L, Xing D, Votaw J, Ely TD, Lambert P, Owens MJ, Camp VM, Malveaux E, Hoffman JM (2000) ^{18}F-Labeled FECNT: a selective radioligand for PET imaging of brain dopamine transporters. Nucl Med Biol 27:1–12
169. Davis MR, Votaw JR, Bremner JD, Byas-Smith MG, Faber TL, Voll RJ, Hoffman JM, Grafton ST, Kilts CD, Goodman MM (2003) Initial human PET imaging studies with the dopamine transporter ligand ^{18}F-FECNT. J Nucl Med 44:855–861
170. Elsinga PH, Hatano K, Ishiwata K (2006) PET tracers for imaging of the dopaminergic system. Curr Med Chem 13:2139–2153
171. Chemel BR, Roth BL, Armbruster B, Watts VJ, Nichols DE (2006) WAY-100635 is a potent dopamine D4 receptor agonist. Psychopharmacol 188:244–251
172. Lang L, Jagoda E, Schmall B, Vuong B-K, Adams HR, Nelson DL, Carson RE, Eckelman WC (1999) Development of fluorine-18-labeled 5-HT_{1A} antagonists. J Med Chem 42:1576–1586
173. Lemaire C, Cantineau R, Marcel Guillaume M, Plenevaux A, Christiaens L (1991) Fluorine-18-altanserin: a radioligand for the study of serotonin receptors with PET: radiolabeling and in vivo biologic behavior in rats. J Nucl Med 32:2266–2272
174. Herth MM, Kramer V, Piel M, Palner M, Riss PJ, Knudsen GM, Roesch F (2009) Synthesis and in vitro affinities of various MDL 100907 derivatives as potential ^{18}F-radioligands for 5-HT_{2A} receptor imaging with PET. Bioorg Med Chem 17:2989–3002
175. Gao Y, Kuwabara H, Spivak CE, Xiao Y, Kellar K, Ravert HT, Kumar A, Alexander M, Hilton J, Wong DF, Dannals RF, Horti AG (2008) Discovery of (−)-7-methyl-2-exo-[3′-(6-[^{18}F] fluoropyridin-2-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane, a radiolabeled antagonist for cerebral nicotinic acetylcholine receptor (α4β2-nAChR) with optimal positron emission tomography imaging properties. J Med Chem 51:4751–4764
176. Yang L, Rieves D, Ganley C (2012) Brain amyloid imaging – FDA approval of florbetapir F18 injection. New Engl J Med 367:885–887
177. Garber K (2012) First FDA-approved beta-amyloid diagnostic hits the market. Nat Biotechnol 30:575
178. Kung HF, Choi SR, Qu W, Zhang W, Skovronsky D (2010) ^{18}F Stilbenes and styrylpyridines for PET imaging of Aβ plaques in Alzheimer's disease: a miniperspective. J Med Chem 53:933–941

179. Kung HF, Lee C-W, Zhuang ZP, Kung MP, Hou C, Plossl K (2001) Novel stilbenes as probes for amyloid plaques. J Am Chem Soc 123:12740–12741
180. Wang W, Oya S, Kung MP, Hou C, Maier DL, Kung HF (2005) F-18 stilbenes as PET imaging agents for detecting β-amyloid plaques in the brain. J Med Chem 48:5980–5988
181. Qu W, Kung MP, Hou C, Benedum TE, Kung HF (2007) Novel styrylpyridines as probes for SPECT imaging of amyloid plaques. J Med Chem 50:2157–2165
182. Zhang W, Oyas S, Kung MP, Hou C, Maier DL, Kung HF (2005) F-^{18}F PEG stilbenes as PET imaging agents targeting Aβ aggregates in the brain. Nucl Med Biol 32:799–809
183. Zhang W, Kung MP, Oya S, Hou C, Kung HF (2007) ^{18}F-labeled styrylpyridines as PET agents for amyloid plaque imaging. Nucl Med Biol 34:89–97
184. Stephenson KA, Chandra R, Zhuang Z-P, Hou C, Oya S, Kung M-P, Kung HF (2007) Fluoropegylated (FPEG): imaging agents targeting Aβ aggregates. Bioconjug Chem 18:238–246
185. Choi SR, Golding G, Zhuang Z, Zhang W, Lim N, Hefti F, Benedum TE, Kilbourn MR, Skovronsky D, Kung HF (2009) Preclinical properties of ^{18}F-AV-45: a PET agent for Aβ plaques in the brain. J Nucl Med 50:1887–1894
186. Wong DF, Rosenberg PB, Zhou Y, Kumar A, Raymont V, Ravert HT, Dannals RF, Nandi A, Brašić JR, Ye W, Hilton J, Lyketsos C, Kung HF, Joshi AD, Skovronsky DM, Pontecorvo MJ (2010) In vivo imaging of amyloid deposition in Alzheimer's disease using the radioligand ^{18}F-AV-45 (florbetapir F 18). J Nucl Med 51:913–920
187. Clark CM, Schneider JA, Bedell BJ, Beach TC, Bilker WB, Mintun MA, Pontecorvo MJ, Hefti F, Carpenter AP, Flitter ML, Krautkramer MJ, Kung HF, Coleman RE, Doraiswamy PM, Fleisher AS, Sabbagh MN, Sadowsky CH, Reiman PEM, Zehntner SP, Skovronsky DM (2011) Use of florbetapir-PET for imaging β-amyloid pathology. J Am Med Assoc 305:275–283
188. Fodero-Tavoletti MT, Brockschnieder D, Villemagne VL, Martin L, Connor AR, Thiele A, Berndt M, McLean CA, Krause S, Rowe CC, Masters CL, Dinkelborg L, Dyrks T, Cappai R (2012) In vitro characterization of [^{18}F]-florbetaben, an Aβ imaging radiotracer. Nucl Med Biol 39:1042–1048
189. Ashford JW, Rosen A, Adamson M, Bayley P, Sabri O, Furst A, Black SE, Weiner M, Barthel H, Sabri O (2011) Florbetaben to trace amyloid-β in the Alzheimer brain by means of PET. J Alzheimer's Dis 26(Suppl 3):117–121
190. Barthel H, Gertz H-J, Dresel S, Peters O, Bartenstein P, Buerger K, Hiemeyer F, Wittemer-Rump SM, Seibyl J, Reininger C, Sabri O (2011) Cerebral amyloid-β PET with florbetaben (^{18}F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. Lancet Neurol 10:424–435
191. Villemagne VL, Ong K, Mulligan RS, Holl G, Pejoska S, Jones G, O'Keefe G, Ackerman U, Tochon-Danguy H, Chan JG, Reininger CB, Fels L, Putz B, Rohde B, Masters C, Rowe CC L (2011) Amyloid imaging with ^{18}F-florbetaben in Alzheimer disease and other dementias. J Nucl Med 52:1210–1217
192. Nelissen N, van Laere K, Thurfjell L, Owenius R, Vandenbulcke M, Koole M, Bormans G, Brooks DJ, Vandenberghe R (2009) Phase 1 study of the Pittsburgh compound B derivative ^{18}F-flutemetamol in healthy volunteers and patients with probable Alzheimer disease. J Nucl Med 50:1251–1259
193. Wong DF, Moghekar Abhay R, Rigamonti D, Brasic JR, Rousset O, Willis W, Buckley C, Smith A, Gok B, Sherwin P, Grachev ID (2013) An in vivo evaluation of cerebral cortical amyloid with ^{18}F-flutemetamol using positron emission tomography compared with parietal biopsy samples in living normal pressure hydrocephalus patients. Mol Imaging Biol 15: 230–237
194. Vandenberghe R, Van Laere K, Ivanoiu A, Salmon E, Bastin C, Triau E, Hasselbalch S, Law I, Andersen A, Korner A, Minthon L, Garraux G, Nelissen N, Bormans G, Buckley C, Owenius R, Thurfjell L, Farrar G, Brooks DJ (2010) ^{18}F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment: a phase 2 trial. Ann Neurol 68:319–329
195. Cselenyi Z, Joenhagen ME, Forsberg A, Halldin C, Julin P, Schou M, Johnstroem P, Varnaes K, Svensson S, Farde L (2012) Clinical validation of ^{18}F-AZD4694, an amyloid-β-specific PET radioligand. J Nucl Med 53:415–424

196. Jureus A, Swahn B-M, Sandell J, Sandell J, Jeppsson F, Johnson AE, Johnstroem P, Neelissen JAM, Sunnemark D, Farde L, Svensson SPS (2010) Characterization of AZD4694, a novel fluorinated Aβ plaque neuroimaging PET radioligand. J Neurochem 114:784–794
197. Li Z, Conti PS (2010) Radiopharmaceutical chemistry for positron emission tomography. Adv Drug Deliv Rev 62:1031–1051
198. Riss PJ, Ferrari V, Brichard L, Burke P, Smith R, Aigbirhio FI (2012) Direct, nucleophilic radiosynthesis of [^{18}F]-trifluoroalkyl tosylates: improved labelling procedures. Org Biomol Chem 10:6980–6986
199. Moon BS, Kil HS, Park JH, Kim JS, Park J, Chi DY, Lee BC, Kim SE (2011) Facile aromatic radiofluorination of [^{18}F]-flumazenil from diaryliodonium slats with evaluation of their stability and selectivity. Org Biomol Chem 9:8346–8355
200. Lee E, Kamlet AS, Powers DC, Neumann CN, Boursalian GB, Furuya T, Choi DC, Hooker JM, Ritter T (2011) A fluoride-derived electrophilic late-stage fluorination reagent for PET imaging. Science 334:639–642
201. Liu W, Huang X, Cheng M-J, Nielsen RJ, Goddard WA III, Groves JT (2012) Oxidative aliphatic C-H fluorination with fluoride ion catalyzed by a manganese porphyrin. Science 337:1322–1325

Chemistry of Fluorinated Pyrroles

Valentine Nenajdenko, Vasiliy M. Muzalevskiy, and Olga V. Serdyuk

Contents

V. Nenajdenko (✉) • V.M. Muzalevskiy
Department of Chemistry, Moscow State University,
Leninskie Gory, Moscow 119992, Russian Federation
e-mail: nenajdenko@gmail.com; muzvas@mail.ru

O.V. Serdyuk
Department of Chemistry and Pharmacy, University of Erlangen-Nuremberg,
Henkestrasse 42, 91054 Erlangen, Germany

Department of Chemistry, Southern Federal University,
Zorge 7, Rostov-on-Don, 344090, Russian Federation

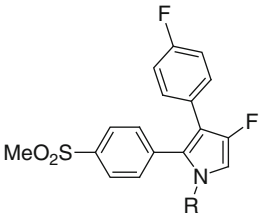
V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_2,

Abstract Synthetic approaches towards pyrroles, bearing fluorine atoms and trifluoromethyl group, are overviewed in this chapter. Literature data are surveyed accordingly to reaction type used to obtain the fluorinated pyrrole moiety. Properties as well as some applications of fluorinated are also reviewed.

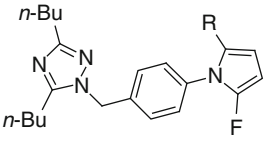
Keywords Pyrroles • Fluorine • Trifluoromethyl group • Synthesis • Fluorinated heterocycles

1 Introduction

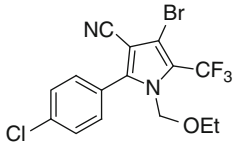
Pyrroles constitute the core of a large number of alkaloids and many other physiologically active compounds, which make them strongly attractive as synthetic targets for further investigation. Fluoropyrrole derivatives are important anti-inflammatory agents [1], stable GnRH receptor antagonists [2], inhibitors of HCV NS5B polymerase [3], Angiotensin II receptor antagonists used in therapy for treating hypertension [4]. Fluorinated pyrrole derivative chlorfenapyr, discovered in 1988, was commercialized in 1995 as a broad-spectrum insecticide [5].



Antiinflammatory Activity



Angiotensin II Antagonist Activity



Chlorfenapyr

This chapter summarizes the major synthetic pathways towards fluoro- and trifluoromethylpyrroles. Biological properties and applications of these compounds are also included. The chapter is organized according to the reaction type used to gain the target fluorinated pyrrole.

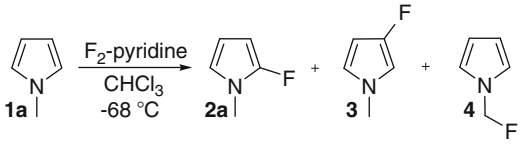
2 Synthesis of Fluorinated Pyrroles

2.1 Fluorination/Trifluoromethylation Methods

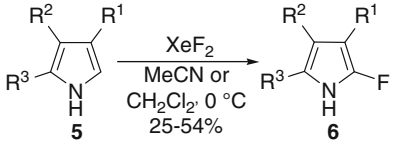
2.1.1 Electrophilic Fluorination

Direct fluorination of pyrrole ring was examined in several works to give a simple pathway to fluoropyrroles. However, high reactivity of pyrrole ring towards electrophiles, resulting in their easy polymerization, leads to fluoropyrroles obtained in low or moderate yields, which is a disadvantage of this approach. Except the

fluorination with elemental fluorine, this method provides regioselectively 2-fluoropyrroles. Thus, treatment of N-methylpyrrole **1a** with F_2 under carefully controlled conditions in $CHCl_3$ afforded both 2- and 3-fluoropyrroles **2,3** together with fluoromethylpyrrole **4** (the yields are not given) [6].



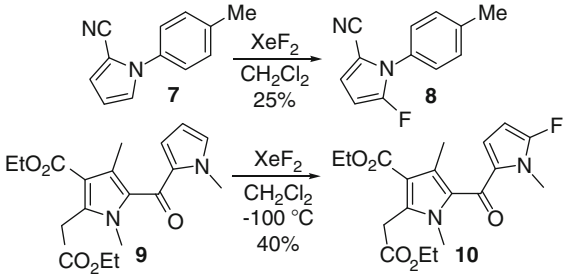
Direct fluorination of pyrroles **5** without NH-protection can be performed with substrates bearing electron-withdrawing substituents, using xenon difluoride. The transformation gives substituted 2-fluoropyrroles **6** in moderate yields [7].



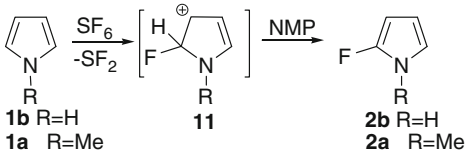
R^1,R^2 = H, CH_2CO_2Me, $CH_2CH_2CO_2Me$

R^3 = CHO, CO_2CH_2Ph, $COCCl_3$, $CONMe_2$

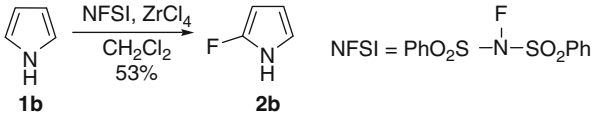
Fluorination of N-substituted pyrroles **7,9** with xenon difluoride was also performed to give substituted products at α-position **8,10** in moderate yields [8].



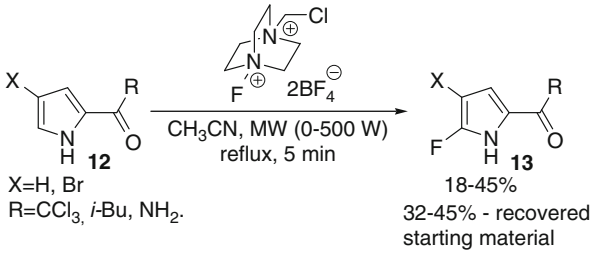
The first synthesis of 2-fluoropyrrole **2b** and N-methylated analogue **2a** was performed in gas phase by electron ionization of SF_6. SF_3^+ species are formed under these conditions providing approach to generate a gentle and effective electrophilic monofluorinating reagent for five-membered heterocyclic compounds [9].



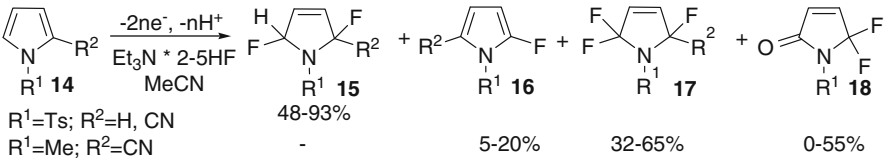
A more convenient method of fluorination is based on the Lewis acid catalyzed reaction with N-fluorobenzenesulfonimide (NFSI). The reaction is catalyzed by $ZrCl_4$ and gives 2-fluoropyrrole **2b** in 53 % yield. The use of a large amount of catalyst can increase the yield of the product; but the amount of unknown by-products also increases [10].



Fluorination of a series of 2-acylpyrroles **12** was also performed using Selectfluor. Treatment of mono- and nonbrominated 2-acylpyrroles **12** with Selectfluor in MeCN under microwave irradiation leads to fluorination of the pyrrole ring at the 5-position. The corresponding fluoropyrroles **13** were isolated in moderate yields. However noticeable amounts of starting materials were also isolated, making real yields much higher [11]. Fluoropyrroles thus obtained were used for the synthesis of fluoroanalogue of hymenidin (see Sect. 3 of this chapter).

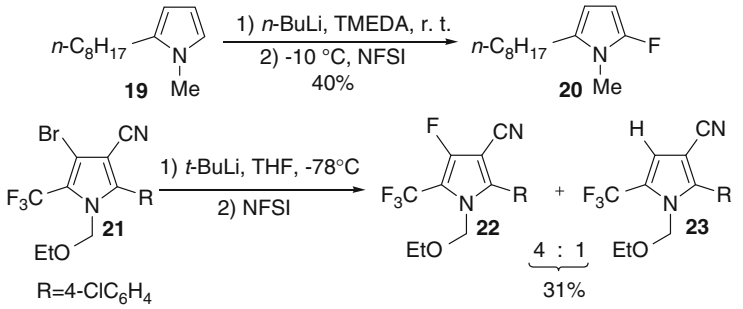


Direct anodic fluorination of 1,2-disubstituted pyrroles **14** gives 5-fluoropyrroles **16** and/or fluorinated adducts **15**, **17**, pyrrolin-2-ones **18**. The transformation is performed with platinum plate electrode in acetonitrile containing supporting fluoride salts Et_3N-nHF [12]. The structure of product depends on supporting fluoride salts.

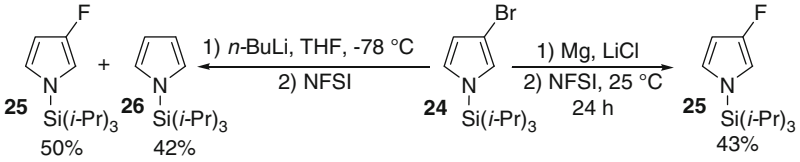


It is known, that convenient approach to fluorinated five-membered heterocycles, including pyrroles, is based on the metallation-fluorination reactions [13]. Thus, 100 % regioselective lithiation of the starting N-methylpyrrole **19** followed by a treatment of the corresponding organolithium derivative with NFSI gives 2-fluoro-5-*n*-octyl-N-methylpyrrole **20** in 40 % yield [13]. Similarly, starting from

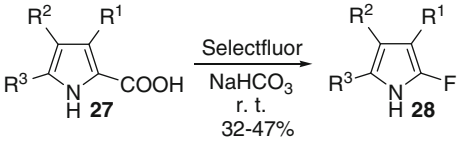
bromopyrrole **21**, highly substituted fluoropyrrole **22** was prepared with admixture of pyrrole **23** [14].



Reaction of NFSI with lithiopyrrole derivative obtained by Br-Li exchange from 3-bromopyrrole **24** afforded the desired 3-fluoro-l-(triisopropylsilyl)pyrrole **25** in 50 % yield and 1-(triisopropylsilyl)pyrrole **26** as a major by-product [14, 15]. The conversion of Grignard reagents into the corresponding fluorinated products using a Br–Mg exchange and a subsequent fluorination procedure with NFSI represents convenient modification of this method providing the fluoropyrrole **25** in 43 % yield [16].

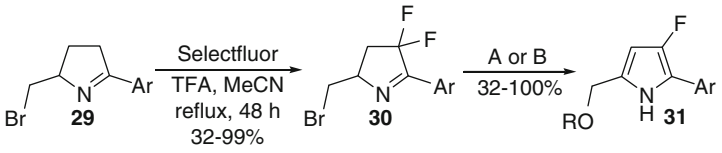


All methods above described are based on the direct fluorination of heterocycle or lithiation followed by fluorination via formal substitution of hydrogen. However, various pyrrole derivatives such as carboxylic acids and halopyrroles can be also used as starting compounds for electrophilic fluorination-decarboxylation. Thus, reaction of α-pyrrolecarboxylic acids **27**, in which the ring is highly substituted by electron-withdrawing or electron-donating groups, with Selectfluor gives the corresponding α-fluoropyrroles **28** in 32–47 % yields [17].



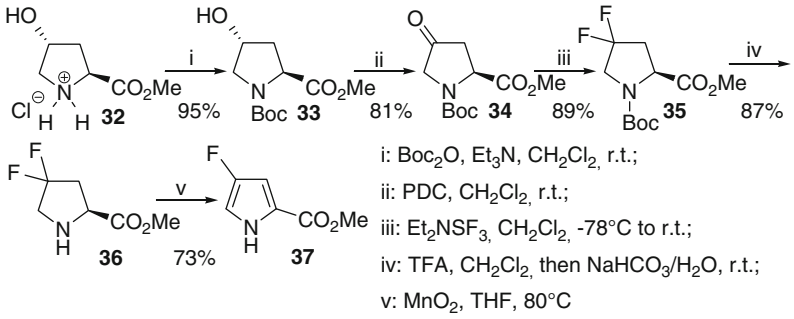
R^1=Me, CH_2CO_2Me, $CH_2CH_2CO_2Me$.
R^2=H, Me, CH_2CO_2Me, $CH_2CH_2CO_2Me$.
R^3=Cbz, CHO, Me.

Another possibility for the synthesis of fluorinated pyrroles is the use of their nonaromatic precursors. Thus, 3,3-difluoro-1-pyrrolines **30** were prepared via electrophilic fluorination of the corresponding 1-pyrrolines **29** by Selectfluor. Reaction of the difluoropyrrolines **30** with sodium alkoxides yielded fluorinated 5-(alkoxymethyl) pyrroles **31** in good yields [18].



Ar = Ph, 4-F-C_6H_4; A: 2M aq. NaOH, ROH, 1h; B: 1M NaOR, ROH, 1h

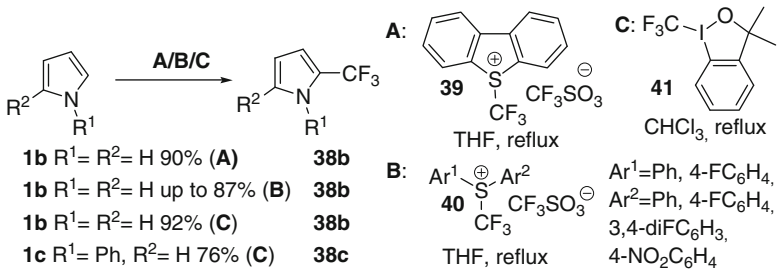
Effective pathway towards 3-fluoropyrrole **37** was elaborated on the base of easily available methyl *trans*-4-hydroxy-L-prolinate **32**. After Boc-protection of this compound followed by oxidation with PDC, ketone obtained **34**, was converted into difluoride **35** by the reaction with DAST. N-Boc deprotection of **35** with trifluoroacetic acid afforded, after basic treatment, free base **36** which was aromatized by activated manganese dioxide into methyl 4-fluoro-1H-pyrrole-2-carboxylate **37** [15, 19].



2.1.2 Electrophilic Trifluoromethylation

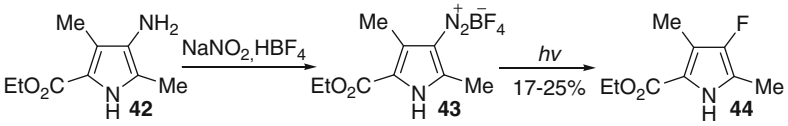
Electrophilic aromatic substitution is also a general method towards trifluoromethylated pyrroles. Umemoto et al. investigated a variety of sulfonium, telluronium, selenonium and oxonium salts as sources of the trifluoromethyl cation. Thus, the sulfonium salt **39** was applied for pyrrole trifluoromethylation. The 2-CF_3-pyrrole **38b** was obtained regioselectively in 90 % yield [20]. Several other sulfonium salts **40** were also used for pyrrole trifluoromethylation [21]. Highest yields were obtained with the most electrophilic salts bearing electron-withdrawing groups in the benzene rings. Perfect regioselectivity was also achieved then hypervalent iodine reagent **41** was used for electrophilic trifluoromethylation of pyrroles [22].

High yields of the target pyrroles and simplicity of experimental technique are significant advantages of electrophilic trifluoromethylation.

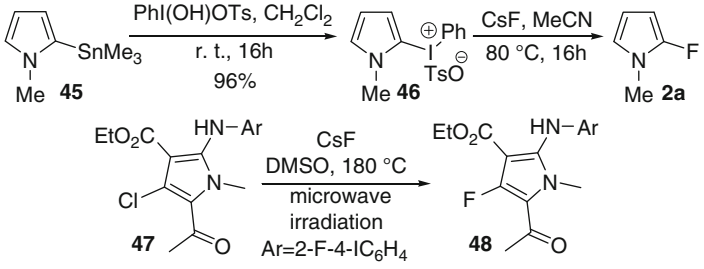


2.1.3 Nucleophilic Fluorination

In contrast to fluorination using electrophiles, nucleophilic fluorination is much rarely presented in the literature. A photochemical modification of the Schiemann reaction has been used for the preparation of 3-fluoropyrroles. Thus, treatment of aminopyrrole derivative **42** with $NaNO_2$ in fluoroboric acid afforded the diazonium tetrafluoroborate **43**. Irradiation of this compound with a high pressure mercury lamp gave 3-fluoropyrrole **44** in 17–25 % yield [23].

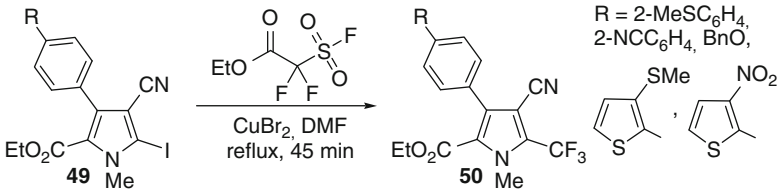


2-Fluoropyrrole **2a** was obtained in good yield through the intermediate iodonium salt **46**, starting from stannane **45** [24]. The reaction represents an example of nucleophilic substitution in iodonium salts by fluoride ion. Similarly, chlorine atom in pyrrole **47** activated by electron-withdrawing CO_2Et and acyl groups was substituted by fluoride in DMSO under microwave irradiation to give fluoropyrrole **48** [25]. The yields of products obtained were not reported.

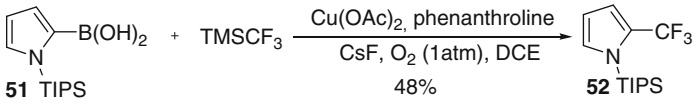


2.1.4 Nucleophilic Trifluoromethylation

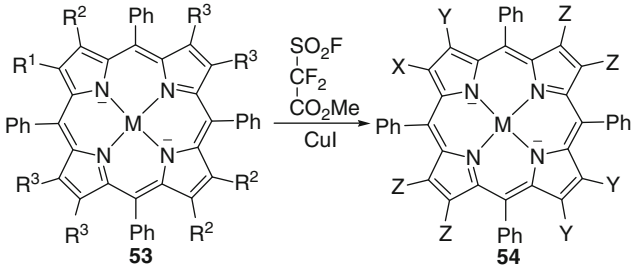
2-Triflurомethyl pyrroles can be also synthesized by nucleophilic trifluoromethylation. In few works the *ipso*-substitution of iodide in compounds **49** by the trifluoromethyl group was reported using a mixture of $FSO_2CF_2CO_2Et$ and $CuBr_2$ as the source of the unstable intermediate trifluoromethyl anion [26]. No yields of compounds **50** were given.



Copper-mediated oxidative cross-coupling of 2-pyrrolylboronic acid **51** with $TMSCF_3$ provided another selective approach to 2-trifluoromethylpyrrole. Reaction proceeds in mild conditions to give *N*-TIPS-2-trifluoromethylpyrrole **52** in 48 % yield [27].



Various trifluoromethylated metalloporphyrins **54** were prepared in high yields by the reaction of brominated metalloporphyrins **53** (copper and nickel complexes) with stoichiometric amounts of FSO_2CF_2COOMe/CuI in the presence of catalytic amounts of a palladium catalyst [28]. Similarly, the $(CF_3)_2Cd$-CF_3CdBr-CuBr system was used as a source of trifluoromethyl anion in the synthesis of some porphyrin derivatives [29].



R^1= Br, R^2= R^3= Y = Z = H, X = CF_3 M = Cu^{2+} 65%; M = Ni^{2+} 70%
R^1= R^2= Br, R^3= Z = H, X= Y = CF_3 M = Cu^{2+} 95%; M = Ni^{2+} 95%
R^1= R^2= R^3= Br, X = Y = Z = CF_3 M = Cu^{2+} 85%; M = Ni^{2+} 90%

Table 1 Synthesis of regioisomeric trifluoromethylpyrroles

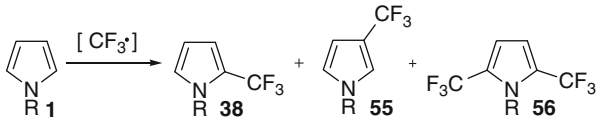
Entry	Educt **1**	R	CF_3 source	CF_3	Yield **38** (%)	Yield **55** or **56**, (%)	References
2	**1a**	Me	CF_3I	CF_3	36	7 (**56**)	[31]
1	**1b**	H	CF_3I	CF_3	33	–	[31]
3	**1d**	Bn	CF_3I	CF_3	71	–	[32]
4	**1e**	*p*-Tol	CF_3I	CF_3	91	–	[32]
5	**1b**	H	CF_2I_2	CF_3	42	2 (**55**)	[33]
6	**1a**	Me	CF_2I_2	CF_3	46	3 (**55**)	[33]
7	**1b**	H	$(CF_3CO_2)_2$	CF_3	72	–	[34]
8	**1b**	H	**70**	CF_3	51	–	[35]
9	**1b**	H	$Te(CF_3)_2$	CF_3	(25:	1(**38b**))[a]	[36]
13	**1a**	Me	CF_3Br	CF_3	52[b]	–	[37]
10	**1b**	H	CF_3Br	CF_3	15[b]	–	[37]
11	**1b**	H	CF_3Br	CF_3	47[c]	–	[37]
12	**1b**	H	CF_3Br	CF_3	65[d]	8 (**55**)	[38]

[a]Yield not given

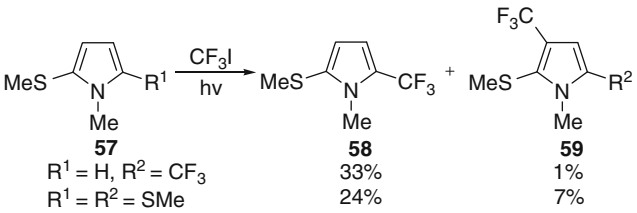
Reducing systems: [b]Zn/SO_2, [c]$Na_2S_2O_4$, [d]HCO_2Na/SO_2

2.1.5 Radical Trifluoromethylation

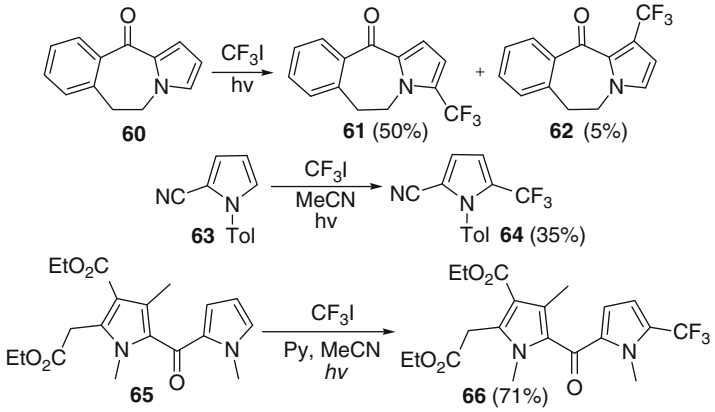
The direct trifluoromethylation of the pyrrole ring is a widely used approach to synthesize trifluoromethylated products [30]. The *N*-methylpyrrole **1a** reacted regioselectively with CF_3Br in acetonitrile under UV irradiation (Hg lamp) giving the 2-CF_3-pyrrole **38a** in 6 % yield. Under similar conditions, the reactions of pyrroles **1a,1b** with CF_3I in acetonitrile [31] resulted in higher yields. Trifluoromethylation of **1b** proceeded regioselectively in 2-position to give **38b** in 33 % yield, while **38a** was isolated in 36 % yield [31] (Table 1, entries 1 and 2). However, excess of CF_3I (2.5 equiv.) was needed to complete the conversion of **1a**. This resulted in the admixture of the bis-trifluoromethylation product **56a** (7 %). In contrast, *N*-benzyl- and *N*-(*p*-tolyl)substituted pyrroles **1d** and **1e** afforded the corresponding derivatives **38d** and **38e** in 71 % and 91 % yields, respectively [32] (Table 1, entries 3 and 4).



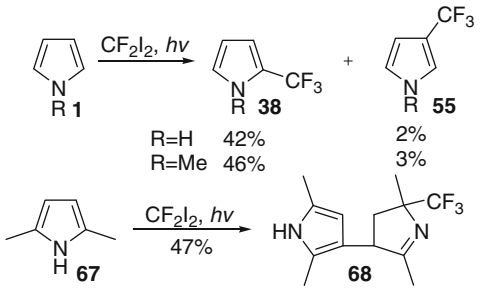
Similarly, in case of the methylthio derivatives **57** maximal yields of **58** were obtained using 2.5 equiv. of CF_3I. However, full consumption of starting material was not achieved and formation of side products **59** was observed [31].



Several other photochemical trifluoromethylations by CF_3I were reported. The regioisomeric substitution products **61** and **62** were formed [32] from the tricyclic pyrrole **60,** whereas regioselective α-trifluoromethylation was observed for pyrroles **63** and **65** to give 2-CF_3-pyrroles **64** [4] and **66** [8] in moderate and good yields.

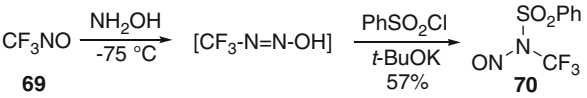


Surprisingly, the reaction of CF_2I_2 with pyrrole (**1b**) and *N*-methylpyrrole (**1a**) gave the trifluoromethylated products **38b** and **38a** in moderate yields under UV irradiation in DMF (Table 1, entries 5 and 6) [33]. In contrast the related reaction with 2,5-dimethylpyrrole **67** gave the trifluoromethylated dimer **68** instead of the desired 2,5-dimethyl-3-trifluoromethylpyrrole.



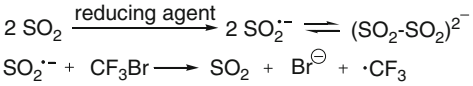
Bis(perfluoroalkanoyl)peroxides were also applied for radical trifluoromethylation of pyrrole **2b** [34]. Performing the reaction in freon 113 at −30 °C was found to be optimal for all peroxides. In this way 2-CF_3-pyrrole **38b** was regioselectively synthesized in 72 % yield (Table 1, entry 7). Lower yields were obtained both at higher temperature and in diethyl ether as a solvent.

The *N*-nitrososulfonamide **70** was shown to be a convenient reagent for radical trifluoromethylation. UV irradiation of **1b** with **70** in the presence of diacetyl as a sensitizer led to **38b** in 51 % yield (Table 1, entry 8). Distinct advantage of this method is easy handling of the solid **70** instead of gaseous CF_3I or of the quite unstable bis(perfluoro-alkanoyl)peroxides. **70** is assessable from trifluoronitroso-methane **69** in a one-pot procedure [35]. $Te(CF_3)_2$ was also used as a trifluoromethyl radical source for trifluoromethylation. The reaction proceeded under UV irradiation and led to a 25:1 mixture of pyrroles **1b** and **2b** (Table 1, entry 9) [36].

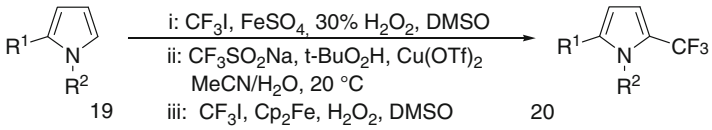


69 **70**

Besides UV irradiation, different reductive systems (Zn/SO_2 couple or $Na_2S_2O_4$) can be used for the initiation of trifluoromethyl radical formation [37]. Using these systems, compound **38b** was synthesized in low or moderate yields (Table 1, entries 10 and 11). **38a** was prepared analogously (entry 13). Initiation by HCO_2Na/SO_2 improved the yield of **38b** up to 65 %, but the admixture of 8 % of the regioisomer **55b** was found (entry 12) [38].



Trifluoromethylation of pyrroles under oxidative conditions was also reported. Thus, the DMSO-CF_3I-$FeSO_4$-H_2O_2 and DMSO-CF_3I-Cp_2Fe-H_2O_2 systems were applied to prepare the 2-CF_3-pyrroles **71** [39], **72** [40], **2b, 73** [41] regioselectively in good to high yields. Similarly, using the combination CF_3SO_2Na/*t*-BuOOH/$Cu(OTf)_2$ in acetonitrile/water, the 2-trifluoromethyl-*N*-acylpyrrole **38f** was prepared in 35 % yield [42].



19 20

71 R^1 = 4-$MeSO_2C_6H_4$, R^2 = 4-FC_6H_4
72 R^1 = 2-MeO-5-ClC_6H_3, R^2 = 4-$MeCO_2C_6H_4$
2f R^1 = H, R_2 = Ac
2b R^1 =R^2=H
73 R^1 =Ac, R^2=Me,

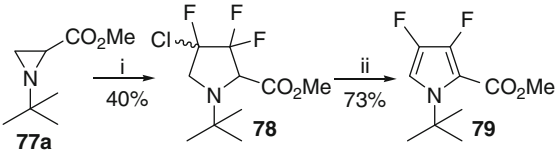
(i) **74** 43%
(i) **75** 43%
(ii) **38f** 35%
(i) **38b** 96%
(iii) **76** 79%

Direct fluorination/trifluoromethylation are very synthetically attractive approaches to prepare fluorinated pyrroles due to it is not necessary to construct the heterocyclic core. Especially this methods are convenient for the synthesis of fluoropyrroles. In contrast, synthesis of trifluoropyrroles is restricted by lower regioselectivity, moderate yields and the application of gaseous CF_3I or quite unstable (bis(trifluoroacetyl)peroxides).

2.2 *Heterocyclizations Leading to Fluorinated Pyrroles*

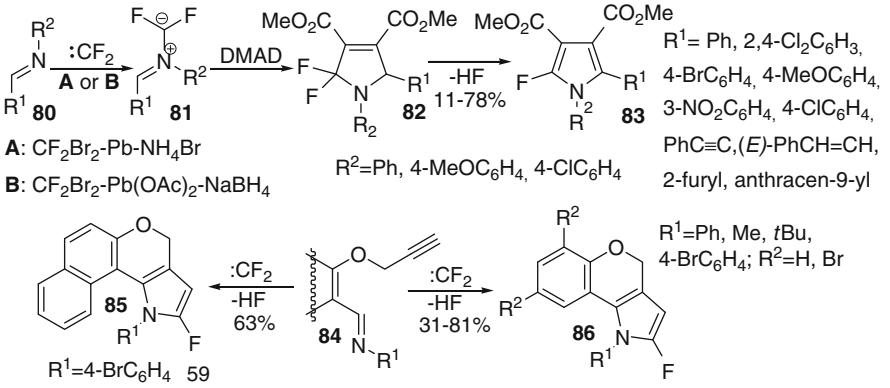
2.2.1 Synthesis of Fluoropyrroles by [3+2] Cycloaddition Reactions

Application of cycloaddition reactions is one of the most prominent strategies in synthesis of cyclic systems. 1,3-Dipolar cycloaddition of azomethine ylides to unsaturated compounds gives rise to a number of pyrrole syntheses. For example, azomethine ylide, generating by the thermal ring-opening of 2-carbomethoxyl-t-butyl-aziridine **77a**, reacts with chlorotrifluoroethene to give a mixture of diastereoisomeric chlorofluoropyrrolidines **78**. Treatment of those with sodium methoxide resulted in formation of 3,4-difluoropyrrole derivative **79** in high yield [43].



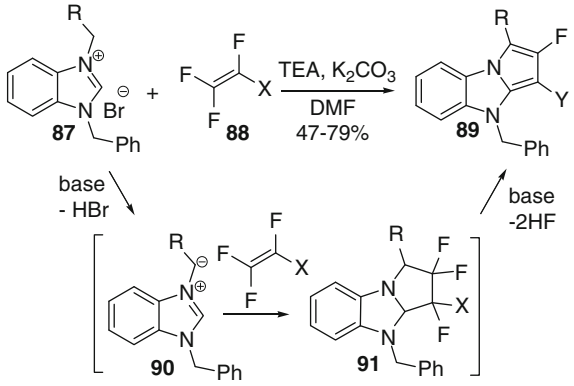
i: FClC=CF_2, 200 °C, 2 h; ii: MeONa, MeOH

Imines **80** react with difluorocarbene in the presence of dimethyl acetylenedicarboxylate (DMAD) producing 2-fluoropyrroles **83** in 11–78 % yields. This domino process was assumed to occur via difluorocarbene attack on the nitrogen lone pair resulting in formation of azomethine ylides **81**, 1,3-dipolar cycloaddition of the latter one to DMAD, and dehydrofluorination of pyrrolines **82** thus formed [44]. Difluorocarbene can be generated by reduction of dibromodifluoromethane with lead powder in the presence of tetrabutylammonium bromide (Method A) or using active lead obtained by reduction of aqueous lead acetate with sodium borohydride (Method B). This reaction can be also performed as intramolecular version to form substituted 2-fluoropyrroles **85**, **86** [45].



Benzimidazolium N-ylides **90**, generated in situ from bromides **87**, react with fluoroalkenes **88** in DMF in the presence of K_2CO_3 and Et_3N, to give fluorinated H-pyrrolo[1,2-a]benzimidazoles **89**. The mechanism of the reaction includes

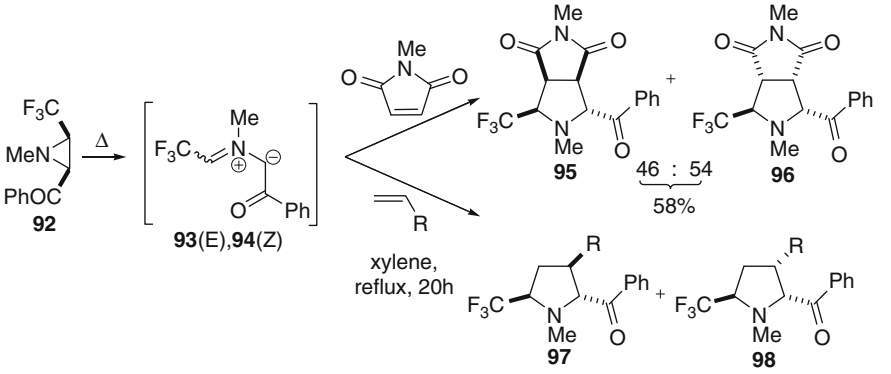
1,3-dipolar [3+2] cycloaddition with formation of pyrrolines **91**, followed by base induced elimination-aromatization [46].



X = Cl, Br, F, CF_3; R = COPh, COOEt, CN; Y=F, CF_3

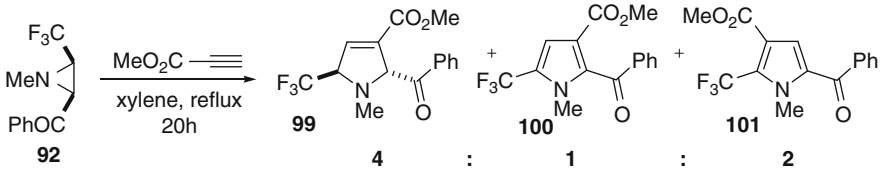
2.2.2 Synthesis of Trifluoropyrroles by [3+2] Cycloaddition Reactions

Azomethine ylides were also used as dipols for the preparation of CF_3-pyrroles by 1,3-dipolar cycloaddition. The ylides **93** and **94** prepared *in situ* from aziridine **92** in refluxing xylene, with excess of *N*-methyl-maleimide gave an 1:1 mixture of the diastereomeric pyrrolidines **95** and **96**. The reactions of **92** with monosubstituted ethenes (styrene, methyl acrylate, acrylonitrile) proceeded regio- and stereoselectively giving only one of the possible isomers. In contrast, the electron-rich vinyl butyl ether led to both possible stereoisomers **97** and **98** in almost 1:1 ratio [47].

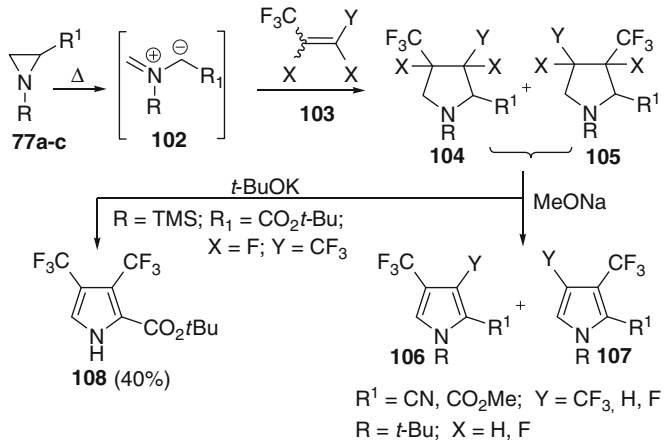


The reaction of **92** with methylpropiolate was not regioselective and led to a 4:1:2 mixture of the pyrroline **99** and the isomeric pyrroles **100** and **101**. The pyrroline **99**

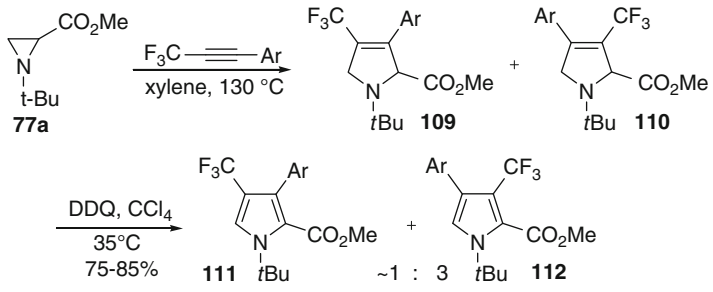
was shown to be an intermediate, which on refluxing in xylene was aromatized into **100**. The regioisomeric pyrroline leading to **101** was not isolated [47].



The addition of azomethine ylides **102** formed by heating of the aziridines **77a,b** (R = *t*-Bu) to the trifluoromethylated alkenes **103** led to mixtures of the diastereomeric pyrrolidines **104** and **105**. Subsequent elimination of HF by treatment with sodium methoxide in methanol gave predominantly the pyrrole **106** and minor amount of the regioisomer **107** [43]. 3,4-Bis(trifluoromethyl)pyrrole **108** with a free nitrogen atom was obtained using *N*-trimethylsilyl aziridine **77c** [48].

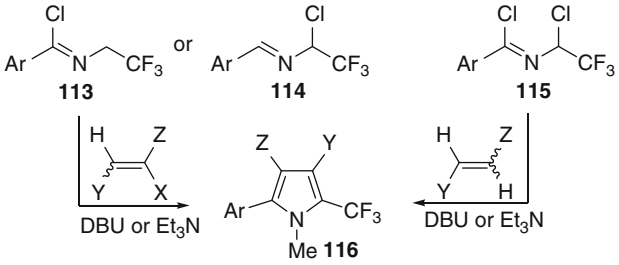


The reaction of azomethine ylide formed from the aziridine **77a** with trifluoromethylaryl acetylenes gave a mixture of dihydropyrroles **109** and **110**, which formed a 1:3 mixture of pyrroles **111** and **112** by oxidation with DDQ [49].



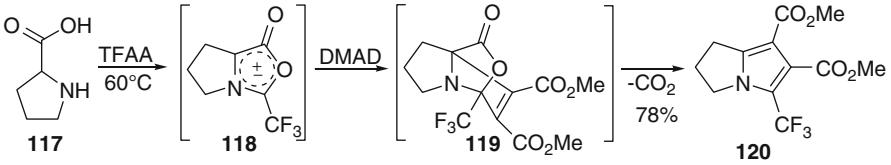
This methodology was further developed using imidoylchlorides **113** as precursors of azomethine ylides [50], which were generated by treatment with bases.

Application of the isomeric chloroimines **114** led to the same pyrroles **116** [51]. The generation of ylides was also possible from dichloroimines **115**, that allowed to involve alkenes without any vinylic halogen atoms. The yields were not given [52].

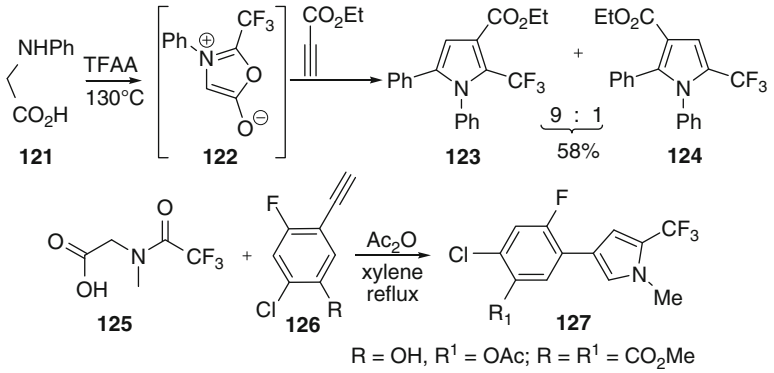


Ar = 4-ClC$_6$H$_4$; X = Cl, Br, I; Y = H, C$_n$F$_{2n}$$^{+1}$; Z = CN, NO$_2$, CO$_2$R

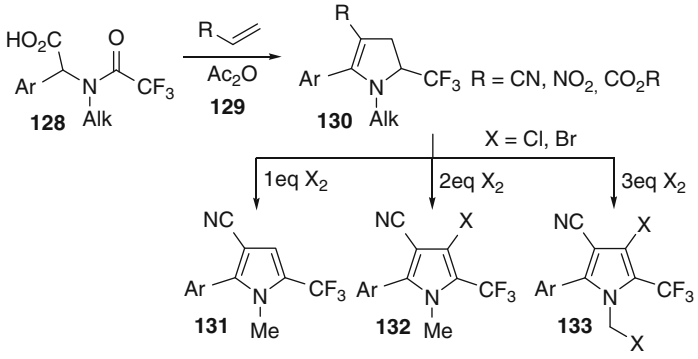
The 1,3-dipolar cycloaddition of acetylenes and alkenes with oxazolones is widely used for the construction of the pyrrole ring. The presence of a CF_3-group in the 1,3-dipolar component opens a pathway to 2-CF_3-pyrroles, while the application of trifluoromethylated dipolarophiles provides 3-CF_3-pyrroles. For example, the dimethyl pyrroledicarboxylate **120** was synthesized in 78 % yield by the reaction of the CF_3-containing oxazolone **118**, prepared from proline **117** and trifluoroacetic anhydride (TFAA), with dimethyl acetylene dicarboxylate (DMAD) [53].



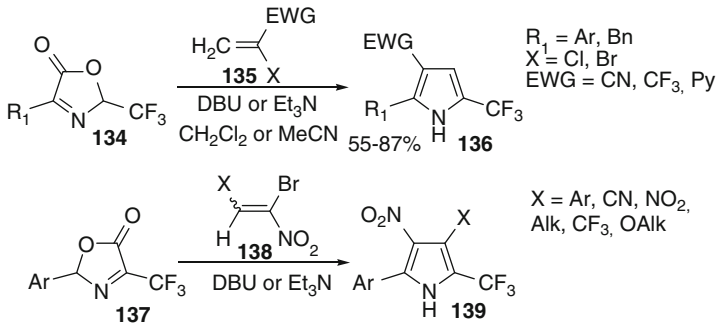
Derivatives of other amino acids were also used for the preparation of pyrroles [54]. Accordingly, the reaction of the unstable **122**, generated in situ from *N*-phenylglycine **121**, with ethyl propiolate gave an inseparable 9:1 mixture of **123** and **124** in 58 % yield. Similarly, the pyrroles **127** were synthesized from trifluoroacetylated sarcosine **125** and the acetylenes **126** [55].



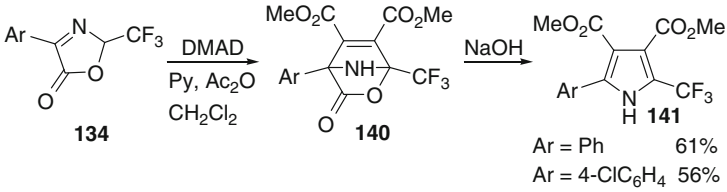
If electron deficient terminal alkenes **129** as dipolarophiles were treated with appropriately protected arylglycine derivatives **128**, the dihydropyrroles **130** were formed as cycloadducts [56]. However, aromatization was easily possible by treatment with oxidants such as bromine or chlorine. Depending on the amount of halogen, pyrroles **131**, monohalopyrroles **132** or dihalopyrroles **133** can be synthesized. Using that strategy, compound **131** (Ar = 4-ClC_6H_4, X = Br) was prepared starting from the corresponding **128** in three steps in 30 % overall yield. This compound is a useful starting material to synthesize the broad-spectrum insecticide chlorfenapyr and analogues [57].



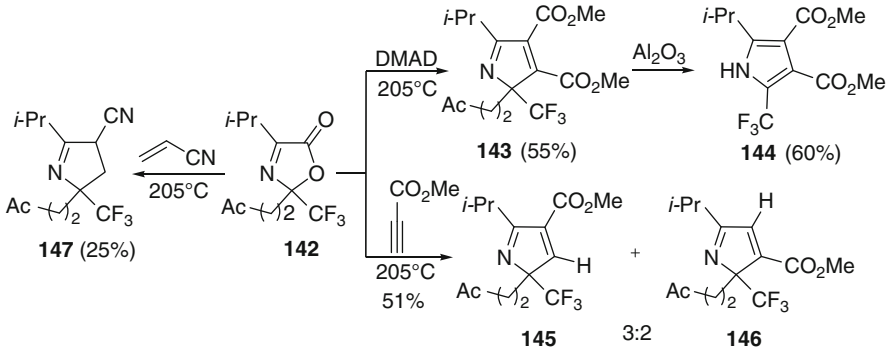
The reaction of oxazolones **134** with electron-deficient alkenes **135** in the presence of a base (DBU or Et_3N) gave the pyrroles **136** in good yields [58]. These base promoted cyclocondensations involve a tandem Michael addition of oxazolones **134** to electron-deficient alkenes **135** followed by intramolecular cyclization and decarboxylation. This method opened up a convenient pathway to synthesize 2-trifluoromethylpyrroles containing electron-withdrawing groups in 4-position. When the reactions were performed in MeCN and Et_3N at reflux, yields rose up to 86–94 % in case of the 4-chlorophenyl substituent [59]. Instead of the alkenes their saturated bromo precursors were also successfully applied [60]. The synthetic scope of this reaction was significantly expanded using reactions of oxazolones **137** with nitroalkenes **138.** The 2-CF_3-pyrroles **139** bearing numerous combinations of aryl, alkyl, alkoxy, nitro and cyano groups can be prepared by this method [61].



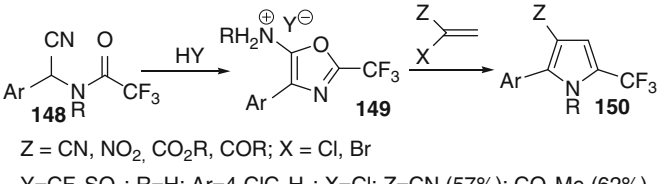
The reaction of oxazolones **134** with DMAD led to adducts **140**, which were transformed into pyrroles **141** after decarboxylation [58].

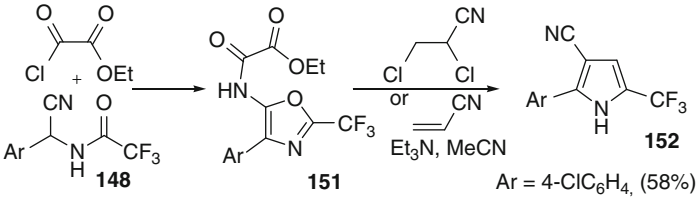


The reaction of the oxazolone **142** (bearing two substituents at C-2 atom) with DMAD led to the nonaromatic pyrroline **143**, which after passing through a column with active Al_2O_3 gave the pyrrole **144** by elimination of methyl vinyl ketone with aromatization. Treatment of **142** with methyl propargylate produced a 3:2 mixture of the regioisomers **145** and **146**, while the reaction with acrylonitrile led to the pyrroline **147** in 25 % yield [62].

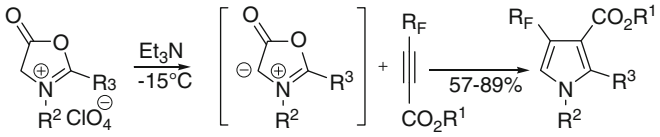


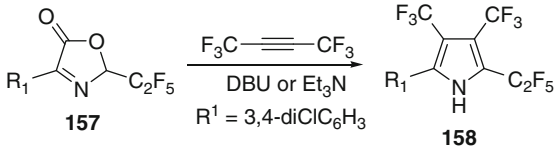
Besides alkyl and aryl oxazolones and their salts, also 5-aminooxazoles **149** [63] as well as the amides of aminooxazoles **151** [64] were used to synthesize trifluoromethylated pyrroles by cycloaddition. This is not surprising taking into account that the aminooxazoles **149** and amides **151** are formal tautomers of the oxazolone imines. Accordingly, a number of CF_3-pyrroles **150** and **152** bearing electron-withdrawing groups at the 4-position have been prepared by this method.





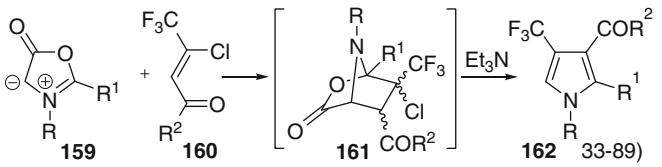
Mesoionic oxazolones **154**, prepared from **153**, allowed the synthesis of 3-CF_3-pyrroles. Thus, their reactions with fluorinated derivatives of ethyl propiolate **155** led to the alkyl pyrrole-3-carboxylates **156** [65]. Similarly, the reaction of compound **157** with hexafluorobut-2-yne gave the pyrrole **158** [66].





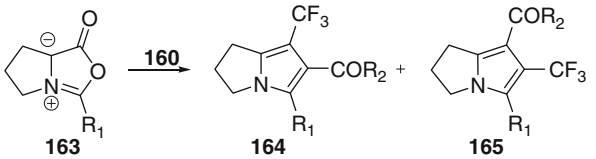
The reaction of the oxazolones **159** with the trifluoromethylated chloroalkenones **160** proceeded regioselectively via the intermediate bicyclic pyrrolidines **161**,

which in the presence of triethylamine eliminated HCl and CO_2, forming the pyrroles **162** in moderate to high yields [67].

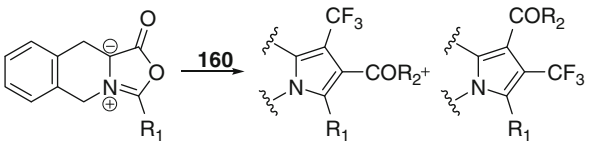


R=Me, Ph; R^1=Ph, Me; R^2=Ph, OBu

Starting from the analogous fused-ring oxazolones **163** and **166** derived from cyclic amino acids, the reaction with the ketone **160** (R^2 = Ph, OBu) afforded mixtures of the regioisomeric dihydropyrrolizines **164** and **165** and the dihydropyrrolo[1,2-b]isoquinolines **167** and **168**, respectively, in high overall yields [67]. In all cases the isomers **164** and **167** dominate in the mixtures.

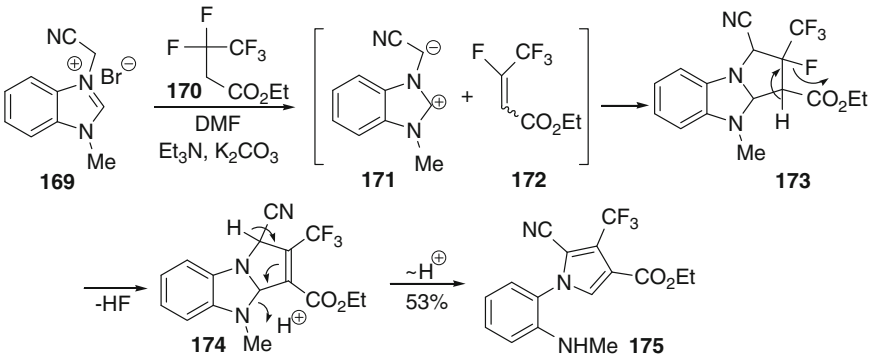


R_1 = Ph; R_2 = Ph	49%	15%
R_1 = Me; R_2 = Ph	56%	12%
R_1 = Ph; R_2 = OBu	49%	36%
R_1 = Me; R_2 = OBu	9%	7%

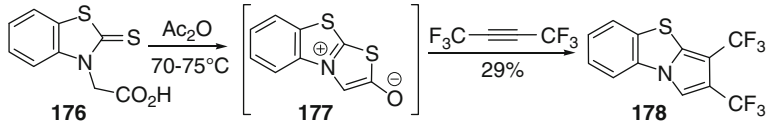


R_1 = Ph; R_2 = Ph	17%	-
R_1 = Me; R_2 = Ph	65%	21%
R_1 = Ph; R_2 = OBu	50%	24%

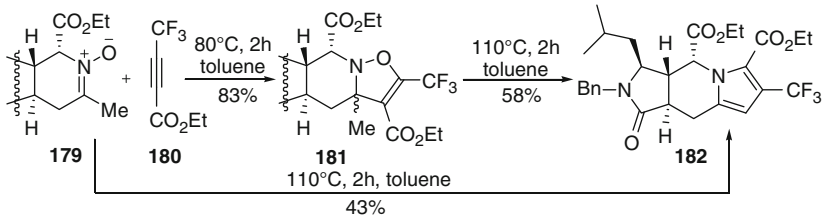
An interesting approach to *N*-[2-(alkylamino)aryl]-3-trifluoromethylpyrroles **175** was elaborated by Zhang et al. [68]. The benzimidazolium salt **169** gave the pyrrole **175** in 53 % yield by treatment with ethyl 3,3,4,4,4-pentafluorobutyrate **169**. Initially the ylide **171** and the activated alkene **172** are formed, which subsequent 1,3-dipolar cycloaddition forms **173**. Elimination of HF continues the reaction to give the intermediate **174**, which by proton migration and ring opening leads to the final pyrrole **175** [68].



Another mesoionic system used as dipolarophile was a cyclic system of anhydro-2-hydroxythiazolo[1,3-b]benzothiazol hydroxide **177**. This compound was prepared *in situ* from thionobenzothiazole **176** by reaction with acetic anhydride. The subsequent reaction with hexafluorobut-2-yne led to the tricyclic 3,4-bis(trifluoromethyl) pyrrole **178** [69].

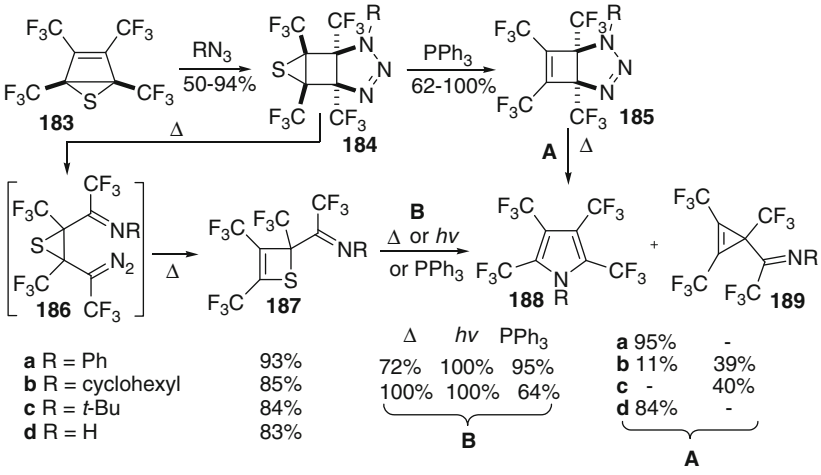


An elegant approach to the "alkaloid-like" heterocycle **182** with a pyrrole moiety was developed using the nitrone **179** in a [3+2]-cycloaddition with ethyl 4,4,4-trifluorobut-2-ynoate (**180**) to give first the 3-methyl-2,3-dihydroisoxazole **181** at 80 °C in toluene. Refluxing in toluene converted **181** to the 3-trifluoromethylpyrrole **182** through a sequence of ring-opening and ring-closure steps with an azomethine-type ylide as a key intermediate. This reaction can also be performed in one step without isolation of **181** [70].

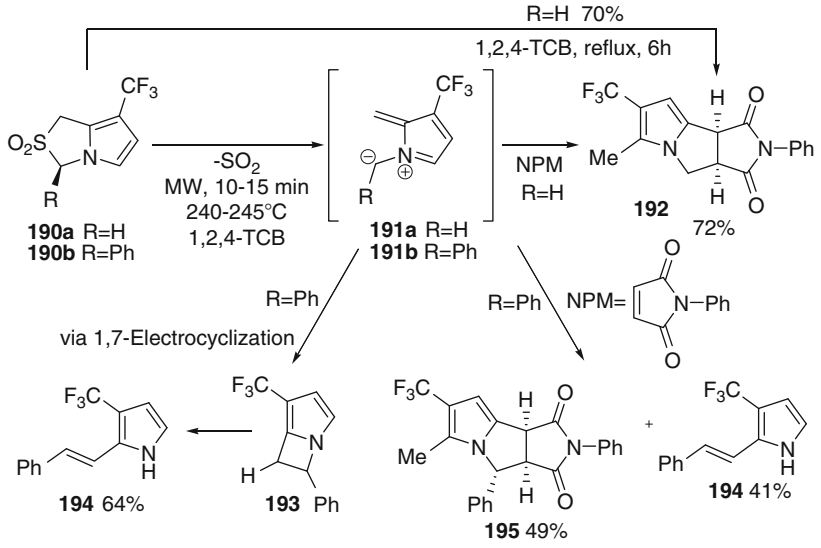


A number of approaches to tetrakis(trifluoromethyl)-pyrroles was developed using tetrakis(trifluoro-methyl)-Dewar-thiophene (**183**) [71]. The 1,3-dipolar cycloaddition with azides led to the tricyclic thiiranes **184**. Subsequent desulfurization by treatment with PPh_3 afforded the cyclobutenes **185** in good to quantitative yields. The result of thermolysis of **185** was strongly depended on the substituent on the amine nitrogen. Pyrroles **188** were formed in high yields (cases **a** and **d**), while only cyclopropene **189**, or a mixture of **188** and **189** (cases **b** and **c**) were isolated. Pyrrole **188a** was also synthesized by the reaction of **183** with aniline in 19 % yield [72].

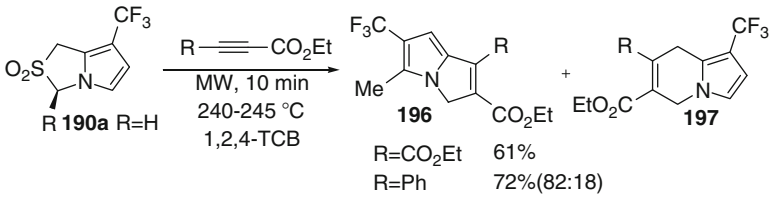
An alternative approach to the pyrroles **188** is based on thermolysis of compounds **184** [71]. The thietimines **187** were formed in high yields via the thiirane **186**, which was isolated and characterized in case of the phenyl compound **186a**. The conversion of the thietimines **187** into the pyrroles **188a** and **188b** was performed by thermolysis, photolysis or by treatment with triphenyl phosphine.



Generated by thermally induced SO_2 extrusion from dioxothiazoles **190** (for the synthesis of **190** see Sect. 2.2.7) under microwave irradiation, azafulvenium methides **191** reacts with dipolarophiles to give CF_3-pyrroles **192**–**195**. Thus, reaction of **191a** with N-phenylmaleimide (NPM) leads to polycyclic CF_3-pyrrole derivative **192** in high yield. Phenyl substituted azafulvenium methide **191b** reacts with NPM to give pyrrole **195** and admixture of 2-styrylpyrrole **194**, which is formed via competitive 1,7-electrocyclization process and can be obtained exclusively by decomposition of **190b** in the absence of NPM [73].



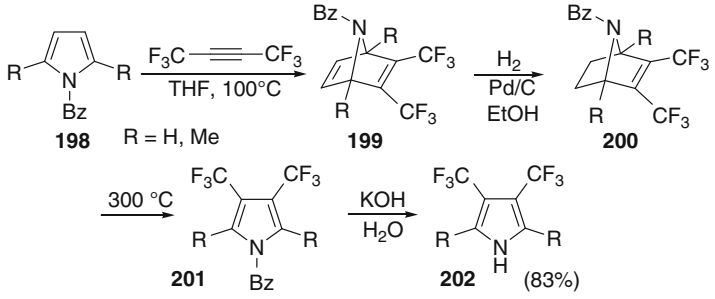
Addition of azafulvenium methides to the triple bond was also realized. Thus, reaction with DMAD afforded bicyclic CF_3-pyrrole **196** in 61 % yield. In case of unsymmetrical ethyl 3-phenylpropiolate the reaction gives a mixture of 1,3- and 1,7-cycloadducts **196** and **197**, respectively, in 72 % overall yield with a ratio of 82:18 [73].



[3 + 2] Cycloaddition reactions open an access to both 2- and 3-trifluoromethylated pyrroles with wide range of additional substituents in pyrrole ring, therefore the method is very useful and general for synthesis of fluorinated pyrroles.

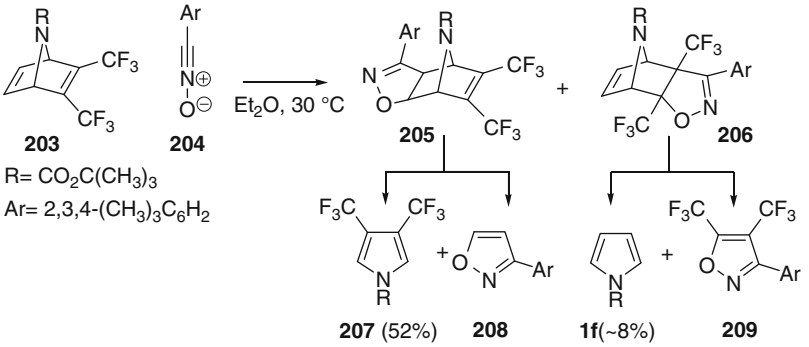
2.2.3 Synthesis of Trifluoromethyl Pyrroles by [4 + 2] Cycloaddition: Cycloreversion Reactions

The sequence of Diels-Alder reactions of nonfluorinated pyrroles with hexafluorobut-2-yne followed by retro Diels-Alder reactions (extrusion of acetylene) was also used for trifluoromethylpyrrole synthesis. However, the 7-azanorbornadiene system was found to be quite thermostable [74], which undergoes cycloreversion only at very high temperature resulting in low yields of trifluoromethylated pyrroles. Hence, additional steps were necessary. For instance, the reduction of the bicyclo[2.2.1] hepta-2,5-diene **199** (formed from **198** and hexafluorobut-2-yne) to **200**, followed by a cycloreversion, afforded the 3,4-bis(trifluoromethyl)pyrrole **201**. Subsequent basic hydrolysis gave the target pyrrole **202**. All reactions proceeded almost quantitatively to give **202** in 83 % overall yield [75].

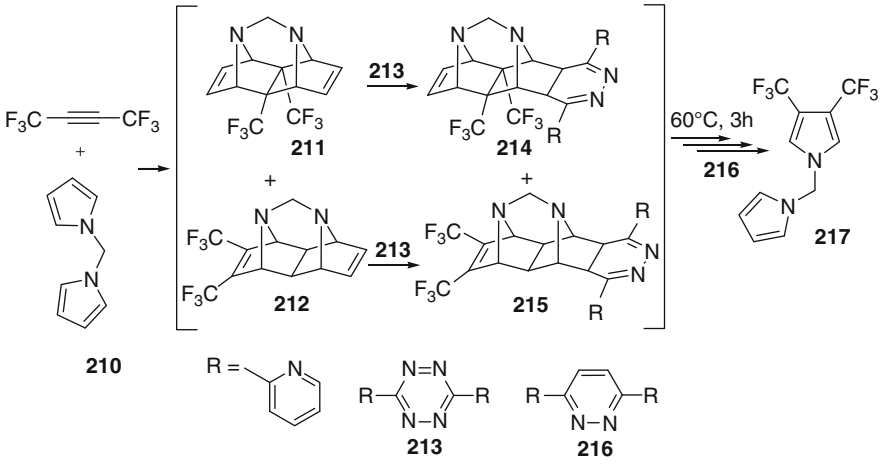


Another variation to facilitate the cycloreversion of trifluoromethylated 7-azabicyclo[2.2.1]heptadienes is their transformation to polycyclic isoxazolines by 1,3-dipolar cycloaddition with nitrile oxides followed by elimination of isoxazole.

Accordingly, the reaction of **203** with benzonitrile oxide (**204**) led to the isoxazolines **205** and **206.** Subsequent retro Diels-Alder reaction of **205** afforded the desired pyrrole **207** in 52 % yield by elimination of the isoxazole **208**. The isomeric isoxazoline **206** gave the pyrrole **1f** in very low yield [48].



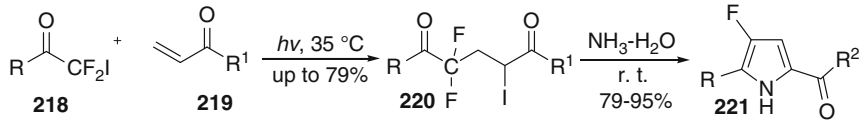
An analogous pathway was used for the synthesis of the pyrrole **217** [76]. The "double" Diels-Alder adducts **211** and **212** of dipyrrolomethane (**210**) were treated with the electron-deficient diene 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (**213**) to give the cycloadducts **214** and **215**. The decay of these compounds proceeded with extrusion of 3,6-di(2-pyridyl)-1,2-pyridazine (**216**) and gave the pyrrole **217**. No yield was given.



2.2.4 Synthesis Based on Carbonyl Compounds

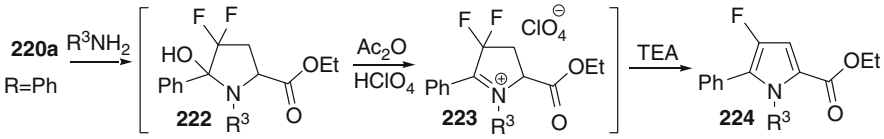
The use of carbonyl function is classic approach in heterocyclic synthesis. In case of fluorinated pyrroles this approach was frequently used. Convenient method for synthesis of pyrroles **221** is based on the reaction of fluorinated δ-keto acid esters or amides **220** with ammonia. In case of methyl and ethyl esters amidolysis was

observed to give the corresponding amides [77]. Starting dicarbonyl compounds **220** are easily available through the radical addition of CF_2I-ketones **218** to alkyl acrylates **219** [78]. Similarly, the reaction of ethyl-4,4-difluoro-2-iodo-5-oxo-5-phenylpentanoate **220a** with primary amines in a one-pot scheme produces a series of β-fluoropyrrole derivatives **224** at ambient temperature. The mechanism is presented below [79]. It includes nucleophilic substitution of I- with amine followed by heterocyclization and aromatization as key steps.



218 **219** **220** **221**

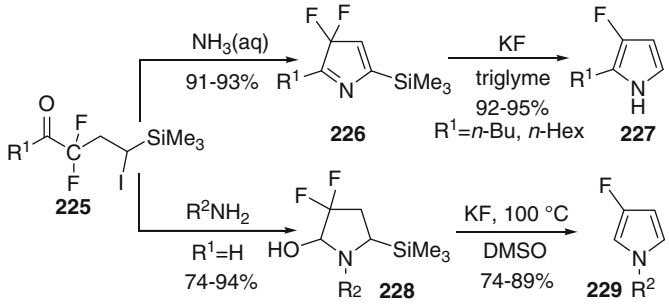
R = Ph, *n*-Bu, *n*-Hex; R^1=NMe_2, R^2=NMe_2; R^1=OEt, OMe; R^2= NH_2



222 **223** **224**

R^3 = H, Me, Et, *cyclo*-Pr, *n*-Bu, *cyclo*-Pn, *cyclo*-Hex, Bn

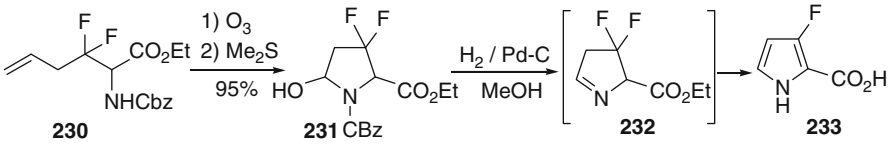
Using α,α-difluoro-γ-iodo-γ-iodotrimethylsilyl ketones or aldehyde **225** as starting compounds, 3,3-difluoro-5-trimethylsilyl-1-pyrrolines **226, 228** were obtained in high yields. Further treatment of them with potassium fluoride gave 4,5-unsubstituted 3-fluoropyrroles **227, 229** in yields up to 95 % [80].



225 **226** **227** **228** **229**

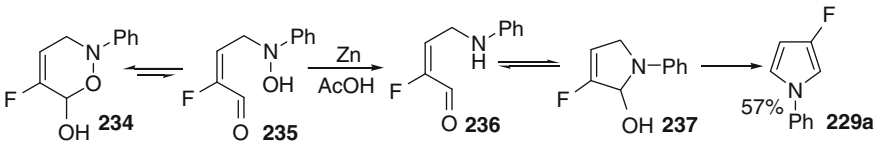
R^2=H,*n*-Bu, *cyclo*-Hex, Bn, Ph, $PhCH_2CH_2$, PMB, 4-Pyridyl

Neutral ozonolysis of compound **230** afforded the cyclic hemiaminal **231** in 95 % yield. Catalytic hydrogenation of **231** in the absence of the acid led to the formation of the pyrrole derivative **233** as a major product [81].

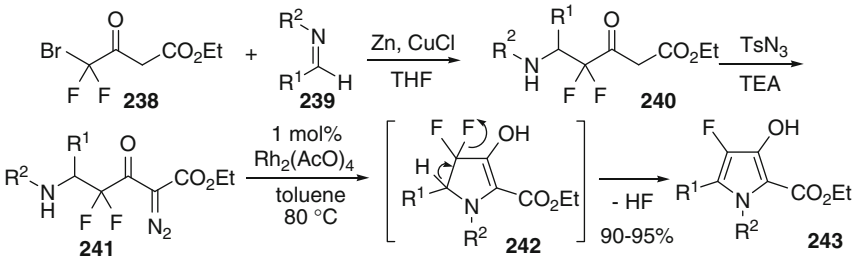


230 **231** **232** **233**

3-Fluoro-1-phenylpyrrole **229a** was effectively prepared starting from compound **234**. Cyclic hemiacetal **234**, existing in equilibrium with its open form **235**, was reduced into amine **237**, which transformed easily into pyrrole **229a** via acid catalyzed cyclization and dehydration [82].

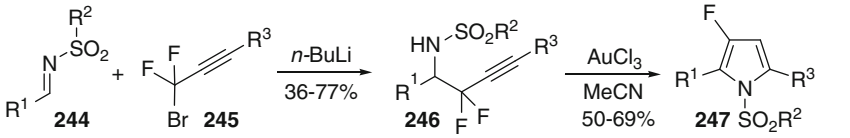


A convenient method for the synthesis of polyfunctionalized 3-fluoropyrroles **243** by $Rh_2(OAc)_4$-catalyzed intramolecular N-H insertion reaction of difluorinated diazo compounds **241** was reported [83]. The starting compounds can be synthesized by Zn-CuCl-promoted Reformatsky-imine addition reaction of 4-bromo-4,4-difluoroacetoacetate **238** with aldimines **239**. Subsequent diazotransfer reaction and $Rh_2(OAc)_4$-catalyzed intramolecular N-H insertion allow the preparation of 3-fluoropyrroles **243** in almost quantitative yield.



R^1=Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-Naphthyl, 2-Furyl; R^2=Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, Bn

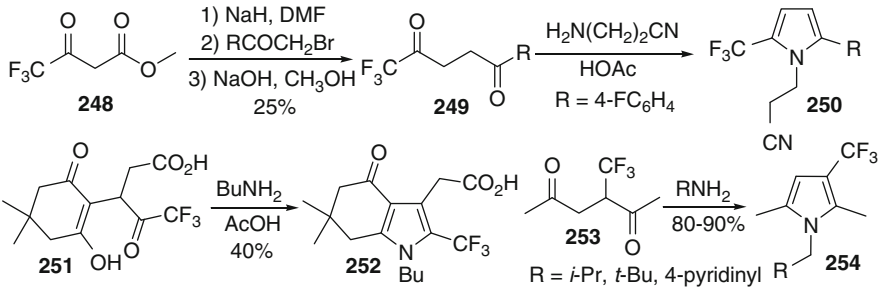
A valuable method for the synthesis of 2-aryl-3-fluoropyrroles **247** is based on a gold-catalyzed cyclization and dehydrofluorination of gem-difluorohomopropargylamines **246**. Difluorinated homopropargylamines **246** can be prepared by the addition of gem-difluoropropargyllithium reagents to arylated *N*-tosylimines **244** [84].



R^1= 4-ClC_6H_4, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$; R^2= Ph, 4-MeC_6H_4; R^3= Ph, TMS

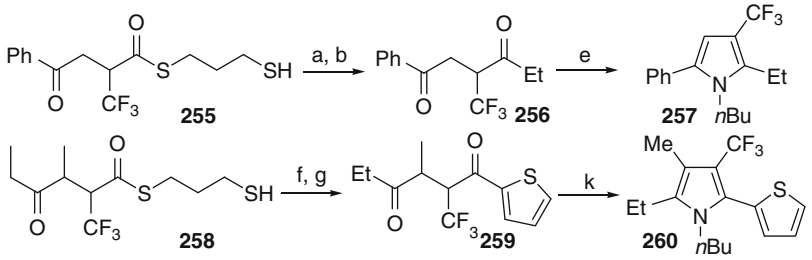
The Paal-Knorr reaction was used for the synthesis of the pyrrole **250** from methyl 4,4,4-trifluoroacetoacetate (**248**) in two steps [85]. Alkylation of **248** with 4-fluorophenacyl bromide gave the 1,4-diketone **249** in 25 % yield after decarboxylation. Its cyclization with 2-cyanoethylamine in acetic acid provided **250**,

which was used without purification in next step. Similarly, the 1,4-diketones **251** and **253** gave the pyrrole derivatives **252** [86] and a series of N-substituted pyrroles **254**, respectively [87].



248 **249** **250** **251** **252** **253** **254**

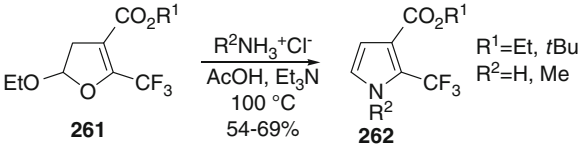
Thiol esters **255** and **258** have proved to be versatile precursors of 3-trifluoromethylpyrroles. Methylation of the mercapto groups of **255** and **258,** followed by subsequent cross-coupling reactions of the resulting thiol esters with organozinc reagents yielded 2-trifluoromethyl-1,4-diketones **256** and **259**, respectively. Classic Paal–Knorr condensation of **256** and **259** afforded highly substituted 3-trifluoromethyl five-membered heteroaromatics **257** and **260** in high yields [88].



255 **256** **257** **258** **259** **260**

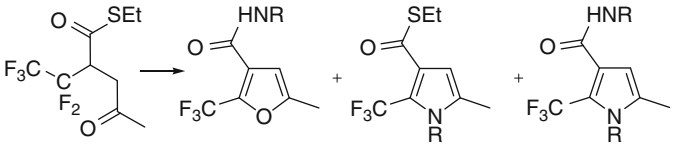
a) MeI (2 equiv), iPr$_2$EtN (2 equiv), acetone, 25°C, 8h, 80%;
b) [PdCl$_2$(PPh$_3$)$_2$] (10 mol%), EtZnI (2 equiv), toluene, reflux, 12h, 65%;
e) nBuNH$_2$ (2 equiv), Ti(OiPr)$_4$ (1.5 equiv), toluene, reflux, 10h, 81%;
f) MeI (2 equiv), iPr$_2$EtN (2 equiv), acetone, 25°C, 8h, 78%;
g) [PdCl$_2$-(dppf)] (10 mol%), (2-thienyl)ZnI·LiCl (5.6 equiv), toluene, 0°C, 1h, 87%, d.r.=3:2;
k) nBuNH$_2$ (4 equiv), Ti(OiPr)$_4$ (3 equiv), toluene, 25°C, 4h, 83%.
dppf=1,1'-bis(diphenylphosphanyl)ferrocene

A versatile approach to 2-CF$_3$-pyrroles was elaborated using dihydrofurans as masked 1,4-dicarbonyl compounds. Condensation of the dihydrofurans **261** with primary amine hydrochlorides gave the corresponding N-substituted pyrroles **262** in good yields [89].



261 **262**

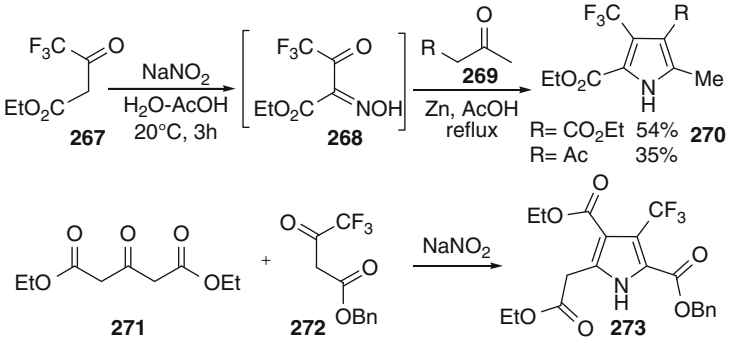
The reactions of the diketone **263** with a number of rather basic amines ($pK_a \sim 9–10$) under different conditions gave mixtures of the furans **264** and the pyrroles **265** and **266** [90]. The reactions with two equivalents of primary amines in ether afforded mixtures of products **264** and **265** (method A). Large excess of pentylamine (8 eq.) increased the yield of furan **264c** and produced the pyrrole **265c** and **266c** as minor products. Without solvent the furan **264c** was not formed and the pyrrole **266c** became the major product. Maintaining the furan **264** in excess amine without solvent at r.t. resulted in its conversion into the corresponding pyrrole **266** in 67 % yield.



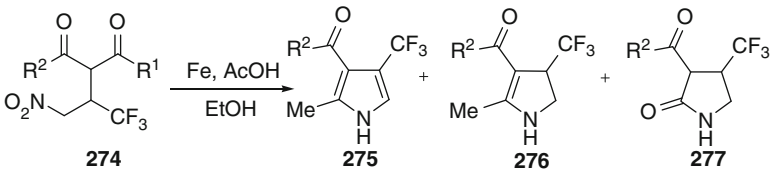
263	**264**	**265**	**266**
A: $PhCH_2$	25%	48%	-
A: *i*Pr	57%	24%	-
A: nC_5H_{11}	40%	35%	-
B: nC_5H_{11}	54%	9%	17%
C: nC_5H_{11}	-	7%	67%

A: 2 eq RNH_2, Et_2O, r.t.; B: 8 eq RNH_2, Et_2O, r.t.; C: 8 eq RNH_2, r.t.

The Knorr pyrrole synthesis was also employed for the synthesis of 3-trifluoropyrroles [91]. Treatment of ethyl trifluoroacetoacetate **267** with sodium nitrite in acetic acid led to the oxime **268**. Refluxing with zinc dust and addition of 1,3-dicarbonyl compounds **269** afforded the 3-trifluoromethylpyrroles **270** in moderate yields. Using more acidic trifluoroacetic acid allowed to lower the reaction temperature to 70 °C [92]. Using a similar approach, the tricarboxylic acid ester **273** was prepared starting from the acetone dicarboxylic acid ester **271** and the fluorinated keto ester **272** [93].

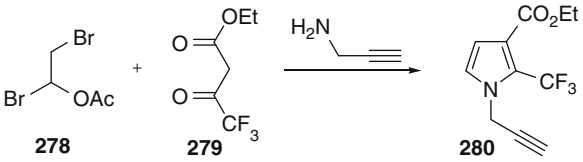


The γ-nitro ketones **274** were also used as precursors in pyrrole synthesis. The reduction of the nitro compounds **274** by iron depending on the conditions and the substrate can give pyrroles **275a,b**, dihydropyrroles **276b** or pyrrolidinones **277c**. It was also found that the di-hydropyrrole **276b** can be transformed into pyrrole **275b** in 25 % yield at reflux in nitrobenzene [94].

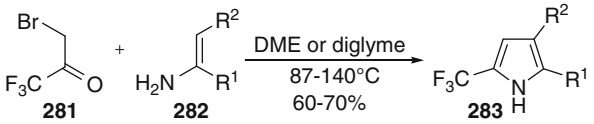


	274		**275**	**276**	**277**
a	R^1=R^2=Me	70°C	27%	-	-
b	R^1=Me, R^2=MeO	70°C	21%	36%	-
	R^1=Me, R^2=MeO	100°C	47%	-	-
c	R^1=R^2= OEt	70°C	-	-	67%

The classic Hantzsch pyrrole synthesis is based on the reaction of ketones bearing electron-withdrawing group in α-position with α-haloketones or aldehydes in the presence of amine or ammonia. For example, the condensation of the masked bromoacetaldehyde **278** with ethyl 4,4,4-trifluoroacetoacetate (**279**) and propargyl amine gave the pyrrole **280** [95]. The yield of pyrrole **280** was not given.

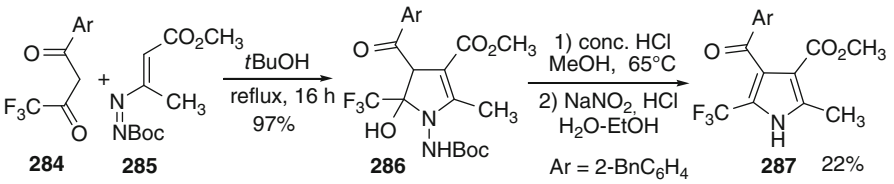


In contrast, the reaction of α-halotrifluoromethyl ketones due to the high electrophilicity of these ketones led to furans [96]. However, in order to synthesize pyrroles, the reaction of such α-haloketones has to be carried out with previously prepared enamines. So, based on reactions of the bromoketone **281** with enamines **282**, a series of 2-CF_3-pyrroles **283** was obtained in good yields [96].

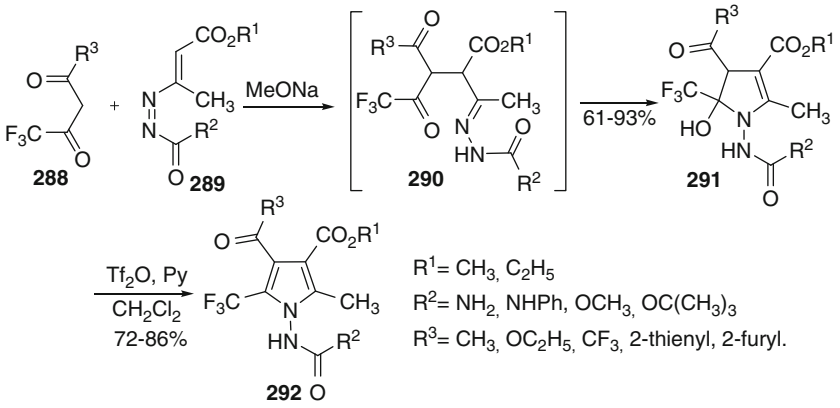


R^1= Me, Ph, 4-ClC_6H_4, 4-MeC_6H_4; R^2= CN, CO_2Me

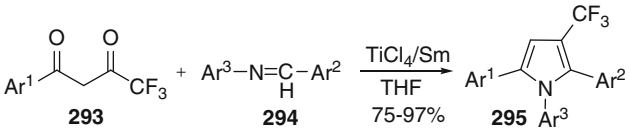
The aim of the following work [97] was the synthesis of the trifluoromethyl analogue **287** of FPL 64176, which is a calcium channel activator. Key step of the synthesis was the reaction of diketone **284** with the azoalkene **285** in refluxing *tert-butanol*. The reaction gave the hydroxypyrroline **286** in quantitative yield. Subsequent treatment with hydrochloric acid followed by reaction with $NaNO_2$ converted the hydroxypyrroline **286** into the target pyrrole **287**.



The reaction of the 1,3-diketones **288** with the azoalkenes **289** led regioselectively to the dihydropyrroles **291** in high yields via the intermediates **290** [98]. The compounds **291** are stable and can be isolated in pure form, but they lost easily water by treatment with triflic anhydride to form the pyrroles **292** [99].

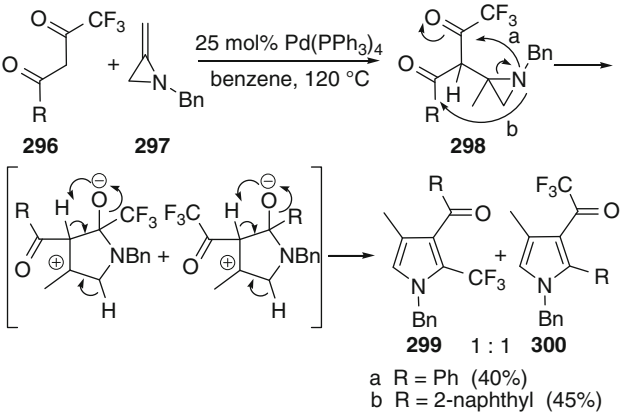


A novel coupling cyclization reaction of 1,3-diketones with imines was applied for the synthesis of polyaryl substituted 3-trifluoromethylpyrroles. The reaction was promoted by a low-valent titanium reagent and afforded the pyrroles **295** in high to quantitative yields. A number of 1,3-diketones **293** and imines **294** provided a variety of pyrroles **295**, bearing different combinations of electron-donating, as well as electron-withdrawing substituents in aromatic rings [100].

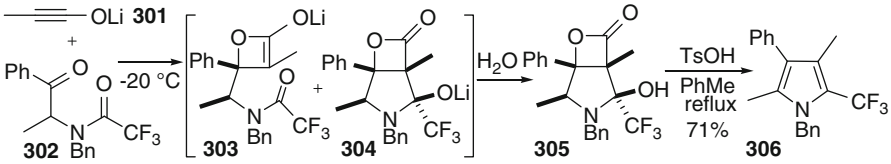


Ar^1=Ph, 2-thienyl; Ar^2, Ar^3=4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 3,4-di$MeOC_6H_3$, 4-ClC_6H_4, 4-FC_6H_4, 3-Cl-4-$MeOC_6H_3$, 4-MeC_6H_4

The Pd(0)-catalyzed reaction of the unsymmetrical 1,3-diketones **296a** and **296b** with *N*-benzylmethyleneaziridine **297** produced the corresponding 2-trifluoromethylpyrroles **299a** or **299b** in moderate yields as 1:1 mixture with trifluoroacetylpyrroles **300a** or **300b** via the intermediate aziridine **298**, which rearrange on pathway **a** or **b** to pyrroline cations to give the products **298** and **300** [101].

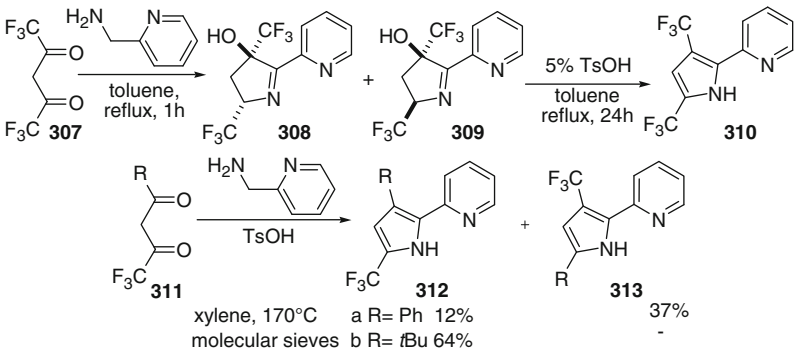


An efficient synthetic method for the preparation of polysubstituted furans, thiophenes and pyrroles using ynolates was developed by Shindo et al. [102]. The cycloaddition of ynolate **301** to amidoketone **302** gave the oxetene **303**, which formed the bicyclic β-lactone **304** by cyclization. Aqueous workup afforded **305**, which was converted to the final 2-trifluoromethylpyrrole **306** in 71 % yield by dehydration with TsOH. The ynolate **301** was prepared *in situ* by treatment of ethyl 2,2-dibromopropanoate with *t*-BuLi at −78 °C.

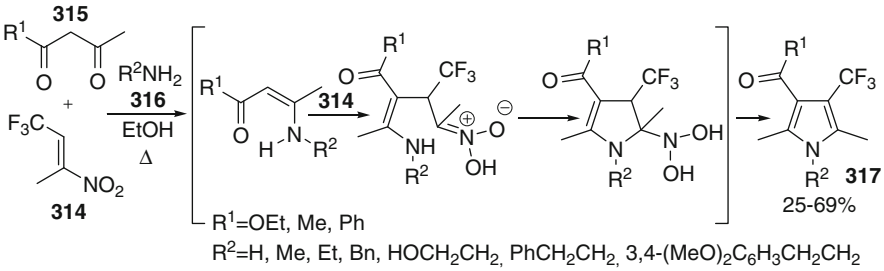


Furthermore, bistrifluoroacetylmethane (**307**) at heating with 2-picolylamine gave a mixture of the diastereomeric dihydropyrroles **308** and **309** in high overall yield [103]. The ratio of the diastereomers depends on the acidic catalyst and the reaction time. Complete dehydration of **308** and **309** resulted in the formation of the pyrrole **310** after 24 h at reflux using *p*-toluenesulfonic acid as catalyst. Similarly, the 1,3-diketone **311a** (R = Ph) gave an 1:3 mixture of the pyrroles **312a** and **313a**, while **311b** (R = *t*-Bu) gave **312b** as the sole product [104]. It should be noted, that 2-(aminomethyl)pyridine appears to be the only amine, which participated in such

a transformation. Neither other isomeric (aminomethyl)-pyridines nor benzylamine reacted in this way.

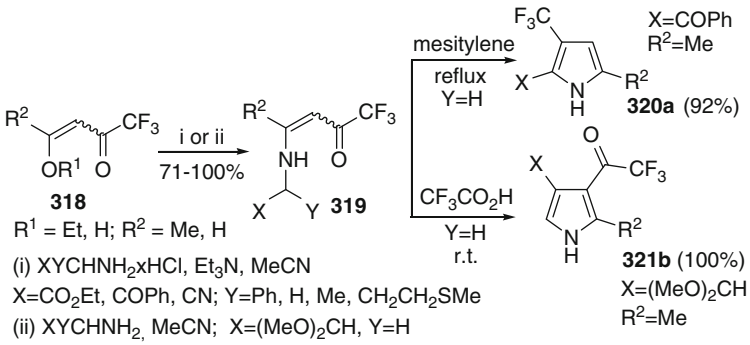


It was shown that the three-component Grob cyclization of (*E*)-1,1,1-trifluoro-3-nitrobut-2-ene **314** with 1,3-dicarbonyls **315** and primary aliphatic amines **316** provides a simple and convenient approach to substituted 4-(trifluoromethyl)pyrroles **317** bearing different electron-withdrawing substituents at the 3-position. Mild conditions and readily available starting materials are distinct advantages of the approach [105].

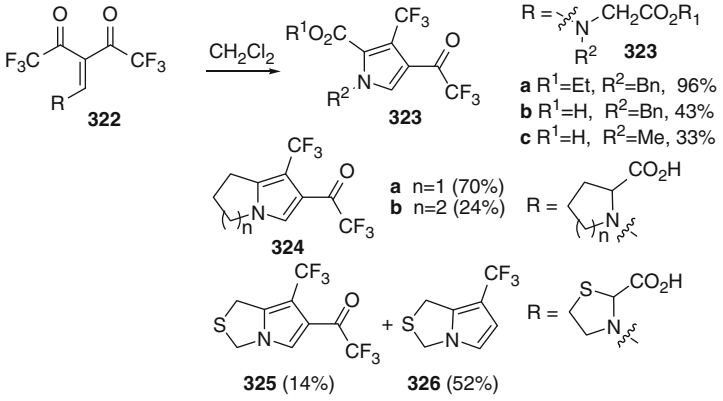


2.2.5 Synthesis Based on α,β-Unsaturated Trifluoromethyl Ketones

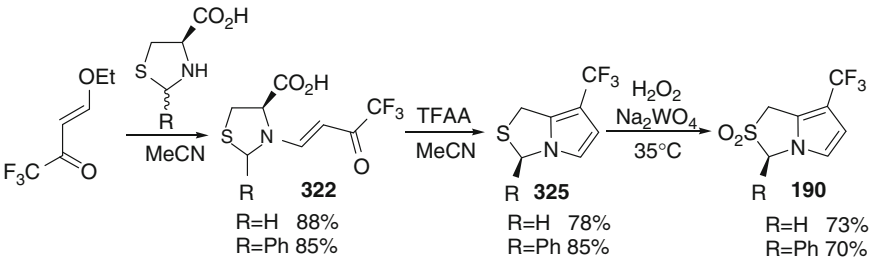
α,β-Unsaturated trifluoromethyl ketones such as **319** were found to be very useful building blocks for the construction of pyrroles [106]. For example, the enaminoketones **319**, which can be prepared in high yields from the enol ethers **318**, gave the 3-trifluoromethylpyrroles **320** or 3-trifluoroacetylpyrroles **321** depending on the reaction conditions [107]. Thus, the cyclization of **319a** afforded the pyrrole **320a** in high yield at reflux in mesitylene, while at standing in trifluoroacetic acid at room temperature the pyrrole **321b** was formed. It should be mentioned, that non-fluorinated analogs of **319** gave 1:1 mixtures of the corresponding pyrroles under these conditions.



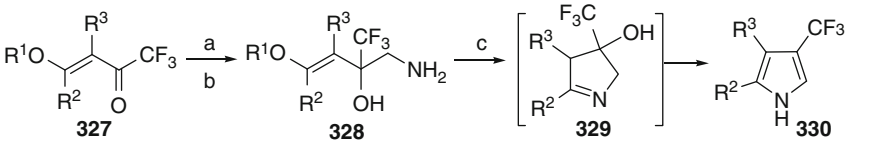
A convenient pathway towards the 3-trifluoromethyl-pyrroles **323** starts from enaminodiketones **322** prepared *in situ* from amino acid derivatives. The derivative of *N*-benzylglycine ethyl ester gave the pyrrole **323a** quantitatively [108]. In the case of *N*-methyl- and *N*-benzylglycine the corresponding pyrroles **209b** and **209c** were obtained in 43 % and 33 % yields. Cyclic amino acid derivatives afforded the bicyclic derivatives **324a** (from proline) and **324b** (from pipecolic acid). In both cases decarboxylation occurred in the aromatization step. Finally, the reaction of a thioproline derivative gave a mixture of pyrroles **325** and **326** [109].



A simple changing of solvent from dichloromethane to acetonitrile allowed to prepare **325** exclusively in higher yield. Compounds **212** were converted into dioxothiazoles **190** by catalytic oxidation and then used as a precursor for generation of azafulvenium methides acting as 1,3-dipols (see Sect. 2.2.3) [73].



Another example dealing with α,β-unsaturated ketones was reported by Gerus et al. [110]. Ketones **327** were smoothly converted to cyanohydrins by treatment with TMSCN, which on reduction with $LiAlH_4$ afforded the aminoalcohols **328**. Acid catalyzed intramolecular cyclization gave **329**, which by dehydration gave the pyrroles **330** generally in good yields.



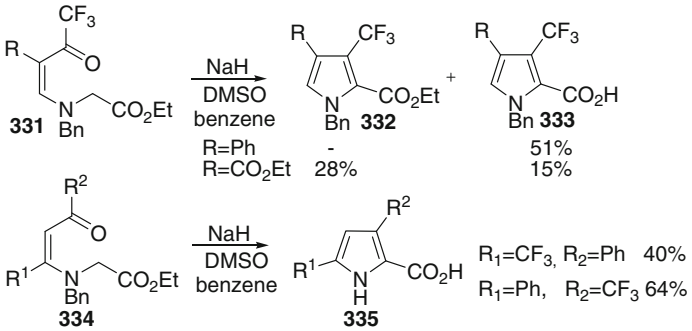
R^1=Me, Et

a: TMSCN, Et_3N, 0-10 °C R^2=H, R^3=H 65%; R^2=Me, R^3=H 55%

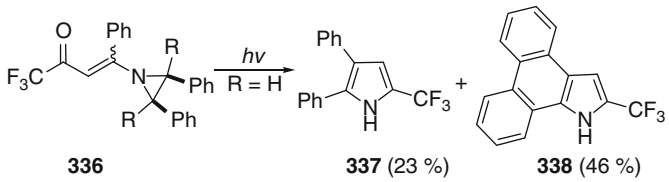
b: $LiAlH_4$, ether, 0-5 °C R^2=H, R^3=Br 5-10%; R^2=Ph, R^3=H 90%

c: HCl, H_2O, MeCN, r.t.

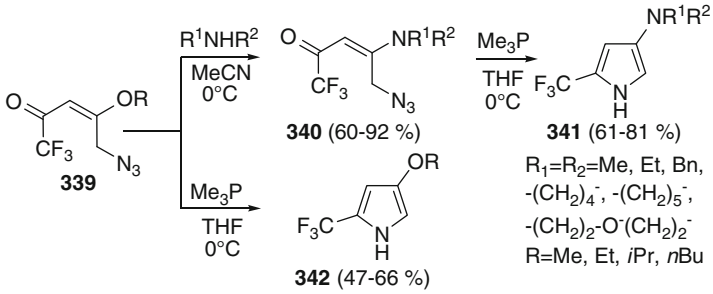
A number of *N*-benzylated 2- and 3-trifluoromethylated pyrroles were prepared using enaminoketones. Accordingly, the treatment of **331** or **334** with NaH-DMSO in benzene led to the corresponding pyrroles **332** and **333** or **335**, respectively, in moderate yields [111].



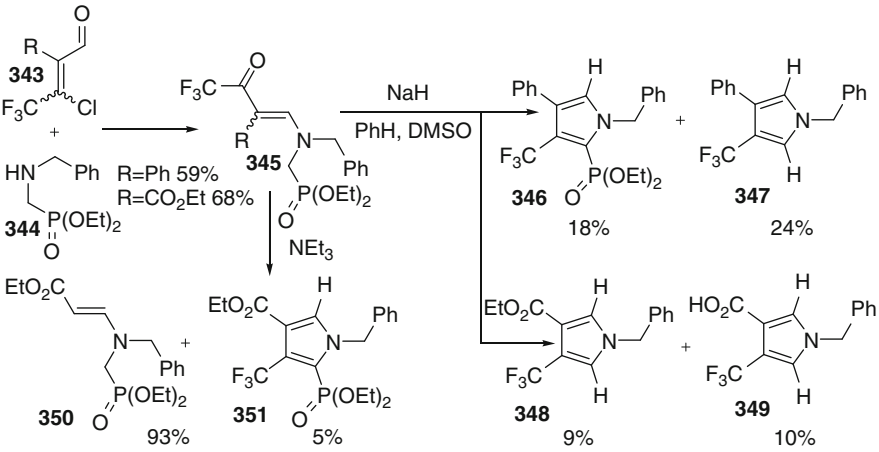
The photolytic rearrangement of aziridine derived enaminoketones **336** was used for the synthesis of a mixture of diphenylpyrrole **337** and dibenzoindole **338** [112].



The 2-trifluoromethylpyrroles **341** and **342** were obtained in high yields starting from **339**. Reaction of the alkoxy azide **339** with a variety of secondary amines formed **340**. Subsequent reduction with trimethylphosphine and cyclizing dehydration gave **341**, while direct reduction of **339** and cyclization led to **342** [113].

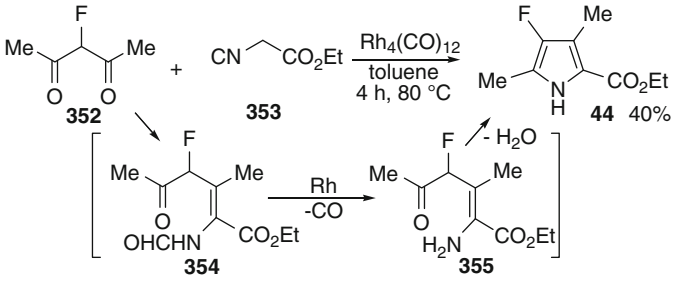


The reaction of ketones **343** with phosphorus analogue of *N*-benzylglycinate **344** allowed to prepare the enaminoketones **345** in good yields. Treatment of **345** with bases led to 3-trifluoromethyl-2-phosphonopyrroles **346** and **351** in low yields via 5-exo-trig cyclization. Formation of nonphosphorylated pyrroles **347** and **349** was also observed making this method less synthetically valuable [114].

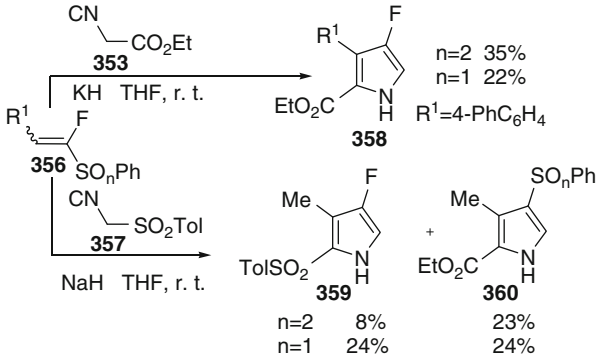


2.2.6 Synthesis Based on Isocyanides

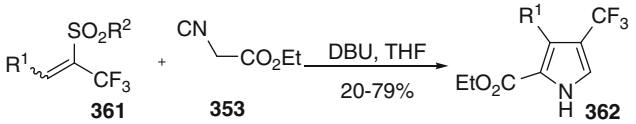
Rhodium catalyzed reactions of ethyl isocyanoacetate **353** with 3-fluoroacetylacetone **352** provides a new facile method for the catalytic synthesis of substituted pyrroles. The key step of the reaction is the activation of the C-H bond of isonitrile **353** induced by the α-heteroatom effect. 3-Fluoropyrrole **44** was obtained in 40 % by this method [115]. The mechanism of the transformation includes rhodium promoted decarbonylation of formamide **354** followed by cyclocondensation of intermediate **355** to form the corresponding pyrrole **44**.



3-Fluoropyrroles **358, 359** were synthesized using addition of isocyanomethylide anions to α-fluoroalkenyl sulfones and sulfoxides **356**. The addition of isocyanoacetate **353** led regioselectively to ethyl 3-fluoropyrroles **358** in moderate yields. In contrast, the addition of tosylmethylisocyanide **357** afforded a mixture of 4-fluoro-3-methyl-2-tosyl-1H-pyrrole **359** with non-fluorinated pyrrole derivative **360** [116].

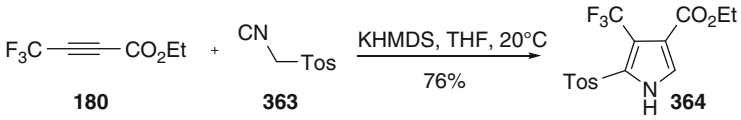


Convenient approach to 3-CF_3-pyrroles is also based on the condensation of electron-deficient alkenes with isocyanomethylide anions. A wide range of pyrroles **362** was synthesized from α-trifluoromethyl(vinyl-sulfones) **361** and ethyl isocyanoacetate **353** [117].

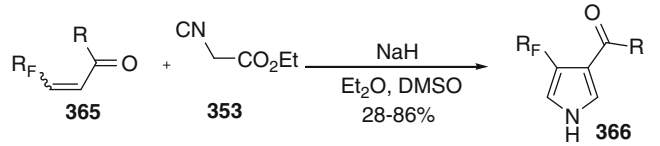


R^1=Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, C_6F_5, 2,6-$Cl_2C_6H_4$, 2-thiophene, CO_2Et, CN; R^2=Ph, *n*-C_6H_{13}

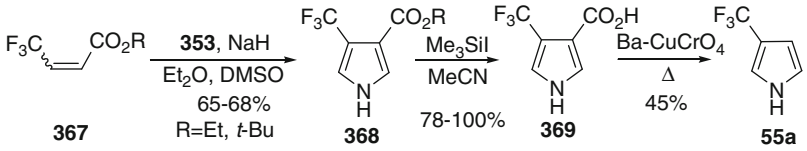
Ethyl 3-trifluoromethylacetylenecarboxylate (**180**) and toluenesulfonylmethyl isocyanide (TOSMIC) **363** provided the 3-CF_3-pyrrole **364** containing a tosyl group in 2-position [118].



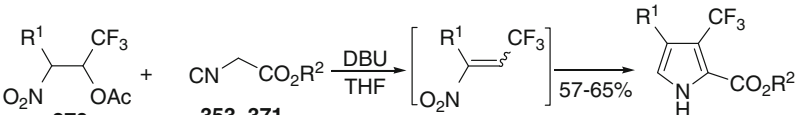
The reaction of perfluoroalkyl substituted α,β-unsaturated ketones **365** or β-trifluoromethylacrylates **367** with ethyl isocyanoacetate **353** gave 3-acylpyrroles **366** [119] or 3-pyrrolylcarboxylates **368** [120] in one step. Subsequent treatment of **368** with trimethylsilyl iodide afforded the acid **369**, which after pyrolysis at copper chromite gave the unsubstituted 3-trifluoromethylpyrrole **55a**.



R=Ph, 4-$CO_2MeC_6H_4$, 4-$CO_2HC_6H_4$, Me, MeO; R_F= CF_3, $CF_2CF_2CF_3$



The reaction of trifluoromethyl substituted β-acetoxy-α-nitroalkanes **370** with isocyanoacetates **353, 371** in the presence of DBU gave the 3-trifluoromethylpyrroles **373** in good yields via the nitroalkenes **372** [121]. The yield was increased up to 100 % employing two equivalents of an even stronger non-nucleophilic base [122].

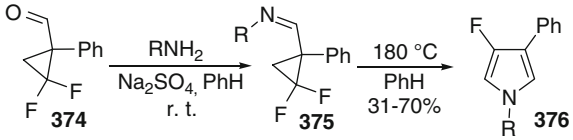


R^1=Me, Et; R^2=Et, *t*-Bu

So, application of isocyanides is one of the best methods for synthesis of fluorinated pyrroles due to high yields, simplicity and mild reaction conditions.

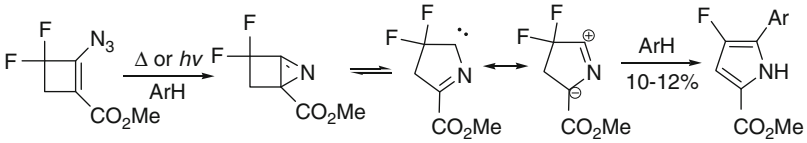
2.2.7 Miscellaneous Approaches to Fluoropyrroles

Thermal rearrangement of N-alkyl- and N-aryl-(2,2-difluoro-1-phenylcyclopropyl) methyleneamines **375** into N-substituted 3-fluoropyrroles **376** was reported by Kagabu. The transformation at high temperature gave regioselectively the corresponding 3-fluoropyrroles **376** in moderate to good yields. Using this method both N-alkyl- and aryl derivatives of pyrrole can be prepared [123].



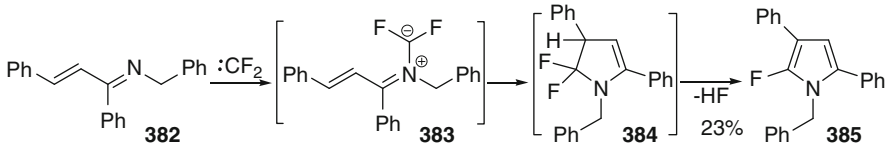
R= Ph, *n*-Bu, *t*-Bu, *cyclo*-Hex, 1-Naphtyl, $Ph(CH_3)_2C$, $4\text{-}MeOC_6H_4CH_2$

An interesting cyclobutene ring expansion reaction was found by Buhr. Being heated or irradiated by UV light, methyl 2-azido-3,3-difluorocyclobut-1-enecarboxylate **377** extrudes nitrogen to give highly strained azirine **378**, which transforms into azomethine ylide **380** through the carbene **379**. The last step of the transformation is the reaction of ylide **380** with solvents leading to methyl 4-fluoro-5-aryl-1H-pyrrole-2-carboxylates **381** in low yield [124].

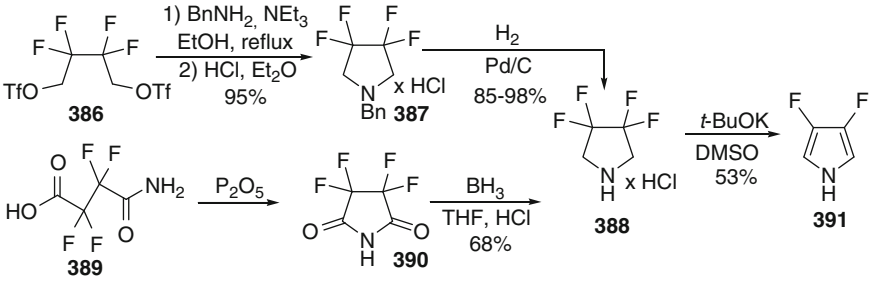


ArH= PhH, furan, mesitylene, 1,4-dimethoxybenzene

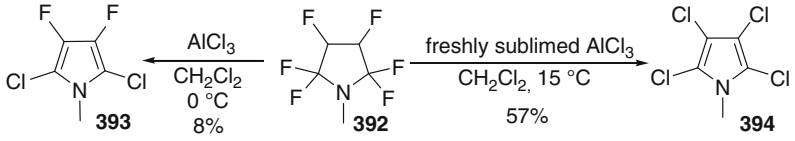
The reaction of azadiene **382** with difluorocarbene gives fluoropyrrole **385** as a major product. Difluorocarbene was generated by reduction of dibromodifluoromethane with active lead in dichloromethane in the presence of tetrabutylammonium bromide under ultrasound irradiation. A possible mechanism includes the formation of difluoroazomethine ylide **383**, 1,5-cyclization of the latter into difluoropyrroline **384**, and subsequent HF elimination [125].



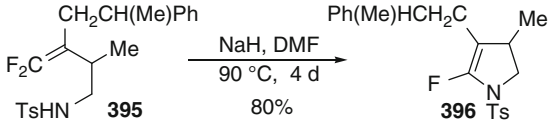
t-BuOK in DMSO was found to be the most efficient basic system for the elimination of HF from **388** to prepare 3,4-difluoropyrrole **391** [43]. Tetrafluoropyrrolidine **388** was prepared starting from **386** or **389**. Thus, **386** was converted into **387** by nucleophilic substitution with benzylamine. Next, **387** was debenzylated by treatment with hydrogen on Pd/C to give **388** [126]. Another pathway to **388** is reduction of tetrafluoromaleimide **390** obtained by cyclization of **389** under P_2O_5 [127].



An interesting transformation was found by Tatlow et al. 1-Methyl-2,5-dichlorodifluoropyrrole **393** was obtained in low yield by treatment of 1-methyl-3H,4*H*-hexafluoropyrrolidine **392** with "old" aluminium chloride, which was of a normal reagent grade. In contrast, using freshly sublimed aluminium chloride gave 1-methyltetrachloropyrrole **394** in good yield [128].



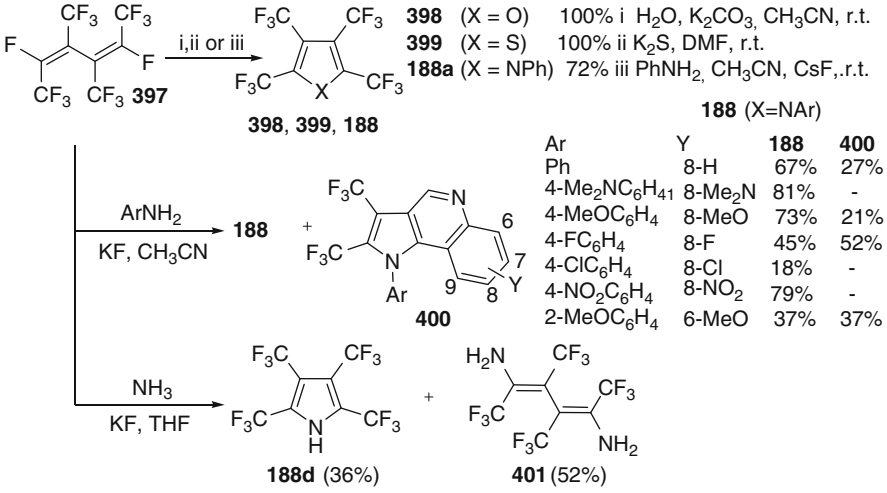
5-Endo-trig cyclizations can be applied for 2-fluoropyrroles synthesis. Thus, treatment of *N*-(3-(difluoromethylene)-2-methyl-5-phenylhexyl)-4-toluenesulfonamide **395** with base provided 5-fluoro-3-methyl-4-(2-phenylpropyl)-1-tosyl-2,3-dihydro-1*H*-pyrrole **396** in 80 % yield [129].



2.2.8 Miscellaneous Approaches to Trifluoromethylpyrroles

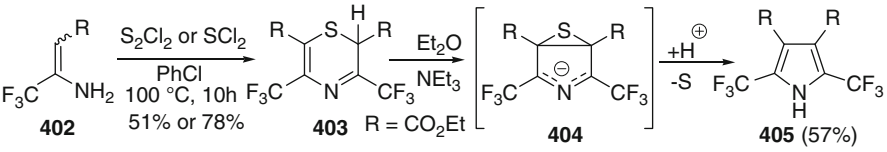
The perfluorohexa-2,4-diene **397** was revealed to be a very useful building block for the preparation of tetrasubstituted pyrroles, thiophenes and furans. Thus, the derivatives **398**, **399**, and **188a** were formed at room temperature [130]. Replacement of the

base by potassium fluoride (in the case of anilines) led to the pyrroloquinolines **400** among other reaction products [131]. Surprisingly, the reaction of the diene **397** with ammonia in the presence of potassium fluoride gave the pyrrole **188d** besides open chain the diaminodiene **401** [130].

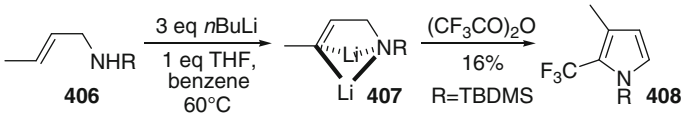


Ar	Y	188	400
Ph	8-H	67%	27%
4-$Me_2NC_6H_{41}$	8-Me_2N	81%	-
4-$MeOC_6H_4$	8-MeO	73%	21%
4-FC_6H_4	8-F	45%	52%
4-ClC_6H_4	8-Cl	18%	-
4-$NO_2C_6H_4$	8-NO_2	79%	-
2-$MeOC_6H_4$	6-MeO	37%	37%

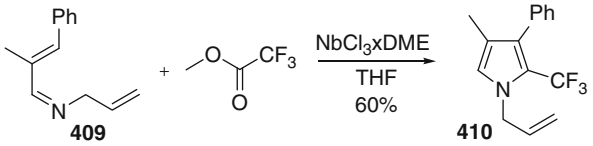
An interesting approach to polysubstituted pyrroles was elaborated based on the enamine **402**, which on heating with S_2Cl_2 or SCl_2 in chlorobenzene led to the thiazine **403** in good yields [132]. Subsequent refluxing of **403** with triethylamine in ether afforded the pyrrole **405** in 57 % yield by sulfur extrusion from the intermediate **404** and acidic workup. Employing one pot technique, the pyrrole **405** was synthesized in 56 % overall yield calculated on the enamine **402**. Other bases (LDA, *s*-BuLi, KH, EtONa) can also be used for conversion of **403** to **405** [133].



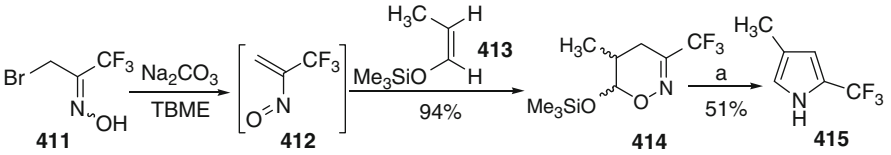
The allylamine **406** was deprotonated with three equiv. of *n*-BuLi using one equivalent of THF as accelerator (benzene, 60 °C) to give the intermediate **407**, which on treatment with trifluoroacetic acid anhydride led to the pyrrole **408** in 16 % overall yield [134].



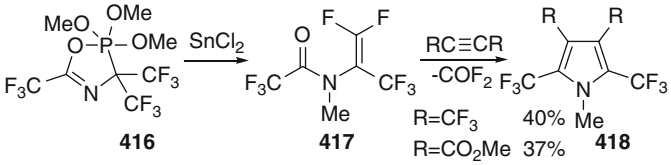
Coupling of the imine **409** with 500 fold excess of methyl trifluoroacetate proceeded smoothly at room temperature in the presence of equimolar amount of the $NbCl_3 \cdot DME$ complex, giving the pyrrole **410** in 60 % yield [135].



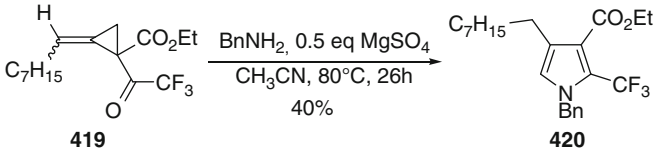
The 1,1,1-trifluoro-2-nitroso-2-propene **412** generated *in situ* by treatment of the α-bromooxime **411** with sodium carbonate, on reaction with the silyl ether **413** gave the 5,6-dihydro-4*H*-1,2-oxazine **414**, which was transformed to the target pyrrole **415** in 51 % yield by treatment with $Mo(CO)_6$ in acetonitrile in the presence of trifluoroacetic acid [136].



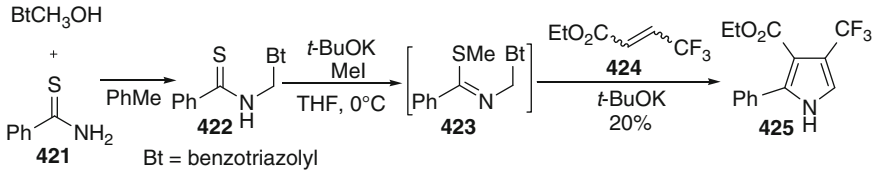
Furthermore, the reaction of the orthophosphonate **416** with $SnCl_2$ gave the trifluoroacetic enamide **417**, which reacted with acetylenes to afford the 2,5-bistrifluoro-methylpyrroles **418** in moderate yields [137].



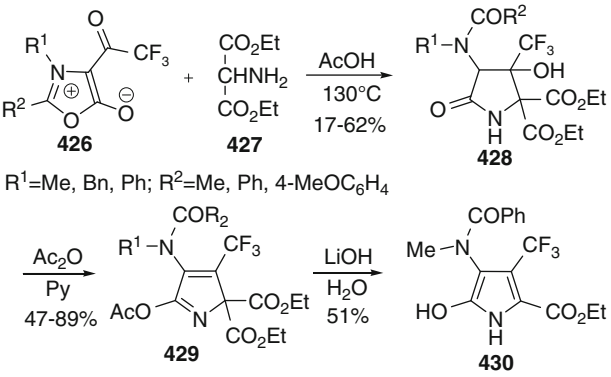
The 2-trifluoromethylpyrrole **420** connected with a long-chain alkyl group in 4-position was obtained in one step in 40 % yield from alkylidenecyclopropyl ketone **419** with excess of benzylamine in the presence of $MgSO_4$ as an additive [138].



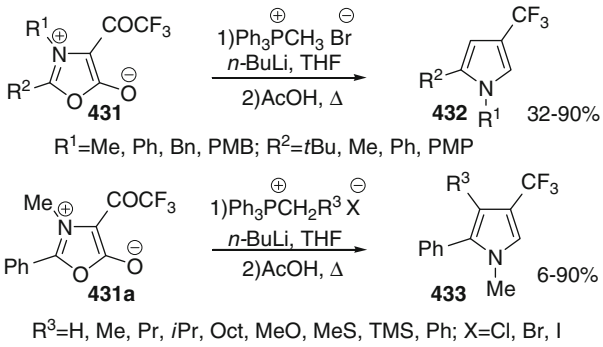
An efficient one-pot pyrrole synthesis was elaborated by Katritzky et al. [139]. The addition of *S*-methylthioimidate **423** to ethyl β-trifluoromethylacrylate **424** was the key step of the reaction leading to **425**. The intermediate **423** was readily prepared from thioamide **421** in two steps via **422**.



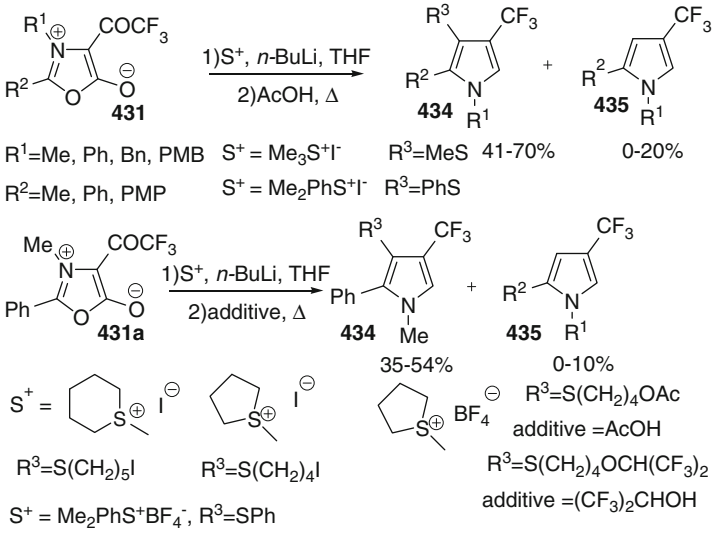
As it was mentioned previously, mesoionic oxazolones were used as dipolarophiles in the synthesis of 2-CF_3-pyrroles. A tandem addition of 1,2-binucleophiles to oxazolones also led to pyrroles, but bearing the CF_3-group in 3-position. For instance, the reaction of the oxazolones **426** with aminomalonate **427** gave the pyrrolidine derivative **428**, which formed **429** by reaction with acetic anhydride. Treatment of **429** with lithium hydroxide resulted in a decarboxylation giving the pyrrole **430** [140].



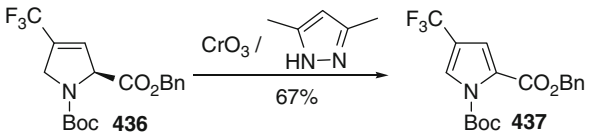
Efficient pathway towards 3-CF_3-pyrroles was elaborated using condensation of mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates **431** with phosphorus ylides. Target pyrroles **432**,**433** with big variety of substituents were easily obtained in the yields up to 90 %. The principal advantage of the method is flexibility in the type of substituents in the pyrrole ring which can be readily achieved by choosing the appropriate N-acyl-N-alkylglycines (precursors of **431**) as the starting material and also the ylides [141].



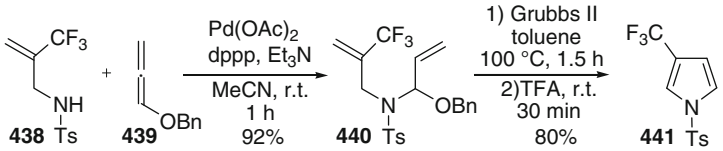
The use of sulfur ylides in the synthesis of trifluoromethylpyrroles from mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates **431** is prove to be also valuable. Reactions proceed to give alkyl(aryl)thio-4-trifluoromethylpyrroles **434** in good yields with an admixture of non-sulfur pyrroles **435** in small amounts [142].



Qiu and co-workers failed to oxidize the dihydropyrrole **436** to the α,β-unsaturated lactam with CrO_3 in pyridine. Instead, the oxidation in the presence of dimethylpyrazol provided the 3-trifluoromethyl-pyrrole **437** in good yield [143].

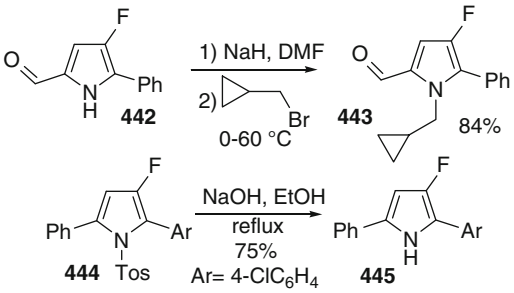


An interesting pathway towards the *N*-tosylated 3-trifluoromethylpyrrole **441** was developed by Rutjes et al. [144]. The palladium catalyzed addition of benzyloxyallene **439** to sulfonamide **438** led to the *N*,*O*-acetal **440** in excellent yield. Subsequent, treatment of **440** with the Grubbs II catalyst followed by acid workup gave the *N*-tosylpyrrole **441** in 80 % yield.

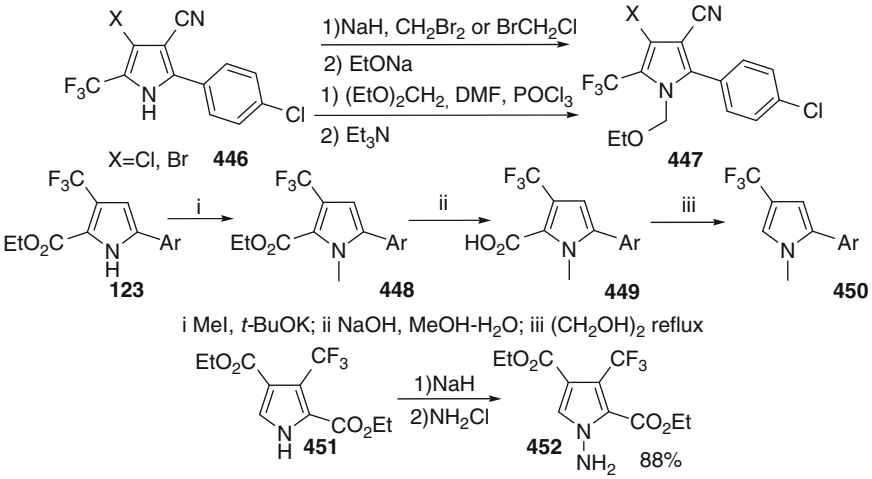


3 Properties and Some Applications of Fluorinated Pyrroles

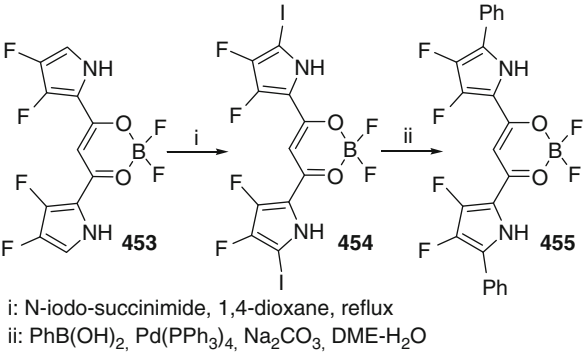
There are not too much examples of fluorinated pyrroles reactivity. Nevertheless one can easily conclude that fluoropyrroles have very similar chemistry in comparison to other pyrroles. Thus, fluorinated pyrrole **442** can be N-alkylated by treatment with alkyl bromides [18]. Inverse process is possible for N-tosyl derivative **445** under basic workup [84].



Trifluoromethylpyrroles were also alkylated. Alkylation of pyrroles **446** led to N-ethoxymethyl derivatives **447** [145, 146]. Similarly, N-methyl derivative of pyrrolecarboxylic ester **448** was obtained, which was further hydrolyzed and decarboxylated [55]. Reaction of **451** with NH_2Cl afforded N-aminopyrrole **452** in 88 % yield [147].

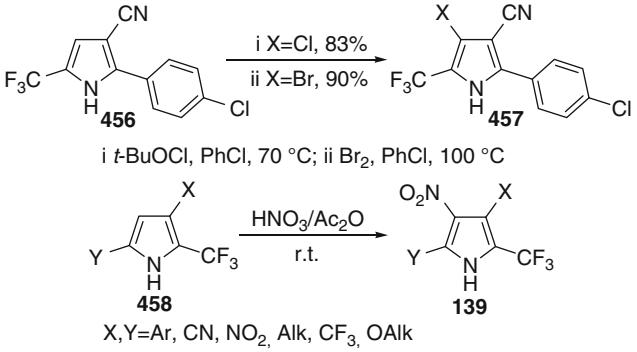


Due to electron-donating properties of pyrrole ring, fluorinated pyrroles react smoothly with electrophiles to give the corresponding functionalized derivatives. Thus, iodination of **453** was carried out under treatment with N-iodo-succinimide in refluxing 1,4-dioxane. Diiododerivative **454** prepared in this way was coupled with phenylboronic acid to give the corresponding polyaromatic compound **455** in 20 % yield under Suzuki reaction conditions [148].

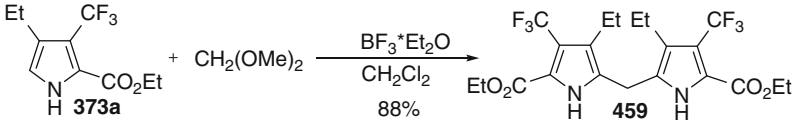


Chlorination and bromination of trifluoromethylpyrroles were carried out by treatment with *t*-BuOCl and Br_2 correspondingly. Deactivating influence of CF_3- and

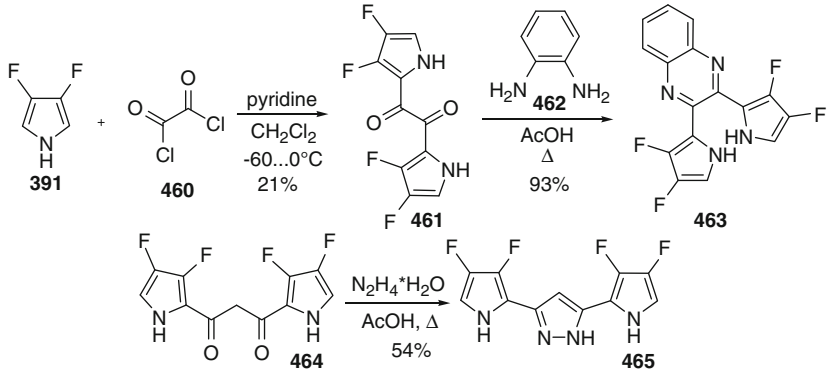
cyano groups explains, why heating was used for halogenation of pyrrole **456** [149]. Nitration of **458** was achieved using acetylnitrate [61].



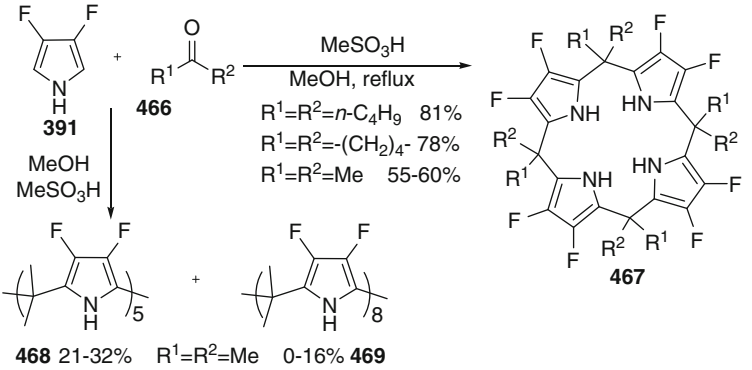
Several efforts were done to perform C-alkylation of pyrrole **373a** by dimethoxymethane [122]. Then PTSA was used as catalyst, about 10 days are needed for full conversion. Using of $(CH_2O)_n$ in EtOH does not lead to pyrrole **459** at all. Nevertheless, using of BF_3xEt_2O in dichloromethane allowed to prepare compound **459** in high yield.



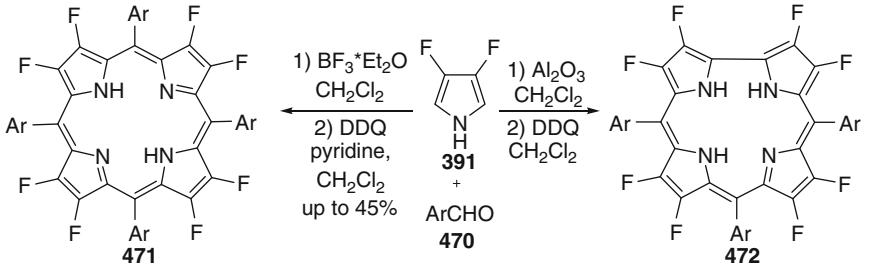
Reaction of 3,4-difluoropyrrole **391** with oxalyl chloride **460** led to the corresponding 1,2-diketone **461**, which was transformed into quinoxaline **463** in high yield by the reaction with 1,2-phenylenediamine **462** [150]. Using reaction of 1,3-diketone **464** with hydrazine, fluorinated dipyrrolylpyrazole **465** was prepared in good yield [151].



The reaction of 3,4-difluoropyrrole **391** with aliphatic ketones **466** afforded fluorinated calix[n]pyrroles. Different fluorinated macrocyclic compounds of this type were prepared using this approach by careful variation of concentration, temperature, and reaction time. Calix[4]pyrrole **467** and calix[5]pyrroles **468** can be prepared as sole products. In contrast, calix[8]pyrrole **469** is always obtained as a mixture with calix[5]pyrrole **468**. Calix[4]pyrroles **467** act as neutral anion receptors and were found to bind anions such as fluoride, chloride, or dihydrogen phosphate with an enhanced affinity compared to their non-fluorinated analogues [150, 152].

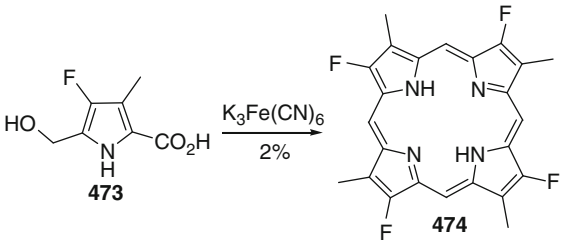


Reaction of 3,4-difluoropyrrole **391** with benzaldehydes **470** followed by oxidation with DDQ led to tetraarylporphyrins **471**. On the base of that reaction sequence a convenient and common pathway towards β-octafluoroporphyrins **471**, bearing meso-tetraaryl substituents, including perfluorinated tetraarylporphyrin was elaborated [153]. In the case of Al_2O_3 catalysis the first step of above mentioned sequence afforded β-octafluorocorroles **472** instead of porphyrins **471** [154].

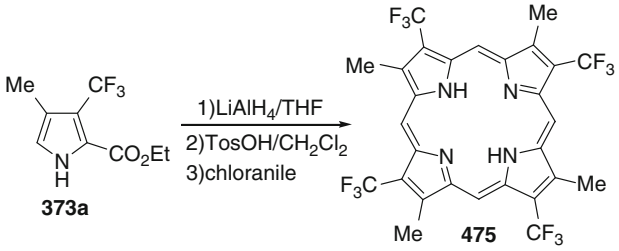


Alternatively fluorinated porphyrin **474** was synthesized by oxidation of 4-fluoropyrrole **473** with $K_3Fe(CN)_6$. The target tetrafluoroporphyrin **474** was prepared in poor yield, however [23]. It should be noted, that due to the high

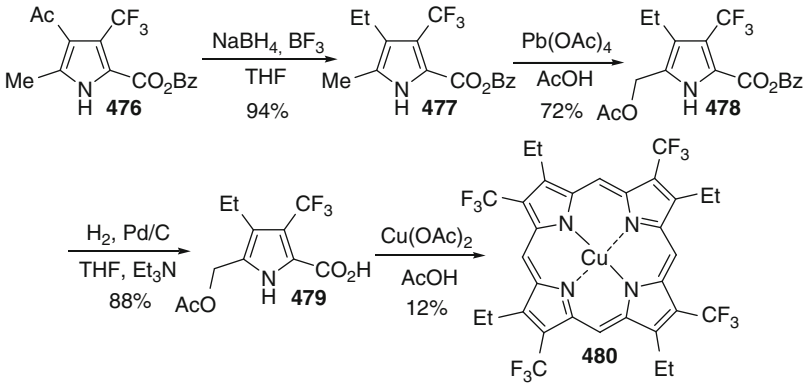
electronegativity of fluorine, fluorinated porphyrins became a valuable tool for the investigation and understanding of the electronic effects in porphyrin structure, opening new horizons for their application.



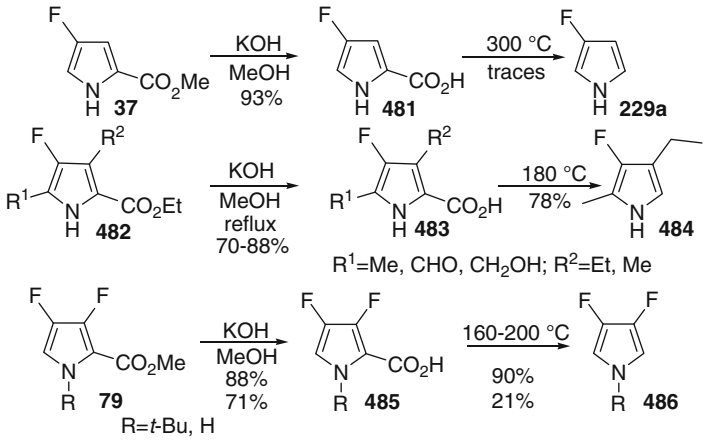
3-Trifluoromethylpyrroles were also used in the fluorinated porphyrins synthesis [121]. Thus, porphyrin **475** was prepared in three steps starting from pyrrole **373a**. At first step reduction of carboxyethyl group was performed. Next, intermolecular alkylation takes place to form CH_2-bridged precursor of porphyrin under PTSA catalysis. The last step is aromatization under treatment with chloranile.



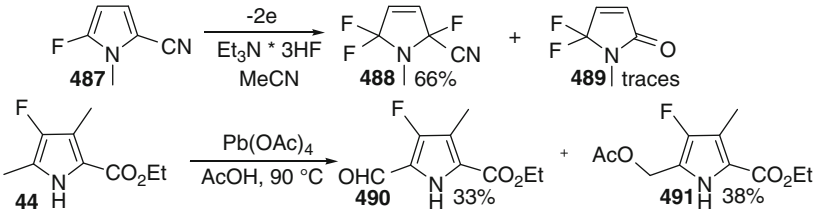
The key step of another porphyrin synthesis is template assembling of the porphyrin core at copper acetate, accompanying with decarboxylation. Starting from pyrrole **476**, porphyrin **480** was prepared in few steps [155, 156].



Other part of fluorinated pyrroles chemistry is connected with chemistry of functional groups transformation attached to fluorinated pyrrole ring. Pyrrole carboxylic acid esters can be easily transformed into acids by alkaline hydrolysis. Pyrrole carboxylic acids undergo decarboxylation at 160–200 °C [23, 157] 3,4-Difluoropyrrole **79** with nitrogen atom, protected with *tert*-butyl group, gave higher yield at decarboxylation step to compare with non-protected one. Unfortunately, only traces of parent 3-fluoropyrrole **229a** were isolated using this method [15]. Nevertheless, this two step transformation represents simple and straightforward approach to fluoropyrroles with unoccupied α-position, which are useful starting materials in synthesis of porphyrins [43].

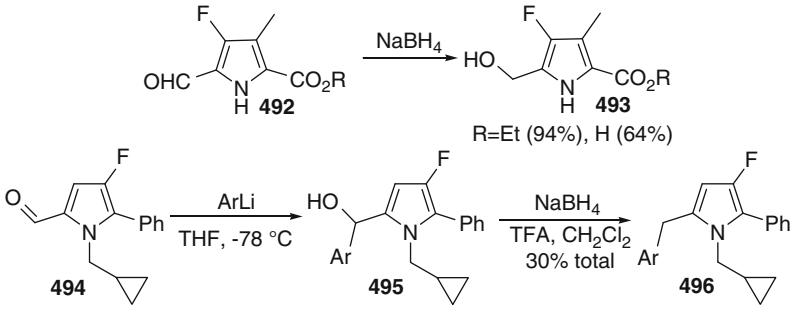


Oxidation and reduction reactions in series of fluorinated pyrroles were also reported. Anodic oxidation of 5-fluoro-1-methyl-1H-pyrrole-2-carbonitrile **487** in acetonitrile in the presence of $Et_3N \cdot 3HF$ complex afforded 2,5,5-trifluoro-1-methyl-2,5-dihydro-1H-pyrrole-2-carbonitrile **488** with traces of 5,5-difluoro-1-methyl-1H-pyrrol-2(5H)-one **489**. α-Methyl group in ethyl 4-fluoro-3,5-dimethyl-1H-pyrrole-2-carboxylate **44** can be selectively oxidized by $Pb(OAc)_4$ in the presence of β-methyl group. The reaction led to a mixture of aldehyde **490** and acetate of the corresponding alcohol **491** in high total yield [23].

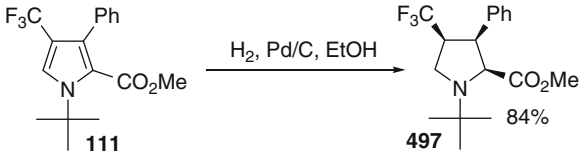


Reduction of 2-formylpyrroles **492** was carried out using $NaBH_4$ in THF to give alcohols **493** in good to high yields [23]. Such alcohols can be further reduced by

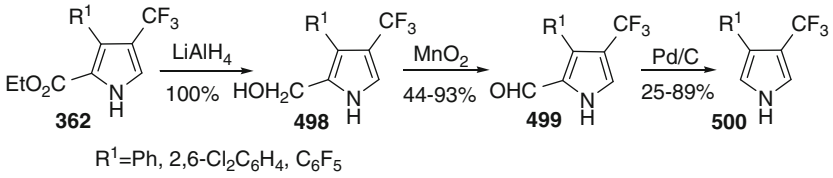
treatment with $NaBH_4$ in CH_2Cl_2 in the presence of TFA. Thus, alcohol **495** obtained by addition of aryllithium to fluorinated pyrrole carbaldehyde **494**, was converted into pyrrole **496** in 30 % total yield [18].



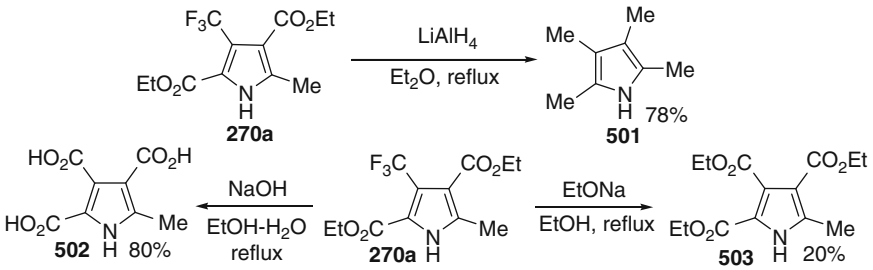
Heterocyclic core of trifluoromethylpyrrole **111** was smoothly reduced by hydrogen under Pd catalysis in EtOH. Pyrrolidine **497** was isolated as the only diastereomer [49].



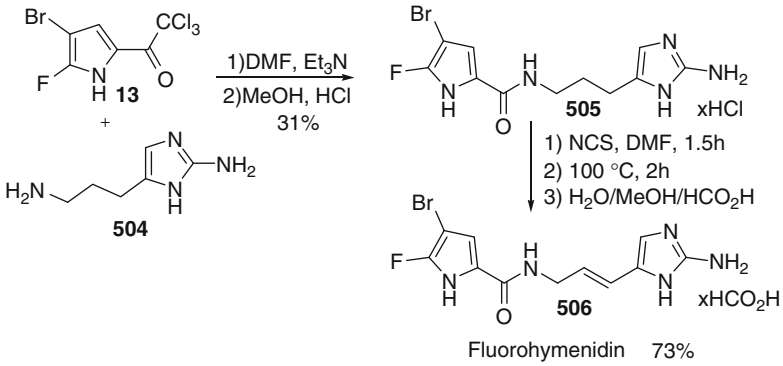
A series of pyrroles **500** with unsubstituted second positions was synthesized using pyrroles **362** as starting materials [158]. Reduction of esters **362** with $LiAlH_4$ afforded alcohols **498**, which were converted into aldehydes **499** by treatment with activated MnO_2. Decarbonylation under Pd/C gave target pyrroles **500**.



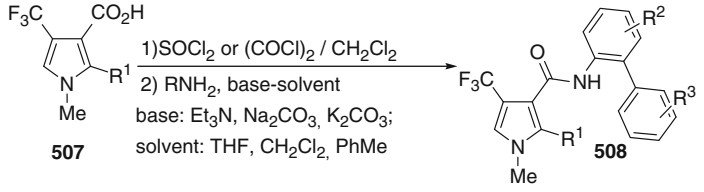
There are few examples of reactions, leading to the loss of fluorine. Thus, treatment of trifluoromethylpyrrole **270a** with excess of $LiAlH_4$ led to reducing of all functional groups to give tetramethylpyrrole **501** in high yield [91]. Another example is basic hydrolysis of pyrrole **270a** in water-ethanol mixture, which led to pyrroletricarboxylic acid **502**. Similarly, its ester **503** was obtained in the reaction of **270a** with sodium ethoxide.



5-Fluorinated trichloromethylketone **13** was used for the synthesis of fluorohymenidin **506**. Hymenidin is bromopyrrole marine alkaloid isolated from the Okinawan marine sponge, and found to be is an antagonist of serotonergic receptors [159]. Coupling of diamine **504** with the **13** led to fluorodihydrohymenidin **505**. Next, vinyl double bond was created via electrophilic chlorination of the 2-aminoimidazole moiety, followed by dehydrochorination. Addition of NCS to **505** in DMF at room temperature selectively formed the corresponding chloroimidazole. Elimination of HCl was induced by heating to 100 °C to give fluorohymenidin formate **506** after reversed phase chromatography (H_2O/MeOH/HCOOH) [11].

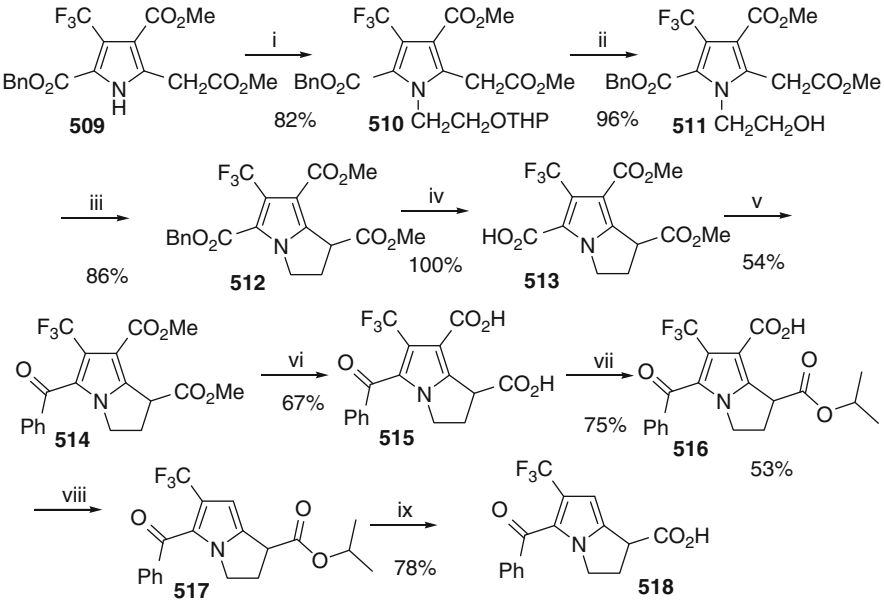


Most applications of trifluoromethylpyrroles connected with pesticide candidates synthesis. In some cases, however, compounds having the 3-trifluoromethyl core posses the fungicidal properties as well. For example amides **508** prepared from **507** was found to reveal such activity [160].



R^1=H, F; R^2=H, F; R^3=H, Cl, F, Br, Me, CF_3, OCF_3, SCF_3

Ketorolac is a non-steroidal anti-inflammatory drug, often used as an analgesic. Fluorinated analogue of ketorolac (compound **518**) was synthesized in nine steps in 11 % total yield starting from **509** [161].



i $BrCH_2CH_2OTHP$, K_2CO_3, NaI, DMF; ii AcOH-H_2O; iii a) Et_3N, $MeSO_2Cl$, CH_2Cl_2; b) NaH, DMF; iv H_2, 10% Pd/C, AcOEt; v $(COCl)_2$, PhMe, PhMgBr, $Fe(acac)_3$; vi EtSLi, HMPTA; vii i-PrOH, HCl; viii CuO, quinoline, 215 °C; ix HCO_2H, $MeSO_3H$

4 Conclusions

Fluorinated pyrroles have been studied intensively in recent years. As a result, a significant number of synthetic approaches to these compounds was elaborated. The most general methods involve direct fluorination/trifluoromethylation of the parent pyrroles, both the [3 + 2]- and the [4 + 2]-cycloaddition reactions, the applications of carbonyl compounds as well as TOSMIC and isocyanoacetates. Though variety of methods are already known, the elaboration of novel preparative pathways towards fluorinated pyrrole derivatives is still ongoing, which is due to the manifold of biological activities of this structural motive and the use as precursors for porphyrins synthesis. It is no doubt, that this branch of synthetic organic chemistry will enjoy a much attention, giving rise to sustainable flow of novel convenient pathways to the synthesis of fluorinated pyrroles.

Acknowledgments Financial support from the Russian Foundation for Basic Research (grants no. 12-03-00292-a and 13-03-01129) are gratefully acknowledged.

References

1. Wilkerson WW, Galbraith W, Gans-Brangs K, Grubb M, Hewes WE, Jaffee B, Kenney JP, Kerr J, Wong N (1994) Antiinflammatory 4,5-diarylpyrroles: synthesis and QSAR. J Med Chem 37:988–998
2. Tucci FC, Zhu YF, Guo Z, Gross TD, Connors PJ Jr, Struthers RS, Reinhart GJ, Wang X, Saunders J, Chen C (2002) A novel synthesis of 7-aryl-8-fluoro-pyrrolo[1,2-a]pyrimid-4-ones as potent, stable GnRH receptor antagonists. Bioorg Med Chem Lett 12:3491–3495
3. Ruebsam F, Webber SE, Tran MT, Tran CV, Murphy DE, Zhao J, Dragovich PS, Kim SH, Li LS, Zhou Y, Han Q, Kissinger CR, Showalter RE, Lardy M, Shah AM, Tsan M, Patel R, Lebrun LA, Kamran R, Sergeeva MV, Bartkowski DM, Nolan TG, Norris DA, Kirkovsky L (2008) Pyrrolo[1,2-b]pyridazin-2-ones as potent inhibitors of HCV NS5B polymerase. Bioorg Med Chem Lett 18:3616–3621
4. Bovy PR, Reitz DB, Collins JT, Chamberlain TS, Olins GM, Corpus VM, McMahon EG, Palomo MA, Koepke JP, Smits GJ, McGraw DE, Gaw JF (1993) Nonpeptide angiotensin II antagonists: N-phenyl-1H-pyrrole derivatives are angiotensin II receptor antagonists. J Med Chem 36:101–110
5. (a) Black BC, Hollingworth RM, Ahammadsahib KI, Kukel CD, Donovan S (1994) Insecticidal action and mitochondrial uncoupling activity of AC-303,630 and related halogenated pyrroles. Pestic Biochem Physiol 50:115–128. (b) Nauen R, Bretschneider T (2002) New modes of action of insecticides. Pestic Outlook 13: 241–245. (c) Dekeyser MA (2005) Acaricide mode of action. Pest Manag Sci 61:103–110
6. Crestoni ME, Fornarini S (1989) Direct fluorination of thiophene and N-methylpyrrole. Gazz Chim Ital 119:203–204
7. (a) Wang J, Scott AI (1994) Fluorination of pyrrolic compounds with xenon difluoride. Tetrahedron Lett 35:3679–3682. (b) Wang J, Scott AI (1994) Synthesis of the 2-fluoro-11-hydroxy analog of porphobilinogen, a new suicide inhibitor of the enzyme porphobilinogen deaminase. Tetrahedron 50:6181–6192
8. Chang MN, Biftu T, Boulton DA, Finke PE, Hammond ML, Pessolano AA, Zambias RA, Bailey P, Goldenberg M, Rackham A (1986) Syntheses and analgesic/antiinflammatory activities of novel 2-[5-aroyl pyrrolo]alkanoic acids. Eur J Med Chem 21:363–369
9. Gozzo FC, Ifa DR, Eberlin MN (2000) Gaseous SF_3+: an efficient electrophilic monofluorinating agent for five-membered heteroaromatic compounds. J Org Chem 65:3920–3925
10. Zhang Y, Shibatomi K, Yamamoto H (2005) Lewis acid catalyzed highly selective halogenation of aromatic compounds. Synlett 18:2837–2842
11. Troegel B, Lindel T (2012) Microwave-assisted fluorination of 2-acylpyrroles: synthesis of fluorohymenidin. Org Lett 14:468–471
12. (a) Tajima T, Ishii H, Fuchigami T (2001) Electrolytic partial fluorination of organic compounds. Part 51: Electrochemical fluorination of 1-methylpyrroles having electron-withdrawing groups at the 2-position: effect of supporting fluoride salts on the fluorinated product selectivity. Electrochem Comm 3:467–471. (b) Tajima T, Ishii H, Fuchigami T (2001) Electrolytic partial fluorination of organic compounds. Part 48: Anodic fluorination of 2-cyano-1-methylpyrrole. Tetrahedron Lett 42:4857–4860. (c) Tajima T, Fuchigami T (2002) A facile synthesis of gem -difluorinated heterocyclic compounds using anodic fluorination of 2-cyano-1-methylpyrrole as a key step synthesis 2597–2600. (d) Tajima T, Nakajima A, Fuchigami T (2006) Electrolytic partial fluorination of organic compounds 83 anodic fluorination of N-substituted pyrroles and its synthetic applications to gem-difluorinated heterocyclic compounds. J Org Chem 71:1436–1441

13. (a) Dvornikova E, Bechcicka M, Kamieńska-Trela K, Krówczyński A (2003) Synthesis and NMR studies of 2- and 3-fluorosubstitued five-membered heterocycles. J Fluor Chem 124:159–168. (b) Samori C, Guerrini A, Varchi G, Fontana G, Bombardelli E, Tinelli S, Beretta GL, Basili S, Moro S, Zunino F, Battaglia A (2009) Semisynthesis, biological activity, and molecular modeling studies of C-ring-modified camptothecins. J Med Chem 52:1029–1039
14. Barnes KD, Hu Y, Hunt DA (1994) Electrophilic fluorination of a highly functionalized pyrrole. Synth Comm 24:1749–1755
15. Leroy J, Porhiel E, Bondon A (2002) Synthesis and characterization of partially b-fluorinated 5, 10, 15, 20-tetraphenylporphyrins and some derivatives. Tetrahedron 58:6713–6722
16. (a) Yamada S, Gavryushin A, Knochel P (2010) Convenient electrophilic fluorination of functionalized aryl and heteroaryl magnesium reagents. Angew Chem Int Ed 49:2215–2218. (b) Yamada S, Knochel P (2010) Large-scale preparation of aromatic fluorides via electrophilic fluorination with functionalized aryl- or heteroarylmagnesium reagents. Synthesis 2490–2494
17. Wang J, Scott AI (1995) Fluoro-decarboxylation of pyrrolecarboxylic acids by F–TEDA–BF_4–a convenient general synthesis of fluoropyrroles. J Chem Soc Chem Commun 2399–2400. doi:10.1039/C39950002399
18. Surmont R, Verniest G, Colpaert F, Macdonald G, Thuring JW, Deroose F, De Kimpe N (2009) New synthesis of 3-fluoropyrroles. J Org Chem 74:1377–1380
19. Demange L, Ménez A, Dugave C (1998) Practical synthesis of Boc and Fmoc protected 4-fluoro and 4-difluoroprolines from trans-4-hydroxyproline. Tetrahedron Lett 39:1169–1172
20. (a) Umemoto T, Ishihara S (1993) Power-variable electrophilic trifluoromethylating agents. S-, Se-, and Te-(trifluoromethyl)dibenzothio-, -seleno-, and -tellurophenium salt system. J Am Chem Soc 115:2156–2164. (b) Umemoto T (1997) MEC reagent brochure. DAIKIN Fine Chemicals Research Center, Tokyo
21. (a) Yang J-J, Kirchmeier RL, Shreeve JM (1998) New electrophilic trifluoromethylating agents. J Org Chem 63:2656–2660. (b) Shreeve JM, Yang J-J, Kirchmeier RL (2001) Preparation of electrophilic trifluoromethylating reagents. US Patent 6,215,021
22. Wiehn MS, Vinogradova EV, Togni A (2010) Electrophilic trifluoromethylation of arenes and N-heteroarenes using hypervalent iodine reagents. J Fluor Chem 131:951–957
23. (a) Onda H, Toi H, Aoyama Y, Ogoshi H (1985) Fluoropyrroles and tetrafluoroporphyrins. Tetrahedron Lett 26:4221–4224. (b) Toi H, Homma M, Onda H, Aoyagi K, Aoyama Y, Ogoshi H (1985) Synthesis of fluorine containing pyrroles and their derivatives. Heterocycles 23:182
24. Martín-Santamaría S, Carroll MA, Carroll CM, Carter CD, Pike VW, Rzepa HS, Widdowson DA (2000) Fluoridation of heteroaromatic iodonium salts-experimental evidence supporting theoretical prediction of the selectivity of the process. Chem Comm 2000:649–650
25. Wallace MB, Adams ME, Kanouni T, Mol CD, Dougan DR, Feher VA, O'Connell SM, Shi L, Halkowycz P, Dong Q (2010) Structure-based design and synthesis of pyrrole derivatives as MEK inhibitors. Bioorg Med Chem Lett 20:4156–4158
26. Albaugh PA, Dominguez-Manzanares E, Hong JE, Hornback WJ, Jiang D, Ornstein PL, Thompson ML, Tromiczak EG, Wu Z, Zarrinmayeh H, Zimmerman DM, Castano MAM, Huffman LG, Miller WD (2005) Pyrrole and pyrazole derivatives as potentiators of glutamate receptors. Patent WO 2005040110
27. Senecal TD, Parsons AT, Buchwald SL (2011) Room temperature aryl trifluoromethylation via copper-mediated oxidative cross-coupling. J Org Chem 76:1174–1176
28. Liu C, Chen Q-Y (2005) Fluoroalkylation of porphyrins: a facile synthesis of trifluoromethylated porphyrins by a palladium-catalyzed cross-coupling reaction. Eur J Org Chem 3680–3686
29. Terazono Y, Dolphin D (2003) Synthesis and characterization of trifluoromethyl-meso-tetraphenylporphyrins. J Org Chem 68:1892–1900

30. Takeo A, Koji K, Masatsugu K, Yoshio S, Junko N, Hisaharu H, Akira S (1988) Photochemical trifluoromethylation of some aromatic and heteroaromatic compounds with trifluoromethyl bromide. Bull Chem Soc Jpn 61:3531–3537
31. (a) Masakazu N, Hiroshi K, Shozo F, Yoshio H, Louis C (1991) Photochemical trifluoromethylation of 1-methylimidazoles and 1-methylpyrroles containing methylthio groups. Bull Chem Soc Jpn 64:2255–2259. (b) Kobayashi Y, Kumadaki I, Ohsawa A, Murakami S, Nakano T (1978) Studies on the organic fluorine compounds. Chem Pharm Bull 26:1247–1249
32. Girard Y, Atkinson J, Joseph G, Belanger P, Fuentes J, Rokach J, Rooney S, Remy D, Hunt C (1983) Synthesis, chemistry and photochemical substitutions of 6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-ones. J Org Chem 48:3220–3234
33. Chen Q-Y, Li Z-T (1993) Photoinduced electron-transfer reaction of difluorodiiodomethane with azaaromatic compounds and enamines. J Chem Soc Perkin Trans 1:645–648
34. Yoshida M, Yoshida T, Kobayashi M, Kamigata N (1989) Perfluoroalkylations of nitrogen-containing heteroaromatic compounds with bis(perfluoroalkanoyl) peroxides. J Chem Soc Perkin Trans I 5:909–914
35. (a) Umemoto T, Miyano O (1982) N-Trifluoromethyl-N-nitrosobenzenesulfonamide a new trifluoromethylating agent. Tetrahedron Lett 23:3929–3930. (b) Umemoto T, Miyano O (1983) Toyo Soda Kenkyu Hokoku 27:69; Chem Abstr 100:67911
36. Naumann D, Kischkewitz J (1990) Trifluoromethylation of furan, thiophene, pyrrole, and p-benzoquinone with CF_3I, $Te(CF_3)_2$, $Sb(CF_3)_3$, $Hg(CF_3)_2$, and $Cd(CF_3)_2$. J Fluor Chem 46:265–281
37. (a) Tordeux M, Langlois B, Wakselman B (1990) Reactions of trifluoromethyl bromide and related halides: Part 10 perfluoroalkylation of aromatic compounds induced by sulphur dioxide radical anion precursors. J Chem Soc Perkin Trans I: 2293–2299. (b) Tordeux M, Wakselman B (1989) Process for the perhaloalkylation of aromatic derivatives. Patent EP 0298803
38. Clavel L, Forat G, Gilbert L, Nantermet R (1991) Perfluoroalkylation of nucleophiles utilizing sulfurous anhydride. Patent FR 2660923
39. Khanna IK, Weier RM, Yu Y, Collins PW, Miyashiro JM, Koboldt CM, Veenhuizen AW, Currie JL, Seibert K, Isakson PC (1997) 1,2-diarylpyrroles as potent and selective inhibitors of cyclooxygenase-2. J Med Chem 40:1619–1633
40. Hall A, Atkinson S, Brown SH, Chessell IP, Chowdhury A, Clayton NM, Coleman T, Giblin GMP, Gleave RJ, Hammond B, Healy MP, Johnson MR, Michel AD, Naylor A, Novelli R, Spalding DJ, Tang SP (2006) Structure-activity relationships of 1,5-biaryl pyrroles as EP1 receptor antagonists. Bioorg Med Chem Lett 16:3657–3662
41. Kino T, Nagase Y, Ohtsuka Y, Yamamoto K, Uraguchi D, Tokuhisa K, Yamakawa T (2010) Trifluoromethylation of various aromatic compounds by CF_3I in the presence of Fe(II) compound, H_2O_2 and dimethylsulfoxide. J Fluor Chem 131:98–105
42. (a) Langlois BR, Laurent E, Roidot N (1991) Trifluoromethylation of aromatic compounds with sodium trifluoromethanesulfinate under oxidative conditions. Tetrahedron Lett 32:7525–7528. (b) Clavel JL, Laurent E, Langlois BR, Roidot N (1991) Reagent and process for the perfluoroalkylation of nucleophilic substrates by sodium perfluoroalkanesulfinates in an oxidising medium. Patent EP 458684
43. (a) Leroy J, Wakselman C (1976) Cycloaddition (2 + 3) d'aziridines avec les perfluoroalcenes Synthese de pyrroles fluorbs. Can J Chem 54:218–225. (b) Leroy J, Rubinstein M, Wakselman C (1984) [2+ 3] Cycloadditions of fluoroolefins: synthesis of 3, 4-difluoro-1-t butyl-pyrrole. J Fluor Chem 25:255–258. (c) Leroy J, Wakselman C (1994) First access to 3,4-difluoro-1H-pyrrole Tetrahedron Lett 35:8605–8608. (d) Woller EK, Smirnov VV, DiMagno SG (1998) A straightforward synthesis of 3, 4-difluoropyrrole. J Org Chem 63:5706–5707
44. (a) Khlebnikov AF, Novikov MS, Dolgikh SA, Magull J (2008) 1,3- vs 1,5-cyclization of azomethine ylides derived from 1-azabuta-1,3-dienes and difluoro- and dichlorocarbenes experimental and quantum-chemical study Arkivoc ix:94–115. (b) Novikov MS, Khlebnikov AF, Sidorina ES, Kostikov RR (1998) A facile tandem carbene-ylide route to 2-fluoropyrrole derivatives. J Fluor Chem 90:117–119

45. (a) Novikov MS, Khlebnikov AF, Voznyi IV, Besedina OV, Kostikov RR (2005) Intramolecular 1,3-dipolar cycloaddition of geminal difluoro azomethine ylides at multiple carbon-carbon bonds. Russ J Org Chem 41:361–369. (b) Novikov MS, Khlebnikov AF, Voznyi IV, Besedina OV, Kostikov RR (2001) The first example of intramolecular cycloaddition of carbene-derived azomethine ylides in a domino reaction of difluorocarbene with Schiff bases. Tetrahedron Lett 42:533–535. (c) Voznyi IV, Novikov MS, Khlebnikov AF, Kopf J, Kostikov RR (2004) Intramolecular 1,3-dipolar cycloaddition to ester carbonyl of azomethinylides prepared from aldimines and difluorocarbene. Russ J Org Chem 40:199–205
46. Wu K, Chen QY (2003) Synthesis of fluorinated indolizines and 4H-pyrrolo [1,2-a] benzimidazoles via 1, 3-dipolar cycloaddition of fluoroalkenes to N-ylides. Synthesis 29–32
47. Tanaka K, Nagatani S, Ohsuga M, Mitshuhashi K (1994) Regio- and stereoselectivity of cycloadditions of trifluoromethylated azomethine ylide. Bull Chem Soc Jpn 67:589–591
48. Leroy J, Cantacuzene D, Wakselman C (1982) Synthesis of 3,4-bis[trifluoromethyl]-1*H*-pyrrole. Synthesis 313–315
49. La Porta P, Capuzzi L, Bettarini F (1994) Synthesis of methyl 3-aryl-4-trifluoromethyl-1H-pyrrole-2-carboxylates. Synthesis 287–290
50. (a) Kameswaran V (1999) Preparation of 2-aryl-5-perfluoroalkylpyrroles from (perfluoroalkylmethyl)arylimidoyl chlorides. US Patent 5,965,773. (b) Kameswaran V (1998) Process for the preparation of 2-aryl-5-(perfluoroalkyl)pyrroles from N-(perfluoroalkylmethyl)arylimidoyl chlorides. US Patent 5,817,834
51. (a) Kameswaran V (2000) Preparation of N-benzylidene-1-chloro-1-perfluoroalkylmethylamines and 2-aryl-5-perfluoroalkylpyrroles. US Patent 6,034,273. (b) Kameswaran V (1999) Preparation of 2-aryl-5-perfluoroalkylpyrroles from N-arylmethylene-1-chloro-1-perfluoroalkylmethylamines. Patent EP 0934929
52. (a) Kameswaran V (2000) Process for the preparation of 2-aryl-5-(perfluoroalkyl)pyrrole compounds from N-[1-chloro-1-(perfluoroalkyl)methyl]arylimidoyl chloride compounds. Patent EP 1035113. (b) Duerr D, Ehrenfreund J, Hall RG, Danko P (1995) Heteroarylpyrroles. Patent WO 9518122
53. Anderson WK, Corey PF (1977) Synthesis and antileukemic activity of 5-substituted 2,3-dihydro-6,7-bis(hydroxymethyl)-1H-pyrrolizine diesters. J Med Chem 20:812–818
54. Padwa A, Burgess EM, Gingrich HL, Roush DM (1982) On the problem of regioselectivity in the 1,3-dipolar cycloaddition reaction of munchnones and sydnones with acetylenic dipolarophiles. J Org Chem 47:786–791
55. Meazza G, Bettarini F, La Porta P, Piccardi P, Signorini E, Portoso D, Fornara L (2004) Synthesis and herbicidal activity of novel heterocyclic protoporphyrinogen oxidase inhibitors. Pest Manag Sci 60:1178–1188
56. Doehner RF, Barton JM, Kuhn DG (1992) 2-phenyl-5-(trifluoromethyl)-2-pyrroline-3-carbonitriles, -3-carboxylates and 3-nitro-2-phenyl-5-(trifluoromethyl)-2-pyrrolines, methods for their preparation and their use as intermediates for insecticides, nematocides and acaricides. US Patent 5,118,816
57. Huang H, Wu X, Wu N (2005) Huaxue Gongye Yu Gongcheng Jishu 26:12; Chem Abstr (2005) 146:358652
58. (a) Tian W, Luo Y, Chen Y, Yu A (1993) A convenient synthesis of 2-trifluoromethylpyrroles via base-promoted cyclocondensation of trifluoromethyloxazolones with electron-deficient alkenes. J Chem Soc Chem Comm 101–102. (b) Wei-Sheng T, Luo Y-R, Chen Y-Q, Zai Y-H (1994) Huaxue Xuebao 52:1126; Chem Abstr (1994) 122:105575. (c) Tian W, Chen Y, Luo Y, Deng X (1991) Chin Chem Lett 2:217; Chem Abstr (1991) 115:114396. (d) Addor RW, Furch JA, Kuhn DG (1991) Process for the preparation of insecticidal, acaricidal and nematicidal 2-aryl-5-(trifluoromethyl)pyrrole compounds. US Patent 5,030,735. (e) Kagiwara K, Saso H, Ichinose K (1997) Jpn Kokai Tokkyo Koho JP 09301962. (f) Hagiwara K, Saso H, Ichinose K, Yokota C, Sano S (1996) Pyridylpyrrole compounds, process for production, and agrohorticultural bactericide. Patent WO 9617841
59. (a) Xu S, Wan Q, Yu Y, Wang X, Xu Z (2003) Preparation of 2-aryl-5-(trifluoride) pyrrole-3-nitrile and its use and preparation of its intermediate thereof Faming Zhuanli Shenqing Gongkai Shuomingshu CN 1439634. (b) Lai H, Mu J, Zeng Q, Li W (2003) Zhejiang Gongye

Daxue Xuebao 31:692; Chem Abstr (2003) 141:243267. (c) Xu S, Jiang M, Yu Y, Wang X, Wan Q, Xu Z (2004) Nanjing Nongye Daxue Xuebao 27:105; Chem Abstr (2004) 144:173068
60. Tian W (1997) Single synthetic method for trifluoromethyl pyrroles compound Faming Zhuanli Shenqing Gongkai Shuomingshu CN 1140713
61. Kuhn DG, Furch JA, Kamhi VM (1992) Diaryl-1H-pyrrolecarbonitriles and diarylnitro-1H-pyrrole derivatives, methods for their preparation and their use as insecticides and acaricides. Patent EP 0487870
62. Steglich W, Gruber P, Heininger HU, Kneidl F (1971) Nitril-Ylide aus Oxazolinonen-5; Nachweis durch Abfangreaktionen und Urnlagerung in 2-Aza-butadiene-λ-3. Chem Ber 104:3816–3830
63. (a) Kameswaran V (1999) Preparation of ammoniumoxazole and aminooxazolium aryl-pyrrole insecticide intermediates. US Patent 5,945,538. (b) Kameswaran V (1998) Process for the manufacture of 2-aryl-5 perfluoroalkylpyrrole derivatives. US Patent 5,777,132. (c) Kameswaran V (1998) Process for the manufacture of 2-aryl-5-perfluoroalkylpyrrole derivatives and intermediates useful therefor. US Patent 5,750,726. (d) Kameswaran V (1998) A process for the manufacture of 2 aryl 5 perfluoroalkylpyrrole derivatives and intermediates useful therefor. Patent EP 816337. (e) Kameswaran V (1999) Preparation of ammoniooxazole and aminooxazolium intermediates for insecticidal arylpyrroles. US Patent 5,925,773
64. (a) Kameswaran V (1997) Oxazole amines as intermediates in the manufacture of insecticidal pyrroles. US Patent 5,631,379. (b) Kameswaran V (1995) Process for the manufacture of insecticidal arylpyrroles via oxazole amine intermediates. US Patent 5,446,170
65. Funabiki K, Ishihara T, Yamanaka H (1995) An efficient and convenient synthesis of 4-polyfluoroalkylated pyrrole-3-carboxylates through 1,3-dipolar cycloaddition reaction of polyfluoro-2-alkynoic acid esters with munchnones. J Fluor Chem 71:5–7
66. Uhr H, Lui N, Erdelen C, Turberg A (1995) Preparation of 2-aryl-3,4,5-tris(trifluoromethyl) pyrroles and related compounds as pesticides. Patent DE 4325132
67. Okano T, Uekawa T, Morishima N, Eguchi S (1991) Synthesis of β-(trifluoromethyl)pyrroles via the cycloaddition of munchnones to electron-deficient trifluoromethylated olefins. J Org Chem 56:5259–5262
68. Zhang X-C, Huang W-Y (1998) Reaction of 1-alkylbenzimidazolium 3-ylides with ethyl 2,2-dihydropolyfluoroalkanoates. Tetrahedron 54:12465–12474
69. Potts KT, Choudhury DR (1978) Mesoionic compounds. 43. Ring annulation utilizing the isomeric anhydro-2- and 3-hydroxythiazolo[2,3-b]benzothiazolium hydroxide mesoionic systems. J Org Chem 43:2697–2700
70. Murray WV, Francois D, Maden A, Turchi I (2007) An azomethine ylide approach to complex alkaloid-like heterocycles. J Org Chem 72:3097–3099
71. Kobayashi Y, Ando A, Kawada K, Ohsawa A, Kumadaki I (1980) Organic fluorine compounds. Part 32. A 1,3-dipolar cycloaddition reaction of tetrakis(trifluoromethyl)(dewar thiophene) and some reactions of the cycloadducts. J Org Chem 45:2962–2966
72. Kobayashi Y, Ando A, Kawada K, Kumadaki I (1980) Organic fluorine compounds 34 Some reactions of valence-bond isomers of tetrakis(trifluoromethyl)pyrroles. J Org Chem 45:2968–2970
73. Nunes MC, Silva MR, Beja AM, Fausto R, Pinho e Melo TMVD (2010) Cycloaddition of trifluoromethyl azafulvenium methides: synthesis of new trifluoromethylpyrrole-annulated derivatives. Tetrahedron Lett 51(2010):411–414
74. Moiseev SV, Vasil'ev NV (2005) Synthesis and cycloaddition of N-substituted pyrroles with polyfluorinated substituents. Russ Chem Bull 54:1948–1953
75. Kaesler RW, LeGoff E (1982) Synthesis of 3,4-bis(trifluoromethyl)pyrroles. J Org Chem 47:4779–4780
76. Visnick M, Battiste MA (1985) Multistage cycloadducts from the condensation of N, N'-dipyrrolylmethane with acetylenic dienophiles: synthesis of the 10,12-diazapentacyclo [7.3.1.04,1205,1306,10]trideca-2,7-diene ring system. J Chem Soc Chem Comm 1621–1622
77. Qiu ZM, Burton DJ (1994) A new approach to the synthesis of beta-fluoropyrrole derivatives. Tetrahedron Lett 35:4319–4322

78. (a) Qiu ZM, Burton DJ (1994) UV initiated addition of iododifluoromethyl ketones to electron-deficient olefins. Tetrahedron Lett 35:1813–1816. (b) Qiu ZM, Burton DJ (1995) Synthesis of gamma-(electron-withdrawing group)-substituted alpha,alpha-difluoro ketones by UV-initiated addition of iododifluoromethyl ketones with electron-deficient alkenes. J Org Chem 60:6798–6805
79. Kim SK, Jun C, Kwak K, Park K, Chai K (2007) Synthesis of N-alkylated 4-fluoro-5-phenylpyrrole-2-carboxylate via isolable pyrroline ionic intermediates. Bull Korean Chem Soc 28:2324–2328
80. (a) Qiu ZM, Burton DJ (1995) α,α-Difluoro-γ-iodo-γ-trimethylsilyl ketones as precursors for the synthesis of α-substituted β-fluoropyrroles. Tetrahedron Lett 36:5119–5122. (b) Kim BM, San Q-Z, Bhatt LR, Kim SK, Chai K-Y (2010) Efficient preparation of 3-fluoropyrrole derivatives. Bull Korean Chem Soc 31:31–34
81. Shi G-Q, Cai W-L (1995) δ, ε-Unsaturated β, β-difluoro-α-keto esters: novel synthesis and utility as precursors of β, β-difluoro-α-amino acids. J Org Chem 60:6289–6295
82. Shi G-Q, Schlosser M (1993) A novel and versatile access to fluorinated carbo-and heterocyclic compounds employing electron-rich fluorodienes as cycloaddition components. Tetrahedron 49:1445–1456
83. Wang Y, Zhu S (2003) Convenient synthesis of polyfunctionalized beta-fluoropyrroles from rhodium(II)-catalyzed intramolecular N-H insertion reactions. Org Lett 5:745–748
84. Surmont R, Verniest G, De Kimpe N (2009) Gold-catalyzed synthesis of 2-aryl-3-fluoropyrroles. Org Lett 11:2920–2923
85. Roth BD, Ortwine DF, Hoefle ML, Stratton CD, Sliskovic DR, Wilson MW, Newton RS (1990) Newton inhibitors of cholesterol biosynthesis 1 trans-6-(2-Pyrrol-1-ylethyl)-4-hydroxypyran-2-ones, a novel series of HMG-CoA reductase inhibitors. 1. Effects of structural modifications at the 2- and 5-positions of the pyrrole nucleus. J Med Chem 33:21–31
86. Nagarajan K, Talwalker PK, Goud AN, Shah RK, Shenoy SJ, Desai ND (1988) Synthesis and oral hypoglycemic properties of 4-oxo-4,5,6,7-tetrahydroindole-3-acetic acids. Ind J Chem Sect B 27:1113–1123
87. Xu G, Singh MP, Gopal D, Sayre LM (2001) Novel 2,5-hexanedione analogues. Substituent-induced control of the protein cross-linking potential and oxidation susceptibility of the resulting primary amine-derived pyrroles. Chem Res Toxicol 14:264–274
88. Kobatake T, Yoshida S, Yorimitsu H, Oshima K (2010) Reaction of 2-(2,2,2-trifluoroethylidene)-1,3-dithiane 1-oxide with ketones under pummerer conditions and its application to the synthesis of 3-trifluoromethyl-substituted five-membered heteroarenes. Angew Chem Int Ed 49:2340–2343
89. Hoffmann MG, Wenkert E (1993) Natural product synthesis in agricultural chemistry. 2. A new and efficient synthesis of 2-trifluoromethyl substituted pyrroles and ethyl-2,3-bis(ethoxycarbonyl)-1H-pyrrole-1-propionate. Tetrahedron 49:1057–1062
90. Bouillon J-P, Henin B, Huot J-F, Portella C (2002) Fluorinated ketene dithioacetals 8 1,1-bis(ethylsulfanyl)perfluorobut-1-ene as starting material for the synthesis of substituted 2-(trifluoromethyl)furans and -pyrroles. Eur J Org Chem 1556–1561
91. Jones RA, Rustidge DC, Cushman SM (1984) Pyrrole studies XXX A critical evaluation of the Knorr synthesis of trifluoromethylpyrroles and the reactivity of diethyl 4-trifluoromethyl-2-methylpyrrole-3,5-dicarboxylate. Synth Commun 14:575–584
92. (a) Ogoshi H, Homma M, Yokota K, Toi H, Aoyama Y (1983) Synthesis of β-trifluoromethylpyrroles. Tetrahedron Lett 24:929–930. (b) Central Glass Co, Ltd (1984) Preparation of pyrrole derivative containing perfluoroalkyl group at beta-position, Japan Jpn Kokai Tokkyo Koho JP 59167568
93. Ward RW, Goudie AC (1983) Pyrrole derivatives. Patent GB 2107304
94. Iwata S, Ishiguro Y, Itsugi M, Mitsuhashi K, Tanaka K (1993) 3,3,3-Trifluoro-1-nitropropene as a novel trifluoromethyl-containing building block. Bull Chem Soc Jpn 66:2432–2435
95. Tessier J, Demoute JP, Taliani L (1986) Pyrrole derivatives, process for their preparation and their application as pesticides. Patent EP 176387

96. (a) Kameswaran V, Jiang B (1997) A simple synthesis of 3-substituted 5-trifluoromethylpyrroles via modified Hantzsch reaction. Synthesis 530–532. (b) Kameswaran V (1992) Synthesis of 2-aryl-5-(trifluoromethyl)pyrroles, useful as pesticides and their intermediates, from enamines and halo ketones. Patent EP 0491137
97. Baxter AJG, Fuher J, Teague SJ (1994) Azoalkene route to methyl 2,5-dimethyl-4-[2-(phenylmethyl)benzoyl]-1H-pyrrole-3-carboxylate (FPL 64176) and analogues: synthesis of 1-(BOC-amino)pyrrole-3-carboxylates and their conversion to 1H-pyrroles via 1-aminopyrroles. Synthesis 207–211
98. Attanasi OA, Filippone P, Guidi B, Mantellini F, Santeusanio S (2001) Regioselective synthesis of stable 2-(trifluoromethyl)-2,3-dihydro-1H-pyrrol-2-ols and derived fluorinated heterocycles. Synthesis 1837–1845
99. Baraznenok IL, Nenajdenko VG, Balenkova ES (2000) Chemical transformations induced by triflic anhydride. Tetrahedron 56:3077–3119
100. Shi D, Dou G, Shi C, Li Z, Ji S-J (2007) Highly regioselective synthesis of substituted pyrroles utilizing low-valent titanium reagent. Synthesis 2007:3117–3124
101. Kathriarachchi KKADS, Siriwardana AI, Nakamura I, Yamamoto Y (2007) Synthesis of 1,2,3,4-tetrasubstituted pyrrole derivatives via the palladium-catalyzed reaction of 1,3-diketones with methyleneaziridines. Tetrahedron Lett 48:2267–2270
102. Shindo M, Yoshimura Y, Hayashi M, Soejima H, Yoshikawa T, Matsumoto K, Shishido K (2007) Synthesis of multisubstituted furans, pyrroles, and thiophenes via ynolates. Org Lett 9:1963–1966
103. Ohkura H, Berbasov DO, Soloshonok VA (2003) Simple and highly diastereoselective synthesis of trifluoromethyl-containing myosmines via reaction between 2-(aminomethyl) pyridine and 1,1,1,5,5,5-hexafluoro-2,4-pentanedione. Tetrahedron Lett 44:2417–2420
104. Klappa JJ, Rich AE, McNeill K (2002) One-step synthesis of 3,5-disubstituted 2-(2-pyridyl) pyrroles by condensation of 1,3-diones and 2-(aminomethyl)pyridine. Org Lett 4:435–437
105. Korotaev VY, Barkov AY, Kotovich IV, Sosnovskikh V, Korotaev VY, Barkov AY, Kotovich IV, Sosnovskikh VY (2012) Three-component synthesis of substituted β-(trifluoromethyl) pyrroles via Grob cyclization of 1,1,1-trifluoro-3-nitrobut-2-ene with 1,3-dicarbonylic compounds and ammonia or primary amines. J Fluor Chem 138:42–47
106. (a) Nenajdenko VG, Sanin AV, Balenkova ES (1997) Preparation of α,β-unsaturated ketones bearing a trifluoromethyl group and their application in organic synthesis molecules 2:186–232. (b) Nenaidenko VG, Sanin AV, Balenkova ES (1999) Methods for the synthesis of α,β-unsaturated trifluoromethyl ketones and their use in organic synthesis. Russ Chem Rev 68:437–458. (c) Druzhinin SV, Balenkova ES, Nenajdenko VG (2007) Recent advances in the chemistry of α,β-unsaturated trifluoromethylketones. Tetrahedron 63:7753–7808
107. Okada E, Masuda R, Hojo M, Inoue R (1992) A facile and convenient synthetic method for N-β-trifluoroacetylvinyl amino acid esters, α-aminoacetophenones and aminoacetonitriles as potentially useful precursors of fluorine-containing pyrroles. Synthesis 533–555
108. Soufyane M, Mirand C, Lévy J (1993) Synthesis of some fluorinated nitrogen heterocycles from (diethylaminomethylene)hexafluoroacetylacetone (DAMFA). Tetrahedron Lett 34:7737–7740
109. Andrew RJ, Mellor JM (2000) Synthesis of (trifluoromethyl)pyrroles and related heterocycles from 4-ethoxy-1,1,1-trifluorobut-3-en-2-one. Tetrahedron 56:7267–7272
110. Shaitanova EN, Gerus II, Kukhar VP (2008) A new synthetic route to 3-polyfluoroalkyl-containing pyrroles. Tetrahedron Lett 49:1184–1187
111. Bartnik R, Bensadat A, Cal D, Faure R, Khatimi N, Laurent A, Laurent E, Rizzon C (1997) Reactivity of trifluoromethylenaminoketones. Synthesis of new trifluoromethylpyrroles. Bull Soc Chim Fr 134:725–734
112. Cebulska Z, Laurent AJ, Laurent EG (1996) Phototransformations of aziridin-1-yl enones and aziridin-1-yl fumarates substituted bya trifluoromethyl group in various positions. Bull Soc Chim Fr 133:209–212
113. Zanatta N, Schneider JM, Schneider PH, Wouters AD, Bonacorso HG, Martins MAP, Wessjohann LA (2006) Regiospecific synthesis of 4-alkoxy and 4-amino substituted 2-trifluoromethyl pyrroles. J Org Chem 71:6996–6998

114. Cal D, Zagórski P (2011) Synthesis of phosphorylated enaminoketones and their application in the preparation of trifluoromethyl-functionalized 2-phosphonopyrroles. Phosphorus Sulfur Silicon 186:2295–2302
115. (a) Takaya H, Kojima S, Murahashi S (2001) Rhodium complex-catalyzed reaction of isonitriles with carbonyl compounds: catalytic synthesis of pyrroles. Org Lett 3:421–424. (b) Gulevich AV, Zhdanko AG, Orru RVA, Nenajdenko VG (2010) Isocyanoacetate derivatives: synthesis, reactivity, and application. Chem Rev 110:5235–5331. (c) Nenajdenko VG (2012) Isocyanide chemistry. Weinheim
116. Uno H, Sakamoto K, Tominaga T, Ono N (1994) A new approach to β-fluoropyrroles based on the Michael addition of isocyanomethylide anions to β-fluoroalkenyl sulfones and sulfoxides. Bull Chem Soc Jap 67:1441–1448
117. Uno H, Tanaka M, Inoue T, Ono N (1999) Preparation of pyrrole-2-carboxylates with electron-withdrawing groups at the 4-position. Synthesis 3:471–474
118. Larionov OV, de Meijere A (2005) Versatile direct synthesis of oligosubstituted pyrroles by cycloaddition of α-metalated isocyanides to acetylenes. Angew Chem Int Ed 44:5664–5667
119. (a) Aoyagi K, Toi H, Aoyama Y, Ogoshi H (1988) Facile syntheses of perfluoroalkylporphyrins electron-deficient porphyrins II. Chem Lett 1891–1894. (b) Aoyagi K, Haga T, Toi H, Aoyama Y, Mizutani T, Ogoshi H (1997) Electron deficient porphyrins III facile syntheses of perfluoroalkylporphyrins including water soluble porphyrin. Bull Chem Soc Jpn 70:937–943
120. Leroy J (1991) Improved synthesis of 3-(trifluoromethyl)pyrrole. J Fluor Chem 53:61–70
121. Ono N, Kawamura H, Maruyama K (1989) A convenient synthesis of trifluoromethylated pyrroles and porphyrins. Bull Chem Soc Jpn 62:3386–3388
122. (a) Tang J, Verkade JG (1994) Nonionic superbase-promoted synthesis of oxazoles and pyrroles: facile synthesis of porphyrins and α-C-Acyl amino acid esters. J Org Chem 59:7793–7802. (b) Verkade J, Tang J (1994) Preparation of pyrrole and oxazole compounds: formation of porphyrins and C-acyl-α-amino acid esters therefrom. US Patent 5,367,084
123. Kagabu S, Tsuji H, Kawai I, Ozeki H (1995) Thermal rearrangement of N-alkyl-, and N-aryl-(2,2-dihalo-1-phenylcyclopropyl)methyleneamines to 1-alkyl-, and 1-aryl-2 (or 3)-halo-4-phenylpyrroles. Bull Chem Soc Jap 68:341–349
124. Buhr G (1973) Ringverengung von Azidocyclobutenen zu Cyclopropancarbonitrilen. Chem Ber 106:3544–3558
125. Novikov MS, Khlebnikov AF, Sidorina ES, Kostikov RR (2000) 1,3-Dipolar cycloaddition of azomethine ylides derived from imines and difluorocarbene to alkynes: a new active Pb-mediated approach to 2-fluoropyrrole derivatives. J Chem Soc Perkin Trans 1:231–237
126. (a) Pfizer Products Inc (2003) Flourinated cyclic amides as dipeptidyl peptidase IV inhibitors. Patent WO 101958. (b) Pfizer Inc (2004) Synthesis of 3,3,4,4-tetrafluoropyrrolidine and novel dipeptidyl peptidase-IV inhibitor compounds. US Patent 2609A1. (c) Pfizer Inc (2005) Fluorinated lysine derivatives as dipeptidyl peptidase IV inhibitors. US Patent 43292. (d) Hulin B, Cabral S, Lopaze MG, Van Volkenburg MA, Andrews KM, Parker JC (2005) New fluorinated pyrrolidine and azetidine amides as dipeptidyl peptidase IV inhibitors. Bioorg Med Chem Lett 15:4770–4773. (e) Nippon Soda CO LTD (2011) Method for producing tetrafluoro compound. US Patent 178323
127. (a) Roberts RD, Ferran HE, Gula MJ, Spencer TA (1980) Superiority of very weakly basic amines as catalysts for alpha-proton abstraction via iminium ion formation. J Am Chem Soc 102:7054–7058. (b) Hine J, Hahn S, Hwang J (1988) The relationship between the Broensted acidities of imides and their hydrogen-bonding acidities toward oxygen bases. J Org Chem 53:884–887
128. Coe PL, Holton AG, Sleigh JH, Smith P, Tatlow JC (1983) Highly fluorinated heterocycles. Part XVI. Polyfluorinated derivatives of 1-methylpyrrolidine, 1-methylpyrrol-3-ine and 1-methylpyrrole. J Fluor Chem 22:287–298
129. Ischikawa J, Wada Y, Fujiwara M, Sakoda K (2002) The nucleophilic 5 -endo-trig cyclization of 1,1 – difluoro-1-alkenes: ring-fluorinated Hetero- and carbocycle synthesis and remarkable effect of the vinylic fluorines on the disfavored process. Synthesis 1917–1936
130. Briscoe MW, Chambers RD, Mullins SJ, Nakamura T, Drakesmith FG (1990) A synthesis of novel perfluorodienes. J Chem Soc Chem Comm 1127–1128

131. Chambers RD, Gray WK, Mullins SJ, Korn SR (1997) Reactions involving fluoride ion. Part 42: Heterocyclic compounds from perfluoro-3,4-dimethylhexa-2,4-diene. J Chem Soc Perkin Trans I: 1457–1463
132. (a) Lee LF, Howe RK (1984) Synthesis of 2H-1,4-thiazine-2,6-dicarboxylates and their conversion to 3,4-pyrroledicarboxylates via sulfur extrusion. J Org Chem 49:4780–4783. (b) Howe R (1983) Herbicidal pyrrole derivatives. Patent EP 0088743
133. Foster R, Gilchrist TL (1991) Rearrangement of sulphonium ylides of the 1H-1,4-thiazine type. J Chem Soc Perkin Trans I 2249–2254
134. Jacobson MA, Willard PG (2002) Synthesis of 2,3-disubstituted pyrroles from 3, N-dilithio-N-(tert-butyldimethylsilyl)-2-buten-1-amine. J Org Chem 67:32–37
135. Roskamp EJ, Dragovich PS, Hartung JB, Pedersen SF (1989) A regioselective synthesis of pyrroles via the coupling of α, β-unsaturated imines with esters or N, N-dimethylformamide promoted by NbCl3(DME). J Org Chem 54:4736–4737
136. Zimmer R, Reissig H (1992) Efficient synthesis of trifluoromethyl-substituted 5,6-dihydro-4H-1,2-oxazines by the hetero-Diels-Alder reaction of 1,1,1-trifluoro-2-nitroso-2-propene and electron-rich olefins. J Org Chem 57:339–347
137. Koshelev VM, Truskanova TD, Chekhlov NV, Vasil'ev NV, Gontar' AF (1989) Synthesis of N-methyl-2,5-bis(trifluoromethyl) pyrroles. Russ Chem Bull 38:1325
138. Lu L, Chen G, Ma S (2006) Ring-opening cyclization of alkylidenecyclopropyl ketones with amines an efficient synthesis of 2,3,4-trisubstituted pyrroles. Org Lett 8:835–838
139. Katritzky AR, Huang T-B, Voronkov MV, Wang MG, Kolb H (2000) Efficient one-pot synthesis of polysubstituted pyrroles. J Org Chem 65:8819–8821
140. Kawase M, Miyamae H, Saito S (1999) Synthesis of functionalized pyrrolidines from mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates and aminomalonate. Heterocycles 50:71–74
141. Saijo R, Hagimoto Y, Kawase M (2010) New synthesis of 3-trifluoromethylpyrroles by condensation of mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates with phosphorus ylides. Org Lett 12:4776–4779
142. Saijo R, Kawase M (2012) The use of sulfur ylides in the synthesis of 3-alkyl(aryl)thio-4-trifluoromethylpyrroles from mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates. Tetrahedron Lett 53:2782–2785
143. Qiu X-L, Qing F-L (2003) Synthesis of cis-4-trifluoromethyl- and cis-4-difluoromethyl-L-pyroglutamic acids. J Org Chem 68:3614–3617
144. De Matteis V, Dufay O, Waalboer DCJ, Van Delft FL, Tiebes J, Rutjes FPJT (2007) An improved ring-closing metathesis approach to fluorinated and trifluoromethylated nitrogen heterocycles. Eur J Org Chem 16:2667–2675
145. Kameswaran V, Barton JM (1992) Process for the manufacture of pesticidal 1-(alkoxymethyl) pyrrole compounds by alkoxymethylation of pyrroles with alkoxides and dihalomethanes. Patent EP 0491136
146. Doehner RF, Barton JM (1994) N-alkoxymethylation of pyrroles with dialkoxymethanes, Vilsmeier reagent, and a tertiary amine. US Patent 5,359,090
147. Hynes JJ, Doubleday WW, Dyckman AJ, Godfrey JD, Grosso JA, Kiau S, Leftheris K (2004) N-amination of pyrrole and indole heterocycles with monochloramine (NH2Cl). J Org Chem 69:1368–1371
148. Haketa Y, Sakamoto S, Chigusa K, Maeda H, Nakanishi T (2011) Synthesis, crystal structures, and supramolecular assemblies of pyrrole-based anion receptors bearing modified pyrrole β-substituents. J Org Chem 76:5177–5184
149. Kameswaran V (1992) Synthesis of 2-aryl-5-(trifluoromethyl)pyrroles, useful as pesticides and their intermediates, from enamines and halo ketones. Patent EP 0491137
150. Anzenbacher P, Try AC, Miyaji H, Jursicova K, Lynch VM, Marquez M, Sessler J (2000) Fluorinated calix[4]pyrrole and dipyrrolylquinoxaline. Neutral anion receptors with augmented affinities and enhanced selectivities. J Am Chem Soc 2000(122):10268–10272

151. Maeda H, Ito Y, Kusunose Y, Nakanishi T (2007) Dipyrrolylpyrazoles: anion receptors in protonated form and efficient building blocks for organized structures. Chem Comm 1136–1138
152. (a) Sessler JL, Anzenbacher P, Shriver JA, Jursikova K, Lynch VM, Marquez M (2000) Direct synthesis of expanded fluorinated calix[n]pyrroles: decafluorocalix[5]pyrrole and hexadecafluorocalix[8]pyrrole. J Am Chem Soc 122:12061–12062. (b) Moyer BA, Sloop FV Jr, Fowler CJ, Haverlock TJ, Kang H-A, Delmau LH, Bau DM, Hossain MdA, Bowman-James K, Shriver JA, Bill NL, Gross DE, Marquez M, Lynch VM, Sessler JL (2010) Enhanced liquid-liquid anion exchange using macrocyclic anion receptors: effect of receptor structure on sulphate-nitrate exchange selectivity. Supramol Chem 22:653–671
153. (a) Biffinger JC, Sun H, Nelson AP, DiMagno SG (2003) Differential substituent effects of β-halogens in water-soluble porphyrins. Org Biomol Chem 1:733–736. (b) Leroy J, Bondon A, Toupet L, Rolando C (1997) 2,3,7,8,12,13,17,18-Octafluoro-5,10,15,20-tetraphenylporphyrin: first synthesis and X-ray crystal structure of the Zn(II) complex. Chem-AEurJ3:1890–1893.(c)WollerEK,DiMagnoSG(1997)2,3,7,8,12,13,17,18-Octafluoro-5,10,15,20-tetraarylporphyrins and their zinc complexes: first spectroscopic, electrochemical, and structural characterization of a perfluorinated tetraarylmetalloporphyrin. J Org Chem 62:1588–1593. (d) Leroy J, Bondon A, Toupet L (1999) 2,3,7,8,12,13,17,18-Octafluoro-5,10,15,20-tetrakis(pentafluorophenyl)porphyrin. Acta Cryst Sect C: Cryst Struct Comm 55:464–466
154. (a) Steene E, Dey A, Ghosh A (2003) β-Octafluorocorroles. J Am Chem Soc 125:16300–16309. (b) Liu H-Y, Lai T-S, Yeung L-L, Chang CK (2003) First synthesis of perfluorinated corrole and its Mn=O complex. Org Lett 5:617–620
155. Homma M, Aoyagi K, Aoyama Y, Ogoshi H (1983) Electron deficient porphyrins. 1. Tetrakis(trifluoromethyl)porphyrin and its metal complexes. Tetrahedron Lett 24:4343–4346
156. Ogoshi H, Homa M, Aoyama Y, Aoyagi K (1984) Electron-deficient porphyrins 1. Perfluoroalkylporphyrins. Heterocycles 21:384
157. (a) Suzuki A, Toi H, Aoyama Y, Ogoshi H (1992) Synthesis of 1-fluoro-1-demethylmesoporphyrin-IX. Heterocycles 33:87–90. (b) Suzuki A, Tomizawa T, Hayashi T, Mizutani T, Ogoshi H (1996) Synthesis of ringfluorinated porphyrins and reconstituted myoglobins with their iron complexes. Bull Chem Soc Jap 69:2923–2933
158. Uno H, Inoue K, Inoue T, Fumoto Y, Ono N (2001) Preparation of α-free pyrroles with perfluorinated groups at β-positions. Synthesis 2255–2258
159. First isolation: Kobayashi J, Ohizumi Y, Nakamura H, Hirata Y (1986) A novel antagonist of serotonergic receptors, hymenidin, isolated from the Okinawan marine sponge Hymeniacidon sp. Experientia 42:1176–1177
160. Walter H (2001) Pyrrolecarboxyamides for the use as fungicides. Patent WO 02/064562
161. Zuniga AC (2004) Synthesis of 5-benzoyl-6-trifluoromethyl-1,2-dihydro-3H-pyrrolo[1,2-a] pyrrole-1-carboxylic acid. Heterocycles 63:2071–2077

Chemistry of Fluorinated Indoles

Vasiliy M. Muzalevskiy, Olga V. Serdyuk, and Valentine G. Nenajdenko

Contents

Abstract The chapter is devoted to the synthesis and application of indoles as well as some their azaanalogues bearing fluorine atoms, trifluoromethyl groups, and perfluorinated aryl fragments.

V.M. Muzalevskiy (✉) • V.G. Nenajdenko
Department of Chemistry, Moscow State University,
Leninskie Gory, Moscow 119992, Russian Federation
e-mail: muzvas@mail.ru

O.V. Serdyuk
Department of Chemistry and Pharmacy, University of Erlangen-Nuremberg,
Henkestrasse 42, 91054 Erlangen, Germany

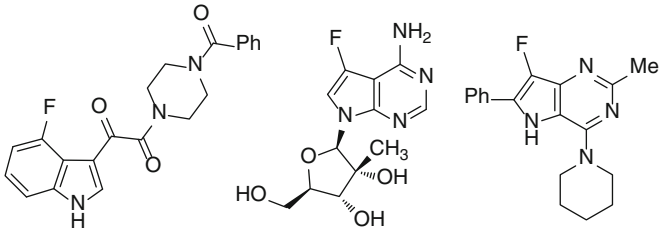
Department of Chemistry, Southern Federal University,
Zorge 7, Rostov-on-Don 344090, Russian Federation
e-mail: oserduke@mail.ru

V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_3,

Keywords Indole • Fluorine • Trifluoromethyl group • Synthesis • Fluorinated heterocycles

1 Introduction

Indoles represent very important subunits of many natural products and pharmacologically active compounds [1]. Fluorinated indole derivatives are inhibitors of HIV-1 [2], CB2 cannabinoid receptor ligands found in the central nervous system [3], and factor Xa preventing thrombus [4]. Some fluorinated azaindoles, for example, fluorinated pyrrolopyrimidines are inhibitors of hepatitis C virus (HCV) RNA replication [5] and Y5 antagonists which are potential antiobesity agents [6]. Herein, we highlighted methods for the synthesis and application of fluoroindoles, trifluromethylpyrroles and some their azaanalogues.

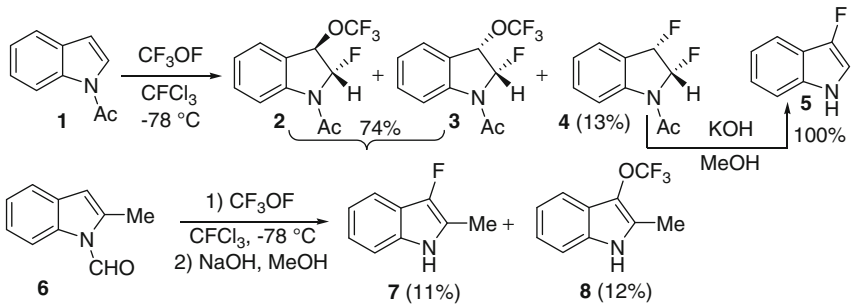


Inhibitor of HIV-1 | Inhibitor of Hepatitis C Virus RNA Replication | Y5 antagonist

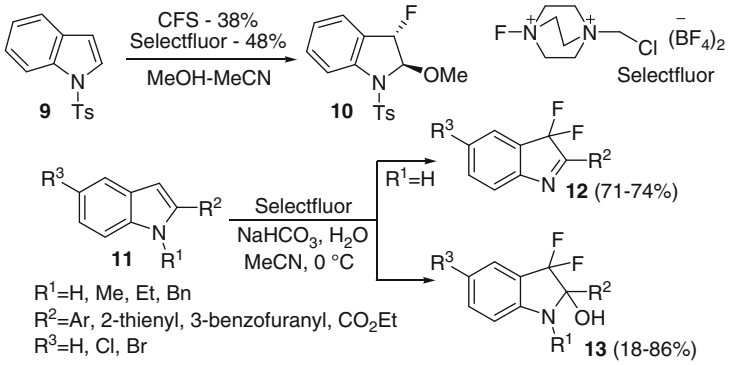
2 Synthesis of Fluoroindoles and Deazapurines

2.1 Functionalization of the Pyrrole Ring

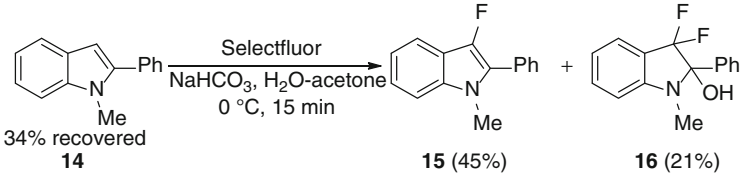
Several reagents were used for the electrophilic fluorination of indole. The first one used for this aim was trifluoromethyl hypofluorite (CF_3OF). Treatment of *N*-acylindole **1** with trifluoromethyl hypofluorite in CF_3Cl at −78 °C afforded a mixture of 2-fluoro-3-trifluoromethoxy- and 2,3-difluoroindoline derivatives **2**–**4** in high combined yield. Subsequent treatment of difluoride **4** with potassium hydroxide in methanol afforded quantitatively 3-fluoroindole **5**. Similarly, starting from 1-formyl-2-methylindole reaction with trifluoromethyl hypofluorite resulted in formation of 2-methyl-3-fluoroindole **7** in low yield in mixture with 2-methyl-3-trifluormethoxyindole **8** [7].



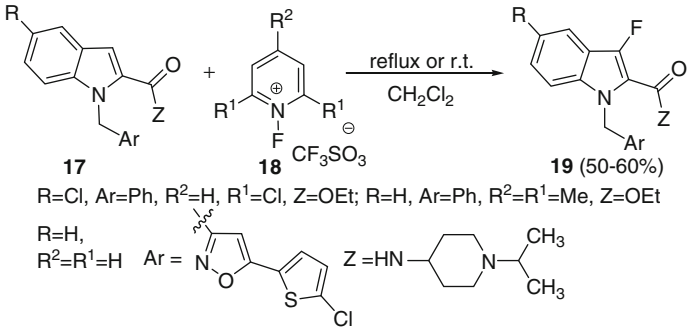
Fluorination of indoles **9** and **11** using cesium fluoroxysulfate ($CsOSO_3F$, CFS) or Selectfluor led to the corresponding 3-fluoroindolines, which are the products of conjugate addition of fluorine and methanol or water. Thus, fluorinated methoxyindolines **10**, and 3-*H*-indoles **12** or hydroxyindolines **13** were obtained in methanolic or aqueous acetonitrile respectively [8a, b].



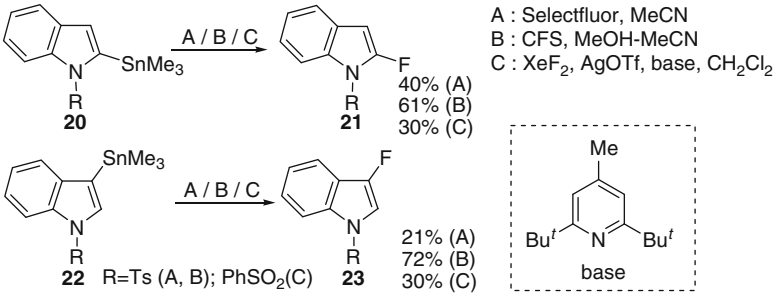
3-Fluoroindole **15** can be also prepared using Selectfluor. When acetonitrile was replaced by acetone and reaction was stopped before the starting *N*-methyl indole **14** was totally consumed, 3-fluoroindole derivative **15** was isolated in 45 % yield together with difluorohydroxyindoline derivative **16**. This experiment led to claim that 3-fluoroindole derivative **15** was a reaction intermediate, subsequent fluorination resulted in the formation of difluoroindolines **12** and **13** [8b].



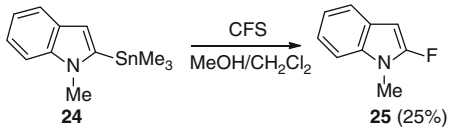
N-Fluoropyridinium triflates **18** are another useful type of fluorinating reagents applied for the preparation of fluorinated indoles. Using these reagents a series of 2-(3-fluoroindolyl)carboxylic acid derivatives **19** was prepared in good yields by treatment of indole-2-carboxylates or carboxamides **17** in dichloromethane [4, 9].



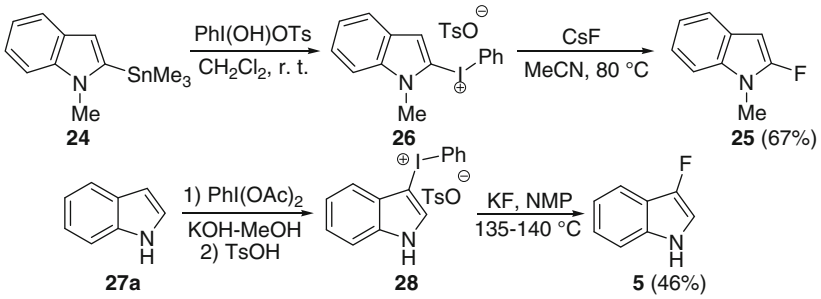
The problem of regioselective installation of fluorine into pyrrole ring of indole was resolved using tin substituted indoles as starting materials. Both 2- and 3-trimethylstannyl-1-(arylsulfonyl)indoles **20** and **22** can be used for fluorination with cesium fluoroxysulfate to afford 2-fluoro and 3-fluoroderivatives in 61 % and 72 % yields correspondingly. Using Selectfluor and xenon difluoride gave fluoroindoles in moderate yields. In addition, reaction of 2-trimethylstannylindole **20** with xenon difluoride afforded admixture of regioisomeric 3-fluoroindole **23** [8, 10].



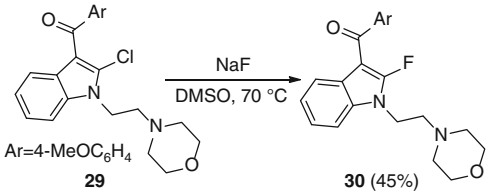
Analogous transformation with cesium fluoroxysulfate in the case of more electron rich 1-methyl-2-(trimethylstannyl)-1*H*-indole **24** leads to 2-fluoro-1-methyl-1*H*-indole **25** in lower yield [8c].



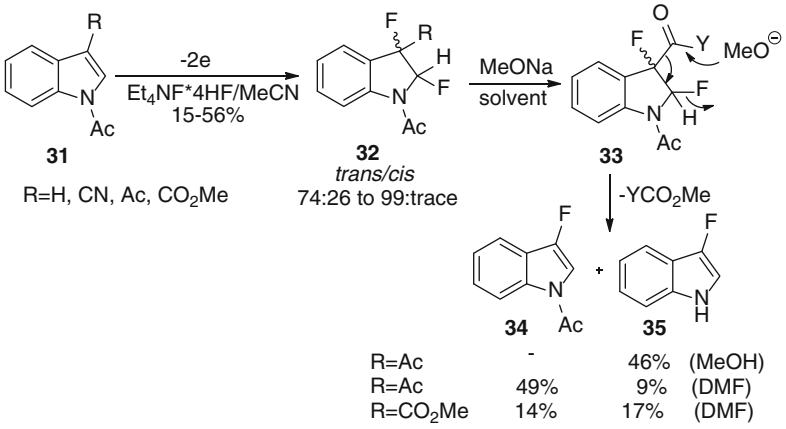
A nucleophilic fluorination approach towards fluoroindoles was also elaborated. Using nucleophilic substitution of phenyliodonium group by fluoride under heating, 2-fluoroindole **25** and 3-fluoroindole **5** were prepared in good yields. The intermediate phenyl(indolyl)iodonium salts **26** and **28** were easily synthesized by treatment of (2-indolyl)trialkylstannane **24** [11] or indole **27a** [12] with the corresponding polyvalent iodine compounds.



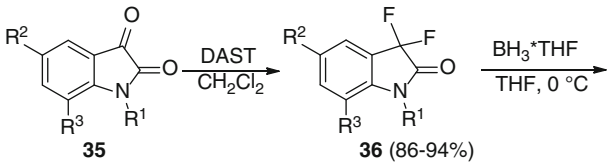
Similarly, 2-fluoroindole **30** derivative was obtained in 45 % yield by nucleophilic substitution of chloride in the 2-chloroindole **29** under heating with sodium fluoride in dimethyl sulfoxide [13]. The nucleophilic substitution proceeds in quite mild conditions for **29** due to the presence of activating nucleophilic substitution keto group in β-position of the indole.



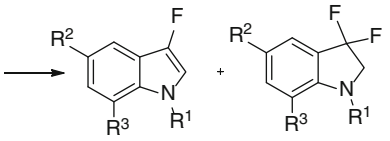
An electrosynthesis of fluorinated indole derivatives was carried out by Fuchigami and co-workers. Anodic fluorination of various *N*-acetyl-3-substituted indole derivatives **31** was performed in acetonitrile to give a mixture of *trans*- and *cis*-2,3-difluoro-2,3-dihydroindoles **32**, which afforded 3-fluoroindoles **35** and **34** after treatment with sodium methoxide [14].



An efficient pathway towards 3-fluoroindoles was proposed starting from isatines **35**. Fluorinated 2-indolinones **36** were obtained in high yields by treatment of isatine derivatives **35** with diethylaminosulfur trifluoride in dichloromethane. In case of electron-donating substituents reduction of **36** with tetrahydrofuran-borane complex led smoothly to 3-fluoroindoles **37** in high yields.



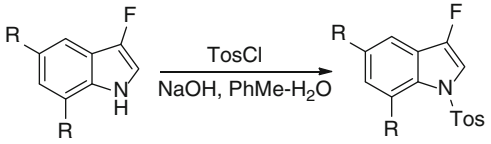
35 **36** (86-94%)



37 **38**

	37 : 38	
R^1=R^2=R^3=H	76%	-
R^1=R^3=H, R^2=Me	70%	-
R^1=Bn, R^2=R^3=H	86%	-
R^1=Me, R^2=R^3=H	90%	-
R^1=H, R^2=NO_2, R^3=H	6%	85%
R^1=H, R^2=R^3=Br	9%	79%

The corresponding difluoroindolines **38** were mostly isolated in case of indoles with electron-withdrawing groups. It was mentioned, that 3-fluoroindoles **5** and **37a** are quite unstable; the much more stable *N*-tosyl derivatives **23** and **39** can be prepared by treatment of **5** and **37a** with tosyl chloride under basic catalysis [15].

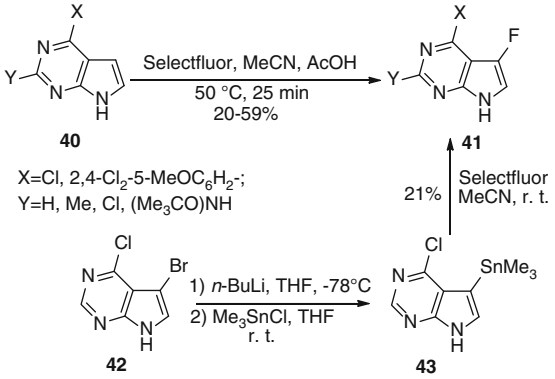


5 R=H
37a R=Me

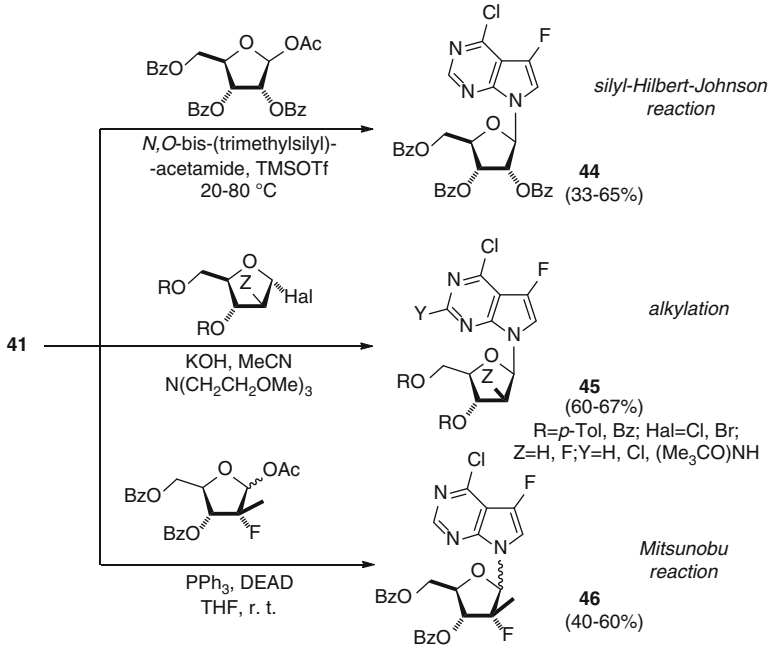
23 (61%)
39 (54%)

7-Deazapurines (pyrrolo[2,3-*d*]pyrimidines) are shape mimics of the parent purines. Hence, one might expect the corresponding ribonucleosides can replace naturally occurring RNA-constituents as substrates or inhibitors. As a result, further modifications of the pyrrolo[2,3-*d*]pyrimidine moiety may provide novel pharmacologically active compounds against human immunodeficiency virus [16]. A great effort was devoted to investigations of 7-fluorinated 7-deazapurines. The fluorination of various 7*H*-pyrrolo[2,3-*d*]pyrimidines **40** with Selectfluor gave selectively 7-fluorinated 7-deazapurines **41** in moderate yields [17]. Alternatively, 7-fluorinated 7-deazapurines **41** were prepared by lithiation of 5-bromo-4-chloro-1*H*-pyrrolo[2,3-*d*]pyrimidine **42**, followed by subsequent treatment of the resulting intermediate with trimethylstannane chloride to give

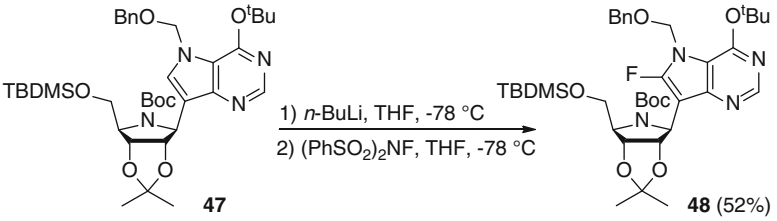
5-trimethylstannane **43**, which affords target 5-fluoroderivative **41** in 21 % yield after the reaction with Selectfluor [5].



The second step of new nucleoside preparation was the modification at the pyrrole nitrogen, using standard techniques of nucleoside synthesis such as the silyl-Hilbert-Johnson (or Vorbrüggen) reaction [17a, c, 18], alkylation under basic conditions [17d, 19] or Mitsunobu reaction [17f, 20]. By means of methods mentioned, a series of nucleosides **44**–**46** was prepared in moderate to good yields.

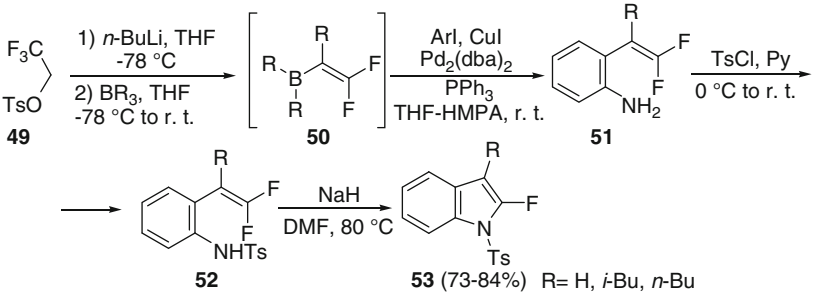


In the case of β-substituted pyrrolo[3,2-*d*]pyrimidines, the fluorine atom can be inserted into the molecule via metallation to α-position to pyrrole ring followed by fluorination. Thus, compound **47** reacted with *n*-butyllithium and *N*-fluorobenzenesulfonimide to produce fluoro derivative **48** in 52 % yield [21].



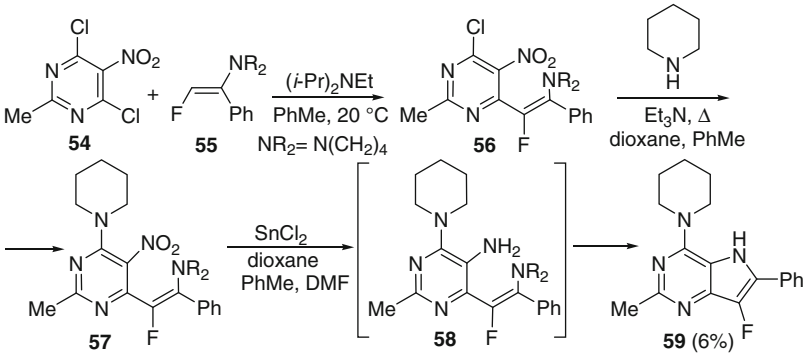
2.2 *Heterocyclization*

β,β-Difluorostyrenes **52** bearing a tosylamido group at the *ortho*-position underwent intramolecular nucleophilic substitution of the fluorine atom *via* a 5-*endo* trigonal process leading to 2-fluorinated indoles **53** [22, 23]. The cyclization is promoted by base, for example sodium hydride. The starting β,β-difluorostyrenes **52** were obtained accordingly to scheme below. Firstly, coupling of 2,2-difluorovinylboranes **50**, generated *in situ* from 2,2,2-trifluoroethyl toluene-*p*-sulfonate **49**, with *N*-butylmagnesio-*o*-iodoaniline were performed in the presence of copper(I) iodide and a palladium catalyst to give alkene **51**. Next, alkene **51** was converted into **52** by the reaction with TsCl.



Another intramolecular cyclization of amine **58** is the last step in the pyrrolo[3,2-*d*]pyrimidine analogue **59** synthesis. Intermediate **58** formed *in situ* from nitro precursor **57** by reduction with tin(II) chloride is a key step of this version of Leimgruber–Batcho synthesis leading to formation of **59** finally. This simple three-step route to **59** started from the coupling of electron-poor dichloronitropyrimidine **54** with β-fluoroenamine **55** to form alkene **56**. Regioselective nucleophilic

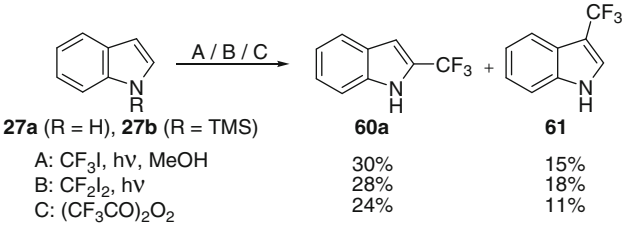
substitution of chlorine with piperidine led to nitro precursor **57**, which transforms into target pyrrolo[3,2-*d*]pyrimidine **59** by reduction in 6 % overall yield [5].



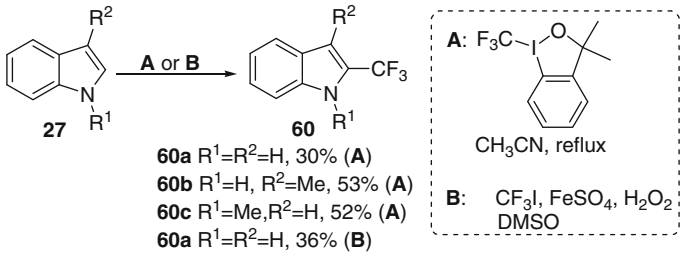
3 Synthesis of Trifluoromethylindoles

3.1 Direct Trifluoromethylation

Radical trifluoromethylation of *N*-trimethylsilylindole **27b** with trifluoroiodomethane proceeded nonselectively into both 2- and 3-positions, with a preference for the 2-trifluoromethylindole formation [24]. Quench of the reaction mixture with methanol afforded the 2- and 3-trifluoromethylndoles **60a** and **61** in 2/1 ratio. Similarly, the trifluoromethylation using difluorodiiodomethane [25] and bis(perfluoroalkanoyl) peroxide [26] led to a mixture of the same products. In all cases, the overall yield of isomeric indoles was moderate.

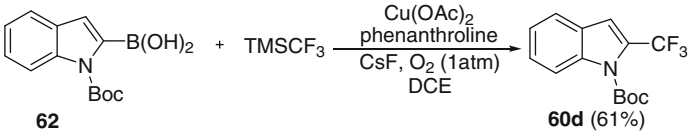


Perfect selectivity was achieved then hypervalent iodine reagent **A** [27] was used for electrophilic trifluoromethylation of indoles. Radical trifluoromethylation using CF_3I-$FeSO_4$-H_2O_2-DMSO system **B** [28] provided also excellent regioselectivity. However, yields of 2-trifluoromethylindoles **60a–c** in both cases were moderate to good.

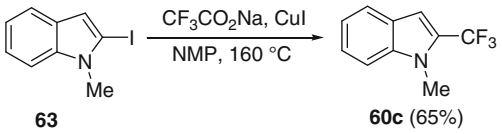


60a R^1=R^2=H, 30% (**A**)
60b R^1=H, R^2=Me, 53% (**A**)
60c R^1=Me,R^2=H, 52% (**A**)
60a R^1=R^2=H, 36% (**B**)

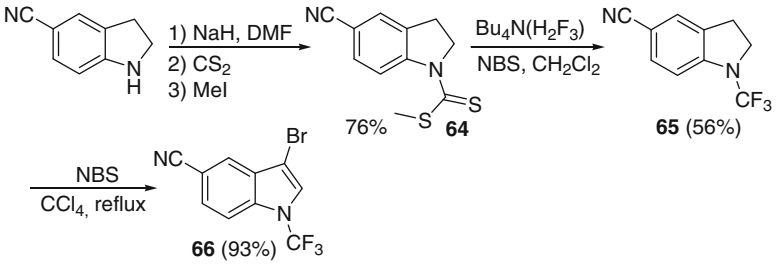
Another selective approach to 2-trifluoromethylindole is copper-mediated oxidative cross-coupling of 2-indolylboronic acid with $TMSCF_3$. Reaction proceeds in mild conditions to give *N*-Boc-2-trifluoromethylindole **60d** in 61 % yield [29].



The nucleophilic trifluoromethylation, which is based on the heating of *N*-methyl-2-iodoindole **63** with 10 equivalents of sodium trifluoroacetate and an equimolar amount of copper(I) iodide in *N*-methylpyrrolidinone, afforded *N*-methyl-2-trifluoromethylindole **60c** in 65 % yield [30].



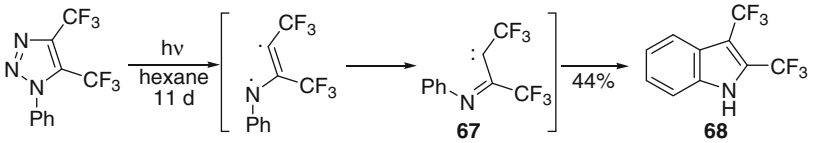
Formal *N*-trifluoromethylation of indole was performed in several steps, starting from indoline. At first step 3-cyanoindoline was treated with NaH, followed by CS_2 and then MeI to form thioderivative **64**. The latter was treated with tetrabutylammonium dihydrogen trifluoride, followed by NBS, to give *N*-CF_3-indoline **65**. Aromatization of **65** was carried out by reaction with NBS in CCl_4 at reflux, leading to *N*-trifluoromethyl-3-bromoindole **66** [31].



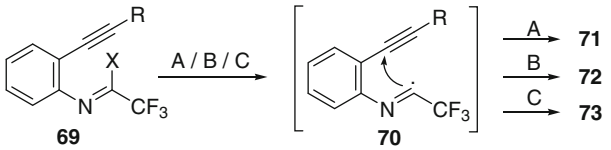
3.2 *Heterocyclizations*

3.2.1 Formation of the C3-C4 Bond

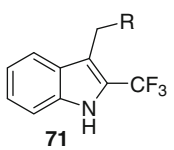
Kobayashi et al. elaborated an unusual pathway for the synthesis of 2,3-bis(trifluoromethyl)indoles [32]. Photolysis of the 1-phenyl-4,5-bis(trifluoromethyl)-1*H*-1,2,3-triazole in hexane proceeded very slowly to afford the indole **68** in 44 % yield. It was proposed, that after homolytic nitrogen extrusion, the carbene **67** was formed. Intramolecular cyclization led to the indole **68**.



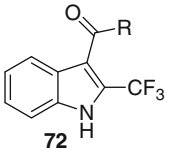
Radical, photochemical and thermolytic generation of *N*-aryltrifluoroacetimidoyl radicals followed by intramolecular cyclization was successfully used to synthesize 2-trifluoromethylindoles [33]. The radical approach was based on treatment of imidoyl iodides **69a** with tributyltin hydride in the presence of 2,2′-azabis(isobutyronitrile) (AIBN). The second method for the generation of *N*-aryltrifluoroacetimidoyl radicals **70** was based on the homolytic cleavage of carbon-iodine or carbon-tellurium bond in imidoyl iodides **69a** and tellurides **69b** under irradiation [34]. The third method involved the thermal homolysis of aza compounds **69c**. All of these methods provided the indoles **71**, **72** and **73**, respectively, in high yields [33, 34].



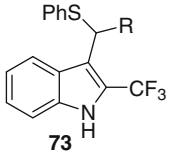
A: (**69a**) X = I; *n*-Bu_3SnH, AIBN, benzene, 80 °C
B: (**69b**) X = I or TePh; THF-H_2O, hν
C: (**69c**) X = N=N-CPh_3; PhSH, toluene, 100 °C



R	
n-Bu	69%
Ph	61%

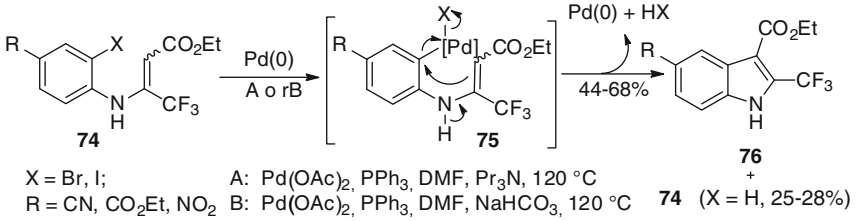


R	Y = I	Y = Te
n-Bu	53%	68%
Ph	68%	67%
$PhCH_2O$	55%	54%

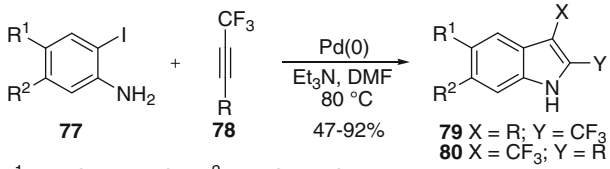


R	
n-Bu	72%
Ph	77%

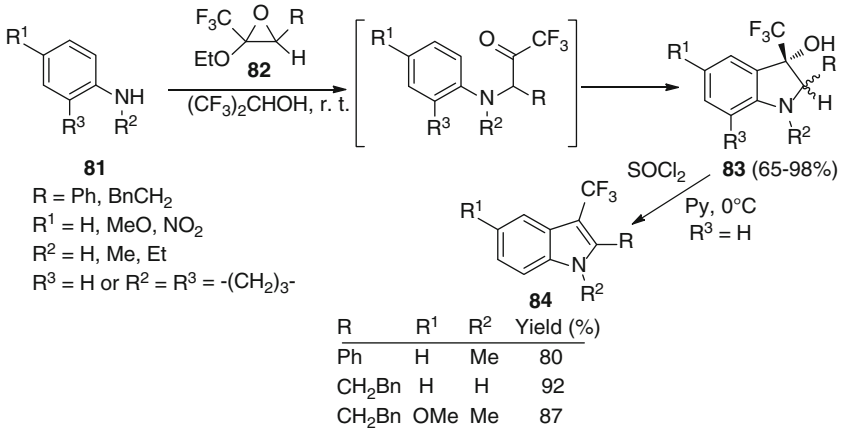
The intramolecular Heck reaction of bromo- or iodoaryl enamines **74** is another versatile key step for the synthesis of indoles. Zero-valent palladium catalysis afforded a mixture of indoles **76** and reduced enamines **74** (X=H) via intermediate formation of **75** depending on the base used [35].



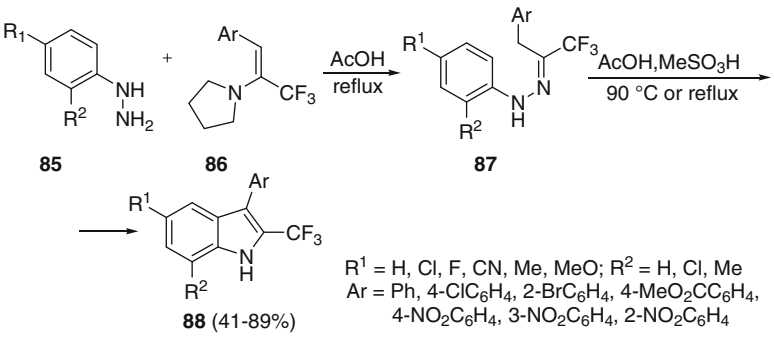
A variation of the intramolecular Heck coupling towards indoles bearing trifluoromethyl and aryl groups in the 2- and 3-positions was described by Chae and co-workers. First the C2-N bond was built, followed by ring closure that forms the C3-C4 bond. Accordingly, the palladium catalyzed addition of the trifluoromethyl(aryl) acetylenes **78** to the *ortho*-iodoanilines **77** afforded a mixture of the indoles **79** and **80** in high overall yield. Depending on the catalyst [20 mol% $Pd(PPh)_3$ or 10 mol% $Pd_2(dba)_3 \cdot CHCl_3$, $P(o\text{-Tol})_3$], one isomeric indole of either **79** or **80** was formed predominantly [36].



Another versatile approach towards 3-trifluoromethylated indoles was elaborated by Rodrigues et al. Anilines **81** reacted with epoxy ethers **82** (prepared by epoxydation of the corresponding vinyl ethers) in hexafluoropropan-2-ol to form mixtures of diastereomeric indolines **83** in high yields. The ratio of the diastereomers varied between 96:4 and 79:21. These diastereomers can be separated easily by column chromatography. The reaction was general and allowed effective preparation of indolines with both electron-donating and electron-withdrawing substituents. Compounds with fused rings were also prepared by this method. Treatment of the major *trans*-diastereomer of **83** with thionyl chloride in pyridine afforded the 3-trifluoromethylindoles **84** in high yields [37].



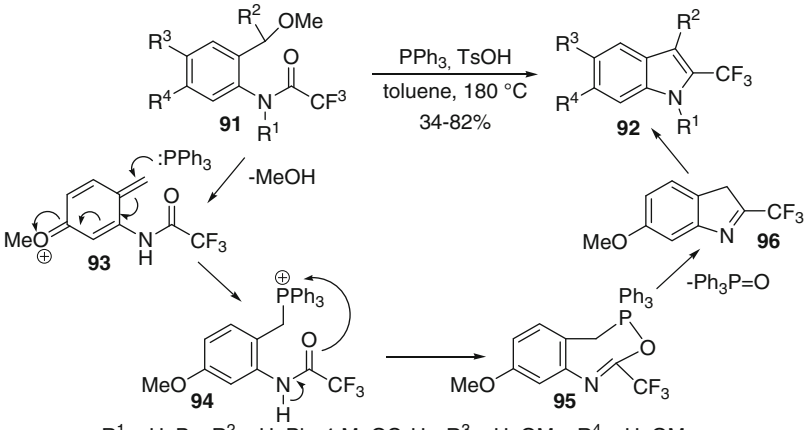
3-Aryl-2-trifluoromethylindoles **88** were prepared regioselectively using trifluoromethyl-2-arylenamines as synthetic equivalents of trifluoromethylated carbonyl compounds in the Fischer indole synthesis. Accordingly, arylhydrazines **85** reacted smoothly with enamines **86** in acetic acid to give the α-trifluoromethylhydrazones **87**. Fischer rearrangement of these hydrazones was performed in refluxing acetic acid the presence of methanesulfonic acid. As a result, a number of 3-aryl-2-trifluoromethylindoles were prepared in moderate to high yields [38]. This approach is first successful example of Fisher rearrangement for trifluoromethylated derivatives.



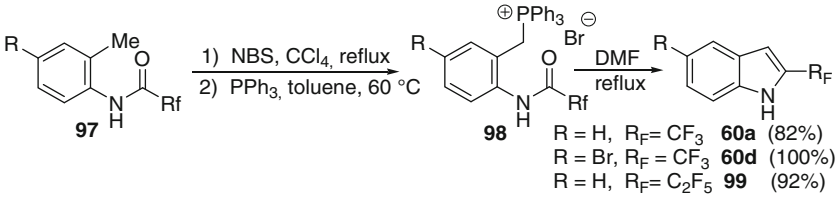
3.2.2 Formation of the C2-C3 Bond

Indole **90** was synthesized by a modified Madelung reaction from the amide **89** by treatment with potassium *tert*-butoxide. The presence of two strong electron-withdrawing groups (CN and CF_3) in **89** facilitated both the deprotonation to the benzyl anion and its intramolecular cyclization under very mild conditions. Formation of **90** was completed in 10 min at room temperature in 81 % yield [39].

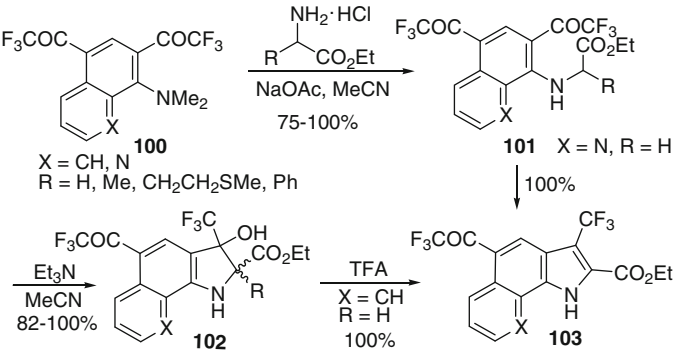
Miyashita and co-workers developed a novel 2-trifluoromethylindole synthesis based on thermolysis of 2-(*N*-acylamino)benzylmethyl ethers **91** in the presence of triphenylphosphine. However, this method has several disadvantages. The presence of a MeO-group in 5-position or 4-methoxyphenyl group at the benzyl carbon atom is necessary for the formation of **92**, otherwise the yields tend to zero. An explanation invokes the necessity of resonance stabilization of the intermediate oxonium ion **93**, which gives the key phosphonium salt **94** after attack by PPh_3. Subsequent intramolecular Wittig reaction leads to **95** which affords the 3-*H*-indole **96**. Isomerization of the latter leads to the target indole **92**. Another significant disadvantage of the method is the four-steps synthetic sequence to reach the starting 2-(*N*-acylamino)benzyl methylethers **91** [40].



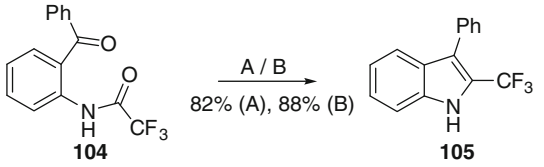
These disadvantages could be overcome by use of the phosphonium salts **98**, which are prepared in two steps from amides **97**. Bromination of **97** with NBS followed by reaction with triphenylphosphine permits to prepare **98** effectively. 2-Perfluoroalkylindoles **60a,d** and **99** were obtained in high yields using this method [40, 41].



Okada and co-workers investigated the reactions of the quinoline and naphthalene bis(trifluoroacetyl) derivatives **100** with amino acid esters in acetonitrile [42]. Two $COCF_3$ groups facilitate extremely nucleophilic substitution in **100** to make dimethylamino group good enough nucleophuge in this case. In the presence of equimolar amounts of sodium acetate (neutral media) the dimethylamino group was substituted with the amino acid ester moiety forming **101**. Subsequent treatment with triethylamine resulted in cyclization of **101** into the condensed dihydropyrrole derivatives **102** as mixtures of diastereomers. Quinoline **101** (X=N) was not isolated, but spontaneously cyclized to give 1*H*-pyrrolo[3,2-*h*]quinoline **102** (X=N). In contrast, naphthalene **101** (X=CH) in basic media was stable enough to be isolated. Treatment of **102** (X=CH) with trifluoroacetic acid gave the 1*H*-benzo[*g*]indole **103** quantitatively.

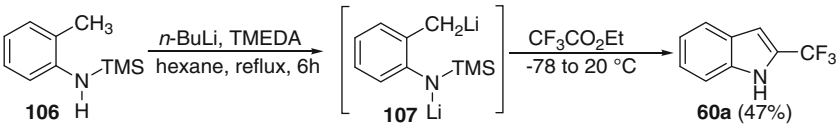


Fürstner and co-workers used the McMurry reaction for the synthesis of 2-trifluoromethyl-3-phenylindole **105** from ketonamide **104**. The reaction was performed either with two equivalents or substoichiometric amounts of titanium(III) chloride. In the latter case, large excesses of trimethylsilyl chloride and zinc were necessary [43].

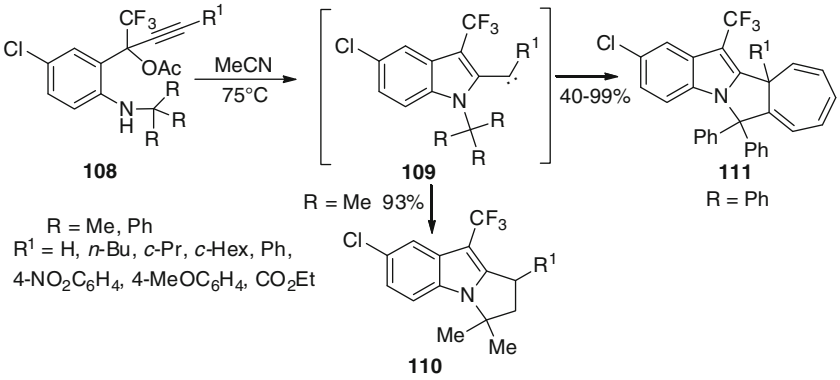


A: 2 equiv. $TiCl_3$, 4 equiv. Zn, THF, reflux
B: 10 mol% $TiCl_3$, 5 equiv. Zn, 5 equiv. TMSCl, MeCN, reflux

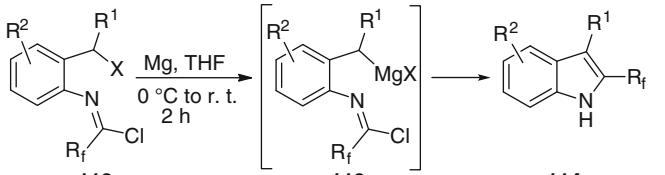
Refluxing of *N*-trimethylsilyltoluidine **106** with *n*-butyllithium in hexane in the presence of TMEDA afforded the dianion **107**, which on treatment with ethyl trifluoroacetate at −78 °C gave 2-trifluoromethylindole **60a** in 47 % yield [30].



An interesting rearrangement was found by Frey et al. Heating the amino alcohol *O*-acetate **108** (R=Me) in acetonitrile led to the tricyclic indole derivative **110**, while the trityl derivative **108** (R=Ph) afforded the dihydrocyclohepta[3,4]pyrrolo[1,2-*a*]indoles **111** in high yields. The authors suggested the carbene **109** as a key reaction intermediate, though the reaction mechanism is still a matter of discussion [44].

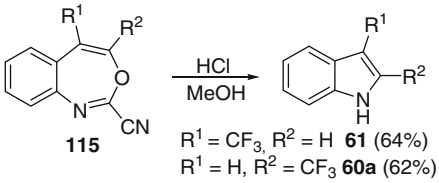


A convenient pathway to 2-fluoroalkyl-substituted indoles **114** was elaborated using the fluorinated *N*-[2-(haloalkyl)aryl]imidoyl chlorides **112** as key intermediates [45]. Treatment of the latter compounds with magnesium in tetrahydrofuran gave the Grignard compounds **113**, which afforded the indoles **114** in high yields by intramolecular cyclization initiated by attack of the nucleophile on imidoyl fragment.

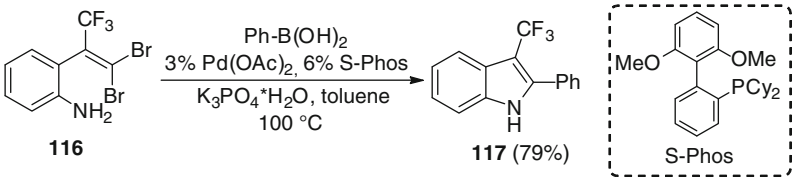


3.2.3 Formation of the C2-N Bond

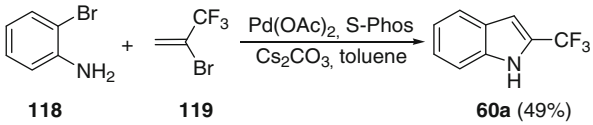
A regioselective pathway to 2- and 3-trifluoromethylindoles based on the ring-opening reaction of compounds **115** was developed by Attanasi and co-workers. After treatment of **115** with HCl in methanol, the corresponding indoles **60a** and **60a** were obtained in good yields. The starting compounds **115** were prepared from trifluoroquinolines in three steps [46].



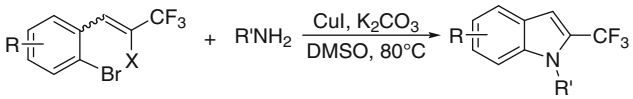
The synthesis of 3-trifluoromethyl-2-phenylindole **117** was accomplished by succeeding palladium catalyzed carbon–carbon cross-coupling of **116** with phenylboronic acid and carbon–nitrogen coupling in the presence of S-Phos [47].



Under similar conditions, 2-trifluoromethylindole **60a** was prepared starting from 2-bromoaniline **118** and 2-bromo-3,3,3-trifluoroprop-1-ene **119** using palladium catalysis [48].



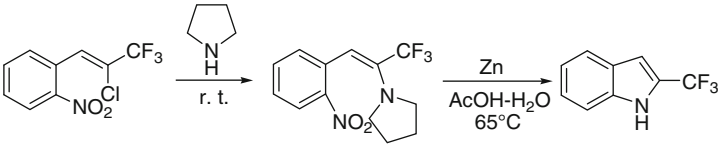
An efficient one-pot synthesis of substituted 2-trifluoromethylindoles was elaborated using copper(I)-catalyzed nucleophilic substitution of vinyl or aryl halogen atoms in styrenes **120** by primary amines. The resulting 2-trifluoromethylindoles **121** were prepared in moderate to good yields. The simplicity of the synthetic procedure and readily available starting materials are significant advantages of this method [49].



120 **121** (39-74%)

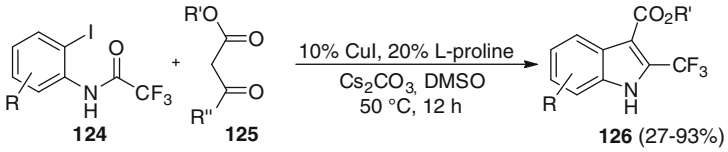
X = Cl, Br; R = H, 5-MeO, 5-EtO, 5,6,7-tri(MeO)
R' = *n*-Hex, *i*-Pr, Et, $Ph(CH_2)_2$, $MeO(CH_2)_2$, $MeO(CH_2)_3$, $3,4\text{-}EtO_2C_6H_3(CH_2)_2$, $3,4\text{-}MeO_2C_6H_3(CH_2)_2$

Another synthetic sequence for the preparation of 2-trifluoromehylindole **60a** was developed. In the first step, the styrene **122** was converted into the enamine **123** in quantitative yield. Subsequent treatment of this enamine with zinc dust under the standard conditions of the Leimgruber-Batcho indole synthesis led to 2-trifluoromethylindole, also in almost quantitative yield. Moreover, a one-pot methodology without isolation of enamine was also applied. In that case, an overall 90 % yield was obtained [50].



122 **123** (98%) **60a** (93%)

A convenient method for the synthesis of 2-trifluoro-methyl-1*H*-indole-3-carboxylic acid esters **126** was elaborated using a cascade coupling, condensation and deacylation sequence. Starting from aryl trifluoacetamides **124** and ketoesters **125**, the corresponding indoles **126** were prepared in good to excellent yields, using a catalytic system of copper(I) iodide and L-proline [51].



124 **125** **126** (27-93%)

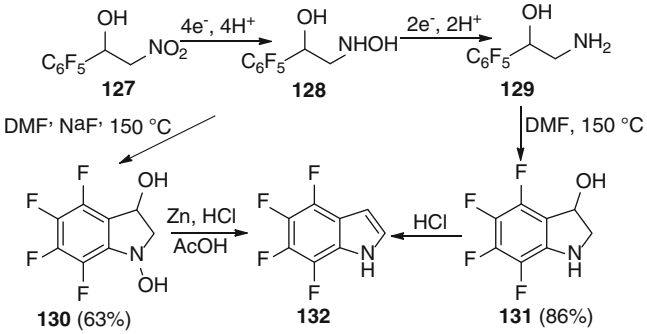
R = NO_2, Ac, Cl, Me, CO_2Me, I, MeO, CH_2CH_2OH
R' = Me, Et, Bn, *t*-Bu, *c*-Hex, allyl
R'' = Me, Ph, *i*-Pr

In conclusion, the synthesis of trifluoromethylated indoles is more difficult and less studied compared to synthesis of indoles bearing C-F bonds, therefore new effective strategies are very desirable to make these compounds to be more accessible building blocks for drug discovery.

4 Synthesis of Indoles with Fluorine Atoms in Carbocycle

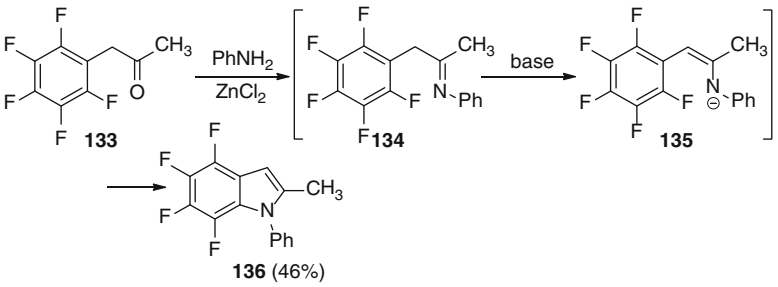
The influence of the fluorine atom on the nature of indole system is lower when fluorine is located on the benzene ring. However, there is significant specificity for indoles having fully fluorinated benzene ring. This part of the chapter is focused on 4,5,6,7-tetrafluoroindole and derivatives.

A common approach to the 4,5,6,7-tetrafluoroindoles is based on the various heterocyclizations starting from pentafluorophenyl precursors. Thus, heating of 1-pentafluorophenyl-2-amino-ethanol **129** in dimethylformamide gives 4,5,6,7-tetrafluoroindole **132** in good yield. The reaction proceeds via intramolecular nucleophilic substitution of the *o*-fluorine atom, followed by dehydration [52].

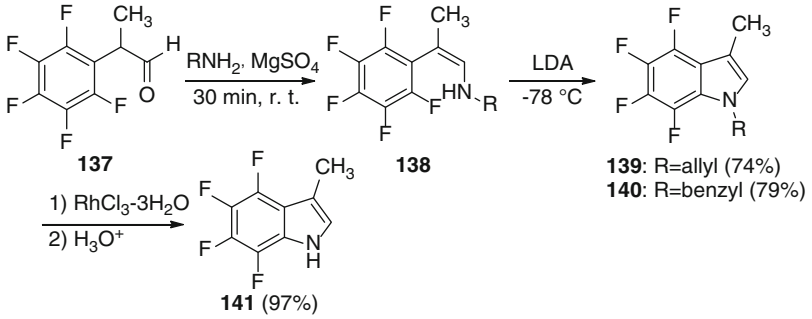


Another possible route for the nucleophilic substitution of the *ortho*-fluorine atom includes intramolecular attack by the hydroxy group of 2-(hydroxyamino)-1-(pentafluorophenyl)ethanol **128**. Heating of compound **128** in *N,N*-dimethylformamide in the presence of sodium fluoride led to cyclizations at the nitrogen to give 1,3-dihydroxy-4,5,6,7-tetrafluoro-indoline **130**. The latter was readily reduced by zinc in acidic media into 4,5,6,7-tetrafluoroindole **132**. The starting amino alcohols **128** and **129** were obtained by the potential-controlled electrochemical reduction of the nitroalcohol **127**, which can be prepared directly from pentafluorobenzaldehyde and nitromethane.

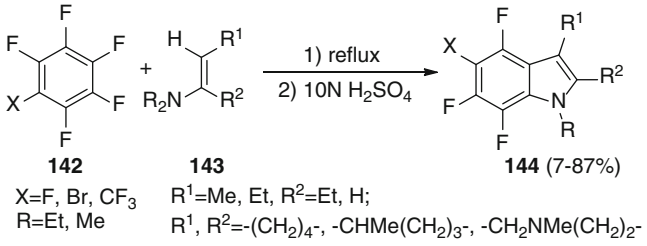
Alternative method for the synthesis of tetrafluoroindole was described in 1968. Ketone **133** was heated under reflux with aniline in the presence of anhydrous zinc chloride in order to prepare the Schiff base **134**. However, the only product isolated was *N*-phenyl-4,5,6,7-tetrafluoro-2-methylindole **136** (<10 %). The yield of **136** was increased up to 47 % by the addition of aniline hydrobromide to the reaction mixture. Thus, the improved synthesis of indole **136** includes heating of the ketone **133**, aniline hydrobromide, anhydrous zinc chloride and aniline under reflux for 2 h [53].



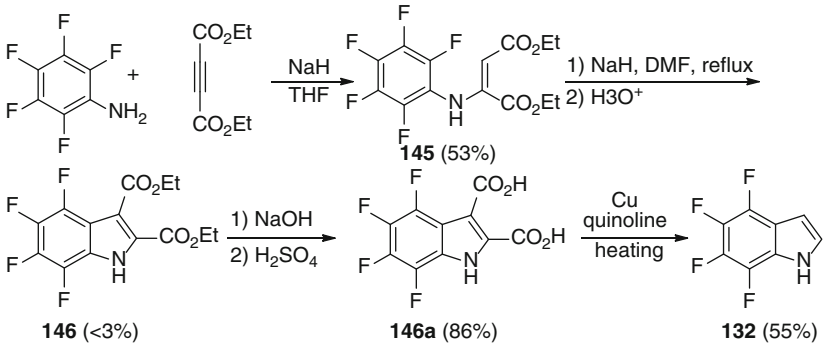
A similar approach was realized by other authors starting from aldehyde **137**. The reaction of the latter one with amines, followed by cyclization of intermediate **138** using lithium diisopropylamide as a base leads to tetrafluoroindole core. Finally, deprotection of **139** or **140** by a rhodium catalyst gave 3-methyl-4,5,6,7-tetrafluoroindole **141**. Overall yield of **141** starting from **138** was 72 % [54].



Intramolecular nucleophilic substitution of fluorine led to the formation of the pyrrole ring in the above mentioned transformations. However, the C-arylation can precede the heterocyclization. For example, condensation of cyclic enamines **143** with perfluorobenzenes **142** gave fluorinated indoles **144** via formation of C-N and C-C bonds. The authors reported that initial C-arylation was in competition with an initial *N*-arylation producing *N*-dialkylaminopoly-fluoroarenes. The "C *versus* N" arylation ratio was found to be dependent upon the nature of the enamine [55].

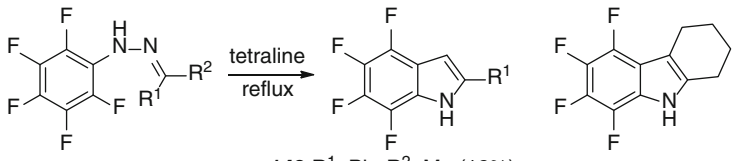


Similar cyclizations based on *N*-arylation are also known. For instance, when pentafluorophenyl substituted aminofumarate **145** (prepared from pentafluoroaniline and diethyl acetylenedicarboxylate) was treated with sodium hydride in dimethylformamide under reflux the indole derivative **146** was isolated. However, the yield of the target indole was very low [56]. Subsequent hydrolysis and decarboxylation provided tetrafluoroindole **132** in 55 % yield.



145 (53%) **146** (<3%) **146a** (86%) **132** (55%)

An unusual formation of indoles via a formal Fischer cyclization of *N*-pentafluorophenyl hydrazones **147** was discovered by Brooke. Generally, the Fischer reaction demands the *ortho*-position be unoccupied. However, in refluxing tetraline, hydrazones **147** were transformed into polyfluoroindoles accompanying with the loss of one *ortho*-fluorine. Hydrazones of acetophenone and cyclohexanone afforded the corresponding indoles **148** and **149** in 12 and 18 % yields respectively. In case of acetaldehyde hydrazone, only a minor amount of parent tetrafluoroindole **132** were isolated. The mechanism of the reaction has not be clarified [57].



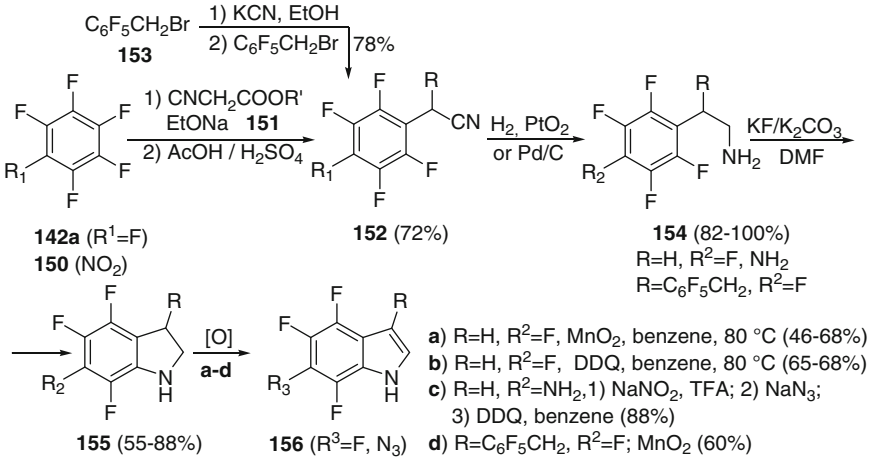
147

148 R^1=Ph, R^2=Me (12%)
132 R^1=H, R^2=Me (1.5%)

149 (18%)

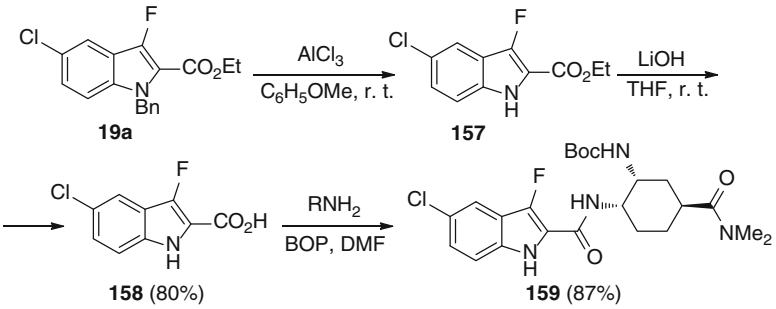
An efficient approach to polyfluoroindole was elaborated starting from hexafluorobenzene **142a** [58] and pentafluoronitrobenzene **150** [59]. In the first step, perfluoroarylacetonitriles **152** were obtained by nucleophilic substitution of fluorine with cyanoacetate **151** followed by acid catalyzed decarboxylation. Alternatively, nitrile **152** could be prepared from pentafluorobenzyl bromide **153** by treatment with potassium cyanide. Next, nitriles **152** were reduced into β-polyfluoroarylethyl amine **154**, which underwent facile cyclizations into fluorinated indolines **155**. The

latter were smoothly aromatized into the corresponding indoles **156** by treatment with manganese (IV) oxide or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

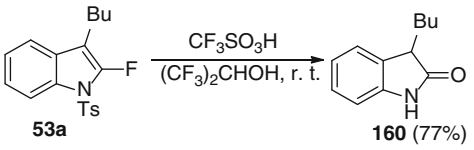


5 Properties

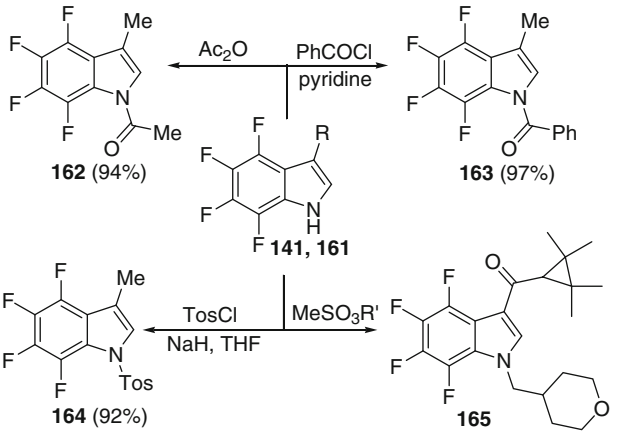
Fluorinated indoles reveal very similar properties in comparison to their non-fluorinated analogues. However, it should be noted that the chemistry of monofluorinated indoles (with fluorine atom attached to both 2 and 3 position) is scarcely studied. For example, 3-fluoroindole derivative **19a** was debenzylated to give indole carboxylic acid ester **157** quantitatively; the latter one was converted into amide **159** by hydrolysis followed by reaction with the corresponding amine in the presence of BOP reagent [9a]. Nitrogen atom in case of 3-fluorosubstituted indole derivatives has usual nucleophilicity and can participate in standard indole reactions, for example reaction with tosyl chloride provided *N*-sulfonylation product in 61 % yield [15].



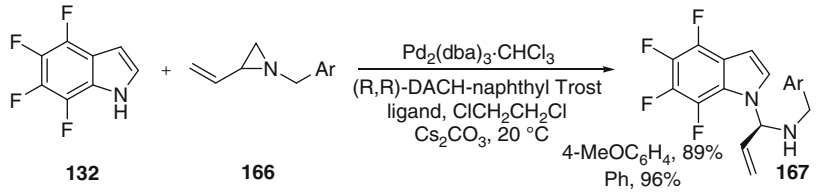
One more example of monofluoroindoles reactivity is hydrolysis of indole derivative **53a** into oxindole **160**, which was achieved under treatment with trifluoromethanesulfonic acid in hexafluoroisopropanol [60].



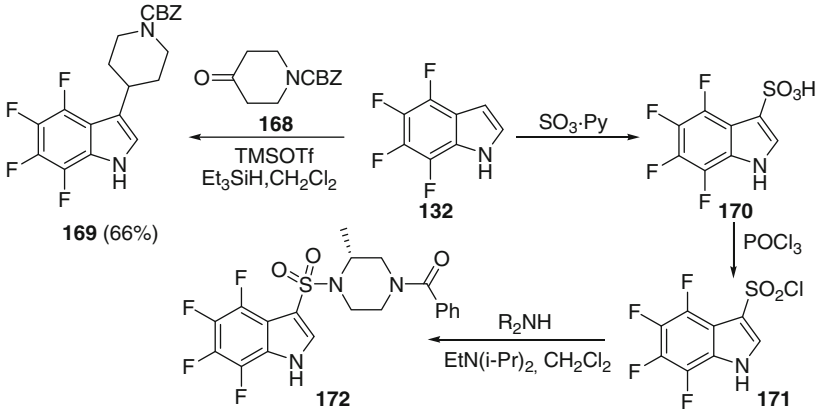
4,5,6,7-Tetrafluoroindoles were also shown to exhibit typical reactivity of indole. N-Substituted 4,5,6,7-tetrafluoroindole derivatives were obtained easily by the reaction of the parent indole with various electrophiles under basic conditions. Reaction of indoles **141** and **161** with acetic anhydride, benzoyl chloride, tosyl chloride and methanesulfonic acid ester afforded the corresponding N-substituted derivatives **162**–**165** in high yields [3, 54b].



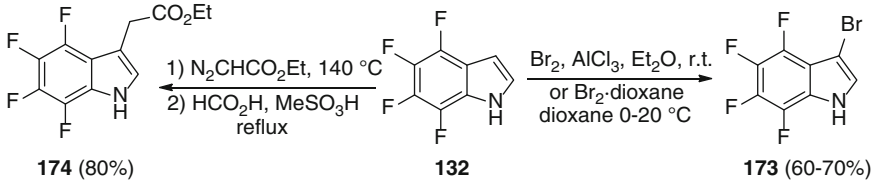
Alternative approach to 4,5,6,7-tetrafluoroindole nitrogen modification was proposed by Trost et al. Reaction of 4,5,6,7-tetrafluoroindole **132** with vinyl azyridines **166** under $Pd_2(dba)_3$ catalysis proceeded with ring-opening to give, stereoselectively, allyl amine derivatives **167** in high yields [61].



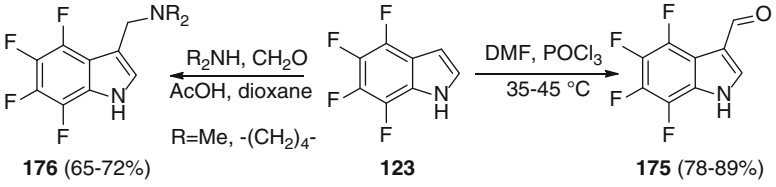
In spite of electron withdrawing action of four fluorine atoms, 4,5,6, 7-tetrafluoroindole **132** reacts with electrophiles under quite mild conditions to give products of substitution at the 3-position. For example, reaction of **132** with *N*-(carbobenzyloxy)piperidin-4-one **168** in the presence of trimethylsilyl triflate and triethylsilane afforded the corresponding piperidine derivative **169** [62]. Using sulfur trioxide-pyridine complex indolyl sulfonic acid **170** was obtained, which was further converted into sulfonyl amide **172** by reaction with phosphorus(V) oxychloride, followed by treatment with derivative of piperazine [2a].



Bromination was carried out using bromine in presence of catalytic amount of aluminum chloride or bromine-dioxane complex at 0–20 °C to form 3-bromoderivative **173** in high yield [63]. Electrophilic carbenoid species, generated at elevated temperature, reacted with polyfluoroindole to form indolyl carboxylic esters **174** after treatment with formic acid [58c].

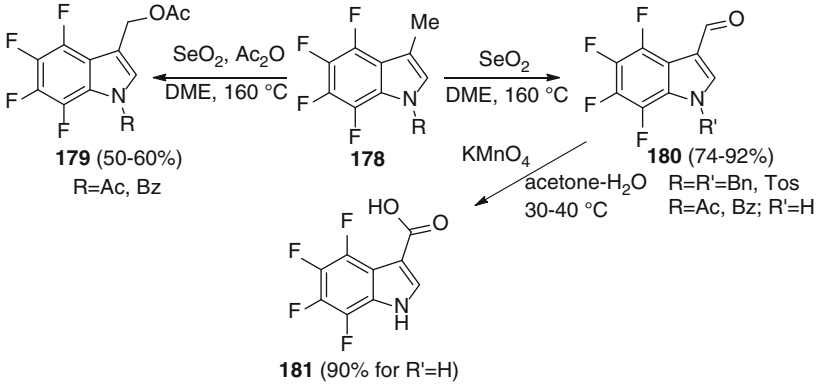


Fluorinated 3-indolyl carbaldehyde **175** was obtained in yields up to 89 % by Vilsmeier-Haack reaction [58c, 63]. Aminomethylation afforded the corresponding fluorinated gramine derivatives **176** in good yields [58c, 63].

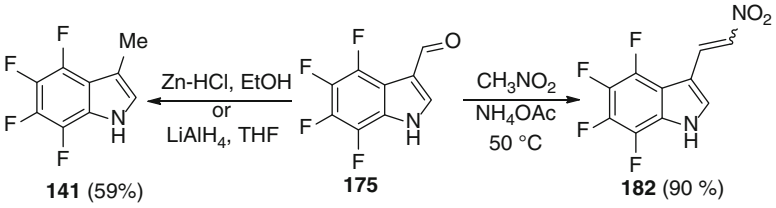


Reaction of chloroacetonitrile with 4,5,6,7-indolyl magnesium bromide, obtained by treatment of tetrafluoroindole with ethylmagnesium bromide, proceeded regioselectively at 3-position to afford the corresponding nitrile **177** in moderate yield [58c].

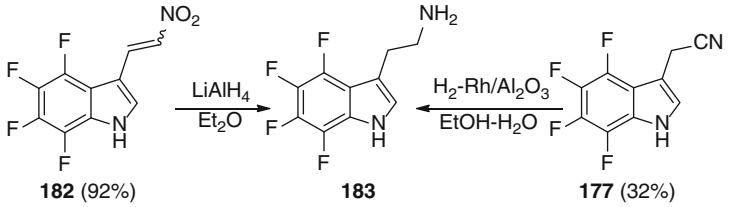
Oxidation of 3-methyltetrafluoroindoles **178** by selenium dioxide in presence of acetic anhydride can be stopped at the alcohol oxidation level step to give acetates **179**. Fluorinated 3-indolylcarbaldehydes **180** were isolated in high yields when the oxidation was performed without addition of acetic anhydride [54]. Further oxidation of aldehyde was achieved by treatment with potassium permanganate to afford 3-indolylcarboxylic acid **181** in high yield [58c].



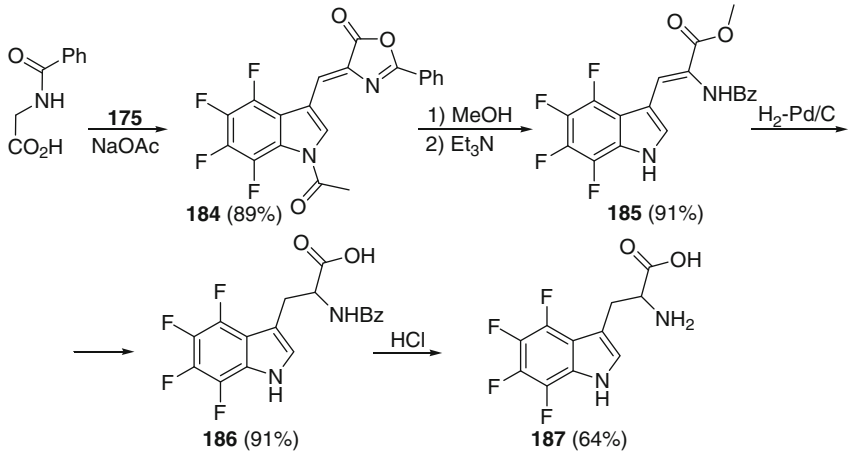
Reduction of the aldehyde **175** with lithium aluminum hydride [63] or zinc in hydrochloric acid [58c] gave fluorinated 3-methylindole **141** in good yield.



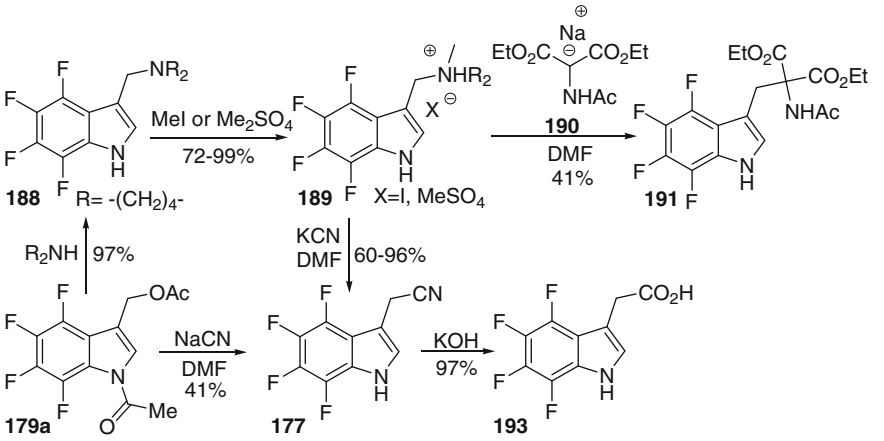
Fluorinated tryptamine **183** was prepared by Rh-catalyzed reduction of the corresponding nitrile **177** by hydrogen [58c]. Alternatively, the compound **183** was synthesized by lithium aluminum hydride reduction of nitroalkene **182**, which was obtained by condensation of aldehyde **175** with nitromethane [54].



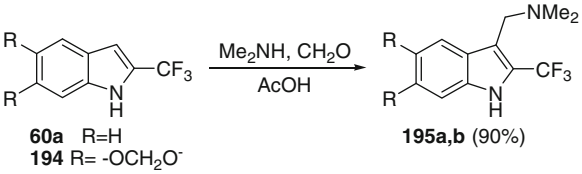
Through a similar reaction sequence, fluorinated tryptophan **187** was synthesized. Condensation of aldehyde **175** with *N*-benzoyl glycine afforded oxazolone **184**, which was converted into unsaturated acid **185**. Reduction of **185** by hydrogen and subsequent acid-catalyzed hydrolysis gave fluorinated tryptophan **187** in good total yield [54].



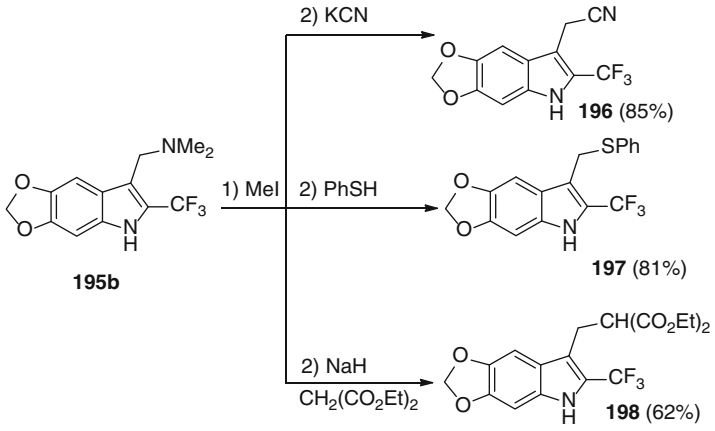
Fluorinated gramine analogue **188** was easily *N*-alkylated by reaction with methyliodide [58c] or dimethylsulfate [54, 63]. The tertiary amine salt **189** and the acetoxy derivative **179a** are suitable substrates for various nucleophilic substitutions. For instance, treatment of **189** or **179a** with potassium cyanide or sodium cyanide afforded the corresponding nitrile **177** [54, 58c] which was hydrolyzed into fluorinated indolyl acetic acid **19**3 [54]. Reaction of acetoxy compound **179a** with secondary amines led to gramine **188**. The corresponding tryptophan derivative **191** was obtained using the sodium salt of diethyl aminomalonate as a nucleophile [58c].



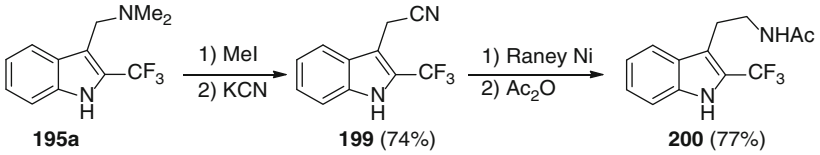
Trifluoromethylindoles undergo similar transformations in comparison to their non-fluorinated analogues as well. Thus, electrophilic substitution at the C-3 position takes place when the C-2 position is occupied by the trifluoromethyl group. The Mannich reaction provided dimethylaminomethyl derivatives in good yields under standard conditions [64].



Quaternization of the compounds **195b** with methyl iodide and subsequent reactions with nucleophiles, e.g. potassium cyanide, thiophenol, and diethyl malonate, gave corresponding products **196**–**198** in 62–85 % yields [64].

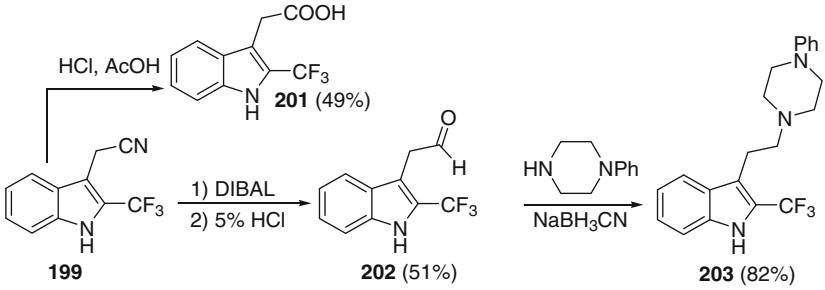


Reduction of the nitrile group of the compound **199** and subsequent reaction with acetic anhydride led to 2-trifluoromethyltryptamine **200** [64]. For the reduction, Raney Ni was used, since hydrides, for example, lithium aluminium hydride, can reduce the trifluoromethyl group as well.



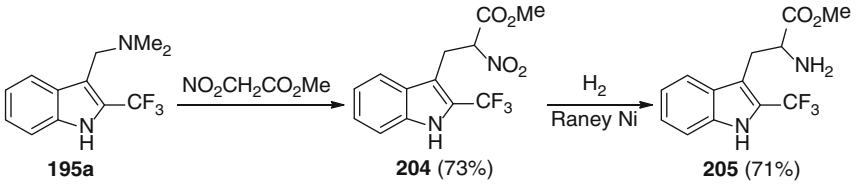
195a **199** (74%) **200** (77%)

Hydrolysis of the nitrile **199** gave 2-trifluoromethylindole-3-acetic acid **201** in moderate yield [60]. A partial reduction of the nitrile group in **199** provided indole-3-acetaldehyde **202** in 51 % yield. The latter was used for the synthesis of the 2-trifluoromethylated analogue of oxypertine (an antipsychotic used in the treatment of schizophrenia) **203** upon treatment with *N*-phenylpiperazine and sodium cyanoborohydride [64].



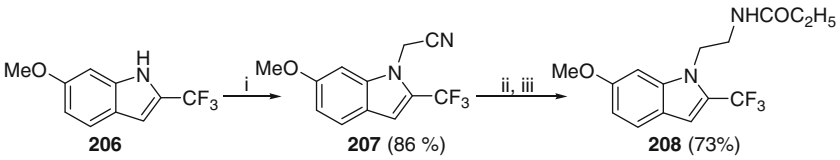
201 (49%) **199** **202** (51%) **203** (82%)

2-Trifluoromethyltryptophan methyl ester **205** was synthesized from nitro derivative **204** obtained via direct reaction of **195a** with methylnitroacetate. Chemoselective reduction of the nitro group was achieved by hydrogenation in the presence of Raney Ni in methanol [60].



195a **204** (73%) **205** (71%)

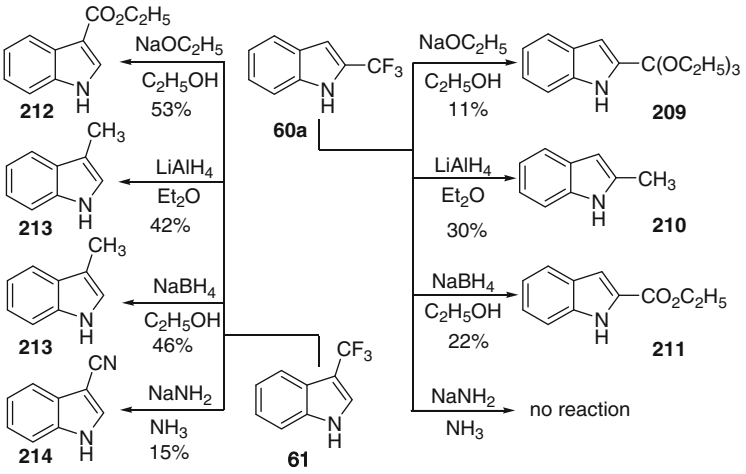
N-Alkylation of indole **206** was achieved by treatment with NaH in DMF, followed by reaction with chloroacetonitrile [65]. Subsequent catalytic reduction of **207** with hydrogen under Raney-Ni followed by reaction with ethylcarbonate led to compound **208**, which was investigated as melatonin receptor ligand.



206 **207** (86 %) **208** (73%)

(i) NaH, $ClCH_2CN$, DMF, 16h; (ii) Re-Ni, H_2, 4 atm; (iii) $(EtCO)_2O$, THF, 50 °C, 6h.

Attanasi et al. investigated reactions of both 2-and 3-trifluoromethylindole involving trifluoromethyl group and leading to loss of fluorine. Treatment of trifluoromethylindoles with $LiAlH_4$ gave methylindoles **210** and **213**.

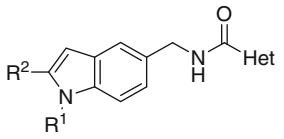


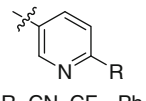
Reaction of 2-trifluoromethylindole with sodium ethoxide led to *ortho*-ether **209**, while ethyl 3-indolylcarboxilate **212** was isolated in case 3-trifluoromethylindole. Reaction of 2-trifluoromethylindole with $NaBH_4$ in ethanol led to ethyl 2-indolylcarboxilate **211**. In contrast, reduction of trifluoromethyl group was observed to form 3-methylindole **213** in case of 3-isomer. Treatment of 3-trifluoromethylindol with sodium amide in liquid ammonia led to 3-cyanoindole **214**, whereas 2-trifluoroindole did not reacted with sodium amide at all [46].

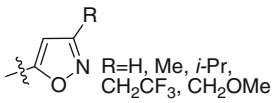
6 Pharmacological Properties of Fluorinated Indoles

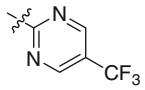
Fluorinated indoles posses a broad scope of physiological activity and they are very prominent candidates for further biological testing and using as drugs. In this part of the chapter pharmacological properties of fluorinated indoles are collected (Table 1). One can see very broad spectrum of biological activity of such structures and synergism bringing both indole fragment and fluorine in a molecule.

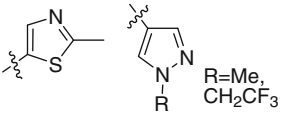
Table 1 Pharmacological properties of fluorinated indoles



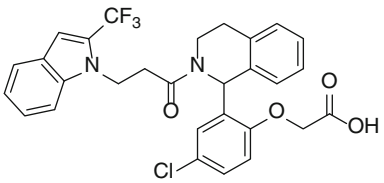




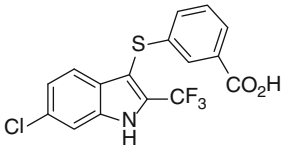




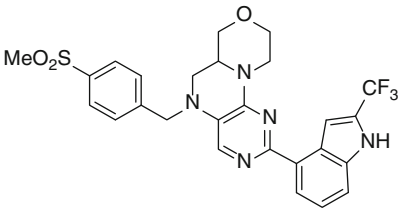
Modulators of nicotinic acetylcholine α7 receptor and KCNQ potassium channel [31]



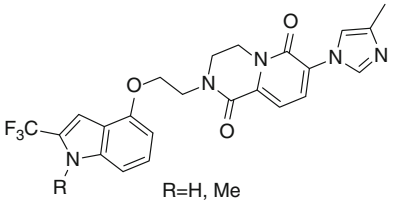
Prostaglandin D2 receptor modulators [66]



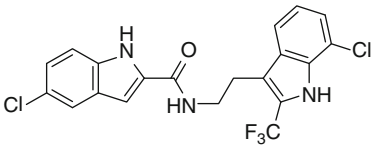
Autotoxin (ATX) inhibitors [67]



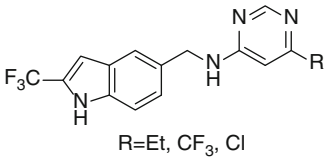
Inhibitor of PI3Kδ [68]



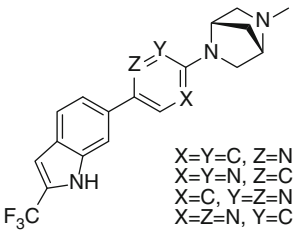
Inhibitor of amyloid beta protein Aβ(1–42) production [69]



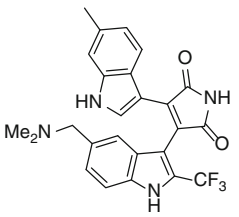
Modulator of human prostaglandin EP_2 receptor [70]



Modulator of nicotinic acetylcholine α7 receptor [71]



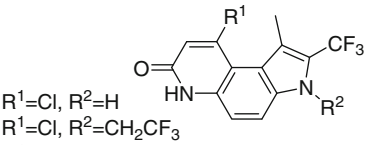
Modulator of α7 neuronal nicotinic receptors (NNRs) [72]



Inhibitor of Protein Kinase Cβ1 (PKCβ1) [73]

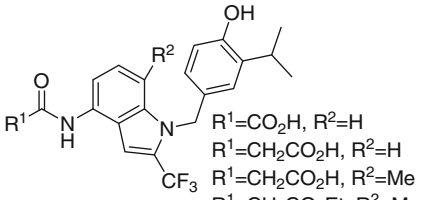
(continued)

Table 1 (continued)



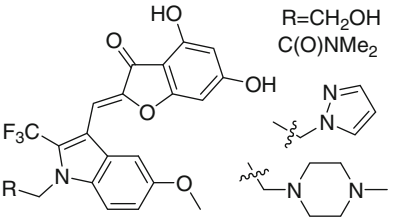
R^1=Cl, R^2=H
R^1=Cl, R^2=CH_2CF_3
R^1=Cl, R^2=$CH_2CH(OH)CF_3$
R^1=Cl, R^2=CH_2CF_3
R^1=CF_3, R^2=$CH_2CF_2CF_3$

Androgen receptor modulator [74]

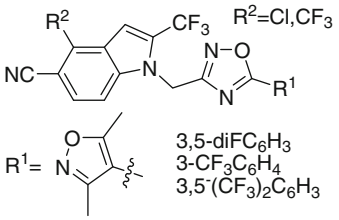


R^1=CO_2H, R^2=H
R^1=CH_2CO_2H, R^2=H
R^1=CH_2CO_2H, R^2=Me
R^1=CH_2CO_2Et, R^2=Me

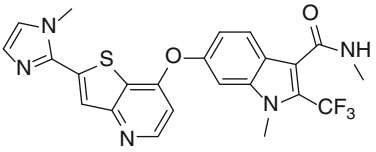
Thyroid hormone receptors (TRα and TRβ) ligand [75]



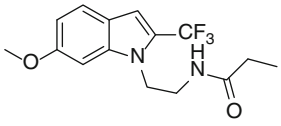
Inhibitor of phosphatidylinositol-3 kinase α (PI3Kα) [76]



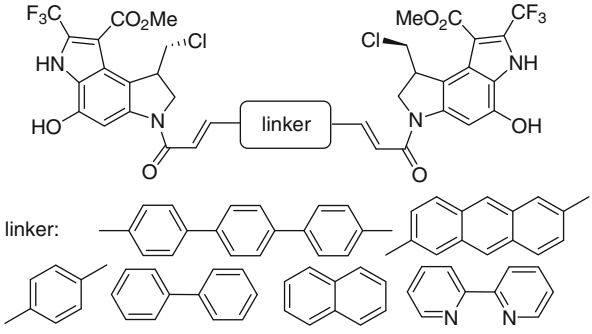
Androgen receptor (AR) agonist [77]



Inhibitor of autophosphorylation receptor [78]



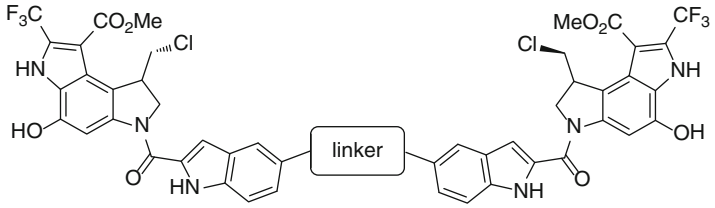
Melatonin receptor ligand [65]



Antiproliferative, antineoplastic, antitumor activity [79]

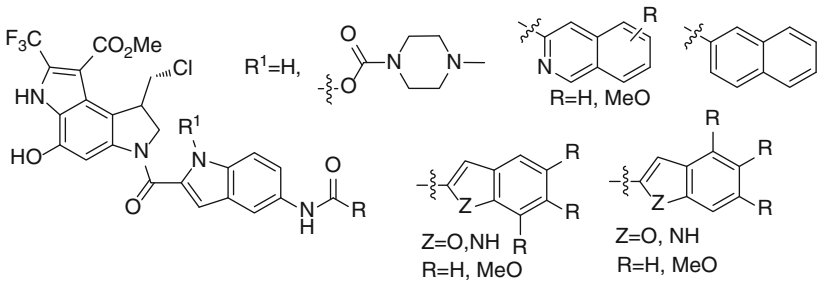
(continued)

Table 1 (continued)

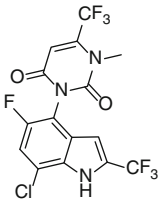


linker: CH_2, CH_2CH_2, -O-, NHC(O)NH-, single bond

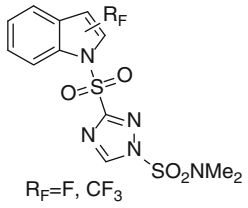
Antitumor activity [80]



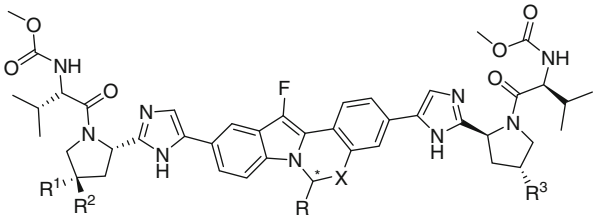
Antitumor activity [79c]



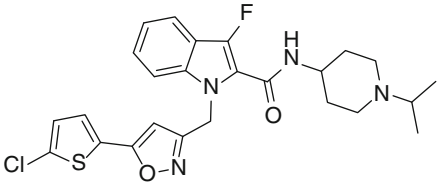
Herbicide [81]



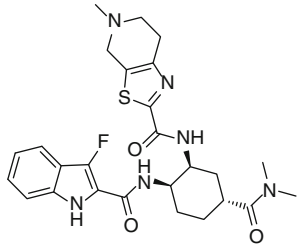
Agricultural and horticultural fungicide [82]



Antiviral against hepatitis C virus [83]



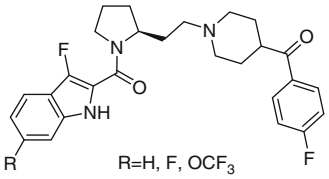
Factor Xa inhibitor [4]



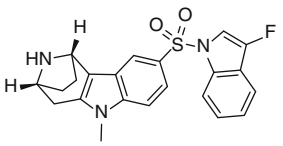
Inhibition of factor Xa, anticoagulant [84]

(continued)

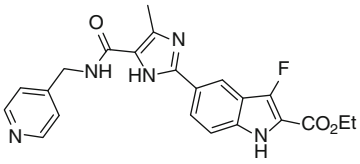
Table 1 (continued)



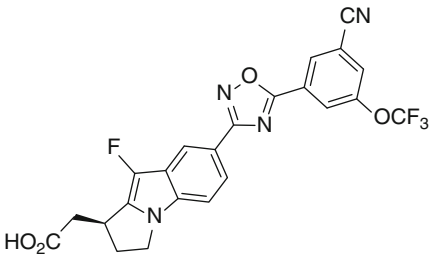
Inhibitors of dopamine D2L receptor, serotonin 5-HT2A receptor, serotonin 5-HT6 receptor, adrenaline α1D receptor [85]



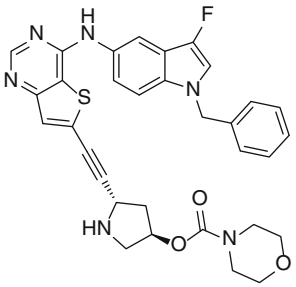
Human 5-HT6 receptor modulator [86]



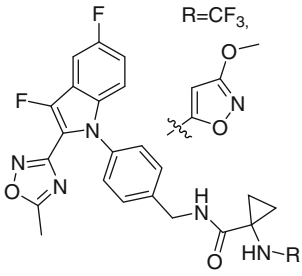
Inhibitor of matrix metalloprotease 13 (MMP13) [87]



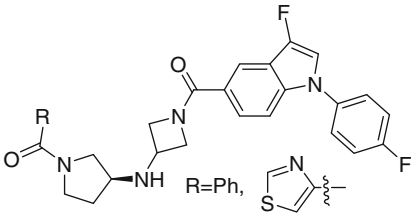
Agonist of the sphingosine-1-phosphate S1P1 receptor [88]



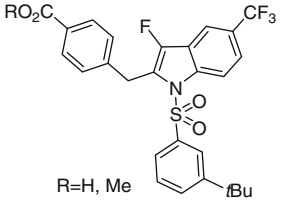
Inhibitor of EGFR and ErbB-2 kinases antiproliferative, cytotoxic for foreskin fibroblast of human [89]



Bradykinin B1 receptor antagonist [90]



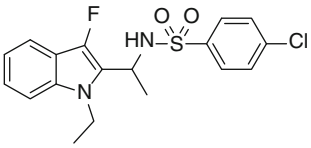
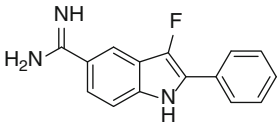
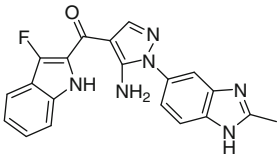
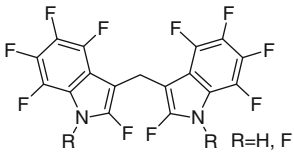
Monoacylglycerol lipase inhibitors [91]



Activators of NURR-1/RXRα and NURR-1/RXRγ heterodimers formation [92]

(continued)

Table 1 (continued)

	
Edg-1 receptor antagonist [93]	ASIC (acid-sensing ion channel) modulator [94]
	
Inhibitor of fibroblast growth factor receptor 1 (FGFR1) [95]	Antiproliferative activity, antiandrogen (R=F). Immune response activator (R=H) [96]

7 Conclusions

Recent decades, fluorinated indoles and their analogues have enjoyed remarkable attention of chemists. However, one can definitely conclude that synthesis of these compounds is still challenging and attractive task.

Acknowledgments Financial support from the Russian Foundation for Basic Research (grants no. 12-03-00292-a and 13-03-01129) are gratefully acknowledged.

References

1. (a) Fan H, Peng J, Hamann MT, Hu JF (2008) Lamellarins and related pyrrole-derived alkaloids from marine organisms. Chem Rev 108:264–287. (b) Schmuck C, Rupprecht D (2007) The synthesis of highly functionalized pyrroles: a challenge in regioselectivity and chemical reactivity. Synthesis 20:3095–3110. (c) Bellina F, Rossi R (2006) Synthesis and biological activity of pyrrole, pyrroline and pyrrolidine derivatives with two aryl groups on adjacent positions. Tetrahedron 62:7213–7211. (d) Jolicoeur B, Chapman EE, Thompson A, Lubell WD (2006) Pyrrole protection. Tetrahedron 62:11531–11563
2. (a) Lu RJ, Tucker JA, Zinevitch T, Kirichenko O, Konoplev V, Kuznetsova S, Sviridov S, Pickens J, Tandel S, Brahmachary E, Yang Y, Wang J, Freel S, Fisher S, Sullivan A, Zhou J, Stanfield-Oakley S, Greenberg M, Bolognesi D, Bray B, Koszalka B, Jeffs P, Khasanov A, Ma YA, Jeffries C, Liu C, Proskurina T, Zhu T, Chucholowski A, Li R, Sexton C (2007) Design and synthesis of human immunodeficiency virus entry inhibitors: sulfonamide as an isostere for the α-ketoamide group. J Med Chem 50:6535–6544. (b) Meanwell NA, Wallace OB, Fang H, Wang H, Deshpande M, Wang T, Yin Z, Zhang Z, Pearce BC, James J, Yeung KS, Qiu Z, Wright JJK, Yang Z, Zadjura L, Tweedie DL, Yeola S, Zhao F, Ranadive S, Robinson BA, Gong YF, Wang HGH, Blair WS, Shi PY, Colonno RJ, Lin PF (2009) Inhibitors of HIV-1 attachment. Part 2: An initial survey of indole substitution patterns. Bioorg Med Chem Lett 19:1977–1981

3. Frost JM, Dart JM, Tietje KR, Garrison TR, Grayson GK, Daza AV, El-Kouhen OF, Miller LN, Li L, Yao BB, Hsieh GC, Pai M, Zhu CZ, Chandran P, Meyer MD (2008) Indol-3-yl-tetramethylcyclopropyl ketones: effects of indole ring substitution on CB_2 cannabinoid receptor activity. J Med Chem 51:1904–1912
4. Nazaré D, Will W, Matter H, Schreuder H, Ritter K, Urmann M, Essrich M, Bauer A, Wagner M, Czech J, Lorenz M, Laux V, Wehner V (2005) Probing the subpockets of factor Xa reveals two binding modes for inhibitors based on a 2-carboxyindole scaffold: a study combining structure-activity relationship and X-ray crystallography. J Med Chem 48:4511–4525
5. Eldrup AB, Prhavc M, Brooks J, Bhat B, Prakash TP, Song Q, Bera S, Bhat N, Dande P, Cook PD, Bennett CF, Carroll SS, Ball RG, Bosserman M, Burlein C, Colwell LF, Fay JF, Flores OA, Getty K, LaFemina RL, Leone J, MacCoss M, McMasters DR, Tomassini JE, Von Langen D, Wolanski B, Olsen DB (2004) Structure-activity relationship of heterobase-modified 2‘–C-methyl ribonucleosides as inhibitors of hepatitis C virus RNA replication. J Med Chem 47:5284–5297
6. Norman MH, Chen N, Chen Z, Fotsch C, Hale C, Han N, Hurt R, Jenkins T, Kincaid J, Liu L, Lu Y, Moreno O, Santora VJ, Sonnenberg JD, Karbon W (2000) Structure-activity relationships of a series of pyrrolo[3,2-*d*]pyrimidine derivatives and related compounds as neuropeptide Y5 receptor antagonists. J Med Chem 43:4288–4312
7. Barton DHR, Hesse RH, Jackman JP, Pechet MM (1977) Fluorination of benzofuran and of N-acylindoles with trifluorofluorooxymethane. J Chem Soc Perkin Trans 1:2604–2608
8. (a) Hodson H, Madge DJ, Slawin ANZ, Widdowson DA, Williams DJ (1994) Electrophilic fluorination in the synthesis of new fluoroindoles. Tetrahedron 50:1899–1906. (b) Lin R, Ding S, Shi Z, Jiao N (2011) An efficient difluorohydroxylation of indoles using Selectfluor as a fluorinating reagent. Org Lett 13:4498–4501. (c) Hodson H, Madge DJ, Widdowson DA, Williams DJ (1992) Regioselective electrophilic fluorination of alkenyl and related stannanes using cesium fluoroxysulfate. Synlett 831–832
9. (a) Yoshikawa K, Yokomizo A, Naito H, Haginoya N, Yoshino T, Osanai K, Ohta T, Kobayashi S, Nagata T, Mochizuki A, Watanabe K, Kanno H (2009) Design, synthesis, and SAR of *cis-1*,2-diaminocyclohexane derivatives as potent factor Xa inhibitors. Part I: Exploration of 5–6 fused rings as alternative S1 moieties. Bioorg Med Chem 17:8206–8220. (b) Umemoto T, Fukami S, Tomizawa G, Harasawa K, Kawada K, Tomita K (1990) Power and structure-variable fluorinating agents. The N-fluoropyridinium salt system. J Am Chem Soc 112:8563–8575
10. Tius MA, Kawakami JK (1995) The reaction of XeF_2 with trialkylvinylstannanes: scope and some mechanistic observations. Tetrahedron 51:3997–4010
11. Martín-Santamaría S, Carroll MA, Carroll CM, Carter CD, Pike VW, Rzepa HS, Widdowson DA (2000) Fluoridation of heteroaromatic iodonium salts-experimental evidence supporting theoretical prediction of the selectivity of the process. Chem Comm 649–650
12. Ermolenko MS, Budylin VA, Kost AN (1978) Nucleophilic substitution in iodonium derivatives of indole. Chem Heterocycl Comp (Engl Transl) 14:752–754
13. Eissenstat MA, Bell MR, D’Ambra TA, Alexander EJ, Daum SJ, Ackerman JH, Gruett MD, Kumar V, Estep KG (1995) Aminoalkylindoles: structure-activity relationships of novel cannabinoid mimetics. J Med Chem 38:3094–3105
14. Yin B, Wang L, Inagi S, Fuchigami T (2010) Electrosynthesis of fluorinated indole derivatives. Tetrahedron 66:6820–6825
15. Torres JC, Garden SJ, Pinto AC, da Silva FSQ, Boechat N (1999) A synthesis of 3-fluoroindoles and 3,3-difluoroindolines by reduction of 3,3-difluoro-2-oxindoles using a borane tetrahydrofuran complex. Tetrahedron 55:1881–1892
16. Guo X, Li Y, Tao L, Wang Q, Dong L, Yu X, An H, Chang J, Wang S, Hu W, Yang Q, Cui Y, Ge Z, Song C, Pan Z (2011) Synthesis and anti-HIV-1 activity of 4-substituted-7-(2′-deoxy-2′-fluoro-4′-azido-β-d-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine analogues. Bioorg Med Chem Lett 22:6770–6772
17. (a) Wang X, Seth PP, Ranken R, Swayze EE, Migawa MT (2004) Synthesis and biological activity of 5-fluorotubercidin. Nucleosides Nucleotides Nucleic Acids 23:161–170. (b) Seela F, Xu K, Chittepu P (2006) Fluorinated pyrrolo[2,3-*d*]pyrimidine nucleosides: 7- fluoro-7-

deazapurine 2′-deoxyribofuranosides and 2′-deoxy-2′-fluoroarabinofuranosyl derivatives. Synthesis 2005–2012. (c) Suydam IT, Strobel SA (2008) Fluorine substituted adenosines as probes of nucleobase protonation in functional RNAs. J Am Chem Soc 130:13639–13648. (d) Seela F, Xu K (2008) Oligonucleotides containing 7-deaza-2′-deoxyinosine as universal nucleoside: synthesis of 7-halogenated and 7-alkynylated derivatives, ambiguous base pairing, and dye functionalization by the alkyne-azide (click) reaction. Helv Chim Acta 91:1081–1200. (e) Chen YL, Yin Z, Duraiswamy J, Schul W, Lim CC, Liu B, Xu HY, Qing M, Yip A, Wang G, Chan WL, Tan HP, Lo M, Liung S, Kondreddi RR, Rao R, Keller TH, Shi PY, Gu H, He H (2010) Inhibition of dengue virus RNA synthesis by an adenosine nucleoside. Antimicrob Agents Chemother 54:2932–2939. (f) Hu W, Song C, Wang Q, Shen Z, Wang S, Chang J, Wang P, Pan Z, Guo X, Yu X (2010) Synthesis and anti-HCV activity of a new 2′-deoxy-2′-fluoro-2′-C-methyl nucleoside analogue. Bioorg Med Chem Lett 24:7297–7298. (g) Kung PP, Richardson P, Hickey MJ, Gajiwala KS, Wang F, Huang B, McClellan G, Wang J, Maegley K, Bergqvist S, Mehta PP, Kania R, Sinnema PJ (2011) Design strategies to target crystallographic waters applied to the Hsp90 molecular chaperone. Bioorg Med Chem Lett 21:3557–3562

18. Seela F, Ming X (2007) 7-Functionalized 7-deazapurine β-D and β-L-ribonucleosides related to tubercidin and 7-deazainosine: glycosylation of pyrrolo[2,3-*d*]pyrimidines with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D or β-L-ribofuranose. Tetrahedron 63:9850–9861
19. Seela F, Xu K, Chittepu P, Ming X (2007) Fluorinated 7-deazapurine 2′-deoxyribonucleosides: modification at the nucleobase and the sugar moiety. Nucleosides Nucleotides Nucleic Acids 26:607–610
20. Shi J, McBrayer TR, Whitaker T, Coats SJ, Zhou L, Zhang H, Detorio MA, Johns M, Bassit L, Schinazi RF, Powdrill MH, Goette M (2011) Synthesis and antiviral activity of 2′-deoxy-2′-fluoro-2′-C-methyl-7-deazapurine nucleosides, their phosphoramidate prodrugs and 5′-triphosphates. Bioorg Med Chem Lett 21:7094–7098
21. Evans GB, Furneaux RH, Lewandowicz A, Schramm VL, Tyler PC (2003) Exploring structure-activity relationships of transition state analogues of human purine nucleoside phosphorylase. J Med Chem 46:3412–3423
22. Ischikawa J, Wada Y, Fujiwara M, Sakoda K (2002) The nucleophilic 5-*endo-trig* cyclization of 1,1-difluoro-1-alkenes: ring-fluorinated hetero- and carbocycle synthesis and remarkable effect of the vinylic fluorines on the disfavored process. Synthesis 1917–1936
23. (a) Ichikawa J, Wada Y, Okauchi T, Minami T (1997) 5-*endo*-trigonal cyclization of *o-substituted gem*-difluorostyrenes: syntheses of 2-fluorinated indoles, benzo[*b*]furans and benzo[*b*]thiophenes. Chem Commun 1537–1538. (b) Ichikawa J, Nadano R, Mori T, Wada Y (2006) 5-*endo-trig* cyclization of 1,1-difluoro-1-alkenes: synthesis of 3-butyl-2-fluoro-1-tosylindole (1*H*-Indole, 3-butyl-2-fluoro-1-[(4-methylphenyl)sulfonyl]-). Org Synth Coll 83:111
24. Girard Y, Atkinson J, Joseph G, Belanger P, Fuentes J, Rokach J, Rooney S, Remy D, Hunt C (1983) Synthesis, chemistry and photochemical substitutions of 6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-ones. J Org Chem 48:3220–3234
25. Chen QY, Li ZT (1993) Photoinduced electron-transfer reaction of difluorodiiodomethane with azaaromatic compounds and enamines. J Chem Soc Perkin Trans 1:645–648
26. Yoshida M, Yoshida T, Kobayashi M, Kamigata N (1989) Perfluoroalkylations of nitrogen-containing heteroaromatic compounds with bis(perfluoroalkanoyl)peroxides. J Chem Soc Perkin Trans 1(5):909–914
27. Wiehn MS, Vinogradova EV, Togni A (2010) Electrophilic trifluoromethylation of arenes and N-heteroarenes using hypervalent iodine reagents. J Fluor Chem 131:951–957
28. Tatsuhito K, Nagase Y, Ohtsuka Y, Yamamoto K, Daisuke Uraguchi D, Tokuhisa K, Yamakawa T (2010) Trifluoromethylation of various aromatic compounds by CF_3I in the presence of Fe(II) compound, H_2O_2 and dimethylsulfoxide. J Fluor Chem 131:98–105
29. Senecal TD, Parsons AT, Buchwald SL (2011) Room temperature aryl trifluoromethylation via copper-mediated oxidative cross-coupling. J Org Chem 76:1174–1176
30. Henegar KE, Hunt DA (1996) Expedient preparations of 2-trifluoromethylindole and its *N*-methyl derivative. Heterocycles 42:1471–1475

31. (a) Lundbeck H (2012) Positive allosteric modulators of nicotinic acetylcholine receptor. Patent A/S; US2012/252853, (A1). (b) Glaxo Group Limited (2009) Indoles as modulators of nicotinic acetylcholine receptors subtype alpha-71. Patent WO2009/127678
32. (a) Kobayashi Y, Kumadaki I, Ohsawa A, Hamana H (1977) 1,3-Dipolar cycloaddition reactions of a diphosphabarrelene. Tetrahedron Lett 18:867–868. (b) Kobayashi Y, Hamana H, Fujino S, Ohsawa A, Kumadaki I (1979) Studies on organic fluorine compounds. 29. Cycloaddition reactions of hexakis(trifluoromethyl)-1,4-diphosphabarrelene. J Org Chem 44:4930–4933
33. Dan-oh Y, Matta H, Uemura J, Watanabe H, Uneyama K (1995) Generation and reactions of trifluoroacetimidoyl radicals. Bull Chem Soc Jpn 68:1497–1507
34. Ueda Y, Watanabe H, Uemura J, Uneyama K (1993) Photolysis of phenyltellurotrifluoroacetimidates; a new approach to generation of α-trifluoroacetimidoyl radicals leading to the synthesis of indole derivatives. Tetrahedron Lett 34:7933–7934
35. (a) Latham EJ, Stanforth SP (1996) Synthesis of indoles and quinolones by sequential Wittig and Heck reactions. Chem Comm 2253–2254. (b) Latham EJ, Stanforth SPJ (1997) Synthesis of indoles and quinolones by sequential Wittig and Heck reactions. Chem Soc Perkin Trans 1:2059–2064
36. (a) Chae J, Konno T, Ishihara T, Yamanaka H (2004) A facile synthesis of various fluorine-containing indole derivatives via palladium-catalyzed annulation of internal alkynes. Chem Lett 33:314–315. (b) Konno T, Chae J, Ishihara T, Yamanaka H (2004) A facile regiocontrol in the palladium-catalyzed annulation of fluorine-containing internal alkynes with variously substituted 2-iodoanilines: a new regioselective synthesis of 2- or 3-fluoroalkylated indole derivatives. J Org Chem 69:8258–8265
37. Rodrigues I, Bonnet-Delpon D, Begue JP (2001) 1-Trifluoromethyl epoxy ethers. Effect of hexafluoro-2-propanol on reactions with secondary aromatic amines: synthesis of 3-trifluoromethyl indole derivatives. J Org Chem 66:2098–2103
38. Muzalevskiy VM, Nenajdenko VG, Shastin AV, Balenkova ES, Haufe G (2009) α-Trifluoromethyl- β-aryl enamines in the synthesis of trifluoromethylated heterocycles by the Fischer and the Pictet-Spengler reactions. Tetrahedron 65:7553–7561
39. Orlemans EOM, Schreuder AH, Conti PGM, Verboom W, Reinhoudt DN (1987) Synthesis of 3-substituied indoles via a modified madeling reaction. Tetrahedron 43:3817–3826
40. Miyashita K, Kondoh K, Tsuchiya K, Miyabe H, Imanishi T (1996) Novel indole-ring formation by thermolysis of 2-(N- acylamino)-benzylphosphonium salts. Effective synthesis of 2-trifluoromethylindoles. J Chem Soc Perkin Trans 1:1261–1268
41. (a) Betschmann P, Burchat AF, Calderwood DJ, Curtin ML, Davidsen SK, Davis HM, Frey RR, Heyman HR, Hirst GC, Hrnciar P, Michaelides MR, Muckey MA, Rafferty P, Wada CK (2005) US Patent Appl Publ US 2005043347. (b) Betschmann P, Burchat AF, Calderwood DJ, Curtin ML, Davidsen SK, Davis HM, Frey RR, Heyman HR, Hirst GC, Hrnciar P, Michaelides MR, Muckey MA, Rafferty P, Wada CK (2005) US Patent Appl Publ US 2005026944
42. (a) Hojo M, Masuda R, Okada E, Miya H (1989) Aromatic nucleophilic nitrogen-nitrogen exchange reaction of N,N-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine with amino acid derivatives: a facile synthesis of fluorine-containing 1H-benzo[*g*]indolines and 1H-benzo[g] indoles. Synthesis 550–552. (b) Okada E, Tsukushi N (1999) Aromatic nucleophilic N-N exchange reaction of N,N-Dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine with various amines: a facile synthetic method for 5,7-bis(trifluoracetyl)-8-quinolylamines. Synlett 210–212. (c) Okada E, Tsukushi N (2000) A facile and convenient synthetic method for fluorine-containing 1H-pyrrolo[3,2-*h*]quinolines. Heterocycles 53:127–134
43. (a) Fuerstner A, Hupperts A, Ptock A, Janssen E (1994) "Site selective" formation of low-valent titanium reagents: an "instant" procedure for the reductive coupling of oxo amides to indoles. J Org Chem 59:5215–5229. (b) Fuerstner A, Hupperts A (1995) Carbonyl coupling reactions catalytic in titanium and the use of commercial titanium powder for organic synthesis. J Am Chem Soc 117:4468–4475
44. (a) Frey LF, Tillyer RD, Ouellet SG, Reamer RA, Grabowski EJJ, Reider PJ (2000) Rapid assembly of substituted dihydrocyclohepta[3,4]pyrrolo[1,2-*a*]indoles via a novel,

carbene-based, rearrangement reaction. J Am Chem Soc 122:1215–1216. (b) Frey LF, Grabowski EJJ, Ouellet SG, Reamer RA, Tillyer RD (2001) Brit UK Patent Appl GB 2353035
45. (a) Hao J, Song X (2005) Faming Zhuanli Shenqing Gongkai Shuomingshu. Patent CN 1660806. (b) Hao J, Wang Z, Ge F (2007) Faming Zhuanli Shenqing Gongkai Shuomingshu. Patent CN 1927834. (c) Ge F, Wang Z, Wan W, Hao J (2007) Grignard cyclization reaction of fluorinated N-arylimidoyl chlorides: a novel and facile access to 2-fluoroalkyl indoles. Synlett 447–450. (d) Wang Z, Ge F, Wan W, Jiang H, Hao J (2007) Fluorinated N-[2-(haloalkyl)-phenyl]imidoyl chloride, a key intermediate for the synthesis of 2-fluoroalkyl substituted indole derivatives via Grignard cyclization process. J Fluor Chem 128:1143–1152
46. Attanasi OA, Filippone P, Guidi B, Mantellini F, Santeusanio S (2001) Regioselective synthesis of stable 2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ols and derived fluorinated heterocycles. Synthesis 1837–1845
47. Fang YQ, Lautens M (2005) Pd-catalyzed tandem C-N/C-C coupling of gem-dihalovinyl systems: a modular synthesis of 2-substituted indoles. Org Lett 7:3549–3552
48. Yamakawa A, Horino Y (2008) Jpn Kokai Tokkyo Koho. Patent JP 2008037760
49. Mokrushin MG, Shastin AV, Muzalevskiy VM, Balenkova ES, Nenajdenko VG (2008) A new synthesis of substituted 2-trifluoromethylindoles. Mendeleev Comm 18:327–328
50. Muzalevskiy VM, Shastin AV, Balenkova ES, Haufe G, Nenajdenko VG (2008) New approaches to the synthesis of 2-(trifluoromethyl)indole and 2-amino-3-(trifluoromethyl)-quinoline. Russ Chem Bull (Engl Transl) 10:2217–2219
51. Chen Y, Wang Y, Sun Z, Ma D (2008) Elaboration of 2-(trifluoromethyl)indoles via a cascade coupling/condensation/deacylation process. Org Lett 10:625–628
52. (a) Petrov VP, Barkhash VA, Shchegoleva GS, Petrova TD, Savchenko TL, Yakobson GG (1968) Dokl Akad Nauk SSSR 178:864. (b) Petrov VP, Barkhash VA (1970) Cyclization of 1-(pentafluorophenyl)-2-aminoalkanols. Chem Heter Comp 6:573–576
53. (a) Brooke GM (1968) Partially fluorinated heterocyclic compounds. Part VIII. New syntheses of benzo[*b*]thiophene and indole derivatives. Tetrahedron Lett 37:4049–4052. (b) Brooke GM, Musgrave WKR, Rutherpord RJD, Smith TW (1971) Partially fluorinated heterocyclic compounds-X. Syntheses of N-phenyl-4,5,6,7-tetrafluoro-2-phenylindole by a new cyclization reaction and attempted synthesis of related compounds by conventional methods. Tetrahedron 27:5653–5658
54. (a) Fujita M, Ojima I (1983) Selenium dioxide oxidation of 3-methyl-4,5,6,7-tetrafluoroindoles: an efficient route to tetrafluoro analogues of 3-formyl and 3-acetoxymethylindole systems. Tetrahedron Lett 24:4573–4576. (b) Ojima I, Kato K, Nakahashi K (1989) New and effective routes to fluoro analogues of aliphatic and aromatic amino acids. J Org Chem 54:4511–4522
55. Blazejewski JC, Wakselman CJ (1980) Condensation of α, β-unsaturated amines with perfluoroarenes. Chem Soc Perkin Trans 1:2845–2850
56. Brooke GM, Rutherford RJD (1967) Partially fluorinated heterocyclic compounds. Part IV. The preparation of 4,5,6,7-tetrafluoroindole by a new cyclisation reaction. J Chem Soc 1189–1191
57. (a) Brooke GMJ (1983) Partially fluorinated heterocyclic compounds. Part 18. Formation of Fischer indole products from acetophenone 1,3,4,5,6,7,8-heptafluoro-2-naphthyl-hydrazone and acetophenone pentafluorophenylhydrazone. The surprising loss of *o*-fluorine. Chem Soc Perkin Trans 1 821–825. (b) Benke FD, Brooke GM (1984) Partially flourinated heterocyclic compounds. Part 19 [1]. The formation of Fischer indole products from a series of hydrozones derived from pentaflourophenylhydrazine and 1,3,4,5,6,7,8-heptaflouro-2-naphthylhydrazine. The surprising loss of *o*-flourine. J Fluor Chem 26:77–86
58. (a) Filler R, Woods SM, Freudenthal AF (1973) 4,5,6,7-Tetrafluoroindole. J Org Chem 38:811–812. (b) Filler R, Chen W, Woods SM (1995) Polyfluoroaralalkylamines: an improved synthesis of 4,5,6,7-tetrafluoroindole. J Fluor Chem 73:95–100. (c) Filler R, Woods SM, White WL (1989) Polyfluoroaralkyl amines. Further studies on the reactivity of 4,5,6,7-tetrafluoroindole. Can J Chem 67:1837–1841

59. Shaffer MW, Platz MS (1989) The preparation and photochemistry of 6-azido-4,5,7-trifluoroindole in toluene. Evaluation of a new reagent for photoaffinity labelling. Tetrahedron Lett 30:6465
60. Tanabe H, Ichikawa J (2010) Transition-metal-catalyzed electrophilic activation of 1,1-difluoro-1-alkenes: oxindole synthesis via intramolecular amination. Chem Lett 39:248–249
61. Trost BM, Osipov M, Dong G (2010) Palladium-catalyzed dynamic kinetic asymmetric transformations of vinyl aziridines with nitrogen heterocycles: rapid access to biologically active pyrroles and indoles. J Am Chem Soc 132:15800–15807
62. Campbell JA, Bordunov V, Broka CA, Dankwardt J, Hendricks RT, Kress JM, Walker KAM, Wang JH (2004) Preparation of 3-arylmethylindoles as selective COX-2 inhibitors. Tetrahedron Lett 45:3793–3796
63. Petrova TD, Savchenko TI, Shchegoleva LN, Ardyukova TF, Yakobson GG (1970) Polyfluorinated heterocyclic compounds VI. Electrophilic substitution in 4,5,6,7-tetrafluoroindole. Chem Heterocycl Comp 6:1251–1254
64. Miyashita K, Kondoh K, Tsuchiya K, Miyabe H, Imanishi T (1997) Synthesis of several 3-substituted 2-trifluoromethylindoles via Mannich reaction of 2-trifluoromethylindoles. Chem Pharm Bull 45:932–935
65. Mor M, Spadoni G, Di Giacomo B, Diamantini G, Bedini A, Tarzia G, Plazzi PV, Rivara S, Nonno R, Lucini V, Pannacci M, Fraschini F, Stankov BM (2001) Synthesis, pharmacological characterization and QSAR studies on 2-substituted indole melatonin receptor ligands. Bioorg Med Chem Lett 9:1045–1057
66. Actelion Pharmaceuticals LTD (2012) 1-Pnenyl-substituted heterocyclic derivatives and their use as prostaglandin D2 receptor modulators. Patent WO2012/4722
67. Amira Pharmaceuticals Inc (2012) Autotaxin inhibitors and uses thereof. Patent WO2012/24620
68. Takeda Pharmaceuticals Comp Ltd (2012) N-substituted oxazinopteridines and oxazinopteridones. Patent US2012/220575
69. Pettersson MY, Johnson DS, Subramanyam C, O'Donnell CJ, Ende CW, Fish BA, Green ME, Mullins PBr, Stiff CM, Tran TP, Navaratnam T (2012) Novel bicyclic pyridinones. Patent US2012/252758
70. Bayer Schering Pharma AG (2010) Extended benzamide derivatives as modulators of the EP2 receptor. Patent US2010/29598
71. Proximagen Ltd (2011) Indole and azaindole modulators of the alfa 7 NACHR. Patent WO2011/45353
72. Tao L, Bunnelle WH, Ryther KB, Anderson DJ, Malysz JH, Rosalind G, Jens H, Hkerud M, Schrimpf MR, Gopalakrishnan MJ, Jianguo PD (2010) Syntheses and structure-activity relationship (SAR) studies of 2,5-diazabicyclo[2.2.1]heptanes as novel α7 neuronal nicotinic receptor (NNR) ligands. Bioorg Med Chem Lett 20:3636–3639
73. Novartis AG (2008) Indolylmaleimide derivatives. Patent WO2008/74752
74. Ligand Pharmaceuticals Incorporated (2009) Androgen receptor modulator compounds and methods. Patent US2009/30027
75. Sanwa Kagaku Kenkyusho Co Ltd (2009) Novel 6–5 bicyclic heterocyclic derivatives and medical use thereof. Patent EP2036887
76. Wyeth (2009) 3-Substituted-1H-indole compounds, their use as MTOR kinase and PI3 kinase inhibitors, and their synthesis. Patent US2009/311217 (A1)
77. Smithkline Beecham Corporation (2008) Chemical compounds. Patent WO2008/42571
78. Pfizer Inc (2003) Benzofused heteroaryl amide derivatives of thienopyridines useful as therapeutic agents, pharmaceutical compositions including the same, and methods for their use. Patent WO2003/106462 (A1)
79. (a) Fukuda Y, Seto S, Furuta H, Ebisu H, Oomori Y, Terashima S (2001) Novel Seco cyclopropa[c] pyrrolo[3,2-e]indole bisalkylators bearing a 3,3′-arylenebisacryloyl group as a linker. J Med Chem 44:1396–1406. (b) Fukuda Y, Furuta H, Kusama Y, Ebisu H, Oomori Y, Terashima S (1999) Novel cyclopropapyrroloindole derivative (AT-3510) bearing methoxycarbonyl and

trifluoromethyl groups. J Med Chem 42:1448–1458. (c) Fukuda Y, Furuta H, Shiga F, Oomori Y, Kusama Y, Ebisu H, Terashima S (1997) Synthesis and antitumor activity of novel cyclopropapyrroloindole(CPI) derivatives bearing methoxycarbonyl and trifluoromethyl groups. Bioorg Med Chem Lett 7:1683–1688

80. (a) Fukuda Y, Furuta H, Kusama Y, Ebisu H, Oomori Y, Terashima S (1998) The novel cyclopropapyrroloindole (CPI) bisalkylators bearing methoxycarbonyl and trifluoromethyl groups. Bioorg Med Chem Lett 8:1387–1390. (b) Fukuda Y, Seto S, Furuta H, Ebisu H, Oomori Y, Terashima S (1998) The novel cyclopropapyrroloindole(CPI) bisalkylators bearing 3,3′-(1,4-phenylene)diacryloyl group as a linker. Bioorg Med Chem Lett 8:2003–2004
81. FMC Corporation (2002) Cycloimido-substituted benzofused heterocyclic herbicides. US Patent 6,352,958
82. Nissan Chemical Industries Ltd (2002) Sulfamoyl compounds and agricultural and horticultural fungicides. US Patent 6,350,748 (B1)
83. (a) Merck Sharp and Dohme Corp (2012) Patent WO2012/41014. (b) Merck Sharp and Dohme Corp (2012) Patent WO2012/40923 (A1). (c) Merck Sharp and Dohme Corp (2010) Inhibitors of hepatitis C Virus replication. Patent WO2010/111483 (A1). (d) Schering Corporation (2012) Fused teracycle derivatives and methods of use thereof for the treatment of viral diseases. Patent WO2012/50848 (A1)
84. Yoshikawa K, Yokomizo A, Naito H, Haginoya N, Yoshino T, Osanai K, Ohta T, Kobayashi S, Nagata T, Mochizuki A, Watanabe K, Kanno H (2009) Design, synthesis, and SAR of *cis*-1,2-diaminocyclohexane derivatives as potent factor Xa inhibitors. Part I: Exploration of 5–6 fused rings as alternative S1 moieties. Bioorg Med Chem 17:8206–8220
85. Dainippon Sumitomo Pharma Co Ltd (2011) N-Acyl cyclic amine derivatives or pharmaceutically acceptable salt thereof. Patent WO2011/111875 (A1), US2012/214790 (A1)
86. Albany Molecular Research Inc (2011) Epiminocycloalkyl[b]indole derivatives as serotonin sub-type 6 (5–HT6) modulators and uses thereof. Patent WO2011/44134
87. Neil A, Gao DA, Heim-Riether A, Keenan LLS, Mugge IA, Taylor SJ, Xiong Z, Yu Y, Zhang Q (2010) Heteroaryl substituted indole compounds useful as MMP-13 inhibitors. Patent WO2010/45188
88. Arena Pharmaceuticals Inc (2011) Disubstituted oxadiazole derivatives useful in the treatment of autoimmune and inflammatory disorders. Patent WO2011/5290 (A1)
89. Kimberly G, Hornberger KR, Hubbard RD, Sammond DM, Smith SC, Dickson HD, Caferro TR, Hinkle KW, Stevens KL, Dickerson SH, Rusnak DW, Spehar GM, Wood ER, Griffin RJ, Uehling DE (2009) Synthesis and evaluation of aniline headgroups for alkynyl thienopyrimidine dual EGFR/ErbB-2 kinase inhibitors. Bioorg Med Chem Lett 19:1332–1336
90. Richter Gedeon NYRT (2012) Indole derivatives. Patent WO2012/59776
91. Zhang YM, Connolly PJ, Lin SC, MacIelag MJ (2012) Amino-pyrrolidine-azetidine diamides as monoacylglycerol lipase inhibitors. Patent US2012/101081 (A1)
92. Laboratoires Fournier SA (2012) Use of indole derivatives as Nurr-1 activators for the application thereof as a medicament for the treatment of Parkinson's disease. Patent US 2012/0232070 (A1)
93. AstraZeneca AB, AstraZeneca UK Ltd (2008) Benzenesulfonamide compounds as EDG-1 antagonists useful in the treatment of cancer. Patent WO2008/59238
94. Merck and Co Inc (2009) 2-Aryl or hetaryl indole derivatives. Patent WO2009/42092
95. Hoffmann-La Roche AG (2012) Aminopyrazole derivative. Patent EP2471786 (A1)
96. Bjeldanes LF, Le HT, Firestone GL (2005) 3,3′-Diindolylmethane antiandrogenic compositions. Patent US2005/58600

Fluorinated Indolizines

Eugene V. Babaev

Contents

Abstract The chapter is devoted to the synthesis and application of indolizines bearing fluorine atoms, perfluorinated alkyl (aryl) groups, and $COCF_3$ fragments.

Keywords Indolizine • Fluorine • Trifluoromethyl group • Synthesis • Fluorinated heterocycles

E.V. Babaev (✉)
Department of Chemistry, Moscow State University,
Leninskie Gory, Moscow 119992, Russian Federation

Moscow Institute of Physics and Technology,
Institutskii per. 9, 141700 Dolgoprudny, Moscow Region, Russia
e-mail: babaev@org.chem.msu.ru

V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_4,

1 Introduction

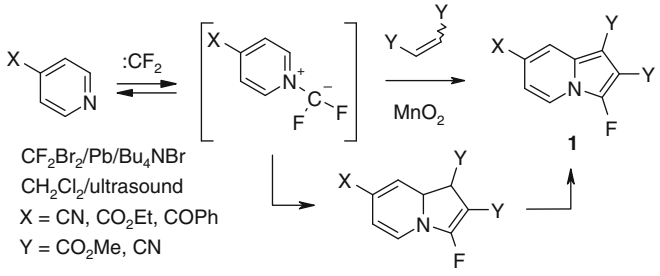
Fluorinated heterocycles have received increasing attention due to their important biological properties. Considerable efforts have been paid to the exploitation of new synthetic routes to these fluorinated compounds. Indolizine is an important fundamental ring system in view of its similarity to indole. This heterocycle occurs commonly as a fully reduced form in natural products. Owing to the increasing importance of fluorine containing heterocycles in biology, pharmacology, and industrial application, synthesis of fluorine-containing indolizines became of considerable interest. In spite of existence of numerous reviews on the chemistry of indolizines [1] no attention have been paid to its fluorinated derivatives. In fact, this area is relatively young (the first research paper on this topic appeared 30 years ago). In spite of many efforts, up to now no indolizines with perfluorinated groups appeared on the market.

The review is organized in the following way. First, indolizines with substituents at pyrrole fragment are covered. This includes indolizines substituted at positions 3 and 1 (since these positions are most easily substituted), and then 2-substituted derivatives. Then, indolizines substituted at pyridine ring are covered: structures with 6(8)-perfluorinated groups are reviewed, and finally, 7- and 5-derivatives are discussed. Major attention is paid to indolizines; benzo-derivatives are also included.

2 Synthesis of Indolizines with Substituent in Pyrrole Fragment

2.1 Indolizines with Substituent at Position 3

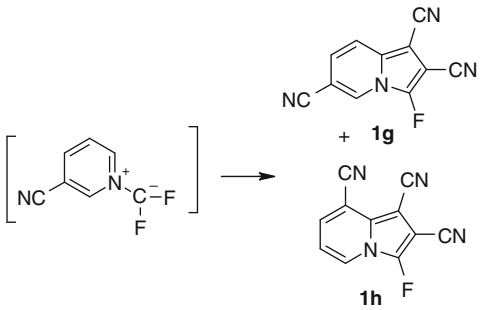
Although the position 3 in the indolizine ring is the most reactive toward electrophilic attack, no direct fluorination of indolizines have been reported. Instead, in the recent work [2] 1,3-dipolar cycloaddition was studied to difluoro-substituted pyridinium ylides.



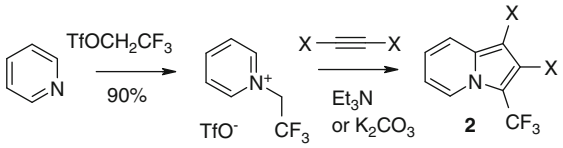
Pyridine	Dipolarophile	Yield (%)
4-COPh	CO_2Me	18 (**1a**)
4-COPh	CN	31 (**1b**)
4-CO_2Et	CO_2Me	23 (**1c**)
4-CO_2Et	CN	28 (**1d**)
4-CN	CO_2Me	48 (**1e**)
4-CN	CN	43 (**1f**)
3-CN	CO_2Me	16 (**1g:1h**) (1:1)

Difluoromethylides were prepared from 4-cyano, 4-benzoyl- and 4-ethoxycarbonyl-substituted pyridines under difluorocarbene generation conditions (ultrasound, CF_2Br_2/Pb/Bu_4NBr) and trapped with dimethyl maleate or fumaronitrile. 3-Fluoroindolizines were isolated as final products of the reaction which involves dehydrofluorination of the primary cycloadducts followed by dehydrogenation by active MnO_2.

These ylides where shown to dissociate to carbene and pyridine with low activation barrier. The equilibrium constant of the reaction increases with increasing electron-withdrawing ability of substituents in the pyridine ring. There was no reaction with unsubstituted pyridine or picolinic acid nitrile. In the reaction of nicotinic acid nitrile with the fumaronitrile a mixture of the regioisomeric products was formed:

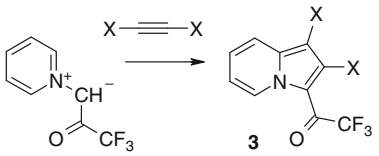


The reaction of N-CH_2CF_3 pyridinium salt with dimethyl acetylenedicarboxylate or perfluorobut-2-yne in the presence of base (Et_3N or K_2CO_3) [3] has provided first formation of indolizines **2** with CF_3-group in position 3.

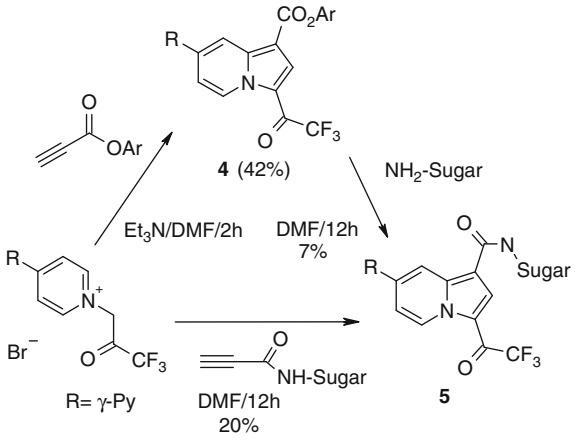


X = CO_2Me (11%); CF_3 (12%)

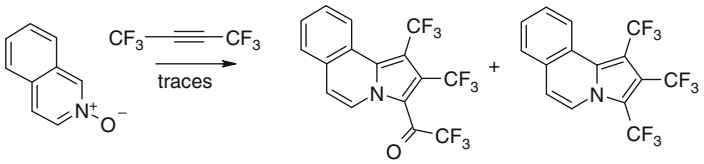
Similarly, the reaction of ylide formed from N-CH_2COCF_3 pyridinium salt and dimethyl acetylenedicarboxylate or perfluorobut-2-yne gave rise to 3-$COCF_3$-indolizines **3** [4].



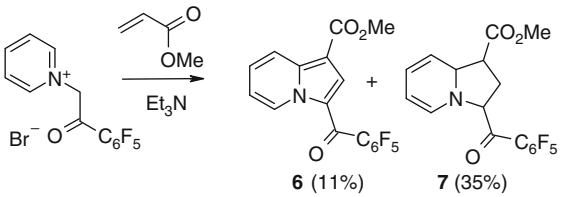
The same methodology was applied to N-CH_2COF_3 γ,γ'-bipyridinium salt leading to intermediate indolizine **4** or final aminosugar **5** with 3-$COCF_3$ group [5].



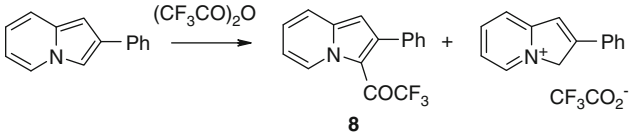
It should be mentioned that isoquinoline 2-oxide reacted with perfluorobut-2-yne similarly forming (among other products) 1,2,3-tris(trifluoromethyl)- and 1,2-bis(trifluoromethy1)-3-trifluoroacethylpyrrolo[2,1-a]isoquinoline [6].



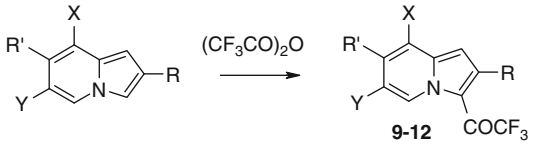
Finally, 3-COC_6F_5 indolizine **6** was obtained together with more saturated product **7** by cycloaddition of the corresponding ylide and methyl acrylate [7].



Meanwhile, it is much easier to prepare indolizines with perfluoroacyl substituent at position 3 by perfluoroacylation reaction. The reaction yields are strongly depended on the basicity of the parent indolizine: thus 2-phenylindolizine underwent trifluoroacetylation to form **8** in 36 %; the rest (60 % after regeneration) was indolizinium cation formed by protonation of starting material [8].

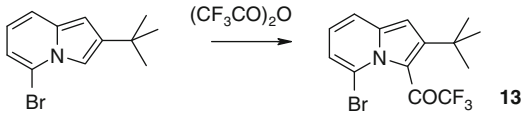


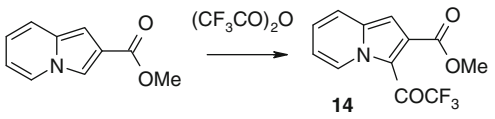
Nitroindolizines having 6- and 8-nitro group in the same reaction led to trifluoroacetyl derivatives **9**–**12** in quantitative yield [9]. It was shown that their basicity is decreased.



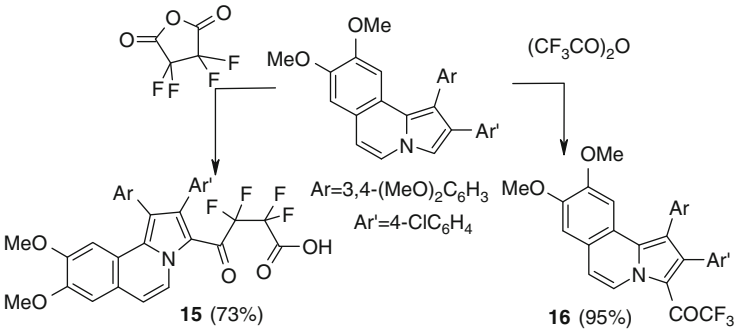
Indolizine		Yield (%)
9	3-$COCF_3$-6-NO_2-2-Ph-7-Me	97
10	3-$COCF_3$-6-NO_2-2-Me	96
11	3-$COCF_3$-8-NO_2-2-Me	100
12	3-$COCF_3$-8-NO_2-2-Ph	100

5-Bromoindolizine underwent trifluoroacetylation selectively at position 3 leading to compound **13**; the yield was 83 % [10]. 2-Carbomethoxyindolizine is transformed to 3-$COCF_3$ derivative **14** in 85 % yield [11].

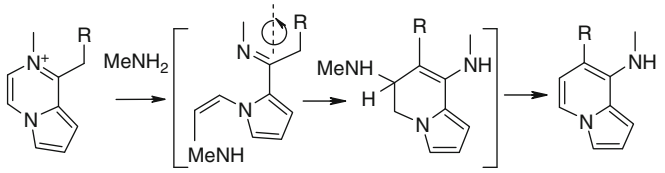




There is only one example of trifluoroacylation in the series of benzoindolizines. 3-Perfluoroacyl derivatives **15** and **16** were obtained in high yield [12] using trifluoroacetic and perfluorosuccinic anhydride as acylating agents.

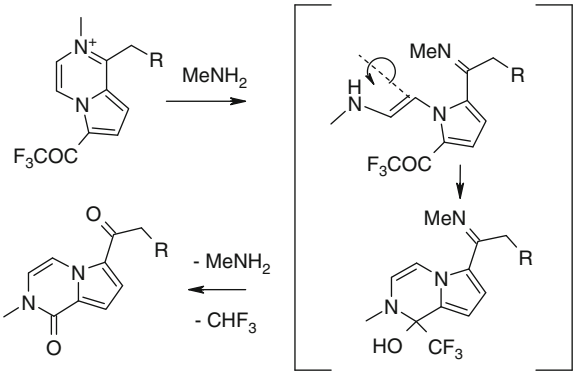


Pyrrolo[1,2-a]pyrazinum (7-azaindolizinium) cations may underwent ring opening and transformation of the pyrazinium fragment under the action of $MeNH_2$. The rearrangement is known as Kost-Sagitullin (enamine) rearrangement.

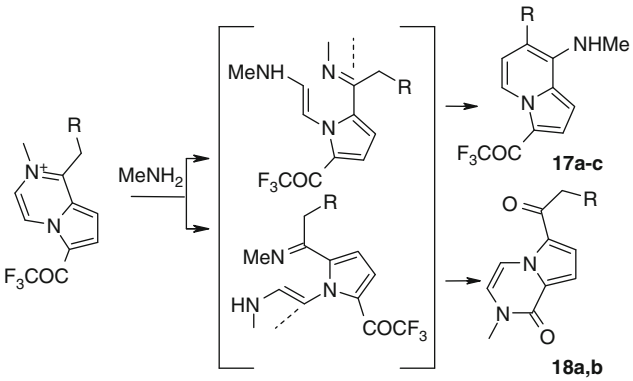


On the other hand, 7-azaindolizinium cations with $COCF_3$ group may be involved in haloformic recyclization leading to oxo-derivatives of pyrrolo[1,2-a]pyrazines.

Here the NHMe-amino group was originated from the reagent.

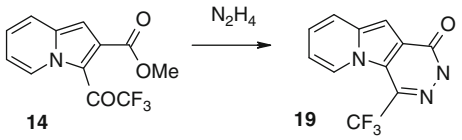


At lower temperature the product **17** of enamine rearrangement to pyridine ring predominated, whereas at higher temperature (and in water solution) the ring transformation occurred with haloformic reaction to form **18** [13].

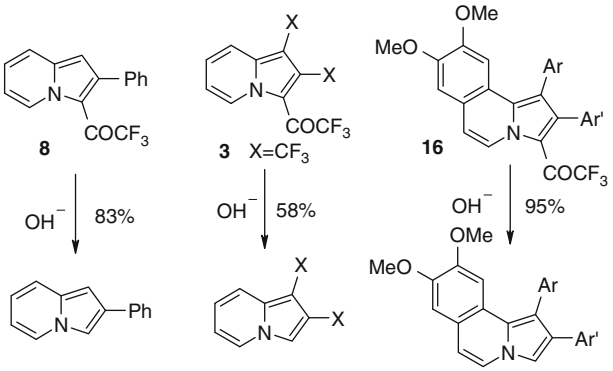


		17:18	
№	R	30 °C	170 °C
a	Et	10:39	45:6
b	n-Pr	15:50	44:10
c	$PhCH_2$	60:0	70:0

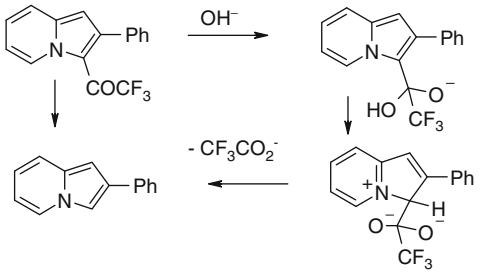
Electrophilic nature of 3-$COCF_3$ group is displayed by the reaction of indolizine **14** with hydrazine forming pyridazinone derivative **19** in the yield 79 % [11].



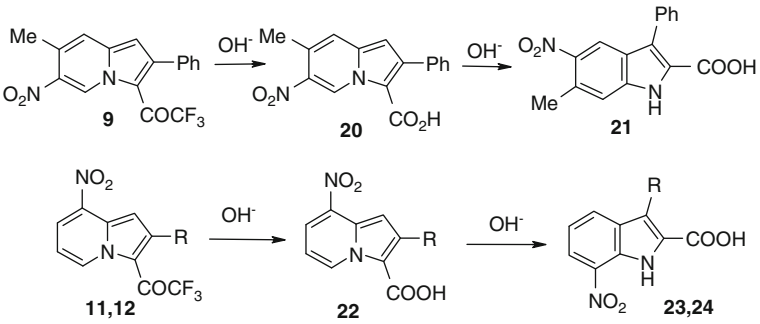
3-Trifuoroacetyl indolizines underwent removal of 3-$COCF_3$ group in good yield by the reaction with cold alkali [9, 4, 12].



It should be mentioned that similar pyrroles, indoles and azulenes bearing $COCF_3$ group all reacted with alkali with haloformic removal of $CHCF_3$; the "strange" behavior of 3-$COCF_3$ indolizines was explained by their higher basicity and possibility of substitution of trifluoroacetate ion by ipso-protonation [14].

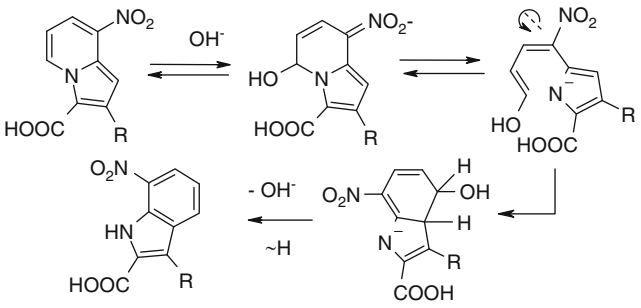


Particularly, this statement was confirmed by reaction of trifluoroacetyl derivatives of 6- and 8-nitroindolizines with alkali. Being less basic these compounds underwent haloformic reaction to form nitroindolizine-2-carboxilic acids. The reaction, however, did not stop at this point and finalized with transformation of pyridine ring (of indolizines) to benzene ring of indoles [9].



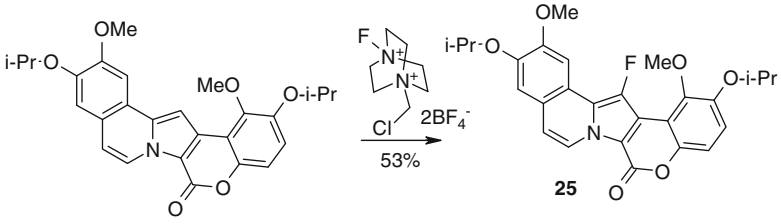
Indolizine	Indole (acid)	Yield of indole (acid), %
9	**21** (**20**)	98 (67)
11	**23** (**22**)	72 (42)
12	**24**	80

It should be mentioned that conversion of indolizines to indole 2-carboxylic acids proceeded in higher yields and in milder conditions (0 °C) than for indolizines without $COCF_3$ group. The overall mechanism is of the ANRORC type:

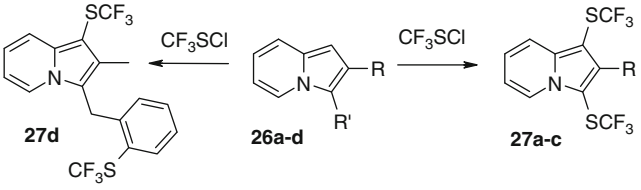


2.2 *Indolizines with Substituent at Position 1*

Position 1 of the indolizine ring is the second one (after position 3) that can be attacked by electrophiles. However, there are no examples of direct fluorination of indolizine ring at position 1. Among the benzoindolizines there is such an example [15] where the desired F-containing scaffold **25** was obtained by use of Selectfluor.

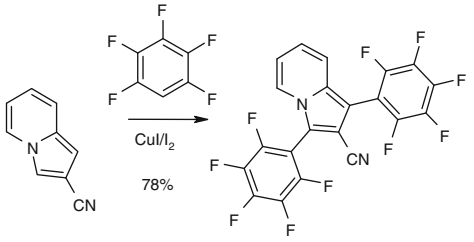


Another example of direct incorporation of perfluorinated substituent at the position 1 is the insertion of CF_3S group using CF_3SCl as electrophile [16]. Reaction proceeded at positions 1 and 3 even in the case of deactivated 3-COMe indolizine quantitatively. In the case of 3-benzylindolizine substitution at C-1 is accompanied by insertion of electrophile in the benzyl fragment as well.

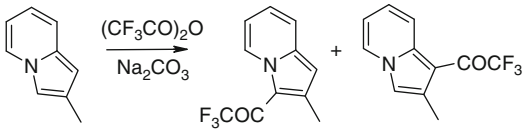


26a	R=R'=H	**27a**
26b	R=H, R'=Me	**27b**
26c	R=Me, R'=Ac	**27c**
26d	R=Me, R'=$PhCH_2$	**27d**

As it was shown recently [17], perfluorophenyl group can be inserted at position 1 and 3 under the cross-coupling conditions. This regioselective reaction took place with pyridine, potassium phosphate, copper (I) iodide, 1,10-phenanthroline and iodine in 1,4-dioxane at 120–130 °C during 74 h.

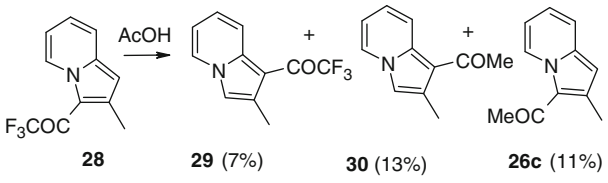


Investigation of the direction of trifluoroacetylation of 2-methylindolizine has shown minor amounts of the 1-substituted isomer formed in addition to the "usual" product of substitution in the 3 position [18].

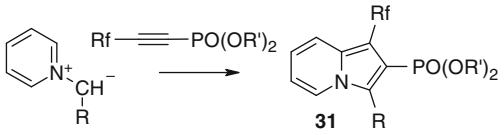


28 (93%) **29** (3.5%)

Furthermore, 1-$COCF_3$ isomer is formed when 3-$COCF_3$ indolizine was heated in CH_3COOH (together with 1- and 3-acetylindolizines) [14]. The reaction mechanism seemed to be intramolecular.



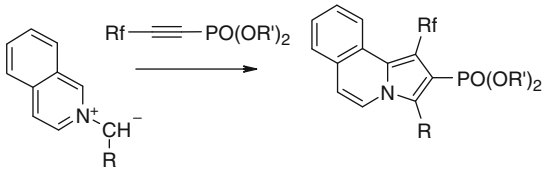
28 **29** (7%) **30** (13%) **26c** (11%)



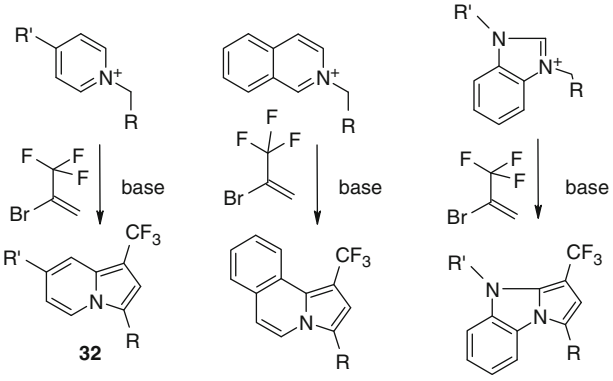
31

Compound	Rf	R'	R	Yield (%)
31a	CF_3	Et	CN	74
31b	CF_3	Pr	CN	70
31c	C_2F_5	Et	CN	73
31d	C_2F_5	Pr	CN	49
31e	CF_3	Et	CO_2Et	47
31f	CF_3	Pr	CO_2Et	51
31g	C_2F_5	Et	CO_2Et	51
1 h	CF_3	Et	COPh	77
31i	C_2F_5	Et	COPh	65
31j	C_3F_7	Et	COPh	70

In addition to direct insertion of perfluorinated group at position 1, there are plenty of methods how to introduce such a group via cycloaddition reaction. Thus, convenient method to perfluoroalkylated indolizinyl-phosphonates **31** was reported [19]. The reaction proceeded regioselectively via the 1,3-cycloaddition of pyridinium N-ylide and perfluoroalkynyl phosphonate in 49–77 % yields. Similar reaction was proposed to obtain pyrrolo[1,2-a]isoquinolinyl phosphonates in 48–78 % yields [20].

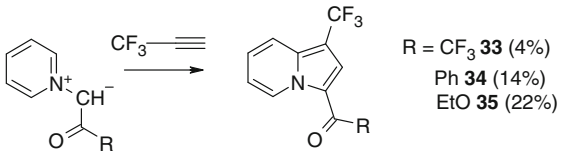


In the reaction of 2-bromo-3,3,3-trifluoropropene with pyridinium ylides cycloaddition occurred readily leading to 1-CF_3 derivatives of indolizines [21]. Similar reaction took place in the cases of pyridazinium and isoquinolinium ylides.

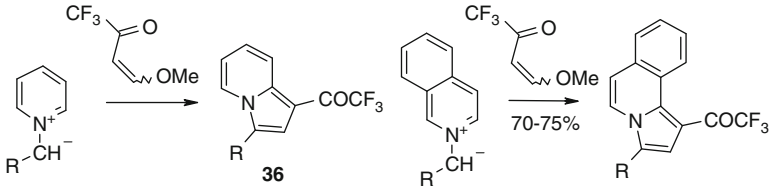


R	R'	Yield (%)	R	R'	Yield (%)
COPh	H	40	COPh	Me	49
COMe	H	24	COMe	Me	27
CO_2Et	H	35			

The reaction of 3-$COCF_3$ pyridinium ylide with 1,1,1-trifluoropropyne proceeded similarly giving 1-CF_3 indolizine in low yield [4]. Similarly behaved other pyridinium ylides with benzoyl and ester groups [22].



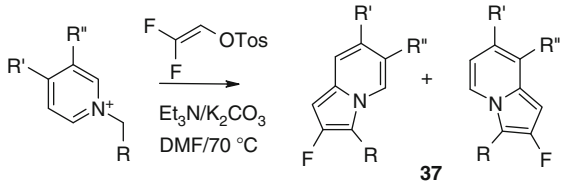
Pyridinium ylides reacted with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one to give the corresponding 1-trifluoroacetyl-substituted indolizines [23]. Isoquinolinium ylides behaved similarly.



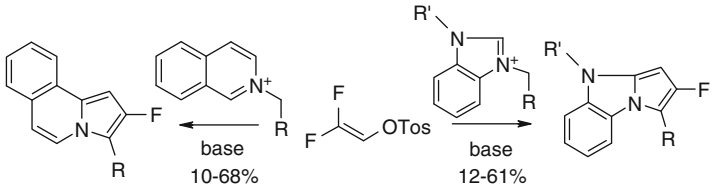
R	Yield (%)
COPh	76 %
CN	74 %
CO_2Et	R=CO_2Et/Me

2.3 *Indolizines with Substituent at Position 2*

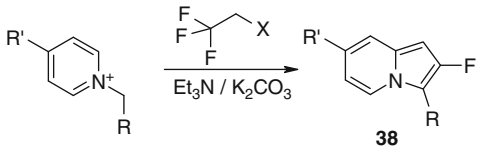
2-Fluoroindolizines are easily available via cycloaddition of fluorinated vinyl tosylates and pyridinium ylides [24]. Using β-substituted pyridinium ylides both isomers (6 and 8) were formed with clear predominance of 8-isomers. One product with 3-CO_2Et group was recently patented as the intermediate [25]. The reaction also proceeded with isoquinolinium and benzimidazolium ylides.



R R' R"	Yield (%)	R R' R"	Yield (%)
COPh H H	34	CO_2Et H COPh	8 (1:1.5)
COPh CH_3 H	23	CN H H	59
COPh H CH_3	37 (1:2)	CN CH_3 H	33
COPh H Br	27 (1:1.5)	CN H CH_3	67 (1:10)
CO_2Et H Br	40 (1:6)	CN H Br	58 (1:1.7)



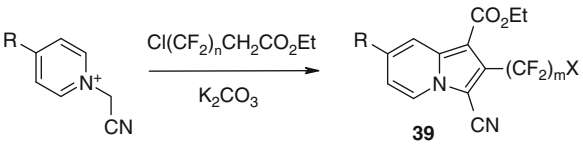
Further modification of the strategy was proposed; 1-chloro-2,2,2-trifluoroethane (bp 6 °C) or 1,1,1,2-tetrafluoroethane (bp –27 °C) gave the corresponding 2-fluoroindolizines **38** via 1,3-dipolar cycloaddition at 80–100 °C in DMSO at atmospheric pressure in normal glassware [26]. The reaction started with the elimination of HF from CF_3CH_2X and can be applied to isoquinolinium ylides.



38

X	R, R'	Yield of 38	X	R, R'	Yield of 38
Cl	COPh, H	45	F	COPh, H	37
Cl	COPh, Me	67	F	CO_2Et, H	47
Cl	CO_2Et, H	82	F	CO_2Et, Me	28
Cl	CO_2Et, Me	76			

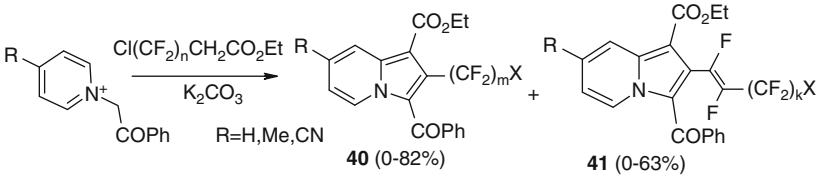
In the presence of base, 2,2-dihydropolyfluoroalkanoates of the type $R_FCF_2CH_2CO_2Et$ reacted with N-(cyanomethyl)pyridinium ylides to give the corresponding indolizine derivatives carrying both a fluoroalkyl and a cyano group [27].



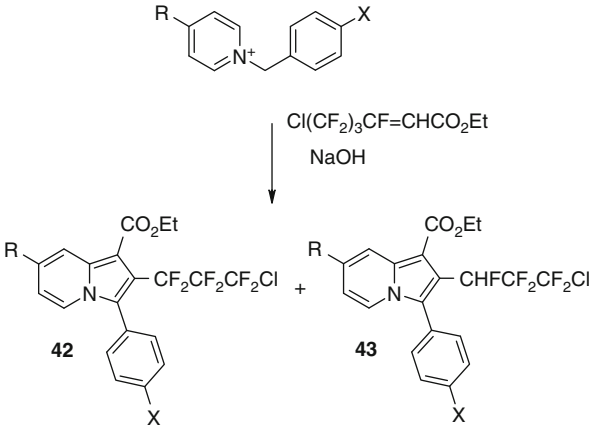
39

R	n	m	X	Yield	R	n	m	X	Yield
H	2	1	H	76	Me	2	1	H	90
H	4	3	Cl	70	Me	4	3	Cl	83
H	6	5	Cl	61	Me	6	5	Cl	88
H	8	7	Cl	52					

Ethyl 2,2-dihydropoly(per)fluoroalkanoates reacted with N-phenacylpyridinium ylides in DMF to give poly(per)fluoroalkyl-substituted indolizines **40** and **41** [28]. Origin of the products **41** is explained by the adduct aromatization.

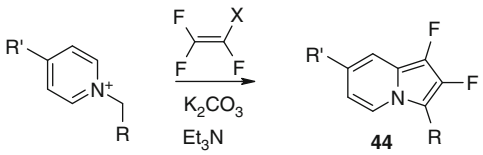


N-Benzylpyridinium ylides (generated in situ from the N-benzylpyridinium bromide and alkali) reacted with ethyl 3-fluoro-3-fluoroalkyl acrylates to give one or two fluoroalkylated indolizine derivatives through 1,3-dipolar cycloaddition followed by an oxidative aromatization or 1,3-H-shift aromatization process [29].



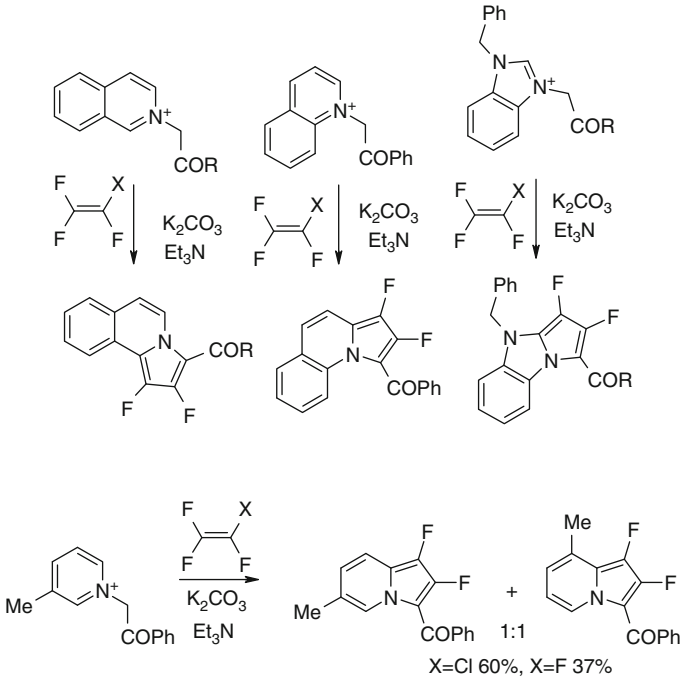
Pyridinium salt	Products and yield (%)	
R=H, X=H	**42a** (18)	**43a** (14)
R=H, X=OMe	**42b** (31)	**43b** (18)
R=H, X=NO_2	**42c** (31)	**43c** (29)
R=CO_2Et, X=H	**42d** (35)	**43d** (8)
R=Me, X=NO	**42e** (5)	–
R=CO_2Et, X=NO_2	**42f** (33)	–

In the presence of K_2CO_3 and Et_3N, pyridinium N-ylides, generated in situ from their halides, reacted with gaseous fluoroalkenes CF_2=CFX (X=Cl, Br) in DMF under atmospheric pressure in normal glassware at 70 °C to give the corresponding 1,2-fluorinated indolizines. Similar results were obtained with tetrafluoroethene in an autoclave [30].

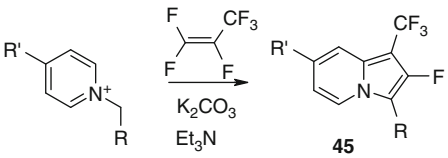


Alkene/X	Ylide, R,R'	Yield
Cl	COPh, H	66
Cl	COPh, Me	64
Cl	CO_2Et, H	37
Br	COPh, H	57
Br	COPh, Me	77
Br	CO_2Et, H	75
F	COPh, Me	32

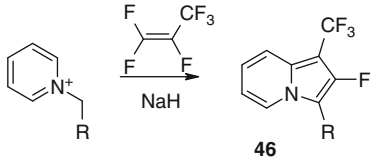
The reaction proceeded also with quinolinium, isoquinolinium and benzimidazolium ylides. In the reaction of ylide obtained from β-picoline the mixture of 6- and 8-isomers was formed.



Similar reaction took place for hexafluoropropene to form 1-CF_3 indolizines. The result was similar to the early one by Banks with $NCH_2CO_2Bu^t$ [31], [32], NCH_2COCF_3 [4] and NCH_2COR [22] pyridinium salts.



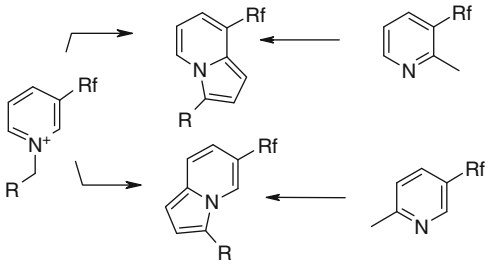
R, R'	Yield of **45** (%)	R	Yield of **46** (%)
COPh, H	62	CO_2Bu^t	37
COPh, Me	71	$COCF_3$	10
CO_2Et, H	57	COPh	12
CO_2Et, Me	53	CO_2Et	13



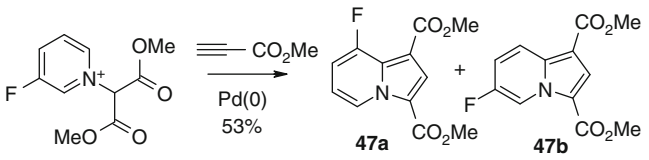
3 Synthesis of Indolizines with Substituent in Pyridine Ring

3.1 Indolizines with Substituent at Position 6 and 8

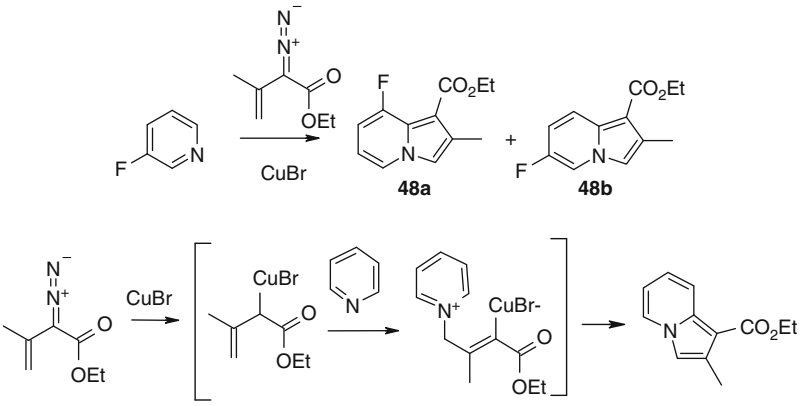
It is difficult to obtain pure isomers containing fluoro (or perfluorinated group) at 6- or 8-position. Since the substituents cannot be inserted directly into the pyridine fragment of indolizine ring, they should already exist in the precursors of the corresponding indolizines. However, this caused loss of regioselectivity (if β-substituted pyridinium salts were used) or necessity to use poorly available β-substituted α-picolines.



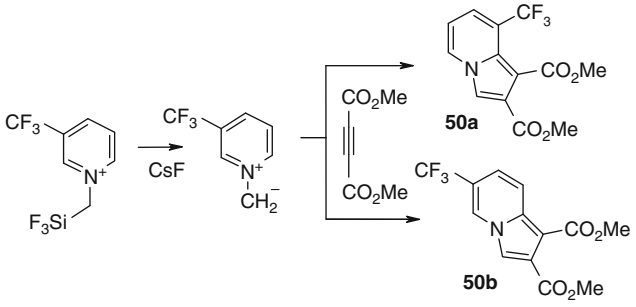
For example, reaction between 3-fluorosubstituted pyridinium N-bis-(methoxycarbonyl)methylide and methyl propiolate [33] proceeded in the yield 53 % giving predominant formation of 8-isomer (**47a:47b** = 65:35). CNDO2 calculations showed that the site selectivity can be rationalized by dipole-dipole interactions.



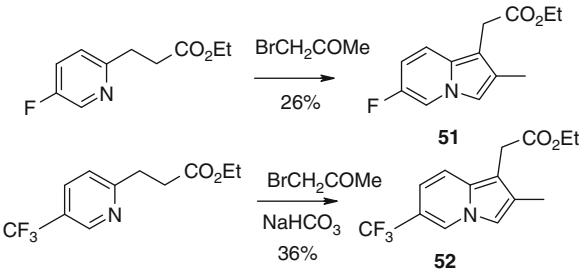
Another example was the copper(I)-catalyzed cycloaddition of ethyl isopropenyldiazoacetate to 3-F-pyridine [34]; reaction took place in the yield 60 % with clear predominance of 8-isomer (**48a:48b** = 3:1). The process represents the first successful example of metal-catalyzed cyclization of a π-deficient heterocyclic system with alkenyldiazo compounds.



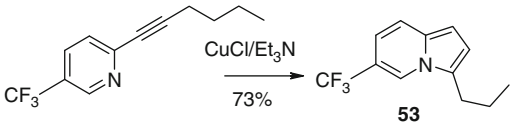
More one example is connected with generation of unsubstituted ylides [35]. As facile precursors for non stabilized pyridinium methylides N-(trimethylsilylmethyl) pyridinium triflates were synthesized. Cesium fluoride induced desilylation of the precursors liberated the nonstabilized pyridinium methylides which were trapped as the cycloadducts to dimethyl acetylenedicarboxylate. Trapping of 3-CF_3-pyridinium ylide gave the mixture of isomers (**50a:50b** = 1:5) in 53 % overall yield.



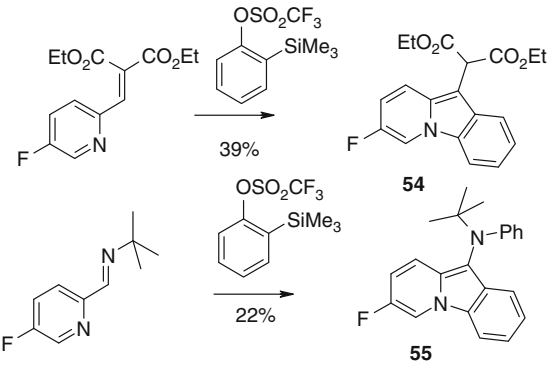
In the patent literature there were two examples of preparation of indolizyl-1-acetic acid according to Chichibabin methodology: the first one – 6-fluoroindilinzine **51** [36] and the second one – 6-CF_3-derivative [37].



Successful cycloisomerization of acyclic alkynyl imines to pyrroles caused an attempt to the cycloisomerization of the cyclic alkynyl imines; thus 2-alkynyl pyridine with CF_3-group gave a product of cyclization, indolizine **53** [38].

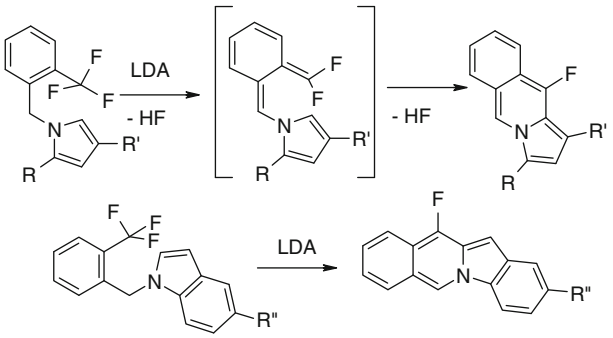


2-(Pyridin-2-yl-methylene)malonates and arynes reacted to produce pyrido[1,2-a]indoles which in some cases (**54**, **55**) correspond to 6-fluoroderivatives of benzoindolizines [39].



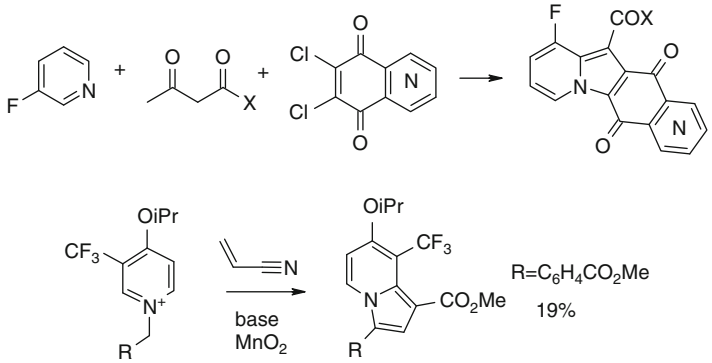
A base-promoted conversion of ortho-trifluoromethyl benzyl derivatives of NH-heterocycles into a respective fluorinated isoquinolines (38–57 % isolated yields) was reported [40]. The reaction is general for the benzylated derivatives of the electron-rich NH heterocycles, particularly indoles. The outcome of the reaction

could be explained by an intermediate formation of a highly reactive quinone methylide species.

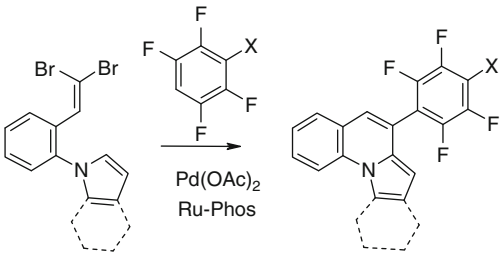


R	R'	R"	Yield, %	R	R'	R"	Yield, %
H	H	–	38	–	–	H	44
Me	H	–	39	–	–	Cl	52
Me	Me	–	48	–	–	OMe	43

In several cases the reported structures of 8-fluoro indolizine were in fact mixtures; however, no analysis of traces of the 6-fluoro isomer was performed. Thus, to the product of reaction of 3-fluoropyridine, CH-acid and active quinone compound the structure of 8-F-indolizine was assigned [41, 42, 43]. Similarly, cycloaddition to β-CF_3-pyridinium ylide is claimed to result in 8-CF_3-derivative of indolizine [25].



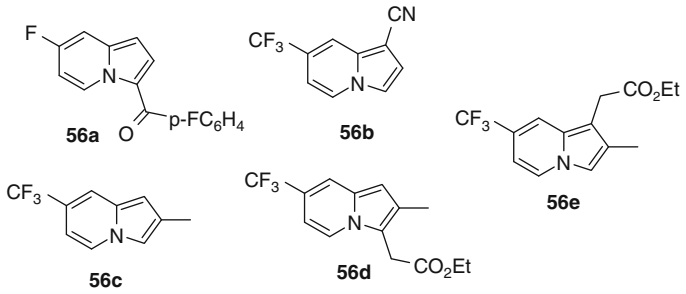
A novel and efficient preparation of 4-polyfluoroaryl substituted pyrrolo[1,2-a] quinolines via a palladium-catalyzed reaction of 1-[2-(2,2-dibromo-ethenyl) phenyl]-1H-pyrrole with polyfluorinated arenes was described [44]. The reaction is also applicable to obtain indoloquinolines with the same substitution pattern.



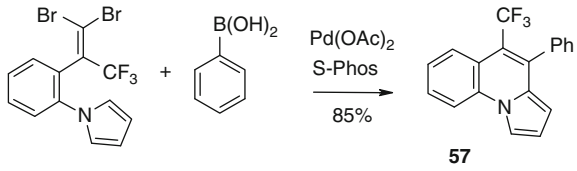
X	Yield, %	X	Yield, %
F	90	Me	68
MeO	80	CF_3	82

3.2 *Indolizines with Substituent at Position 7*

7-F or 7-CF_3 indolizines can be found only in the patent literature, namely compounds **56a** [45], **56b** [25], **56c**, **56d** [46] and **56e** [37].

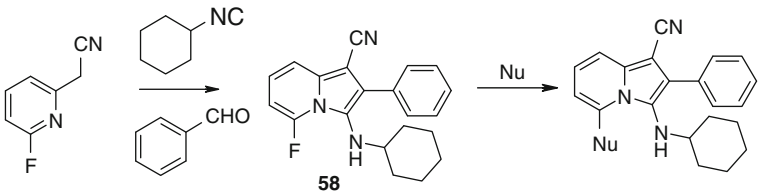


A water-accelerated palladium-catalyzed reaction of gem-dibromoolefins with a boronic acid via a tandem Suzuki-Miyaura coupling and direct arylation was reported [47]. One of the products, **57**, corresponded to 7-CF_3 derivative of benzoindolizine.



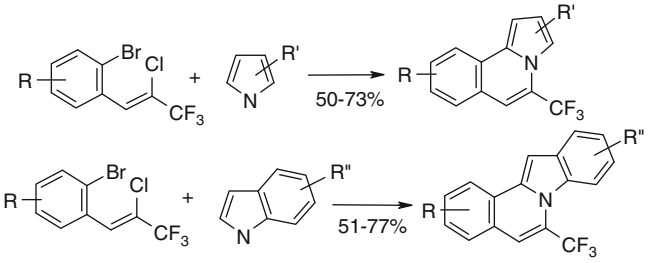
3.3 *Indolizines with Substituent at Position 5*

The only reaction which allowed introducing fluorine atom at position 5 of indolizine ring was the Ugi-type reaction [48]. The resulting 5-fluoroinolizine **58** was sensitive to nucleophiles giving rise to mini-library of 5-subsituted derivatives.



Indolizine (Nu)	Yield, %	Indolizine (Nu)	Yield, %
F (**58**)	65	$O(CH_2)_3NMe_2$	17
SCH_2CO_2Me	98	1-Morpholinyl	61
SCH_2CO_2H	95	$NH(CH_2)_2NMe_2$	48
SMe	49		

Finally, a palladium- and copper-catalyzed tandem N-H/C-H bond functionalization reaction of ortho-(2-chlorovinyl)bromobenzenes with indoles and pyrroles has been developed [49].



A variety of CF_3-containing indolo- and pyrrolo[2,1-a]isoquinolines were prepared in moderate to good yields via the cyclization of 1-bromo-2-(2-chloro-3,3,3-trifluoroprop-1-enyl)benzenes with indoles and pyrroles.

4 Conclusion

Fluorinated indolizines remained relatively rare class of compounds. In contrast to indolizines substituted at pyrrole fragment the structures having a perfluoro-substituent in the pyridine ring are less available. This is caused by the fact that 3

and 1 substituted indolizines are easily available by direct insertion of fluorine containing group. It should be mentioned that 1-, 2- and 3-substituted indolizines could be easily obtained by 1,3-dipolar cycloaddition reactions, whereas there is lack of general methods to the structures substituted in pyridine ring.

Acknowledgments This work was funded by RFBR (grant 12-03-00644-a).

References

1. (a) Flitsch W (1984) Pyrroles with fused six-membered heterocyclic rings: a-fused. . In: Katritzky A, Rees CW (ed) Comprehensive heterocyclic chemistry 4:443–496. (b) Swinborne P-J, Hunt JH, Klinkert G. (1978) Advances in indolizine chemistry. Adv Heteroc Chem 23:103–167. (c) Prostakov NS, Baktibaev OB (1975) Usp Khim 9:1649–1687. (d) Mosby WL (1961) Heterocyclic systems with bridgehead nitrogen atom, Part I. Interscience, New York, pp 239–371. (e) Borrows ET, Holland DO (1948) The chemistry of pyrrocolines and of the octahydropyrrocolines. Chem Rev 42:611–643. (f) Kost AN, Sagitullin RS, Gromov SP (1977) Nucleophilic amination and recyclization of the indolizine nucleus. Heterocycles 7:997–1001
2. Kobylianskii IJ, Novikov MS, Khlebnikov AF (2011) Formation and reactivity of gem-difluoro-substituted pyridinium ylides: experimental and DFT investigation. J Fluor Chem 3:175–180
3. Banks RE, Mohialdin SN (1988) Synthesis of indolizines from N-(2,2,2-trifluoroethyl)-pyridinium triflate; evidence for the generation of pyridinium (trifluoromethyl)methylide. J Fluor Chem 38:289–294
4. Banks RE, Mohialdin SN (1986) Synthesis of indolizines from pyridinium (trifluoroacetyl) methylide and fluorinated dipolarophiles. J Fluor Chem 34:275–280
5. Lungu NC, Depret A, Delattre F, Surpateanu GG, Cazier F, Woisel P, Shirali P, Surpateanu G (2005) Synthesis of a new fluorinated fluorescent β-cyclodextrin sensor. J Fluor Chem 3:385–388
6. Kobayashi Y, Kumadaki I, Fujino S (1977) 1,3-Dipolar cycloaddition reaction of aromatic N-oxide with hexafluorobutyne. Heterocycles 2:871–876
7. Shinji Y, Emiko O (2008) An unusual reaction of a pyridinium ylide with 1,1-dicyanoethylene derivatives. Chem Lett 6:628–629
8. Babaev EV (1987) Synthesis, structure and ambiphilic reactivity of nitroindolizines. PhD thesis, Moscow University, Moscow, 182 pp
9. (a) Bobrovskii SI, Babaev EV, Bundel YuG (1987) Recyclization of 3-acyl-6(8)-nitroindolizines to 2-acyl(carboxy)-5(7)- nitroindoles. Zh Org Khim (Russ) 10:2240–2241. (b) Babaev EV, Bobrovskii SI, Bundel YuG (1988) Recyclization of 2-phenyl-6(8)-nitro-3-trifluoracetylindolizine forming 3-phenyl-5(7)-nitroindole-2-carboxylic acid. Chem Heteroc Comp 11:1307. (c) Terenin VI, Babaev EV, Yurovskaya MA, Bundel YuG (1992) New recyclizations and transformations of azines. Chem Heteroc Comp 6:658–670
10. Kuznetsov AG, Bush AA, Babaev EV (2007) Synthesis and reactivity of 5-Br(I)-indolizines and their parallel cross-coupling reactions. Tetrahedron 4:749–756
11. American Home Products Corporation (1998) Saturated and unsaturated pyridazino[4,5-B] indolizines useful as antidementia agents. US Patent 5,756,501
12. Krivoshein AE, Krivorotov DV, Vorob'ev MV, Petrov ML, Polukeev VA (2007) Reaction of perfluorocarboxylic anhydrides with 2-(4-chlorophenyl)-1-(3,4-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-a]isoquinoline. Russ J Gen Chem 2:319–320
13. Terenin VI, Ivanov AS (2007) Effect of the trifluoroacetyl group on the direction of the recyclization of the pyrazine ring in 6-trifluoroacetylpyrrolo[1,2-a]pyrazinium salts. Chem Heterocyc Comp 11:1460–1465

14. Bobrovskii SI, Lushnikov DE, Bundel' YuG (1989) De-acylation, re-acylation and isomerization of 2-methyl-3-trihalogenacetyl indolizines. Zh Org Khim 10:2251–2252 (Russ)
15. Ohta T, Fukuda T, Ishibashi F, Iwao M (2009) Design and synthesis of lamellarin D analogues targeting topoisomerase I. J Org Chem 21:8143–8153
16. Mirek J, Haas A (1982) The reaction of indolizines and acetylindolizines with trifluoromethylsulfenyl chloride. J Fluor Chem 19:67–70
17. Do H-D, Daugulis O (2011) A general method for copper-catalyzed arene cross-dimerization. J Am Chem Soc 34:13577–13586
18. Bobrovskii SI, Lushnikov DE, Bundel' YG (1989) Structure and ambiphilic reactivities of indolizines. 5. Acylation of 2-methylindolizine. Chem Heterocycl Comp 12:1360–1364
19. Shen Y, Zhang Y, Jiang G-F (2002) A convenient synthesis of perfluoroalkylated indolizinylphosphonates. Synthesis 6:714–716
20. Shen Y, Zhang Y, Sun J (2002) Regiospecific synthesis of perfluoroalkylated pyrrolo[2,1-a] isoquinolinyl phosphonates. J Fluor Chem 2:157–162
21. Zhang X-C, Huang W-Y (1999) A one-step approach to 1-(fluoroalkyl)indolizine derivatives. Synthesis 1:51–54
22. Banks RE, Khaffaff SN (1991) Fluorocarbon derivatives of nitrogen. Part 18. Synthesis of fluorinated indolizines through reactions of pyridinium ethoxycarbonylmethylide or pyridinium phenacylide with perfluoropropene, perfluorobut-2-yne and 3,3,3-trifluoro-propyne. J Fluor Chem 3:407–418
23. Zhu S-Z, Qin C-Y, Wang Y-L, Chu Q-L (1999) Preparation of 1-trifluoroacetyl indolizines and their derivatives via the cycloaddition of pyridinium N-ylides with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one. J Fluor Chem 2:183–188
24. Fang X, Wu Y-M, Deng J, Wang S-W (2004) Synthesis of monofluorinated indolizines and their derivatives by the 1,3-dipolar reaction of N-ylides with fluorinated vinyl tosylates. Tetrahedron 25:5487–5494
25. Shimizu K, Iizuka M, Kissei Pharmaceutical Co Ltd (2012) Patent US2012/15972
26. Wu K, Chen Q-Y (2003) A facile synthetic method for 2-fluoroindolizines from 1-chloro-2,2,2-trifluoroethane (HCFC-133a) and 1,1,1,2-tetrafluoroethane (HFC-134a). J Fluor Chem 2:171–174
27. Zhang X-C, Huang W-Y (1998) Cycloaddition reactions of N-(cyanomethyl)pyridinium ylides with 2,2-dihydropolyfluoroalkanoates. J Fluor Chem 1:13–16
28. Zhang X-C, Huang W-Y (1998) A convenient synthesis of polyfluoroalkyl-substituted pyrazolo[1,5-a]pyridine, pyrrolo[1,2-b]pyridazine and indolizine derivatives. J Fluor Chem 1:57–64
29. Peng W, Zhu S (2001) Reactions of N-benzyl-pyridinium or -isoquinolinium ylides with ethyl 3-fluoro-3-(fluoroalkyl)acrylates to give fluoroalkylsubstituted indolizine and pyrrolo[2,1-a] isoquinoline derivatives. J Chem Soc Perkin Trans 1 23:3204–3210
30. Wu K, Chen Q-Y (2003) Synthesis of fluorinated indolizines and 4H-pyrrolo[1,2-a]benzimidazoles via 1,3-dipolar cycloaddition of fluoroalkenes to N-ylides. Synthesis 1:35–40
31. Banks RE, Hitchen SM, Thomson J (1982) Reactions of pyridinium t-butoxycarbonylmethylide with perfluoropropene and some fluoroaromatics. J Fluor Chem 20:127–132
32. Banks RE, Thomson J (1985) Reaction of pyridinium t-butoxycarbonylmethylide with perfluoropropene and with some fluoroaromatic compounds: synthesis of some fluorinated indolizines. J Chem Res Miniprint 2:671–689
33. Matsumoto K, Ikemi Y, Konishi H, Shi X-L, Uchida T (1988) Site selectivity in the 1,3-dipolar cycloaddition reaction of unsymmetric pyridinium bis(methoxycarbonyl)methylides with methyl propiolate. Heterocycles 11:2557–2562
34. Barluenga J, Lonzi G, Riesgo L, Lopez LA, Tomas M (2010) Pyridine activation via copper(I)-catalyzed annulation toward indolizines. J Am Chem Soc 38:13200–13202
35. Tsuge O, Kanemasa S, Kuraoka S, Takenaka Shigeori (1984) N-(Trimethylsilylmethyl)-pyridinium trifluoromethanesulfonates as facile precursors for nonstabilized pyridinium methylides. Chem Lett 13:279–280

36. Hynd G, Argenta Discovery Limited (2008) CRTH2 antagonists. Patent WO2008/74966
37. Hynd G, Ray NC, Finch H, Middlemiss D, Cramp MC, Blaney PM, Williams K, Griffon Y, Harrison TK, Crackett P (2009) Indolizine derivatives. Patent US2009/163534
38. Kel'in AV, Sromek AW, Gevorgyan V (2001) A novel Cu-assisted cycloisomerization of alkynyl imines: efficient synthesis of pyrroles and pyrrole-containing heterocycles. J Am Chem Soc 9:2074–2075
39. Rogness DC, Markina NA, Waldo JP, Larock RC (2012) Synthesis of pyrido[1,2-a]indole malonates and amines through aryne annulation. J Org Chem 6:2743–2755
40. Kiselyov AS (2006) A convenient procedure for the synthesis of fused fluoro isoquinolines. Tetrahedron 4:543–548
41. Shen D-Q, Wu N, Li Y-P, Wu Z-P, Huang Z-S, Gu L-Q, An L-K, Zhang H-B (2010) Design, synthesis, and cytotoxicity of indolizinoquinoxaline-5,12-dione derivatives, novel DNA topoisomerase IB inhibitors. Austr J Chem 7:1116–1121
42. Shen D-Q, Wu Z-P, Wu X-W, An Z-Y, Bu X-Z, Gu L-Q, Huang Z-S, An L-K (2010) Synthesis and antiproliferative activity of indolizinophthalazine-5,12-dione derivatives, DNA topoisomerase IB inhibitors. Eur J Med Chem 9:3938–3942
43. Cheng Y, An L-K, Wu N, Wang X-D, Bu X-Z, Huang Z-S, Gu L-Q (2008) Synthesis, cytotoxic activities and structure–activity relationships of topoisomerase I inhibitors: indolizinoquinoline-5,12-dione derivatives. Bioorg Med Chem 8:4617–4625
44. Ye S, Wu J, Liu J (2012) Generation of 4-polyfluoroaryl pyrrolo[1,2-a]quinolines via C-H bond activation. Chem Comm 41:5028–5030
45. Synta Pharmaceuticals Corp (2004) Synthesis of indolizines. Patent WO2004/24727
46. Hund G, Argenta Discovery Ltd (2007) Indolizine derivatives as ligands of the CRTH2 receptor. Patent WO2007/31747
47. Chai DI, Lautens M (2009) Tandem Pd-catalyzed double C-C bond formation: effect of water. J Org Chem 8:3054–3061
48. Bedjeguelal K, Bienayme H, Dumoulin A, Poigny S, Schmitt P, Tam E (2006) Discovery of protein-protein binding disruptors using multi-component condensations small molecules. Bioorg Med Chem Lett 15:3998–4001
49. Sun L-L, Liao Z-Y, Tang R-Y, Deng C-L, Zhang X-G (2012) Palladium and copper cocatalyzed tandem N-H/C-H bond functionalization: synthesis of CF_3-containing indolo- and pyrrolo[2,1-a]isoquinolines. J Org Chem 6:2850–2856

Fluorinated Furans and Benzofurans

Alexander V. Butin, Igor V. Trushkov, Olga V. Serdyuk, and Vladimir T. Abaev

Contents

Abstract Synthesis, reactions, and application of furans and benzofurans bearing a fluorine atom and a trifluoromethyl group are reviewed.

A.V. Butin (✉)
Department of Chemistry, Perm State University, Bukireva 15,
Perm 614990, Russian Federation
e-mail: alexander_butin@mail.ru

I.V. Trushkov
Department of Chemistry, M. V. Lomonosov Moscow State University,
Leninskie Gory, 1-3, Moscow 119991, Russian Federation

O.V. Serdyuk
Department of Chemistry and Pharmacy, Chair of Organic Chemistry I,
University of Erlangen-Nuremberg, Henkestrasse 42, 91054 Erlangen, Germany

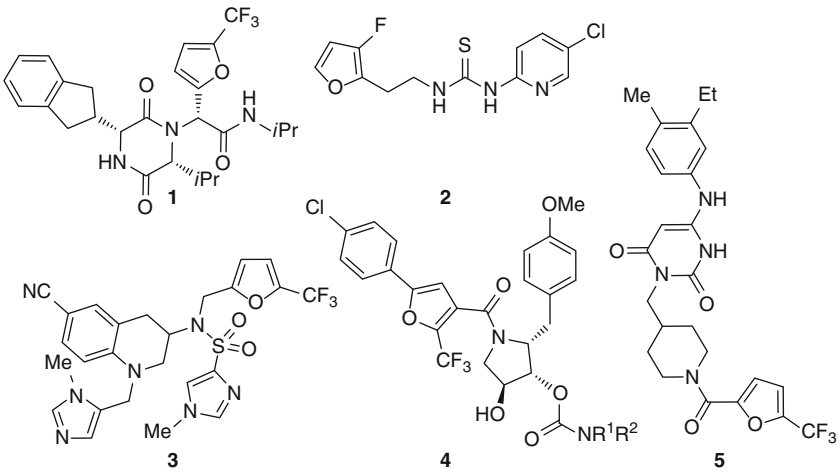
V.T. Abaev
Department of Chemistry, North-Ossetian State University, Vatutina 46,
Vladikavkaz 362025, Russian Federation

V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_5,

Keywords Fluorofurans • Trifluoromethylfurans

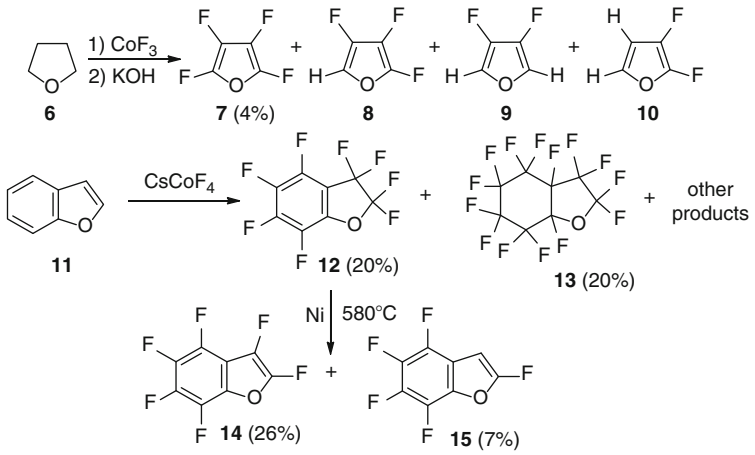
1 Introduction

Furans and benzofurans bearing a fluorine atom or a trifluoromethyl group attract significant attention due to their important pharmacological properties. For example, 2-trifluoromethylfuran **1** is oxytocin antagonist [1], 3-fluorofuran **2** inhibits HIV-1 reverse transcriptase at nanomolar level [2]. 2-Trifluoromethylfuran **3** reveals antimalarial activity [3], derivatives **4** and **5** demonstrate antibacterial properties [4, 5], etc. [6–12]. The main progress in the synthesis of fluorinated furans was summarized recently [13]. The present review covers methods for the synthesis of furans and benzofurans with a fluorine atom or a trifluoromethyl group, as well as their application, excluding patent data.



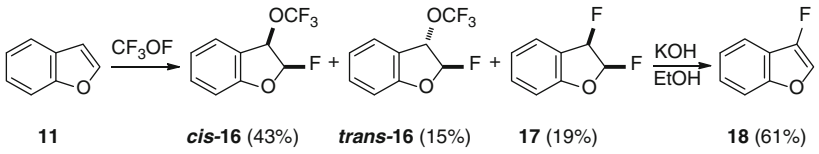
2 Synthesis of Fluorofurans and Fluorobenzofurans

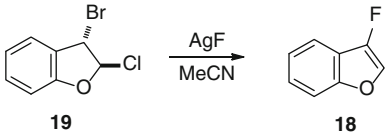
It is well known, that the direct fluorination of furan proceeds non-selectively. Application of fluorine diluted with an inert gas to the furan monofluorination was found to be unsuitable [14]. Moreover, the reaction of 2,5-diarylfurans with Selectfluor proceeded via oxidative ring opening to produce *cis*-enediones [15]. Reaction of tetrahydrofuran **6** with cobalt(III) fluoride or potassium tetrafluorocobaltate(III) ($KCoF_4$) followed by the treatment with alkali afforded a mixture of perfluorofuran **7**, both trifluorofurans and three difluorofurans. All products were isolated in very low yields [16–18].



Similarly, fluorination of benzofuran **11** with cesium tetrafluorocobaltate(III) led to a mixture of nonaromatic products. Heating the product **12** over nickel gauze at 580 °C yielded hexa- and pentafluorobenzo[*b*]furans **14** and **15** [19].

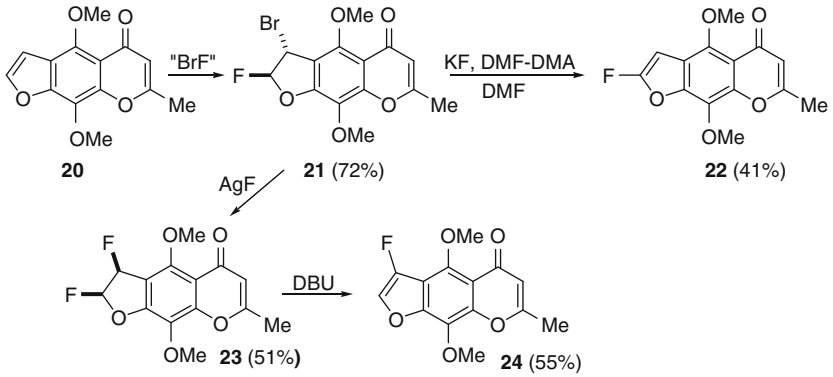
Other addition/elimination sequence was utilized for monofluorination of benzofuran and its derivatives. Thus, the reaction of benzofuran **11** with trifluoromethyl hypofluorite (CF_3OF) furnished 2-fluoro-3-trifluoromethoxy-2,3-dihydrobenzofurans **16** (43 % *cis*- and 15 % *trans*-isomer) and *cis*-difluoroderivative **17** (19 %). Treatment of the derivative **17** with ethanolic potassium hydroxide produced 3-fluorobenzofuran **18** in 61 % yield [20]. 3-Fluorobenzofuran **18** was also synthesized from the compound **19** using silver fluoride as fluorinating and dehydrohalogenating reagent at the second step [21].



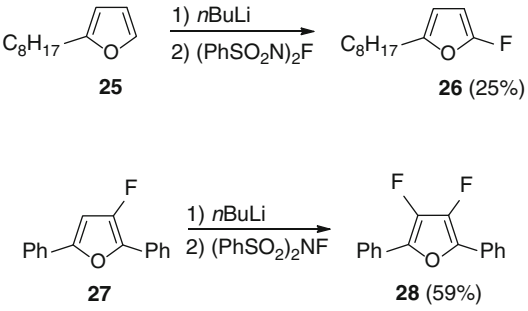


A related procedure for benzofuran monofluorination was developed starting from khellin **20**. The reaction with BrF generated *in situ* yielded product **21**, which dehydrobromination with KF/DMF-DMA system produced 2-fluorokhellin **22** along with 3-bromoderivative. Transformation of **21** into *cis*-difluoride **23** followed

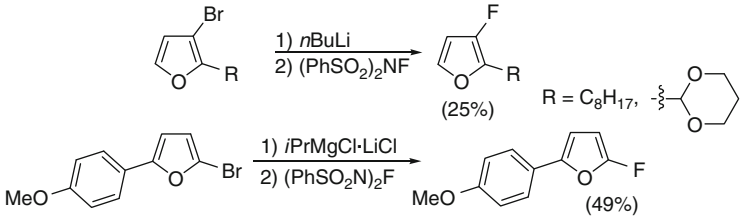
by the treatment with DBU afforded 3-fluorokhellin **24** [22]. The study of *anti*- and *syn*-elimination from 2,3-dihalo-2,3-dihydrobenzofurans showed that halide was eliminated from the C2 atom exclusively; *cis*-isomer reacted faster than *trans*-one; electron-withdrawing chlorine substituent at the C5 atom of benzofuran ring accelerated elimination [23].



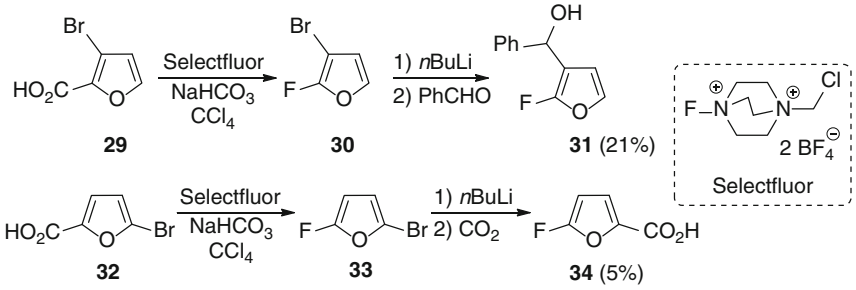
Selective monofluorination of furan can be performed via lithiation followed by the treatment with *N*-fluorobis(benzenesulfonyl)amine. For example, 2-octylfuran **25** was transformed into 2-fluoro-5-octylfuran **26** in 25 % yield [24]. When both α-positions are substituted, a fluorine atom can be introduced into the β-position. Thus, fluorination of **27** furnished 3,4-difluorofuran **28** in 59 % yield [25].



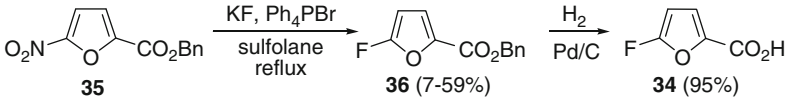
Another method for the fluorofuran synthesis is transmetallation of the corresponding aryl halide with *n*BuLi [2, 24] or *i*PrMgCl [26, 27] followed by addition of positive fluorine source, for example, *N*-fluorobis (benzenesulfonyl)amine.



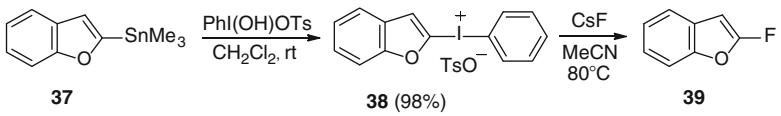
Fluorodecarboxylation was also used for the introduction of fluorine into the furan ring. Thus, treatment of **29** with Selectfluor afforded 3-bromo-2-fluorofuran **30**. Subsequent transmetallation with *n*BuLi and quench with benzaldehyde furnished alcohol **31** in 21 % overall yield. Similarly, 5-bromo-2-furoic acid **32** was transformed into 2-bromo-5-fluorofuran **33** and then to 2-benzoyl-5-fluorofuran [28] and 5-fluoro-2-furoic acid **34** [29].



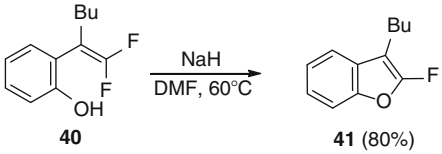
A related fluorodenitration was shown to proceed efficiently allowing for transformation of benzyl 5-nitrofuran-2-carboxylate **35** into 5-fluoro derivative **36** in 59 % yield. The reaction did not proceed with methyl or *tert*-butyl esters as well as in the case of free acid or nitrile. Hydrogenolysis of benzyl ester allowed to obtain acid **34** as well [29].



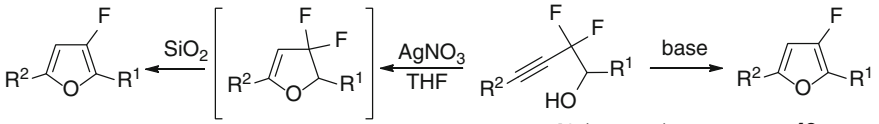
Reaction of cesium fluoride with (benzofuran-2-yl)phenyliodonium tosylate **38**, which can be easily synthesized from (benzofuran-2-yl)trimethyltin **37** in quantitative yield, produced 2-fluorobenzofuran **39**. (2-Furyl)phenyliodonium salt afforded furan and fluorobenzene (the yield was not given) [30].



Base-induced cyclization of *o*-(2,2-difluoroalkenyl)phenol **40** was demonstrated to be an efficient method for the synthesis of 2-fluoro substituted benzofuran **41** [31, 32].



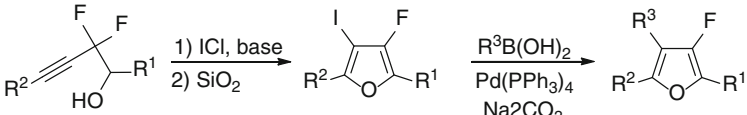
Cyclization of difluorohomopropargylic alcohols **42** afforded 3-fluorofurans **43** in good yields. Reaction was induced by either DBU, potassium *tert*-butoxide [25, 33], or silver nitrate [34]. Iodocyclization of alcohols **42** yielded the corresponding 3-fluoro-4-iodofurans **44** which were further involved into the Suzuki reaction yielding 3-fluorofurans **45** in good to high yields [35]. A related halocyclization of 2-fluorobut-3-yn-1-ones **46** in the presence of gold(I) chloride and zinc(II) bromide produced 3-fluoro-4-halofurans **47** in 62–78 % yields [36, 37].



43 (20-68%) **42** (42-90%) **43**

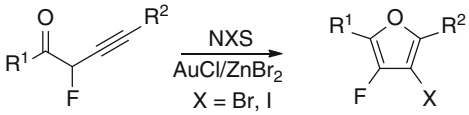
R^1 = aryl, $BnOCH_2$
R^2 = H, Ph, $(i\text{Pr})_3\text{Si}$, $n\text{C}_6\text{H}_{13}$, $BnOCH_2$

R^1 = Et, CH_2=CH, Het
R^2 = Ph, $n\text{C}_5\text{H}_{11}$



42 **44** (46-76%) **45** (50-98%)

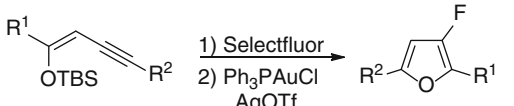
R^1= Ph, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, $BnOCH_2$; R^2= Ph, *n*-C_6H_{13}, $BnOCH_2$;
R^3= Ph, 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-$HOCC_6H_4$, 4-CNC_6H_4, 3,4-$(OCH_2O)C_6H_4$, PhCH=CH, 3-thienyl



46 **47** (62-78%)

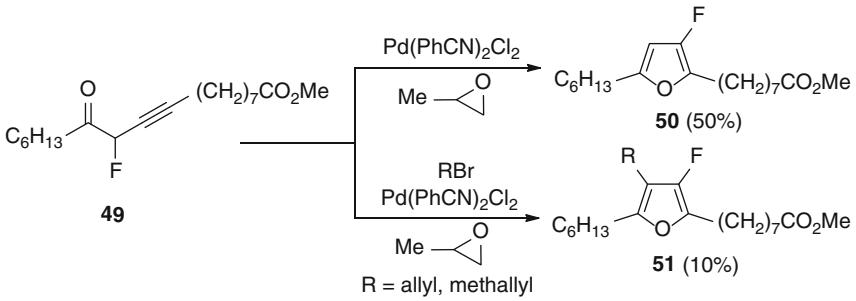
R^1= Ph, 4-FC_6H_4, 4-BrC_6H_4; R^2= 4-MeC_6H_4, *c*C_3H_5, 4-*t*-BuC_6H_4

Similar fluorocyclization of but-3-yn-1-ones using Selectfluor was found to be inefficient. However, the transformation of ketone into silyl enolate **48** allowed one to perform the cyclization with formation of 3-fluorofurans **43** in 52–96 % yields [37, 38]. 3-Fluorofuran derived fatty esters **50**, **51** were obtained from alkynone **49** using a similar reaction catalyzed by $(PhCN)_2PdCl_2$ in propylene oxide [39].

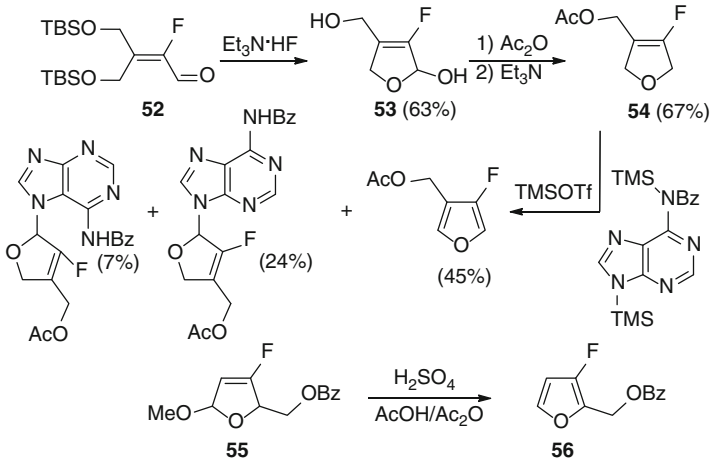


48 **43** (52-96%)

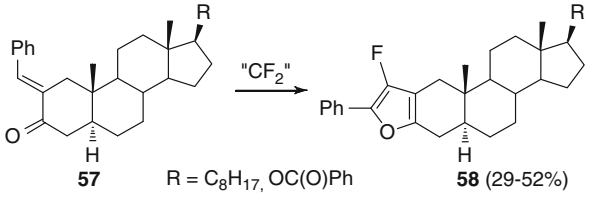
R^1= Et, Ph, 4-FC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$; R^2=Ph, 4-MeC_6H_4, *c*C_3H_5, 4-*t*BuC_6H_4



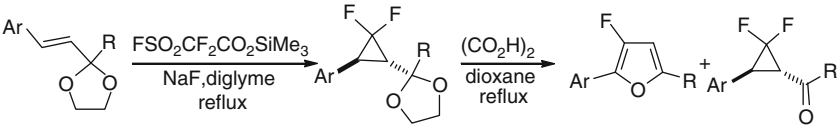
Desilylative cyclizations of **52** yielded lactol **53**. Further acetylation with acetic anhydride followed by the treatment with N6-benzoyladenine derivative resulted in formation of 3-acetoxymethyl-4-fluorofuran in 45 % yield [40]. A similar reaction of 2-methoxy-2,5-dihydrofuran **55** with silylated pyrimidine bases or the treatment of **55** with an acid led to fluorofuran **56** [41].



The reaction of difluorocarbene, generated by thermal decomposition of sodium chlorodifluoroacetate, with 2-benzylidene-5α-cholestan-3-one **57** and related substrates afforded 3-fluoro-2-phenylfuran fused to steroid fragment via C4-C5 bond **58**. 2-Benzylidenecyclohexanone reacted similarly with difluorocarbene yielding 3-fluoro-2-phenyl-4,5,6,7-tetrahydrobenzofuran in low yield [42].



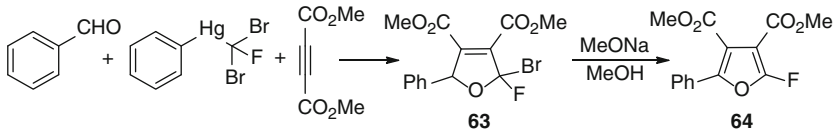
This formal [4 + 1] cycloaddition proceeded through cyclopropanation followed by rearrangement of acylcyclopropane to dihydrofuran and HF elimination. It was shown that reaction of 2-styryl-1,3-dioxolanes **59** with difluorocarbene, generated from $FSO_2CF_2CO_2SiMe_3$ under the treatment with sodium fluoride, furnished difluorocyclopropanes **60**. Further heating with oxalic acid produced 3-fluorofurans **61** or the corresponding cyclopropyl ketones **62** depending on substituents in starting compounds [43]. Moreover, bromide induced ring opening of 1-benzoyl-2,2-difluoro-3-phenylcyclopropane (**62**, Ar=R=Ph) was accompanied by formation of 3-fluoro-2,5-diphenylfuran in 7 % yield [44].



59 **60** (40-72%) **61** (1-55%) **62** (36-78%)

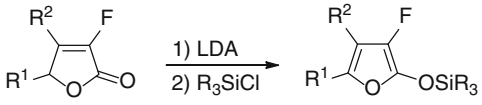
Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$CF_3C_6H_4$; R = H, Me, Ph

Reaction of carbene, generated from $PhHgCBr_2F$, with benzaldehyde and dimethyl acetylenedicarboxylate afforded 2-bromo-2-fluoro-2,3-dihydrofuran **63**. The compound **63** was aromatized by treatment with sodium methoxide producing fluorofuran **64**. The reaction proceeded via intermediate carbonyl ylide that was trapped with dimethyl acetylenedicarboxylate in the subsequent [3 + 2] cycloaddition reaction [45].



63 **64**

Fluorinated butenolides **65** were easily transformed into 2-siloxy-3-fluorofurans **66** by reaction with silyl chlorides [46–48].



65 **66** (48-70%)

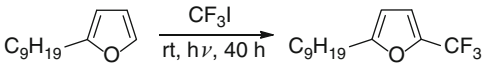
R^1= H, Ph; R^2=Cl, Ph; R_3SiCl = Me_3SiCl, *t*$BuMe_2SiCl$

3 Synthesis of Trifluoromethyl-Substituted Furans and Benzofurans

Methods for the synthesis of trifluoromethyl-substituted furans and benzofurans can be divided into several groups: direct trifluoromethylation of heterocycle, transformation of functional groups of hetarene into trifluoromethyl substituent, Diels-Alder/retro-Diels-Alder sequence, and various methods for the furan ring formation from precursors bearing trifluoromethyl moiety.

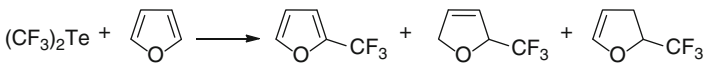
3.1 Trifluoromethylation of Furan Derivatives

Trifluoromethylation of furans and benzofurans is less studied to compare with other aromatic heterocycles. Generally, it can be performed as radical, electrophilic or nucleophilic process depending on the nature of trifluoromethyl source and reaction conditions. Thus, treatment of 2-nonylfuran **67** with trifluoromethyl iodide in acetonitrile under irradiation afforded the α-trifluoromethylated product **68** in 51 % yield [49].



67 **68** (51%)

Photochemical and thermal trifluoromethylation of furan **69** was performed using trifluoromethyl iodide, as well as $Te(CF_3)_2$, $Hg(CF_3)_2$, and $Sb(CF_3)_3$. Under these conditions, the best yields of 2-(trifluoromethyl)furan **70** (51 and 74 %) were achieved using $Te(CF_3)_2$ [50].

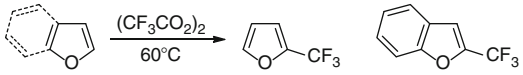


69 **70**

120°C	46% : traces : traces
150°C	74% : traces : 0
160°C	64% : traces : traces

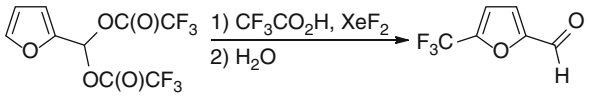
Other systems for generation of electrophilic perfluoroalkyl radicals were also applied to the synthesis of perfluoroalkylfurans. Thus, trifluoromethylation of furan and benzofuran with trifluoromethyl iodide in DMSO afforded the 2-trifluoromethyl derivatives in 16 and 30 % yield correspondingly [51]. Better results were reported for the photocatalytic $Ru(bpy)_3Cl_2$-TMEDA system. Trifluoromethylation of

2-ethylfuran under visible light irradiation proceeded in 92 % yield with low catalyst loading (1 mol %) [52]. Trifluoromethylation of furan and benzofuran was also performed via the thermal decomposition of bis(trifluoroacetyl) peroxide [53].



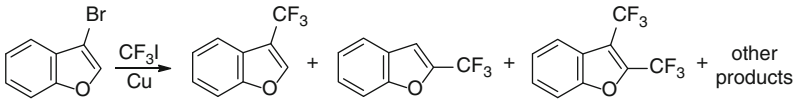
11,69 **70** (53%) **71** (47%)

One more common source of trifluoromethyl radical is trifluoroacetic acid-xenone difluoride system. For example, treatment of furfural or its bis(trifluoroacetate) **72** with trifluoroacetic acid and XeF_2 followed by hydrolysis furnished 5-(trifluoromethyl)furfural **73** in moderate yield [54].



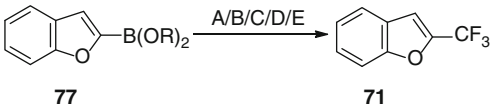
72 **73** (30%)

Trifluoromethylation of 3-bromobenzofuran **74** with trifluoromethyl iodide and copper powder produced a mixture of products including (trifluoromethyl)benzofurans **71**, **75**, and **76** [55]. Yields of products depend on the reaction conditions significantly [56].



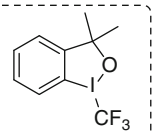
74	**75**	**71**	**76**
Pyridine	9%	27%	45%
DMF (140°C)	66%	11%	0%

The employment of more nucleophilic benzofuranylboronic acid **77** as a substrate for trifluoromethylation and a copper salt as an additive has advantages due to the mild conditions (40–70 °C), rate acceleration, better selectivity and yields. It was proposed that trifluoromethylcopper species are responsible for this effect. The trifluoromethyl group can be delivered to copper center as a radical and this approach was exemplified by using trifluoromethyl iodide, copper(I) acetate and visible-light photocatalyst $Ru(bpy)_3Cl_2 \cdot 6H_2O$ [57] or CF_3SO_2Na/*t*-BuOOH/CuCl system [58] where 2-trifluoromethylbenzofuran **71** was obtained in 56 and 77 % yield correspondingly. Employment of a CF_3SiMe_3/KF/CuOTf system as a source of trifluoromethyl anion was also suitable; benzofuran **71** was obtained in 76 % yield [59]. Examples of electrophilic trifluoromethylating reagents including Togni's reagent and trifluoromethylsulphonium salts were also reported [60–62].



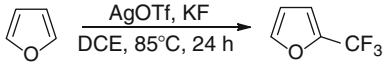
77 **71**

A: CF_3I, CuOAc, $Ru(bpy)_3Cl_2{*}6H_2O$, K_2CO_3, hν, DMF (56%)
B: CF_3SO_2Na/*t*BuOOH/CuCl (77%)
C: CF_3SiMe_3/KF/CuOTf (76%)
D: $Ph_2S^+CF_3\,OTf^-$, Cu, $NaHCO_3$ (66%)
E: Togni´s reagent, Cu(I), base, 1,10-phenanthroline (76%)



Togni´s reagent

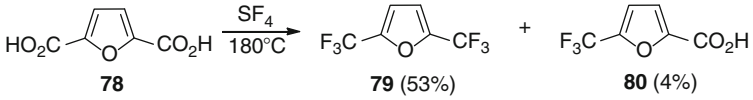
Trifluoromethylation of furan with Me_3SiCF_3/KF/AgOTf was shown to proceed in low yields, on the contrary to trifluoromethylation of other aromatics [63].



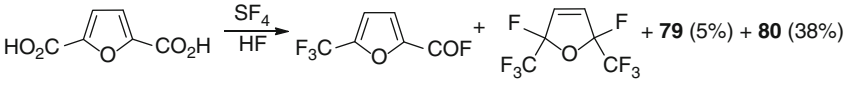
69 **70** (16%)

3.2 Synthesis of Trifluoromethylfurans from Furoic Acids

Treatment of 2,5-furandicarboxylic acid **78** with five equivalents of sulfur tetrafluoride provided 2,5-bis(trifluoromethyl)furan **79** as a major product [64]. Other furoic acid derivatives were also transformed into trifluoromethylfurans using sulfur tetrafluoride [65–71]. If the reaction was performed in the presence of anhydrous HF, furan dearomatization products were formed. Thus, diacid **78** gave fluoroanhydride **81** and dihydrofuran derivative **82** along with **79** and **80**. Yields of the products depend on ratio of reagents and reaction temperature [64, 65].

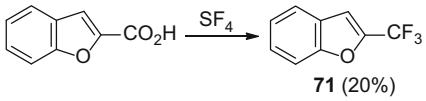


78 **79** (53%) **80** (4%)



78 **81** (10%) **82** (4%)

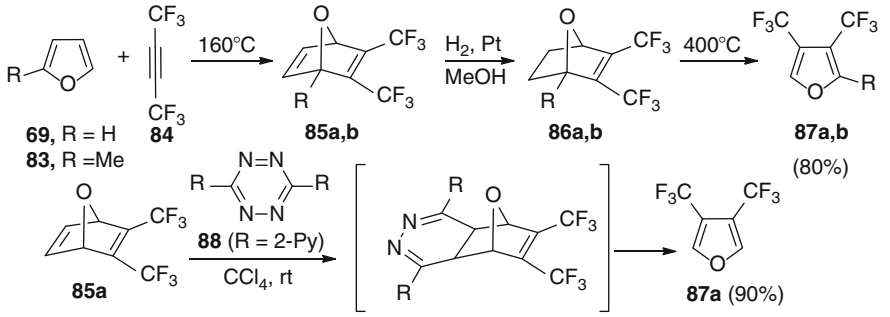
Treatment of 2-benzofurancarboxylic acid with sulfur tetrafluoride was found to produce 2-(trifluoromethyl)benzofuran **71** in 20 % yield; 3-(trifluoromethyl)benzofuran **75** could not be synthesized by this method [55].



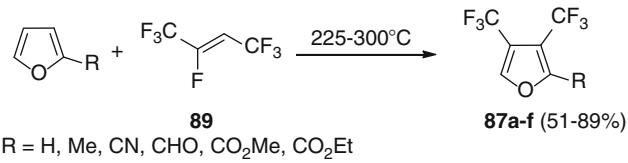
71 (20%)

3.3 Diels-Alder/Retro-Diels-Alder Sequence

Diels-Alder reaction/retro-Diels-Alder sequence can be applied to the synthesis of furans with unusual substitution pattern. For example, the reaction of furan **69** and 2-methylfuran **83** with hexafluorobut-2-yne **84** afforded 7-oxanorbornadienes **85**, which were further transformed into 3,4-bis(trifluoromethyl)furans **87** through the intermediate **86** [72–75]. Temperature of retro-Diels-Alder reaction should be relatively high in this case. However, this drawback can be circumvented by the addition of tetrazine **88**. It was shown that reaction of **85a** with this reagent proceeds at room temperature giving rise to 3,4-bis(trifluoromethyl)furan **87a** through the Diels-Alder cycloaddition and double retro-Diels-Alder reaction [76].



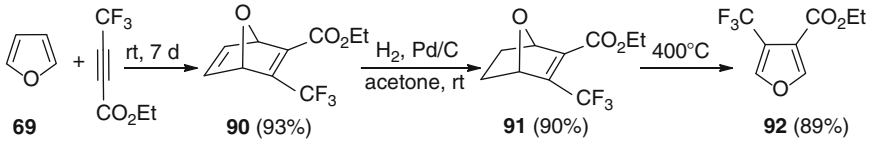
Compound **84** is expensive, and its preparation is quite challenging. Instead, heptafluorobutene **89** was proposed as an alternative for the same transformation as it can be readily synthesized from hexachlorobutadiene and KF. It was shown that heating of **89** with various furans produced compounds **87a-f** in moderate to good yields. The exception was 2-furoic acid which underwent decarboxylation under reaction conditions furnishing **87a** in 39 % yield. Nevertheless, the acid **87 g** can be obtained by indirect way through basic hydrolysis of esters **87c** (R=CO_2Me) and **87d** (R=CO_2Et). In reaction of **89** with 2-cyanofuran, compound **87a** (21 %) was isolated as a product of hydrolysis and decarboxylation together with **87e** (R=CN, 71 %). Hydrofluorination of cyano-group with subsequent elimination of cyanogen fluoride accounts for the unusual formation of the latter compound. Authors pointed out that **87** are formed through cycloaddition of **89** to furan followed by HF elimination rather than elimination-cycloaddition sequence [77].



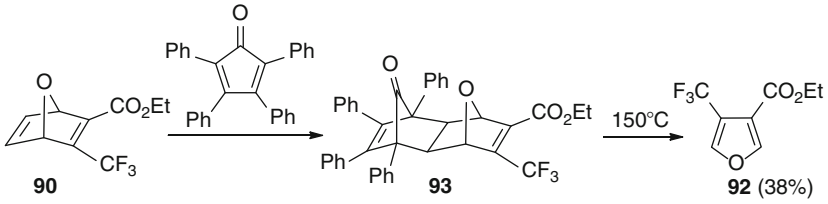
89
R = H, Me, CN, CHO, CO_2Me, CO_2Et

87a-f (51-89%)

Similarly, Diels-Alder/retro-Diels-Alder sequence was utilized to the synthesis of ethyl 4-(trifluoromethyl)furan-3-carboxylate **92** starting from furan and ethyl trifluorobut-2-ynoate via intermediate products **90** and **91** [78]. Cycloadduct **90** was also transformed into **92** by two-step procedure including its Diels-Alder reaction with tetracyclone and thermolysis of adduct **93** [79].

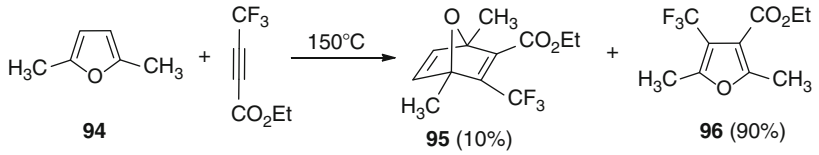


69 **90** (93%) **91** (90%) **92** (89%)



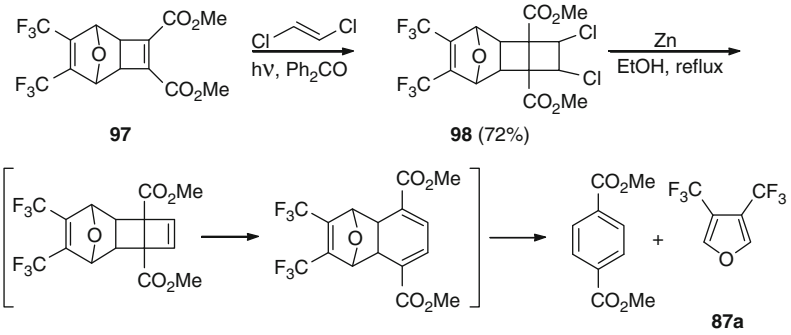
90 **93** **92** (38%)

Hydrogenation of the intermediate 7-oxanorbornadiene is not always a necessary step. Thus, reaction of ethyl trifluorobutynoate with 2,5-dimethylfuran **94** at 150 °C for 24 h afforded a mixture of cycloadduct **95** and tetra-substituted furan **96** in a ratio of 1:9 [80].

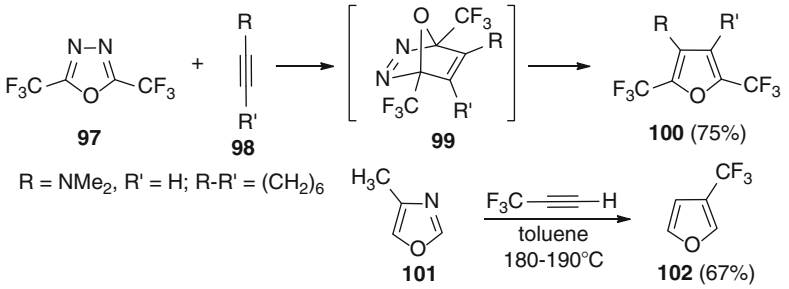


94 **95** (10%) **96** (90%)

Other rings were also used for related transformations. For example, derivative **87a** was synthesized from tricyclic compound **97** through [2 + 2] cycloaddition leading to **98** followed by Zn induced dechlorination which led to domino-reaction, which last step is retro-Diels-Alder reaction [81]. Starting material was synthesized via the reaction of **85a** with dimethyl acetylenedicarboxylate.

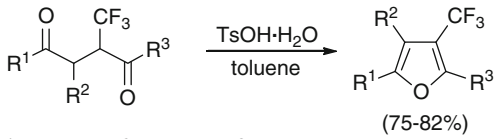


Heating of 1,3,4-oxadiazole **97** with alkynes **98** furnished the corresponding furans **100** in good yields [82, 83]. Similarly, reaction of 4-methyloxazole **101** with trifluoropropyne gave rise to 3-(trifluoromethyl)furan **102** [84].

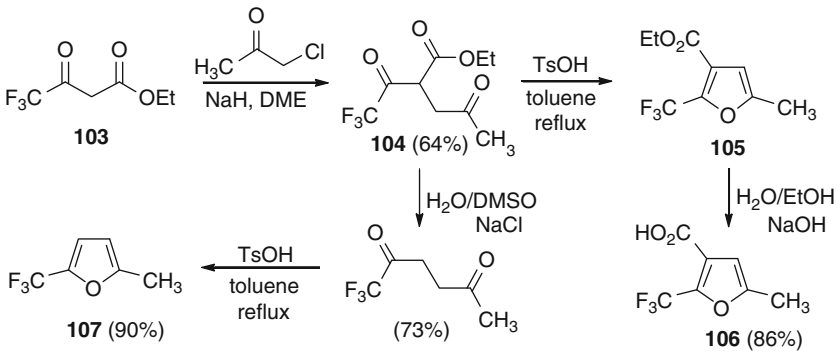


3.4 Cyclization Leading to Trifluoromethyl-Substituted Furans

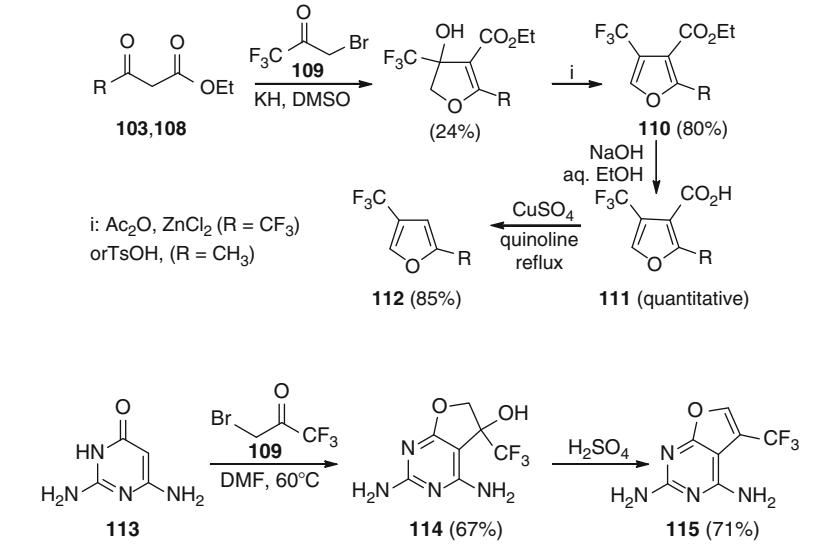
Other common approach towards trifluoromethylated furans is based on a cyclization of the corresponding 1,4-diketones [85]. Various methods were used for the synthesis of starting trifluoromethyl-substituted 1,4-diketones. Thus, alkylation of ethyl 4,4,4-trifluoroacetate **103** with chloroacetone produced 1,4-diketone derivative **104**. The latter underwent cyclizations either directly [86] or after decarboxylation [87] yielding furans **105**–**107**.



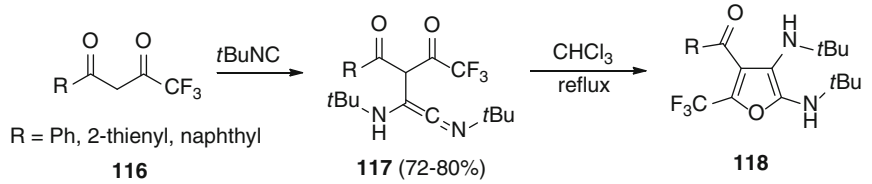
R^1 = Ph, Et; R^2 = H, Me; R^3 = Et, 2-thienyl



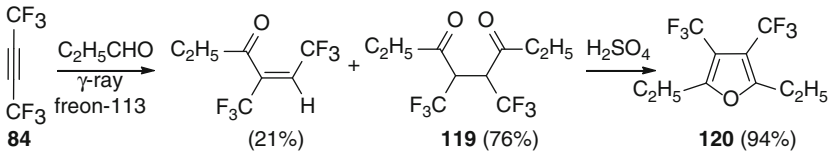
Isomeric furans **110**–**112** were obtained by reaction of **103** or ethyl acetoacetate **108** with 1,1,1-trifluoro-3-bromoacetone **109** [87, 88]. Reaction of **109** with 2,6-diaminopyrimidin-4-one **113** produced bicyclic adduct **114** aromatization of which gave furo[2,3-*d*]pyrimidine **115** [89, 90].



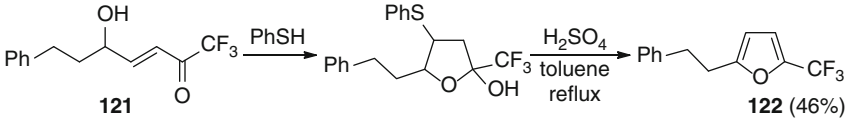
A related cyclization of β-ketoketimines **117**, obtained by reaction of *tert*-butyl isocyanide with 4-aryl-1,1,1-trifluorobutan-2,4-diones **116**, afforded 2,3-diamino-4-aroyl-5-(trifluoromethyl)furans **118** [91].

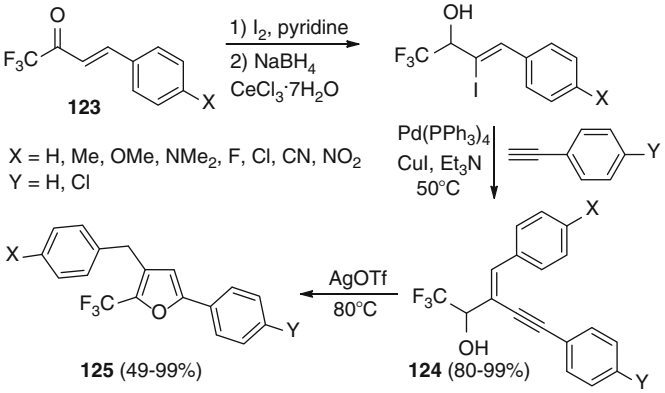


γ-Ray irradiation of a mixture of hexafluorobutyne **84** and propionaldehyde gave 1,4-diketone **119** which was efficiently cyclized into furan **120** in 94 % yield [92].

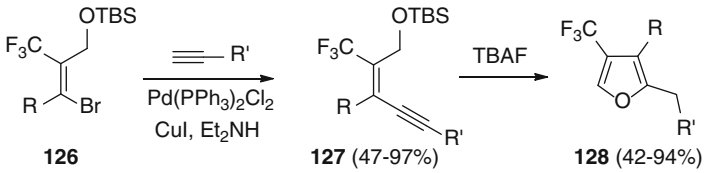


Thiol-mediated cyclizations of γ-hydroxy-α,β-unsaturated trifluoromethyl ketones **121** was utilized to the preparation of trifluoromethylfuran **122** [93]. α,β-Unsaturated trifluoromethyl ketones **123** were transformed into 3-alkylidene-4-yn-2-ols **124** which underwent silver-catalyzed cyclization into furans **125** [94].



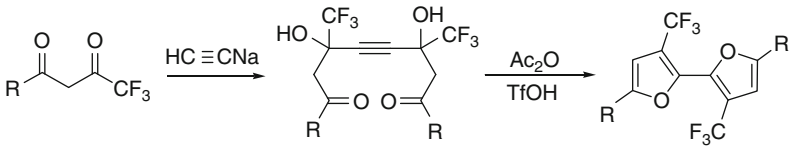


A related cyclization of silyl ethers **127**, synthesized by Sonogashira reaction from bromides **126**, into furans **128** was initiated by fluoride ion [95].



R = H, Me, Bn; R' = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$MeO_2CC_6H_4$, CH_2OBn, nC_5H_{11}

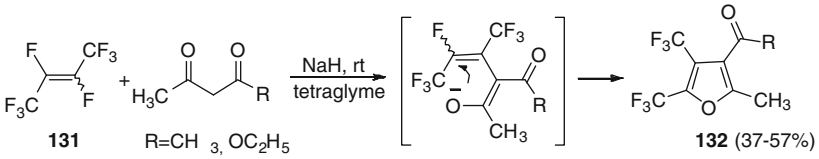
2,2′-Bifuryl derivatives bearing trifluoromethyl groups in β-positions of both furan rings **130** were synthesized by cyclization of oct-4-yne-1,8-diones **129** obtained by reaction of sodium acetylide with 1-trifluoromethyl-1,3-diones **116** [96].



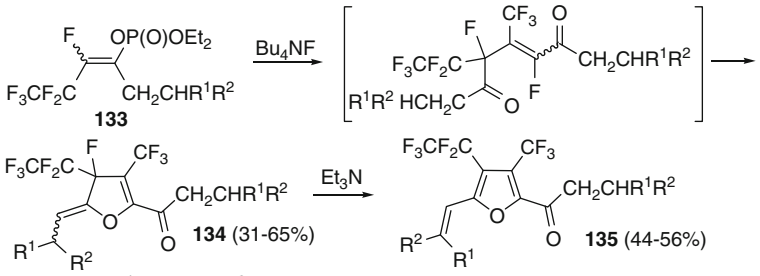
116 **129** (73%) **130** (31%)

R = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-naphthyl, (*E,E*)-PhCH=CH-CH=CH-

The increased ability of polyfluorinated compounds to undergo fluorine substitution was used for the synthesis of trifluoromethyl-substituted furans. Reaction of perfluorobut-2-ene **131** with acetylacetone or acetoacetic ester furnished 2,3-bis(trifluoromethyl)furans **132** through two sequential fluorine substitutions [97]. Similarly, fluoride-ion catalyzed reaction of fluorinated enol phosphates **133** led to dihydrofurans **134** which treatment with a base produced furans **135** in 44–56 % yields [98].



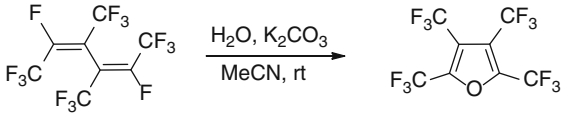
131 R=CH 3, OC_2H_5 **132** (37-57%)



133 **134** (31-65%) **135** (44-56%)

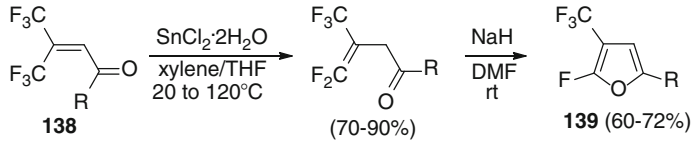
R^1 = H, Me; R^2 = Me, Et, *n*Bu, *i*Pr

Tetrakis(trifluoromethyl)furan **136** was obtained by basic hydrolysis of perfluoro-3,4-dimethylhexa-2,4-diene **137** in 54 % yield [99–101].



136 **137** (54%)

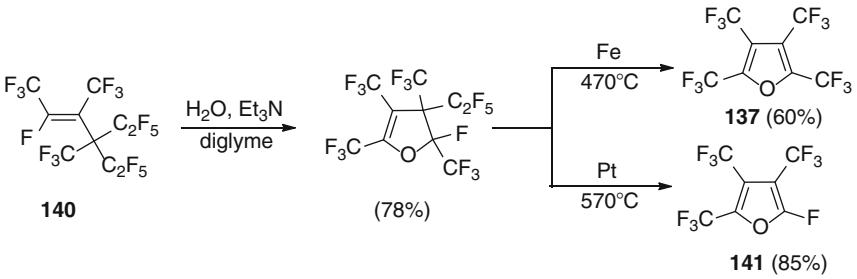
A number of 5-substituted 2-fluoro-3-trifluoromethylfurans **139** was synthesized using sequential treatment of β,β-bis(trifluoromethyl)-α,β-unsaturated ketones **138** with tin(II) chloride and sodium hydride [102–104].



138 (70-90%) **139** (60-72%)

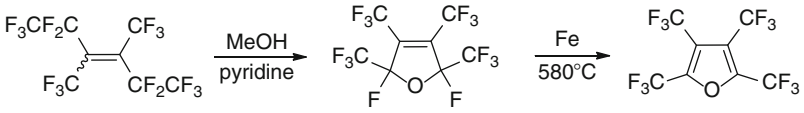
R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 2-MeOC$_6$H$_4$, 5-Me-2-furyl, 2-thienyl

Perfluorotetramethylfuran **137** and perfluorotrimethylfuran **141** were obtained from pentamer of tetrafluoroethylene **140** in two steps. The first step of the reaction is hydration with formation of fluorinated dihydrofuran derivative. The subsequent heating in the presence of iron or platinum catalyst resulted in **137** or **141** in high yields [105].



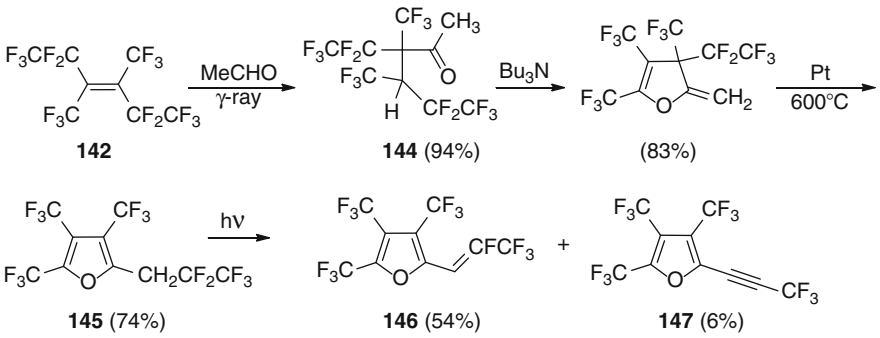
140 (78%) **137** (60%) **141** (85%)

The reaction of perfluoro-3,4-dimethylhex-3-ene **142** with methanol in the presence of a base yielded cyclic product **143** which was transformed into perfluorotetramethylfuran **137** by heating over iron at 580 °C [106, 107] or treatment with sodium amalgam [108].

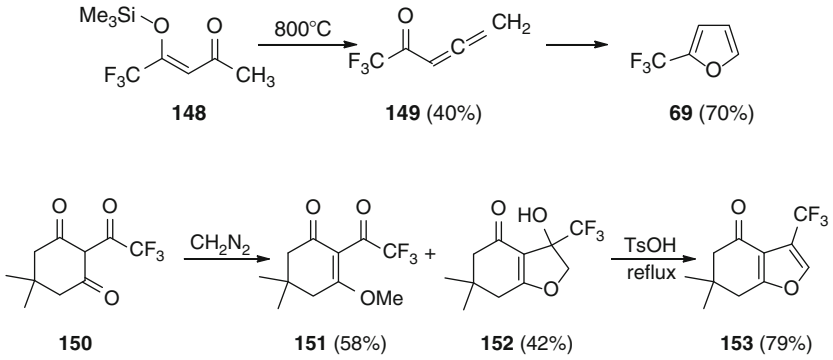


142 **143** (56%) **137** (79%)

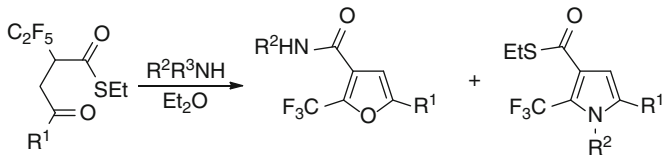
Perfluoro-2,3,4-trimethyl-5-propylfuran **145** was prepared from ketone **144**, obtained from compound **142** via γ-ray induced addition of acetaldehyde, using base-induced cyclization followed by pyrolysis. Irradiation of **145** gave products **146** (54 %) and **147** (6 %) [109].



Other methods were also used for the synthesis of trifluoromethylfurans. Thus, flash vacuum thermolysis of silyl enol ether of 1,3-diketone **148** at 800 °C afforded furan **69** (70 %) via intermediate allenic ketone **149** [110]. Another synthesis of trifluoromethylated furan from 1,3-diketone comprised reaction of diazomethane with 2-(trifluoroacetyl)dimedone **150**. This approach produced dihydrofuran **152** in a mixture with methylated product **151**. Compound **151** underwent aromatization into **153** under heating with *p*-toluenesulfonic acid [111].



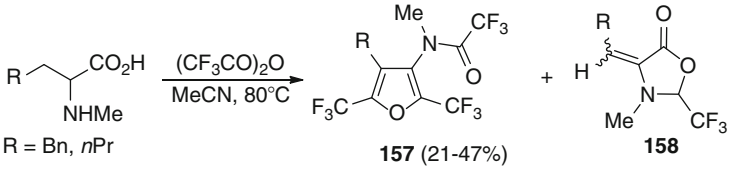
An unusual formation of furans **155** (together with the corresponding pyrroles **156**) was observed when compound **154** was treated with two equivalents of primary amine. Ratio of products depends on amine properties. Thus, if the amine acts as a base, the reaction proceeds via the intermediate enolate and an intramolecular Michael addition/fluoride elimination sequence. Further nucleophilic displacement of the ethylsulfanyl group gives 3-carboxamide furans **155**. If the amine acts as a nucleophile, a Michael addition/elimination followed by an intramolecular condensation leads to the corresponding pyrrole **156** via the enaminone [112, 113].



154 **155** (25-57%) **156** (24-48%)

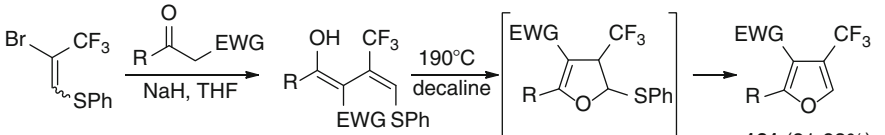
R^1 = Me, Ph; R^2 = Bn, *i*Pr, nC_5H_{11}; R^3= H, *i*Pr

Similarly, the reaction of *N*-methylnorleucine and *N*-methyl-homophenylalanine with trifluoroacetic anhydride led to 3-aminofurans **157** as main products and oxazolidinones **158** as minor products [114]. Reaction of bromoalkene **159** with CH-acids gave dienes **160** which underwent thermal cyclization into the corresponding furans **161** in 81–93 % yields [72].



R = Bn, *n*Pr

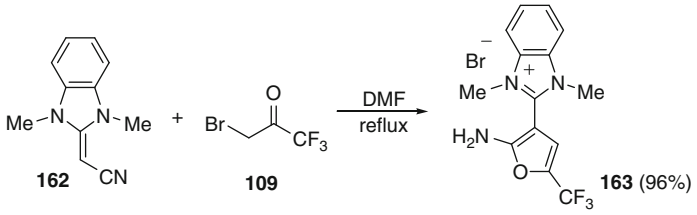
157 (21-47%) **158**



159 EWG = CN, CO_2Et **160** **161** (81-93%)

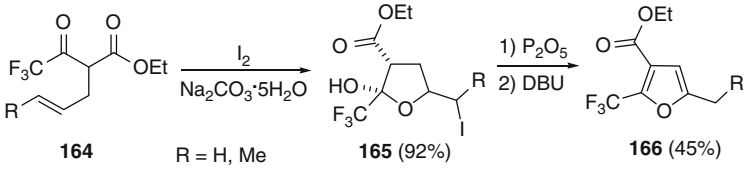
R = Me, Et, *n*Pr, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$MeO_2CC_6H_4$, 3-MeC_6H_4, 2-PhC_6H_4

Condensation of **109** with nitrile **162** produced furan **163** in 96 % yield [115]. The derivative **163** is formed through initial C-alkylation of compound **162** with the α-bromo ketones followed by hydrogen bromide assisted enolization and intramolecular addition of the hydroxy group to the nitrile. The latter step is accompanied by the positive charge transfer to the benzimidazole moiety.



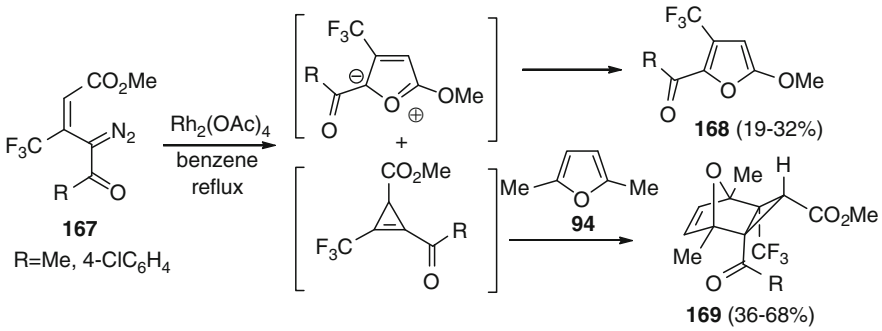
162 **109** **163** (96%)

Iodolactonization of γ,δ-unsaturated trifluoroacetoacetates **164** yielded tetrahydrofurans **165** which were then aromatized into furans **166** [116].



164 R = H, Me **165** (92%) **166** (45%)

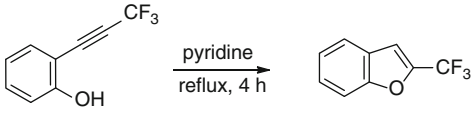
Catalytic decomposition of diazoketones **167** with $Rh_2(OAc)_4$ in the presence of 2,5-dimethylfuran **94** gave a mixture of trifluoromethylfurans **168** and tricyclic compounds **169** derived from [2+4] cycloaddition of 2,5-dimethylfuran and intermediate cyclopropene [117].



167 R=Me, 4-ClC_6H_4 **168** (19-32%) **169** (36-68%)

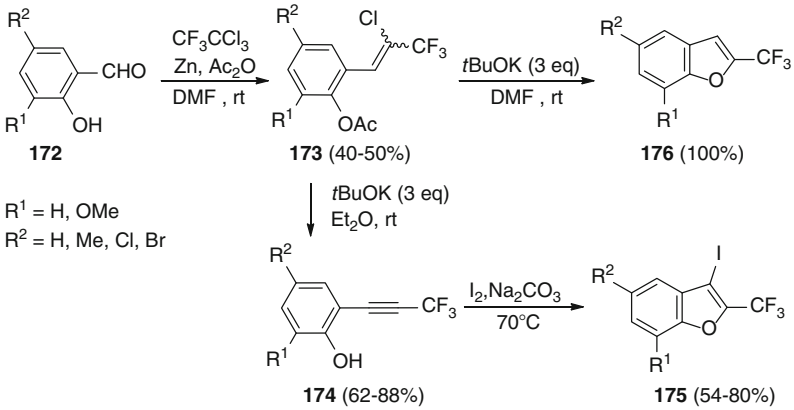
3.5 *Cyclization Leading to Trifluoromethyl-Substituted Benzofurans*

Common methods for the furan ring construction were applied to preparation of trifluoromethyl-substituted benzofurans starting from the substrates bearing appropriately located CF_3-group. Thus, 2-(trifluoropropynyl)-phenol **170** was cyclized into trifluoromethylbenzofuran **171** by heating with pyridine [118].

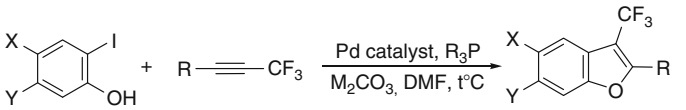


170 **171** (30%)

Treatment of β-chloro-β-trifluoromethylstyrenes **173**, obtained from salicylaldehydes **172**, with potassium *tert*-butoxide in DMF produced trifluoromethylbenzofurans **176** in excellent yields. On the other hand, iodocyclization of **174** into **175** took place under very mild conditions in 54–80 % yields [119].

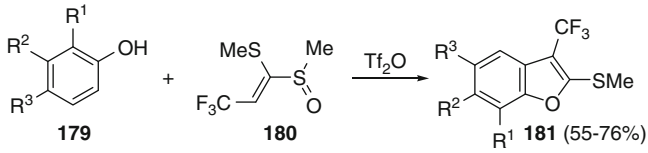


Intermolecular reaction of *o*-iodophenols **176** with trifluoromethylacetylenes **177** promoted by Pd catalysts afforded 3-(trifluoromethyl)benzofurans **178** [120, 121].



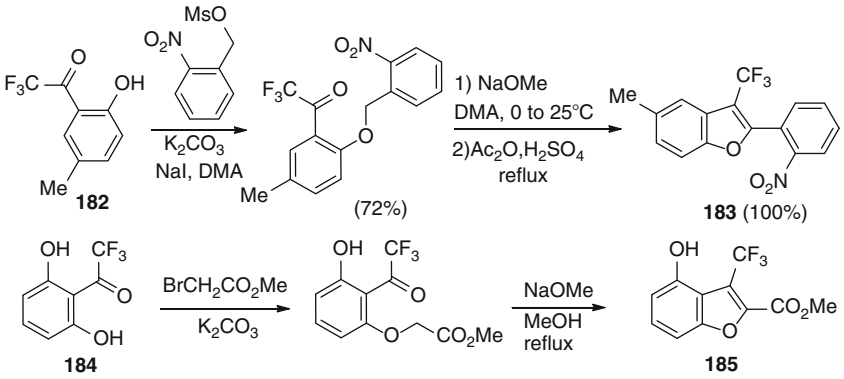
X = H, Cl, Me, CN; Y = H; X-Y = CH=CH-CH=CH;
R = 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-EtO$_2$CC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 1-(HO)*c*Hex

Reaction of phenols **179** with 1,1-bis(methylthio)-2-trifluoromethylethene *S*-oxide **180** and trifluoromethanesulfonic anhydride gave 2-methylthio-3-(trifluoromethyl) benzofurans **181** [122].

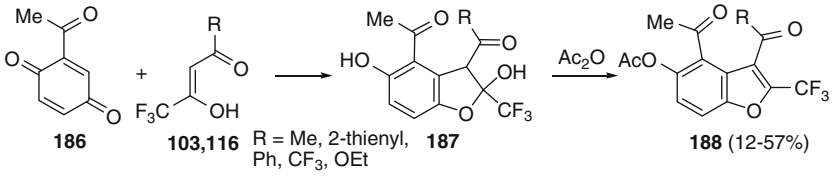


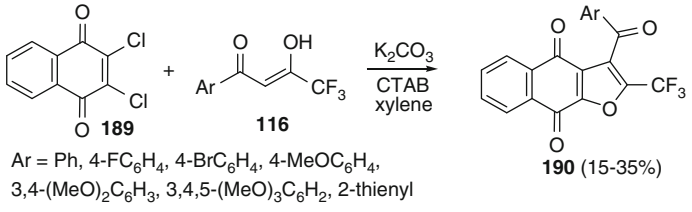
R^1 = H, Me; R^2 = H , Me, *t*Bu, OMe, CF$_3$; R^1-R^2, R^2-R^3 = CH=CH-CH=CH;
R^3 = H, *n*Bu, Br, CN, CF$_3$, CO$_2$Et

Alkylation of *o*-hydroxytrifluoroacetophenones **182** and **184** with *o*-nitrobenzyl mesylate and methyl bromoacetate, respectively, followed by Madelung-like cyclization produced 3-(trifluoromethyl)benzofurans **183** and **185** [123, 124].



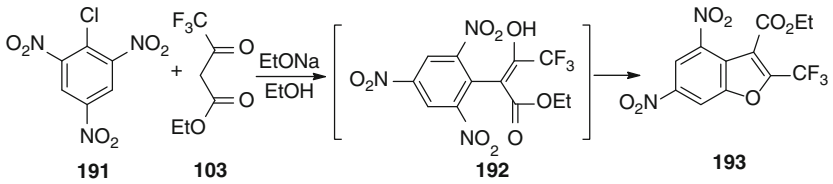
Reaction of benzoquinone **186** with fluorinated 1,3-diketones **116** or ketoester **103** gave 2-trifluoromethyl-2,3-dihyrobenzofurans **187** which underwent dehydration into the corresponding benzofurans **188** [125]. The related reaction of aroyl(trifluoroacetyl)methane **116** with 2,3-dichloro-1,4-naphthoquinone **189** yielded naphtho[2,3-*b*]furan-4,9-diones **190** in moderate yields under phase-transfer conditions [126].





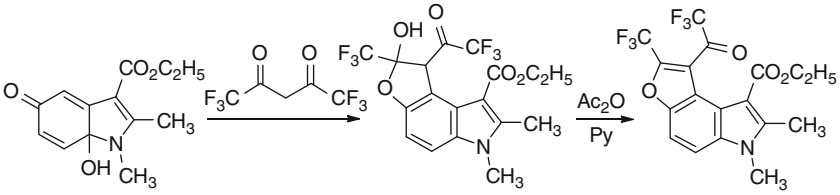
Ar = Ph, 4-FC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 2-thienyl

Substitution of both chlorine atom and nitro group in the reaction of picryl chloride **191** with trifluoroacetoacetate **103** led to benzofuran **193** [127].



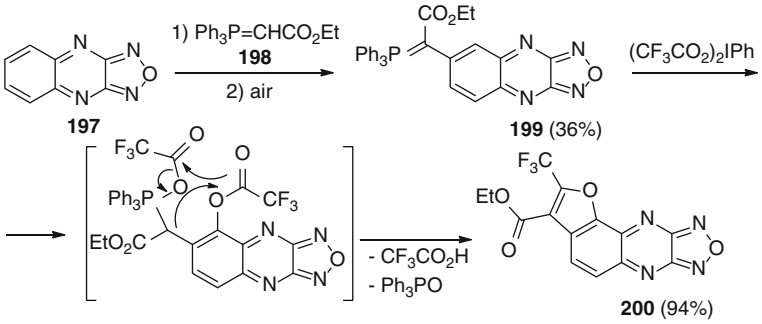
191 **103** **192** **193**

Treatment of cyclic semiaminal **194** with hexafluoroacetylacetone produced compound **195** which was further dehydrated to furo[3,2-*e*]indole **196** using acetic anhydride/pyridine mixture [128].



194 **195** (60%) **196** (80%)

The oxidative reaction of furazano[3,4-*b*]quinoxaline **197** with ylide **198** furnished new phosphonium ylide **199** that underwent smooth transformation into benzofuran derivative **200** under the treatment with $PhI(O_2CCF_3)_2$. Obviously, trifluoroacetoxylation with subsequent intramolecular Wittig-like reaction led to the formation of this unusual product [129].

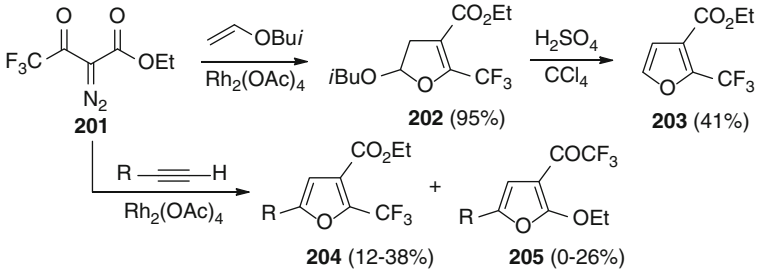


197 **199** (36%) **200** (94%)

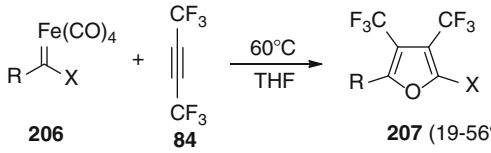
3.6 Miscellaneous

1,3-Dipolar cycloaddition of ethyl 2-diazo-4,4,4-trifluoroacetoacetate **201** with isobutyl vinyl ether produced dihydrofuran **202** which underwent elimination affording 2-trifluoromethylfuran **203** [130]. A related reaction with alkynes directly

produced 2-(trifluoromethyl)furan-3-carboxylates **204** together with 2-ethoxy-3-(trifluoroacetyl)furans **205** [131]. The reaction proceeds through the intermediate formation of metal carbene complex. Reaction of stable iron(0) carbene complex **206** with hexafluorobutyne **84** led to 3,4-bis(trifluoromethyl)furans **207** [132].

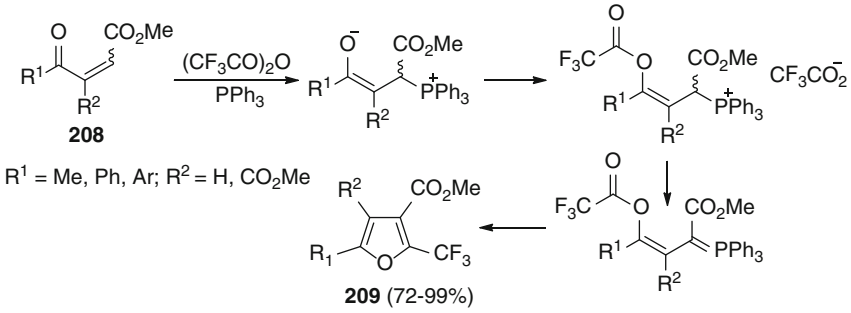


R = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-C$_4$H$_9$C$_6$H$_4$, (*E*)-PhCH=CH



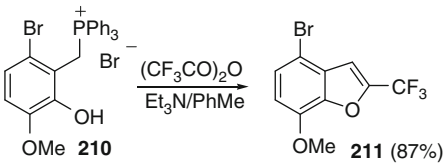
R = Ph, 3-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, *t*Bu; X = OEt, NMe$_2$

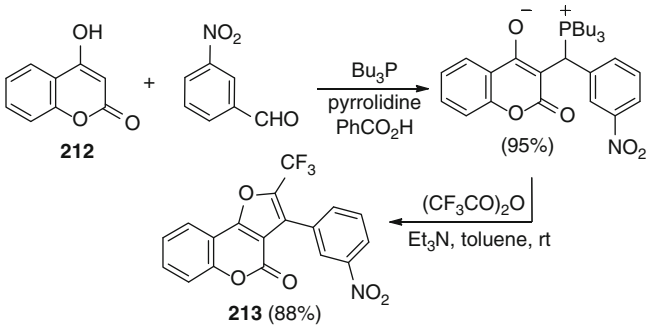
Treatment of 3-acylacrylates and 2-acylfumarates **208** with trifluoroacetic anhydride and PPh$_3$ yielded 3,4,5-substituted 2-(trifluoromethyl)furans **209**. The plausible mechanism of the reaction includes slow Michael addition of triphenylphosphine to enone fragment with fast trifluoroacetylation of resulted adduct and subsequent intramolecular Wittig olefination. An alternative mechanism via trifluoroacetyl radical arising from interaction of trifluoroacetic anhydride and triphenylphosphine is also possible [133].



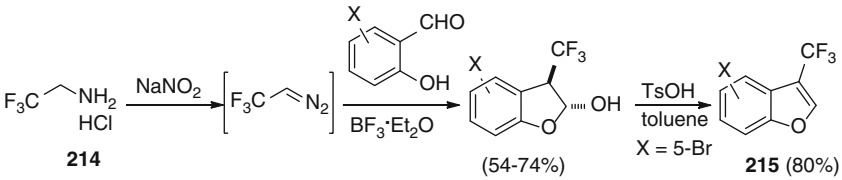
4-Bromo-7-methoxy-2-(trifluoromethyl)benzofuran **211** was synthesized by reaction of (*o*-hydroxybenzyl)triphenylphosphonium bromide **210** with trifluoroacetic anhydride and base under reflux [134]. A similar approach was utilized for

synthesis of polysubstituted furo[3,2-*c*]coumarin **213** bearing a trifluoromethyl group at the C(2) atom from 4-hydroxycoumarin **212** [135].



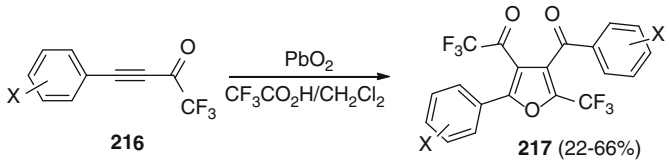


A series of 3-CF_3-benzofurans **215** was synthesized by transformation of trifluoroethylamine **214** into the corresponding diazo compound followed by the BF_3-catalyzed reaction with salicylaldehydes and dehydration [136].



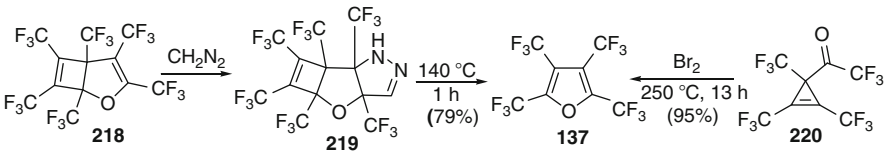
X = H, 5-MeO, 7-EtO, 7-BnO, 5-Me, 7-Me, 5-Cl, 5-Br, 5-NO_2, 5-Br-7-MeO

Oxidative dimerization of 1-aryl-2-(trifluoroacetyl)acetylenes **216** with lead(IV) oxide afforded furan derivatives **217** in 22–66 % [137, 138].

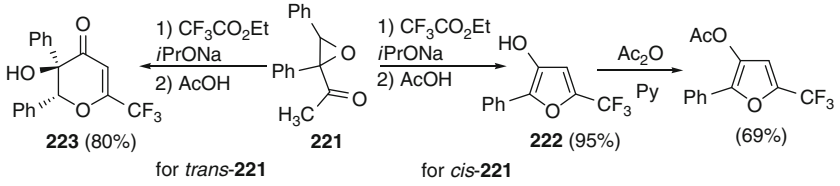


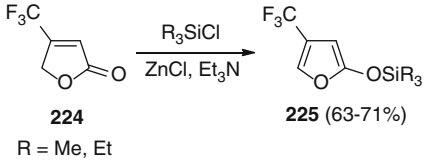
X = 4-MeO, 3-F-4-MeO, 2,4-Me_2

Tetrakis(trifluoromethyl)furan **137** was obtained in 79 % yield by thermolysis of tricyclic compound **219** which was synthesized from valence-bond isomer of hexakis(trifluoromethyl)oxepin **218** via the reaction with diazomethane [139]. This compound was also obtained by bromine-induced isomerization of 3-trifluoroacetyl-1,2,3-tris(trifluoromethyl)cyclopropane **220** [140].



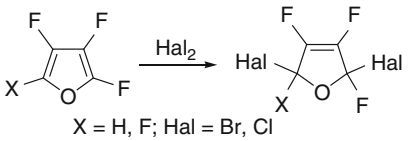
Reaction of *cis*-2-acetyl-2,3-diphenyloxirane **221** with ethyl trifluoroacetate afforded 3-hydroxy-2-phenyl-5-trifluoromethylfuran **222**. Oppositely, *trans*-isomer was cyclized under the same conditions into pyran derivative **223** [141]. Silylation of trifluoromethylated butenolide **224** gave 2-siloxyfurans **225** in 63–71 % yield [142].



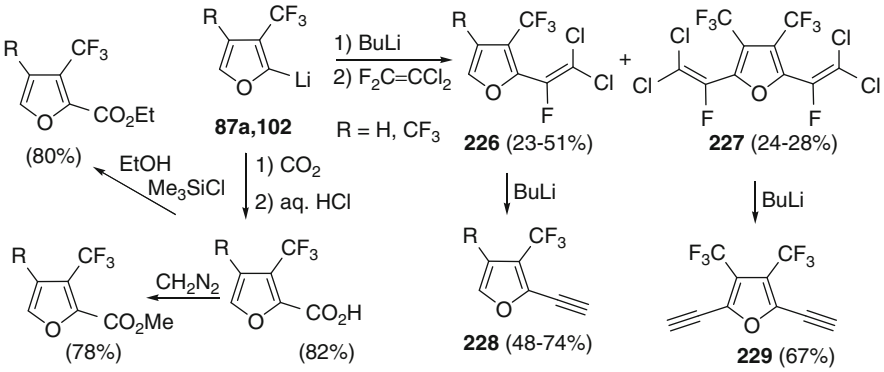


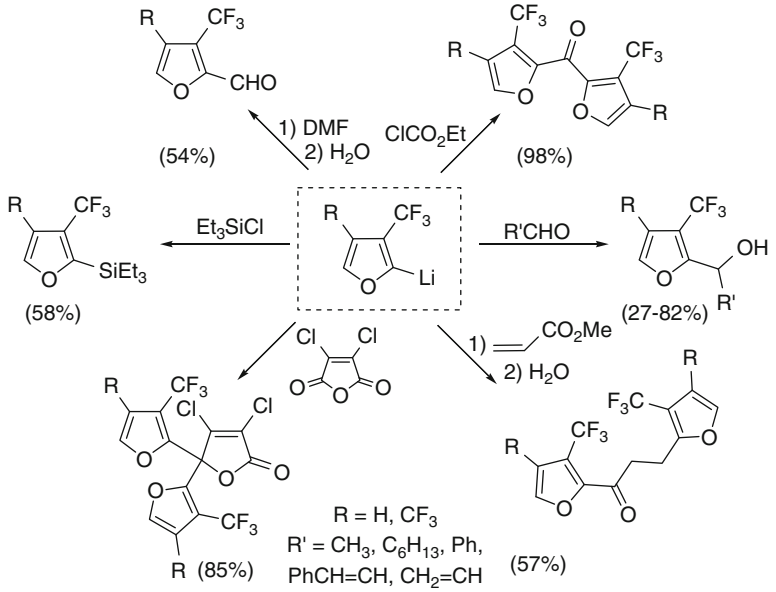
4 Reactions of Fluoro- and Trifluoromethyl-Substituted Furans

Polyfluorofurans are unstable even at room temperature. Tetrafluorofuran and 2,5-difluorofurans are polymerized affording white solids; trifluorofurans, 2,3- and 3,4-difluorofurans decomposed with the evolution of HF [18]. Introduction of fluorine atoms slightly decreases nucleophilicity of the furan ring. For example, bromine, chlorine, acetyl nitrate react rapidly with tetrafluorofuran and 2,3,4-trifluorofuran to give a mixture of the *cis*- and *trans*-2,5-adducts. When furans were treated with iodine monochloride, products of 2,5-chlorination were also isolated. However, polyfluorofurans failed to react with HCl and HBr [18].

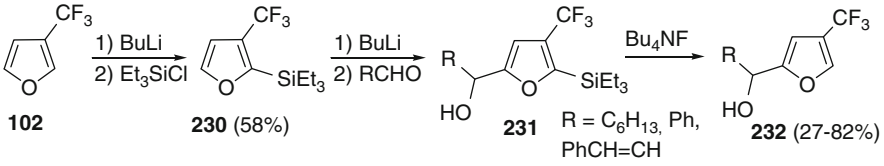


3,4-Bis(trifluoromethyl)furan **87a** did not react with bromine, however lithiation allowed one to insert Br-atom regioselectively at the C2 position [143]. Many other electrophilic reagents can be involved into the reaction with lithiated furan derivatives, for example, carbon dioxide, aldehydes, silyl chlorides, various Michael acceptors, etc. [74, 84, 144]. Treatment of vinylation products **226**, **227** with alkyllithium afforded the corresponding alkynes **228**, **229** [64, 143].

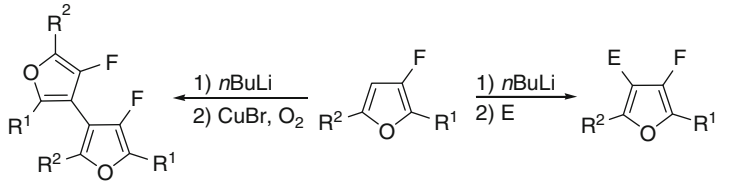




To introduce a substituent into the C5 position of furan **102**, intermediate protection of C2 atom by silyl group was proposed. Silylated derivative **230** was lithiated and treated with aldehydes furnishing products **231** which were desilylated to **232** using tetrabutylammonium fluoride [84].

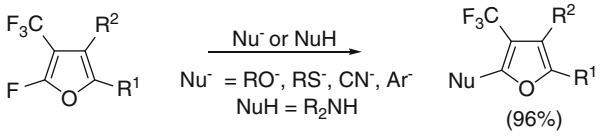


Lithiation of 2,5-disubstituted 3-fluorofurans **43** allowed one to introduce new substituents at C4 atom producing **233** or perform oxidative dimerization to **234** [25].

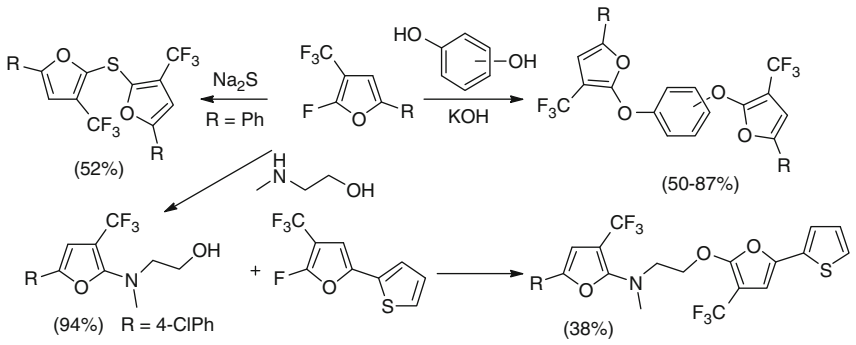


R^1 = Et, aryl; R^2 = Ph, nC_5H_{11} E = PhCHO, PhCOCl, DMF, CO_2, NBS, NFSI

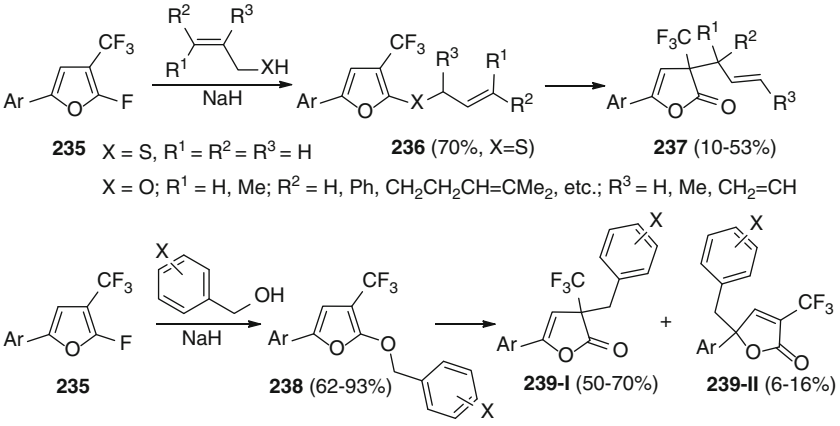
A perfluoroalkyl group activates fluorine atom in 2-fluoro-3-trifluoromethylfurans to nucleophilic substitution with a broad range of nucleophiles [102–105]. Fluorine can be efficiently substituted by alkoxy or phenoxy groups, aliphatic or heterocyclic thiols and amines or reduced with lithium aluminium hydride. The C-nucleophiles like cyanide or malonate anion as well as phenylithium and phenylmagnesium bromide can also be involved into the reaction.



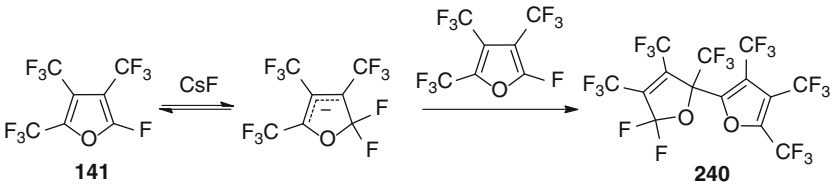
Application of binucleophilic reagents, such as resorcine, hydroquinone, aminoethanol derivatives and others, led to formation of dimeric trifluoromethyl-substituted furans [102, 104].



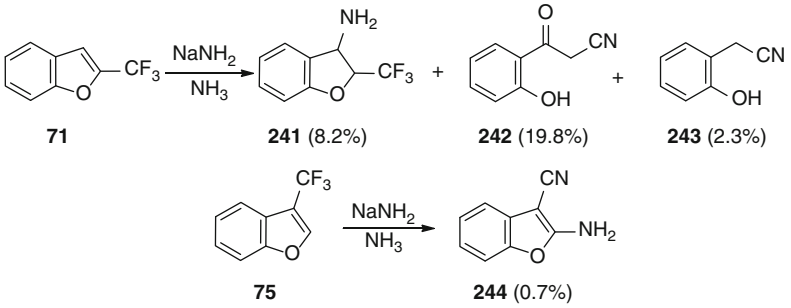
Reaction of 2-fluoro-3-trifluoromethylfurans **235** with allyl alcohols followed by Claisen rearrangement directly produced butenolides **237** [145, 146]. Oppositely, allyl mercaptane formed stable substitution product **236** [146]. A similar transformation was reported for benzyl alcohols. While benzhydryl and (2-thienyl)methyl groups migrated at room temperature directly furnishing butenolides **239**, in the case of benzyloxy derivatives, heating at 120 °C was required to reach the transformation. On the other hand, stable up to 140 °C products **238** were formed in the reaction of benzylamine, benzyl mercaptane, and 2-(hydroxymethyl)pyridine [147].



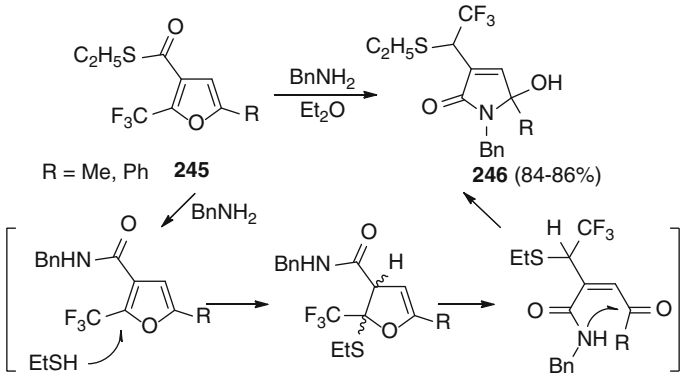
Nucleophilic attack of cesium fluoride induced dimerization of perfluorotrimethylfuran [105]. Due to the strong electrophilic properties, perfluorinated furan ring easily undergoes addition of fluoride anion with the subsequent release in a second nucleophilic substitution step with another molecule of perfluoro-2,3,4-trimethylfuran.



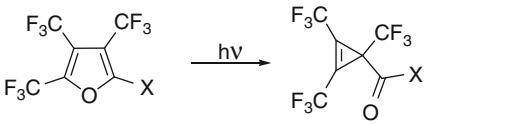
Heating of 2- and 3-(trifluoromethyl)benzofuran **71**, **75** with alcoholic sodium hydroxide solution under reflux yielded the corresponding acids in poor yields. Significant tar formation was observed due to the ring opening. Products of the ring opening **241**–**243** were isolated in reaction of **71** with sodium amide in liquid ammonia. Oppositely **75** gave the compound **244** in very low yield [55].



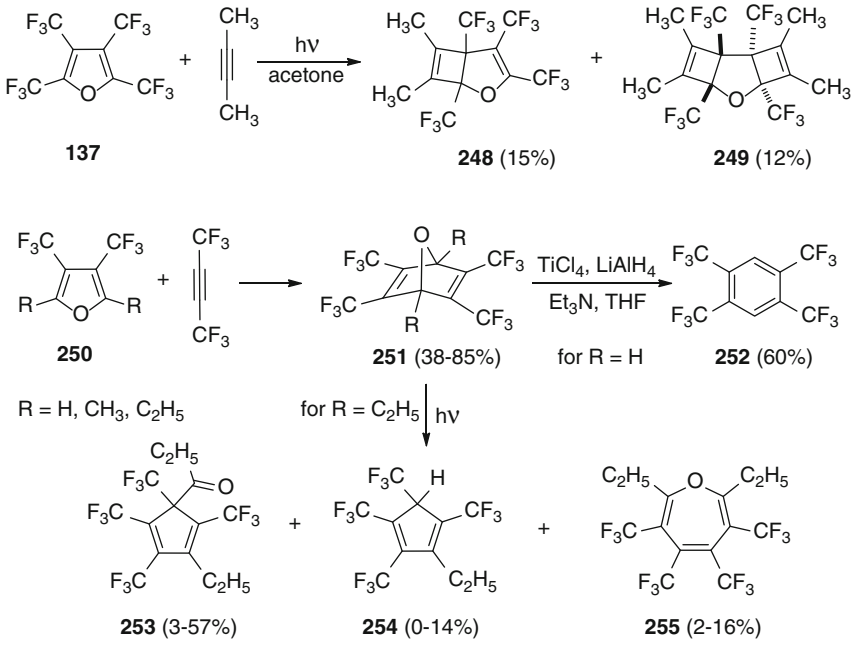
Reaction of furans **245** with benzylamine is accompanied by recyclization leading to pyrrolidones **246**. The first step of the reaction includes amidation with benzylamine with release of ethanethiol. The furan ring, which is activated by both the trifluoromethyl substituent and the amide function, acts as a Michael acceptor with thiol to give the dihydroderivative. Such an intermediate might undergo ring opening followed by a 1,3-proton migration to afford the γ-keto amide and cyclization to lactam **246** [148].



Tetrakis(trifluoromethyl)furan **137** was reported to be inert in a reaction with common dienophiles and stable to irradiation, unlike the most other furans [139, 149]. However, later it was shown that **137** rearranged into cyclopropenyl ketone **220** under irradiation with high pressure Hg-lamp. Similarly, furan **141** was transformed into acyl fluoride **247** [105].

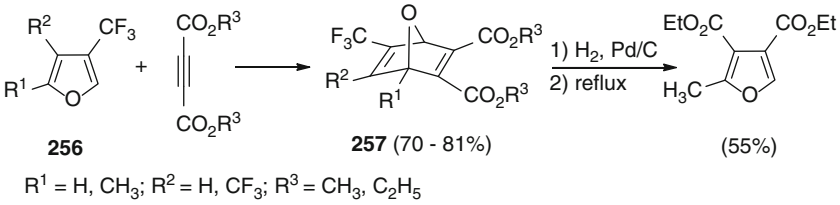


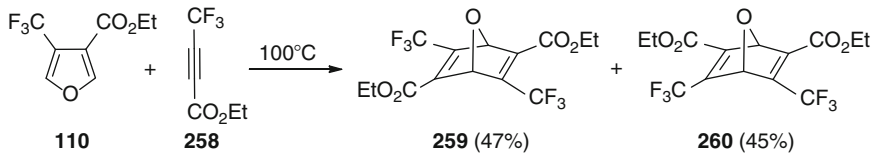
Acetone-sensitized photoreaction of **137** with butyne-2 gave products of mono- **248** and bis [2+2] cycloaddition **249** [149]. Oppositely, 3,4-bis(trifluoromethyl) furans **250** participate in the Diels-Alder reaction. They reacted with hexafluorobut-2-yne **84** giving 7-oxanorbornadiene **251** [72, 73, 77, 150]. Treatment of **251** with $TiCl_4/LiAlH_4/Et_3N$ system led to the formation of tetrakis(trifluoromethyl)benzene **252** [77]. Irradiation of **251** produced mixture of cyclopentadienes **253** and **254** as well as oxepin **255** in variable ratios depending on the solvent [150].



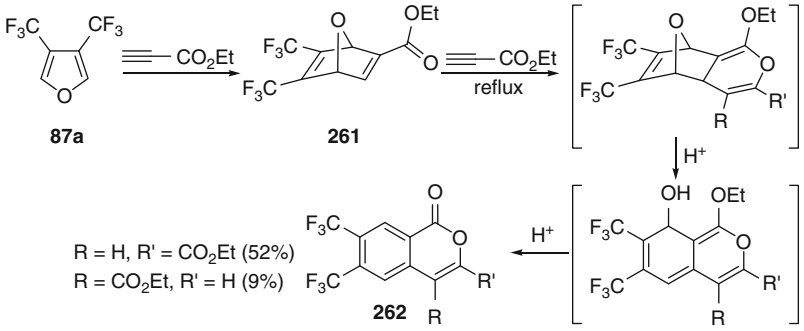
Similarly, a reaction of furans **256** with DMAD or DEAD furnished oxanorbornadienes **257** [88, 151]. Depending on substitution mode, these norbornadienes can

be partially hydrogenated and involved into retro-Diels-Alder reaction [88]. A related Diels-Alder reaction of furan **110** with DMAD and hexafluorobut-2-yne proceeded smoothly with formation of the corresponding 7-oxanorbornadienes in excellent yields. When asymmetric dienophile **258** was utilized, a mixture of regioisomeric cycloadducts **259**, **260** was obtained in 92 % overall yield [78].

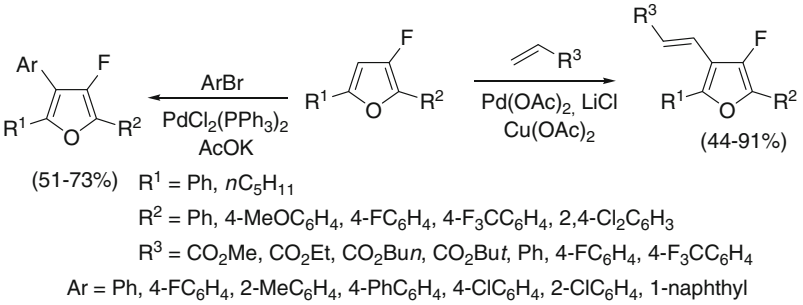




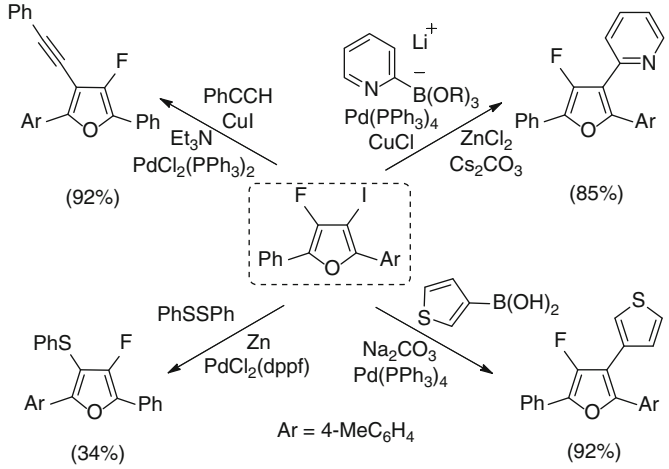
On the contrary, when **87a** was reacted with ethyl propynoate, isocoumarins **262** were obtained. In this case the Diels-Alder cycloadduct **261** reacted as diene with another ethyl propynoate molecule. Tricyclic pyran underwent oxygen bridge opening followed by ethanol elimination presumably catalyzed by acidic Pyrex reaction tube walls [75, 78, 151]. Reaction of **110** with ethyl propynoate yielded complex mixture of unidentified products [78].



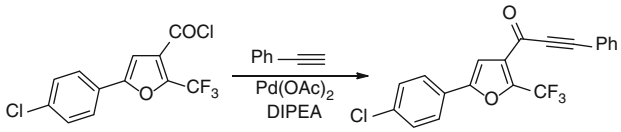
Fluorine atom activates furan ring to oxidative Heck reaction with various alkenes [152] and to Pd-catalyzed arylation of the neighboring carbon atom [153].



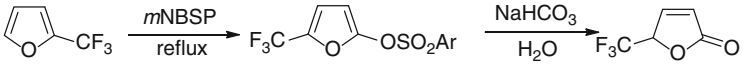
Another way to 4-aryl-3-fluorofurans is Suzuki reaction of 3-fluoro-4-iodofurans. Other cross-coupling reactions of fluoroiodofuran were also described. Thus, Sonogashira coupling gave phenylethynyl fluorofuran, the Suzuki-Miyaura coupling reaction with the thiophene-3-boronic acid conducted using classical conditions produced (thienyl)fluorofuran. Employment of lithium (pyridin-2-yl) triisopropoxyborate allowed for the introduction of a conventionally unreactive moiety. Coupling with diphenyl disulfide carried out under reductive conditions produced phenylthiofuran in poor yield [37].



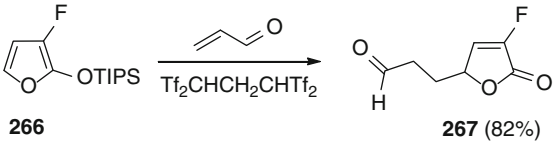
Palladium-catalyzed reaction of 5-aryl-2-(trifluoromethyl)furan-3-carbonyl chloride **263** with phenylacetylene afforded derivative **264** which is a convenient precursor for synthesis of pyrazoles, pyrimidines, and other heterocyclic systems bearing trifluoromethylated furan as substituent [154].

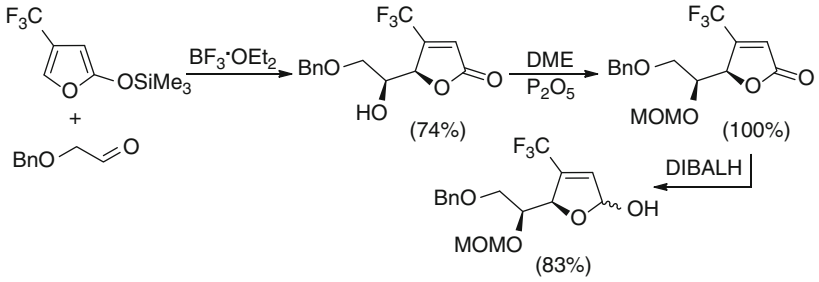


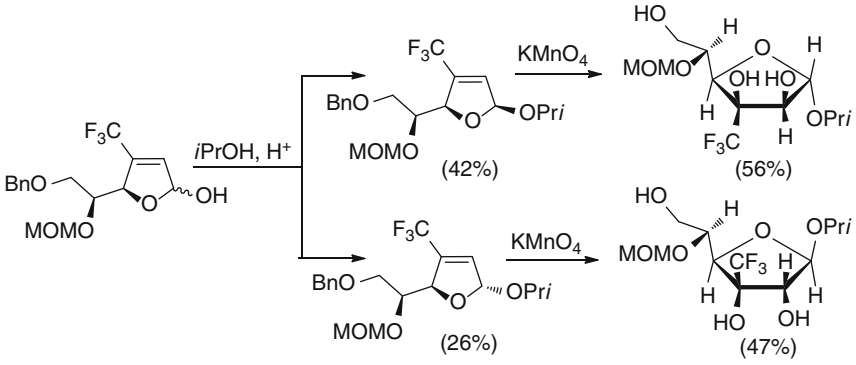
The oxidative transformation of 2-trifluoromethylfuran **69** into butenolide **265** was performed using *m*-nitrobenzenesulfonyl peroxide (*m*-NBSP) followed by hydrolysis under basic conditions. Deprotonated butenolide was shown to be good nucleophile in Michael addition to various substrates [155].



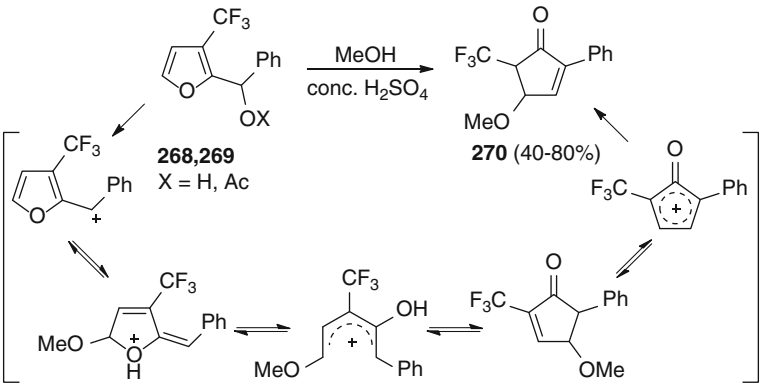
α-Fluoro-γ-butenolide **267** was synthesized from 3-fluoro-2-siloxyfuran **266** using vinilogous Mukayama-Michael reaction with α,β-unsaturated aldehydes [156]. Similar reaction was utilized for the synthesis of trifluoromethylated sugars [142].



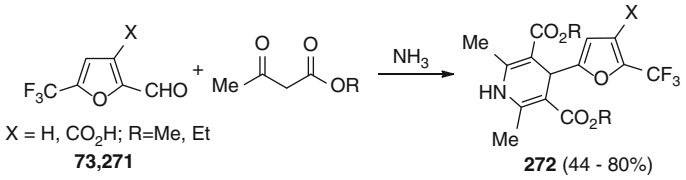


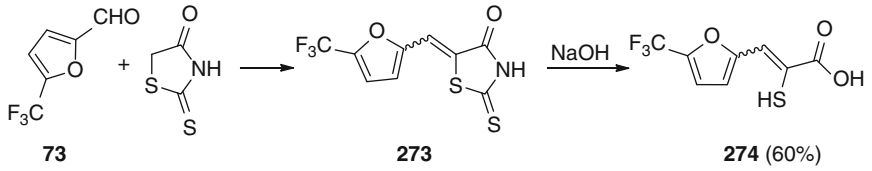


Under treatment with strong acid, 2-furyl(phenyl)carbinol **268** and acetate **269** recyclized into cyclopentenone **270**; the related alkyl(furyl)carbinols gave product of dehydration [84].

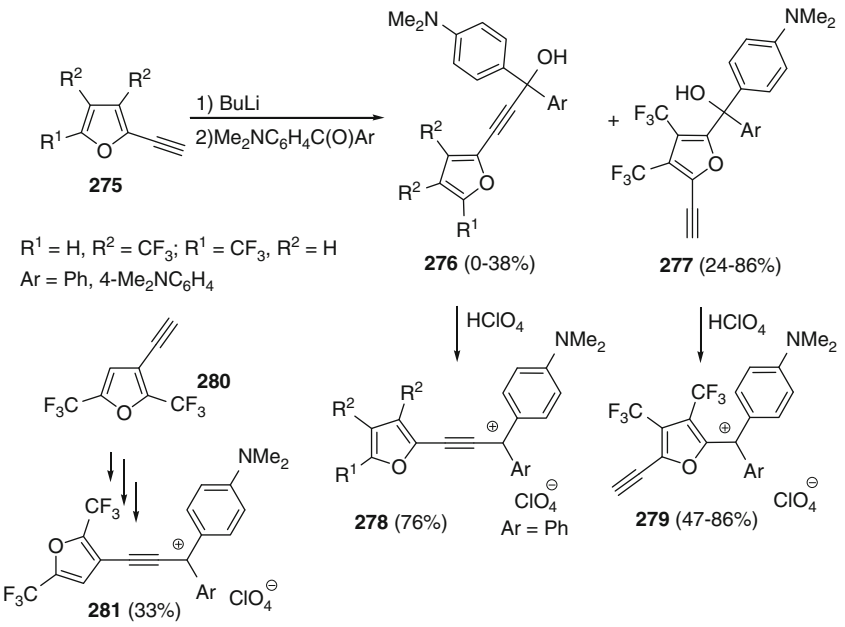


Condensation of **73** and related aldehyde **271** with acetoacetate and NH_3 afforded 1,4-dihydropyridines **272** [157]. Reaction of **73** with rhodanine followed by basic hydrolysis of **273** led to α-mercapto-β-(5-trifluoromethyl-2-furyl)acrylic acid **274** [158].

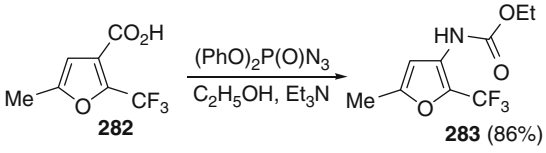


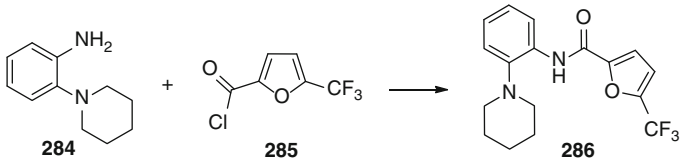


Lithiation of ethynyl(trifluoromethyl)furans **275** followed by the reaction with diaryl ketones produced diaryl(2-arylethynyl)carbinols **276** and triarylcarbinols **277**. Further treatment with $HClO_4$ yielded the corresponding dyes **278**, **279**. Similarly, furan **280** was transformed into dye **281** [159].



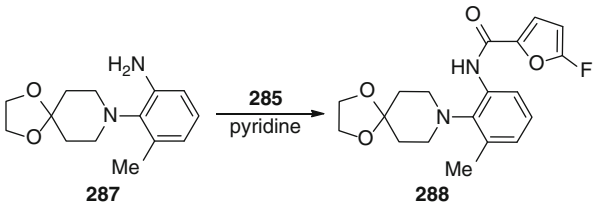
Curtius rearrangement was applied to synthesis of 3-ethoxycarbonylamino-5-methyl-2-(trifluoromethyl)furan **283** from 3-furoic acid **282** [160]. Other transformations of side chains and functional groups in trifluoromethyl-substituted furans were also reported. They are intensively used to search novel bioactive compounds due to the high potential of fluorinated furans as pharmacological agents. Thus, 2-piperidinoaniline **284** was acylated with 5-trifluoromethyl-2-furoyl chloride **285** searching for new inhibitors of colony-stimulated factor-1 receptor, but product **286** appeared to be devoid of significant activity [161].



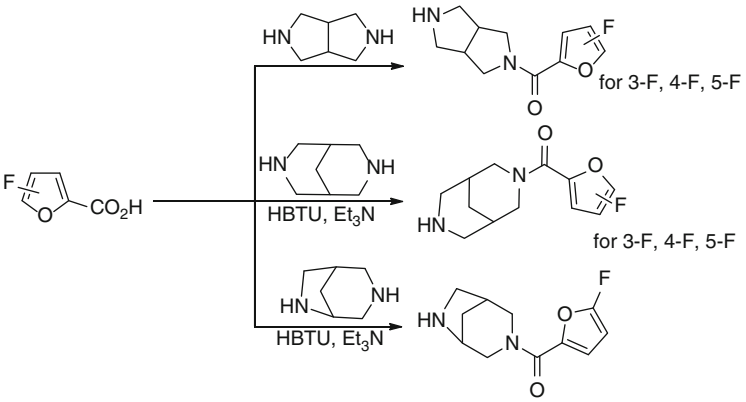


5 Application of Fluoro- and Trifluoromethyl-Substituted Furans

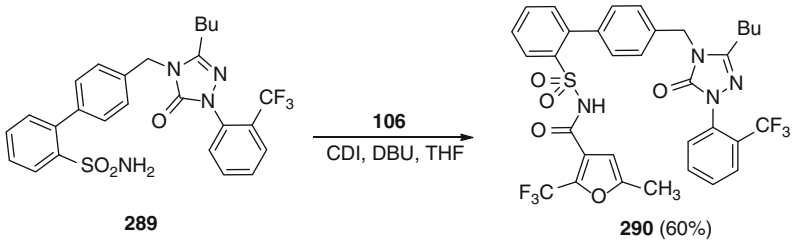
The section highlights synthesis of compounds demonstrated physiological activities using fluoro- or trifluoromethyl-substituted furans as starting compounds. Acylation of aniline **287** with 5-fluorofuran-2-carbonyl chloride gave amide **288** which inhibited c-jun *N*-terminal kinase at submicromolar level [162].

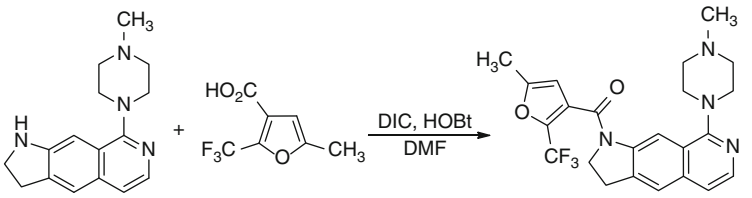


Reaction of the corresponding acid **34**, as well as 3-fluoro- and 4-fluoro-2-furoic acids with bicyclic diamines was used for preparation of nicotinic acetylcholine receptor agonists and antagonists with binding affinity to α4β2 receptor subtype, which is target for the treatment of Alzheimer's disease, schizophrenia, major depression, etc., as low as 3 nM [163].

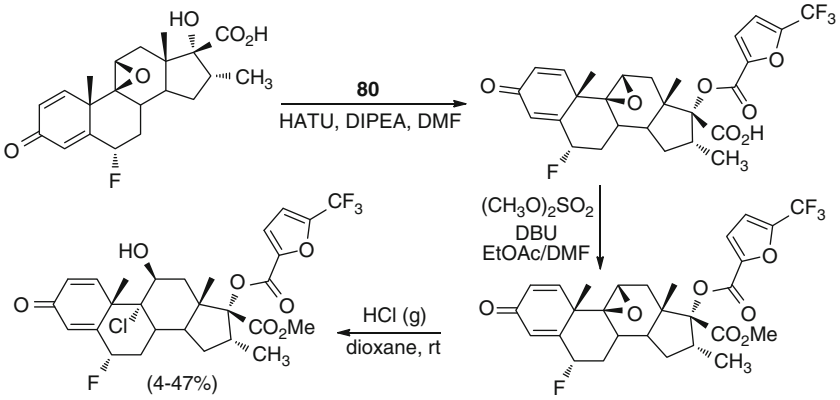


Condensation of 5-methyl-2-trifluoromethyl-3-furoic acid **106** with triazolinonesulfamide **289** led to imide **290** which demonstrated affinity to angiotensin AT_1 receptor at nanomolar level [164]. Acylation of pyridoindole **291** with acid **106** afforded amide **292** showing binding ability to serotonin receptors [165].

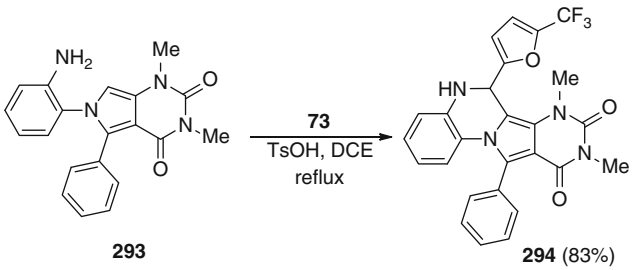




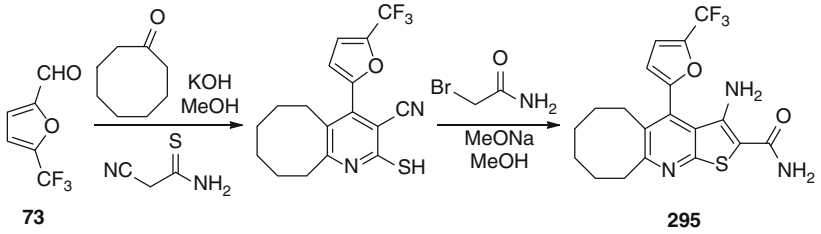
5-Trifluoromethyl-2-furoic acid **80** was employed for the synthesis of novel glucocorticoid androstene ester with 4.8 times higher TNFα potency than those for budesonide which is a steroid for the treatment of asthma [166].



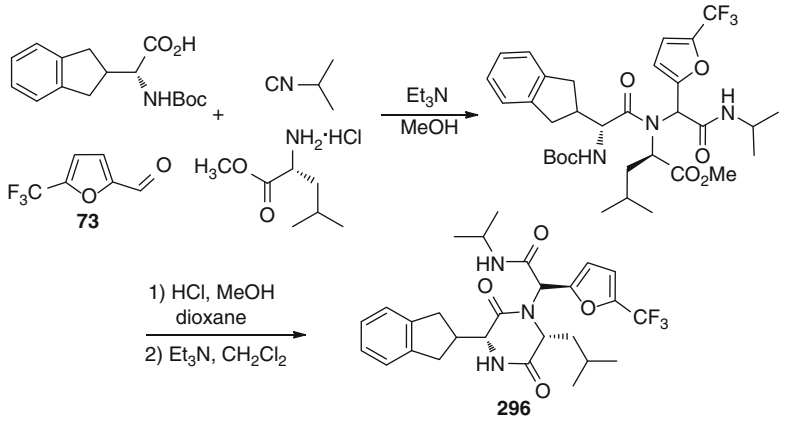
Condensation of 5-(trifluoromethyl)furfural **73** with compound **293** gave polycyclic product **294** inhibiting cystic fibrosis transmembrane conductance regulator chloride channel at submicromolar level [167].



Reaction of **73** with cyclooctanone followed by consecutive treatment of product with 2-cyanothioacetamide and 2-bromoacetamide produced cyclooctathieno-pyridine **295** which inhibits eukaryotic elongation factor-2 kinase with IC_{50} 0.3 μmol/L and can be applied for the treatment of breast carcinoma [168].

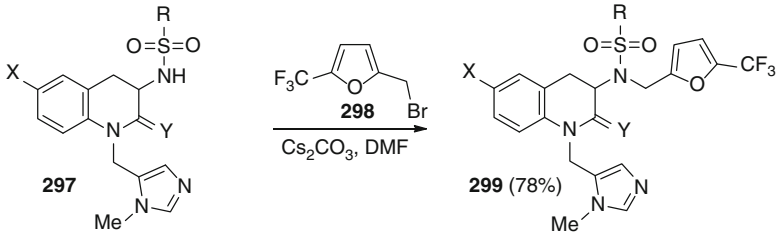


Ugi reaction of **73** with isopropyl isocyanide, *N*-Boc-2-(indan-2-yl)glycine and leucine methyl ester was applied to the synthesis of compound **296 –** oxytocin antagonist with pK_i 10.0 [1].



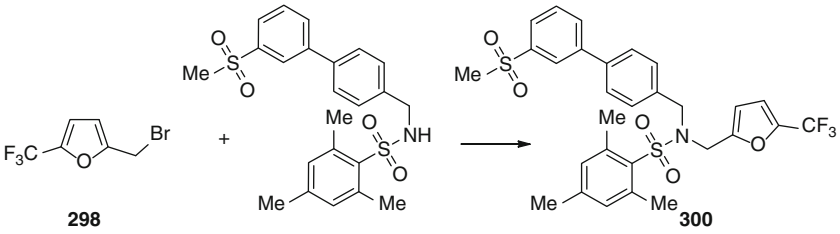
Alkylation of tetrahydroquinolines **297** (Y=H_2) with 5-(trifluoromethyl)furfuryl bromide **298** afforded derivative **299** which inhibited protein farnesyltransferase

and demonstrated antimalarial activity at submicromolar level [3]. The related tetrahydroquinolone **299** (Y=O, X=CN, R=1-methylimidazol-4-yl) was synthesized in two steps via the reaction between **298** and **297** (X=Br) and bromine substitution with $Zn(CN)_2/Pd(PPh_3)_4$ [169].

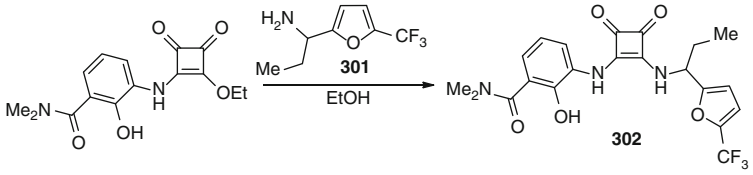


X = CN, Ph, Y = CH_2, O, R = 2-Py, 1-Me-imidazol-4-yl

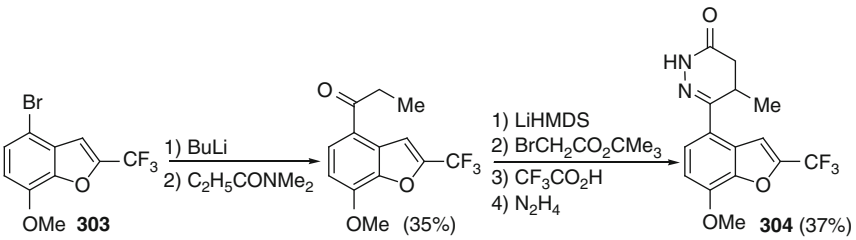
Compound **298** was applied to the synthesis of *N*-4-biphenylmethyl-*N*-furfurylsulfonamide **300** demonstrating liver X receptor β-binding with pIC_{50} of ca. 7.5 [170].



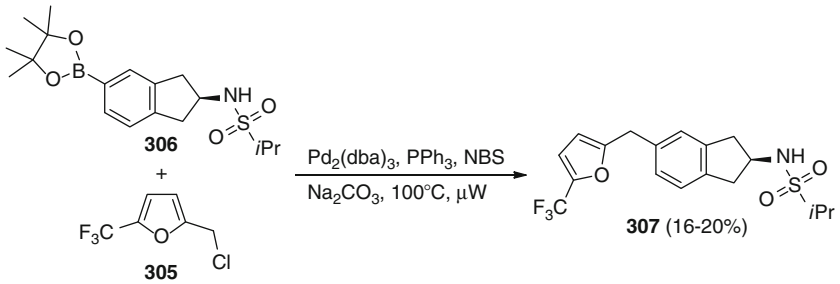
α-Ethyl-5-trifluoromethylfurfurylamine **301** was a starting material in the preparation of highly active and selective CXCR2 antagonist **302** [171].



Oppositely, reaction of 2-(trifluoromethyl)benzofuran **303** was a first step in the synthesis of compound **304** inhibiting phosphodiesterases PDE3A and PDE4B at 19.8 and 0.38 μmol/L respectively [134].



Cross-coupling of furfuryl chloride **305** with (indan-5-yl)pinacolylborane **306** gave benzylfuran **307** which was shown to be a modulator of AMPA receptor with EC_{50} of ca. 1 μmol/L [172].



6 Conclusions

Obviously, the majority of the efficient methods for fluorinated furans synthesis has been described over the last 20 years. The development of modern fluorinating agents, organometallic chemistry, and homogeneous catalysis provided new possibilities for the preparation of fluoro- and perfluoroalkylfurans, which find their application in pharmacology, agriculture, and material science.

References

1. Liddle J, Allen MJ, Borthwick AD, Brooks DP, Davies DE, Edwards RM, Exall AM, Hamlett C, Irving WR, Mason AM, McCafferty GP, Nerozzi F, Peace S, Philp J, Pollard D, Pullen MA, Shabbir SS, Sollis SL, Westfall TD, Woollard PM, Wu C, Hickey DMB (2008) The discovery of GSK221149A: a potent and selective oxytocin antagonist. Bioorg Med Chem Lett 18:90–94
2. Cantrell AS, Engelhardt P, Högberg M, Jaskunas RS, Johansson NG, Jordan CL, Kangasmetsä J, Kinnick MD, Lind P, Morin JM, Muesing MA, Noreen R, Öberg B, Pranc P, Sahlberg C, Ternansky RJ, Vasileff RT, Vrang L, West SJ, Zhang H (1996) Phenethylthiazolylthiourea (PETT) compounds as a new class of HIV-1 reverse transcriptase Inhibitors. 2. Synthesis and

further structure-activity relationship studies of PETT analogues. J Med Chem 39:4261–4274
3. Bendale P, Olepu S, Suryadevara PK, Bulbule V, Rivas K, Nallan L, Smart B, Yokoyama K, Ankala S, Pendyala PR, Floyd D, Lombardo LJ, Williams DK, Buckner FS, Chakrabarti D, Verlinde CLMJ, Van Voorhis WC, Gelb MH (2007) Second generation tetrahydroquinoline-based protein farnesyltransferase inhibitors as antimalarials. J Med Chem 50:4585–4605
4. Shi S, Zhu S, Gerritz SW, Esposito K, Padmanabha R, Li W, Herbst JJ, Wong H, Shu YZ, Lam KS, Sofia MJ (2005) Solid-phase synthesis and anti-infective activity of a combinatorial library based on the natural product anisomycin. Bioorg Med Chem Lett 15:4151–4154
5. Kuhl A, Svenstrup N, Ladel C, Otteneder M, Binas A, Schiffer G, Brands M, Lampe T, Ziegelbauer K, Rübsamen-Waigmann H, Haebich D, Ehlert K (2005) Biological characterization of novel inhibitors of the gram-positive DNA polymerase IIIC enzyme. Antimicrob Agents Chemother 49:987–995
6. Jenkins TJ, Guan B, Dai M, Li G, Lightburn TE, Huang S, Freeze BS, Burdi DF, Jacutin-Porte S, Bennett R, Chen W, Minor C, Ghosh S, Blackburn C, Gigstad KM, Jones M, Kolbeck R, Yin W, Smith S, Cardillo D, Ocain TD, Harriman GC (2007) J Med Chem 50:566–584
7. Hevener KE, Mehboob S, Su P-C, Truong K, Boci T, Deng J, Ghassemi M, Cook JL, Johnson ME (2011) Discovery of a novel and potent class of F. Tularensis enoyl-reductase (fabl) inhibitors by molecular shape and electrostatic matching. J Med Chem 55:268–279
8. Yun W, Ahmad M, Chen Y, Gillespie P, Conde-Knape K, Kazmer S, Li S, Qian Y, Taub R, Wertheimer SJ, Whittard T, Bolin D (2011) Discovery and optimization of 2-phenyloxazole derivatives as diacylglycerol acyltransferase-1 inhibitors. Bioorg Med Chem Lett 21:7205–7209
9. Elworthy TR, Kertesz DJ, Kim W, Roepel MG, Quattrocchio-Setti L, Smith DB, Tracy JL, Chow A, Li F, Brill ER, Lach LK, McGee D, Yang DS, Chiou S-S (2004) Lactams as EP_4 prostanoid receptor subtype selective agonists. Part 1: 2-pyrrolidinones – stereo-chemical and lower side-chain optimization. Bioorg Med Chem Lett 14:1655–1659
10. Elworthy TR, Brill ER, Caires CC, Lim W, Lach LK, Tracy JL, Chiou S-S (2005) Lactams as prostanoid receptor ligands. Part 4: 2-piperidones as selective EP_4 receptor agonists. Bioorg Med Chem Lett 15:2523–2526
11. Hutinec A, Rupcic R, Ziher D, Smith KS, Milhous W, Ellis W, Ohrt C, Ivezic Schönfeld Z (2011) An automated, polymer-assisted strategy for the preparation of urea and thiourea derivatives of 15-membered azalides as potential antimalarial chemotherapeutics. Bioorg Med Chem 19:1692–1701
12. Gammill RB, Bell FP, Bell LT, Bisaha SN, Wilson GJ (1990) Antiatherosclerotic agents. A structurally novel bivalent inhibitor of AcylCoA: cholesterol O-acyltransferase with systemic activity. J Med Chem 33:2685–2687
13. Serdyuk O, Butin A, Abaev V (2010) Synthesis of fluorofurans and perfluoroalkylfurans. J Fluor Chem 131:296–319
14. Cerichelli G, Crestoni ME, Fornarini S (1990) The fluorination of five-membered heteroaromatic compounds with elemental fluorine. Gazz Chim Ital 120:749–755
15. Blank SJ, Stephens CE (2006) Oxidative ring opening of 2,5-diarylfurans by selectfluor®. Tetrahedron Lett 47:6849–6850
16. Burdon J, Tatlow JC, Thomas DF (1966) Tetrafluorofuran. Chem Commun 48–49. doi:10.1039/C19660000048
17. Burdon J, Chivers GE, Mooney EF, Tatlow JC (1969) Partial fluorination of tetrahydrofuran with cobalt trifluoride. J Chem Soc (C) 1739–1746
18. Burdon J, Chivers GE, Tatlow JC (1970) Highly fluorinated heterocycles. Part III. The preparation and reactions of some polyfluorofurans. J Chem Soc (C) 2146–2151
19. Bailey J, Plevey RG, Tatlow JC (1975) Hexafluorobenzo[*b*]furan. Tetrahedron Lett 16:869–870
20. Barton DHR, Hesse RH, Jackman GP, Pechet MM (1977) Fluorination of benzofuran and of N-acylindoles with trifluorofluorooxymethane. J Chem Soc Perkin Trans 1:2604–2608

21. Perugini R, Ruzziconi R, Sebastiani GV (1983) Synthesis of 2,3-dihalogeno-2,3-dihydrobenzofurans: regioselectivity and stereochemistry. Gazz Chim Ital 113:149–152
22. Nash SA, Gammill RB (1987) The synthesis of 2- and 3-fluorokhellin. Tetrahedron Lett 28:4003–4006
23. Baciocchi E, Ruzziconi R, Sebastiani GV (1983) Anti and syn eliminations from 2,3-dihalo-2,3-dihydrobenzofurans. The role of the substrate structure and the base-solvent system on the reaction mechanism. J Am Chem Soc 105:6114–6120
24. Dvornikova E, Bechcicka M, Kamenska-Trela K, Krowczynski A (2003) Synthesis and NMR studies of 2- and 3-fluorosubstituted five-membered heterocycles. J Fluor Chem 124:159–168
25. Li P, Chai Z, Zhao G, Zhu S-Z (2008) Synthesis of 3-fluoro-2,5-disubstituted furans and further derivative reactions to access fluorine-containing 3,3′-bifurans and tetrasubstituted furans. Synlett 2547–2551
26. Yamada S, Gavryushin A, Knochel P (2010) Convenient electrophilic fluorination of functionalized aryl and heteroaryl magnesium reagents. Angew Chem Int Ed 49:2215–2218
27. Yamada S, Knochel P (2010) Large-scale preparation of aromatic fluorides via electrophilic fluorination with functionalized aryl- or heteroarylmagnesium reagents. Synthesis 2490–2494
28. Forrest AK, O'Hanlon PJ (1995) The preparation and lithiation of bromofluorofurans via a novel fluorodecarboxylation. Tetrahedron Lett 36:2117–2118
29. Song R, Lin W, Jiang Q (2011) A convenient synthesis of 5-fluorofuran-2-carboxylic acid. Tetrahedron Lett 52:4965–4966
30. Martin-Santamaria S, Carroll MA, Carroll CM, Carter CD, Pike VW, Rzepa HS, Widdowson DA (2000) Fluoridation of heteroaromatic iodonium salts – experimental evidence supporting theoretical prediction of the selectivity of the process. Chem Commun 649–650
31. Ichikawa J, Wada Y, Fujiwara M, Sakoda K (2002) The nucleophilic 5-endo-trig cyclization of 1,1-difluoro-1-alkenes: ring-fluorinated hetero- and carbocycle synthesis and remarkable effect of the vinylic fluorines on the disfavored process. Synthesis 1917–1936
32. Ichikawa J, Wada Y, Okauchi T, Minami T (1997) 5-endo-trigonal cyclization of *o-substituted* gem-difluorostyrenes: syntheses of 2-fluorinated indoles, benzo[*b*]furans and benzo[b]thiophenes. Chem Commun 1537–1538
33. Sham HL, Betebenner DA (1991) A new and concise synthesis of 3-fluoro-2,5-disubstituted furans. J Chem Soc Chem Commun 1134–1135
34. Arimitsu S, Hammond GB (2007) Selective synthesis of fluorinated furan derivatives via $AgNO_3$-catalyzed activation of an electronically deficient triple bond. J Org Chem 72:8559–8561
35. Arimitsu S, Jacobsen JM, Hammond GB (2008) Synthesis of 2,4,5-trisubstituted 3-fluorofurans via sequential iodocyclization and cross-coupling of gem-difluorohomopropargyl alcohols. J Org Chem 73:2886–2889
36. Li Y, Wheeler KA, Dembinski R (2011) Electrophilic cyclizations of 2-fluoroalk-3-yn-1-ones: room-temperature synthesis of diversely 2,5-disubstituted 3,4-fluorohalofurans. Eur J Org Chem 2767–2771
37. Li Y, Wheeler KA, Dembinski R (2012) Room temperature syntheses of entirely diverse substituted β-fluorofurans. Org Biomol Chem 10:2395–2408
38. Li Y, Wheeler KA, Dembinski R (2010) Gold(I)-catalyzed cycloisomerization of 2-fluoroalk-3-yn-1-ones: synthesis of 2,5-substituted 3-fluorofurans. Adv Synth Catal 352:2761–2766
39. Lie MSF, Jie K, Lau MML, Lam CNW (2003) Synthesis of novel tri- and tetrasubstituted C_{18} furan fatty esters. Lipids 38:1293–1297
40. Moon HR, Kim HO, Jeong LS (2002) Synthesis of 2′,3′-didehydro-2′,3′-dideoxy-2′-flu-oro apionucleosides as potential antiviral agents. J Chem Soc Perkin Trans 1:1800–1804
41. Lee K, Zhou W, Kelley LLC, Momany C, Chu CK (2002) Synthesis of unsaturated fluoride containing D- and L-pyranosyl nucleosides. Tetrahedron Asymmetry 13:1589–1598

42. Derenberg M, Hodge P (1971) Reaction of difluorocarbene with 2-benzylidenecyclohexanones to afford phenylfluorofurans. Chem Commun 233–234
43. Xu W, Chen Q-Y (2003) A novel approach of cycloaddition of difluorocarbene to α, β-unsaturated aldehydes and ketones: synthesis of gem-difluorocyclopropyl ketones and 2-fluorofurans. Org Biomol Chem 1:1151–1156
44. Xu W, Dolbier WR, Salazar J (2008) Ionic liquid, surrogate hydrogen bromide reagent for ring opening of cyclopropyl ketones. J Org Chem 73:3535–3538
45. Wang H, Gu W, Zhang G, Huan Z, Chen J-P (1999) Revisiting the reactions of halocarbenes with tetraphenylcyclone. J Chem Res (M) 1501–1509
46. Paleta O, Volkov A, Hetflejs J (2000) Fluorinated butanolides and butenolides, part 5. Synthesis and nucleophilic reactions of 3-chloro-2-fluoro-2-buten-4-olide as tetronic acid analogue. Conjugate addition of hard nucleophiles and vinylic halogen displacement with soft phosphorus nucleophiles. J Fluor Chem 102:147–157
47. Pomeisl K, Cejka J, Kvicala J, Paleta O (2007) Synthesis of 3-fluorofuran-2(H)-ones based on Z/E photoisomerisation and cyclisation of 2-fluoro-4-hydroxybut-2-enoates. Eur J Org Chem 5917–5925
48. Pomeisl K, Kvicala J, Paleta O (2006) Convenient synthesis of 3-fluoro-4,5-diphenylfuran-2(5H)-one from benzoin ethers. Novel and efficient Z-E isomerisation and cyclisation of 2-fluoroalkenoate precursors, substitution of vinylic fluorine. J Fluor Chem 127:1390–1397
49. Girard Y, Atkinson JG, Belanger PC, Fuentes JJ, Rokach J, Rooney CS, Remy DC, Hunt CA (1983) Synthesis, chemistry, and photochemical substitutions of 6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-ones. J Org Chem 48:3220–3234
50. Naumann D, Kischkewitz J (1990) Trifluormethylierubgsreaktionen von CF_3I, $Te(CF_3)_2$, $Sb(CF_3)_3$, $Hg(CF_3)_2$, und $Cd(CF_3)_2 \cdot D$ mit furan, thiophen, pyrrol und p-benzochinon. J Fluor Chem 46:265–281
51. Kino T, Nagase Y, Ohtsuka Y, Yamamoto K, Uraguchi D, Tokuhisa K, Yamakawa T (2010) Trifluoromethylation of various aromatic compounds by CF_3I in the presence of Fe(II) compound, H_2O_2 and dimethylsulfoxide. J Fluor Chem 131:98–105
52. Iqbak N, Choi S, Ko E, Cho EJ (2012) Trifluoromethylation of heterocycles via visible light photoredox catalysis. Tetrahedron Lett 53:2005–2008
53. Sawada H, Nakayama M, Yoshida M, Yoshida T, Kamigata N (1990) Trifluoromethylation of aromatic compounds with bis(trifluoroacetyl) peroxide. J Fluor Chem 46:423–431
54. Popkov SV, Kuzenkov AV (2005) Synthesis of trifluoromethyl-substituted heteroaroma-tic aldehydes. Russ Chem Bull 54:1672–1674 (Izv Akad Nauk, Ser Khim 1623–1625)
55. Kobayashi Y, Kumadaki I, Hanzawa Y (1977) Studies on organic fluorine compounds. XXII. Synthesis and reactions of (trifluoromethyl)benzofurans. Chem Pharm Bull 25:3009–3012
56. Kobayashi Y, Kumadaki I (1980) Studies on organic fluorine compounds. Part 27. Abnormal reactions in the trifluoromethylation of aromatic compounds with trifluoromethyl iodide and copper powder. J Chem Soc Perkin Trans 1:661–664
57. Ye Y, Sanford MS (2012) Merging visible-light photocatalysis and transition-metal catalysis in the copper-catalyzed trifluoromethylation of boronic acids with CF_3I. J Am Chem Soc 134:9034–9037
58. Ye Y, Künzi SA, Sanford MS (2012) Practical method for the Cu-mediated trifluoromethylation of arylboronic acids with CF_3 radical derived from $NaSO_2CF_3$ and *tert*-butyl hydroperoxide (TDHP). Org Lett 14:4979–4981
59. Chu L, Qing F-L (2010) Copper-mediated oxidative trifluoromethylation of boronic acids. Org Lett 12:5060–5063
60. Zhang C-P, Cai J, Zhou C-B, Wang X-P, Zheng X, Gu Y-C, Xiao J-C (2011) Copper-mediated trifluoromethylation of arylboronic acids by trifluoromethyl sulfonium salts. Chem Commun 47:9516–9518
61. Liu T, Shen Q (2011) Copper-catalyzed trifluoromethylation of aryl and vinyl boronic acids with an electrophilic trifluoromethylating reagent. Org Lett 13:2342–2345

62. Liu T, Shao X, Wu Y, Shen Q (2012) Highly selective trifluoromethylation of 1,3-disubstituted arenes through iridium-catalyzed arene borylation. Angew Chem Int Ed 51:540–543
63. Ye Y, Lee SH, Sanford MS (2011) Silver-mediated trifluoromethylation of arenes using $TMSCF_3$. Org Lett 13:5464–5467
64. Nishida M, Fujii S, Aoki T, Hayakawa Y, Muramatsu H, Morita T (1990) Synthesis and polymerization of ethynylthiophenes and ethynylfurans containing trifluoromethyl groups. J Fluor Chem 46:445–459
65. Grigorash RV, Lyalin VV, Alekseeva LA, Yagupol'skii LM (1977) 5-Trifluoromethyl-furan derivatives. Chem Heterocycl Comp 13:1280–1282 (Khim Geterotsikl Soed 1607–1609)
66. Lyalin VV, Grigorash RV, Alekseeva LA, Yagupolskii LM (1975) Fluorination of furantetracarboxylic acid by sulfur tetrafluoride. Russ J Org Chem 11:456–457 (Zh Org Khim 11:460–461)
67. Lyalin VV, Grigorash RV, Alekseeva LA, Yagupolskii LM (1975) Mono(trifluoromethyl) furans and bis(trifluoromethyl)furans. Russ J Org Chem 11:1073–1077, Zh Org Khim 11:1086–1090
68. Yagupolskii LM, Vechirko EP, Kondratenko NV, Liepinsh EE, Shpaer EG, Zhuk RA (1981) Synthesis of 2-trifluoromethyltetrahydrofuran and 2-perfluoro-tert-butyltetrahydrofuran and their pyrimidinenucleoside analogs. Russ J Org Chem 17:167–170 (Zh Org Khim 17:186–191)
69. Lyalin VV, Grigorash RV, Alekseeva LA, Yagupolskii LM (1984) Reaction of 3,4-furandicarboxylic acid derivatives with sulfur tetrafluoride in a hydrogen fluoride medium. Russ J Org Chem 20:769–772 (Zh Org Khim 20:846–849)
70. Nowak I, Dmowski W, Manko WA (1995) Unusual reaction of sulphur tetrafluoride: conversion of the methyl group into difluoromethyl and trifluoromethyl groups. J Fluor Chem 75:115–116
71. Sherman WR, Freifelder M, Stone GR (1960) Three 2-fluoroalkyl-5-nitrofurans. J Org Chem 25:2048–2049
72. Weis CD (1962) A diene-retrodiene-diene reaction. The synthesis of 2,3,5,6-tetrakis-(trifluoromethyl)-7-oxabicyclo[2.2.1]-2,5-heptadiene. J Org Chem 27:3693–3695
73. Jiang B, Zhang F, Xiong W (2002) The regio- and stereoselective addition of carbon nucleophiles to trifluoromethyl phenylsulfanyl acetylene: a novel and expeditious approach to 3-trifluoromethyl furans. Tetrahedron Lett 43:665–667
74. Abubakar AB, Booth BL, Tipping AE (1991) Reaction of 2-lithio-3,4-bis(trifluoromethyl) furan with electrophiles. J Fluor Chem 55:189–198
75. Abubakar AB, Booth BL, Suliman NNE, Tipping AE (1992) Some reactions of 3,4-bis(trifluoromethyl)furan and its precursor, 2,3-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]-hepta-2,5-diene: novel isocoumarin formation from thermal reaction of the furan with ethyl propionate. J Flu Chem 56:359–371
76. Wilson WS, Warrener RN (1972) A mild retro-$[\pi 4_S + \pi 2_S]$ cleavage route to furans and fulvenes. J Chem Soc Chem Commun 211–212
77. Chambers RD, Roche AJ, Rock MH (1996) Polyhalogenated heterocyclic compounds. Part 41. Cycloaddition reactions involving hexafluorobut-2-yne and 1,1,1,2,4,4,4-heptafluorobut-2-ene. J Chem Soc Perkin Trans 1:1095–1100
78. Barlow MG, Suliman NNE, Tipping AE (1995) A high-yield synthesis of 3-carboethoxy-4-trifluoromethylfuran and some Diels-Alder reactions of this furoate with acetylenic dienophiles. J Fluor Chem 70:59–69
79. Nezis A, Fayn J, Cambon A (1991) Obtention de 3-F-alkyl-4-ethoxycarbonyl furanes. J Fluor Chem 53:297–299
80. Nezis A, Fayn J, Cambon A (1991) Synthese d'heterocycles F-alkyles par reaction de Diels-Alder sur les F-alkyl propynoates. J Fluor Chem 53:285–295
81. Warrener RN, Wang J-M, Weerasuria KDV, Russell RA (1990) Transfer technology III: the synthesis of bridged cyclic polyenes using a new retrosynthetic algorithm as a guide. Tetrahedron Lett 31:7069–7072

82. Thalhammer F, Wallfahrer U, Sauer J (1988) 1,3,4-Oxadiazole als heterocyclische 4π-komponenten in Diels-Alder-reaktionen. Tetrahedron Lett 29:3231–3234
83. Seitz G, Gerninghaus C (1994) Cycloadditions of 1,3,4-oxadiazoles. Pharmazie 49:102–106
84. Kawada K, Kitagawa O, Kobayashi Y (1985) Studies on organic fluorine compounds. XLV. Synthesis and regioselective substitution reaction of 3-trifluoromethylfuran. Chem Pharm Bull 33:3670–3674
85. Kobatake T, Yoshida S, Yorimitsu H, Oshima K (2010) Reaction of 2-(2,2,2-trifluoroethylidene)-1,3-dithiane 1-oxide with ketones under Pummerer conditions and its application to the synthesis of 3-trifluoromethyl-substituted five-membered heteroarenes. Angew Chem Ed 49:2340–2343
86. Bambury RE, Yaktin HK, Wyckoff KK (1968) Trifluoromethylfurans. J Heterocycl Chem 5:95–100
87. Smith JO, Mandal BK, Filler R, Beery JW (1997) Reaction of ethyl 4,4,4-trifluoroacetate enolate with 3-bromo-1,1,1-trifluoroacetone: synthesis of 2,4-bis(trifluoromethyl)furan. J Fluor Chem 81:123–128
88. Bambury RE, Miller LF (1970) Trifluoromethylfurans. II. J Heterocycl Chem 7:269–273
89. Gibson CL, Paulini K, Suckling CJ (1997) Synthesis of potential inhibitors of GTP-cyclohydrolase I: an efficient synthesis of 8-substituted 7-deazaguanines. Chem Commun 371–372
90. Gibson CL, Ohta K, Paulini K, Suckling CJ (1997) Specific inhibitors in vitamin biosynthesis. Part 10. Synthesis of 7- and 8-substituted 7-deazaguanines. J Chem Soc Perkin Trans 1:3025–3031
91. Mosslemin MH, Yavari I, Anary-Abbasinejad M, Nateghi MR (2004) Reaction between tert-butyl isocyanide and 1,1,1-trifluoro-4-aryl-butane-2,4-diones. Synthesis of new trifluoromethylated furan derivatives. J Fluor Chem 125:1497–1500
92. Nishida M, Hayakawa Y, Matsui M, Shibata K, Muramatsu H (1991) Synthesis of 2,5-diethyl-3,4-bis(trifluoromethyl)furan and its derivatives. J Heterocycl Chem 28:225–229
93. Linderman RJ, Jamois EA, Tennyson SD (1994) Synthesis of and analysis of thiol additions to β-alkyl-α, β-unsaturated trifluoromethyl ketones. J Org Chem 59:957–962
94. Zhang D, Yuan C (2007) Reaction of 1,2-unsaturated trifluoromethyl ketones and their conversion to 1-(trifluoromethyl)furan derivatives. Eur J Org Chem 3916–3924
95. Zhang J, Zhao X, Li Y, Lu L (2006) Highly efficient synthesis of 4-trifluoromethylfuran derivatives via a sequential deprotection-annulation reaction. Tetrahedron Lett 47:4737–4739
96. Usachev BI (2011) First nucleophilic addition of acetylide to 1,3-diketonate anions: reaction of 1-aryl-4,4,4-trifluorobutane-1,3-diones with sodium acetylide. Tetrahedron Lett 52:6726–6728
97. Chambers RD, Kirk JR, Powell RL (1983) Polyhalogenoheterocyclic compounds. Part 35. Reactions of fluorinated alkenes and cycloalkenes with enolate anions. J Chem Soc Perkin Trans 1:1239–1242
98. Kuroboshi M, Shinozaki T, Ishihara T, Ando T (1987) A convenient synthesis of fluorine-containing highly-substituted furans through new fluoride ion-catalyzed reaction of 1-alkyl-F-1-alkenyl phosphates. Chem Lett 1621–1622
99. Briscoe MW, Chambers RD, Mullins, SJ, Nakamura T, Drakesmith FG (1990) A synthesis of novel perfluorodienes. J Chem Soc Chem Commun 1127–1128
100. Briscoe MW, Chambers RD, Mullins SJ, Nakamura T, Vaughan JFS (1994) Reactions involving fluoride ion. Part 39. Reactions of perfluorinated dienes with oxygen and sulphur nucleophiles. J Chem Soc Perkin Trans 1:3119–3124
101. Chambers RD, Vaughan JFS, Mullins SJ, Nakamura T, Roche AJ (1995) Fluorinated dienes. J Fluor Chem 72:231–233
102. Burger K, Helmreich B (1992) Ein neues Verfahren zur positionsselektiven Einführung von Trifluormethylgruppen in Heteroaromaten: Synthese von 3-Trifluormethylfuran. J Prakt Chem 334:311–316

103. Burger K, Helmreich B (1992) Synthesis of 3-trifluoromethylfurans from β,β-bis(trifluoromethyl) α,β-unsaturated ketones and tin(II) chloride. J Chem Soc Chem Commun 348–349
104. Burger K, Helmreich B, Hennig L, Spengler J, Albericio F, Fuchs A (2007) Partially fluorinated heterocycles from 4,4-bis(trifluoromethyl)-hetero-1,3-dienes via C–F bond activation – synthesis of 2-fluoro-3-(trifluoromethyl)furans. Monatsh Chem 138:227–236
105. Chambers RD, Lindley AA, Fielding HC (1978) Photochemical transformations of perfluoro-tri- and -tetra-methylfurans. J Fluor Chem 12:337–340
106. Chambers RD, Lindley AA, Philpot PD, Fielding HC, Hutchinson J, Whittaker G (1978) Perfluorinated derivatives of furan via novel cyclisation reactions of perfluoro-olefins. J Chem Soc Chem Commun 431–432
107. Chambers RD, Lindley AA, Philpot PD, Fielding HC, Hutchinson J, Whittaker G (1979) Reactions involving fluoride ion. Part 16. Nucleophilic attack on a perfluorotetraalkylethylene and a synthesis of perfluorotetramethylfuran. J Chem Soc Perkin Trans 1:214–219
108. Briscoe MW, Chambers RD, Mullins SJ, Nakamura T, Vaughan JFS, Drakesmith FG (1994) Reactions involving fluoride ion. Part 38. New fluorinated dienes by defluorination. J Chem Soc Perkin Trans 1:3115–3118
109. Bartlett S, Chambers RD, Kelly NM (1980) A novel furan synthesis. Tetrahedron Lett 21:1891–1892
110. Jullien J, Pechine JM, Perez F, Piade JJ (1982) Flash vacuum thermolysis of β-keto-trimethylsilyl-enol-ethers. Synthesis of allenic and furanic derivatives. Tetrahedron 38:1413–1416
111. Khlebnikova TS, Isakova VG, Lakhvich FA (2009) Reaction of 2-perfluoroalkanoyl-cyclohexane-1,3-diones with diazomethane. Russ J Org Chem 45:519–522 (Zh Org Khim 45:534–537)
112. Bouillon J-P, Henin B, Huot J-F, Portella C (2002) 1,1-Bis(ethylsulfanyl)perfluorobut-1-ene as starting material for the synthesis of substituted 2-trifluoromethylfurans and –pyrroles. Eur J Org Chem 1556–1561
113. Bouillon J-P, Kikelj V, Tinant B, Harakat D, Porterlla C (2006) Synthesis of new trifluoromethylated furans, dihydrofurans and butenolides starting from γ-ketothioesters and diisopropylamine. Synthesis 1050–1056
114. Hess U, König WA (1981) Synthese von Furanderivaten aus N-Methylaminosäuren. Liebigs Ann Chem 1606–1609
115. Denisenko AV, Tverdokhlebov AV, Tolmachev AA, Volovenko YM, Shishkina SV, Shishkin OV (2010) Synthesis of masked 2-amino-3-furancarboxaldehydes. Synthesis 1009–1013
116. Begue J-P, Bonnet-Delpon D, Dogbeavou R, Ourevitch M (1993) Trifluoromethylated furans via iodocyclisation of γ-unsaturated ethyl trifluoroacetates. J Chem Soc Perkin Trans 1:2787–2791
117. Zakharova VM, Nikolaev VA (2007) Rhodium(II)-catalyzed intramolecular reactions of methyl 4-diazo-5-oxo-3-trifluoromethylalk-2-enoates in the presence of 2,5-dimethylfuran. Russ J Org Chem 43:930–932 (Zh Org Khim 43:931–933)
118. Yoneda N, Matsuoka S, Miyaura N, Fukuhara T, Suzuki A (1990) Preparation of 1-aryl- or 1-alkenyl-2-(perfluoroalkyl)acetylenes. Bull Chem Soc Jpn 63:2124–2126
119. Zhou H, Niu J-J, Xu J-W, Hu S-J (2009) Novel route to 2-trifluoromethylated benzofurans. Synth Commun 39:716–732
120. Jiang Z-X, Qing F-L (2003) Sodium carbonate as carbon dioxide source for the synthesis of cyclic carbonates containing the trifluoromethyl group. J Fluor Chem 123:57–60
121. Konno T, Chae J, Ishihara T, Yamanaka H (2004) A first regioselective synthesis of 3-fluoroalkylated benzofurans via palladium-catalyzed annulation of fluorine-containing internal alkynes with variously substituted 2-iodophenol. Tetrahedron 60:11695–11700
122. Kobatake T, Fujino D, Yoshida S, Yorimitsu H, Oshima K (2010) Synthesis of 3-trifluoromethylbenzo[*b*]furans from phenols via direct ortho functionalization by extended Pummerer reaction. J Am Chem Soc 132:11838–11840

123. Kaltenbronn JS, Quin J, Reisdorph BR, Klutchko S, Reynolds EE, Welch KM, Flynn MA, Doherty AM (1997) Benzofuran derivatives as ET_A-selective, non-peptide endothelin antagonists. Eur J Med Chem 32:425–431
124. Judd DB, Dowle MD, Middlemiss D, Scopes DIC, Ross BC, Jack TI, Pass M, Tranquillini E, Hobson JE, Panchal TA, Stuart PG, Paton JMS, Hubbard T, Hilditch A, Drew GM, Robertson MJ, Clark KL, Travers A, Hunt AAE, Eddershaw PJ, Bayliss MK, Manchee GR, Donnelly MD, Walker DG, Richards SA (1994) Bromobenzofuran-based non-peptide antagonists of angiotensin II: GR138950, a potent antihypertensive agent with high oral bioavailability. J Med Chem 37:3108–3120
125. Kuckländer U, Herweg-Wahl U, Poll W, Rickerich L (1988) Darstellung und Eigenschaften von fluorierten Benzofuran-Derivaten. Chem Ber 121:1841–1845
126. Davydov DV, Beletskaya IP (2004) Synthesis of naphtho[2,3-*b*]furan-4,9-diones having a trifluoromethyl group under conditions of phase-transfer catalysis. Russ J Org Chem 40:134–136 (Zh Org Khim 40:143–145)
127. Onys'ko PP, Proklina NV, Prokopenko VP, Gololobov YG (1987) Intramolecular substitution of *o*-nitro group in 2,6-dinitrobenzene derivatives. Russ J Org Chem 23:549–552 (Zh Org Khim 23:606–610)
128. Kuckländer U (1983) Zur Umsetzung eines cyclishen Halbaminals mit CH-aciden Verbindungen. Arch Pharm 316:449–453
129. Gallos JK, Lianis PS, Nicolaides DN (1989) Reactions of furazano[3,4-*b*]quinoxalines with phosphorus ylides and an unusual oxidative transformation of the transylidation product. J Heterocycl Chem 26:1415–1420
130. Wang Y, Zhu S (2001) A simple synthesis of fluoroalkyl substituted dihydrofurans by rhodium(II)-catalyzed 1,3-dipolar reactions. Tetrahedron 57:3383–3387
131. Pang W, Zhu S, Xin Y, Jiang H, Zhu S (2010) $Rh_2(OAc)_4$ catalyzed formation of fluorine-containing polysubstituted furans from diazocompounds and aromatic alkynes. Tetrahedron 66:1261–1266
132. Akhani RK, Atiq-ur-Rehman, Schnatter WFK (2009) Incorporation of hexafluorobutyne into furans or phenols via reaction with iron(0) carbine or vinylketene complexes. Tetrahedron Lett 50:930–932
133. Wang Y, Luo Y-C, Hu X-Q, Xu P-F (2011) A powerful cascade approach for expeditious synthesis of trifluoromethylated furans. Org Lett 13:5346–5349
134. Ochiai K, Takita S, Eiraku T, Kojima A, Iwase K, Kishi T, Fukuchi K, Yasue T, Adams DR, Allcock RW, Jiang Z, Kohno Y (2012) Phosphodiesterase inhibitors. Part 3: design, synthesis and structure-activity relationships of dual PDE3/4-inhibitory fused bicyclic heteroaromatic-dihydropyridazinones with anti-inflammatory and bronchodilatory activity. Bioorg Med Chem 20:1644–1658
135. Lee C-J, Jang Y-J, Wu Z-Z, Lin W (2012) Preparation of functional phosphorus zwitterions from activated alkanes, aldehydes, and tributylphosphine: synthesis of polysubstituted furo[3,2-*c*]coumarins. Org Lett 14:1906–1909
136. Morandi B, Carreira EM (2011) Expedient preparation of trifluoromethyl-substituted benzofuranols. Org Lett 13:5984–5985
137. Rudenko AP, Aristov SA, Vasil'ev AV (2004) Oxidative heterocyclization of 4-(4-methoxy-3-fluorophenyl)-1,1,1-trifluorobut-3-yn-2-one in a system CF_3CO_2H-CH_2Cl_2-PbO_2. Russ J Org Chem 40:1221 (Zh Org Khim 40:1268)
138. Aristov SA, Vasil'ev AV, Rudenko AP (2006) Oxidation of aromatic compounds: XIV. Oxidation of arylethynyl ketones in the system CF_3CO_2H-CH_2Cl_2-PbO_2. Russ J Org Chem 42:66–72 (Zh Org Khim 42:74–80)
139. Kobayashi Y, Hanzawa Y, Nakanishi Y, Kashiwagi T (1978) Conversion of a valence-bond isomer of hexakis(trifluoromethyl)oxepin to tetrakis(trifluoromethyl)furan. Tetrahedron Lett 19:1019–1022
140. Boriack CJ, Laganis ED, Lemal DM (1978) Perfluorotetramethylfuran. Tetrahedron Lett 19:1015–1018

141. Tyvorskii VI, Pukin AV, Bobrov DN (2001) Condensation of stereoisomeric 2-acetyl-2,3-diphenyloxiranes with ethyl trifluoroacetate. Chem Heterocycl Comp 37:540–545 (Khin Geterotsikl Soed 592–597)
142. Kawada K, Kitagawa O, Taguchi T, Hanzawa Y, Kobayashi Y, Iitaka Y (1985) Studies on organic fluorine compounds. XLVII. Synthesis of trifluoromethylated sugars through the aldol reaction of 2-trimethylsilyloxy-4-trifluoromethylfuran. Chem Pharm Bull 33:4216–4222
143. Okano T, Ueda T, Ito K, Kodaira K, Hosokawa K, Muramatsu H (1986) Synthesis of so-me ethynyltrifluoromethylfurans and their polymerization. J Fluor Chem 31:451–459
144. Grigorash RV, Lyalin VV, Alekseeva LA, Yagupolskii LM (1978) Tetrakis(trifluoro-methyl) furan. Russ J Org Chem 14:2414–2415 (Zh Org Khim 14:2623–2624)
145. Burger K, Fuchs A, Hennig L, Helmreich B (2001) Low temperature domino reaction. A ready access to trifluoromethyl substituted butenolides and their thioanalogues. Tetrahedron Lett 42:1657–1659
146. Burger K, Hennig L, Fuchs A, Greif D, Spengler J, Albericio F (2005) Domino reactions with fluorinated five-membered heterocycles – syntheses of trifluoromethyl substituted butenolides and γ-ketoacids. Monatsh Chem 136:1763–1779
147. Burger K, Fuchs A, Hennig L, Helmreich B, Greif D (2001) Domino reactions with 2-fluoro-3-trifluoromethylfurans and –thiophenes. Monatsh Chem 132:929–945
148. Bouillon J-P, Tinant B, Nuzillard J-M, Porterlla C (2004) Synthesis of new 3-(1-ethylsulfanyl-2-perfluoroalkyl)-5-hydroxy-5-methyl (or 5-phenyl)-1,5-dihydro-pyrrol-2-ones starting from γ-keto thioesters and amines. Synthesis 711–721
149. Kobayashi Y, Hanzawa Y (1978) Reaction of tetrakis(trifluoromethyl)furan and its photo-adduct. Tetrahedron Lett 19:4301–4302
150. Nishida M, Hayakawa Y, Matsui M, Shibata K, Muramatsu H (1992) Synthesis and photochemical reaction of 1,4-dialkyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclo-hepta-2,5-diene. J Heterocycl Chem 29:113–116
151. Abubakar AB, Booth BL, Tipping AE (1990) Novel Diels-Alder cycloaddition involving two α, β-unsaturated esters in the formation of isocoumarins from the reaction of ethyl propynoate with 3,4-bis(trifluoromethyl)furan. J Fluor Chem 47:353–359
152. Li P, Gu J-W, Ying Y, He Y-M, Zhang H-f, Zhao G, Zhu S-Z (2010) Palladium-catalyzed alkenylation of fluoro-substituted furans via C-H activation to form tetrasubstituted furans. Tetrahedron 66:8387–8391
153. Li P, Chai Z, Zhao G, Zhu S-Z (2009) Pd-catalyzed direct arylation of 3-fluorofurans utilizing the neighboring effect of fluorine atom: facile synthesis of tetrasubstituted monofluorofurans. Tetrahedron 65:1673–1678
154. Baxendale IR, Schou SC, Sedelmeier J, Ley SV (2010) Multi-step synthesis by using modular flow reactors: the preparation of yne-ones and their use in heterocyclic synthesis. Chem Eur J 16:89–94
155. Yoshida M, Imai R, Komatsu Y, Morinaga Y, Kamigata N, Iyoda M (1993) Convenient preparations and Michael reactions of 4-fluoroalkylated but-2-en-4-olides. J Chem Soc Perkin Trans 1:501–504
156. Yanai H, Takahashi A, Taguchi T (2010) 1,4-Addition of silicon dienoates to α,β-unsaturated aldehydes catalyzed by in situ-generated silicon Lewis acid. Chem Commun 46:8728–8730
157. Kastron VV, Dubur GY, Vitolin' RO, Kimenis AA (1979) Synthesis and pharmacological activity of 4-furyl-1,4-dihydropyridines. Pharm Chem J 13:611–616 (Khim-Farm Zh, 13, N6:57–62)
158. Wagner J, Vitali P, Schoun J, Giroux E (1977) Metal complexation by α-mercapto-β-aryl acrylic acids. Can J Chem 55:4028–4036
159. Muramatsu H, Okumura A, Shibata K, Matsui M (1994) Synthesis, absorption spectra, and photostability of triarylmethane dye ethynylogues containing trifluoromethyl group(s). Chem Ber 127:1627–1632

160. Baumann M, Baxendale IR, Ley SV, Nikbin N, Smith CD, Tierney JP (2008) A modular flow reactor for performing Curtius rearrangements as a continuous flow process. Org Biomol Chem 6:1577–1586
161. Patch RJ, Brandt BM, Asgari D, Baindur N, Chadha NK, Georgiadis T, Cheung WS, Petrounia IP, Donatelli RR, Chaikin MA, Player MR (2007) Potent 2′-aminoanilide inhibitors of cFMS as potential anti-inflammatory agents. Bioorg Med Chem Lett 17:6070–6074
162. Shin Y, Chen W, Habel J, Duckett D, Ling YY, Koenig M, He Y, Vojkovsky T, LoGrasso P, Kamenecka TM (2009) Synthesis and SAR of piperazine amides as novel c-jun N-terminal kinase (JNK) inhibitors. Bioorg Med Chem Lett 19:3344–3347
163. Mazurov AA, Miao L, Bhatti BS, Strachan J-P, Akireddy S, Murthy S, Kombo D, Xiao Y, Hammond P, Zhang J, Hauser TA, Jordan KG, Miller CH, Speake JD, Gatto GJ, Yohannes D (2012) Discovery of 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane (TC-6683, AZD1446), a novel highly selective α4β2 nicotinic acetylcholine receptor agonist for the treatment of cognitive disorders. J Med Chem 55:9181–9194
164. Ashton WT, Chang LL, Flanagan KL, Hutchins SM, Naylor EM, Chakravarty PK, Patchett AA, Greenlee WJ, Chen T-B, Faust KA, Chang RSL, Lotti VJ, Zingaro GJ, Schorn TW, Siegl PKS, Kivlighn SD (1994) Triazolinone biphenylsulfonamide derivatives as orally active angiotensin II antagonists with potent AT_1 receptor affinity and enhanced AT_2 affinity. J Med Chem 37:2808–2824
165. Heightman TD, Gaster LM, Pardoe SL, Pilleux J-P, Hadley MS, Middlemiss DN, Price GW, Roberts C, Scott CM, Watson JM, Gordon LJ, Holland VA, Powles J, Riley GJ, Stean TO, Trail BK, Upton N, Austin NE, Ayrton AD, Coleman T, Cutler L (2005) 8-Piperazinyl-2,3-dihydropyrrolo[3,2-*g*]isoquinolines: potent, selective, orally bioavailable 5-HT_1 receptor ligands. Bioorg Med Chem Lett 15:4370–4374
166. Sandham DA, Barker L, Beattie D, Beer D, Bidlake L, Bentley D, Butler KD, Craig S, Farr D, Ffoulkes-Jones C, Fozard JR, Haberthuer S, Howes C, Hynx D, Jeffers S, Keller TH, Kirkham PA, Maas JC, Mazzoni L, Nicholls A, Pilgrim GE, Schaebulin E, Spooner GM, Stringer R, Tranter P, Turner KL, Tweed MF, Walker C, Watson SJ, Cuenoud BM (2004) Synthesis and biological properties of novel glucocorticoid androstene C-17 furoate esters. Bioorg Med Chem 12:5213–5224
167. Snyder DS, Tradtrantip L, Yao C, Kurth MJ, Verkman AS (2011) Potent, metabolically stable benzopyrimido-pyrrolo-oxazine-dione (BPO) CFTR inhibitors for polycystic kidney disease. J Med Chem 54:5468–5477
168. Lockman JW, Reeder MD, Suzuki K, Ostanin K, Hoff R, Bhoite L, Austin H, Baichwal V, Willardsen JA (2010) Inhibition of eEF-2K by thieno[2,3-*b*]pyridine analogues. Bioorg Med Chem Lett 20:2283–2286
169. Bulbule VJ, Rivas K, Verlinde CLMJ, Van Voorhis WC, Gelb MH (2008) 2-Oxotetrahydroquinoline-based antimalarials with high potency and metabolic stability. J Med Chem 51:384–387
170. Zuercher WJ, Buckholz RG, Campobasso N, Collins JL, Galardi CM, Gampe RT, Hyatt SM, Merrihew SL, Moore JT, Oplinger JA, Reid PR, Spearing PK, Stanley TB, Stewart EL, Wilson TM (2010) Discovery of tertiary sulfonamides as potent liver X receptor antagonists. J Med Chem 53:3412–3416
171. Yu Y, Dwyer MP, Chao J, Aki C, Chao J, Purakkattle B, Rindgen D, Bond R, Mayer-Ezel R, Jakway J, Qiu H, Hipkin RW, Fossetta J, Gonsiorek W, Bian H, Fan X, Terminelli C, Fine J, Lundell D, Merritt JR, He Z, Lai G, Wu M, Taveras A (2008) Synthesis and structure-activity relationships of heteroaryl substituted-3,4-diamino-3-cyclobut-3-ene-1,2-dione CXCR2/CXCR1 receptor antagonists. Bioorg Med Chem Lett 18:1318–1322
172. Jamieson C, Maclean JKF, Brown CI, Campbell RA, Gillen KJ, Gillespie J, Kazemier B, Kiczun M, Lamont Y, Lyons AJ, Moir EM, Morrow JA, Pantling J, Rankovic Z, Smith L (2011) Structure based evolution of a novel series of positive modulators of the AMPA receptor. Bioorg Med Chem Lett 21:805–811

Fluorinated Thiophenes and Their Analogues

Olga V. Serdyuk, Vladimir T. Abaev, Alexander V. Butin, and Valentine G. Nenajdenko

Contents

O.V. Serdyuk (✉)
Department of Chemistry and Pharmacy, University of Erlangen-Nuremberg, Henkestrasse 42, 91054, Erlangen, Germany

Department of Chemistry, Southern Federal University, Zorge 7, Rostov-on-Don 344090, Russian Federation
e-mail: oserduke@mail.ru

V.T. Abaev
Department of Chemistry, North-Ossetian State University, Vatutina 46, Vladikavkaz 362025, Russian Federation

A.V. Butin
Department of Chemistry, Perm State University, Bukireva 15, Perm 614990, Russian Federation

V.G. Nenajdenko
Department of Chemistry, Moscow State University, Leninskie Gory, Moscow 119992, Russian Federation

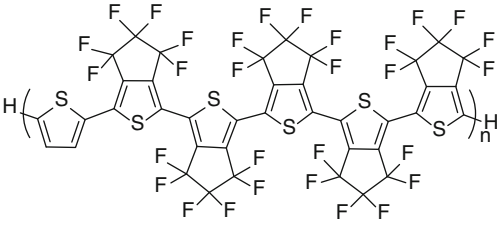
V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_6,

Abstract The chapter is devoted to the synthesis and application of thiophenes (selenophenes) and benzothiophenes bearing fluorine atoms, CF_3 groups, and perfluorinated aryl fragments.

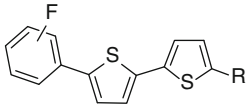
Keywords Thiophene • Fluorine • Trifluoromethyl group • Synthesis • Fluorinated heterocycles

1 Introduction

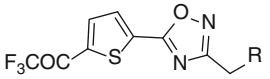
Fluorinated thiophene derivatives are widely used as soluble semiconductors [1], polymers [2], blue light emitting materials [3], and liquid crystals [4]. Some of them represent potent selective class II histone deacetylase (HDAC) inhibitors [5], agonists of sphingosine-1-phosphate (S1P) receptors [6], and some reveal fungicidal properties [7], anti-inflammatory, and immunoregulatory activity [8]. In addition, thiophene-substituted perfluorocyclopentenes are being investigated as thermally irreversible photochromic compounds having a high resistance to fatigue [9]. Herein, we describe methods for the preparation of thiophenes with a fluorine atom in the 2- and 3-position, and polyfluorothiophenes. These methods are classified into functionalization of the thiophene ring and heterocyclizations. This principle of classification is also applied for thiophenes with a perfluoroalkyl group, their benzoanalogues, and benzothiophenes with four fluorine atoms on the carbocycle.



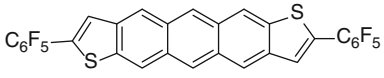
Oligomers applied in organic light-emitting diodes (OLEDs) and organic field-effect transistors (OFETs)



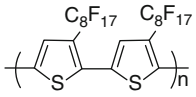
Liquid crystals



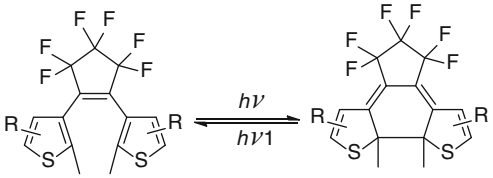
Selective class II histone deacetylase (HDAC) inhibitor



DFMADT - semiconductor for organic thin-film transistors (OTFTs)



First supercritical-CO_2-soluble conjugated polymer

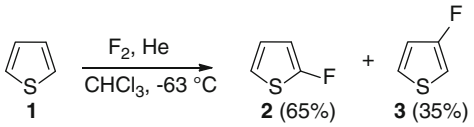


Photochromic memory

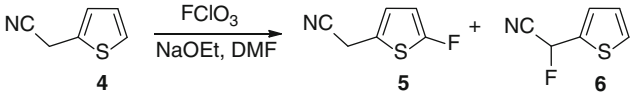
2 Synthesis of Fluorothiophenes

2.1 Functionalization of the Thiophene Ring

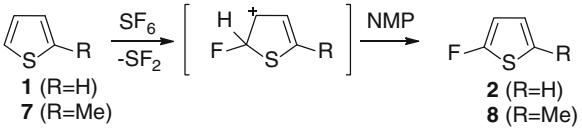
Direct fluorination of thiophene with molecular fluorine (F_2) is inconvenient as it is not selective process, owing to the extreme reactivity of molecular fluorine. For example, the reaction of thiophene **1** with fluorine at −63 °C (5 % F_2 in He) gave a mixture of 2- and 3-fluorothiophene **2** and **3** in a 2:1 ratio [10]. The synthesis of 3-fluorothiophene **3** is challenging due to the higher reactivity of the 2-position of thiophene. When a tenfold excess of fluorine was used, the 3-substituted isomer **3** (68 %) was three times more abundant then the 2-substituted product **2**.



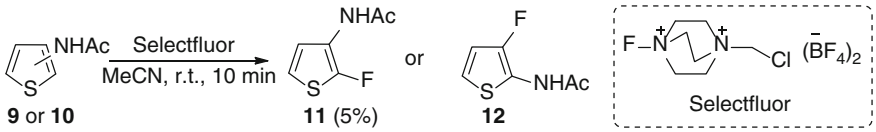
The treatment of 2-(thiophene-2-yl)acetonitrile **4** with perchloryl fluoride ($FClO_3$) in N,N-dimethylformamide in the presence of sodium ethoxide was also not selective. The formation of 2-(5-fluorothiophen-2-yl)acetonitrile **5** was accompanied by fluorination of the methylene group to give 2-fluoro-(2-thiophen-2-yl) acetonitrile **6** [11].



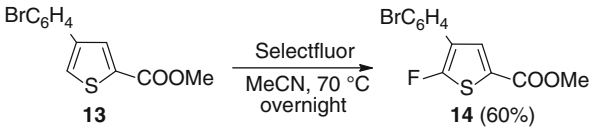
Gaseous SF_3^+ is a gentle and effective electrophilic monofluorinating reagent for five-membered heterocyclic compounds. The reaction of thiophenes **1**,**7** with gaseous SF_3^+, generated by electron ionization of sulfur hexafluoride and acting as a source of fluorine cation (F^+), is one more example of a direct fluorination process [12].



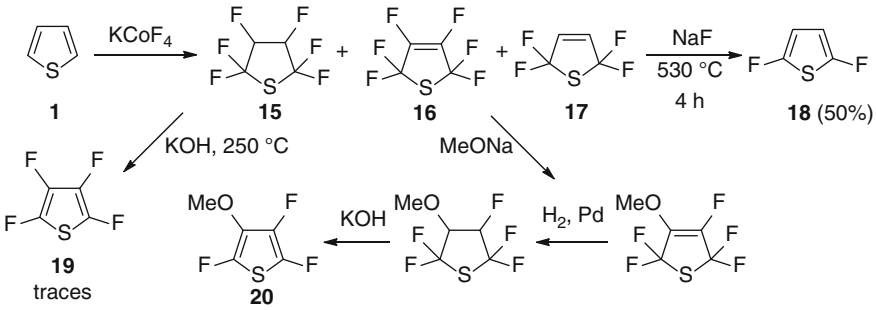
1-(Chloromethyl)-4-fluoro-1,4-diazobicyclo[2.2.2]octane tetrafluoroborate (Selectfluor™) can also serve as selective fluorinating reagent. Thus 3-acetamidothiophene **9** was fluorinated in the 2-position exclusively on treatment with Selectfluor™, but the yield of **11** was 5 % [13]. Fluorination of the isomeric 2-acetamidothiophene **10** gave the 3-fluorinated product **12** in low yield.



However, the 60 % conversion was achieved using Selectfluor for the overnight performed fluorination reaction of methyl thiophene-2-carboxylate derivative **13** [14].

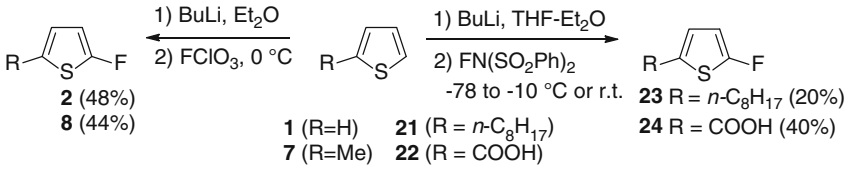


Thiophene **1** was fluorinated with potassium tetrafluorocobaltate(III) ($KCoF_4$) to give a mixture of hexafluorotetrahydrothiophene **15** and 2,2,5,5-tetrafluoro-2,5-dihydrothiophene **17** as major products. When hexafluorotetrahydrothiophene **15** was bubbled through molten potassium hydroxide, tetrafluorothiophene **19** was formed in low yield. When sodium methoxide was used, substitution of fluoride took place [15]. 2,5-Difluorothiophene **18** was obtained in 50 % yield by heating of 2,2,5,5-tetrafluoro-2,5-dihydrothiophene **17** with sodium fluoride at 530 °C. These conditions were found to be optimal, since the reaction did not occur at moderate temperatures (<480 °C). However, at 530 °C side reactions also took place, thus accounting for the only moderate yield of 2,5-difluorothiophene **18** [16].

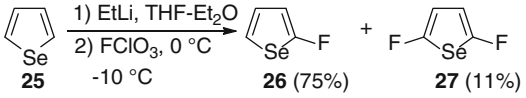


A more convenient approach to the synthesis of fluorothiophenes was based on the reaction of their organolithiums (easily prepared by metallation or halogen-metal exchange) with electrophilic fluorinating reagents such as perchloryl fluoride [17] or N-fluorodibenzenesulfonimide [18]. The yields of target fluorinated thiophenes **2**, **8** and **23**, **25** were moderate. This approach was proposed by Gronowitz and Rosén [19] for the preparation of various substituted 2-fluorothiophenes and 3-fluorothiophenes. Complications can arise in the case of halogen-metal exchange: rearrangement can occur if the thienyllithium is thermodynamically unstable. The

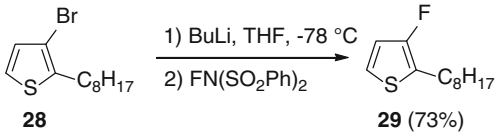
metallation of 2- and 3-fluorothiophenes followed by reaction with electrophiles was found to provide substituted 2-fluorothiophenes and 3-fluorothiophenes, since fluorine does not interfere in the metallation or in the halogen-metal exchange.



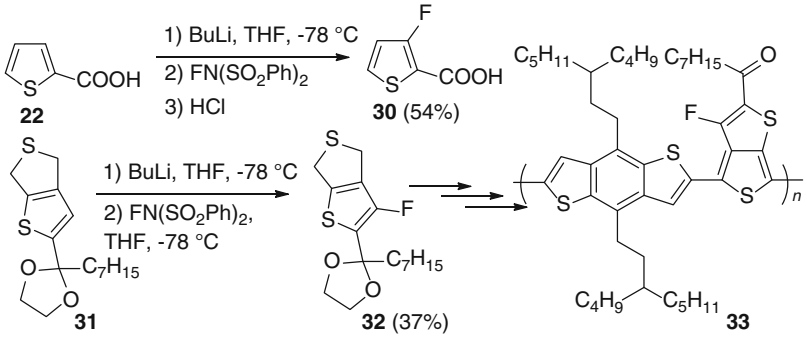
Fluorination of 2-selenophenyllithium **25** with perchloryl fluoride gave a mixture of 2-selenophene **26** and 2,5-difluoroselenophene **27** [20].



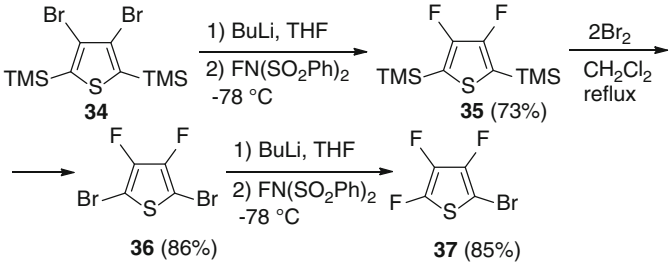
3-Fluorothiophene derivatives were easily obtained starting from the corresponding 3-bromothiophenes (Br-Li exchange). For example, the reactions of 3-thienyllithium obtained from **28** with N-fluorodibenzenesulfonimide as electrophilic fluorinating reagent led to the 3-fluorosubsituted thiophene **29** [18, 21].



In some cases, the direct metallation was also applied for the synthesis of 3-fluorothiophenes. Thus, 3-fluorothiophene-2-carboxylic acid **30** was prepared in two steps from the corresponding thiophene-2-carboxylic acid **22** by treatment with *n*-butyllithium followed by reaction with N-fluorodibenzenesulfonimide [22]. This approach was applied to the synthesis of monomer **32** for thieno[3,4-*b*]thiophene polymers **33** used in organic solar cells [23].

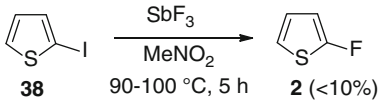


Another convenient approach is based on the use of N-fluorodibenzenesulfonimide. 2,3-Difluoro-, 2,4-difluoro- [18], 3,4-difluoro-, and 2,3,4-trifluorothiophenes can be prepared by this method. Thus, lithiation of 2,5-di(trimethylsilyl)-3,4-dibromothiophene **34** with *n*-BuLi followed by treatment with N-fluorodibenzenesulfonimide provides 3,4-difluoro-2,5-bis(trimethylsilyl)-thiophene **35**. The latter was transformed into 2,5-dibromo-3,4-difluorothiophene **36**. 1-Bromo-2,3,4-trifluorothiophene **37** was prepared similarly [24].



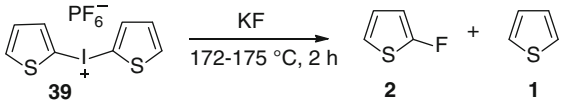
34 **35** (73%) **36** (86%) **37** (85%)

The first reported method for the preparation of 2-fluorothiophene **2** was the reaction of 2-iodothiophene **38** with SbF_3 in nitromethane. However, the method was inconvenient since it gave the target 2-fluorothiophene **2** in less than 10 % yield [25].



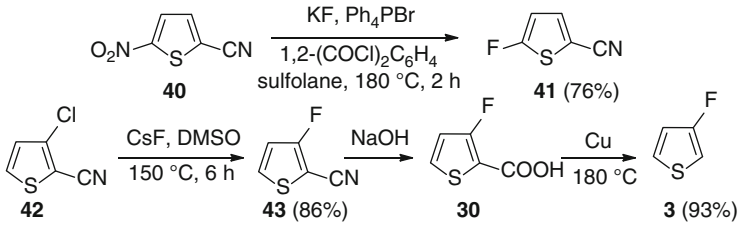
38 **2** (<10%)

A more useful approach to fluorothiophenes was based on transformations of iodonium salts. 2-Thienyliodoniym salts, for example dithiophen-2-yliodonium hexafluorophosphate **39**, afford 2-fluorothiophene **2** (37 %) and thiophene **1** (20 %) after treatment with potassium fluoride and heating at 172–175 °C [26].

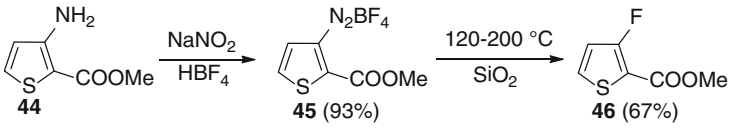


39 **2** **1**

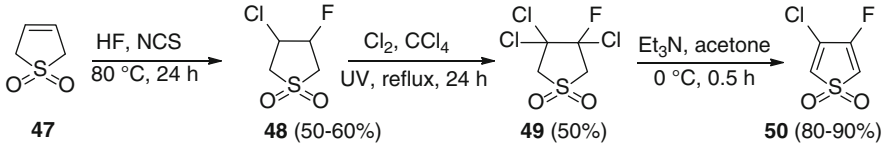
It is known that nitro group is a good leaving group for aromatic nucleophilic substitution and can be substituted by fluoride. For example, 5-nitrothiophene-2-carbonitrile **40** reacted with potassium fluoride in the presence of tetraphenylphosphonium bromide and phthaloyl dichloride in sulfolane at 180 °C providing 5-fluoro-2-cyanothiophene-2-carbonitrile **41** in 76 % yield [14, 27]. The reaction of 2-cyano-3-chlorothiophene **42** with CsF in dimethylsulfoxide gave 2-cyano-3-fluorothiophene **43** in 86 % yield. Subsequent hydrolysis by sodium hydroxide and decarboxylation gave 3-fluorothiophene **3** in 93 % yield [28].



One more method for the synthesis of 3-fluorothiophene is based on the thermal decomposition of a diazonium tetrafluoroborate (Schiemann reaction), which has been successfully used in the synthesis of a variety of fluorobenzenes. The reaction was carried out by heating of thiophene diazonium salt **45** in dry xylene (48 %) [29] or in a mixture with silica gel under vacuum (67 %) [13, 30].

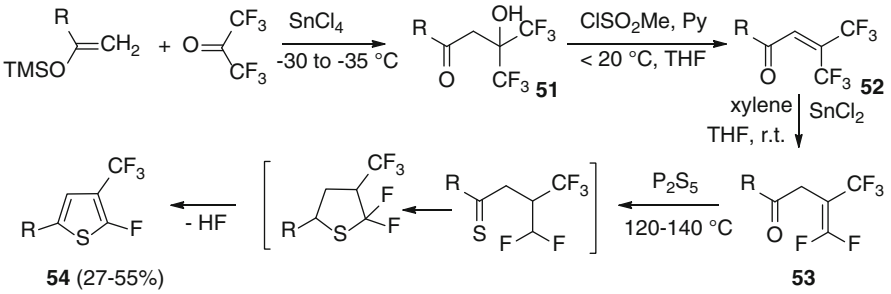


The straightforward synthetic route to 3-chloro-4-fluorothiophene-1,1-dioxide **50** involved chlorofluorination of 3-sulfolene **47**, photochemical chlorination, and dehydrochlorination of 3,3,4-trichloro-4-fluorosulfolane **49** [31].

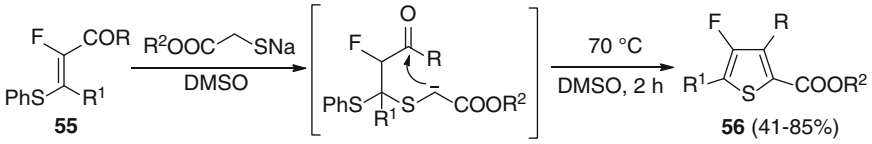


2.2 *Heterocyclization*

The transformation of 4,4-difluoro-3-trifluoromethylbut-3-ene-1-ones **53**, easily prepared from hexafluoroacetone (HFA), into 2-fluoro-3-trifluoromethylthiophenes **54** proceeded on heating with phosphorus pentasulfide [32]. Yields of 2-fluoro-3-trifluoromethylthiophenes **54** depend on the reaction conditions and the progress of the transformation should be monitored by ^{19}F NMR spectroscopy. The starting compounds were formed by elimination of water from hexafluoroacetone aldols **51** obtained by reaction of HFA with enol silyl ethers in the presence of Lewis acid such as $SnCl_4$. The unsaturated ketones **52** were reduced with $SnCl_2$ and **53** were cyclized to the desired thiophenes **54** with phosphorus pentasulfide [33].

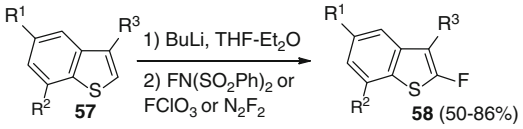


The reaction of (Z)-α-fluoro-β-(phehylthio)butanones **55** with methyl or ethyl thioglycolate in dimethylsulfoxide led to substituted 3-fluorothiophenes **56** in moderate to high yields. The authors proposed nonclassical nucleophilic vinylic substitution mechanism, occurring through an enolate intermediate. The first step of the sequence is the Michael addition that gives enolate; subsequent cyclization and aromatization leads to the target 3-fluorothiophenes **56** [34].



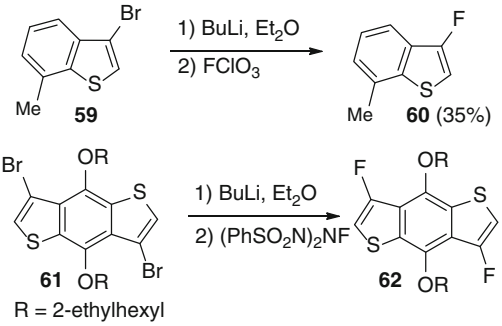
3 Synthesis of Fluorobenzothiophenes

Methods for the synthesis of fluorobenzothiophenes are rare. A lithiation-fluorination sequence by treatment of benzothiophenes **57** with *n*-BuLi followed by fluorination with perchloryl fluoride [35], N_2F_2 [36], or N-fluorodibenzenesulfonimide afforded 2-fluorobenzo[*b*]thiophenes **58** in good yields [37].

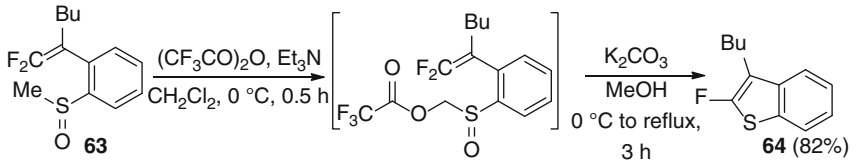


3-Fluorobenzo[*b*]thiophenes **60** and **62** were synthesized from the lithiated precursors by treatment with perchloryl fluoride [35] or N-fluorodibenzenesulfonimide

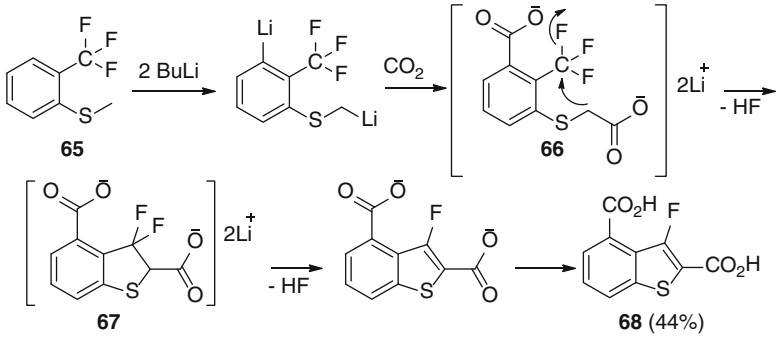
in good yields [38]. The lithium derivatives were obtained from 3-bromobenzo[*b*] thiophene derivatives **59** and **61** and *n*-butyllithium.



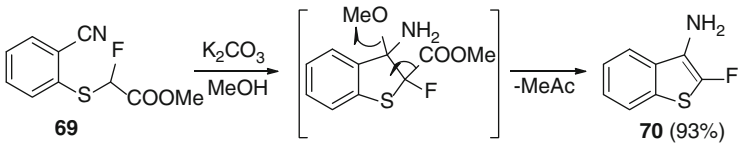
Fluorobenzo[*b*]thiophenes synthesis was also accomplished through a 5-*endo-trig* cyclization. Successive reaction of β,β-difluoro-*o*-methylsulfinylstyrene **63** first with trifluoroacetic anhydride and triethylamine in dichloromethane and then with potassium carbonate provided 2-fluorobenzo[*b*]thiophene **64** in 82 % yield [39].



3-Fluorobenzothiophene derivative **68** was prepared in 44 % yield starting from 4-(methylthio)-l-(trifluoromethyl)benzene **65** by double metallation with *n*-BuLi and subsequent reaction with CO_2. The primary intramolecular cyclization of **66** was anchimerically assisted by the carboxylate anion in *ortho* position and gave rise to a nucleophilic substitution of the fluorine atom by the SCH^- anion. The resulting intermediate **67** aromatized after acidification into 3-fluorobenzo[*b*]thiophene **68** [40].



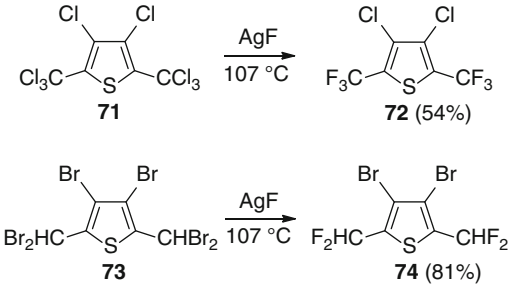
Fluorinated benzo[*b*]thiophene derivative **70** was synthesized in 93 % yield by the intramolecular cyclization of anodically fluorinated open-chain sulfide **69** containing the 2-cyanophenyl group [41].



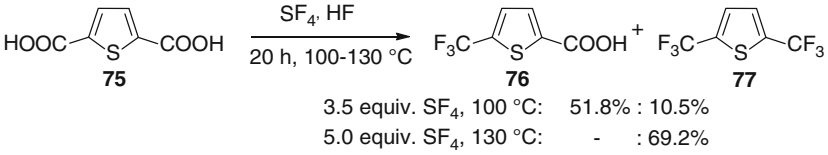
4 Synthesis of Perfluoroalkylthiophenes

4.1 Functionalization of the Thiophene Ring

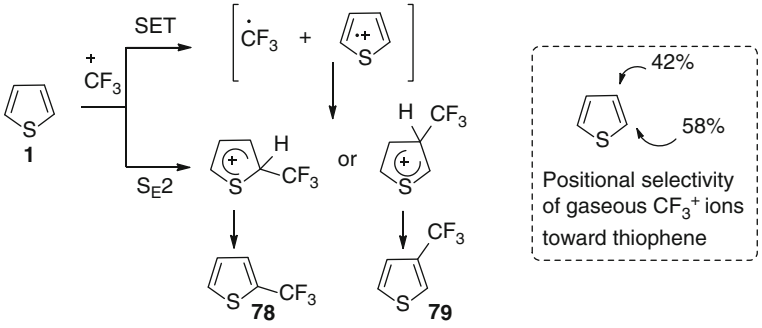
A perfluoroalkyl group can be incorporated onto the thiophene ring directly, or a haloalkyl substituent can be transformed into a perfluoroalkyl moiety. For example, treatment of 2,5-bis(trichloromethyl)-3,4-dichlorothiophene **71** with AgF resulted in exchange of chlorine by fluorine in the CCl_3-groups. It should be noted that no exchange took place for the chlorine atoms attached directly to the thiophene ring. In a similar way, brominated 2,5-dimethylthiophene **73** gave a 2,5-bis(difluoromethyl) thiophene derivative **74** under the same conditions [42].



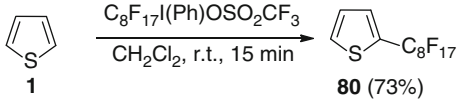
A very useful method for the introduction of a CF_3 group onto the thiophene ring is the transformation of a carboxylic group with SF_4. Depending on the conditions, thiophene-2,5-dicarboxylic acid **75** reacted with SF_4 and HF to produce 5-(trifluoromethyl)thiophene-2-carboxylic acid **76** and 2,5-bis(trifluoromethyl)-thiophene **77**. At lower temperature, the compound **76** was the major product, while **77** was obtained at 130 °C with five equivalents of SF_4 [43].



The direct trifluoromethylation of thiophene can be performed under electrophilic and radical conditions. The electrophilic reaction proceeded in the gas phase using trifluoromethyl cations obtained from CF_4 under radiolysis (^{60}Co γ-rays) [44]. The selectivity trend for thiophene in the gas phase follows the order C2 > C3 > S1. The major products of this transformation were found to be monosubstituted trifluoromethylthiophenes **78** and **79** (<20 % yield) [45]. It has been proposed that the trifluoromethylation proceeds through electrophilic substitution and single-electron transfer mechanisms.

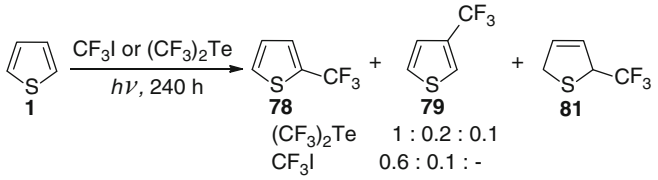


Electrophilic perfluoroalkylation has been performed with the use of iodonium salts $R_fI(Ar)X$, where the perfluoroalkyl group is bonded with a positively charged heteroatom. The trifluoromethylation of thiophene **1** with $C_8F_{17}I(Ph)OSO_2CF_3$ in dichloromethane at room temperature proceeds in 73 % yield in the presence of 2,6-di-*tert*-butyl-4-methylpyridine as a base [46].

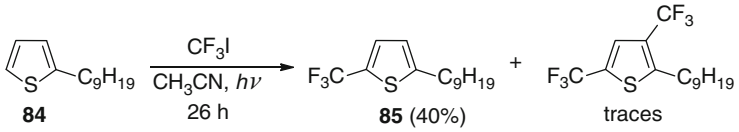


Radical perfluoroalkylation is more versatile because it can be performed under thermal, photolytic, oxidative, and reductive conditions. For example, the photochemical reaction of thiophene **1** with bis(trifluoromethyl)tellurium or trifluoromethyliodide yields 2-trifluoromethylthiophene **78** as the major product. The most suitable reagent in this case was found to be bis(trifluoromethyl)tellurium. Similarly, perfluoroalkylation of thiophene with perfluorodecyl iodide under thermal

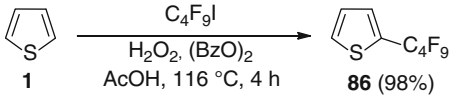
conditions (175 °C, 24 h, steel bomb) provided predominantly the 2-substituted isomer **82**. The latter was the sole product when the reaction was carried out at higher temperature [47].



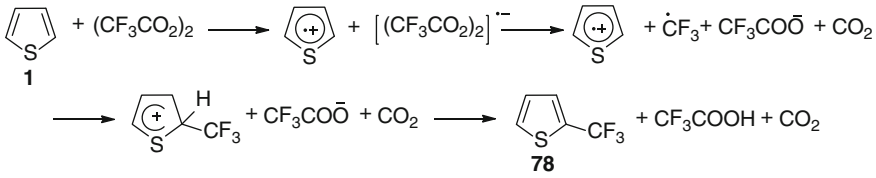
2-Nonylthiophene **84** was trifluoromethylated with trifluoromethyliodide in acetonitrile under irradiation to produce 2-nonyl-5-trifluoromethylthiophene **85**. A trace amount of 3,5-bis(trifluoromethyl)-2-nonylthiophene was also formed in this reaction. However, the conversion was not complete and starting thiophene (25 %) was recovered [48].



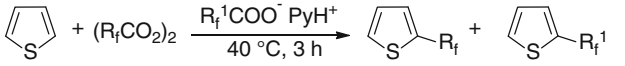
Nonafluoro-4-iodobutane can serve as a source of nonafluorbutyl radical under oxidative conditions. The reaction with thiophene **1** was carried out under reflux in AcOH in the presence of hydrogen peroxide and benzoyl peroxide. Other solvents appeared to be less effective, probably because hydrogen abstraction from the solvent by nonafluorbutyl radical competes with the attack of thiophene [49].



Perfluoroalkylation is often performed with bis(perfluoralkanoyl)peroxides, e.g. bis(trifluoroacetyl)peroxide and bis(heptafluorobutyryl)peroxide, which are thermally stable, convenient to use, and can be obtained from the corresponding anhydrides and hydrogen peroxide in Freon 113 ($CFCl_2CF_2Cl$) as a solvent. Perfluorooxaalkanoylperoxides provide the same reactivity. The mechanism of the transformation includes oxidation of thiophene to radical cation, followed by reaction with perfluoro radical to produce 2-perfluoroalkylthiophenes [50].

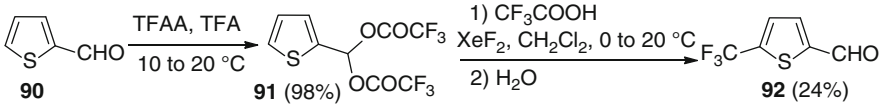


Interestingly, the perfluoroalkyl group can be incorporated onto the thiophene ring even if the corresponding peroxide cannot be synthesized. For example, when thiophene was treated with bis(perfluoralkanoyl)peroxide in the presence of pyridinium perfluoroalkanoate, not only the perfluoroalkyl group of the peroxide, but also the perfluoroalkyl group of perfluoroalkanoate was incorporated [51].



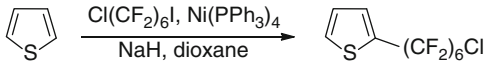
$R_f = C_3F_7$, $R_f^1 = C_7F_{15}$ **87:88** = 18%:23%
$R_f = C_7F_{15}$, $R_f^1 = C_3F_7$ **88:87** = 20%:17%
$R_f = C_3F_7$, $R_f^1 = C_9F_{19}$ **87:89** = 32%:20%
$R_f = CF_3$, $R_f^1 = C_7F_{15}$ **78:88** = 48%:67%

It is well known that xenon fluoride trifluoroacetate, obtained from XeF_2 and trifluoroacetic acid, is able to generate trifluoromethyl radicals which allow introduction of the trifluoromethyl group onto the aromatic ring at room temperature. The trifluoromethylation of thiophene-2-carbaldehyde bistrifluoro-acetate **91** gave 5-trifluoromethyl-thiophene-2-carbaldehyde **92** in 24 % yield [7].



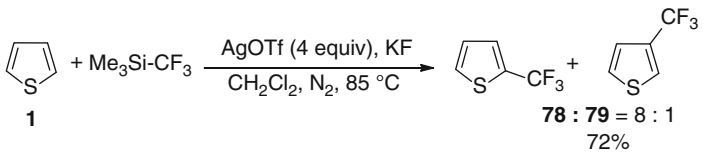
90 **91** (98%) **92** (24%)

Fluoroalkylation reaction can also be performed using transition-metals catalysis. In the presence of a catalytic amount of tetrakis(triphenylphosphine)nickel, polyfluoroalkyl iodide reacted with thiophene to produce the 2-substituted isomer **93** as the sole product. To complete the reaction, addition of sodium hydride was required to absorb hydroiodic acid by-product [52].

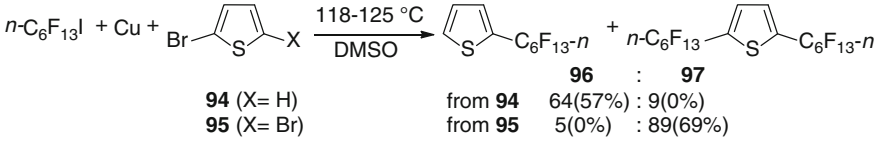


1 **93** (37%)

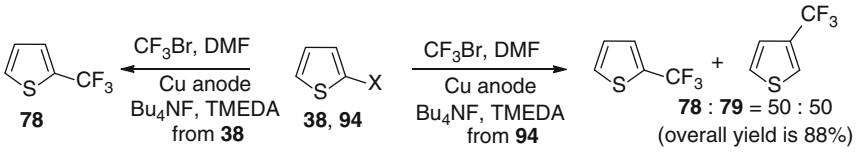
The silver-mediated trifluoromethylation of thiopene with $TMSCF_3$ gave 2- and 3-trifluoroderivatives **78** and **79** in 72 % total yield. The authors proposed that the reaction proceeds via $AgCF_3$ intermediates [53].



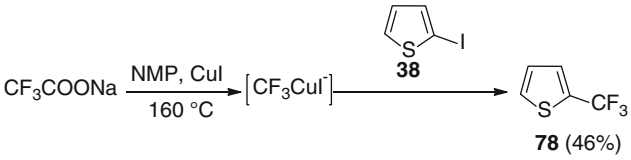
The copper-promoted substitution of halogen atoms on the thiophene ring provides another method for perfluoroalkylation. For example, 2-perfluorohexylthiophene **96** and 2,5-bis(perfluorohexyl)-thiophene **97** were obtained from the corresponding bromothiophenes **94** and **95** and perfluorohexyl iodide in dimethylsulfoxide (isolated yields are given in parentheses) trough reaction with the organocopper intermediate, perfluorohexyl copper(I) [54]. More detailed information about fluorinated organometallics and their use in organic synthesis was presented in a review [55], and some examples of copper promoted perfluoroalkylation of halothiophenes are also described in papers [2b, 8, 56].



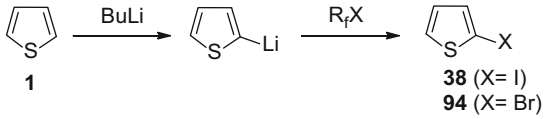
Another method of trifluoromethylation was based on the electrochemical reaction (copper anode) of 2-bromothiophene **94** with bromotrifluoromethane in DMF. In comparison to usual methods leading to trifluoromethylcopper, this one offered an advantage because it allowed the use of CF_3Br instead of the more expensive CF_3I. However, the reaction was not selective and gave a mixture of 2- and 3-isomers **78** and **79**. The use of 2-iodothiophene **38** as a starting material was found to be more effective: 2-trifluoromethylthiophene **78** was obtained in 60 % yield [57].



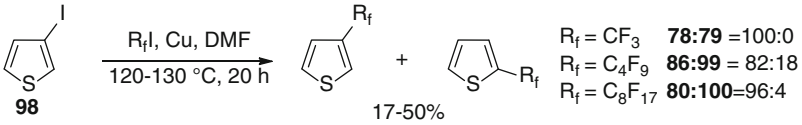
Sodium trifluoroacetate, in the presence of copper(I) iodide, was also used as trifluoromethyl source to replace halogen by trifluoromethyl group in the thiophene system. Sodium trifluoroacetate was decarboxylated, forming fluoroform, when heated alone in aqueous N-methylpyrrolidin-2-one. The addition of copper(I) iodide increased the rate of decarboxylation dramatically. The mechanism of this process was explored and an intermediate $[CF_3CuI]^-$ was proposed. Introduction of higher perfluoroalkyl groups from their corresponding sodium perfluoroalkane carboxylates was also shown to be possible [58].

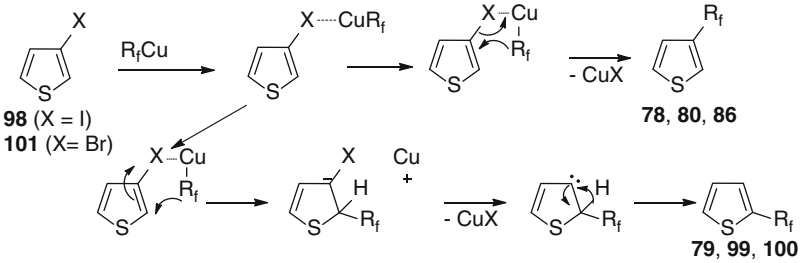


The reaction of 2-thienyllithium with perfluoroalkyliodides and bromides gave 2-halothiophenes **38**, **94** rather than corresponding perfluoroalkylated thiophene [59].



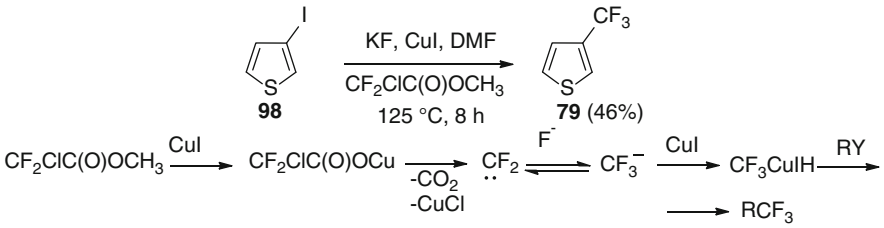
The copper-catalyzed substitution of a halogen atom was used for the preparation of 3-perfluoroalkylthiophenes. Usually, the reaction involves the heating of 3-iodothiophene **98** with perfluoroalkyliodide in N,N-dimethylformamide or dimethylsulfoxide [54]. In some cases, however, it was not possible to obtain useful quantities of the three-substituted products. When the perfluoroalkyl group was not trifluoromethyl, two isomers were formed due to the addition of the perfluoroalkyl anion to the C(2)–C(3) double bond. The ratio of isomers was also influenced by the nature of halogen: iodine, which is better leaving group than bromine, gave a lower percentage of rearrangement [60].



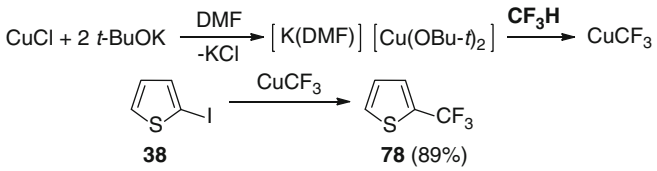


An improved method of 3-trifluoromethylthiophene **79** synthesis was the reaction of methyl-2-chloro-2,2-difluoroacetate with 3-iodothiophene **98** in the presence of copper(I) iodide and potassium fluoride in N,N-dimethylformamide. The reaction was carried out at 125 °C and gave 3-trifluoromethylthiophene **79** in 46 % as the sole product [61]. The proposed mechanism includes the formation of the copper(I)

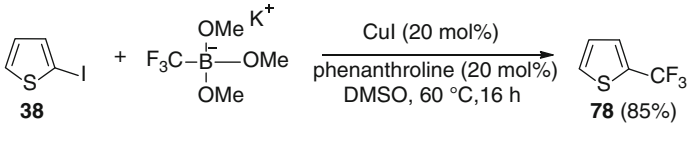
iodide salt or a complex, followed by its decarboxylation to yield difluorocarbene; the latter then reacts with fluoride to establish an equilibrium with trifluoromethyl anion. In the presence of copper(I) iodide, the equilibrium was readily shifted to give trifluoromethyl copper species CF_3CuI^-, which reacted with halides to afford the final products [62].

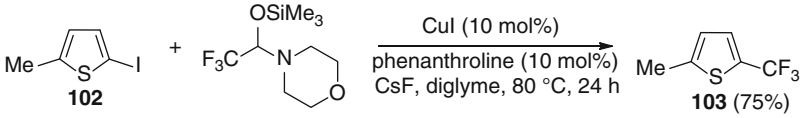


The reaction of direct cupration of fluoroform provides a source for the introduction of the trifluoromethyl group into organic molecules, including thiophene [63].

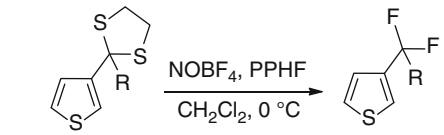


Recently, it was demonstrated that a small amount of copper(I) iodide-phenanthroline complex efficiently catalyzes aromatic trifluoromethylation of 2-iodothiophenes **38** and **102** leading to 2-trifluoromethylated products **78** and **103** in 75–85 % yields [64].





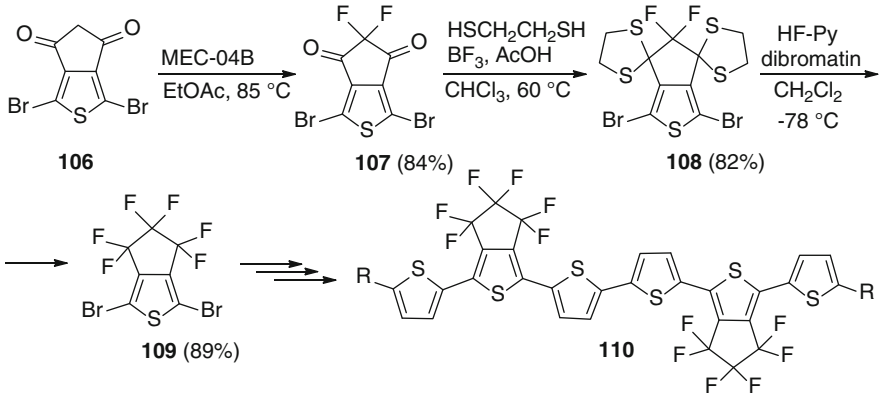
Dithioacetales **104** have been transformed into difluoromethyl derivatives **105**: a one-pot desulfurative fluorination of dithiolane led to the synthesis of difluoroalkylthiophene. Treatment of the dithioacetales **104a, b** with pyridinium polyhydrogen fluoride (PPHF) and nitrosyl tetrafluoroborate at 0 °C led to 3-(1,1-difluoroheptyl) thiophene **105a** (40 %) or 3-(1,1-difluorononyl)thiophene **105b** (30 %) [65].



104a,b
R = C_6H_{13}, C_8H_{17}

105a,b
(30-40%)

Fluorination of a carboxylic group with sulfur tetrafluoride was applied to the incorporation of the trifluoromethyl and difluoromethyl group onto the thiophene ring [43, 66]. As it was mentioned, 2,5-bis(trifluoromethyl)thiophene **77** was obtained by the reaction of thiophene-2,5-dicarboxylic **75** acid with five equivalents of sulfur tetrafluoride at 130 °C. This approach can also be used for the synthesis of oligothiophenes annelated with hexafluorocyclopentene **110**. The latter have good electron-donating properties and inherently low electron affinities, and have widespread applications as hole-transporting materials to various electronics such as organic light-emitting diodes (OLEDs), organic field-effect transistors (OFETs), and organic solar cells. The synthesis of such thiophenes includes three steps.



106

107 (84%)

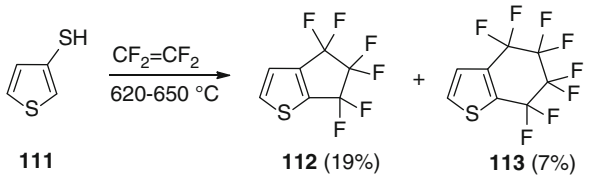
108 (82%)

109 (89%)

110

The first is fluorination of cyclopenta[*c*]thiophene-4,6-dione **106** by treatment with *N*-fluoro-6-(trifluoromethyl)pyridinium-2-sulfonate (MEC-04B) in ethyl acetate to give 1,3-dibromo-5,5-difluorocyclopenta[*c*]thiophene-4,6-dione **107** in 84 % yield. Then, conversion of the two carbonyl groups to difluoromethylene groups was accomplished via formation of the bis-1,3-dithiolane derivative **108** followed by desulfurative fluorination with hydrofluoric acid-pyridine complex and dibromatin (1,3-dibromo-5,5-dimethylhydantoin) in dichloromethane to afford 1,3-dibromohe xafluorocyclopenta[*c*]thiophene **109** in a two-step yield of 73 % [1d, 67].

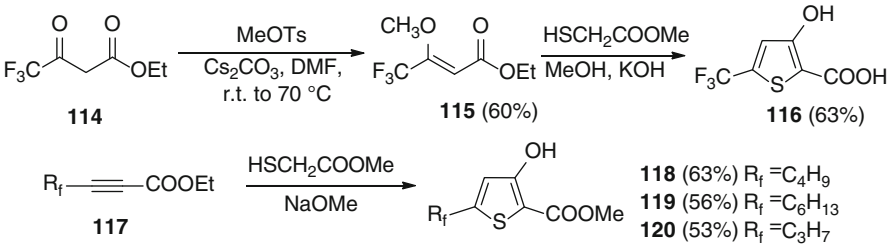
2-Substituted thiophenes were found to react with tetrafluoroethylene (TFE) at high temperatures to produce 4,4,5,5,6,6-hexafluorocyclopenta[*b*]thiophene **112**. In such a reaction, 3-thiophenethiol **111** gave rise to the major product **112**, along with 4,4,5,5,6,6,7,7-octafluorocyclohexa[*b*]thiophene **113**. Yields of the products were low [68].



111 **112** (19%) **113** (7%)

4.2 Heterocyclization and Cycloaddition

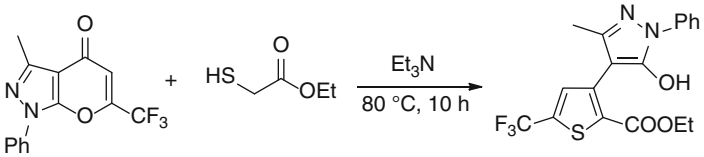
The most versatile method for synthesis of 2-trifluoromethylthiophenes is based on heterocyclizations with the participation of methyl thioglycolate ($HSCH_2COOMe$). For example, 2-trifluoromethylthiophene **116** was formed as a result of condensation of trifluoromethyl-substituted α,β-unsaturated ester **115** and methyl thioglycolate in the presence of a base. 2-Trifluoromethyl- and (perfluoroalkyl)thiophenes were prepared by reaction with α-fluoroalkylacetates in good yields [69]. A similar transformation took place when fluoroalkylpropynoates **117** were treated with methyl thioglycolate under basic conditions [70].



114 **115** (60%) **116** (63%)

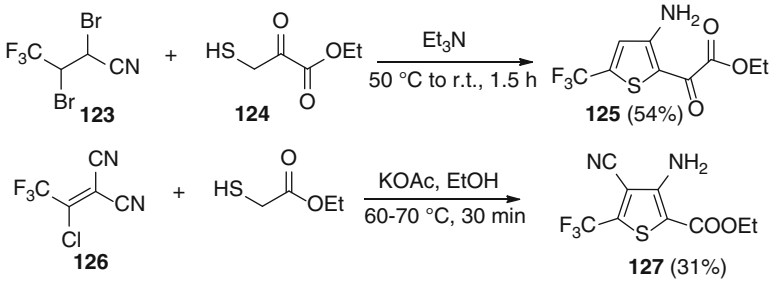
117

6-Trifluoromethylpyranopyrazole **121** reacted at C(6) atom with excess of methyl mercaptoacetate in the presence of triethylamine to form a derivative **122** of trifluoromethyl thiophene bonded with a pyrazole fragment. The reaction took place via pyran ring opening and intramolecular aldol-type condensation [71].

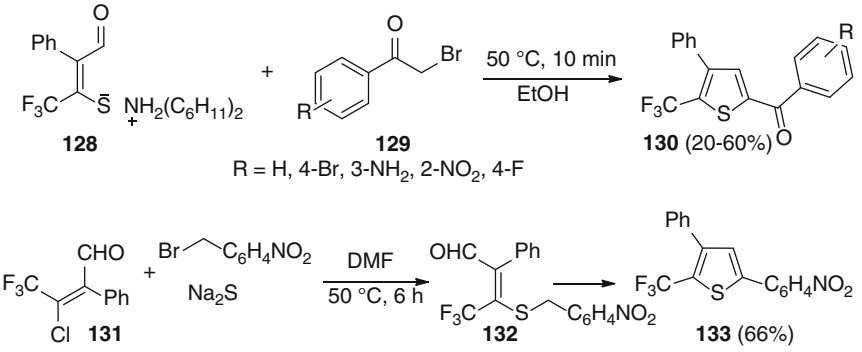


121 **122** (31%)

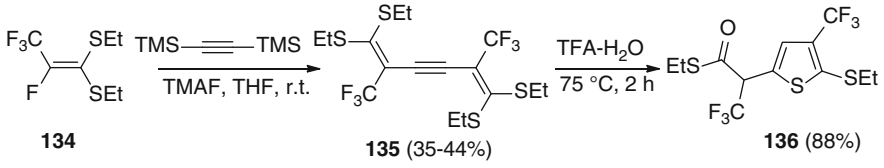
Ethyl mercaptopyruvate **124** was also transformed into 2-trifluoromethylthiophene **125** in 54 % yield by reaction with 2,3-dibromo-4,4,4-trifluorobutanenitrile **123** in the presence of triethylamine at 50 °C [72]. The condensation of a trifluoromethylethylene **126** derivative with ethyl thioglycolate in ethanol proceeded analogously [73].



Additionally, sulfur and perfluoroalkyl functionalities can both be present in the same starting molecule. For example, nucleophilic attack of trifluoromethylated thiolate **128** on phenacyl bromides **129** followed by spontaneous aldol cyclization gave 5-substituted 2-trifluoromethylthiophene **130** in yields of 20–60 % [74]. 4,4,4-Trifluoro-3-(4-nitrobenzylthio)-2-phenylbut-2-enal **132** obtained from trifluorosubstituted β-chlorovinylaldehyde **131** afforded the trifluoromethylthiophene product **133** in 66 % yield on heating in N,N-dimethylformamide [75].

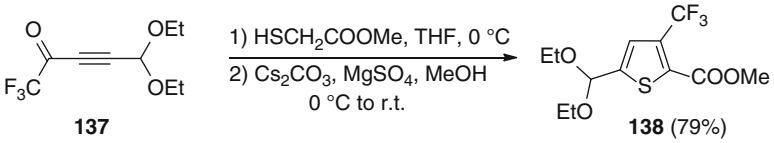


Some heterocyclizations have been used for the preparation of 3-perfluoroalkylthiophenes. As an illustration, treatment of 1,1,6,6-tetrakis(ethylsulfanyl)-2,5-bis(trifluoromethyl)-hexa-1,5-dien-3-yne **135** with a mixture of trifluoroacetic acid and water for 2 h at 75 °C led to the thiophene derivative **136** in high yield. The starting compound **135** was obtained by reaction of perfluoroketene dithioacetal **134** with bis(trimethylsilyl)acetylene [76].



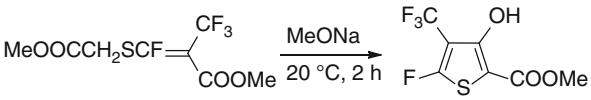
2,3,5-Trisubstituted thiophene **138** was synthesized in good yields using a tandem Michael addition and intramolecular Knoevenagel condensation strategy starting

from readily available acetylenic ketone **137** in the presence of cesium carbonate and magnesium sulfate as a base to initiate the reaction [77].



137 **138** (79%)

1,3,3,3-Tetrafluoro-2-(methoxycarbonyl)propenyl methoxycarbonylmethyl sulfide **139**, with its activated α-methylene group, underwent intramolecular cyclocondensation in the presence of sodium methoxide as a catalyst to form 3-trifluoromethylthiophene **140** in 37 % yield. The fluorine atom at the 2-position was substituted by a methoxy group when an excess of sodium methoxide was used [78].



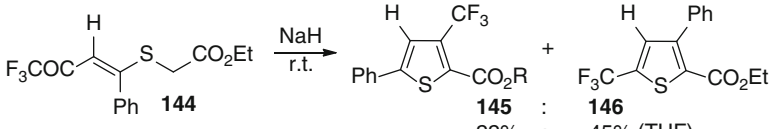
139 **140** (37%)

The reaction of mercaptomethyleniminium salts **141** with trifluoroacetic anhydride in the presence of triethylamine yielded substituted 2-aminothiophenes, including 3-trifluoromethyl heterocycle **143**. The starting mercaptomethyleniminium salts were prepared by S-alkylation of thioacetamides. When triethylamine was not used in the reaction, it was possible to isolate the intermediate ketene-S,N-aminals **142** and cyclize them under basic conditions [79].

141 **142** **143** (46%)

R^1, R^1 = -$(CH_2)_2$-O-$(CH_2)_2$-, R^2 = 4-MeC_6H_4, Ar = 4-$NO_2C_6H_4$

Ethyl-2-(4,4,4-trifluoro-3-oxo-1-phenylbut-1-enylthio)acetate **144** gave 3-trifluoromethylthiophene derivative **145** in moderate yield upon treatment with sodium hydride in benzene in the presence dimethylsulfoxide. The same reaction in tetrahydrofuran yielded a mixture of 2- and 3-trifluoromethylthiophene **146** and **145** with a predominance of the 2-isomer **146** [80].

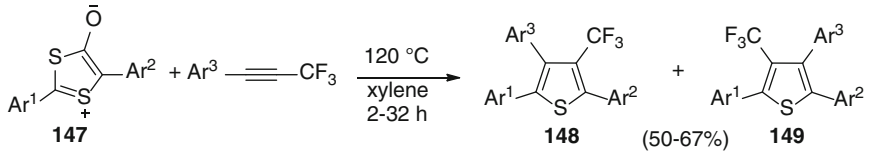


144 **145** : **146**

R = Et or H 22% : 45% (THF)

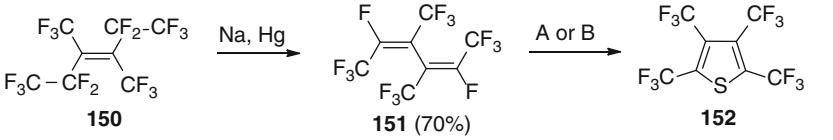
67% : - (DMSO, PhH)

Triaryl-ß-trifluoromethylthiophenes **148**, **149** were synthesized from 1,3-dithiolium-4-olates **147** and various 1-aryl-3,3,3-trifluoro-1-propynes. The 1,3-dipolar cycloaddition was carried out by heating in xylene at 120 °C. Interestingly, when the substituents Ar^1 and Ar^2 in the mesoionic 1,3-dithiolium-4-olates were swapped, the isomer ratio was completely reversed. The observed regioselectivity was explained by HOMO-LUMO interactions of the reacting species [81].



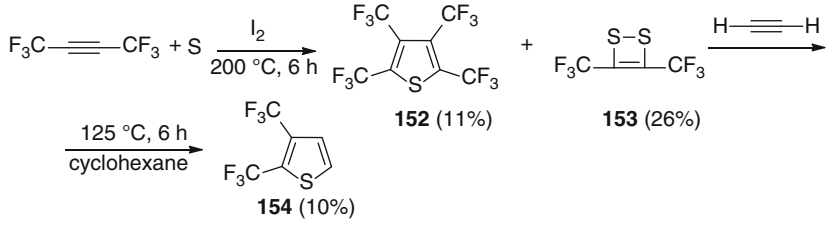
Ar = 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-$MeSC_6H_4$, 4-$MeSO_2C_6H_4$, 2-ClC_6H_4

1,2,3,4-Tetrakis(trifluoromethyl)buta-1,3-diene **151** was employed for the preparation of 2,3,4,5-tetrakis(trifluoromethyl)thiophene **152**. The transformation can be performed by treatment of the diene with potassium sulfide in N,N-dimethylformamide at room temperature [82] or by heating at reflux with thiourea in acetonitrile [83]. The starting diene **151** was obtained from perfluoro-3,4-bis(trifluoromethyl)hex-3-ene **150**.

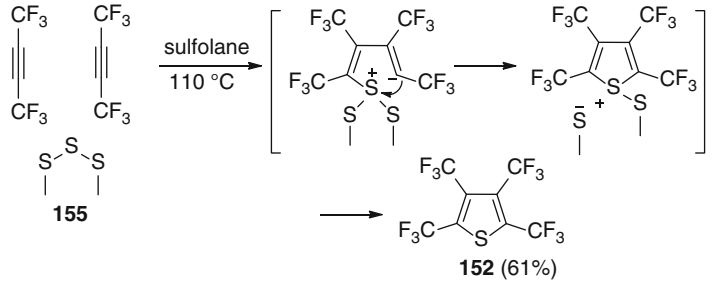


A: K_2S, DMF, r.t. (72%)
B: $(NH_2)_2CS$, MeCN, reflux (51%)

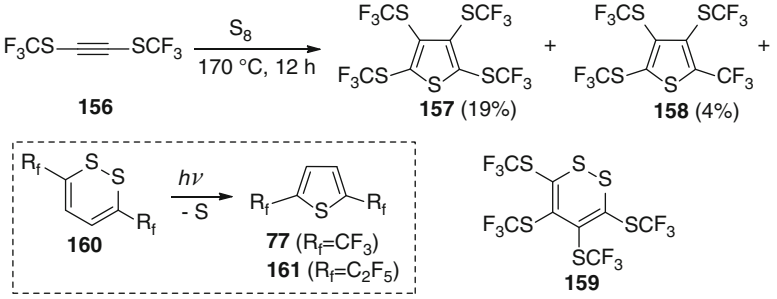
2,3,4,5-Tetrakis(trifluoromethyl)thiophene **152** was also obtained by addition of sulfur to hexafluoro-2-butyne at 110–200 °C [84]. The process is supposed to involve reaction of an intermediate dithietene **153** with starting hexafluoro-2-butyne at high temperature. This mechanism was supported by the preparation of 2,3-bis(trifluoromethyl)thiophene **154** and tetrakis(trifluoromethyl)thiophene **152** from dithietene **153** and the corresponding alkynes [85].



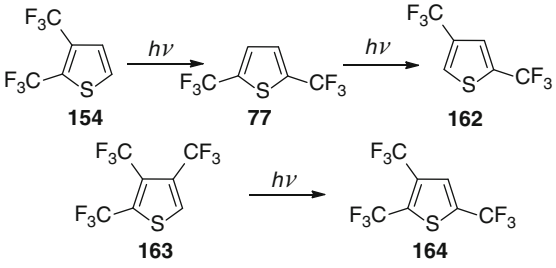
The reaction with dimethyltrisulfide **155** as sulfur source occurred at 110 °C in sulfolane giving tetrakis(trifluoromethyl)thiophene **152**. No other sulfur heterocycles were detected and the authors presumed that a different process was taking place under these conditions. They concluded that a nucleophilic cyclisation process operates with the *cis*-addition occurring because sulfur is both a bulky and a neutral nucleophile [84].



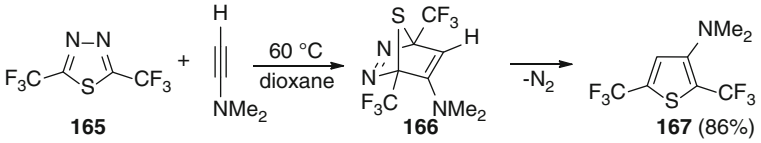
Photolysis or heating of bistrifluoromethylthioacetylene **156** with sulfur afforded 2,3,4,5-tetrakis(trifluoromethylthio)thiophene **157** in low yield. The transformation was determined to proceed via an intermediate 1,2-dithiin derivative **159**; this was supported by the reaction of 3,6-bis(perfluoroalkyl)-1,2-dithiins **160** that produced 2,5-bis(perfluoroalkyl)thiophenes **77**, **161** under irradiation [86].



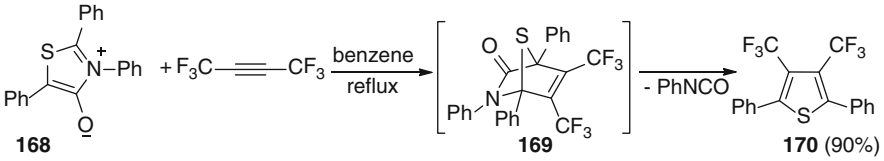
The photolysis of bis(trifluoromethyl)thiophenes **154** and **77** and tristrifluoromethylated thiophene provides a simple way to produce isomeric structures, but usually these procedures are not synthetically useful for the preparation of thiophene derivatives [87].



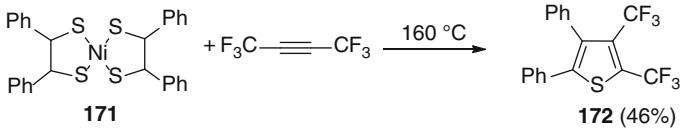
A convenient synthesis of 2,5-bis(trifluoromethyl)thiophene **167** involved the [4+2]-cycloaddition reaction of acetylenes to 2,5-bis(trifluoromethyl)-1,3,4-thiadiazole **165** and subsequent elimination of nitrogen. The reaction proceeded under sufficiently mild conditions and led to 2,5-bis(trifluoromethyl)thiophene **167** in high yield [88].



Another type of cycloaddition used to produce, in this case, 3,4-bis(trifluoromethyl)thiophene **170** was the reaction of hexafluoro-2-butyne with mesoionic thiazolium system **168**. Phenyl isocyanate was eliminated from the initial adduct, giving the substituted thiophene in more than 90 % yield [89].

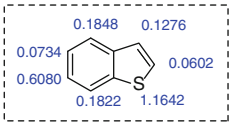


The reaction of bis(dithiobenzyl)nickel **171** with alkynes yielded thiophene derivative **172**. In view of the improved method of preparation of the complexes, this reaction has been applied to the synthesis of difficult-to-access substituted thiophene derivatives. Complexes are air-stable and easily available from benzoin and phosphorus pentasulfide [90].

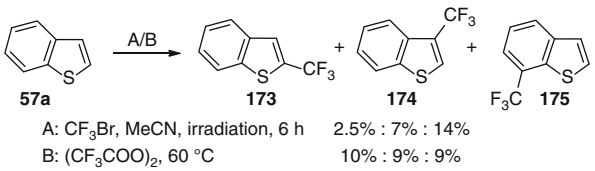


5 Synthesis of Perfluoroalkylbenzothiophenes

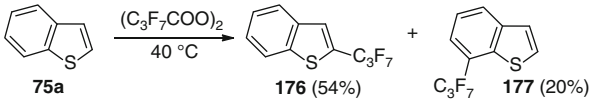
Direct trifluoromethylation of benzo[*b*]thiophene is not selective. For instance, photochemical reaction with bromotrifluoromethane yielded a mixture of 3-, 4- and 7-trifluoromethylbenzo[*b*]thiophenes (**173**, **174** and **175**), which correlates with the values of electron density in the molecule [91].



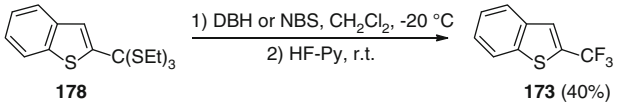
HOMO electron densities of benzo[*b*]thiophene



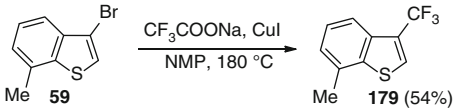
Oxidative trifluoromethylation with bis(trifluoroacetyl)peroxide provided a similar result, while the reaction with bis(heptafluorobutyryl)peroxide afforded 3-heptafluoropropylbenzo[*b*]thiophene **176** as a major product (54 %) with some 7-substituted isomer **177** [50].



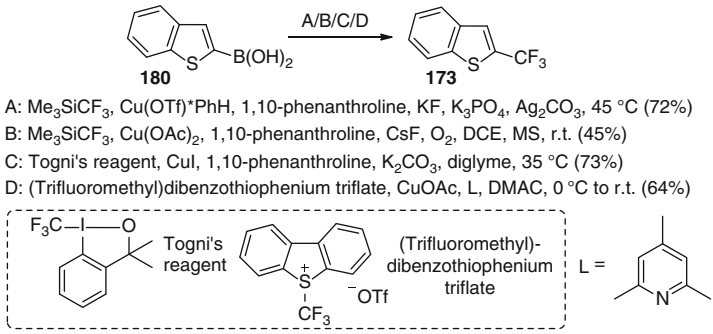
A more effective method for the preparation of 2-trifluoromethylbenzo[*b*]thiophene **173** involved the treatment of orthothioester **178** with 1,3-dibromo-5,5-dimethylhydantoin (DBH) or N-bromosuccinimide (NBS) followed by hydrofluoric acid-pyridine complex. The target compound was obtained by this method in 40 % yield [92].



Through direct trifluoromethylation, 7-methyl-3-trifluoromethyl-benzo[*b*]thiophene **179** was prepared in 54 % yield from 7-methyl-3-bromobenzo[*b*]thiophene **59**. The reaction took place with sodium trifluoroacetate and copper(I) iodide in N-methylpyrrolidone at 180 °C [35].

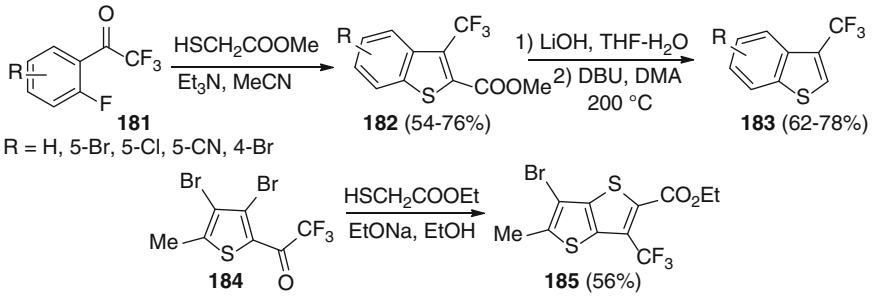


Recently, simple copper-catalyzed trifluoromethylation of aryl boronic acids under mild conditions was developed. Using (trifluoromethyl)trimethylsilane (Me_3SiCF_3) [93], trifluoromethyldibenzothiophenium triflate [94], or Togni's reagent [95], 2-trifluoromethylbenzo[*b*]thiophene **173** was prepared in 45–73 % yields.

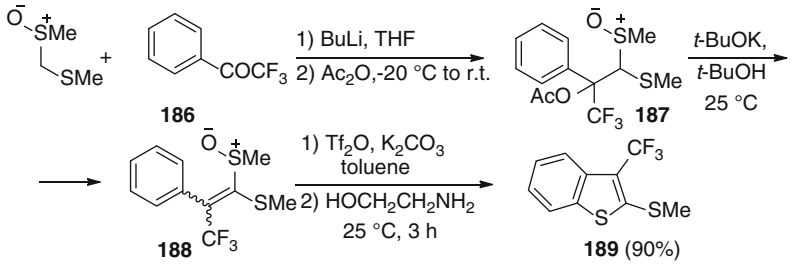


A straightforward method for the synthesis of 5- or 6-substituted 2-trifluoromethylbenzo[*b*]thiophenes involved the reaction of *ortho*-fluorinated trifluoroacetophenones **181** with methyl thioglycolate [96]. The starting trifluoroacetophenones **181** were prepared from fluorobenzenes and ethyl trifluoroacetate. The key transformation proceeded in the presence of triethylamine at room temperature in acetonitrile and produced methyl 3-trifluoromethylbenzo[*b*]thiophene-2-carboxylates **182** in good yields. The products **182** were easily transformed into their corresponding 3-trifluoromethylbenzo[*b*]thiophenes **183**.

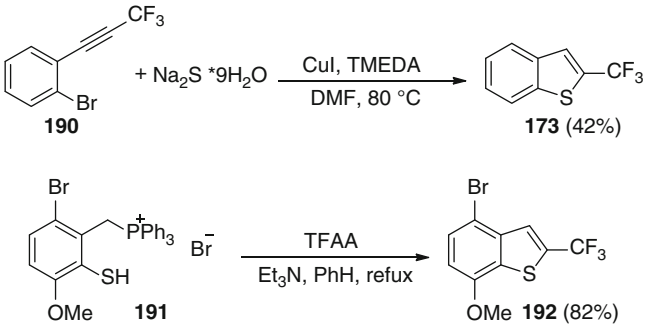
A similar approach was used for the preparation of the thienothiophene derivative **185**: the treatment of the trifluoroacetyl-substituted thiophene **184** with ethyl thioglycolate gave the condensed thiophene [97] bearing a trifluoromethyl group [98].



An alternative approach to benzo[*b*]thiophene derivatives includes treatment of an aryl-substituted ketene dithioacetal monoxide **188** with trifluoromethanesulfonic anhydride [99] (Tf_2O) in the presence of K_2CO_3 in toluene at 25 °C, followed by addition of ethanolamine to the reaction mixture, provided benzo[*b*]thiophenes, including 3-trifluoromethylbenzo[*b*]thiophene **189**, in good yields. The cyclization proceeded through formation of reactive sulfonium electrophile [100]. The synthesis of the starting material **188** was also facile and scalable, starting from aryl ketone **186** and formaldehyde dimethyl dithioacetal S-oxide (FAMSO) [101].



In 2011 a copper-catalyzed thiolation annulation reaction of 2-bromo alkynylbenzenes **190** with sodium sulfide has been developed. This approach provided 2-substituted benzo[*b*]thiophenes in moderate to good yields [102]. Also, synthesis of the 2-trifluoromethyl benzothiophene **192** was carried out in high yield using the thiophenol equivalent of the phenolic phosphonium bromide salt **191** [103].

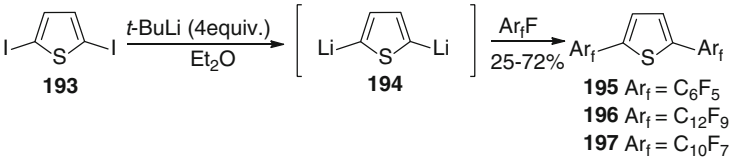


6 Synthesis of Perfluoroarylthiophenes

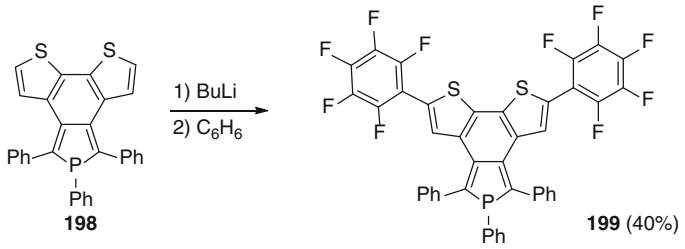
Usually, methods used for the synthesis of 2-perfluoroarylthiophenes synthesis are also applicable for the preparation of 3-perfluoroarylthiophenes. Although not numerous, they include reactions with organometallic reagents, cross-coupling reactions, and heterocyclization.

6.1 Organometallic Synthesis

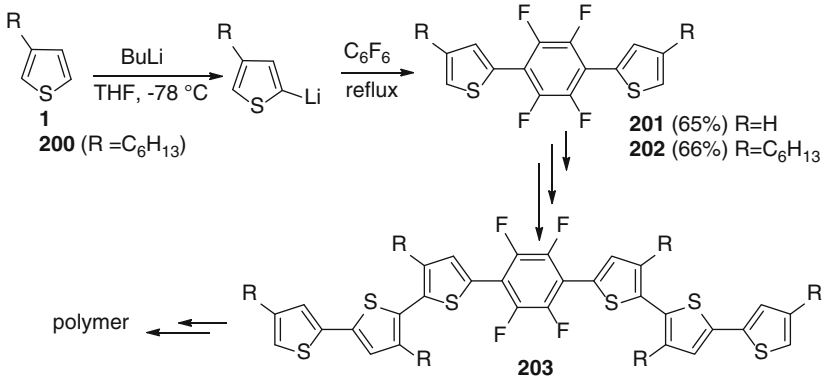
Perfluoroaryl thiophene derivatives **195–197** were obtained by nucleophilic aromatic substitution via thienyllithium intermediates **194**. The reaction is quite simple and is widely used for the preparation of various fluoroaromatics [59].



Lithiated bithiophene also gave rise to pentafluorophenyl derivative **199** in moderate yield. The S_NAr-type reaction proceeded with hexafluorobenzene in 8 h. The starting compound was obtained from the corresponding thiophene on treatment with *n*-butyllithium [104].

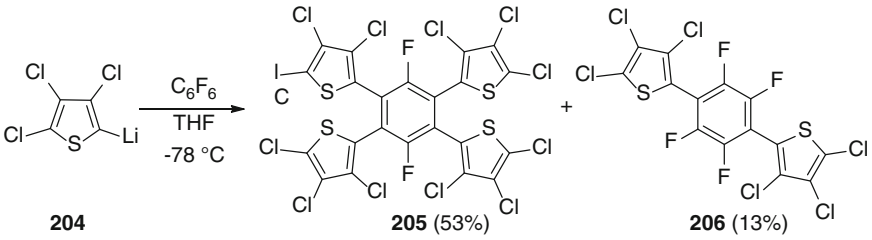


2-Thienyllitium and 4-hexyl-2-thienyllithium reacted with hexafluorobenzene to give the triaryl derivatives **201** (65 %) and **202** (66 %), respectively. The procedure is noteworthy since the lithiation of 3-hexylthiophene was regiospecific and resulted in the isolation of a single isomer. The compounds **201**, **202** have been used as precursors for oligothiophene **203** synthesis and preparation of polymeric materials [105].

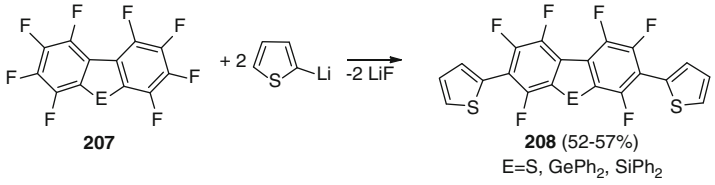


Similarly, lithiated chlorothiophenes reacted with hexafluorobenzene to produce fluoroaryl derivatives. Addition of hexafluorobenzene to trichloro-2-thienyllithium **204** in tetrahydrofuran at −78 °C gave 1,2,4,5-tetrakis(trichloro-2-thienyl) difluorobenzene **205** and 1,4-bis(trichloro-2-thienyl)tetrafluorobenzene **206**. A

similar reaction in diethyl ether at −15 to −20 °C also gave both **205** (44 %) and **206** (20 %) products [106].

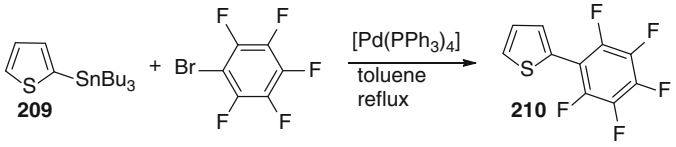


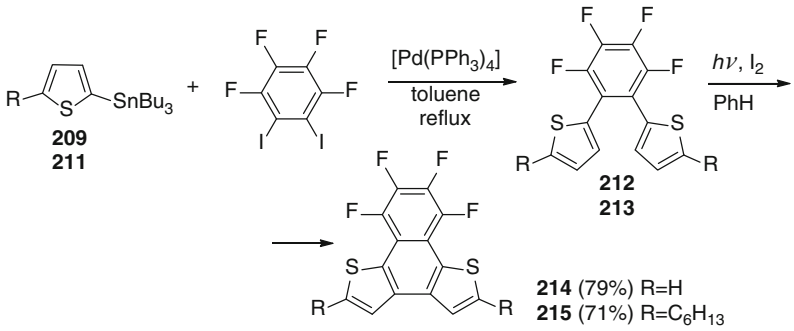
2,7-Disubstituted hexafluoro-9-heterofluorenes **208** were synthesized via nucleophilic aromatic substitution (S_NAr) reactions of 2-thienyllithium with various octafluoroheterofluorenes **207**. These compounds are of interest as possible building blocks for materials with useful electron-transport properties, since they possess relatively low LUMO energy levels [107].



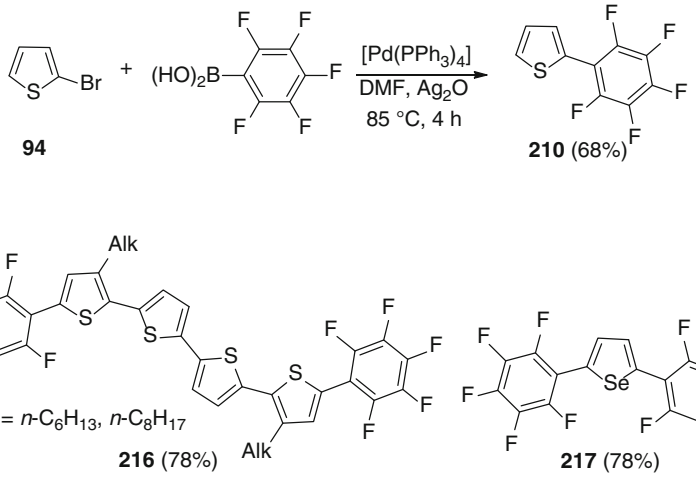
6.2 *Cross-Coupling*

More often, cross-coupling reactions are applied for the preparation of perfluoroarylthiophenes. Cupper and palladium catalysts are common for arylation. For example, palladium-catalyzed Stille coupling with iodo- and bromosubstituted fluoroarenes gave the fluoroarene-modified thiophenes which can act as organic semiconductors [108]. The palladium-catalyzed reaction was performed with the corresponding stannylated thiophenes (e.g. **209**, **211**) in toluene under reflux. Numerous thiophene derivatives have been obtained by this method. Product yields for these transformations ranged from moderate to good (45–80 %) [109].

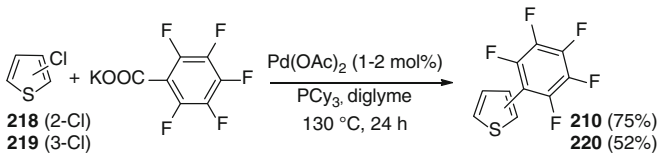




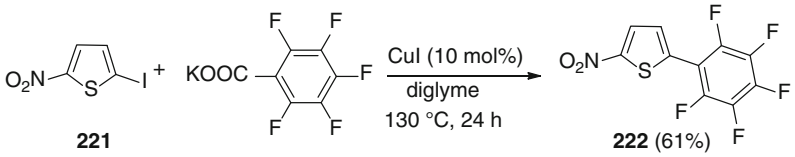
2-(Pentafluorophenyl)thiophene **210** and its derivatives were also synthesized by a palladium catalyzed Suzuki reaction between pentafluoroiodobenzene and thiophene boronic acid derivative. However, considering the ready accessibility of 2-halothiophenes by electrophilic substitutions of thiophenes, commercially available pentafluorophenylboronic acid is the counterpart of choice for the Suzuki coupling. The use of DMF as a solvent and potassium phosphate as a base in the presence of palladium catalyst allowed for the synthesis of a wide range of compounds, including thiophene-fused system and oligothiophenes with various chain lengths, such as **216**, as well as several selenophene homologues, for example **217** [110].



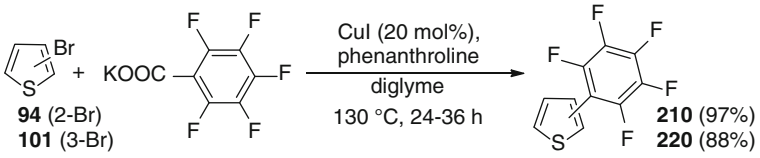
The palladium-catalyzed decarboxylative coupling of potassium pentafluorobenzoate with aryl chlorides, bromides and triflates was shown to be a useful method for the synthesis of polyfluorobiaryls from readily accessible polyfluorobenzoate salts. For instance, 2- and 3-chlorothiophens **218**, **219** reacted with potassium pentafluorobenzoate to produce pentafluorophenyl derivatives **210** and **220**. The reaction proceeded in refluxed diglyme in the presence palladium acetate(II) [111].



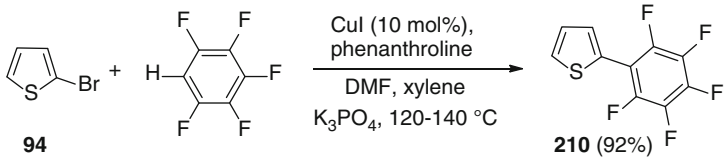
A similar coupling proceeded with 2-iodo-5-nitrothiophenene **221** in the presence of a copper catalyst. A possible explanation for the outstanding performance of diglyme is that it can coordinate to K^+, thereby facilitating the complexation between CuI and pentafluorobenzoate.



This protocol was applicable to aryl iodides but not to less reactive aryl bromides. This problem was solved by using 1,10-phenanthroline as a ligand: 2- and 3-bromothiophenes **94** and **101** formed the corresponding pentafluorophenyl derivatives in good yields in the presence of a copper-phenanthroline catalytic system [112].

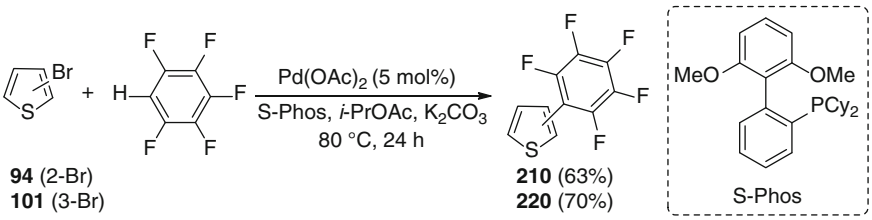


All of the methods presented above are based on cross-couplings of halogenated thiophenes and different pentafluorophenyl derivatives. However, the arylation of polyfluorobenzene C-H bonds can also be used for the synthesis of perfluoroarylthiophenes. For example, 2-bromothiophene **94** and pentafluorobenzene gave 2-(perfluorophenyl)thiophene **210** in 92 % yield in the presence of phenanthroline [113].



A similar monoarylation was performed with 2- and 3-bromothiophenes **94** and **101** under palladium-catalyzed conditions in good yields. The use of a more

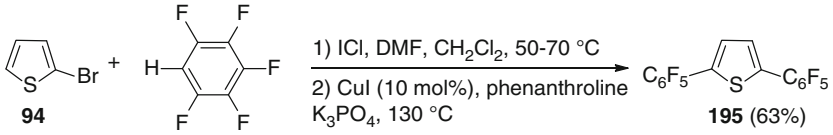
effective palladium catalyst with the phosphine ligand S-Phos allowed for the temperature of this transformation to be reduced to 80 °C [114].



94 (2-Br)
101 (3-Br)

210 (63%)
220 (70%)

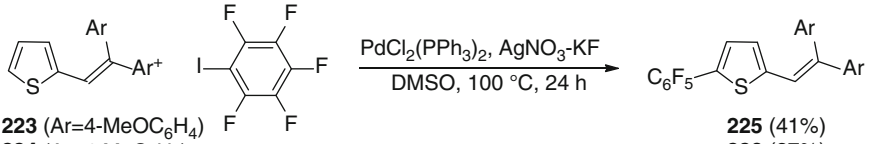
2,5-Bisperfluorophenylthiophene **195** was obtained by a one-pot sequential iodination and copper-catalyzed cross-coupling of arene C–H bonds. The first step was the electrophilic halogenations with incorporation of the iodine atom. Then, copper-catalyzed arylation allowed for a highly regioselective heterocoupling, thereby leading to the diarylated product **195** [115].



94

195 (63%)

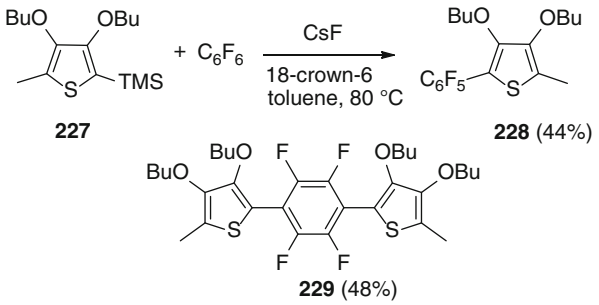
The previous three examples involved the couplings of halogenated thiophenes with different substrates. However, it is also possible to perform coupling between thiophene and halogen-substituted arenes. The reaction of thiophene derivatives **223**, **224** with pentafluoroiodobenzene proceeded in the presence of bis(triphenylphosphine)palladium(II) dichloride and silver nitrate [116].



223 (Ar=4-MeOC$_6$H$_4$)
224 (Ar=4-MeC$_6$H$_4$)

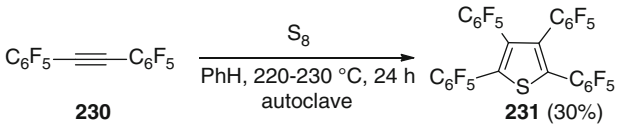
225 (41%)
226 (37%)

The transition-metal-free carbon-carbon bond formation by fluoride activation of silicon-carbon bonds has been used for coupling of perfluoroarenes and trimethylsilylthiophene derivative **227**. In the case of 2,5-bis(trimethylsilyl)thiophenes, the ratio of isolated products indicated that the first and second attacks on perfluorobenzene proceeded with the same rate, or that conversion of the second TMS group can be more rapid than that of the first [117].

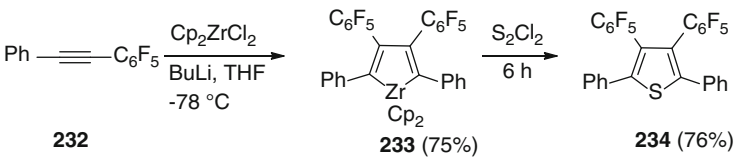


6.3 *Heterocyclization*

The heterocyclization of substituted alkynes with sulfur was also shown to be applicable for the preparation of perfluoroarylthiophenes. When a mixture of 1,2-bis(perfluorophenyl)ethyne **230** and sulfur was heated in benzene at 220–230 °C the tetrakis(perfluorophenyl)thiophene **231** was formed in 30 % yield [118].

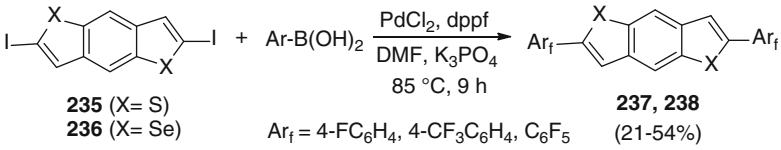


Another pathway to perfluoroalkylthiophenes involved the cyclization of zirconocene obtained from pentafluorophenyl-substituted alkynes. The fluorophenyl-substituted alkynes was synthesized by coupling of the appropriate fluoroaryl iodide with a terminal alkyne catalyzed by tetrakis(triphenylphosphine)-palladium(0) and CuI. Reaction of the resulting alkyne **232** with Negishi's zirconocene synthon at low temperature followed by warming to room temperature afforded zirconacyclopentadienes **233** in high yields. The reaction of the latter with S_2Cl_2 gave thiophene **234** in high yield [119].

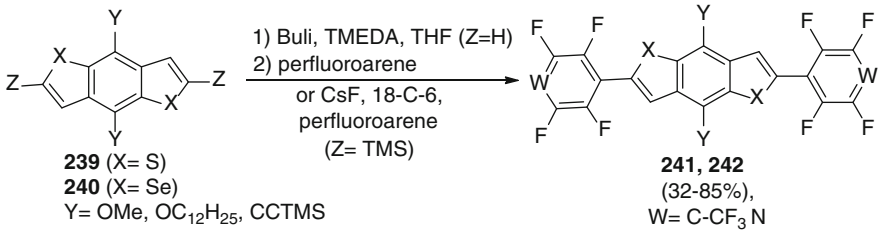


7 Synthesis of Perfluoroarylbenzothiophenes

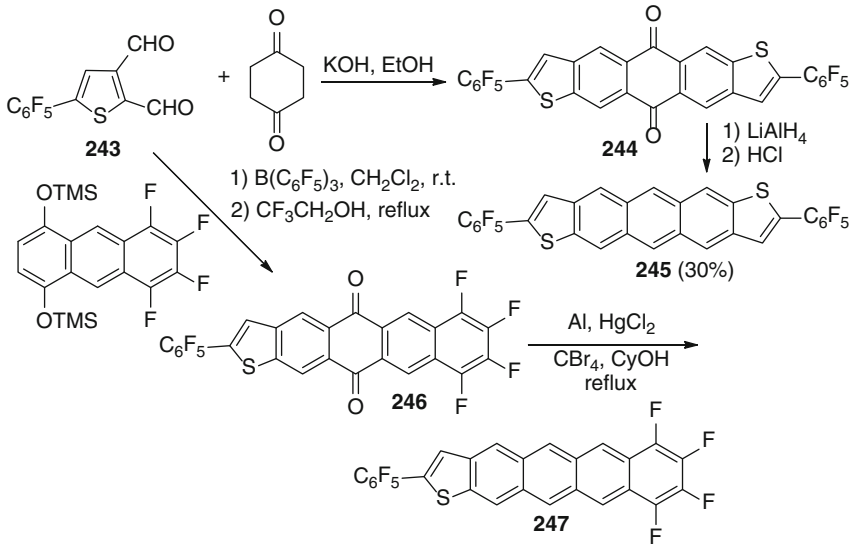
The known approaches to perfluoroarylbenzothiophenes are generally based on the cross-couplings and reactions with organometallic reagents. For example, benzo[1,2-b:4,5-*b′*]dithiophene **235** and -diselenophene **236**, which are known p-channel semiconducting materials, were modified via palladium-catalyzed Suzuki-Miyaura coupling reaction. The reaction proceeded in moderate yields and gave compounds **237**, **238** which can act as n-semiconductors [120].



Another method for the synthesis of 2,6-diphenylbenzo[1,2-*b*:4,5-*b′*]dithiophene **241** and diselenophene fluorinated derivatives **242** was based on the reaction of their bismetalates with perfluoroarenes. The same transformation was also performed with trimethylsilyl derivatives using a catalytic amount of cesium fluoride in the presence of 18-crown-6 [121].

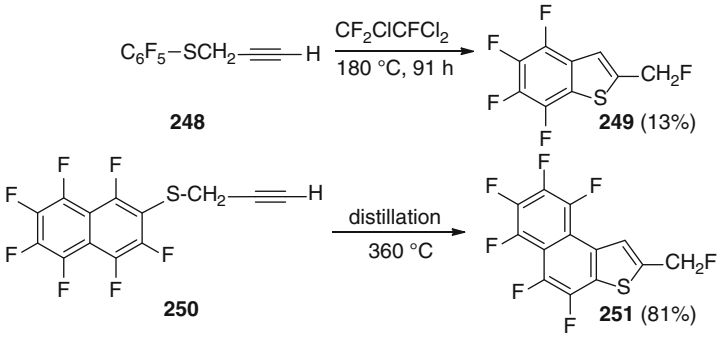


The synthesis of functionalized anthradithiophenes was achieved through condensation of thiophenes derivatives with cyclohexane-1,4-dione. The starting 5-perfluorophenyl-2,3-thiophenedicarboxaldehyde was prepared in 45 % yield by Stille coupling of 5-(tributylstannyl)-2,3-bis(1,3-dioxolan-2-yl)thiophene with bromopentafluorobenzene. The reaction of thiophenedicarboxaldehyde with cyclohexane-1,4-dione gave intermediate quinone **244** that produced dipentafluorophenylanthradithiophene **245** on reduction. The latter is a semiconductor for organic thin-film transistors (OTFTs) [109]. A similar reaction with a 5,6,7,8-tetrafluoroanthracene derivative leads to 7,8,9,10-tetrafluoro-2-pentafluorophenyltetraceno[2,3-*b*]thiophene **247**.



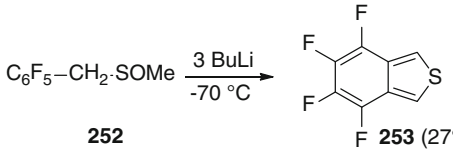
8 Benzothiophenes with Perfluorinated Carbocycle

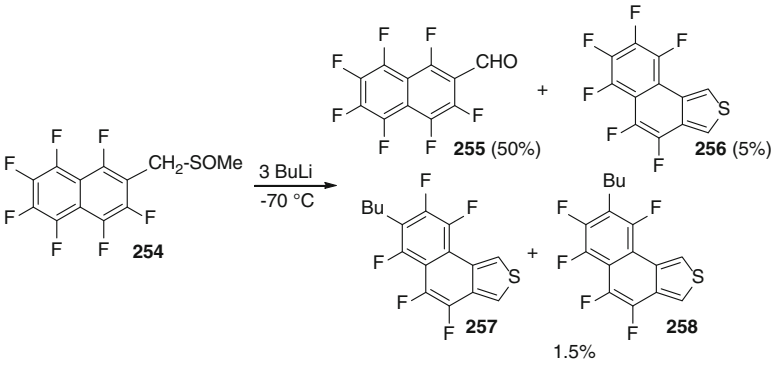
Benzothiophenes with a fully fluorinated carbocycle are usually prepared by way of cyclization reactions. For example, when pentafluorophenyl prop-2-ynyl sulfide **248** in Freon 113 was heated at 180 °C 4,5,6,7-tetrafluoro-2-fluoromethylbenzo[*b*] thiophene **249** was obtained in low yield. A similar isomerisation of the naphthalene compound **250** was more efficient and gave the 2-fluoromethyl derivative **251** in 41 % yield. Distillation of the starting compound under vacuum through silica-filled tube led to the target compound **251** in 81 % yield [122].



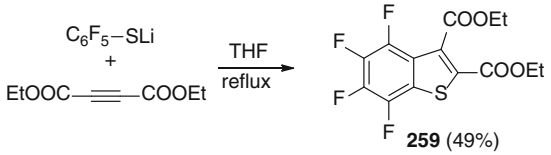
More often, such compounds are synthesized via cyclization induced by organometallics. For example, 2,3,4,5,6-pentafluorobenzyl methyl sulfoxide **252** gave 4,5,6,7-tetrafluorobenzo[*c*]thiophene **253** on treatment with BuLi in THF at −70 °C. The mechanism invokes the nucleophilic replacement of *ortho*-fluorine by CH_2Li and

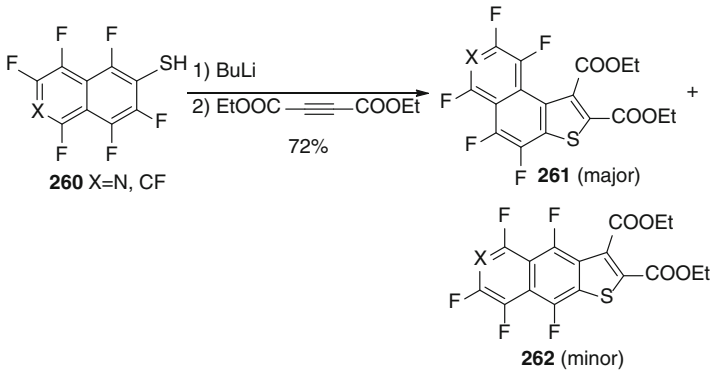
aromatization. Treatment of the naphthalene sulphoxide **254** with BuLi gave 4,5,6,7,8,9-hexafluoronaphtho[1,2-*c*]thiophene **256** in inseparable mixture of the 7- and 8-butyl derivatives **257** and **258**, as well as the aldehyde **255** in 50 % yield [123].





In 1967, the formation of diethyl 4,5,6,7-tetrafluoro-benzo[*b*]thiophen-2,3-dicarboxylate **259** in 49 % yield, by the reaction of lithium pentafluorobenzenethiolate with diethyl acetylenedicarboxylate in THF under reflux, was reported [124]. Later, the cyclization reaction was shown to occur under very mild conditions (−70 to −58 °C) in 74 % yield [125]. A similar reaction of lithium 1,3,4,5,6,7,8-heptafluoro-2-naphthalenethiolate and its isoquinoline derivative with dimethyl acetylenedicarboxylate was reported to give polyfluorinated condensed products **261** and **262** [126].





9 Conclusion

Fluorinated thiophene derivatives have found a broad application as biologically intriguing molecules and especially as modern organic materials. However, methods for their synthesis are still limited. The direct fluorination or trifluoromethylation of thiophene is either not selective or proceeds in low yields. The most convenient approach to fluorothiophenes and their benzoanalogues involves lithiation-fluorination reactions. Other common methods are based on heterocyclizations with participation of methyl thioglycolate, or cycloaddition reactions. The scarce methods for fluorinated thiophenes synthesis give a chance for synthetic chemists to elaborate new, better pathways to these intriguing and useful compounds.

References

1. (a) Yoon MH, DiBenedetto SA, Facchetti A, Marks TJ (2005) Organic thin-film transistors based on carbonyl-functionalized quaterthiophenes: high mobility n-channel semiconductors and ambipolar transport. J Am Chem Soc 127:1348–1349; (b) Subramanian S, Park SK, Parkin SR, Podzorov V, Jackson TN, Anthony JE (2008) Chromophore fluorination enhances crystallization and stability of soluble anthradithiophene semiconductors. J Am Chem Soc 130:2706–2707; (c) Tang ML, Reichardt AD, Wie P, Bao Z (2009) Correlating carrier type with frontier molecular orbital energy levels in organic thin film transistors of functionalized acene derivatives. J Am Chem Soc 131:5264–5273; (d) Ie Y, Umemoto Y, Kaneda T, Aso Y (2006) Electronegative oligothiophenes based on a hexafluorocyclopentene-annelated thiophene unit. Org Lett 8:5381–5384; (e) Ie Y, Nitani M, Ishikawa M, Nakayama K, Tada H, Kaneda T, Aso Y (2007) Electronegative oligothiophenes for n-type semiconductors: difluoromethylene-bridged bithiophene and its oligomers. Org Lett 9:2115–2118
2. (a) Li L, Collard DM (2005) Tuning the electronic structure of conjugated polymers with fluoroalkyl substitution: alternating alkyl/perfluoroalkyl-substituted polythiophene. Macromolecules 38:372–378; (b) Facchetti A, Yoon MH, Stern CL, Hutchison GR, Ratner MA, Marks TJ (2004) Building blocks for n-type molecular and polymeric electronics. Perfluoroalkyl- versus alkyl-functionalized oligothiophenes (nTs; n =2-6). Systematic synthesis, spectroscopy, electrochemistry, and solid-state organization. J Am Chem Soc 126:13480–13501
3. Geramita K, McBee J, Shen Y, Radu N, Tilley TD (2006) Synthesis and characterization of perfluoroaryl-substituted siloles and thiophenes: a series of electron-deficient blue light emitting materials. Chem Mater 18:3261–3269
4. Matharu AS, Cowling SJ, Wright G (2007) Laterally fluorinated liquid crystals containing the 2,2′-bithiophene moiety. Liq Cryst 34:489–506
5. (a) Scarpelli R, Di Marco A, Ferrigno F, Laufer R, Marcucci I, Muraglia E, Ontoria JM, Rowley M, Serafini S, Steinkühler C, Jones P (2008) Studies of the metabolic stability in cells of 5-(trifluoroacetyl)thiophene-2-carboxamides and identification of more stable class II histone deacetylase (HDAC) inhibitors. Bioorg Med Chem Lett 18:6078–6082; (b) Muraglia E, Altamura S, Branca D, Cecchetti O, Ferrigno F, Orsale MV, Palumbi MC, Rowley M, Scarpelli R, Steinkühler C, Jones P (2008) 2-Trifluoroacetylthiophene oxadiazoles as potent and selective class II human histone deacetylase inhibitors. Bioorg Med Chem Lett 18:6083–6087
6. (a) Yan L, Budhu R, Huo P, Lynch CL, Hale JJ, Mills SG, Hajdu R, Keohane CA, Rosenbach MJ, Milligan JA, Shei GJ, Chrebet G, Bergstrom J, Card D, Mandala SM (2006)

2-Aryl(pyrrolidin-4-yl)acetic acids are potent agonists of sphingosine-1-phosphate (S1P) receptors. Bioorg Med Chem Lett 16:3564–3568; (b) Hale JJ, Lynch CL, Neway W, Mills SG, Hajdu R, Keohane CA, Rosenbach MJ, Milligan JA, Shei GJ, Parent SA, Chrebet G, Bergstrom J, Card D, Ferrer M, Hodder P, Strulovici B, Rosen H, Mandala S (2004) A rational utilization of high-throughput screening affords selective, orally bioavailable 1-benzyl-3-carboxyazetidine sphingosine-1-phosphate-1 receptor agonists. J Med Chem 47:6662–6665; (c) Nakamura T, Asano M, Sekiguchi Y, Mizuno Y, Tamaki K, Kimura T, Nara F, Kawase Y, Shimozato T, Doi H, Kagari T, Tomisato W, Inoue R, Nagasaki M, Yuita H, Oguchi-Oshima K, Kaneko R, Watanabe N, Abe Y, Nishi T (2012) Discovery of CS-2100, a potent, orally active and $S1P_3$-sparing $S1P_1$ agonist. Bioorg Med Chem Lett 22:1788–1792

7. Popkov SV, Kuzenkov AV (2005) Synthesis of trifluoromethyl-substituted heteroaromatic aldehydes. Russ Chem Bull (Engl Transl) 54:1672–1674
8. Tsuji K, Nakamura K, Ogino T, Konishi N, Tojo T, Ochi T, Seki N, Matsuo M (1998) Studies on anti-inflammatory agents. VI. Synthesis and pharmacological properties of 2,3-diarylthiophenes. Chem Pharm Bull 46:279–286
9. Irie M (2000) Chem Rev 100:1685–1716
10. (a) Crestoni ME, Fornarini S (1989) Direct fluorination of thiophene and N-methylpyrrole. Gazz Chim Ital 119:203–204; (b) Cerichelli G, Crestoni ME, Fornarini S (1990) The fluorination of five-membered heteroaromatic compounds with elemental fluorine. Gazz Chim Ital 120:749–755
11. Malabarba A, Somma S, Berti M, Cavalleri B (1984) 7-(D, L-α-fluoro-2-thienylacetamido) cephalosporanic acid (L 14655), a new semisynthetic cephalosporin. Synthesis and preliminary biological evaluation. Farmaco 39:1050–1060
12. Gozzo FC, Ifa DR, Eberlin MN (2000) Gaseous SF_3^+: an efficient electrophilic monofluorinating agent for five-membered heteroaromatic compounds. J Org Chem 65:3920–3925
13. Kobarfard F, Kauffman JM, Boyko WJ (1999) Attempted synthesis of aminofluorothiophenes. J Heterocycl Chem 36:1247–1251
14. Badland M, Compère D, Courté K, Dublanchet AC, Blais S, Manage A, Peron G, Wrigglesworth R (2011) Thiophene and bioisostere derivatives as new MMP12 inhibitors. Bioorg Med Chem Lett 21:528–530
15. Burdon J, Cambell JG, Parsons IW, Tatlow JC (1969) Tetrafluorothiophen. J Chem Soc D Chem Comm 1:27–28
16. Burdon J, Parsons IW (1979) Highly fluorinated heterocycles. Part XIV. The conversion of 2,2,5,5-tetrafluoro-3-thiolen into 2,5-difluorothiophene: an apparent example of the thermal elimination of molecular fluorine. J Fluor Chem 13:159–162
17. Schuetz RD, Taft DD, O'Brien JP, Shea JL, Mork HM (1963) Fluorinated heterocyclics. J Org Chem 28:1420–1422
18. (a) Dvornikova E, Bechcicka M, Kamieńska-Trela K, Krówczyński A (2003) Synthesis and NMR studies of 2- and 3-fluorosubstitued five-membered heterocycles. J Fluorine Chem 124:159–168; (b) Lai G, Guo T (2008) A convenient and efficient preparation of 2-acetyl-4,5-difluorothiophene. Synth Comm 38:72–76; (c) Foister S, Marques MA, Doss RM, Dervan PB (2003) Shape selective recognition of T·A base pairs by hairpin polyamides containing N-terminal 3-methoxy (and 3-chloro) thiophene residues. Bioorg Med Chem 11:4333–4330; (d) Torrado A, Lamas C, Agejas J, Jiménez A, Díaz N, Gilmore J, Boot J, Findlay J, Hayhurst L, Wallace L, Broadmore R, Tomlinson R (2004) Novel selective and potent 5-HT reuptake inhibitors with 5-HT1D antagonist activity: chemistry and pharmacological evaluation of a series of thienopyran derivatives. Bioorg Med Chem 12:5277–5295; (e) Higashiguchi K, Matsuda K, Asano Y, Murakami A, Nakamura S, Irie M (2005) Photochromism of dithienylethenes containing fluorinated thiophene rings. Eur J Org Chem 91–97; (f) Pike VW, Rash KS, Chen Zh, Pedregal C, Statnick MA, Kimura Y, Hong J, Zoghbi SS, Fujita M, Toledo MA, Diaz N, Gackenheimer SL, Tauscher JT, Barth VN, Innis RB (2011) Synthesis and evaluation of radioligands for imaging brain nociceptin/orphanin FQ peptide (NOP) receptors with positron emission tomography. J Med Chem 54:2687–2700

19. Gronowitz S, Rosén U (1971) Nuclear magnetic resonance of aromatic heterocycles. III. On the synthesis of substituted fluorothiophenes. Chem Scr 1:33–43
20. Gronowitz S, Johnson I, Hörnfeld AB (1973) Fluorinated heterocycles. Chem Scr 3:94–96
21. Chonan T, Takahashi K (2004) The synthesis of difluoro and dimethyl derivatives of 2,6-bis(dicyanomethylene)-2,6-dihydro-4H-cyclopenta[2,1-*b*:3,4-*b*′]dithiophen-4-one (CPDT-TCNQ) and the conducting properties of the metallic salts based on the dimethyl derivative. Bull Chem Soc Jpn 77:1487–1497
22. Taylor EC, Zhou P (1997) A facile synthesis of 3-fluorothiophene-2-carboxylic acid. Org Prep Proced Int 29:221–223
23. (a) Liang Y, Feng D, Wu Y, Tsai ST, Li G, Ray C, Yu L (2009) Highly efficient solar cell polymers developed via fine-tuning of structural and electronic properties. J Am Chem Soc 131:7792–7799; (b) Wakim S, Alem S, Li Zh, Zhang Y, Tse SC, Lu J, Ding J, Tao Y (2012) New low band gap thieno[3,4-*b*]thiophene-based polymers with deep HOMO levels for organic solar cells. J Mater Chem 21:10920–10928
24. Sakamoto Y, Komatsu S, Suzuki T (2001) Tetradecafluorosexithiophene: the first perfluorinated oligothiophene. J Am Chem Soc 123:4643–4644
25. Van Vleck RT (1949) Preparation of fluorothiophene. J Am Chem Soc 71:3256–3257
26. Onys'ko PP, Kim TV, Kiseleva OI, Rassukana YV, Gakh AA (2009) Cascade iodination-fluorination synthesis of 2-fluorothiophene and 5-fluoro-2-thienyliodonium salts. J Fluor Chem 130:501–504
27. Chambers RJ, Marfat A (2000) An improved synthesis of 5-fluorothiophene-2-carboxylic acid. Synth Comm 30:3629–3632
28. Kassmi AE, Fache F, Lemaire M (1994) A convenient synthesis of 3-fluorothiophene. Synth Comm 24:95–101
29. Corral C, Lasso A, Lissavetzky J, Alvarez-Isúa AS, Valdeolmillos AM (1985) The behaviour of vicinal alkyl aminothiophenecarboxylates in the sandmeyer and schiemann reaction. Heterocycles 23:1431–1435
30. (a) Kiryanov A, Seed AJ, Sampson P (2001) Ring fluorinated thiophenes: applications to liquid crystal synthesis. Tetrahedron Lett 42:8797–8800; (b) Pomerantz M, Turkman N (2008) A facile and improved synthesis of 3-fluorothiophene. Synthesis 2008:2333–2336.
31. Dmowski W, Manko VA, Nowak I (1998) 3-Chloro-4-fluorothiophene-1,1-dioxide. A new synthetically useful fluorodiene. J Fluor Chem 88:143–151
32. (a) Burger K, Helmreich B, Jendrewski O (1994) 3-Trifluoromethylthiophens from hexafluoroacetone. J Fluorine Chem 66:13–15; (b) Burger K, Helmreich B, Popkova VY, German LS (1994) Synthesis of 2-fluoro-3-trifluoromethylthiophene and 3-trifluoromethylthiophene from hexafluoroacetone. Heterocycles 39:819–832
33. Ishihara T, Shinjo H, Inoue Y, Ando T (1983) Regiospecific α-hexafluoroisopropylidenation of ketones using hexafluoroacetone. J Fluor Chem 22:1–19
34. Andrès DF, Laurent EG, Marquet BS (1997) Reaction of thioglycolate with α-fluoro-β-(phenylthio)enones (or-enals): synthesis of substituted β-carboxy-γ-fluorothiophenes. Tetrahedron Lett 38:1049–1052
35. Nussbaumer P, Petranyi G, Stütz A (1991) Synthesis and structure-activity relationships of benzo[*b*]thienylallylamine antimycotics. J Med Chem 34:65–73
36. Bensoam J, Mathey F (1977) Etude preliminaire de la difluorodiazine N_2F_2 comme agent de fluoration en synthese organique; conversion de quelques cetones cycliques en α-fluorocetones. Tetrahedron Lett 32:2797–2800
37. Belley M, Douida Z, Mancuso J, De Vleeschauwer M (2005) Aromatic ring-opening of 2-fluorobenzothiophenes by alkyllithiums. Synlett 2005:247–250
38. Son HJ, Wang W, Xu T, Liang Y, Wu Y, Li G, Yu L (2011) Synthesis of fluorinated polythienothiophene-co-benzodithiophenes and effect of fluorination on the photovoltaic properties. J Am Chem Soc 133:1885–1894
39. (a) Ischikawa J, Wada Y, Okauchi T, Minami T (1997) 5-*endo*-Trigonal cyclization of *o-substituted gem*-difluorostyrenes: syntheses of 2-fluorinated indoles, benzo[*b*]furans and

benzo[*b*]thiophenes. Chem Comm 1537–1538; (b) Ischikawa J, Wada Y, Fujiwara M, Sakoda K (2002) The nucleophilic 5-*endo-trig* cyclization of 1,1-difluoro-1-alkenes: ring-fluorinated hetero- and carbocycle synthesis and remarkable effect of the vinylic fluorines on the disfavored process. Synthesis 2002:1917–1936

40. Cabiddu MG, Cabiddu S, Cadoni E, Corrias R, Fattuoni C, Floris C, Melis S (1997) Metallation reactions XXII. Regioselective metallation of (trifluoromethyl)(alkylthio)benzenes. J Organometall Chem 531:125–140
41. Yin B, Inagi S, Fuchigami T (2011) Electrosynthesis of fluorinated benzo[*b*]thiophene derivatives. Synlett 2011:1313–1317
42. Ulrich H, Kober E, Rätz R, Schroeder H, Grundmann C (1962) Synthesis of polyfluorinated heterocycles by indirect fluorination with silver fluorides. V. Fluorothiophene. J Org Chem 27:2593–2595
43. Nishida M, Fujii S, Aoki T, Hayakawa Y (1990) Synthesis and polymerization of ethynylthiophenes and ethynylfurans containing trifluoromethyl groups. J Fluor Chem 46:445–459
44. Bucci R, Laguzzi G, Pompili ML, Speranza M (1991) Gas-phase heteroaromatic substitution. 12. Reaction of free trifluoromethyl cation with simple five-membered heteroarenes in the gas phase. J Am Chem Soc 113:4544–4550
45. Herrera OS, Nieto JD, Lane SI, Oexler EV (2003) The gas-phase reaction of the CF_3 radical with thiophene. Can J Chem 81:1477–1481
46. (a) Umemoto T, Kuriu Y, Shuyama H (1981) Perfluoroalkylation of aromatic compounds with $R_fI(Ph)OSO_2CF_3$. Chem Lett 10:1663–1666; (b) Umemoto T, Nakamura T (1984) Synthesis of double FITS reagents. Chem Lett 13:983–984
47. (a) Naumann D, Kischkewitz J (1990) Trifluoromethylierungsreaktionen von CF_3I, $Te(CF_3)_2$, $Sb(CF_3)_3$, $Hg(CF_3)_2$, und $Cd(CF_3)_2 \cdot D$ mit Furan, Thiophen, Pyrrol und p-Benzochinon. J Fluor Chem 46:265–281; (b) Cowell A, Tamborski C (1981) Fluoroalkylation of aromatic compounds. J Fluor Chem 17:345–356
48. Girard Y, Atkinson JG, Bélanger PC, Fuentes JJ, Rokach J, Rooney SC, Remy DC, Hunt CA (1983) Synthesis, chemistry, and photochemical substitutions of 6,11-dihydro-5H-pyrrolo[2,1-]*b*[3]benzazepine-11-ones. J Org Chem 48:3220–3234
49. Bravo A, Bjørsvik HR, Fontana F, Liguori L, Mele A, Minisci F (1997) New methods of free-radical perfluoroalkylation of aromatics and alkenes. Absolute rate constants and partial rate factors for the homolytic aromatic substitution by n-perfluorobutyl radical. J Org Chem 62:7128–7136
50. (a) Sawada H, Nakayama M, Yoshida M, Yoshida T, Kamigata N (1990) Trifluoromethylation of aromatic compounds with bis(trifluoroacetyl) peroxide. J Fluor Chem 46:423–431; (b) Sawada H, Yoshida M, Hagii H, Aoshima K, Kobayashi M (1986) Perfluoroalkylation of furan, thiophene, and pyridines with bis(heptafluorobutyryl) peroxide. Bull Chem Soc Jpn 59:215–219; (c) Yoshida M, Yoshida T, Kamigata N, Kobayashi M (1988) Heptafluoropropylation of various substituted thiophenes with bis(heptafluorobutyryl) peroxide. Preparation of 3-heptafluoropropylthiophene. Bull Chem Soc Jpn 61:3549–3552; (d) Sawada H, Nakayama M (1991) Synthesis of aromatic compounds containing perfluorooxaalkyl groups. J Fluor Chem 51:117–129
51. Yoshida M, Sasage S, Kamigata N, Sawada H, Nakayama M (1989) Nucleophilic displacement of bis(perfluoroalkanoyl) peroxides with perfluoroalkanoate. Bull Chem Soc Jpn 62:2416–2418
52. Zhou QL, Huang YZ (1989) Direct fluoroalkylation of aromatic compounds catalyzed by tetrakis(triphenylphosphine)nickel. J Fluor Chem 43:385–392
53. Ye Y, Lee SH, Sanford MS (2011) Silver-mediated trifluoromethylation of arenes using $TMSCF_3$. Org Lett 13:5464–5467
54. Chen GJ, Tamborski C (1990) Polufluoroalkylation of bromoheterocyclic compounds via perfluoroalkylcopper intermediates. J Fluor Chem 46:137–159
55. Burton DJ, Yang ZY (1992) Fluorinated organometallics: perfluoroalkyl and functionalized perfluoroalkyl organometallic reagents in organic synthesis. Tetrahedron 48:189–275

56. (a) Oishi M, Kondo H, Amii H (2009) Aromatic trifluoromethylation catalytic in copper. Chem Comm 1909–1911; (b) McCairn MC, Turner ML (2007) Rapid synthesis and fluorous-phase purification of α-perfluorohexyloligothiophenes. Tetrahedron Lett 48:1045–1047
57. (a) Paratian JM, Sibille S, Périchon J (1992) An efficient electrochemical trifluoromethylation of aromatic halides with bromotrifluoromethane and a sacrificial copper anode an efficient electrochemical trifluoromethylation of aromatic halides with bromotrifluoromethane and a sacrificial copper anode. J Chem Soc Chem Comm 53–54; (b) Paratian JM, Labbé E, Sibille S, Périchon J (1995) Electrosynthesis of (trifluoromethyl)copper complexes from bromotrifluoromethane: reactivities with various organic halides. J Organometallic Chem 489:137–143
58. Carr GE, Chambers RD, Holmes TF, Parker DG (1988) Sodium perfluoroalkane carboxylates as sources of perfluoroalkyl groups. J Chem Soc Perkin Trans 1:921–926
59. Jones E, Moodie IM (1969) (Perfluoroacy1)thiophens. Part II. Fluorination of hexafluoro-1,3-di-(2-thenoy1)propane. J Chem Soc C 1969:2051–2053
60. (a) Leroy J, Rubinstein M, Wakselman C (1985) Copper-mediated perfluoroalkylation of halogenothiophenes. J Fluor Chem 27:291–298; (b) Li L, Counts KE, Kurosawa S, Teja AS, Collard DM (2004) Tuning the electronic structure and solubility of conjugated polymers with perfluoroalkyl substituents: poly(3-perfluorooctylthiophene), the first supercritical CO_2-soluble conjugated polymer. Adv Mater 16:180–183
61. (a) Ritter SK, Hill BK, Odian MA, Dai J, Noftle RE, Gard GL (1999) Synthesis and characterization of thiophenes with fluorinated substituents. J Fluor Chem 93:73–79; (b) Ritter SK, Noftle RE, Ward AE (1993) Synthesis, characterization, and oxidative polymerization of 3-(fluoromethyl)thiophenes. Chem Mater 5:752–754
62. Duan JX, Su DB, Chen QY (1993) Trifluoromethylation of organic halides with methyl halodifluoroacetates. A process via difluorocarbene and trifluoromethide intermediates. J Fluor Chem 61:279–284
63. Zanardi A, Novikov MA, Martin E, Benet-Buchholz J, Grushin VV (2011) Direct cupration of fluoroform. J Am Chem Soc 133:20901–20913
64. (a) Knauber T, Arikan F, Röschenthaler GV, Gooßen LJ (2011) Copper-catalyzed trifluoromethylation of aryl iodides with potassium (trifluoromethyl)trimethoxyborate. Chem Eur J 17:2689–2697, (b) Kondo H, Oishi M, Fujikawa K, Amii H (2011) Copper-catalyzed aromatic trifluoromethylation via group transfer from fluoral derivatives. Adv Synth Catal 353:1247–1252
65. (a) Turkman N, An L, Pomerantz M (2010) Synthesis of 2,5-dibromo-3-(1,1-difluoroalkyl) thiophenes. Org Lett 12:4428–4430; (b) Kiryanov AA, Sampson P, Seed AJ (2001) Synthesis and mesomorphic properties of 1,1-difluoroalkylsubstituted biphenylthienyl and terphenyl liquid crystals. A comparative study of mesomorphic behavior relative to alkyl, alkoxy and alkanoyl analogs. J Mater Chem 11:3068–3077
66. Haas A, Plümer R, Schiller A (1985) Fluorierung ungesättigter Aldehyde rnit Schwefeltetrafluorid. Chem Ber 118:3004–3010
67. (a) Umemoto Y, Ie Y, Saeki A, Seki S, Tagawa S, Aso Y (2008) Electronegative Oligothiophenes fully annelated with hexafluorocyclopentene: synthesis, properties, and intrinsic electron mobility. Org Lett 10:1095–1098
68. (a) Platonov VE, Maksimov AM, Yakobson GG (1977) Formation of 4,4,5,5,6,6-hexafluoroc yclopenta[*b*]thiophene upon copyrolysis of 2-substituted thiophenes with tetrafluoroethylene. Russ Chem Bull (Engl Transl) 26:2220; (b) Maksimov AM, Platonov VE, Yakobson GG (1986) Formation and some chemical reactions of 4,4,5,5,6,6-hexafluorocyclopenta[*b*]thiophene. Russ Chem Bull (Engl Transl) 35:125–128
69. (a) Karp GM, Samant D, Mukhopadhyay S, Condon ME, Kleemann A (2000) Preparation of 4-hydroxy-2-trifluoromethylthiophene: a novel bioisostere of α,α,α-trifluoro-*m*-cresol. Synthesis 1078–1080; (b) Hromatka O, Binder D, Eichinger K (1974) Über die Synthese von Amino-trifluormethyl-thiophencarbonsäure-äthylestern. Monatsh Chem 105:127–134; (c) Binder D, Noe CR, Baumann K, Wildburger JMF (1985) Thiophen als Strukturelement phys-

iologisch aktiver Substanzen, 15. Mitt. Das Thiophenanalogon eines anxiolytisch wirksamen 1,2,4-Triazolo[4,3-b]pyridazins. Arch Pharm 318:243–249; (d) Guan HP, Luo BH, Hu CM (1997) An effective synthesis of 2-trifluoromethyl- or 2-(1,1-difluoroalkyl)thiophenes. Synthesis 461–464; (e) Meng Zh, Kulkarni BA, Kerekes AD, Mandal AK, Esposite SJ, Belanger DB, Reddy PA, Basso AD, Tevar S, Gray K, Jones J, Smith EB, Doll RJ, Siddiqui MA (2011) Bioisosteric approach to the discovery of imidazo[1,2-a]pyrazines as potent Aurora kinase inhibitors. Bioorg Med Chem Lett 21:592–598

70. Chauvin A, Greiner J, Pastor R, Cambon A (1986) A facile synthesis of aromatic trifluoromethyl compounds via orthothio esters. Tetrahedron 42:663–668
71. Sosnovskikh VYa, Barabanov MA, Usachev BI, Irgashev RA, Moshkin VS (2005) Synthesis and some properties of 6-di(tri)fluoromethyl- and 5-di(tri)fluoroacetyl-3-methyl-1-phenylpyrano[2,3-*c*]pyrazol-4(1*H*)-ones. Russ Chem Bull (Engl Transl) 54:2846–2850
72. Hu S, Huang Y, Poss MA, Gentles RG (2005) A novel route to the 5,6-dihydro-4H-thieno[3,2-b]pyrrol-5-one ring system involving an intermediate substituted-thiophene synthesis. J Heterocyclic Chem 42:661–667
73. Fernandez MC, Castaño A, Dominguez E, Escribano A, Jiang D, Jimenez A, Hong E, Hornback WJ, Nisenbaum ES, Rankl N, Tromiczak E, Vaught G, Zarrinmayeh H, Zimmerman DM (2006) A novel class of AMPA receptor allosteric modulators. Part 1: design, synthesis, and SAR of 3-aryl-4-cyano-5-substituted-heteroaryl-2-carboxylic acid derivatives. Bioorg Med Chem Lett 16:5057–5061
74. Alvernhe GM, Greif D, Laurent AJ, Pulst M, Weissenfels M (1995) Reactivity of β-trifluoromethyl β-thioacrolein with various electrophiles. J Fluor Chem 70:121–125
75. Greif D, Eilitz U, Pulst M, Riedel D, Wecks M (1999) Perfuoralkylsubstituierte β-Chlorvinylaldehyde: eine neue Klasse von building blocks zur Synthese fluorierter Heterocyclen. J Fluor Chem 94:91–103
76. Nocentini T, Brulé C, Bouillon JP, Gouault-Bironneau S, Portella C (2007) Fluoride-induced coupling of perfluoroketene dithioacetals with silyl alkynes: a way towards new polyfunctionalized trifluoromethyl building blocks. J Fluor Chem 128:1300–1305
77. Obrecht D, Gerber F, Sprenger D, Masquelin T (1997) A novel approach towards 2,3,5-trisubstituted thiophenes *via* tandem Michael addition/intramolecular Knoevenagel condensation. Helv Chim Acta 80:531–537
78. Kovregin AN, Sizov AY, Ermolov AF (2002) Synthesis of substituted thiophenes based on fluorine-containing β-functionalized vinyl sulfides. Russ Chem Bull (Engl Transl) 51:1028–1030
79. Liebscher J, Feist K (1985) Formylation products of thioamides; Part 11. A novel route to substituted 2-aminothiophenes by the reaction of S-alkylated thioamides with carboxylic acid derivatives. Synthesis 1985:412–414
80. Bartnik R, Bensadat A, Cal D, Faure R, Khatimi N, Laurent A, Laurent É, Rizzon C (1997) Réactivité des trifluorométhylénaminocéones. Synthèse de nouveaux trifluorométhylpyrroles. J Bull Soc Chim Fr 134:725–734
81. Meazza G, Zanardi G, Guglielmetti G, Piccardi P (1997) Synthesis of 2,3,5-triaryl-4-trifluoromethyl thiophenes. J Fluor Chem 82:175–180
82. Briscoe MW, Chambers RD, Mullins SJ, Nakamura T, Drakesmith FG (1990) A synthesis of novel perfluorodienes. J Chem Soc Chem Comm 1990:1127–1128
83. (a) Briscoe MW, Chambers RD, Mullins SJ, Nakamura T, Vaughan JFS (1994) Reactions involving fluoride ion. Part 39. Reactions of perfluorinated dienes with oxygen and sulphur nucleophiles. J Chem Soc Perkin Trans 1:3119–3124; (b) Chambers RD, Vaughan JFS, Mullins SJ, Nakamura T, Roche AJ (1995) Fluorinated di-enes. J Fluor Chem 72:231–233
84. (a) Chambers RD, Jones CGP, Silvester MJ, Speigt DB (1984) Reactivite des hydryl-1 F-alcynes et des F-alkynyl-2 esters: synthese et etudes spectroscopiques de nouveaux F-alkyl pyrazoles. J Fluorine Chem 25:47–56; (b) Verkoczy B, Sherwood AG, Safarik I, Strausz OP (1983) Thiirene formation in the reactions of sulfur atoms with alkynes. Can J Chem 61:2268–2281

85. (a) Krespan CG (1961) Bis(polyfluoroalky1)acetylenes. IV. Fluorinated dithietenes and related heterocyclic compounds from bis(polyfluoroalky1)acetylenes and sulfur. J Am Chem Soc 83:3434–3437; (b) Krespan CG, McKusick BC (1961) Bis-(polyfluoroalky1)-acetylenes. V. Addition of Bis(trifluoromethyl)-1,2-dithietene to olefins and acetylenes. J Am Chem Soc 83:3438–3440
86. (a) Haas A, Krächter HU (1988) Darstellung und Reaktionen Trifluormethylchalkogenyl-substituierter Alkine. Chem Ber 121:1833–1840; (b) Haas A, Klare C, Krächter HU (1985) (Perhalogenmethyltio)heterocyclen. XIX. Darstellung und Eigenschaften von Tetrakis(trifluormethylthio)thiophen, Tetrakis(trifluormethylthio-1,2-dithiin, 2,3,4-Tris(trifluormethylthio)-5-trifluormethyl-thiophen und 1-Chlor-terakis(trifluormethylthio)pyrrol. J Heterocycl Chem 22:1631–1633; (c) Lorance ED, Glass RS, Block E, Li X (2003) Synthesis, electrochemistry, and gas-phase photoelectron spectroscopic and theoretical studies of 3,6-bis(perfluoroalkyl)-1,2-dithiins. J Org Chem 68:8110–8114
87. (a) Kobayashi Y, Kawada K, Ando A, Kumadaki I (1984) Photoisomerization of bis(trifluoromethyl)thiophenes. Tetrahedron Lett 25:1917–1920; (b) Kobayashi Y, Kawada K, Ando A, Kumadaki I (1983) Photoisomerization of trifluoromethylated thiophenes. Heterocycles 20:174
88. Thalhammer F, Wallfahrer U, Sauer J (1988) 1,3,4-Oxadiazole als Heterocyclische 4π-Komponenten in Diels-Alder-Reaktionen. Tetrahedron Lett 29:3231–3234
89. Potts KT, Houghton E, Singh UP (1974) Mesoionic compounds. XXXI. The preparation and cycloaddition reactions of the *anhydro*-4-hydroxythiazolium hydroxide system with acetylenic dipolarophiles. J Org Chem 39:3627–3630
90. Schiauzer GN, Mayweg VP (1965) Preparation, reactions, and structure of bisdithio-α-diketone complexes of nickel, palladium, and platinum. J Am Chem Soc 87:1483–1489
91. Akiyama T, Kato K, Kajitani M, Sakagughi Y, Nakamura J, Hayashi H, Sugimori A (1988) Photochemical trifluoromethylation of some aromatic and heteroaromatic compounds with trifluoromethyl bromide. Bull Chem Soc Jpn 61:3531–3537
92. Matthews DP, Whitten JP, McCarthy JR (1986) A facile synthesis of aromatic trifluoromethyl compounds via orthothio esters. Tetrahedron Lett 27:4861–4864
93. (a) Chu L, Qing FL (2010) Copper-mediated oxidative trifluoromethylation of boronic acids. Org Lett 12:5060–5063; (b) Senecal TD, Parsons AT, Buchwald SL (2011) Room temperature aryl trifluoromethylation via copper-mediated oxidative cross-coupling. J Org Chem 76:1174–1176; (c) Jiang X, Chu L, Qing FL (2012) Copper-catalyzed oxidative trifluoromethylation of terminal alkynes and aryl boronic acids using (trifluoromethyl)trimethylsilane. J Org Chem 77:1251–1257
94. Xu J, Luo DF, Xiao B, Liu ZJ, Gong TJ, Fu Y, Liu L (2011) Copper-catalyzed trifluoromethylation of aryl boronic acids using a CF_3^+ reagent. Chem Comm 47:4300–4302
95. (a) Liu T, Shen Q (2011) Copper-catalyzed trifluoromethylation of aryl and vinyl boronic acids with an electrophilic trifluoromethylating reagent. Org Lett 13:2342–2345; (b) Liu T, Shao X, Wu Y, Shen Q (2012) Highly selective trifluoromethylation of 1,3-disubstituted arenes through iridium-catalyzed arene borylation. Angew Chem Int Ed 51:540–543
96. (a) Okada E, Masuda R, Hojo M, Imazaki N, Miya H (1992) Reactions of tetrakis(trifluoromethyl)dewar thiophene. Heterocycles 34:103–110; (b) Owton WM (2003) Synthesis of substituted 3-trifluoromethylbenzo[*b*]thiophenes. Tetrahedron Lett 44:7147–7149; (c) Iaroshenko VO, Erben F, Mkrtchyan S, Hakobyan A, Vilches-Herrera M, Dudkin S, Bunescu A, Villinger A, Sosnovskikh VYa, Langer P (2011) 4-Chloro-3-(trifluoroacetyl)- and 4-chloro-3-(methoxalyl)coumarins as novel and efficient building blocks for the regioselective synthesis of 3,4-fused coumarins. Tetrahedron 67:7946–7955
97. (a) Nenajdenko V, Gribkov D, Sumerin V, Balenkova E (2003) A novel synthesis of dithieno[2,3-*b*:3′,2′-*d*]thiophene and its bromo derivatives. Synthesis, 124–128; (b) Nenajdenko VG, Sumerin VV, Chernichenko KYu, Balenkova ES (2004) A new route to annulated oligothiophenes. Org Lett 20:3437–3439; (c) Chernichenko KYu, Balenkova ES, Nenajdenko VG (2008) From thiophene to Sulflower. Mendeleev Comm 18:171–179

98. Krayushkin MM, Stoyanovich FM, Zolotarskaya OYu, Murav'ev IV, Martynkin AYu, Vorontsova LG, Starikova ZA, Ivanov VL, Uzhinov BM (2001) Photochromic dihetarylethenes. 6. Photochromic derivatives of thieno[3,2-*b*]thiophene. Russ Chem Bull (Engl Transl) 50:110–115
99. Baraznenok IL, Nenajdenko VG, Balenkova ES (2000) Chemical transformations induced by triflic anhydride. Tetrahedron 56:3077–3119
100. (a) Nenajdenko VG, Vertelezkij PV, Balenkova ES (1996) Activation of sulfoxides with triflic anhydride. Synthesis of dialkylaryl sulfonium salts and sulfur heterocycles. Sulfur Lett 20:75–84; (b) Nenajdenko VG, Vertelezkij PV, Koldobskij AB, Alabugin IV, Balenkova ES (1997) J Org Chem 62:2483–2486; (c) Nenajdenko VG, Vertelezkij PV, Gridnev ID, Shevchenko NE, Balenkova ES (1997) Reaction of dimethyl sulfide ditriflate with alkenes. Synthesis of sulfur derivatives of nortricyclane. Tetrahedron 53:8173–8180; (d) Shevchenko NE, Karpov AC, Zakurdaev EP, Nenajdenko VG, Balenkova ES (2000) Synthesis of methylthio-substituted heterocycles using the complex of trifluoromethanesulfonic anhydride with dimethyl sulfide. Chem Het Comp (Engl Transl) 137–143; (e) Nenajdenko VG, Shevchenko NE, Balenkova ES, Alabugin IV (2003) 1,2-Dications in organic main group systems. Chem Rev 131:229–282; (f) Shevchenko NE, Nenajdenko VG, Balenkova ES (2003) Triflic anhydride-promoted cyclization of sulfides: a convenient synthesis of fused sulfur heterocycles. Synthesis 1191–2001; (g) Nenajdenko VG, Balenkova ES (2003) New synthetic capabilities of sulfonium salts. Rus J Org Chem (Engl Transl) 39:291–330; (h) Nenajdenko VG, Vertelezkij PV, Balenkova ES (1997) Synthesis of β-dimethylsulfonium- and β-methylthio-substituted vinyl triflates by reaction of acetylenes with dimethyl sulfide ditriflate. Synthesis 351–355
101. Yoshida S, Yorimitsu H, Oshima K (2007) Synthesis of benzo[*b*]thiophenes by cyclization of arylketene dithioacetal monoxides under Pummerer-like conditions. Org Lett 9:5573–5576
102. Sun LL, Deng CL, Tang RY, Zhang XG (2011) CuI/TMEDA-catalyzed annulation of 2-bromo alkynylbenzenes with Na_2S: synthesis of benzo[*b*]thiophenes. J Org Chem 76:7546–7550
103. Ochiai K, Takita S, Eiraku T, Kojima A, Iwase K, Kishi T, Fukuchi K, Yasue T, Adams DR, Allcock RW, Jiang Z, Kohn Y (2012) Phosphodiesterase inhibitors. Part 3: design, synthesis and structure-activity relationships of dual PDE3/4-inhibitory fused bicyclic heteroaromatic-dihydropyridazinones with anti-inflammatory and bronchodilatory activity. Bioorg Med Chem 20:1644–1658
104. Matano Y, Miyajima T, Fukushima T, Kaji H, Kimura Y, Imahori H (2008) Comparative study of the synthesis, structures, and optical and electrochemical properties of bithiophene-fused benzo[*c*]phospholes. Chem Eur J 14:8102–8115
105. Crouch DJ, Skabara PJ, Heeney M, McCulloch I, Coles SJ, Hursthouse MB (2005) Hexyl-substituted oligothiophenes with a central tetrafluorophenylene unit: crystal engineering of planar structures for p-type organic semiconductors. Chem Comm 2005:1465–1467
106. Dua SS, Howells RD, Gilman H (1974) Reactions of hexafluorobenzene with some organometallic reagents. J Fluor Chem 4:381–386
107. Geramita K, McBee J, Tilley TD (2009) 2,7-Substituted hexafluorohetero-fluorenes as potential building blocks for electron transporting materials. J Org Chem 74:820–829
108. (a) Yoon MH, Facchetti A, Stern CE, Marks TJ (2006) Fluorocarbon-modified organic semiconductors: molecular architecture, electronic, and crystal structure tuning of arene-versus fluoroarene-thiophene oligomer thin-film properties. J Am Chem Soc 128:5792–5801; (b) Casado J, Hernández V, Ruiz Delgado MC, Ortiz RP, López Navarrete JT, Facchetti A, Marks TJ (2005) Incisive structure-spectroscopic correlation in oligothiophenes functionalized with (±) inductive/mesomeric fluorine groups: joint Raman and DFT study. J Am Chem Soc 127:13364–13372
109. (a) Cho DM, Parkin SR, Watson MD (2005) Partial fluorination overcomes herringbone crystal packing in small polycyclic aromatics. Org Lett 7:1067–1068; (b) Facchetti A, Yoon MH, Stern CE, Katz HE, Marks TJ (2003) Building blocks for n-type organic electronics: regiochemically modulated inversion of majority carrier sign in perfluoroarene-modified polythiophene semiconductors. Angew Chem Int Ed 42:3900–3903; (c) Chen MC, Kim C,

Chen SY, Chiang YJ, Chung MC, Facchetti A, Marks TJ (2008) Functionalized anthradithiophenes for organic field-effect transistors. J Mater Chem 18:1029–1036; (d) Chernichenko KYu, Sumerin VV, Shpanchenko RV, Balenkova ES, Nenajdenko VG (2006) "Sulflower": a new form of carbon sulfide. Angew Chem Int Ed 45:7367–7370; (e) Dadvand A, Cicoira F, Chernichenko KYu, Balenkova ES, Osuna RM, Jolin VH, Rosei F, Nenajdenko VG, Perepichka DF (2008) Heterocirculenes as a new class of organic semiconductors. Chem Comm 2008:5354–5356

110. (a) Morimoto M, Kobatake S, Irie M (2003) Aryl-perfluoroaryl interaction in photochromic diarylethene crystals. Cryst Growth Des 3:847–854; (b) Takimiya K, Niihara N, Otsubo T (2005) Syntheses of 2-(pentafluorophenyl)thiophene derivatives via the palladium-catalyzed Suzuki reaction. Synthesis 2005:1589–1592
111. Shang R, Xu Q, Jiang YY, Wang Y, Liu L (2010) Pd-catalyzed decarboxylative cross coupling of potassium polyfluorobenzoates with aryl bromides, chlorides, and triflates. Org Lett 12:1000–1003
112. Shang R, Fu Y, Wang Y, Xu Q, Yu HZ, Liu L (2009) Copper-catalyzed decarboxylative cross-coupling of potassium polyfluorobenzoates with aryl iodides and bromides. Angew Chem Int Ed 48:9350–9354
113. Do HQ, Daugulis O (2008) Copper-catalyzed arylation and alkenylation of polyfluoroarene C-H bonds. J Am Chem Soc 130:1128–1129
114. Lafrance M, Shore D, Fagnou K (2006) Mild and general conditions for the cross-coupling of aryl halides with pentafluorobenzene and other perfluoroaromatics. Org Lett 8:5097–5100
115. Do HQ, Daugulis O (2009) Copper-catalyzed arene C–H bond cross-coupling. Chem Comm 2009:6433–6435
116. Arai N, Miyaoku T, Teruya S, Mori A (2008) Synthesis of thiophene derivatives via palladium-catalyzed coupling reactions. Tetrahedron Lett 49:1000–1003
117. Wang Y, Watson MD (2006) Transition-metal-free synthesis of alternating thiophene-perfluoroarene copolymers. J Am Chem Soc 128:2536–2537
118. Choi KS, Akiyama I, Hoshino M, Nakayama J (1993) A convenient synthesis of 1,2-dithietes and 1,2-dithioxo compounds stabilized by buttressing and resonance effects, respectively, by sulfuration of alkynes and elemental sulfur. Bull Chem Soc Jpn 66:623–629
119. Johnson SA, Liu FQ, Suh MC, Zürcher S, Haufe M, Mao SSH, Tilley TD (2003) Regioselective coupling of pentafluorophenyl substituted alkynes: mechanistic insight into the zirconocene coupling of alkynes and a facile route to conjugated polymers bearing electron-withdrawing pentafluorophenyl substituents. J Am Chem Soc 125:4199–4211
120. (a) Takimiya K, Kunugi Y, Konda Y, Niihara N, Otsubo T (2004) 2,6-Diphenylbenzo[1,2-b:4,5-*b′*]dichalcogenophenes: a new class of high-performance semiconductors for organic field-effect transistors. J Am Chem Soc 126:5084–5085; (b) Takimiya K, Kunugi Y, Ebata H, Otsubo T (2006) Molecular modification of 2,6-diphenylbenzo[1,2-*b*:4,5-*b′*]dichalcogenophenes by introduction of strong electron-withdrawing groups: conversion from p- to n-channel OFET materials. Chem Lett 35:1200–1201
121. Wang Y, Parkin SR, Watson MD (2008) Benzodichalcogenophenes with perfluoroarene termini. Org Lett 10:4421–4424
122. Brooke GM, Cooperwaite JR (1985) Partially fluorinated heterocyclic compounds. Part 21. Isomerisations of pentafluorophenyl and 1,3,4,5,6,7,8-heptafluoro-2-naphthyl prop-2-ynyl sulphides: differing courses of reactions of the naphthyl sulphides and ethers in glass and nickel apparatus. Considerations of mechanism. J Chem Soc Perkin Trans 1:2643–2649
123. Brooke GM, Mawson SD (1990) Partially fluorinated heterocyclic compounds. Part 27. The synthesis of 4,5,6,7-tetrafluorobenzo[*c*]thiophene and 4,5,6,7,8,9-hexafluoronaphtho[1,2-*c*] thiophene; some chemistry and electrochemistry. J Chem Soc Perkin Trans 1:1919–1923
124. Brooke GM, Quasem MA (1967) Partially fluorinated heterocyclic compounds. Part II. The preparation of 4,5,6,7-tetrafluorobenzo[*b*]thiophen by a new cyclisation reaction. J Chem Soc C 865–869

125. Brooke GM, Quasem MA (1973) Partially fluorinated heterocyclic compounds. Part XI. The reactions of lithium pentafluorobenzenethiolate with acetylenic compounds giving benzo[*b*] thiophen derivatives and/or olefins. J Chem Soc Perkin Trans 1:429–432
126. (a) Brooke GM (1989) Partially fluorinated heterocyclic compounds. Part 26. An investigation into the mode of cyclization in the reaction of lithium 1,3,4,5,6,7,8-heptafluoro-2-naphthalenethiolate with dimethyl acetylenedicarboxylate. J Fluorine Chem 43:393–403; (b) Brooke GM, Drury CJ (1994) Partially fluorinated heterocyclic compounds. Part 30. Cyclisation reactions of lithium 1,3,4,5,7,8-hexafluoro-6-isoquinolinethiolate and lithium 2,3,5,6,7,8-hexafluoro-4-quinolinethiolate with dimethyl acetylene dicarboxylate. J Fluor Chem 67:143–147

Fluorinated Pyrazoles and Indazoles

Santos Fustero, Antonio Simón-Fuentes, Oscar Delgado, and Raquel Román

Contents

S. Fustero (✉)
Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain

Laboratorio de Moléculas Orgánicas, Centro de Investigación Príncipe Felipe, E-46012 Valencia, Spain
e-mail: fustero@uv.es

A. Simón-Fuentes • R. Román
Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain

O. Delgado
Neuroscience Medicinal Chemistry Department, Janssen Research and Development, E-45007 Toledo, Spain

V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_7,

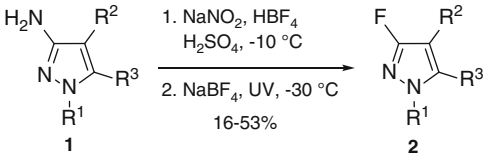
Abstract The synthesis of fluorine containing pyrazoles has been boosted in the past decades due to the interesting properties that confer these building blocks in pharmaceutical and agricultural active ingredients. There are two main methods for the synthesis of fluorine-containing organic compounds, namely, the direct replacement of an atom or functional group such as diazo, hydroxyl, halogen or hydrogen by fluorine, and the modification of fluorine-containing building blocks. In the case of fluorinated pyrazoles the latter approach is the most commonly applied. This chapter deals primarily with the pivotal procedures that allow the preparation of fluoro- and fluoroalkyl- pyrazoles. Their benzocondensed derivatives, indazoles, have been studied to a much lesser extent. The fundamental applications of this class of compounds in different fields are also discussed.

Keywords Pyrazole • Indazole • Fluorine • Synthesis

1 Synthesis of 3-/5-Fluoropyrazoles

1.1 By Nucleophilic Substitution Reactions

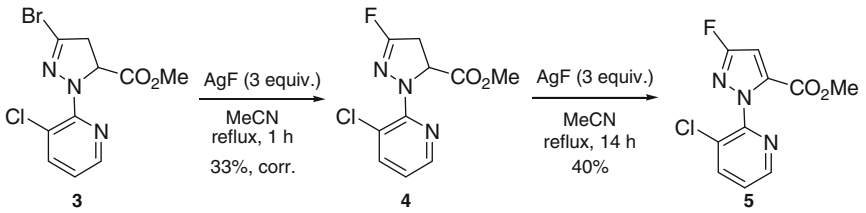
The Balz-Schiemann photolytic dediazoniation of pyrazolodiazonium salts using ultraviolet irradiation at low temperature, in the presence of tetrafluoroboric acid, was used in order to obtain 3-/5-fluoropyrazole derivatives **2** [1]. Although poor yields were observed in general (Scheme 1), the presence of an electron-withdrawing group at the C-4 (R^2=NO_2) improved the process significantly [1c].



R^1 = H, Me; R^2 = H, NO_2; R^3 = H, F

Scheme 1

Halogen exchange has been the most widely used process for fluorine incorporation at C-3 and C-5 of the pyrazole ring. For instance, bromine-fluorine exchange in the 3-bromopyrazoline **3** was described as an alternative approach for the preparation of the 3-fluoropyrazole derivative **5**, a precursor of insecticidal fluorinated anthranilic diamides [2]. Silver fluoride was used as both fluorine source and oxidation reagent of the pyrazoline ring (Scheme 2).

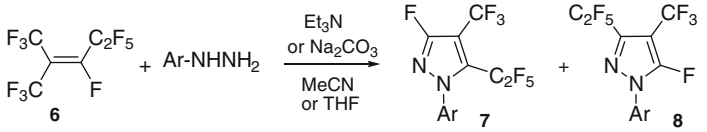


Scheme 2

Chlorine-fluorine exchange was mentioned in some patents as the most adequate procedure for C-5 fluorination [3]. In all cases, KF was employed as fluorine source, and reaction mixtures were warmed from 100 to 200 °C for many hours. The presence of an electron-withdrawing substituent such as a carbonyl group at C-4 seems to facilitate the progress of the reaction.

1.2 Using Fluorinated Building Blocks

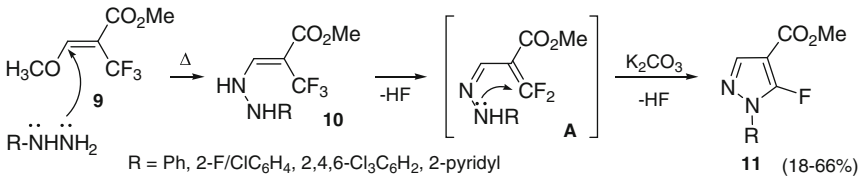
It has been reported that condensation of perfluoro-2-methyl-2-pentene **6** with hydrazones [4], arylhydrazines and propionylhydrazine [5] in basic media (Na_2CO_3 or Et_3N), lead to 5-fluoropyrazole derivatives as single products in good to excellent yield. However, a study carried out by Furin and co-workers [6] using **6** and a variety of arylhydrazines, in the presence of triethylamine, showed that, in all cases, mixtures of 3- and 5-fluoropyrazole derivatives **7** and **8** (Scheme 3) were obtained. The regioisomeric ratios were dependent on the reaction conditions and arylhydrazine used. Two different reaction pathways were proposed for explaining these results.



Ar = Ph, 2-/4-$O_2NC_6H_4$, 2,4-$(O_2N)_2C_6H_3$, F_5C_6, 4-CF_3-2,3,5,6-F_4C_6

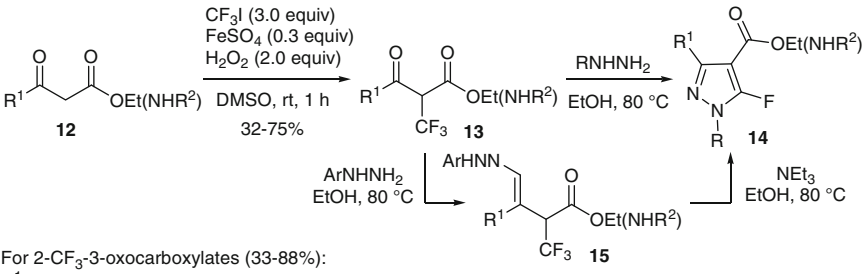
Scheme 3

On the other hand, condensation of methyl 3-methoxy-2-(trifluoromethyl) acrylate **9** with arylhydrazines under weakly basic conditions allowed the synthesis of methyl 1-aryl-5-fluoropyrazole-4-carboxylates **11** (Scheme 4); the lower yields were obtained with arylhydrazines bearing electron-withdrawing substituents [7]. The process involves hydrogen fluoride elimination followed by intramolecular nucleophilic addition from the 3-hydrazinoacrylates **10** previously formed. When alkylhydrazines were employed, no heterocyclic compounds were isolated.



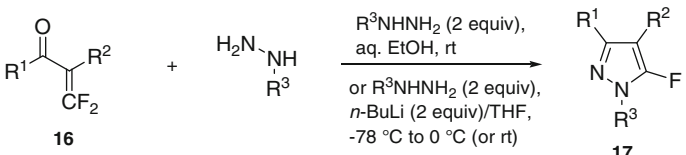
Scheme 4

Similar to **A** intermediates (Scheme 4) were proposed to explain the formation of 1,3-disubstituted 5-fluoropyrazole-4-carboxylates (or carboxamides) **14** from 2-(trifluoromethyl)-3-oxo-carboxylates (or carboxamides) **13** and alkyl(aryl) hydrazines (Scheme 5). Trifluoromethylcarboxylates and carboxamides were prepared in moderate yield by trifluoromethylation of 3-oxocarboxylates and carboxamides **12** with CF_3I in the presence of the Fenton reagent [8]. Treatment of **13** with arylhydrazines in EtOH at 80 °C yielded 3-(arylhydrazono)-2-(trifluoromethyl)carboxylate(carboxamide) intermediates **15** as the only isolated products. These were then converted into the products **14** by treatment with NEt_3. The 5-fluoropyrazoles were directly obtained from intermediates **13** with the more nucleophilic alkylhydrazines. This approach is highly versatile and more simple than the previously reported procedures for the preparation of fungicides with a 5-fluoropyrazole-4-carboxamide framework [3].



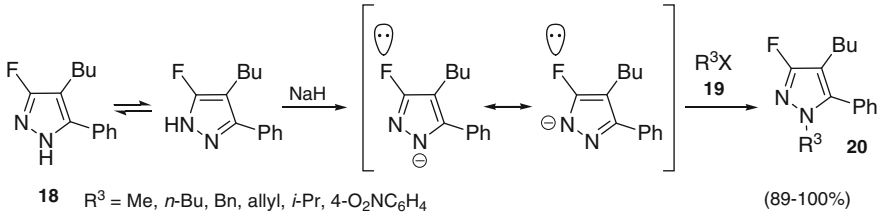
Scheme 5

An alternative method for the synthesis of 5-fluoropyrazoles is depicted in Scheme 6. The target molecules **17** were obtained in high yields (76–95 %) and excellent regioselectivities (96/4-100/0) upon condensing 2,2-difluorovinyl ketones **16** with alkyl and arylhydrazines [9]. Reactions with alkylhydrazines occurred in aqueous ethanol at rt whereas, with arylhydrazines, the use of *n*-butyllithium was requisite to generate the anion of the hydrazine (Scheme 6).



Scheme 6

The fluorine atom has been also employed as a directing group for the alkylation of *N*-unsubstituted pyrazoles [9]. In this context, Ichikawa and co-workers have shown that treatment of 4-butyl-3-fluoro-5-phenylpyrazole **18** with a strong base followed by the addition of a variety of electrophiles **19** leads to the more hindered 1-alkyl-5-phenylpyrazole isomers **20** in excellent yields, and regioselectivities up to 90/10. In contrast, there is no regiocontrol in the *N*-alkylation of the fluorine-free pyrazole analogue. These results revealed that the site of the electrophilic attack in the deprotonated pyrazole was governed by the repulsive interaction between the lone pair of the fluorine atom and the negative charge on the nitrogen closer to the fluorine (Scheme 7).



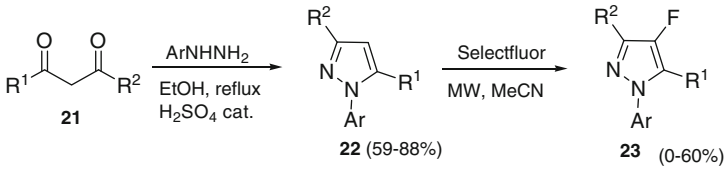
Scheme 7

2 Synthesis of 4-Fluoropyrazoles

2.1 By Fluorination of the Pyrazole Ring

The 4-position of the pyrazole ring is the most nucleophilic and readily undergoes electrophilic substitution. Nevertheless, the direct fluorination at this position is often a difficult task because of the high reactivity of the pyrazole ring toward electrophiles and the high oxidative properties of the electrophilic fluorinating reagents. Elemental fluorine either in acetic acid [10], or diluted in nitrogen [11], has been employed for the C-4 fluorination of 3-alkoxycarbonylpyrazoles in up to 52 % yield. Selectfluor® is the most extensively used electrophilic fluorinating agent for this purpose. Several 3,5-substituted pyrazole carboxylates, intermediates in the synthesis of potentially pharmacological active molecules, were fluorinated at C-4 with this reagent in refluxing acetonitrile in poor to moderate yield [12].

More recently, a study on the influence of the substituents in the reactivity of 1-aryl-3,5-substituted pyrazoles **22** in microwave-mediated fluorinations with Selectfluor® at C-4 of the pyrazole ring was reported [13]. In general, deactivated pyrazoles were unreactive or gave lower yields than more electron-rich derivatives (Scheme 8). Moreover, side products derived from fluorination of aryl or methyl substituents at N-1 and C-3 were isolated. Noteworthy, this was not the case at C-5, probably due to the steric interference between the substituent and the fluorine source. Results were compared with those obtained via C-2 fluorination of 1,3-diketones **21** followed by *in situ* condensation with arylhydrazines (see below).



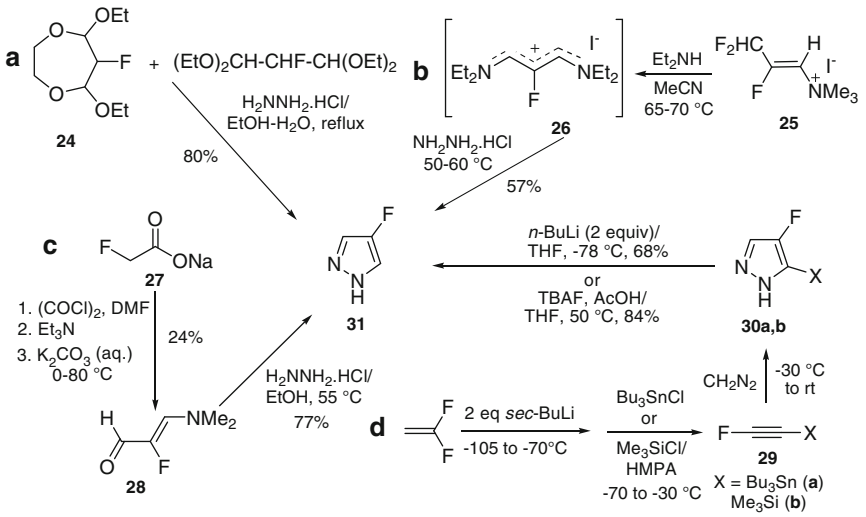
R^1	R^2	Ar	Yield (%)
Me	Me	Ph	60
Me	4-$O_2NC_6H_4$	Ph	40
Me	CF_3	Ph	40
Ph	CF_3	Ph	0
Me	CH_3	4-$O_2NC_6H_4$	49
Me	CF_3	4-$O_2NC_6H_4$	13
Me	Me	2,4-$(O_2N)_2C_6H_3$	30
Me	Me	4-$MeOC_6H_4$	20
Ph	Me	4-$MeOC_6H_4$	53
CF_3	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	0

Scheme 8

2.2 *Using Fluorinated Building Blocks*

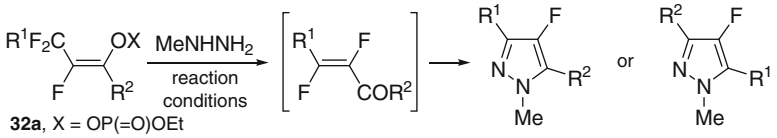
The synthesis of 4-fluoropyrazole (**31**) has been described by several authors. The condensation of either **24** [14] (Scheme 9a) or **26** [15] (Scheme 9b) with hydrazine hydrochloride led to the target compound in 80 % and 57 % yield, respectively. Starting from sodium fluoroacetate (**27**), **31** was obtained through a four-step sequence in 19 % overall yield [16]. More recently, a modification of this procedure allowed the preparation of this compound in only two steps and with identical overall yield (Scheme 9c) [17]. On the other hand, Hanamoto and co-workers [18] obtained pyrazole **31** by either *n*-BuLi-destannylation of **30a** (X=Bu_3Sn) or TBAF-desilylation of 4-fluoro-5-trimethylsilylpyrazole **30b** (X=Me_3Si), in 68 % and 84 %, respectively. Precursors **30** were obtained by 1,3-dipolar cycloadditions of diazomethane with *in situ* prepared fluoro(tributylstannyl)- or fluoro(trimethylsilyl) acetylene **29** (Scheme 9d). 4-Fluoro-1-methylpyrazole was also prepared in 90 % yield by condensation between β-fluorovinamidinium iodide and methylhydrazine [15]. By contrast, diazotization of 4-amino-1-metylpyrazole followed by

photochemical irradiation of the diazonium salt in tetrafluoroboric acid yielded the same compound but in poor yield (8 %) [1a].



Scheme 9

The cyclocondensation between fluorinated 1,3-dielectrophilic compounds and hydrazines has been the pivotal methodology employed for the preparation of 4-fluoropyrazole derivatives. 2,3,3-Trifluoroalkenyl phosphates **32a** [19], sulfonates **32b** [20] and silyloxy derivatives **32c** [21], synthetic equivalents of 2,3-difluoroalkenyl ketones, were used by some authors as fluorinated building blocks for the regioselective synthesis of fluoropyrazoles **33a-c** (Scheme 10). Reactions could be carried out in the presence of a base or an excess of hydrazine to neutralize the hydrogen fluoride generated in the process. This approach was applied to the synthesis of polyfluorinated homo-*C*-nucleoside analogues [22].



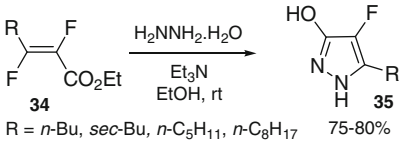
32a, X = OP(=O)OEt
32b, X = Ts
32c, X = SiR'2R''

reaction conditions: **32a**: THF, rt, 10-14 h; **32b**: TBAF, DMSO, 70 °C, 1 h; **32c**: Et_2O, rt

R^1	R^2	**33a** (%)	R^1	R^2	**33b** (%)	R^1	R^2	**33c** (%)
CF_3	$CH_3(CH_2)_5$	91	H	H	71	C_2F_5	Ph	95
CF_3	Ph	82	H	Ph	88	C_2F_5	4-ClC_6H_4	94
CF_3	*c*-C_6H_{11}	90	H	4-$MeOC_6H_4$	83	C_2F_5	4-FC_6H_4	89
CF_3	$CH_3(CH_2)_2$	90	H	4-$EtO_2CC_6H_4$	86	C_2F_5	4-$MeOC_6H_4$	97
						C_2F_5	*n*-C_5H_{11}	67

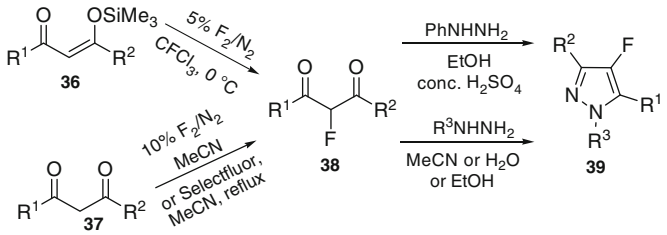
Scheme 10

In a similar fashion, ethyl 3-alkyl-*trans*-2,3-difluoro-2-acrylates **34** underwent a Michael addition with hydrazine monohydrate in the presence of triethylamine affording 5-alkyl-3-hydroxy-4-fluoropyrazoles **35** in good yield (Scheme 11) [23].



Scheme 11

2-Fluorinated-1,3-dicarbonyl and related compounds have been extensively used as fluorinated building blocks in the synthesis of 4-fluoropyrazoles. These substrates were prepared by electrophilic fluorination of the corresponding β-dicarbonyl precursors. Thus, treatment of silyl enol ethers of trifluoromethyl-1,3-diketones **36** and 1-phenyl-1,3-butanedione **37** with 5 % F_2 in N_2 allowed the synthesis of 2-fluoro-1,3-diketones **38**, that were isolated and subsequently condensed with phenylhydrazine in the presence of concentrated sulphuric acid. As a result, 4-fluoro-3-trifluoromethyl(methyl)pyrazole derivatives **39** were isolated as exclusive regioisomers in good yield (Scheme 12) [24]. Recently, this approach was adapted into a single, sequential telescoped two-step continuous gas/liquid-liquid/liquid flow process involving direct fluorination (10 % F_2 in N_2 in MeCN) in the first stage and subsequent condensation with hydrazines (Scheme 12) [25]. The hydrazine was added to the continuous flow process dissolved in acetonitrile, water or ethanol depending on the solubility of the hydrazine derivative. Alternatively, Sloop and co-workers [13] obtained 1-aryl-4-fluoropyrazole analogues **39** (R^3=Ar) by selective fluorination of 1,3-diketones **37** with Selectfluor®, followed by *in situ* condensation of the resulting 2-fluoro-β-diketones **38** with arylhydrazines (Scheme 12). The cyclization was catalyzed by the ammonium salt byproduct of the fluorination. This strategy precluded the occurrence of side reactions; no fluorination of alkyl or aryl groups was observed.

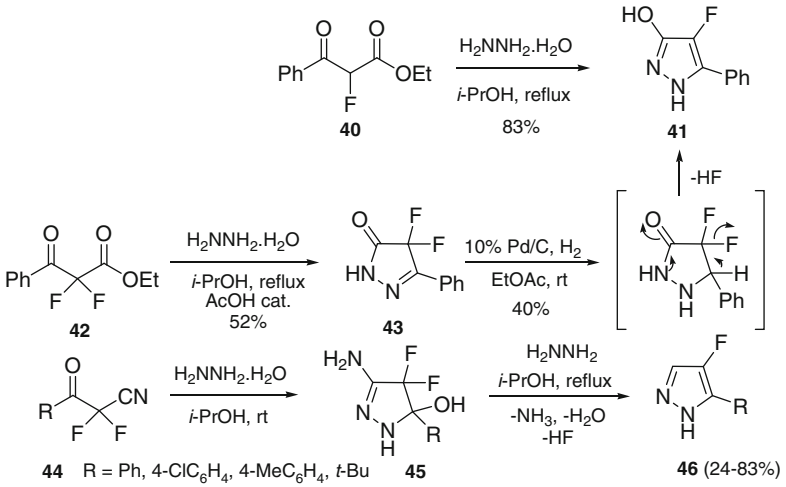


R^1	R^2	R^3	(%)[a]	R^1	R^2	R^3	(%)[b]	R^1	R^2	R^3	(%)[c]
Me	CF_3	Ph	86	Me	Me	H	77	Me	CF_3	Ph	60
Et	CF_3	Ph	70	Me	Me	Me	83	Me	4-$O_2NC_6H_4$	Ph	50
i-Pr	CF_3	Ph	71	Me	Me	Ph	72	Me	Me	Ph	55
t-Bu	CF_3	Ph	68	Et	Et	H	72	Ph	CF_3	Ph	56
CF_3	CF_3	Ph	69	Me	*t*-Bu	H	71	Me	CF_3	4-$O_2NC_6H_4$	40
Ph	CF_3	Ph	70	*t*-Bu	*t*-Bu	H	74	Me	Me	4-$MeOC_6H_4$	70
Ph	Me	Ph	74	Me	Ph	H	69	Ph	Me	4-$MeOC_6H_4$	55
								CF_3	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	45

[a] Yield from ref. 24. [b] Yield from ref. 25. [c] Yield from ref. 13

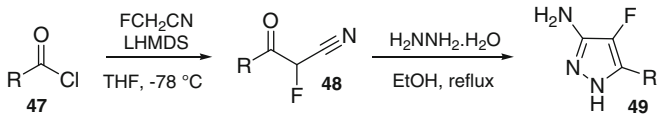
Scheme 12

De Kimpe and co-workers [26] synthesized 4-fluoro-3-hydroxy-5-phenylpyrazole **41** by condensation of ethyl benzoylfluoroacetate **40**, or ethyl benzoyldifluoroacetate **42**, with hydrazine in refluxing *i*-PrOH. While starting from monofluorinated **40**, the product **41** was formed in 83 % yield, the condensation using the difluorinated **42** led to the formation of pyrazolone **43**. The target product **41** could be then obtained by hydrogenation of **43** via a pyrazolidin-3-one intermediate, which readily underwent dehydrofluorination. Surprisingly, when this strategy was applied to the synthesis of the 3-amino analogue by condensation of benzoyldifluoroacetonitrile **44** with hydrazine, the deaminated 4-fluoro-5-phenylpyrazole **46** (R=Ph) was isolated. Similar results were obtained starting from other 2,2-difluoro-3-oxopropanenitriles **44** (Scheme 13).



Scheme 13

Some 3-amino-4-fluoropyrazoles **49** have been used to synthesize compounds with potential application in medicinal chemistry and agrochemistry. Although procedures for fluorination of the pyrazole ring of aminopyrazoles using fluorinating agents have been reported, such reactions suffer from low applicability and poor yields. Recently, Cocconcelli and co-workers [27] synthesized a small set of compounds **49** by condensation of alkanoyl- and arylfluorobenzonitriles **48** with hydrazine hydrate in refluxing ethanol. The α-fluoro-β-ketonitrile intermediates **48** were prepared by reaction of the corresponding acyl chlorides **47** with fluoroacetonitrile using lithium bis(trimethylsilyl)amide (LHMDS) as base at −78 °C in THF. The target products were obtained in fair to good yields (Scheme 14). Remarkably, the order of addition of the reagents (first fluoroacetonitrile, second the acyl chloride and then the base) was fundamental for the success of the process.

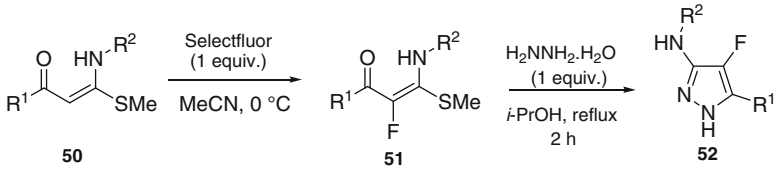


LHMDS: Lithium bis(trimethylsilyl)amide

R = *c*-propyl, *c*-pentyl, *t*-Bu, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-EtC_6H_4, 3-pyridyl, (6-CF_3)-3-pyridyl, 2-quinolyl, 2-tiophenyl

Scheme 14

An alternative strategy to 3-amino-4-fluoropyrazoles was based on the cyclocondensation of β-methylthio-β-enaminoketones with hydrazines. The monofluorinated building blocks **51** were prepared by treatment of the *N*-aryl(benzyl)-β-methylthio-β-enaminoketone precursors **50** with Selectfluor® [28]. Subsequent condensation of **51** with hydrazine led to the desired 3-aryl(benzyl)amino-4-fluoropyrazoles **52** in good yield (Scheme 15). With methylhydrazine, a 1:1 mixture of 3- and 5-aminopyrazoles was obtained (R^1=Ph, R^2=PMP), whereas with phenylhydrazine, the 5-aminopyrazole was the only observed regioisomer (R^1=Ph, R^2=PMP). In contrast to the *N*-benzyl protecting group, which was easily removed by catalytic hydrogenation, the *N*-*p*-methoxyphenyl (PMP) could not be cleaved by a variety of reagents.



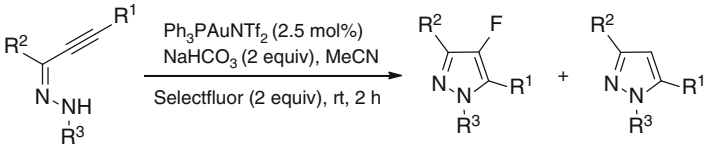
R^1	R^2	51 (%)	52 (%)
Ph	Ph	73	81
Ph	PMP[a]	91	88
Ph	Bn	n.i.[b]	57
2- furyl	Ph	93	70
$CH(OMe)_2$	Ph	73	73
4-FC_6H_4	PMP[a]	n.i.[b]	68
Me	Ph	63	82

[a] PMP: *p*-methoxyphenyl.[b] n.i.: not isolated

Scheme 15

In the last decade, metal-catalyzed intramolecular nitrogen addition to alkynes has been introduced as a new methodology for the preparation of pyrazole derivatives. Liu, Xu and co-workers [29] have developed a mild and efficient protocol for the synthesis of 4-fluorinated pyrazoles via gold(I)-catalyzed tandem aminofluorination of alkynes **53** in the presence of Selectfluor® (Scheme 16). In all cases (except for R^2=H), mixtures of 4-fluorinated **54** and nonfluorinated pyrazoles **55** (**54**:**55** = 2.1:1

to 8.3:1) were produced. This method has a broad substrate scope. The best catalytic activity and chemoselectivity were obtained when acetonitrile was used as solvent and $NaHCO_3$ as base.



53 54 55

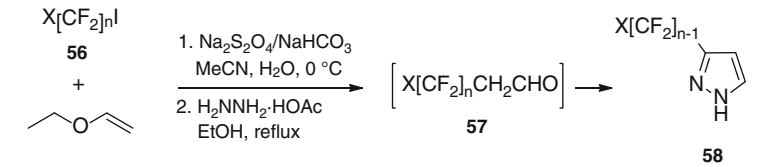
R^2 = Me/ R^3 = Ph			R^1 = R^3 = Ph			R^1 = Ph/ R^2 = Me		
R^1	54:55	(%)*	R^2	54:55	(%)*	R^3	54:55	(%)*
4-MeC_6H_4	7.2:1	85	Me	6.2:1	81	2,4-ClC_6H_3	3.6:1	56
4-MeOC_6H_4	5.6:1	81	Et	6.1:1	67	4-O_2NC_6H_4	7.0:1	64
2-MeOC_6H_4	6.3:1	83	*n*-Pr	4.6:1	63	Me	2.7:1	49
4-EtOC_6H_4	5.0:1	80	H	100:0	90	H	2.1:1	45
4-EtC_6H_4	4.0:1	73	*t*-Bu	4.9:1	64			
4-(*n*-C_5H_{11})C_6H_4	3.8:1	75						
4-ClC_6H_4	2.8:1	64						
3-ClC_6H_4	4.5:1	73						
4-BrC_6H_4	3.3:1	69						
2-thiophenyl	8.3:1	87						
n-Bu	4.5:1	78						
Bn	3.8:1	74						
t-Bu	5.1:1	75						
TMS	2.1:1	43						

* Yield

Scheme 16

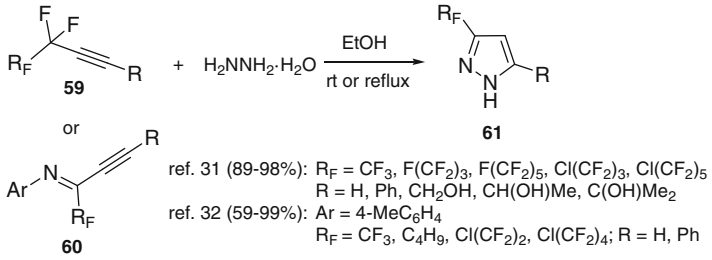
3 Synthesis of 3- and 5-Fluoroalkylpyrazoles

3-Fluoroalkyl-1*H*-pyrazoles **58** were synthesized in excellent yields in one-pot procedure starting from polyfluoroalkyl iodides **56** [30]. The treatment of **56** with ethylvinyl ether led to their corresponding fluoroalkyl aldehyde intermediates **57**, which upon condensation with hydrazine acetic acid under mild conditions gave pyrazoles **58** (Scheme 17).



Scheme 17

3-Perfluoroalkyl-5-substituted-1*H*-pyrazoles **61** can be obtained in excellent yields by reaction of either perfluoroalkylacetylenes **59** [31] or *N*-aryl per(poly) fluoroalkyl phenyl acetylenic imines **60** [32] with hydrazine hydrate in EtOH (Scheme 18). The loss of two molecules of hydrogen fluoride in the former case, and arylamine in the latter, led to the final products. As it has been mentioned above, this strategy can be also applied for the preparation of polyfluorinated derivatives (see Scheme 3), by reaction of perfluoro-2-methyl-2-pentene with hydrazones [4] or arylhydrazines [5, 6] in a basic medium.



Scheme 18

3.1 Synthesis of 3- and 5-Trifluoromethylpyrazoles

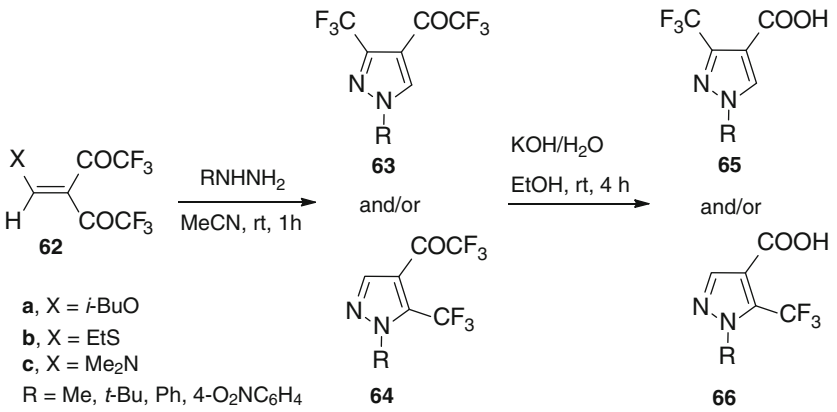
Among fluoroalkylpyrazoles, trifluoromethyl containing derivatives are regarded as privileged building block due to the properties that this group can confer to molecules. 3(5)- and 4-Trifluoromethyl, and 3,5-bis(trifluoromethyl)pyrazoles are commercially available, and it is not surprising that they are often used as the starting materials in medicinal chemistry. In addition to the procedures described above (Schemes 17, 18), the synthesis of 5-substituted 3-trifluoromethyl-1*H*-pyrazoles was carried out with excellent yields starting from pentafluoroethyl iodide. The process involves the reaction of pentafluoroethyl radical with an alkyne, followed by condensation of the adduct with hydrazine hydrate with the loss of two molecules of hydrogen fluoride [33]. 3(5)-Trifluoromethyl-5(3)-(phenyl/butyl/hexyl) pyrazoles were adequately prepared (76–92 % yield) by reaction of hydrazine and trifluoroacetyl acetylenes [34]. The difluoromethylated derivatives were obtained under the same reaction conditions.

Ethyl 5-trifluoromethylpyrazole-3-carboxylate was quantitatively prepared in a 1,3-dipolar cycloaddition between ethyl diazoacetate and sulphur (or bromo) derivatives of 3,3,3-trifluoropropene that act as easier to handle synthetic equivalents of 3,3,3-trifluoropropyne [35]. On top of all these studies, the most common strategy for the preparation of 3- and 5-trifluoromethylpyrazoles entails the [3 + 2] heterocyclization of trifluoromethyl building blocks derived from β-(amino/alkoxy/thioxy) vinylketones and 1,3-dicarbonyl with monosubstituted hydrazines. Mixtures of regioisomers are often obtained depending on the substrate, the substituent of the hydrazine, and the reaction conditions [36].

3.1.1 Using β-(Amino/Alkoxy/Thioxy/Halo)Vinyl Trifluoromethylketones

In principle, the heterocyclization between these β-substituted ketones and monosubstituted hydrazines proceeds by a Michael addition-elimination on the β-carbon atom by the more nucleophilic nitrogen of the hydrazine, followed by cyclodehydration to give mixtures of 3-trifluoromethyl and 5-trifluoromethylpyrazoles. In general, condensation reactions with methylhydrazine lead to the 3-trifluoromethylpyrazole derivatives as only or major regioisomers, whereas with aryl or heterocyclic aromatic hydrazines, the formation of 5-trifluoromethylpyrazole prevails.

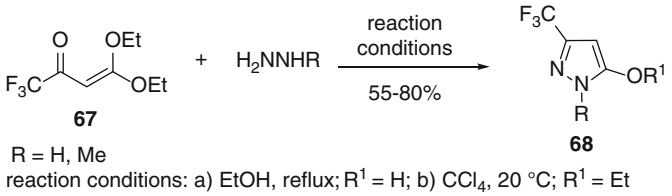
Hojo and co-workers prepared 3- and 5-trifluoromethyl-4-trifluoroacetylpyrazoles **63** and **64** by reaction of β,β-bis(trifluoroacetyl)vinyl ethers **62a**, sulfides **62b**, and amines **62c** with hydrazines in acetonitrile [37]. While the condensation reactions with methylhydrazine led to the 3-trifluoromethylpyrazoles **63** as only isomers in high yields, identical reaction conditions with phenylhydrazine resulted in mixtures of regioisomers **63** and **64**, in a 1:5 to 1:19 ratio. In contrast, condensations between either **62b** or **62c** with *t*-butylhydrazine hydrochloride or **62a** with *p*-nitrophenylhydrazine yielded the 5-trifluoromethyl regioisomers **64** as a single product in high yields (Scheme 19). All pyrazoles were then hydrolyzed to the corresponding pyrazole-4-carboxylic acids **65** and **66** in excellent yields.



Scheme 19

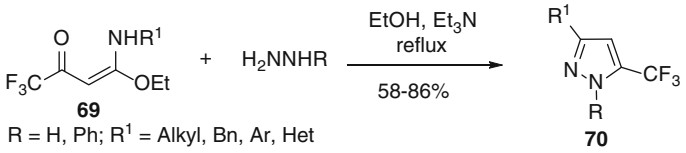
Similar levels of regiocontrol were observed in the condensation of 4-(*N,N*-diethylamino)-1,1,1-trifluoro-3-phenyl-3-buten-2-one and methyl-, phenyl-, and *p*-nitrophenyl hydrazines in acetonitrile (58–83 % yield). With methylhydrazine, the major isomer was the 3-trifluoromethyl-1-methyl-4-phenylpyrazole (ratio: 2.5:1), whereas with phenylhydrazine, the 5-trifluromethylpyrazole analogue was the predominant component in a 11:1 mixture of isomers. This regioisomer was the only product observed when *p*-nitrophenylhydrazine was used [38].

Depending on the solvent used, the condensation between β,β-diethoxyvinyltrifluoromethylketone **67** and hydrazine gave either 5-ethoxy- or 5-hydroxy-3-trifluoromethylpyrazoles **68** (Scheme 20) [39]. When methylhydrazine was employed as nucleophile the process was shown to be regioselective, resulting in the formation of 3-trifluoromethylpyrazole.



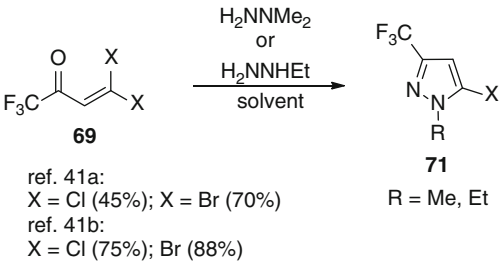
Scheme 20

In contrast, the condensation of β-alkyl(aryl)amino-β-ethoxyltrifluoromethylenones **69** with phenylhydrazine led to the sole isolation of 5-trifluoromethylpyrazole regioisomers **70** (Scheme 21) [40].



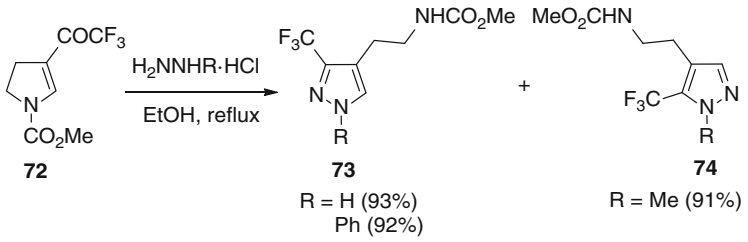
Scheme 21

The incorporation of a chlorine or bromine atom at the pyrazole ring offers considerable potential for diversification of these scaffolds *via* substitution and coupling processes. Levskovskaya and co-workers prepared 5-chloro(bromo)-3-trifluoromethylpyrazoles **71** in acceptable yields by condensation of β,β-dihalotrifluoromethylenone **69** (X=Cl, Br) and *N,N*-dimethylhydrazine and ethylhydrazine (Scheme 22) [41].



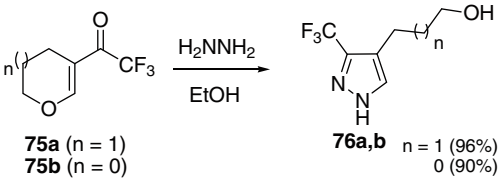
Scheme 22

This approach allows the preparation of more functionalized pyrazoles when the leaving group at the β-carbon of the trifluoromethylenone is embedded in a ring [42]. The condensation of the 3-trifluoroacetyldihydropyrrole **72** with hydrazine or phenylhydrazine in acidic medium afforded 3-trifluoromethylpyrazoles **73** in almost quantitative yield. The regioselectivity could be reversed by using methylhydrazine in the presence of pyridine · HCl, in this case obtaining 5-trifluoromethylpyrazole **74** (Scheme 23) as the major product [42a]. The whole process can be described as a ring-chain-transfer, in which the cycle in the substrate becomes an alkylic substituent in the final pyrazole adduct.



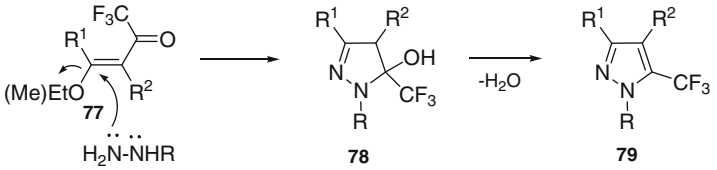
Scheme 23

Similar results were obtained from β-trifluoroacetyl- dihydropyran **75a** (n = 1) and dihydrofuran **75b** (n = 0) and hydrazine (Scheme 24). With this protocol both hydroxyethyl and hydroxypropyl chains can be incorporated at C-4 [42b].



Scheme 24

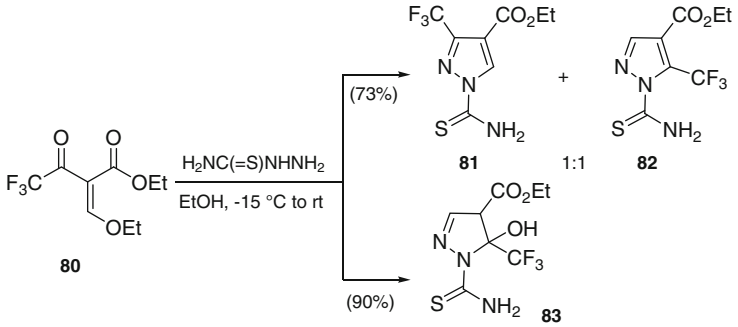
Some authors [43] have described the isolation of 5-trifluoromethyl-5-hydroxypyrazolines **78** (Scheme 25), instead of final products **79**, when reactions were carried out in neutral media (MeOH or EtOH; at room temperature or reflux) with monosubstituted hydrazines that react through the NH_2 group (see also Sect. 3.1.2). The 5-trifluoromethylpyrazoles **79** can be then obtained by the use of a dehydrating agent (H_2SO_4 reflux; AcOH reflux, P_2O_5, $SOCl_2$).



ref. 43a: R = C(=S)NH_2; R^1 = H, Me, Ph, 4-Me/Br/$O_2NC_6H_4$; R^2 = H, Me
ref. 43b: R = C(=NH)NH_2·H_2CO_3; R^1 = Me, *n*-Pr, *t*-Bu, Ph, 4-Me/Cl/Br/$MeOC_6H_4$; R^2 = H
ref. 43c: R = C_6F_5, C_6HF_4, C(=O)CF_2Br, C(=O)C_3F_7; R^2 = H, $(CH_2)_nCH_2OH$; R^1 = H
ref. 43d: R = (4-CF_3-6-Me)-2-pyrimidyl; R^1 = H, Me, Ph; R^2 = H
ref. 43e: R = Ph; R^1 2-thienyl, 2-furyl; R^2 = H
ref. 43f: R= (7-Cl)-4-quinolyl; R^1 = Ph, 4-Me/F/Cl/Br/MeO/$O_2NC_6H_4$, 4-biphenyl; R^1 = H

Scheme 25

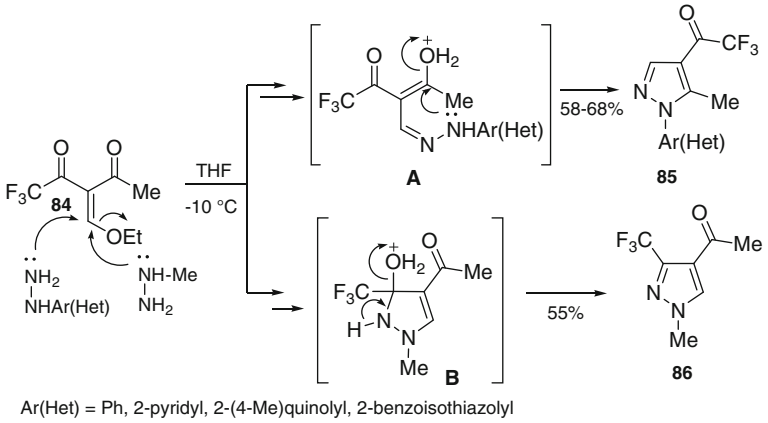
Furthermore, other authors have reported dissimilar results for reactions carried out under identical reaction conditions. For instance, Sanfilippo and co-workers [44] obtained a 1:1 mixture of 3- and 5-trifluoromethylpyrazoles **81** and **82** (73 % overall yield) in the condensation of ethyl 2-ethoxymethylene-3-oxo-4,4,4-trifluorobutanoate **80** with thiosemicarbazide in EtOH at −15 °C to room temperature. On the contrary, Tice and co-workers [45] reported that the 5-trifluoro-5-hydroxypyrazoline derivative **83** (90 % yield) was the only product obtained following an identical synthetic protocol (Scheme 26).



Scheme 26

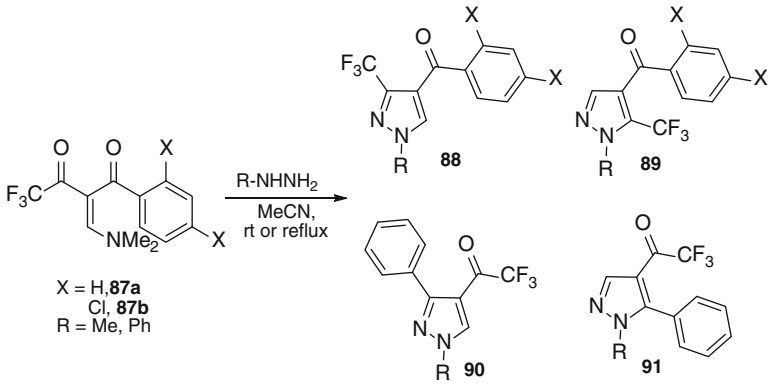
Following a similar strategy, when the substrate contains two ketone functionalities with different electronic properties, the outcome of the reaction in terms of regioselectivity, can be controlled by the substituent of the hydrazine. One example, shown in Scheme 27, is the reaction of 3-acetyl-4-ethoxy-1,1,1-trifluorobut-3-en-2-one **84** with phenyl- and aromatic heterocyclic hydrazines, in THF at −10 °C. While 4-trifluoroacetylpyrazoles **85** were obtained as exclusive products (58–68 %), the reaction of **84** with methylhydrazine led to the sole formation of 4-acetyl-3-trifluoromethylpyrazole **86** [46]. In both cases, the reaction proceeds through the initial attack of the more nucleophilic nitrogen atom of the hydrazine (NH_2 for the aromatic hydrazines and NH for methylhydrazine) to the β-carbon to the carbonyl and subsequent addition of the other nitrogen atom to the more

electrophilic $COCF_3$ (with methylhydrazine; intermediate **B**) or to the less reactive COMe (with aromatic hydrazines; intermediate **A**).



Scheme 27

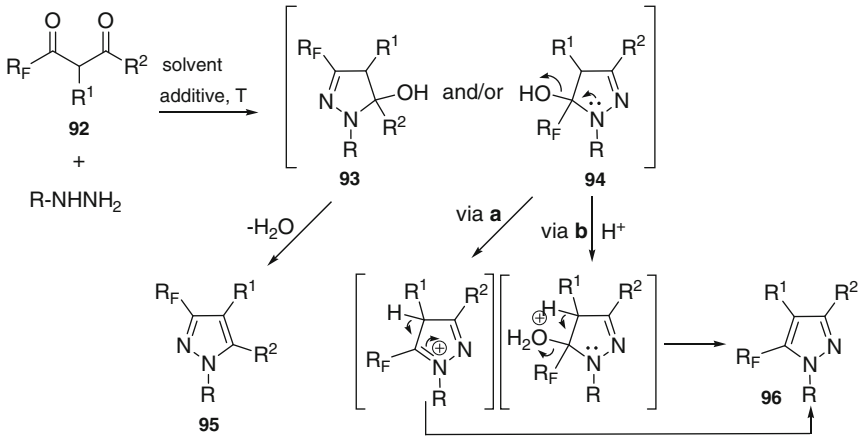
In connection with these observations, Mirand and co-workers [38] studied the influence of electron-withdrawing substituents in the regioselectivity of heterocyclization reactions involving fluorinated enaminodiketones and monosubstituted hydrazines. To this end they prepared **87a** and the 2,4-dichlorophenyl analogue **87b**. The reaction of **87a** with methylhydrazine in acetonitrile afforded a mixture of three pyrazoles **88, 89** and **90** in a 3:1:1 ratio (81 % overall yield). Treatment of the same diketone **87a** with phenylhydrazine gave a mixture of **89** (54 %) and **91** (28 %) (Scheme 28). In contrast, the condensation of the dichlorophenyl derivative **87b** with either methyl- or phenylhydrazine afforded mixtures of **88** and **89** as only components, but in different ratios depending on the hydrazine (3-/5- ratio = 2.75:1 with methylhydrazine; 3-/5- ratio = 1:21 with phenylhydrazine).



Scheme 28

3.1.2 Using Trifluoromethyl 1,3-Dicarbonyl Compounds

The condensation of fluoroalkyl 1,3-diketones **92** with monosubstituted hydrazines has been the most popular synthetic approach towards fluoroalkyl 3,5-disubstituted pyrazoles of general structure **95** and **96** (Scheme 29) [47]. The influence of the electronic and steric properties on the regioselectivity of the condensation of a variety of fluoroalkyl 1,3-dicarbonyl compounds with aryl and heterocyclic aromatic hydrazines is summarized on Table 1.



Scheme 29

In many cases, mixtures of the 3- and 5-fluoroalkyl regioisomers were obtained. However, when reactions were performed in neutral alcoholic media, 5-fluoroalkyl-5-hydroxypyrazoline intermediates **94** were isolated instead of the dehydrated final products **96** (entries 1, 6, 7, 9; Table 1) [48]. This observation could be explained on the basis of the influence of the fluoroalkyl group adjacent to the hydroxyl group that stabilizes the hydroxypyrazoline **94**, preventing the dehydration process (via **a**). In addition, the dehydration involves a cationic intermediate, whose formation could explain why, when R is an electron-withdrawing group, the dehydration does not occur or occurs with difficulty. In contrast, in an acidic medium, **94** was not observed, probably because the dehydration follows a different mechanism (via **b**). In acidic EtOH solution (H_2SO_4 catalyst), at room temperature or at reflux, the 3-trifluoromethylpyrazole **95** was the major or the only regioisomer observed in the condensation of phenylhydrazine with trifluoromethyl-1,3-diketones bearing aryl, heteroaryl, and alkyl substituents (for R^2=Me; ratio **95/96** = 1:1) [24]. Similar results were obtained by Norris [48d] and Singh [48e] in the heterocyclization of 4,4,4-trifluoro- and 4,4-difluoro-1-phenyl-1,3-butanediones with phenyl and 4-methanosulfonylpyridin-2-yl hydrazines in boiling 2-propanol. In all cases, the reactions were carried out in the presence of H_2SO_4 (entries 6 and 7; Table 1).

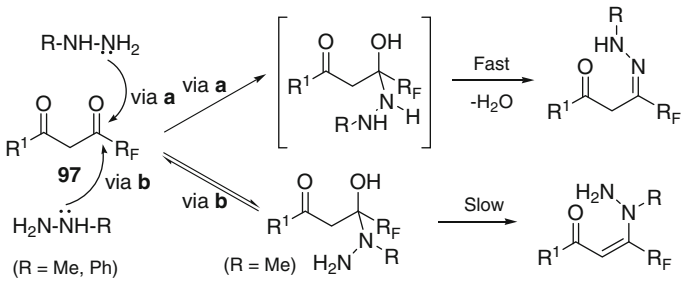
Table 1 Synthesis of fluoroalkyl pyrazoles by condensation between fluoroalkyl 1,3-diketones and monosubstituted hydrazines

Ent	R_F	R^1	R^2	R	Cond.	Ratio 95:94 or 95:96	Yield (%)	References
1	CF_3	H	Me, 2-thienyl	C_6F_5, HC_6F_4, ClC_6F_4	EtOH; rt or reflux	0:100–1:2	57–72	[48c]
2	CF_3	H	Me, Et, *i*-Pr, *i*-Bu, *t*-Bu, *n*-hexyl, Ph, 2(or 4)-Me/MeO/F/$O_2NC_6H_4$, NCC_6H_4, 2-naphtyl/pyrrolyl/furyl/thienyl/pyridyl	Ph	EtOH; rt or reflux H_2SO_4	100:0–1:1	60–100	[24]
3	CF_3	H	2-$MeOC_6H_4$, 3-Me/MeO/NCC_6H_4, 4-Me/Et/FC_6H_4, 2-/3-/4-pyridyl	4-MeC_6H_4	Si-TsOH; EtOH; μW; 160 °C; 5 min	–	42–95	[51]
4	CF_3, CHF_2	H, Et	4-MeO/Br/$O_2NC_6H_4$, Ph	Ph, 4-Br/$H_2NO_2SC_6H_4$	DMAc, 10 N HCl, rt, 24 h	86:14–>99.8:0.2	59–98	[49]
5	CF_2Br	H	Ph, 4-Me/$MeOC_6H_4$, 3-thienyl	4-O_2N/H_2NSO_2/$MeHNSO_2Bn$	DMF, conc. H_2SO_4 100 °C; 2–7 h	94:6–99:1	69–86	[50]
6	CF_3, CHF_2	H	Ph	Ph, 4-methanosulfonylpyridin-2 yl	*i*-PrOH, 85 °C 1–6 days	3:1–8:1	97–100	[48d]
					i-PrOH,85 °C H_2SO_4, 1 h	15:2–100:0	65–98	
7	CF_3	H	Ph, 4-MeO/F/Cl/Br/$O_2NC_6H_4$	Ph, 4-$O_2NC_6H_4$, 6-(Me/F) benzo-thiazol-2-yl, 4methylquinolin-2-yl	EtOH, reflux	R=Ph: 2.5:1–100:0 Remaining hydrazines: 1:1.5–0:100	75–82	[48e]
					EtOH, H_2SO_4, reflux	1.5:1–100:0	6–87	
8	CF_3	H	2-thienyl	Me	AcOH-EtOH, reflux	100:0	60	[52]
9	CF_3, CF_2Me, CF_2CF_3	H	Me, Ph, 4-MeO/ClC_6H_4, 2,4-$Cl)_2C_6H_3$, 2-furyl	Me, Ph	EtOH, rt, 45 min	1:1–6:1	52–99	[48f]
					TFE, rt, 45 min	3:1–99:1	40–99	
					HFIP, rt, 45 min	4:1–>99:<1	61–99	

Excellent regioselectivities were also obtained using polar aprotic solvents, instead of alcohols, in the presence of a protic acid. The condensation reactions of 1-aryl-4,4,4-trifluoro and 1-aryl-4,4-difluoro-1,3-butanediones with arylhydrazines in *N,N*-dimethylacetamide (DMA) in the presence of 10 N HCl aq. (50 mol%), at room temperature, led to 3-fluoroalkylylpyrazole derivatives **95** in good yields and with regioselectivities ranging from 88:12 to >99.8:0.2 (entry 4; Table 1) [49] Wu and co-workers [50] reported a highly regioselective synthesis of 3-bromodifluoromethylpyrazoles (from 94:6 to >99:1) by condensing of 1-aryl-4-bromo-4,4-difluoro-1,3-butanediones in dimethylformamide (DMF) at 100 °C in the presence of catalytic amounts of concentrated H_2SO_4 (entry 5; Table 1).

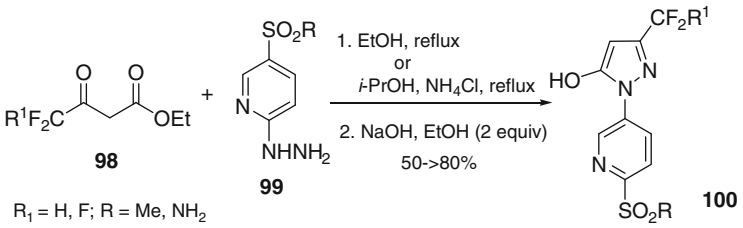
By changing the acid source to silica-supported *p*-toluenesulfonic acid, a series of 1,5-diaryl-3-trifluoromethylpyrazoles **95** were synthesized through the microwave-assisted addition of tolylhydrazine to aryltrifluoromethyl-1,3-diketones in EtOH (entry 3; Table 1) [51]. Reactions were completed in 5 min, and a workup step could be avoided in the isolation of the targeted pyrazoles.

Condensations of fluorinated 1,3-diketones and methylhydrazine are scarce in the literature. In boiling AcOH-EtOH, 4,4,4-trifluoro-1-(2-thienyl)butane-1,3-dione reacted with methylhydrazine yielding 3-trifluoromethyl-1-methyl-5-(2-thienyl)pyrazole as only product in 60 % yield [52]. Fustero and co-workers [48f] reported an elegant and regioselective process that gives fluorinated 1-methylpyrazoles starting from fluoroalkyl 1,3-diketones and methylhydrazine. When reactions were performed in EtOH at room temperature, mixtures of 3-fluoroalkylpyrazoles **95** and 5-fluoroalkyl-5-hydroxypyrazolines **94** were obtained with poor regioselectivities (1:1 to 1:3). Remarkably, using the more acidic alcohols trifluoroethanol (TFE; pKa = 12.4) and hexafluoroisopropanol (HFIP; pKa = 9.3) as solvents, instead of EtOH (pKa = 15.9), regioselectivities improved to 99:1 in favour of the 3-fluoroalkylpyrazole isomers **95**. An NMR experiment revealed the competition between the two nucleophiles, methylhydrazine and EtOH, toward the more electrophilic α-fluorinated carbonyl group, whereas such competition was not observed when the non-nucleophilic TFE or HFIP were added. These results could explain the dramatic increase in the regioselectivities when the fluorinated solvents were used. Interestingly, both methyl- and phenylhydrazine led to 3-fluoroalkylpyrazoles as major regioisomers, despite the fact that NH_2 is the more nucleophilic nitrogen in phenylhydrazine but not in methylhydrazine. This apparent anomaly in the case of methylhydrazine was explained by considering that the attack of the more nucleophilic NH group on the more reactive carbonyl group of **97** (Scheme 30) resulted in the formation of a hemiaminal (via **b**) that does not dehydrate easily to yield the hydrazone and can revert to the starting materials. This dehydration is disfavoured because of the presence of the fluoroalkyl group. In contrast, the NH_2 group of methylhydrazine attacks the fluoroalkylated carbonyl group, leading to the irreversible hydrazone formation (via **a**), in agreement with Elguero's observation that the kinetic controlling step is the first dehydration [53].



Scheme 30

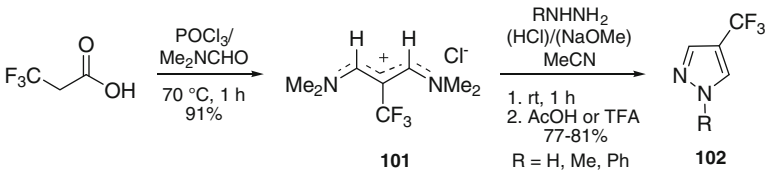
Generally speaking, the condensation reaction between alkyl trifluoroacetoacetates and monosubstituted hydrazines proceeds by the initial attack of the NH_2 of the hydrazine to the more electrophilic $COCF_3$, followed by cyclization, leading to either 5-hydroxypyrazoles or their tautomers 5-pyrazolones. Thus, the condensation of ethyl 4,4,4,-trifluoroacetoacetate **98** (R^1=F) with 2-pyridylhydrazines **99** in refluxing EtOH or *i*-PrOH, followed by treatment with sodium hydroxide, afforded regioselectively 1-substituted 3-trifluoromethyl-5-hydroxypyrazoles **100** in moderate yield (Scheme 31) [54]. The 2-difluoromethyl-5-hydroxypyrazoles analogues **100** (R^1=H) were prepared in the same manner starting from ethyl 4,4-difluoroacetoacetate.



Scheme 31

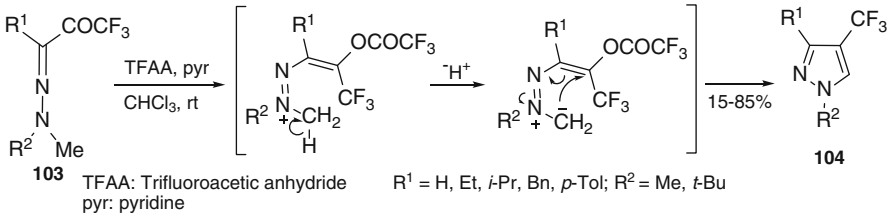
4 Synthesis of 4-Fluoroalkylpyrazoles

Several methods have been described for the preparation of pyrazole containing fluoroalkyl groups at C-4. 1*H*-, 1-Methyl, and 1-phenyl 4-trifluoromethylpyrazoles **102** were regioselectively obtained by condensation of the β-trifluoromethyl vinamidinium salt **101** with hydrazine, methylhydrazine, and phenylhydrazine, respectively (Scheme 32) [55].



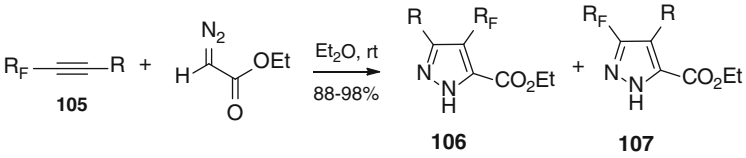
Scheme 32

Hojo and co-workers reported the synthesis of 4-trifluoromethylpyrazoles **104** by trifluoroacetic anhydride (TFAA) induced cyclization of trifluoroacetylated hydrazones **103** in pyridine [56]. Both TFAA and pyridine proved necessary for the success of the reaction. It is noteworthy that the cyclization occurs on the *N*-methyl group (Scheme 33). A speculative mechanism involving a *N*-methylide intermediate was proposed in order to explain the obtained results.



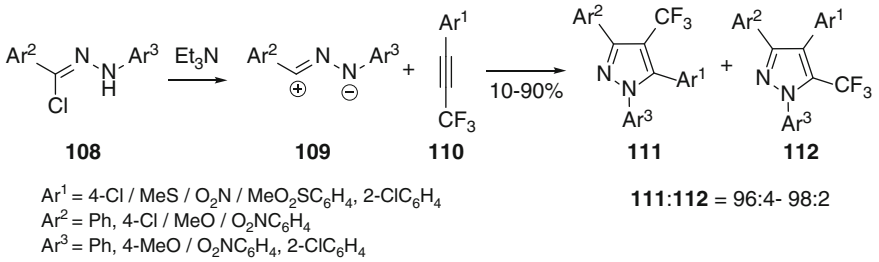
Scheme 33

The 1,3-dipolar cycloaddition using fluoroalkylacetylenes as dipolarophiles represents the key method to preparing diverse 4-fluoroalkylpyrazoles. The addition of ethyl diazoacetate to fluorine-containing acetylenes **105**, in diethyl ether at room temperature, afforded mixtures of 4- and 3-fluoroalkylpyrazoles **106** and **107** in high yield but with poor control over the regioselectivity in general (Scheme 34). Both products were easily separated chromatographically [57].



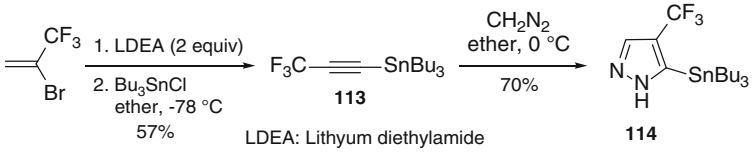
Scheme 34

Higher regioselectivities were obtained in the preparation of 1,3,5-triaryl-4-trifluoromethylpyrazoles **111** by 1,3-cycloaddition between diarylnitrileimines **109** and a variety of substituted 1-aryl-3,3,3-trifluoro-1-propynes **110** [58]. Nitrileimines **109** were formed *in situ* from the corresponding α-halohydrazones **108** (Scheme 35). The regioselectivity was no affected by the nature of the aryl substituents both in the alkyne and the nitrileimine. Lower regioselectivities were observed when nitrileoxides, sydnones and azides were employed as 1,3-dipoles.



Scheme 35

The 1,3-dipolar cycloaddition of tributyl(3,3,3-trifluoro-1-propynyl)stannane **113** with diazomethane allowed the regioselective synthesis of 5-(tributyl)stannyl-4-trifluoromethylpyrazole **114** (Scheme 36) [59], and interesting building-block for the synthesis of a variety of 5-substituted 4-trifluoromethylpyrazoles by cross-coupling reactions (see Sect. 7.1).



Scheme 36

5 Fluoro- and Fluoroalkylindazoles

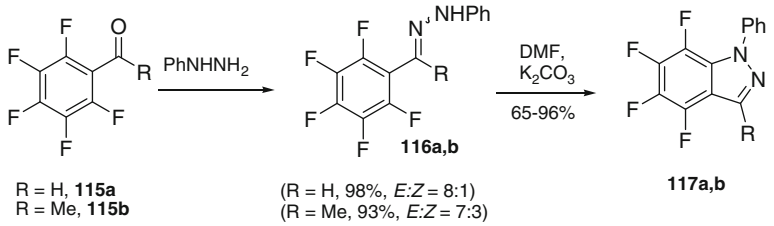
Indazoles (benzo[*c*]pyrazoles) have been studied to a much lesser extent than the related pyrazoles. Yet, molecular entities containing this structural motif have started to flourish recently in the context of pharmaceutical sciences and materials [60]. In particular, the preponderance of fluorine containing indazoles in journals and chemical patent literature is very limited. For the sake of clarity, fluoroindazoles will be classified in four categories, depending on the exact location of the fluorine atom within the bicyclic core:

(a) Indazoles fluorinated at the phenyl ring, more often in all four positions (4,5,6,7-tetrafluoroindazoles)

(b) Indazoles fluorinated at the pyrazole ring (3-fluoroindazoles)
(c) Indazoles containing a fluoroalkyl group at C-3 (3-fluoroalkylindazoles)
(d) Indazoles containing a fluoroalkyl group at N1 (1-fluoroalkylindazoles)

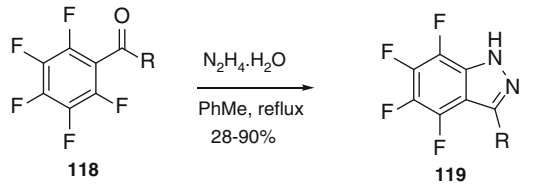
5.1 Synthesis of 4,5,6,7-Tetrafluoroindazoles

In general, indazoles exist in a single tautomeric form (*1H*-) with the exception of some *C*-substituted examples. There are two main methods for the synthesis of indazoles which can be exploited also in the preparation of the fluorinated counterparts: the diazotization of 2-alkylanilines and the cyclization of *ortho*-substituted hydrazones. The former usually requires acidic conditions and works best with electron deficient aromatic substrates while the latter employs hydrazine and involves the formation of one or two bonds of the pyrazole ring starting from cyclohexanones or mono or bifunctional arenes [61, 62]. In the first report describing the preparation of 4,5,6,7-tetrafluoro-1-phenylindazole, pentafluorobenzaldehyde **115a** (R=H) was treated with phenylhydrazine resulting in the formation of the corresponding phenylhydrazone **116a** in excellent yield (98 %) with a 8:1 *E:Z* ratio [63]. While the *Z*-isomer was cyclised to the desired indazole **117a** upon treatment with potassium carbonate in DMF at room temperature, higher temperatures (100 °C) were required in order to observe the complete conversion of the *E*-isomer (Scheme 37). The same reaction sequence was carried out starting from 2,3,4,5,6-pentafluoroacetophenone **115b** (R=Me), leading to C3-substituted indazole **117b** in 60 % yield over two steps.



Scheme 37

Other derivatives unsubstituted at *N*1 **119** were synthesized in one step by condensation of hydrazine monohydrate and pentafluoroaryl ketones **118** in excellent yield (Scheme 38) [64]. Interestingly, in the case of methyl pentafluorobenzoate **118** (R=OMe), the desired indazole is obtained in low yield (28 %) due to the fact that substitution of the fluorine by hydrazine occurs *ortho*- and *para*- to the ester group; so, besides 4,5,6,7-tetrafluoro-1H-indazol-3-ol (**119**, R=OH)), the methyl 2,3,5,6-tetrafluoro-4-hydrazinylbenzoate is also formed.

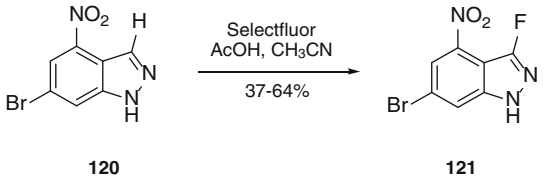


R = Ph, C_6F_5, OCH_3, CF_3 R = Ph, C_6F_5, OH, CF_3

Scheme 38

5.2 *Synthesis of 3-Fluoroindazoles*

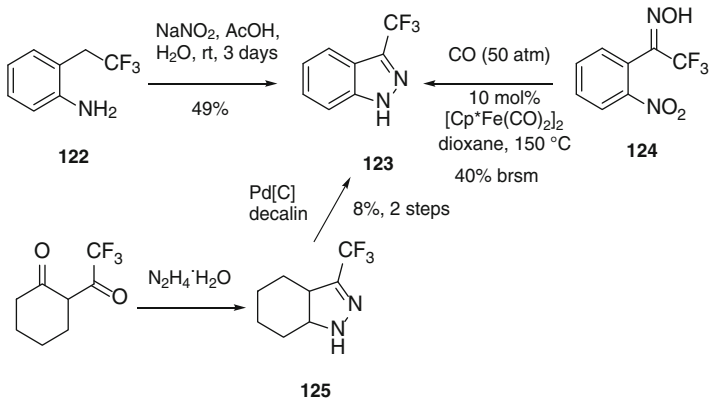
Incorporation of a fluorine at C-3 can be achieved by treatment of a preformed (*3H*)-indazole with electrophilic fluorinating reagents. In the context of a medicinal chemistry programme, scientists at GSK carried out the fluorination of 4-nitro-6-bromo-(*1H*)-indazole (**120**) with Selectfluor® in a mixture of acetonitrile and acetic acid (Scheme 39). Best yields (64 %) were observed when the reaction mixture was submitted to microwave irradiation [65]. The scope of this synthetic transformation is somewhat limited, since the regioselectivity is controlled by the presence of two electron withdrawing groups on the phenyl ring.



Scheme 39

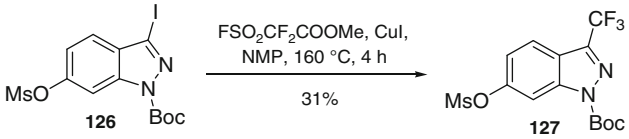
5.3 *Synthesis of 3-Fluoroalkylindazoles*

The synthesis of 3-trifluoromethyl-1*H*-indazole (**123**) was originally reported in 1975 using a standard condensation procedure [66]. Other procedures that lead to this compound are depicted in Scheme 40. Although the yields are low to moderate, these examples demonstrate that fluorinated indazoles can also be constructed relying on a *N-N* bond forming reaction (diazotization). For instance, treatment of the aniline **122** with sodium nitrite in AcOH gave the desired product in 49 % as a 1:1 mixture with an unidentified side product [67]. Alternatively *ortho*-nitroketoxime **124** were converted to *1H*-indazole **123** upon reaction with carbon monoxide with $[Cp^*Fe(CO)_2]_2$ as catalyst [68]. This reductive cyclization, albeit low yielding, offers the advantage of being carried out under neutral conditions. Finally, the aromatization of the tetrahydroindazole precursor **125** yielded the same trifluoromethyl indazole **123** in poor overall yield.



Scheme 40

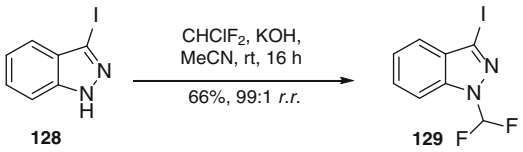
Methods that allow the incorporation of trifluoromethyl group onto haloarenes and haloheteroarenes have emerged in recent years [69]. Only one example has been reported in the context of fluoroalkylindazoles. The copper mediated coupling of a Boc-protected 3-iodoindazole **126** and a suitable source of CF_3 (2-fluorosulfonyl-2,2-difluroroacetic acid methyl ester) led to the formation of the coupling product **127** in low yield (31 %) (Scheme 41) [70]. It is believed that with the recent discovery of synthetic technologies for the palladium and copper catalyzed incorporation of the CF_3 group onto sp^2-carbon atoms, this approach will be further optimized in the near future.



Scheme 41

5.4 Synthesis of 1-Fluoroalkylindazoles

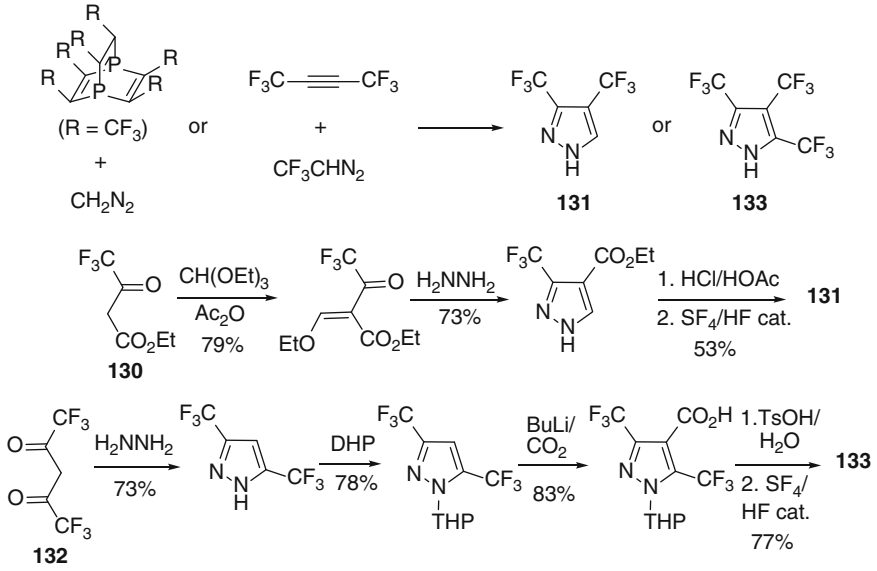
In the context of a medicinal chemistry programme, it was required the incorporation of a difluoromethyl group onto the nitrogen of the indazole. It was shown that the fluorinated grouping provided greater metabolic stability relative to the corresponding 1H-indazole derivative [71]. After extensive optimization it was found that chlorodifluoromethane could be employed for the selective incorporation at *N*1 of the difluoromethyl group in 3-iodoindazole **128** (Scheme 42). Acetonitrile was identified as the preferred solvent together with aqueous KOH as the base. By using this protocol 1-difluoromethyl-3-iodoindazole **129** was synthesized in 66 % in low scale and 59 % yield on a 20-g scale.



Scheme 42

6 Miscellaneous

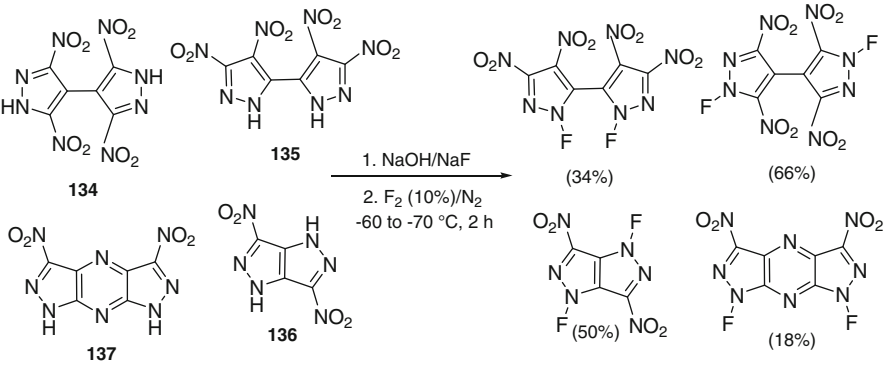
Syntheses of 3,4-bis(trifluoromethyl) **131** and 3,4,5-(tris)trifluoromethylpyrazole **133** were reported in the second half of the past century [72]. These procedures involved the use of gaseous starting materials such as diazomethane, bis(trifluoromethyl) acetylene, or trifluoromethyldiazomethane (Scheme 43). Recently, two practical syntheses to **131** and **133**, based on the transformation of the carboxylic group into the trifluoromethyl group by sulphur tetrafluoride (SF_4), were reported (Scheme 43) [73]. These procedures allowed the gram-scale preparation of **131** (30 % overall yield from commercially available **130**) and **133** (36 % overall yield from commercially available **132**). Physical properties such as *NH*-acidities or fluorescence were determined for both compounds.



DHP: Dihydropyrane, THP: Tetrahydropyrane

Scheme 43

Dalinger and co-workers [74] have reported a regioselective *N*-fluorination of Na-salts of polynitrated bipyrazoles **134**, **135** and pyrazole-based fused heterocycles **136**, **137** with fluorine-nitrogen mixture (10 % F_2) at −60 to −70 °C in NaOH solution in the presence of NaF (Scheme 44). The fluorination occurred only at the nitrogen atom which is most distant from the nitro group.

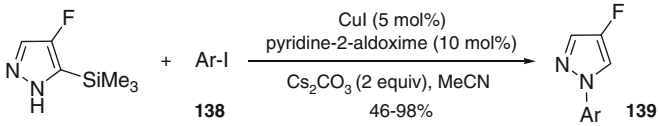


Scheme 44

7 Applications

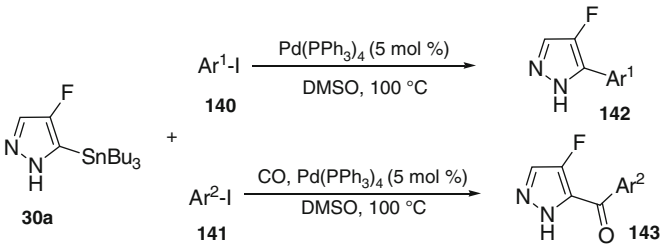
7.1 C-N and C-C Cross-Coupling Reactions

In the last years, metal-catalyzed cross-coupling reactions have emerged as a powerful tool for the construction of C-C and C-N bonds. In this context, 4-fluoro-5-trimethylsilyl-1*H*-pyrazole (**30b**) was used as fluorinated building block in a copper iodide-catalyzed *N*-arylation with a variety of aryl iodides **138** (Ullmann-type reaction) affording *N*-aryl-4-fluoropyrazoles **139** in high yields [18a]. Interestingly, these coupling reactions occurred at 60–70 °C using pyridine-2-aldoxime as ligand. It is noteworthy that some functional groups such as ketone, ester, ether or nitro were compatible with the reaction conditions (Scheme 45).



Scheme 45

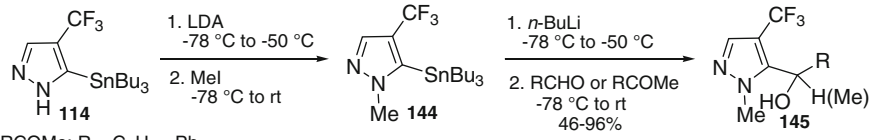
Palladium-catalyzed C-C cross-coupling reactions between 5-tributylstannyl-4-fluoro-1*H*-pyrazole (**30a**) and aryl iodides **140** and **141** led to the corresponding 5-aryl-4-fluoro-1*H*-pyrazoles **142** in high yields [18c]. The versatility of the process was demonstrated when reactions were conducted under an atmosphere of carbon monoxide (CO). The corresponding 5-acyl-4-fluoro-1*H*-pyrazoles **143** arising from a carbonylative cross-coupling reaction were obtained in variable yields (Scheme 46). As in the C-N cross-coupling reactions mentioned above, a variety of functional groups were tolerated in the process.



Ar^1	Yield (%)	Ar^2	Yield (%)
4-$MeCO_2C_6H_4$	91	4-$EtO_2CC_6H_4$	91
4-$EtO_2CC_6H_4$	78	4-$F_3CC_6H_4$	67
4-$F_3CC_6H_4$	92	4-NCC_6H_4	62
4-$MeOC_6H_4$	59	4-$O_2NC_6H_4$	47
4-$O_2NC_6H_4$	84	Ph	78
Ph	99	2-EtC_6H_4	83
2-$MeO_2CC_6H_4$	83	2-ClC_6H_4	36
2-ClC_6H_4	89	2-FC_6H_4	16
2,4-$Me_2C_6H_3$	94	2,4-$Me_2C_6H_3$	95
3-$MeOC_6H_4$	74	3-$MeOC_6H_4$	74
		2-thienyl	84
		2-pyridyl	35

Scheme 46

As it was indicated above, 5-(tributyl)stannyl-4-trifluoromethylpyrazole (**114**) was used as suitable building-block for the preparation of some 5-substituted-4-trifluoromethylpyrazoles [75]. Compound **114** was regioselectively converted into its 1-methyl derivative **144** in almost quantitative yield upon treatment with LDA followed by addition of methyl iodide. Transmetallation with *n*-BuLi and quenching of the resulting lithiated species with a range of aldehydes and ketones gave a range of 5-(1-hydroxy) alkylpyrazoles **145** (Scheme 47). Other electrophiles such as *S*-phenyl benzenethiosulfate and phenyl isocianate afforded the corresponding adducts in good yield.



RCOMe: R = C_9H_{19}, Ph.
RCHO: R = Ph, 4-MeO/Ph/ $CF_3C_6H_4$, 3,4-$(MeO)_2C_6H_3$, 2-tolyl, CH=CHPh, CH=CHMe, C_9H_{19}, 3-pentyl.

Scheme 47

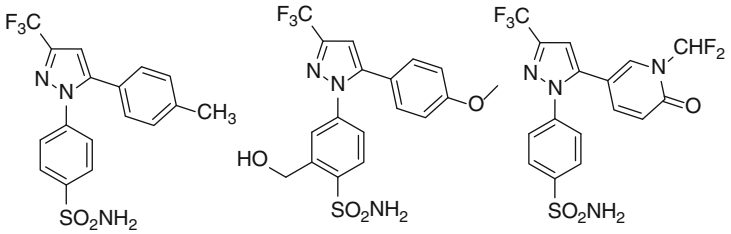


Fig. 1 Inhibitors of COX-2 and LOX-2

7.2 Pharmaceuticals and Agrochemicals

The presence of fluorine atoms in drug candidates has increased dramatically over the past two decades. The special nature of fluorine might confer a range of properties to different molecular scaffolds, such as enhanced binding interactions, increased metabolic stability or changes in physicochemical properties. In this regard, the trifluoromethyl group has become a privileged unit because of its ability to effectively fine-tune pharmacokinetic properties of molecular entities.

3-Trifluoromethyl- and 3,5-bis(trifluoromethyl)-containing pyrazole motifs are present in numerous pharmacologically relevant compounds. Celecoxib [76] (commercialized as Celebrex) is a nonsteroidal anti-inflammatory drug (NSAID) introduced into the clinical practice for the treatment of rheumatoid arthritis and osteoarthritis in humans. It belongs to a 1,5-diaryl-3-trifluoromethylpyrazole class of selective cyclooxygenase-2 (COX-2) inhibitors bearing a benzenesulfonamide function at *N*1 (Fig. 1a). Further structural modifications at *N*1 and C-5, allowed the preparation of selective COX-2 inhibitors [77]. Some particular modifications, such as the incorporation of a hydroxymethyl group at the phenyl group at *N*1, together with the incorporation of a *p*-methoxyphenyl group at C-5 led to a considerable increase in potency with respect to celecoxib (Fig. 1b) [78].

The pharmacological profile of this series was enhanced by the incorporation of *N*-difluoromethyl-1,2-dihydropyrid-2-one at C-5. The compound shown (Fig. 1c) displayed dual selective COX-2/lipooxygenase-2 (LOX-2) inhibitory activities [79]. Replacement of *p*-tolyl moiety by a *N*-(4-nitrooxybutyl)piperidyl or *N*-(4-nitrooxybutyl)-1,2,3,6-tetrahydropyridyl group revealed a new chemical series of

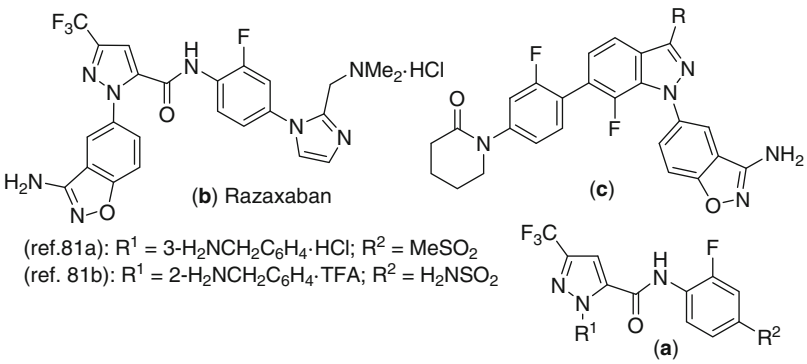


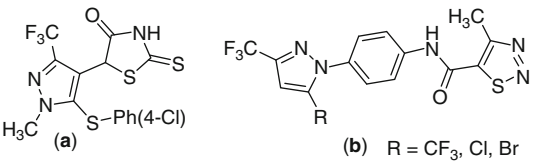
Fig. 2 Inhibitors of factor Xa

hybrid nitric oxide (NO) releasing anti-inflammatory (AI) coxib prodrugs (NO-coxib) with an AI potency profile that was similar to aspirin [80].

The 1-aryl-3-trifluorometylpyrazole-5-carboxamide group is present in many of the orally available blood coagulation factor Xa inhibitors. Pinto and co-workers found in their medicinal chemistry program that a fluorinated pyrazole was an optimal five-membered heterocyclic core. Thus, two members of the 3-trifluoromethylpyrazole-5-carboxamide series were advanced to preclinical development (Fig. 2a) [81]. An additional structural modification, the incorporation of an aminobenzisoxazole moiety at *N*1 instead of the benzylamine group, led to the discovery of razaxaban (Fig. 2b), a potent, selective, and orally bioavailable inhibitor of factor Xa with in vivo efficacy in antithrombotic models [82]. The amide hydrolysis observed *in vivo* could be modulated by introducing bicyclic core variants at the carboxamide portion, such as 1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one or 1,4,5,6-tetrahydropyrazolo-[3,4-*c*]pyridine-7-one [83].

In the context of a study of selective factor Xa inhibitors for thromboembolic diseases, a key 7-fluoroindazolyl moiety was employed [84]. It was reasoned that fluoro group on the indazole scaffold could be used as a replacement of the carbonyl group of an amide that was found in previously reported factor Xa inhibitors (Fig. 2a). According to the solid state structure of a factor Xa cocrystal containing an example of the 7-fluoroindazole series, showed the 7-fluoro atom hydrogen-bonding with the N–H of Gly216 in the peptide backbone. The presence of the F atom did also have an effect in inhibitory potencies, being 60-fold greater for the 7-fluoroindazoles (Fig. 2c) versus non-fluorinated counterparts.

A series of 5-[(3-trifluoromethyl)-1*H*-pyrazol-4-yl)methylene)-2-thioxothiazolidin-4-ones were evaluated as ADAMTS-5 (aggrecanase-2) inhibitors. It is believed that by preventing the degradation of aggregan, a major component of cartilage, the progression of osteoporosis can be arrested. The most representative compound of this series is depicted in Fig. 3a [85]. In an alternative effort, a structure-activity relationship (SAR) study around 3-trifluoromethyl-1-methylpyrazoles allowed the discovery of potent and selective calcium-release-activated calcium (CRAC) channel inhibitors. Interestingly, the incorporation of an additional trifluoromethyl



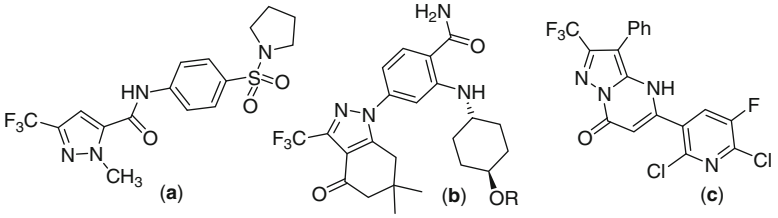


Fig. 3 Inhibitors of ADAMTS-5 (**a**), and CRAC channel (**b**)

Fig. 4 Non-nucleoside inhibitor of the measles virus RNA-dependent RNA polymerase complex (**a**), inhibitor of heat shock protein 90 (**b**), and activator of KCNQ potassium channel (**c**)

group at the pyrazole ring increased the in vitro potency (Fig. 3b) [86]. Other electron-withdrawing groups (Cl, Br) were equally effective. Related 4′-[3,5-bis (trifluoromethyl)pyrazol-1-yl]carboxyanilides were previously identified as nuclear factor of activated T-cells (NFAT) transcription factor regulators [87].

The 3-trifluoromethyl-1-methylpyrazole motif is also present in non-nucleoside inhibitors of the measles virus RNA-dependent RNA polymerase complex (Fig. 4a) [88]. Measles virus is one of the most infectious pathogens known to date. Quantitative structure-activity relationships (QSAR) suggests that the pyrazole-CF_3 most likely sits in a pocket housing cationic Arg, His or Lys. Other biologically relevant trifluoromethylpyrazole derivatives include some fused systems. The 3-trifluoromethylindazol-4-one derived 2-aminobenzamides (Fig. 4b) showed strong binding affinity to heat shock protein 90 (Hsp90) and has recently entered clinical trials as antitumor agents [89]. More recently, 2-trifluoromethypyrazolo[1,5-a]pyrimidin-7(4H)-ones (Fig. 4c) have been patented as potent activators (openers) of KCNQ2/3 potassium channels [90].

Progressive degenerative osteoarthritis is the most common cause of chronic pain in dogs. Deracoxib (Fig. 5a), a 1,5-diaryl-3-difluoromethylpyrazole derivative, is a moderately potent canine COX-2 inhibitor in the market [91]. Some potent and selective analogues of deracoxib included a 5-methanesulfonylpyridinyl group at *N*1 [92]. Along these lines, the incorporation of both a cyano group at C-4 and a *cis*-dimethylmorpholine at C-5 of the pyrazole ring increased the *in vitro* and *in vivo* activities in dogs and cats (Fig. 5b, c) [93]. Furthermore, a trifluoromethyl derivative (Fig. 5d) is under clinical evaluation against the same disease [94].

Other biologically active trifluoromethylated pyrazoles and derivatives thereof are shown in Fig. 6. Members of the 5-trifluoromethyl-3*H*-pyrazol-3-ones chemical series (one example is depicted as the hydroxyl tautomer; Fig. 6a) have been shown to be antidiabetic agents. 5-Trifluoromethyl-5-hydroxypyrazolines containing a

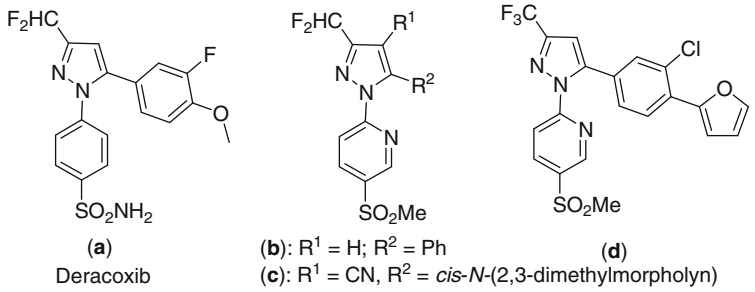


Fig. 5 Canine COX-2 inhibitors

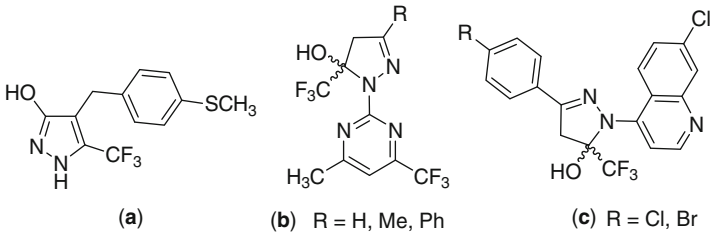


Fig. 6 Antidiabetic agent (**a**); analgesics (**b**), and antimalarials (**c**)

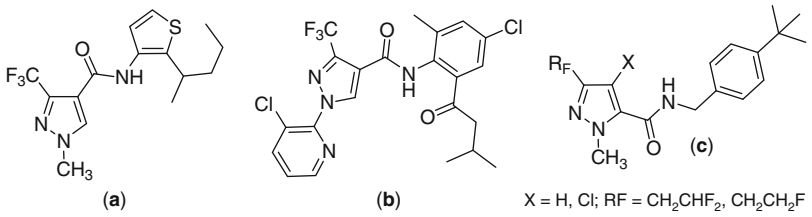


Fig. 7 Fungicide (**a**), insecticide (**b**), and acaricides (**c**)

pyrimidine substituent at *N*1 are potential analgesics and antipyretics (Fig. 6b) [43d]. Analogues of the popular quinoline antimalarial chloroquine, in which the diamino side chain was replaced by pyrazoles and hydroxypyrazolines, showed interesting activities *in vitro* (Fig. 6c) [95].

Fluoro- and fluoroalkylpyrazole templates are also present in important agrochemicals, two examples being the marketed fungicide penthiopyrad [96] (Fig. 7a) and the insecticidal anthranilic diamide (Fig. 7b) [97]. Fustero and co-workers prepared a small set of analogues of the commercially available acaricide tebufenpyrad with several fluorinated side chains at the pyrazole C-3 [98]. Some of these compounds displayed higher acaricidal activity than the parent compound tebufenpyrad (Fig. 7c).

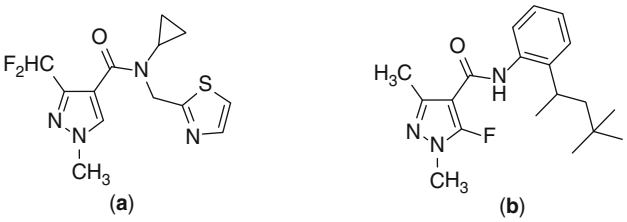


Fig. 8 Fungicide (**a**), and bactericide (**b**)

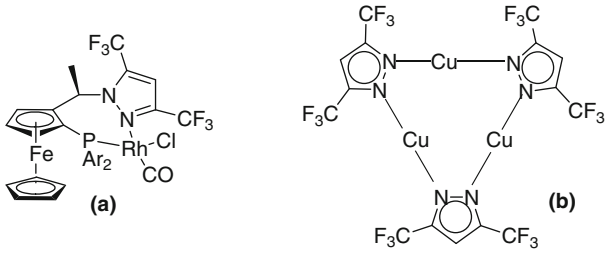


Fig. 9 Complexes with trifluoromethylated pyrazoles

The preparation of a range of 3-difluoromethyl-1-methylpyrazole-4-carboxamides and 5-fluoro-1,3-dimethyl-4-carboxamides and carboxanilides are described in some patents. These compounds display important activities as fungicides (Fig. 8a) and bactericides (Fig. 8b) [99]. Finally, the 3-trifluoromethylthyopyrazole motif is present in some pesticide hydrazide derivatives [100], and oxazolidines bearing a 3-trifluoromethyl-1-methyl-5-(2,2,2-trifluoro)ethoxypyrazole substituent show activity as herbicides [101].

7.3 Ligands in Coordination Chemistry

3-Trifluoromethyl and 3,5-bis(trifluoromethyl)pyrazoles has been widely used as ligands in coordination chemistry. Among them, the pyrazolide anions have emerged as the most versatile ligands in this field [102]. Different research groups have reported the synthesis and structural characterization of complexes of transition metals with trifluoromethylpyrazoles. For instance, Togni and co-workers prepared rhodium complexes with a ferrocenyl ligand in order to reveal the role of electronic effects on the enantioselectivity of the hydroboration reaction (Fig. 9a) [103]. The electron-withdrawing properties of these ligands were exploited by Dias and co-workers in the preparation of stable complexes of ethylene and carbon monoxide with silver and copper tris(pyrazolyl)borate, respectively [104]. Carty and co-workers reported the synthesis and structure of the complex [$(CO)_3$Ru(3,5-$(CF_3)_2$pyrazolate] and its use for the chemical vapor deposition (CVD) of ruthenium metal [105].

Moreover, Jones and co-workers prepared a series of 3,5-bis(trifluoromethyl)pyrazolate derivatives of Rh, Ir, Pd, and Pt as potential volatile precursors for the CVD of these metals [106].

Finally, Dias and co-workers carried out a systematic study of trinuclear, dinuclear, and mononuclear complexes of Cu(I) and Ag(I) with fluorinated pyrazole ligands (Fig. 9b) and found that these complexes exhibit bright, tunable luminescence [107]. Due to this behaviour, these complexes were selected as potential candidates for emitting materials in molecular light-emitting devices (LEDs). Fluorinated ligands not only increase the volatility of these ligands but might also improve properties such as thermal and oxidative stability, and reduced concentration quenching of luminescence to metal adducts. Moreover, the trinuclear metal pyrazolates also exhibit interesting π acid/base properties, which are highly dependent on the pyrazole ring substituents and the metal atom. While $\{[3,5\text{-}(CH_3)_2Pz]Au\}_3$ has been shown to be a π base, the fluorinated analogue $\{[3,5\text{-}(CF_3)_2Pz]Au\}_3$ possesses π acidity [108].

Acknowledgments We would like to thank MICINN (CTQ2010-19774) of Spain and Generalitat Valenciana (PROMETEO/2010/061) for their financial support.

References

1. (a) Vilarrasa F, Gálvez G, Calafell M (1975) Synthesis of fluoroazoles. An Quim 71:631–632; (b) Fabra F, Vilarrasa J, Coll J (1978) Fluoropyrazoles. III. Synthesis and ^{1}H and ^{19}F Nmr spectra of 3-, 4-, and 5-fluoro-1-mrthylpyrazole. J Heterocycl Chem 15: 1447–1449; (c) Fabra F, Fos E, Vilarrasa J (1979) Fluoroazoles IV. Fluorine-19-fluorine 19 coupling constants in the azole series. Synthesis of 3,4-, 4,5-, and 3,5-difluoropyrazoles. Tetrahedron Lett 34:3179–3180
2. Clark DA, Lahm GP, Smith BK, Barry JD, Clagg DG (2008) Synthesis of insecticidal fluorinated anthranilic diamides. Bioorg Med Chem 16:3163–3170
3. See, e.g.: (a) Nishida S, Ohsumi T, Tsushima K, Matsuo N, Maeda K, Inoue S (1988) Pyrazolecarboxamide derivatives, and fungicides containing them as effective ingredients. Patent: US 4742074; (b) McLoughlin JI, Metz S (1993) Pyrazolecarboxanilide agrochemical fungicides. Patent: WO 9311117; (c) Elbe HL, Bielefeldt D, Tiemann R, Dutzmann S, Stenzel K, Kugler M, Wachtler P (1998) 1,3-Dimethyl-5-fluoropyrazole-4-carboxamides and their use in controlling unwanted microorganisms in plants. Patent: DE 19629826; (d) Nakatani M, Ito M, Kimijima K, Miyazaki M, Fujinami M, Ueno R, Takahashi S (2004) Preparation of isoxazoline derivatives as herbicides. Patent: EP 1405853; (e) Pazenok S (2009) Preparation of 1-alkyl-3-haloalkylpyrazole-4-carboxylic acids. Patent: WO 2009112157
4. Ikeda I, Kogame Y, Okahara M (1985) Synthesis of novel pyrazoles containing perfluoroalkyl groups by reactions of perfluoro-2-methylpent-2-ene and hydrazones. J Org Chem 50:3640–3642
5. Furin GG, Chi KW, Protsuk NI, Lopyrev VA (2001) Reactions of perfluoro(5-aza-4-nonene) with hydrazine and some its derivatives. Russ J Org Chem 37:1621–1628
6. Chi KW, Kim SJ, Park TH, Gatilov YV, Bagryanskaya IY, Furin GG (1999) Synthesis of fluorinated *N*-arylpyrazoles with perfluoro-2-methyl-2-pentene and arylhydrazines. J Fluor Chem 98:29–36
7. Volle JN, Schlosser M (2000) Fluorine-sacrificial as an access to 5-fluoropyrazoles. Eur J Org Chem 823–828
8. Ohtsuka Y, Uraguchi D, Yamamoto K, Tokuhisa K, Yamakawa T (2012) Synthesis of 2-(trifluoromethyl)-1,3-dicarbonyl compounds through direct trifluoromethylation with CF_3I and their application to fluorinated pyrazoles syntheses. Tetrahedron 68:2636–2649

9. Ichikawa J, Kobayashi M, Noda Y, Yokota N, Amano K, Minami T (1996) Regiocontrolled syntheses of 3- or 5-fluorinated pyrazoles from 2,2-difluorovinyl ketones. J Org Chem 61:2763–2769
10. Purrington ST, Kagen BS, Patrick TB (1986) Application of elemental fluorine in organic synthesis. Chem Rev 86:997–1018
11. Storer R, Ashton CJ, Baxter AD, Hann MM, Marr CLP, Mason AM, Mo CL, Myers PL, Noble SA, Penn CR, Weir NG, Woods JM, Coe PL (1999) The synthesis and antiviral activity of 4-fluoro-1-β-D-ribofuranosyl-1H-pyrazole-3-carboxamide. Nucleoside Nucleotide 18:203–216
12. (a) Katoch-Rouse R, Pavlova OA, Caulder T, Hoffman AF, Mukhin AG, Horti AG (2003) Synthesis, structure-activity relationship, and evaluation of SR141716 analogues: development of central cannabinoid receptor ligands with lower lipophilicity. J Med Chem 46:642–645; (b) Dressen D, Garofalo AW, Hawkinson J, Hom D, Jagodzinski J, Marugg JL, Neitzel ML, Pleiss MA, Szoke B, Tung JS, Wone DWG, Wu J, Zhang H (2007) Preparation and optimization of a series of 3-carboxamido-5-phenacylaminopyrazole bradykinin B1 receptor antagonists. J Med Chem 50:5161–5167; (c) Skinner PJ, Cherrier MC, Webb PJ, Shin YJ, Gharbaoui T, Lindstrom A, Hong V, Tamura SY, Dang HT, Pride CC, Chen R, Richman JG, Connolly DT, Semple G (2007) Fluorinated pyrazole acids are agonists of the high affinity niacin receptor GPR109a. Bioorg Med Chem Lett 17:5620–5623
13. Sloop JC, Jackson JL, Schmidt RD (2009) Microwave-mediated pyrazole fluorinations using Selectfluor®. Heteroat Chem 20:341–345
14. Molines H, Wakselman C (1989) Fluoromalonaldehyde bis(dialkyl acetals): synthesis by carbene condensation and transformation to dialkyl fluoromalonates and fluorinated heterocyclic compounds. J Org Chem 54:5618–5620
15. Shi X, Ishihara T, Yamanaka H, Gupton JT (1995) Reactions of β-fluorovinamidinium salt with bifunctional hetero nucleophiles. A new synthetic route to fluorinated heterocycles. Tetrahedron Lett 36:1527–1530
16. (a) Reichardt C, Halbritter K (1975) Syntheses with substituted malondialdehydes. XIX. Synthesis of fluoro-substituted carbocyclic and heterocyclic compounds. Justus Liebigs Ann Chem 470:483; (b) Reichardt C, Halbritter K (1970) Syntheses with substituted malondialdehydes. VII. Fluoro- and iodo-malonaldehyde. Justus Liebgsg Ann Chem 99:107
17. England K, Mason H, Osborne R, Roberts L (2010) An improved synthesis of a novel α1A partial agonist including a new two-step synthesis of 4-fluoropyrazole. Tetrahedron Lett 51:2849–2851
18. (a) Hanamoto T, Koga Y, Kido E, Kawanami T, Furuno H, Inanaga J (2005) Palladium catalyzed cross-coupling reaction of 5-tributylstannyl-4-fluoropyrazole. Chem Commun 2041–2043; (b) Hanamoto T, Iwamoto Y, Yamada K, Anno R (2007) *N*-arylation of 4-fluoro-5-trimethylsilyl-1*H*-pyrazole. J Fluor Chem 128:1126–1130; (c) Hanamoto T, Suetake T, Koga Y, Kawanami T, Furuno H, Inanaga J (2007) Synthesis and reactions of 5-tributylstannyl-4-fluoro-1*H*-pyrazole. Tetrahedron 63:5062–5070
19. Ishihara T, Okada Y, Kuroboshi M, Shinozaki T, Ando T (1988) A new effective and convenient route of fluorinated nitrogen heterocyclic compounds by the use of enol phosphates derived from F-alkyl ketones. Chem Lett 819–822
20. Funabiki K, Ohtsuki T, Ishihara T, Yamanaka H (1995) Reactions of 1-substituted-polyfluoro-1-propenyl *p*-toluenesulfonates with bifunctional nitrogen nucleophiles. A new expedient access to monofluorinated nitrogen heterocycles. Chem Lett 239–240
21. Bouillon JP, Didier B, Dondy B, Doussot P, Plantier-Royon R, Portella C (2001) Efficient synthesis of 4-fluoro-5-(perfluoroalkyl)pyrazoles from organofluorosilicon building blocks. Eur J Org Chem 187–192
22. Chanteau F, Plantier-Royon R, Portella C (2004) Synthesis of fluorinated homo-*C*-nucleoside analogues from new carbohydrate-derived acylsilanes. Synlett 512–516
23. Zhang Q, Lu L (2000) A novel synthetic route to ethyl 3-substituted-*trans*-2,3-difluoro-2-acrylates and their reactions with nucleophiles. Tetrahedron Lett 41:8545–8548
24. Sloop JC, Bumgardner CL, Loehle WD (2002) Synthesis of fluorinated heterocycles. J Fluor Chem 118:135–147

25. Breen JR, Sandford G, Yufit DS, Howard JAK, Fray J, Patel B (2011) Continuous gas/liquid-liquid/liquid flow synthesis of 4-fluoropyrazole derivatives by selective direct fluorination. Beil J Org Chem 7:1048–1054
26. Surmont R, Verniest G, De Kimpe N (2010) New synthesis of fluorinated pyrazoles. Org Lett 12:4648–4651
27. Cocconcelli G, Ghiron C, Haydar S, Micco I, Zanaletti R (2010) Synthesis of novel 4-fluoro-2H-pyrazol-3-ylamines. Synth Commun 40:2547–2555
28. Surmont R, Verniest G, De Schrijver M, Thuring JW, ten Holte P, Deroose F, De Kimpe N (2011) Synthesis of 3-amino-4-fluoropyrazoles. J Org Chem 76:4105–4111
29. Qian J, Liu Y, Zhu J, Jiang B, Xu Z (2011) A novel synthesis of fluorinated pyrazoles via gold(I)-catalyzed tanem aminofluorination of alkynes in the presence of selectfluor. Org Lett 13:4220–4223
30. Tang XQ, Hu CM (1994) Direct synthesis of 3-(fluoroalkyl)pyrazoles from polyfluoroalkyl aldehydes. J Chem Soc Perkin Trans 1:2161–2163
31. Tang XQ, Hu CM (1995) Synthesis of 3-perfluoroalkyl-, including 3-trifluoromethyl-, substituted pyrazoles from perfluoroalkylacetylenes. J Fluor Chem 73:129–131
32. Yu HB, Huang WY (1998) A novel precursor for per(poly)fluoroalkyl heterocycles from *N*-aryl per(poly)fluoroalkyl imidoyl iodides. J Fluor Chem 87:69–73
33. Tang XQ, Hu CM (1994) A novel and practical method for the synthesis of 3-trifluoromethylated pyrazoles. J Chem Soc Chem Commun 631–632
34. Linderman RJ, Kirollos KS (1989) An efficient method for the synthesis of trifluoromethyl substituted heterocycles. Tetrahedron Lett 30:2049–2052
35. Planquaert MA, Redon M, Janousek Z, Viehe HG (1996) 2-Phenylthio-3,3,3-trifluoropropene, its sulfoxide and sulfone. Synthesis and reactivity in 1,3-dipolar cycloadditions. Tetrahedron 52:4383–4396
36. (a) Fustero S, Sánchez-Roselló M, Barrio P, Simón-Fuentes A (2011). From 2000 to mid-2010. A fruitful decade for the synthesis of pyrazoles. Chem Rev 111:6084–7034; (b) Fustero S, Simón-Fuentes A, Sanz-Cervera JF (2009). Recent advances in the synthesis of pyrazoles. A review. Org Prep Proc Int 41: 253–290
37. Okada E, Masuda R, Hojo M (1992) Facile synthetic methods for 3- and 5-trifluoromethyl-4-trifluoroacetylpyrazoles and their conversion into pyrazole-4-carboxylic acids. Heterocycles 34:791–798
38. Touzot A, Soufyane M, Berber H, Toupet L, Mirand C (2004) Synthesis of trifluoromethylated pyrazoles from trifluoromethylenaminones and monosubstituted hydrazines. J Fluor Chem 125:1299–1304
39. Martins MAP, Pereira CMP, Zimmermann NEK, Cunico W, Moura S, Beck P, Zanatta N, Bonacorso HG (2003) Regiospecific synthesis of poly fluorinated heterocycles. J Fluor Chem 123:261–265
40. Martins MAP, Cunico W, Brondani S, Peres RL, Zimmermann NEK, Rosa FA, Fiss GF, Zanatta N, Bonacorso HG (2006) Synthesis of novel 3-amino-5-(trifluoromethyl)azoles: a convenient method of obtaining *N*-(azol-3-yl)amines. Synthesis 1485–1493
41. (a) Levkovskaya GG, Bozhenkov GV, Larina LI, Mirskova AN (2002) New synthesis and properties of 3-alkyl, 3-chloroalkyl, 3-perfluoroalkyl, and 3-aryl-1-methyl-5-halopyrazoles from chloro(bromo)vinyl ketones and *N,N*-dimethylhydrazone. Russ J Org Chem 38:1501–1506; (b) Bozhenkov GV, Levkovskaya GG, Mirskova AN, Dolgushin GV, Larina LI, Ushakov PE (2003) Chloro(bromo)vinyl ketones and 2,2-dichloroacrolein in reactions with hydrazines. Russ J Org Chem 39:1069–1075
42. (a) Kawase M, Hyrabayashi M, Saito S, Yamamoto K (1999) Heterocyclization of 4-trifluoroacetyl-2,3-dihydropyrroles with hydrazines and amidines: a new access to trifluoromethylated pyrazoles and pyrimidines bearing a β–aminoethyl side chain. Tetrahedron Lett 40:2541–2544; (b) Jones BG, Branch SK, Thompson AS, Threadgill MD (1996) Synthesis of a series of trifluoromethylpyrazoles and determination of pKa of acidic and basic trifluoromethyl heterocycles by ^{19}F NMR spectroscopy. J Chem Soc Perkin Trans 1: 2685–2691

43. (a) Bonacorso HG, Wastowski AD, Zanatta N, Martins MAP, Naue JA (1998) Haloacetylated enol ethers 10. Condensation of β-alkoxyvinyl trifluoromethyl ketones with thiosemicarbazide. Synthesis of new trifluoromethyl 4,5-dihydro-1*H*-1-pyrazolethiocarboxyamides. J Fluorine Chem 92:23–26; (b) Bonacorso HG, Wentz AP, Zanatta N, Martins MAP (2001) Regiospecific cyclization of β-methoxyvinyl trifluoromethyl ketones with aminoguanidine: a convenient method to obtain trifluoromethylated 2-[1*H*-pyrazol-1-yl]pyrimidines. Synthesis 1505–1508; (c) Song L, Chu Q, Zhu S (2001) Regioselective synthesis of fluorinated pyrazole derivatives from trifluoromethyl-1,3-diketone. J Fluor Chem 111:201–205; (d) Zanatta N, Flores DC, Madruga CC, Faoro D, Flores AFC, Bonacorso HG, Martins MAP (2003) Regiospecific cyclization of 4-alkoxyvinyl trifluoro(chloro)methyl ketones with 6-trifluoro(chloro)methyl-2-hydrazine pyrimidines. A convenient method to obtain trifluoro(chloro)methylated 2-(5-hydroxy-5-trifluoro(chloro)methyl 4,5-dihydro-1H-pyrazol-1-yl)pyrimidines. Synthesis 894–898; (e) Flores AFC, Brondani S, Pizutti L, Martins MAP, Zanatta N, Bonacorso HG (2005) Haloacetylated enol ethers, 19: Synthesis of 3-(2-thienyl)- and 3-(2-furyl)-5-trihalomethyl substituted azoles. Synthesis 2744–2750; (f) Bonacorso HG, Cechinel CA, Oliveira MR, Costa MB, Martins MAP, Zanatta N, Flores AFC (2005) An efficient and regiospecific preparation of trifluoromethyl-substituted 4-(1H-pyrazol-1-yl)-7-chloroquinolines. J Heterocycl Chem 42:1055–1061
44. Sanfilippo PJ, Urbanski MJ, Beers KN, Ecardt A, Falotico R, Ginsberg MH, Oxford S, Press JB, Tigre J, Tomko K, Andrade-Gordon P (1995) Novel thiazole-based heterocycles as selective inhibitors of fibrinogen-mediated platelet aggregation. J Med Chem 38:34–41
45. Donohue BA, Michelotti EL, Reader JC, Reader V, Stirling M, Tice CM (2002) Design, synthesis, and biological evaluation of a library of 1-(2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxamides. J Comb Chem 4:23–32
46. Singh SP, Kumar D (1997) A facile synthesis of 5-methyl-1-(phenyl/heterocyclyl)-4-trifluoroacetylpyrazoles. J Chem Research (S) 142–143
47. For the synthesis of 3,5-bis(trifluoromethyl)pyrazoles, see, e.g.: Claire PPK, Coe P, Jones CJ, McCleverty JA (1991) 3,5-Bis(trifluoromethyl)pyrazole and some *N*-substituted derivatives. J Fluor Chem 51:283–289
48. (a) Singh SP, Kapoor JK, Kumar D, Threadgill MD (1997) Reaction of hydrazinoquinolines with trifluoromethyl-β-diketones: structural and mechanistic studies. J Fluor Chem 83:73–79; (b) Singh SP, Kumar D, Jones BG, Threadgill MD (1999) Formation and dehydration of a series of 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazoles. J Fluor Chem 94:199–203; (c) Song L, Chu Q, Zhu S (2001) Synthesis of fluorinated pyrazole derivatives from β-alkoxyvinyl trifluoroketones. J Fluor Chem 107:107–112; (d) Norris T, Colon-Cruz R, Ripin DHB (2005) New hydroxyl-pirazoline intermediates, subtle region-selectivity and relative reaction rate variations observed during acid catalyzed and neutral pyrazole cyclization. Org Biomol Chem 3:1844–1849; (e) Singh SP, Kumar V, Aggarwal R, Elguero J (2006) The reaction of aryl and heteroarylhydrazines with aryltrifluoromethyl β-diketones. J Heterocycl Chem 43:1–12; (f) Fustero S, Román R, Sanz-Cervera JF, Simón-Fuentes A, Cuñat AC, Villanova S, Murguía M (2008) Improved regioselectivity in pyrazole formation through the use of fluorinated alcohols as solvents: synthesis and biological activity of fluorinated tebufenpyrad analogs. J Org Chem 73:3523–3529
49. Gosselin F, O'Shea PD, Webster RA, Reamer RA, Tillyer RD, Grabowski EJJ (2006) Highly regioselective synthesis of 1-aryl-3,4,5-substituted pyrazoles. Synlett 3267–3270
50. Yang X, Shui S, Chen X, He H, Wu F (2010) Synthesis of bromodifluoromethyl substituted pyrazoles and isoxazoles. J Fluor Chem 131:426–432
51. Humphries PS, Finefield JM (2006) Microwave-assisted synthesis utilizing supported reagents: a rapid and versatile synthesis of 1,5-diarylpyrazoles. Tetrahedron Lett 47:2443–2446
52. Yonetoku Y, Kubota H, Okamoto Y, Toyosima A, Funatsu M, Ishikawa J, Takeuchi M, Ohta M, Tsukamoto SI (2006) Novel potent and selective calcium-released-activated calcium (CRAC) channel inhibitors. Part 1: synthesis and inhibitory activity of 5-(1-methyl-3-trifluoromethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamides. Bioorg Med Chem 14:4750–4760

53. Singh SP, Kumar D, Batra H, Naithani R, Rozas I, Elguero J (2000) The reaction between hydrazines and β-dicarbonyl compounds: proposal for a mechanism. Can J Chem 78:1109–1120
54. Shavnya A, Sakya SM, Munich ML, Rast B, DeMello KL, Jaynes BH (2005) Efficient fluoride-mediated synthesis of 5-alkyl amino- and ether-substituted pyrazoles. Tetrahedron Lett 46:6887–6891. For the regioselective synthesis of 1-alkyl-5-fluoroalkyl-3-hydroxypyrazoles, see: Hamper BC, Kurtzweil ML, Beck JP (1992) Cyclocondensation of alkylhydrazines and β-substituted acetylenic esters: Synthesis of 3-hydroxypyrazoles. J Org Chem 57:5680–5686
55. Yamanaka H, Takekawa T, Morita K, Ishihara T, Gupton J (1998) Preparation of novel β-trifluoromethyl vinamidium salt and its synthetic application to trifluoromethylated heterocycles. Tetrahedron Lett 37:1829–1832
56. Kamitori Y, Hojo M, Masuda R, Ohara S, Kawasaki K, Yoshikawa N (1988) Convenient synthesis of 4-trifluoromethylpyrazoles by cyclization of trifluoroacetylated hydrazones. Tetrahedron Lett 29:5281–5284
57. Zheng J, Wang Z, Shen Y (1993) A facile synthesis of fluoroalkylpyrazoles. J Fluor Chem 61:17–21
58. (a) Meazza G, Zanardi G (1994) Synthesis of triaryl-4-trifluoromethylpyrazoles via 1,3-dipolar cycloaddition. J Fluor Chem 67:183–187; (b) Meazza G, Zanardi G, Piccardi P (1993) A convenient and versatile synthesis of 4-trifluoromethyl-substituted pyrazoles. J Heterocycl Chem 30:365–71
59. Hanamoto T, Hakoshima Y, Egashira M (2004) Tributyl(3,3,3-trifluoro-1-propynyl)stannane as an efficient reagent for the preparation of various trifluoromethylated heterocyclic compounds. Tetrahedron Lett 45:7573–7576
60. Elguero J, Goya P, Jagerovic N, Silva AMS (2002) Pyrazoles as drugs: facts and fantasies. In: Attanasi OA, Spinelli D (eds) Targets in heterocyclic systems. Italian Society of Chemistry, Roma
61. Elguero J (1996) In: Katritzky AR, Rees CW, Scriven EFV (eds) Comprehensive heterocyclic chemistry II. Oxford, Elsevier
62. Stadlbauer W (2002) In: in science of synthesis. Georg-Thieme, NewYork
63. Petrenko NI, Gerasimova TN (1990) Stereoisomers of pentafluorobenzaldehyde and pentafluoroacetophenone phenylhydrazones. J Fluor Chem 49:359–366
64. Hathaway BA, Day G, Lewis M, Glaser R (1998) Synthesis, structure, electrostatic properties and spectroscopy of 3-methyl-4,5,6,7-tetrafluoro-1H-indazole. An experimental and ab initio computational study. J Chem Soc, Perkin Trans 2:2713–2719; (b) Claramunt RM, López C, Pérez-Medina C, Pérez-Torralba M, Elguero J, Escames G, Acuña-Castroviejo D (2009) Fluorinated indazoles as novel selective inhibitors of nitric oxide synthase (NOS): synthesis and biological evaluation. Bioorg Med Chem 17:6180–6187; (c) Teichert J, Oulié P, Jacob K, Vendier L, Etienne M, Claramunt RM, López C, Pérez-Medina C, Alkorta I, Elguero J (2007) The structure of fluorinated indazoles: the effect of the replacement of a H by a F atom on the supramolecular structure of NH-indazoles. New J Chem 31:936–946
65. (a) Baldwin IR, Down KD, Faulder P, Gaines S, Hamblin JN, Le J, Lunniss CJ, Parr NJ, Ritchie TJ, Robinson JE, Simpson JK, Smethurst CAP (2009) Benzylpyrazol derivatives as inhibitors of P13 kinases. Patent: WO 2009147188; (b) Baldwin IR, Down KD, Faulder P, Gaines S, Hamblin JN, Le J, Lunniss CJ, Parr NJ, Ritchie TJ, Robinson JE, Simpson JK, Smethurst CAP (2011) Benzylpyrazol derivatives as inhibitors of P13 kinases. Patent: WO 2011067365
66. Dupre V, Pechmeze J, Sureau R (1975) Neue fluorierte Indazolderivate und Verfahren zu ihrer Herstellung. Ger Offen 25:13801; (1976) Chem Abs 84:17337
67. Zhu GD, Gong J, Gandhi VB, Woods K, Luo Y, Liu X, Guan R, Klinghofer V, Johnson EF, Stoll VS, Mamo M, Li Q, Rosenberg SH, Giranda VL (2007) Design and synthesis of pyridine–pyrazolopyridine-based inhibitors of protein kinase B/Akt. Bioorg Med Chem 15:2441–2452
68. O'Dell DK, Nicholas KM (2004) Synthesis of 1H-indazoles by reductive cyclization of o-nitro-ketoximes. Heterocycles 63:373–382

69. (a) Grushin VV, Marshall WJ (2006) Facile Ar–CF_3 bond formation at Pd. strikingly different outcomes of reductive elimination from [$(Ph_3P)_2Pd(CF_3)Ph$] and [(Xantphos)$Pd(CF_3)Ph$]. J Am Chem Soc 128:12644–12645; (b) Ball ND, Kampf JW, Sanford MS (2010) Aryl-CF3 bond-forming reductive elimination from palladium (IV). J Am Chem Soc 132:2878–2879; (c) Ye Y, Ball ND, Kampf JW, Sanford MS (2010) Oxidation of a cyclometalated Pd(II) dimer with "CF3+": formation and Reactivity of a catalytically competent Monomeric Pd(IV) aquo complex. J Am Chem Soc 132:14682–14687; (d) Wang X, Truesdale L, Yu JQ (2010) Pd(II)-catalyzed ortho-trifluoromethylation of arenes using TFA as a promoter. J Am Chem Soc 142:3648–3649; (e) Cho EJ, Senecal TD, Kinzel T, Zhang Y, Watson DA, Buchwald SL (2010) The palladium-catalyzed trifluoromethylation of aryl chlorides. Science 328:1679–1681
70. Nakano S, Taisuke I, Yamanishi K, Wada Y, Morimoto A (2010) Indazole compounds. Patent: US 2010160256
71. Pelc M, Huang W, Trujillo J, Baldus J, Turner S, Kleine P, Yang S, Thorarensen A (2010) An efficient and regioselective difluoromethylation of 3-iodoindazole with chlorodifluoromethane. Synlett 219–222
72. See, e.g.: (a) Kobayashi Y, Hamana H, Fujino S, Ohsawa A, Kumadaki I (1979) Studies in organic fluorine compounds. 29. Cycloaddition of hexakis(trifluoromethyl)-1,4-diphosphsbarrelene. J Org Chem 44:4930–4933; (b) Atherton JH, Fields RJ (1968) Cycloaddition reactions of 2,2,2-trifluorodiazoethane. J Chem Soc C 1507–1513
73. Gerus II, Mironetz RX, Kondratov IS, Bezdudny AV, Dmytriv YV, Shishkin OV, Starova VS, Zaporozhets OA, Tolmachev AA, Mykhailiuk PK (2012) "Reported, but still unknown". A closer look into 3,4-bis- and 3,4,5-tris(trifluoromethyl)pyrazoles. J Org Chem 77:47–56
74. Dalinger IL, Shkineva TK, Bastadse IA, Popota GP, Shevelev SA (2011) *N*-fluoro derivatives of nitrated pyrazole-containing fused heterocycles. Mendeleev Commun 21:48–49
75. Hanamoto T, Egashira M, Ishizuka K, Furuno H, Inanaga J (2006) Synthesis and reactions of 1-methyl-5-tributylstannyl-4-trifluoromethylpyrazole. Tetrahedron 62:6332–6338
76. Penning TD, Talley JJ, Bertenshaw SR, Carter JS, Collins PW, Docter S, Graneto MJ, Lee LF, Malecha JW, Miyashiro JM, Rogers RS, Rogier DJ, Yu SS, Anderson GD, Burton EG, Cogburn JN, Gregory SA, Koboldt CM, Perkins WE, Seibert K, Veenhuizen AW, Zhang YY, Isakson PC (1997) Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (SC-58365, celecoxib). J Med Chem 40:1347–1365
77. (a) Habeeb AG, Rao PNP, Knaus EE (2001) Design and synthesis of celecoxib and rofecoxib analogues as selective cyclooxygenase-2 (COX-2) inhibitors: replacement of sulfonamide and methylsulfonyl pharmacophores by an azido bioisostere. J Med Chem 44:3039–3042; (b) Singh SK, Vobbalareddy S, Shivaramakrishna S, Krishnamraju A, Rajjak SA, Casturi SR, Akhila V, Rao YK (2004) Methanesulfonamide group at position-4 of the C-5-phenyl ring of 1,5-diarylpyrazole affords a potent class of cyclooxygenase-2 (COX-2) inhibitors. Bioorg Med Chem Lett 14:1683–1688
78. (a) Singh SK, Reddy PG,; Rao KS, Lohray BB, Misra P, Rajjak SA, Rao YK, Venkateswarlu A (2004) Polar substitutions in the benzenesulfonamide ring of celecoxib afford a potent 1,5-diarylpyrazole class of COX-2 inhibitors. Bioorg Med Chem Lett 14:499–504 (b) Singh SK, Vobbalareddy S, Kalleda SR, Rajjak SA, Casturi SR, Datla SR, Mamidi RNVS, Mullangi R, Bhamidipati R, Ramanujan R, Akella V, Yelewarapu KR (2004) 2-Hydroxymethyl-4-[5-(4-methoxyphenyl)-3-trifluoromethyl-1*H*-1-pyrazolyl]-1-benzenesulfonamide (DRF-4367): an orally active COX-2 inhibitor identified through pharmacophoric modulation. Org Biomol Chem 2:2442–1450
79. Chowdhury MA, Abdellatif KRA, Dong Y, Das D, Suresh MR, Knaus EE (2009) Synthesis of celecoxib analogues possessing a *N*-difluoromethyl-1,2-dihydropyrid-2-one 5-lipoxygenase pharmacophore: biological evaluation as dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity. J Med Chem 52:1525–1529
80. Chowdhury MA, Abdellatif KRA, Dong Y, Yu G, Huang Z, Rahman M, Das D, Velázquez CA, Suresh MR, Knaus EE (2010) Celecoxib analogs possessing a *N*-(4-nitrooxybutyl) piperidin-4-yl or *N*-(4-nitrooxybutyl)-1,2,3,6-tetrahydropyridin-4-yl nitric oxide donor

moiety: synthesis, biological evaluation and nitric oxide release studies. Bioorg Med Chem Lett 20:1324–1329

81. (a) Pinto DJP, Orwat MJ, Wang S, Fevig JM, Quan ML, Amparo E, Cacciola J, Rossi KA, Alexander RS, Smallwood AM, Luettgen JM, Liang L, Aungst BJ, Wright MR, Knabb RM, Wong PC, Wexler RR, Lam PYS (2001) Discovery of 1-[3-(aminomethyl)phenyl]-*N*-[3-fluoro-2′-(methylsulfonyl)-[1,1′-biphenyl]-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide (DPC423), a highly potent, selective, and orally bioavailable inhibitor of blood coagulation factor Xa. J Med Chem 44:566–578; (b) Pruitt JR, Pinto DJP, Galemmo RA, Alexander RS, Rossi KA, Wells BL, Drummond S, Bostrom LL, Burdick D, Bruckner R, Chen H, Smallwood AM, Wong PC, Wright MR, Bai S, Luettgen JM, Knabb RM, Lam PYS, Wexler RR (2003) Discovery of 1-(2-aminomethylphenyl)-3-trifluoromethyl-*N*-[3-fluoro-2′-(aminosulfonyl)[1,2′-biphenyl)]-4-yl]-1*H*-pyrazole-5-carboxamide (DPC602), a potent, selective, and orally bioavailable factor Xa inhibitor. J Med Chem 46:5298–5315
82. Quan ML, Lam PYS, Han Q, Pinto DJP, He MY, Li R, Ellis CD, Clark CG, Teleha CA, Sun JH, Alexander RS, Bai S, Luettgen JM, Knabb RM, Wong PC, Wexler RR (2005) Discovery of 1-(3′-aminobenzisoxazol-5′-yl)-3-trifluoromethyl-*N*-[2-fluoro-4-[(2′-dimethylaminomethyl) imidazol-1-yl]phenyl]-1*H*-pyrazole-5-carboxamide hydrochloride (razaxaban), a highly potent, selective, and orally bioavailable factor Xa inhibitor. J Med Chem 48:1729–1744
83. (a) Fevig JM, Cacciola J, Buriak JJr, Rossi KA, Knabb RM, Luettgen JM, Wong PC, Bai SA, Wexler RR, Lam PYS (2006) Preparation of 1-(methoxyphenyl)-1*H*-pyrazolo[4,3-*d*] pyrimidin-7(6*H*)-ones as potent, selective and bioavailable inhibitors of coagulation factor Xa. Bioorg Med Chem Lett 16:3755–3760; (b) Pinto DJP, Orwat MJ, Quan ML, Han Q, Galemmo RA Jr, Amparo E, Wells B, Ellis CD, He MY, Alexander RS, Rossi KA, Smallwood A, Wong PC, Luettgen JM, Rendina AR, Knabb RM, Mersinger L, Kettner C, Bai S, He K, Wexler RR, Lam PYS (2006) 1-[3-aminobenzisoxazol-5′-yl]-3-trifluoromethyl-6-[2′-(3-(*R*)-hydroxy-*N*-pyrrolidinyl)methyl-[1,1′]-biphen-4-yl]-1,4,5,6-tetrahydropyrazolo-[3,4-*c*]-pyridin-7-one (BMS-740808) a highly potent, selective, efficacious, and orally bioavailable inhibitor of blood coagulation factor Xa. Bioorg Med Chem Lett 16:4141–4147; (c) Li YL, Fevig JM, Cacciola J, Buriak J Jr, Rossi KA, Jona J, Knabb RM, Luettgen JM, Wong PC, Bai SA, Wexler RR, Lam PYS (2006) Preparation of 1-(3-aminobenzo[*d*]isoxazol-5-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones as potent, selective, and efficacious inhibitors of coagulation factor Xa. Bioorg Med Chem Lett 16:5176–5182; (d) Qiao JX, Cheng X, Smallheer JM, Galemmo RA, Drummond S, Pinto DJP, Cheney DL, He K, Wong PC, Luettgen JM, Knabb RM, Wexler RR, Lam PYS (2007) Pyrazole-based factor Xa containing *N*-arylpiperidinyl P4 residues. Bioorg Med Chem Lett 17:1432–1437
84. Lee YK, Parks DJ, Lu T, Thieu TV, Markotan T, Pan W, McComsey DF, Milkiewicz KL, Crysler CS, Ninan N, Abad MC, Giardino EC, Maryanoff BE, Damiano BP, Player MR (2009) 7-Fluoroindazoles as potent and selective inhibitors of actor Xa. J Med Chem 51:282–297
85. Gilbert AM, Bursavich MG, Lombardi S, Georgiadis KE, Reifenberg E, Flannery CR, Morris EA (2007) 5-((1*H*-Pyrazol-4-yl)methylene-2-thioxothiazolidin-4-one inhibitors of ADAMTS-5. Bioorg Med Chem Lett 17:1189–1192
86. (a) Yonetoku Y, Kubota H, Okamoto Y, Toyoshima A, Funatsu M, Ishikawa J, Takeuchi M, Ohta M, Tsukamoto S (2006) Novel potent and selective calcium-release-activated calcium (CRAC) channel inhibitors. Part 1: Synthesis and inhibitory activity of 5-(1-methyl-3-trifluoromethy-1*H*-pyrazol-5-yl)-2-thiophenecarboxamides. Bioorg Med Chem 14:4750–4760; (b) Yonetoku Y, Kubota H, Okamoto Y, Ishikawa J, Takeuchi M, Ohta M, Tsukamoto S (2006) Novel potent and selective calcium-release-activated calcium (CRAC) channel inhibitors. Part 2: Synthesis and inhibitory activity of aryl-3-trifluoromethylpyrazoles. Bioorg Med Chem 14:5370–5383; (c) Yonetoku Y, Kubota H, Miyazaki Y, Okamoto Y, Funatsu M, Yoshimura-Ishikawa N, Ishikawa J, Yoshino T, Takeuchi M, Ohta M (2008) Novel potent and selective Ca^{+2} release-activated Ca^{+2} (CRAC) channel inhibitors. Part 3: Synthesis and CRAC channel inhibitory activity of 4′-[(trifluoromethyl)pyrazol-1-yl]carboxanilides. Bioorg Med Chem 16:9457–9466

87. Djuric SW, BaMaung N, Basha A, Liu H, Luly JR, Madar DJ, Sciotti RJ, Tu NP, Wagenaar FL, Wiedeman PE, Zhou X, Ballaron S, Bauch J, Chen YW, Chiou XG, Fey T, Gauvin D, Gubbins E, Hsieh GC, Mersh KC, Mollison KW, Pong M, Shaughnessy TK, Sheets MP, Smith M, Trevillyan JM, Warrior U, Wegner CD, Carter GW (2000) 3,5-Bis(trifluoromethyl) pyrazoles. A novel class of NFAT transcription factor regulator. J Med Chem 43:2975–2981
88. (a) Sun A, Chandrakumar N, Yoon JJ, Plemper RK, Snyder JP (2007) Non-nucleoside inhibitors of the measles virus RNA-dependent RNA polymerase complex activity: synthesis and in vitro evaluation. Bioorg Med Chem Lett 17:5199–5203; (b) Sun A, Yoon JJ, Yin Y, Prussia A, Yang Y, Min J, Plemper RK, Snyder JP (2008) Potent non-nucleoside inhibitors of the measles virus RNA-dependent RNA polymerase complex. J Med Chem 51:3731–3741
89. Huang KH, Veal JM, Fadden P, Rice JW, Eaves J, Strachan JP, Barabasz AF, Foley BE, Barta TE, Ma W, Silinski MA, Hu M, Partridge JM, Scott A, DuBois LG, Freed T, Steed PM, Ommen AJ, Smith ED, Hughes PF, Woodvard AR, Hanson GJ, McCall WS, Markworth CJ, Hinkley L, Jenks M, Geng L, Lewis M, Otto J, Pronk B, Verleysen K, Hall SE (2009) Discovery of novel 2-aminobenzamide inhibitors of heat shock protein 90 as potent, selective and orally active antitumor agents. J Med Chem 52:4288–4305
90. Qi J, Zhang F, Mi Y, Fu Y, Xu W, Zhang D, Wu Y, Du X, Jia Q, Wang K, Zhang H (2011) Design, synthesis and biological activity of pyrazolo[1,5-a]pyrimidin-7(4H)-ones as novel Kv7/KCNQ potassium channel activators. Eur J Med Chem 46:934–943
91. Millis DL, Weigel JP, Moyers T, Buonomo FC (2002) Effect of derecoxib, a new COX-2 inhibitor, on the prevention of lameness induced by chemical synovitis in dogs. Vet Ther 3:453–464
92. (a) Li J, DeMello KML, Cheng H, Sakya SM, Bronk BS, Rafka RJ, Jaynes BH, Ziegler CB, Kilroy C, Mann DW, Nimz EL, Lynch MP, Haven ML, Kolosko NL, Minich ML, Li C, Dutra JK, Rast B, Crosson RM, Morton BJ, Kirk GW, Callaghan KM, Koss DA, Shavnya A, Lund LA, Seibel SB, Petras CF, Silvia A (2004) Discovery of a potent, selective and orally active canine COX-2 inhibitor, 2-(3-difluoromethyl-5-phenyl-pyrazol-1-yl)-5-methanesulfonylpyridine. Bioorg Med Chem Lett 14:95–98; (b) Li J, Lynch MP, DeMello KL, Sakya SM, Cheng H, Rafka RJ, Bronk BS, Jaynes BH, Kilroy C, Mann DW, Haven ML, Kolosko NL, Petras C, Seibel SB, Lund LA (2005) In vitro and in vivo profile of 2-(3-difluoromethyl-5-phenyl-pyrazol-1-yl)-5-methanesulfonylpyridine, a potent, selective, and orally canine COX-2 inhibitor. Bioorg Med Chem 13:1805–1809
93. (a) Sakya SM, DeMello KML, Minich ML, Rast B, Shavnya A, Rafka RJ, Koss DA, Cheng H, Li J, Jaynes BH, Ziegler CB, Mann DW, Petras CF, Seibel SB, Silvia AM, George DM, Lund LA, St. Denis S, Hickman A, Haven ML, Lynch MP (2006) 5-Heteroatom substituted pyrazoles as canine COX-2 inhibitors. Part 1: Structure-activity relationship studies of 5-alkylamino pyrazoles and discovery of a potent, selective, and orally active analog. Bioorg Med Chem Lett 16:288–292; (b) Sakya SM, Hou X, Minich ML, Rast B, Shavnya A, DeMello KML, Cheng H, Li J, Jaynes BH, Mann DW, Petras CF, Seibel SB, Haven M (2007) 5-Heteroatom substituted pyrazoles as canine COX-2 inhibitors. Part III: Molecular modeling studies on binding contribution of 1-(5-methylsulfonyl)pyrid-2-yl and 4-nitrile. Bioorg Med Chem Lett 17:1067–1072
94. Cheng H, DeMello KML, Li J, Sakya SM, Ando K, Kawamura K, Kato T, Rafka RJ, Jaynes BH, Ziegler CB, Stevens R, Lund LA, Mann DW, Kilroy C, Haven ML, Nimz EL, Dutra JK, Li C, Minich ML, Kolosko NL, Petras C, Silvia AM, Seibel SB (2006) Synthesis and SAR of heteroaryl-phenyl-substituted pyrazole derivatives as highly selective and potent canine COX-2 inhibitors. Bioorg Med Chem Lett 16:2076–2080
95. Cunico W, Cechinel CA, Bonacorso HG, Martins MAP, Zanatta N, de Souza MVN, Freitas IO, Soares RPP, Kettli AU (2006) Antimalarial activity of 4-(5-trifluoromethyl-1*H*-pyrazol-1-yl)chloroquine analogues. Bioorg Med Chem Lett 16:649–653
96. Culbreath AK, Brenneman TB, Kemerait RC Jr, Hammes GG (2009) Effect of the new pyrazole carboxamide fungicide penthiopyrad on late leaf spot and steam rot of peanut. Pest Manag Sci 65:66–73

97. Lahm GP, Selby TP, Freudenberger JH, Stevenson TM, Myers BM, Seburyamo G, Smith BK, Flexner L, Clark CE, Cordova D (2005) Insecticidal anthranilic diamides: a new class of potent ryanodine receptor activators. Bioorg Med Chem Lett 15:4898–4906
98. Fustero S, Román R, Sanz-Cervera JF, Simón-Fuentes A, Bueno J, Villanova S (2008) Synthesis of new fluorinated tebufenpyrad analogs with acaricidal activity through regioselective pyrazole formation. J Org Chem 73:8545–85552
99. See, e.g.: (a) Dunkel R, Gary S, Grosjean-Cournoyer MC, Ronolfi P, Tuch A (2008) Preparation of fungicide *N*-cycloalkyl carboxamide derivatives. Patent: WO 2008015189; (b) Elbe HL, Rieck H, Dunkel R, Zhu-Ohlbach Q, Mauler-Machnik A, Wachendorff-Neumann U, Kuck KH (2003) Preparation of 1*H*-pyrazole-4-carboxanilides as agricultural fungicides and bactericides. Patent: WO 2003010149; (c) Elbe HL, Rieck H, Dunkel R, Wachendorff-Neumann U, Mauler-Machnik A, Kuck KH, Kugler M, Jaetsch T (2002) Preparation of *N*-biphenylpyrazolecarbox amides as bactericides. Patent: WO 2002008195; (d) Elbe HL, Mauler-Machnik A, Stenzel KU, Kuck KH, Kugler M, Jaetsch T (2000) Pyrazolecarboxanilides. Patent: DE 19840322
100. Ikegami H, Jachmann M, Nokura Y, Iwata C (2007) Hydrazide compound and pesticidal use of the same. Patent: WO 2007043677
101. Black J, Boehmer JE, Chrystal EJT, Kozakiewicz AM, Plant A (2007) Novel herbicides. Patent: WO 2007071900
102. For comprehensive reviews on the application of pyrazoles as ligands in coordination chemistry, see: (a) Ojwach SO, Darkwa J (2010) Pyrazole and (pyrazol-1-yl)metal complexes as carbon-carbon coupling catalysts. J Inorg Chim Acta 363:1947–1964; (b) Halcrow MA (2009) Pyrazoles and pyrazolides-flexible synthons in self-assembly. Dalton Trans 2059–2073
103. Schnyder A, Togni A, Wiesli U (1997) Electronic effects in asymmetric catalysis. Synthesis and structure of model rhodium complexes containing ferrocenyl ligands for use in the hydroboration reaction. Organometallics 16:255–260
104. (a) Dias RHV, Wang Z, Jin W (1997) Synthesis and chemistry of [hydrotris(3,5-bis(trifluoromethyl) pyrazolyl)borato]silver (I) complexes. Inorg Chem 36:6205–6215; (b) Dias RHV, Kim HJ, Lu, HL, Rajeshwar K, de Tacconi NR, Derecskei-Kovacs A, Marynick DS (1996) Investigation of the electronic and geometric effects of trifluoromethyl substituents on tris(pyrazolyl)borate ligands using manganese(I) and copper(I) complexes. Organometallics 15:2994–3003
105. Song YH, Chen YL, Chi Y, Liu CS, Ching WL, Kai JJ, Chen RS, Huang YS, Carty AJ (2003) Deposition of conductive Ru and RuO_2 thin films employing a pyrazolate complex $[Ru(CO)_3(3,5\text{-}(CF_3)_2Pz]_2$ as the CVD source reagent. Chem Vap Depos 9:162–169
106. Wang Z, Abernethy CD, Cowley AH, Jones JN, Jones RA, Macdonald CLB, Zhang L (2002) Synthesis and structures of 3,5-bis(trifluoromethyl)pyrazol derivatives of Rh(I), Ir(I), Pd(II) and Pt(II). J Organomet Chem 666:35–42
107. (a) Dias HVR, Diyabalanage HVK, Rawashdeh-Omary MA, Franzman MA, Omary MA (2003) Bright phosphorescence of a trinuclear copper(I) complex: luminiscence thermocroism, solvatochroism, and "concentration luminochroism". J Am Chem Soc 125:12072–12073; (b) Omary MA, Rawashdeh-Omary MA, Diyabalanage HVK, Dias HVR (2003) Blue phosphors of dinuclear and mononuclear copper(I) and silver(I) complexes of 3,5-bis(trifluoromethyl) pyrazolate and the related bis(pyrazolyl)borate. Inorg Chem 42:8612–8614
108. Omary MA, Rawashdeh-Omary MA, Gonser MWA, Elbjereirami O, Grimes T, Cundari T, Diyabalanage HVK, Gamage CSP, Dias HVR (2005) Metal effect on the supramolecular structure, photophysics, and acid–base character of trinuclear pyrazolato coinage metal complexes. Inorg Chem 44:8200–8210

Fluorinated Imidazoles and Benzimidazoles

Gordon W. Gribble, Sudipta Roy, and Sujata Roy

Contents

Abstract Synthetic approaches towards the preparation of various fluoro-functionalized imidazoles and benzimidazoles are discussed in this chapter.

Keywords Benzimidazole • Fluorination • Fluoroalkylation • Imidazole • Trifluoromethylation

1 Introduction

Imidazoles and benzimidazoles are privileged scaffolds that are present in many biologically active molecules, natural products, pharmaceuticals, and agrochemicals (Figs. 1, 2, 3 and 4) [1, 2]. The imidazole-containing essential amino acid histidine is the precursor of histamine. Histidine and histamine play critical roles in many physiological functions. Anti-histamine drugs (H_1-receptor antagonists or inverse agonists) are popular allergy medications [e.g. fexofenadine (Allegra),

G.W. Gribble (✉) • S. Roy • S. Roy
Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA
e-mail: Gordon.W.Gribble@dartmouth.edu

V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_8,

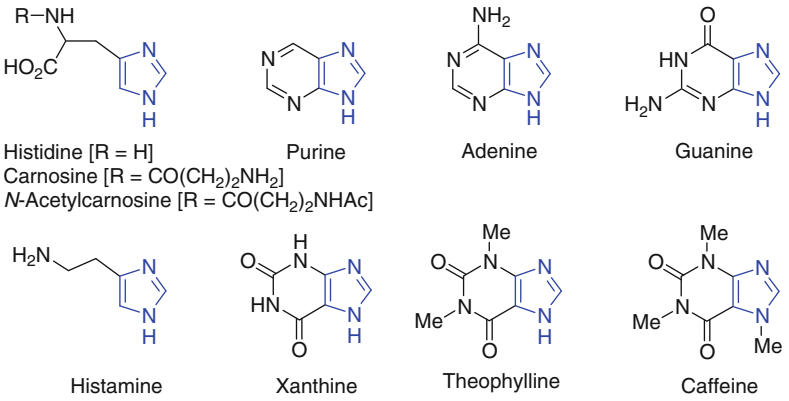


Fig. 1 Naturally-occurring compounds bearing imidazole core

loratadine (Claritin), diphenhydramine (Benadryl), cetirizine (Zyrtec)]. Purines (adenine, guanine), xanthine, theophylline, caffeine, carnosine, and *N*-acetylcarnosine (NAC) have the imidazole nucleus in their skeletons (Fig. 2). Although a large number of pharmaceuticals and agrochemicals contain an imidazole or benzimidazole core, as shown in Figs. 2, 3 and 4, the number of pharmaceuticals and agrochemicals bearing fluorinated imidazoles and benzimidazoles is relatively small (approximately 25–30 % of pharmaceuticals and agrochemicals contain fluorine) [3]. This might be partially attributed to the difficulty in the rapid preparation of a large number of targeted fluorinated imidazole and benzimidazole analogs during the discovery process.

Imidazole-based ligands and *N*-heterocyclic carbenes have shown remarkable catalytic effects on many organic reactions [4]. Fluoroalkyl-derivatized imidazolium-based ionic liquids are becoming increasing important in the material science area. Besides relative thermal stability and potential use as green solvents, imidazolium ionic liquids are also useful in biphasic reaction catalysis, conductive membranes, dye-sensitized solar cells, atom transfer radical polymerization, and as water purification agents [5]. Furthermore, 2-trifluoromethyl-4,5-dicyanoimidazole lithium salt (LiTDI) shows promising results in rechargeable lithium battery technology [6].

As the most electronegative element, fluorine polarizes the C–F bond which enhances the bond strength (CH_3–**F:** 109 kcal/mol, Ph–**F:** 127 kcal/mol *vs.* CH_3–**I:** 58 kcal/mol, CH_3–**Br:** 71 kcal/mol) and decreases bond length ($_{sp3}$C–**F:** 1.39 Å, $_{sp2}$C–**F:** 1.34 Å vs. $_{sp3}$C–**I:** 2.15 Å, $_{sp3}$C–**Br:** 1.95 Å and $_{sp3}$C–**H:** 1.09 Å, $_{sp2}$C–**H:** 1.08 Å) [7]. The effect of fluorine on the physical properties of imidazole is exemplified by the lower pKa of 2- and 4-fluoroimidazoles (pKa ~ 2.4 – 2.5) compared to imidazole (pKa ~ 6.9). Likewise, pKa of 2- and 4-(difluoromethyl) imidazoles are lower (3.4 and 4.1, respectively) than the pKa of 2- and 4-methylimidazoles (~7.5–7.9).

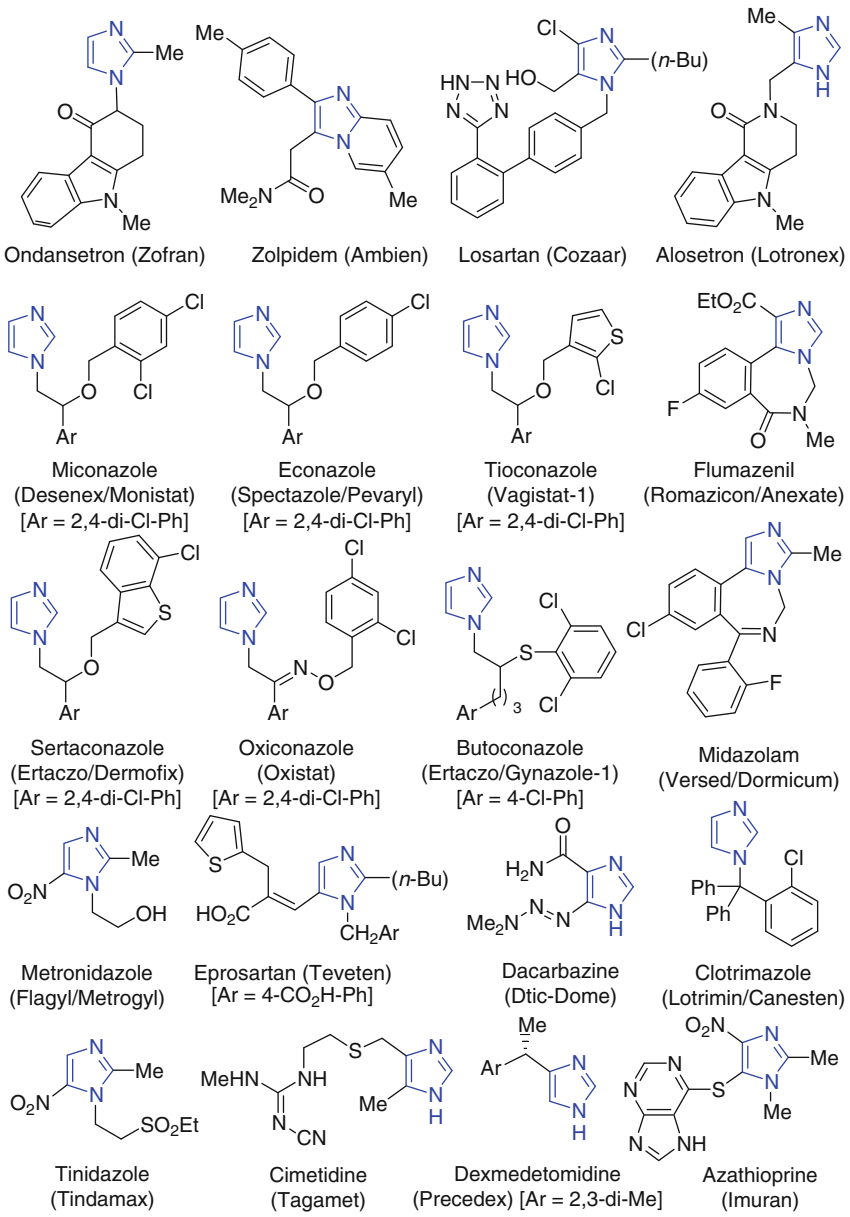


Fig. 2 Representative imidazole-bearing pharmaceuticals

In this chapter, we discuss the various synthetic strategies that allow for the preparation of a wide variety of fluorine-containing imidazoles and benzimidazoles.

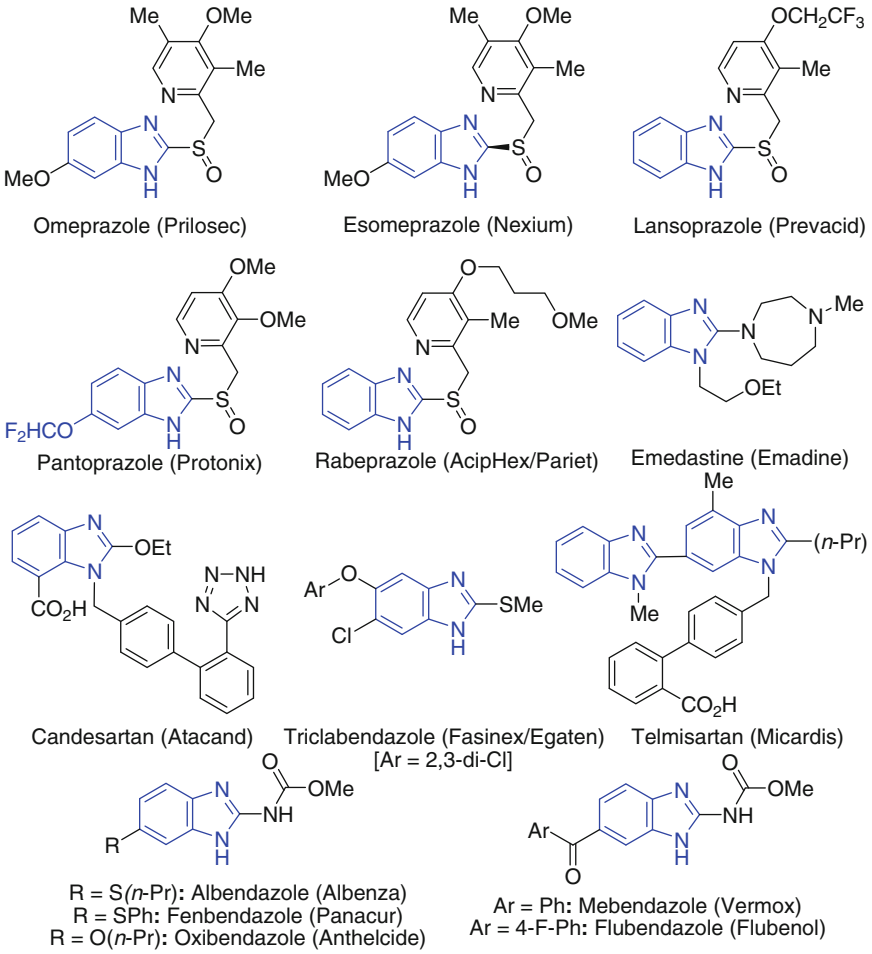


Fig. 3 Representative benzimidazole-bearing pharmaceuticals

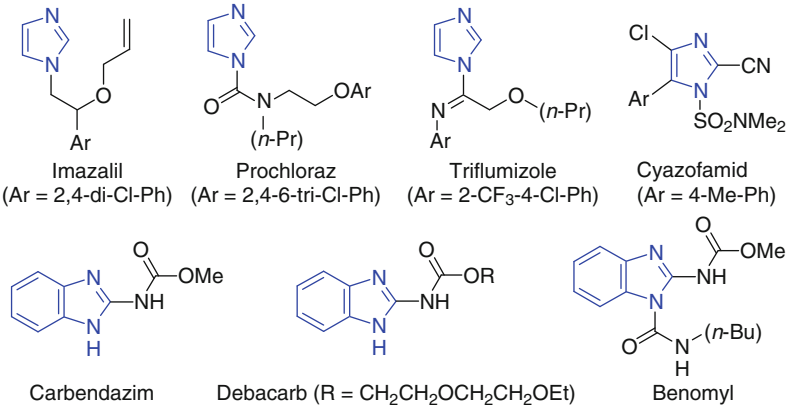
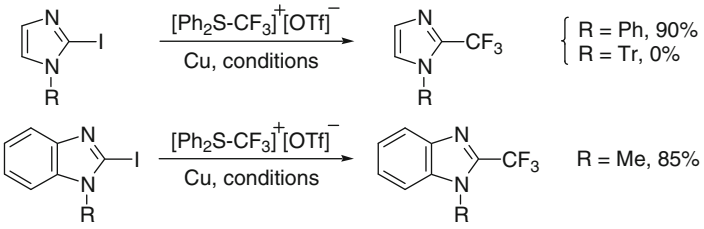


Fig. 4 Representative imidazole/benzimidazole-bearing agrochemicals

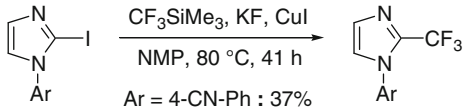
2 Synthesis of 2-Trifluoromethylimidazoles, Benzimidazoles and Related Analogs

The copper-catalyzed trifluoromethylation of *N*-phenyl-2-iodoimidazole and *N*-methyl-2-iodobenzimidazole using *S*-(trifluoromethyl)diphenyl iodonium triflate afforded the corresponding C-2 trifluoromethylated derivatives in 85–90 % yields (Scheme 1) [8]. Interestingly, the trifluoromethylation of *N*-tritylimidazole failed, even at 80 °C, presumably due to the steric effect of the trityl group.



Scheme 1

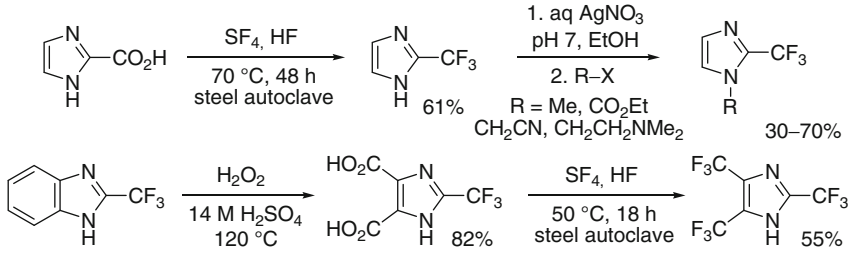
During the preparation of novel imidazoles as potential therapeutics for the treatment of inflammation, Mano and co-workers used Urata-Fuchikami's trifluoromethylation method to convert a 2-iodoimidazole to its trifluoromethylated derivative (Scheme 2) [9]. However, only a moderate yield was obtained for this reaction.



Scheme 2

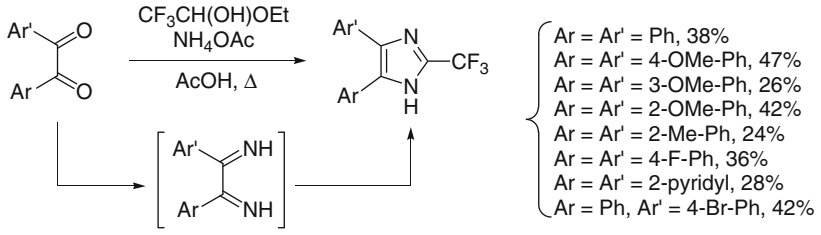
In an early approach to the synthesis of 2-trifluoromethylimidazole, Tatlow and co-workers employed SF_4 for the conversion of imidazole-2-carboxylic acid to *N*-unprotected 2-trifluoromethylimidazole (Scheme 3) [10]. The prerequisite imidazole-2-carboxylic acid was prepared from *N*-benzylimidazole via low-temperature C-2 lithiation using MeLi, followed by quenching with CO_2 and subsequent debenzylation. 2-Trifluoromethylimidazole is prone to undergo hydrolysis upon treatment with aqueous sodium hydroxide to give sodium imidazole-2-carboxylate [11]. Thus, *N*-alkylation of 2-trifluoromethylimidazole was carried out by mixing 2-trifluoromethylimidazole with silver nitrate to quantitatively precipitate the silver salt of 2-trifluoromethylimidazole, which was subsequently treated with alkylating agents, such as bromomethane, ethyl bromoacetate, *N*,*N*-dimethyl-*2*-chloroethylamine, and chloroacetonitrile to afford the corresponding *N*-alkyl-2-trifluoromethylimidazoles.

Treatment of 2-trifluoromethylimidazole-4,5-dicarboxylic acid, prepared by the oxidation of 2-trifluoromethylbenzimidazole, with SF_4–HF also afforded 2,4,5-tris(trifluoromethyl)imidazole in moderate yield. Synthetic manipulations of dicarboxylic acid also gave *N*-methyl-2-(trilfluoromethyl)imidazole-4-carboxylic acid [12].



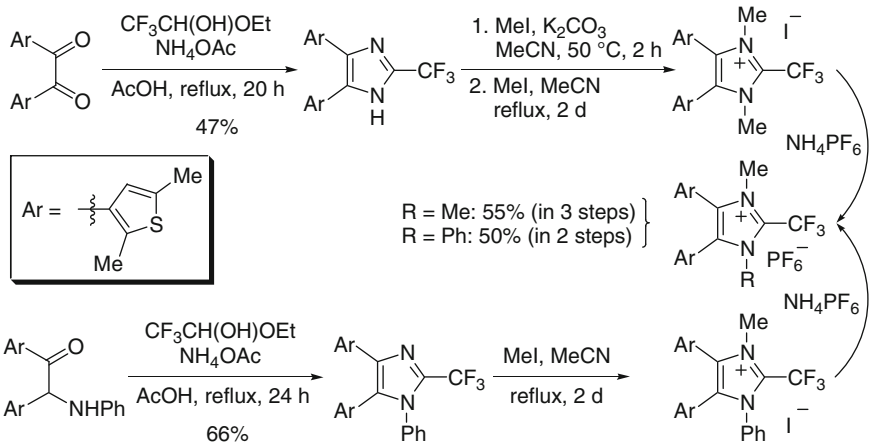
Scheme 3

One of the popular and widely used methods for the synthesis of 2-trifluoromethylimidazole involves the Radziszewski reaction (Debus-Radziszewski reaction) [2a]. Following the Davidson's modifications (using ammonium acetate in acetic acid instead of ammonia in alcohol) [13a], Lombardino and Wiseman prepared a series of 2-trifluoromethylimidazoles via the condensation of α-dicarbonyl compounds and trifluoroacetaldehyde ethyl hemiacetal (Scheme 4) [13b]. The reaction presumably proceeds via the formation of a diimide intermediate that subsequently undergoes condensation with the aldehyde to afford the final product. An anhydrous condition is highly recommended for better yields of imidazoles.



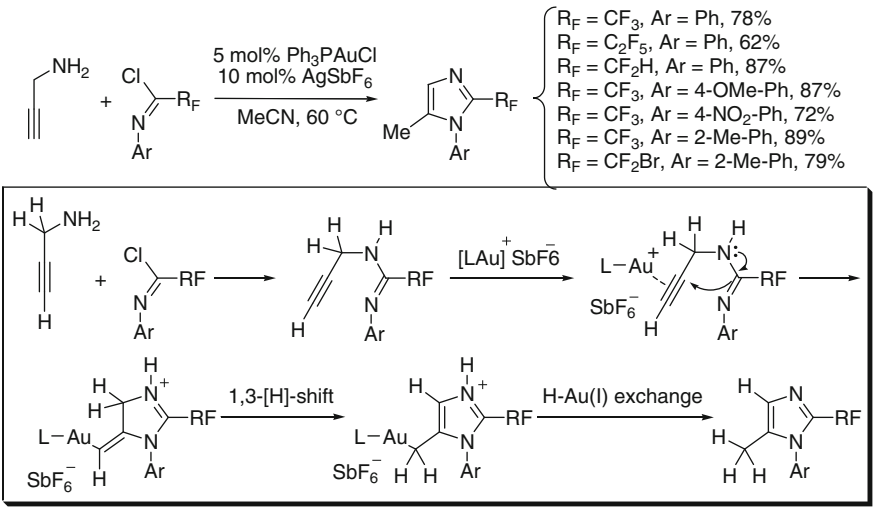
Scheme 4

During photochromic studies of dithienylethene-containing imidazolium derivative, Yam and co-workers prepared 4,5-di(thienyl)-2-trifluoromethylimidazoles and related hexafluorophosphates (Scheme 5) [14]. The condensation of a 1,2-diketone or α-aminoketone with trifluoroacetaldehyde hemiacetal afforded the desired 3,4-disubstituted-2-(trifluoromethyl)imidazoles. The *N*-methylation of the unsubstituted nitrogen(s) followed by treatment with ammonium hexafluorophosphate afforded the corresponding imidazolium salts.



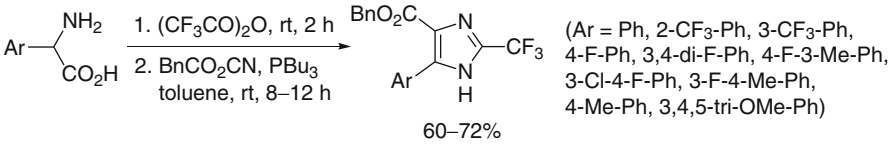
Scheme 5

The Au(I)-catalyzed cyclization of the fluorinated *N*-aryl-*N*′-propargyl amidines afforded *N*-aryl-2-fluoroalkylimidazoles (Scheme 6) [15]. These fluorinated propargyl amidines are unstable under strong basic conditions. The gold-catalyzed 5-exo-dig cyclization of propargyl amidines not only produced the desired imidazoles in excellent yields, but these mild conditions also accommodate various functional groups. Slightly lower yields were obtained for the aryl-amidines bearing an electron-withdrawing group compared to the electron-donating group whereas steric effects did show much influence on the product yields. In this one-pot process, the Au cation coordinates with the alkyne to provide a vinyl-gold intermediate.



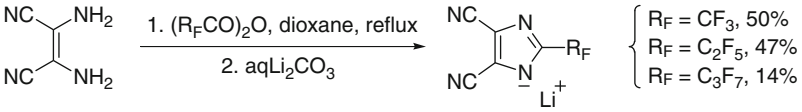
Scheme 6

Using a two-step procedure, Flynn synthesized a variety of benzyl 5-aryl-2-(trifluoromethyl)imidazole-4-carboxylates from the corresponding aryl glycines (Scheme 7) [16].



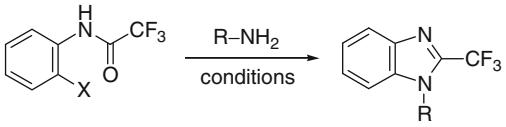
Scheme 7

Three lithium 4,5-dicyano-2-(perfluoroalkyl)imidazoles were prepared by Niedzicki by treating the corresponding imidazole with aqueous lithium carbonate (Scheme 8) [6a]. The prerequisite 4,5-dicyano-2-(perfluoroalkyl)imidazoles were prepared by the reaction of diaminomalononitrile with trifluoroacetic anhydride in refluxing dioxane.



Scheme 8

Ma reported a Cu-catalyzed aryl amination and condensation cascade to prepare 2-trifluoromethylbenzimidazole from 2-halotrifluoroacetanilides (Scheme 9) [17a]. Sterically less hindered primary amines underwent coupling with both electron-rich and electron-deficient 2-iodotrifluoroacetanilides at room temperature to afford the corresponding 2-trifluoromethylbenzimidazoles (Condition A). Although the *ortho*-NHCOCF3 group significantly promotes the amination reactions [17b], further heating was required for sterically hindered amines to facilitate the intramolecular cyclization of the nascent coupling products to afford 2-trifluoromethylbenzimidazoles (Condition B). In general, heating in acetic acid gave better results for these condensation reactions than directly heating in DMSO. The amination of 2-bromotrifluoroacetanilides with primary amines was also effective at room temperature, presumably due to the same *ortho*-substituent effect, and thus smoothly afforded the corresponding 2-trifluoromethylbenzimidazoles after heating the intermediates in acetic acid (Condition C). Buchwald synthesized *N*-hexyl-2-trifluoromethylbenzimidazole via amination of 2-iodotrifluoroacetanilide with *n*-hexylamine; [18] however, no additional ligand was required to facilitate this transformation (Scheme 9, Condition D).

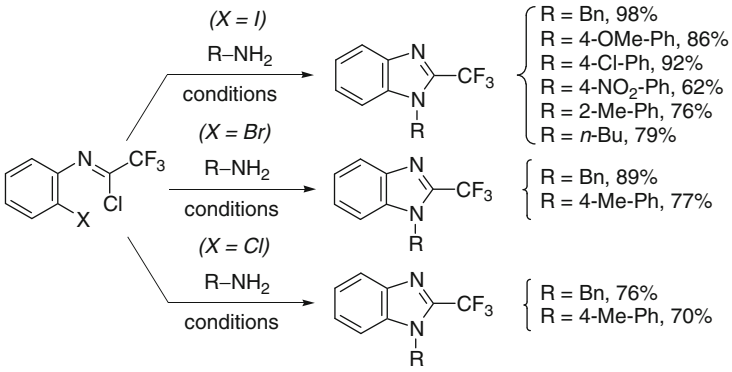


X = I: R = *n*-Hex, 90% (Condition A)
X = I: R = allyl, 90% (Condition A)
X = I: R = $(CH_2)_2OH$, 92% (Condition A)
X = I: R = *c*-Hex, 94% (Condition B)
X = I: R = Ph, 74% (Condition B)
X = I: R = $CH(Bn)CO_2Me$, 61% (Condition B)
X = Br: R = *n*-Hex, 80% (Condition C)
X = Br: R = *c*-Hex, 90% (Condition C)
X = Br: R = $(CH_2)_2OH$, 90% (Condition C)
X = I: R = *n*-Hex, 86% (Condition D)

Condition A**:** 5 mol% CuI, 10 mol% *L*-proline, K_2CO_3 (2 eq), DMSO, rt, 10–24 h.
Condition B**:** i) 5 mol% CuI, 10 mol% *L*-proline, K_2CO_3 (2 eq), DMSO, 25–40 °C, 17–36 h; ii) 50–70 °C, AcOH, 2–12 h.
Condition C**:** i) 5 mol% CuI, 10 mol% *L*-proline, K_2CO_3 (2 eq), DMSO, rt, 10–24 h; ii) 50 °C, AcOH, 1–5 h.
Condition D: i) 5 mol% CuI, Cs_2CO_3 (2 eq), DMF, rt, 18h; ii) AcOH, 50 °C, 2 h.

Scheme 9

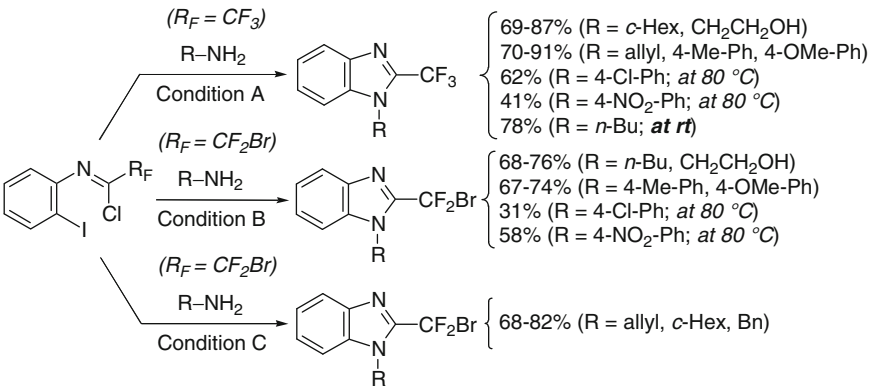
Zhang synthesized 2-trifluoromethylbenzimidazoles via a copper-catalyzed tandem C–N bond forming process (Scheme 10) [19]. Thus, the reaction of *N*-(2-halophenyl)trifluoroacetimidoyl chlorides, prepared from 2-haloanilines and trifluoroacetic acid, with primary amines in the presence of catalytic CuI–TMEDA afforded the corresponding *N*-substituted 2-trifluoromethylbenzimidazoles. The activation of the C–Cl bond by the CF_3 group made these trifluoroacetimidoyl chlorides eager to engage in the double amination reactions with both aliphatic and aromatic amines. In contrast, the reaction of analogous *N*-(2-iodophenyl)trifluoroacetimidoyl chloride with benzylamine failed to yield the corresponding benzimidazole.



Conditions: 10 mol% CuI, 20 mol% TMEDA, Cs_2CO_3 (2 eq), toluene, 110 °C, 8 h.

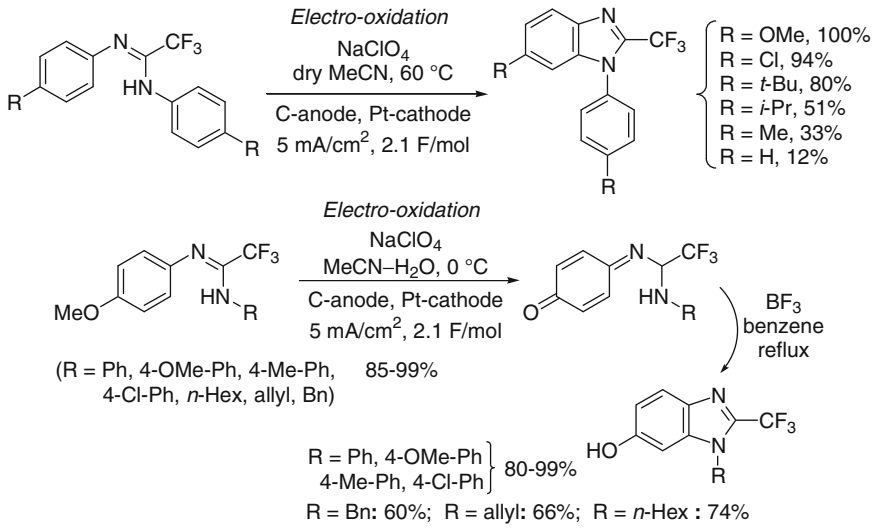
Scheme 10

Using the Cu(I)-catalyzed tandem reactions of imidolyl chlorides with amines, Wu synthesized several 2-fluoroalkylbenzimidazoles (Scheme 11) [20]. K_2CO_3 (or K_3PO_4) was a suitable base for this transformation and no additional ligands were used in these reactions. Both aliphatic and aromatic amines successfully coupled with imidoyl chlorides to afford the corresponding 2-(trifluoromethyl)- and 2-(bromodifluoromethyl)benzimidazoles. Furthermore, *N*-butyl-2-trifluoromethylbenzimidazole was prepared in good yield at room temperature via the coupling of *N*-(2-iodophenyl) trifluoroacetimidoyl chloride and *n*-butylamine. This ligand-free Cu-catalyzed coupling was also effectively used for the preparation of regioisomerically pure 5-nitro- and 6-nitro-2-(bromodifluoromethyl)benzimidazoles.



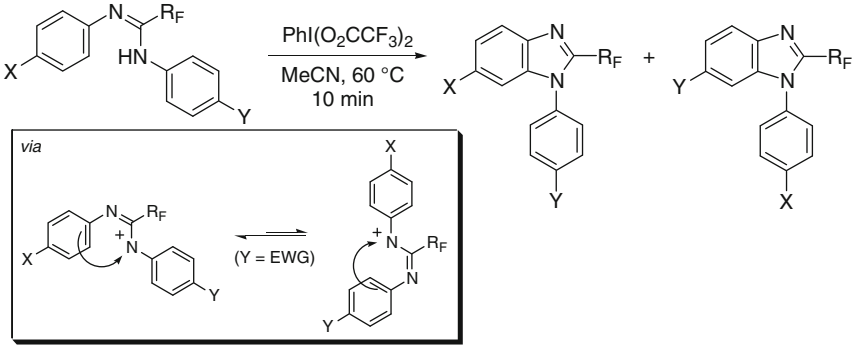
Scheme 11

Uneyama reported the synthesis of 2-trifluoromethylbenzimidazoles via electro-oxidative C–N bond formation in symmetrical imidamides (Scheme 12) [21]. The reactions were conducted in dry acetonitrile and higher temperature generally favored product formation. While the imidamides bearing 4-methoxyphenyl, 4-chlorophenyl, and 4-*tert*-butyl-phenyl substituents gave excellent yields (80–100 %), 4-isopropylphenyl and 4-methylphenyl-containing imidamides afforded lower yields, presumably due to the removal of the benzylic proton from the cation radical; thus resulting in oligomerization or polymerization of the substrates. Related *N,N′*-diphenylimidamides also afforded a low yield (12 %) of the corresponding 2-trifluoromethylbenzimidazole where the substrate predominantly underwent polymerization under the reaction conditions. In contrast to the electro-oxidation of symmetrical imidamides bearing two 4-methoxyphenyl substituents, the electro-oxidation of unsymmetrical *N*-(4-methoxyphenyl)-*N′*-arylimidamides produced complex mixtures of two isomeric benzimidazoles and *p*-benzoquinone imines. Nonetheless, conducting the electro-oxidation in aqueous acetonitrile predominantly afforded the *p*-benzoquinone imines, even with *N*-(4-methoxyphenyl)-*N′*-phenylimidamide. The BF_3-catalyzed cyclization of *p*-benzoquinone imines afforded the corresponding 6-hydroxy-2-(trifluoromethyl)benzimidazoles.



Scheme 12

The oxidative cyclization of *N*,*N*′-diarylimidamides using phenyliodine (III) bis(trifluoroacetate)/[bis(trifluoroacetoxy)iodo]benzene (PIFA/BTI) afforded the corresponding *N*-aryl-2-fluoroalkylbenzimidazoles (Scheme 13) [22a]. Symmetrical *N*,*N*′-diarylfluoroalkyl ethanimidamides gave the corresponding 2-fluoroalkylbenzimidazoles in moderate to good yields (Table 1, entries 1,2,4), except for the imidamides bearing a nitro group in both aryl rings (entry 3). For unsymmetrical imidamides, the cyclization of the nitrenium ion intermediate generally occurred through the relatively electron-rich benzene ring (entries 5–12). Later, these researchers also reported the phenyliodine (III) diacetate/(diacetoxyiodo)benzene (PIDA/DIB) mediated oxidative cyclization of *N*-aryl amidines to afford the 2-fluoroalkylbenzimidazoles (Scheme 14) [22b]. The *N*-arylfluoroalkylacetamidines were obtained from the corresponding imidoyl chlorides using ammonia. The *N*-phenylamidines, bearing substituents at the *ortho* and *para* position of the benzene ring, gave the corresponding benzimidazoles in good yields. However, the amidines, bearing a meta-substituted benzene ring produced an

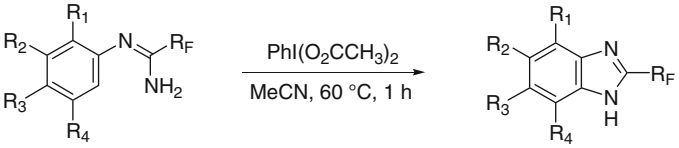


Scheme 13

Table 1 Synthesis of *N*-aryl-2-fluoroalkylbenzimidazole from imidamides

Entry	R_F	X	Y	6-X product (%)	6-X/6-Y[a]
1	CF_3	H	H	83	–
2	CF_3	Cl	Cl	90	–
3	CF_3	NO_2	NO_2	0	–
4	CF_2Br	H	H	62	–
5	CF_2Br	H	NO_2	87	>99:1
6	CF_2Br	H	CO_2Et	83	>99:1
7	CF_2Br	H	COMe	78	>99:1
8	CF_2Br	H	Cl	69	1.44:1
9	CF_2Br	H	Br	63	1.27:1
10	CF_2Br	H	I	83	1:1.2
11	CF_2Br	H	Me	73	1:6.7
12	CF_2Br	H	OMe	54	<1:99

[a]Determined by ^{19}F NMR



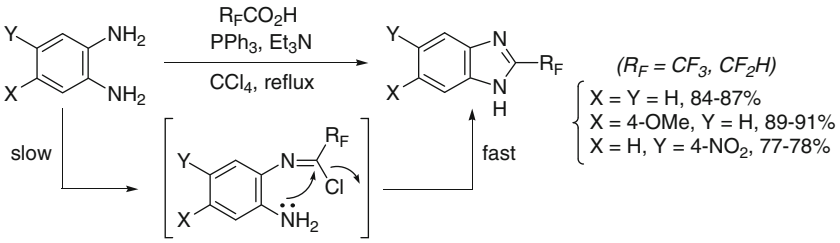
$R_F = CF_3$; $R_3 = CF_3$, CN; $R_1 = R_2 = R_4 = H$: 83-97%
$R_F = CF_2Br$; R_3 = H, Br, Cl, CF_3; $R_1 = R_2 = R_4 = H$: 80-87%
$R_F = CF_2Br$; R_3 = CN, Ac, CO_2Et, NO_2; $R_1 = R_2 = R_4 = H$: 92-97%
$R_F = CF_2Br$, R_3 = Me, OMe, I; $R_1 = R_2 = R_4 = H$: 65-70%
$R_F = CF_2Br$; R_1 = Me, I, CF_3; $R_2 = R_3 = R_4 = H$: 78-90%
$R_F = CF_2Br$; R_2 = Me, CF_3; $R_1 = R_3 = R_4 = H$: 84-88%

Scheme 14

inseparable mixture of 5(6)-substituted (major) and 4(7)-substituted (minor; steric effect) regioisomers under similar conditions.

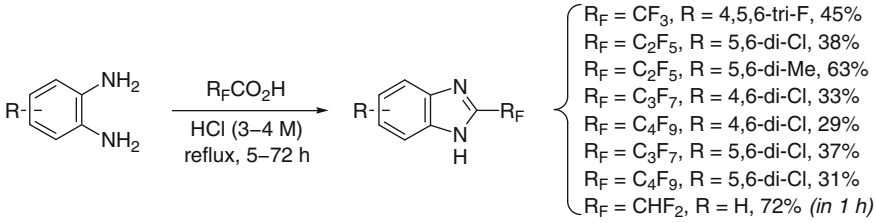
The reaction of *o*-phenylenediamine with trifluoroacetic acid and difluoroacetic acid afforded 2-(trifluoromethyl)- and 2-difluoromethylbenzimidazoles, respectively (Scheme 15) [23]. In the presence of excess triethylamine, the nucleophilic attack of the *ortho*-amino group to the electrophilic imidoyl chloride, formed in situ, afforded the 2-fluoroalkylimidazoles. In general, the electronic properties of the substituents on the benzene ring determine the regioisomeric outcome of the benzimidazoles in this one-pot process. Thus, an electron-donating methoxy group increases the electron density and nucleophilicity of the *para*-amino group in *o*-phenylenediamine and facilitates the formation of imidoyl chloride at the *para*-position of the methoxy group leading eventually to the formation of the 6-methoxy regioisomer. In contrast, an electron-withdrawing nitro group decreases the electron density and nucleophilicity of the *para*-amino group in *o*-phenylenediamine and, thus, formation of

imidoyl chloride occurs through the nucleophilic attack of the other amino group which is responsible for the formation of 5-nitro regioisomer. The position of the methoxy and nitro substituents was further confirmed by X-ray crystallography.



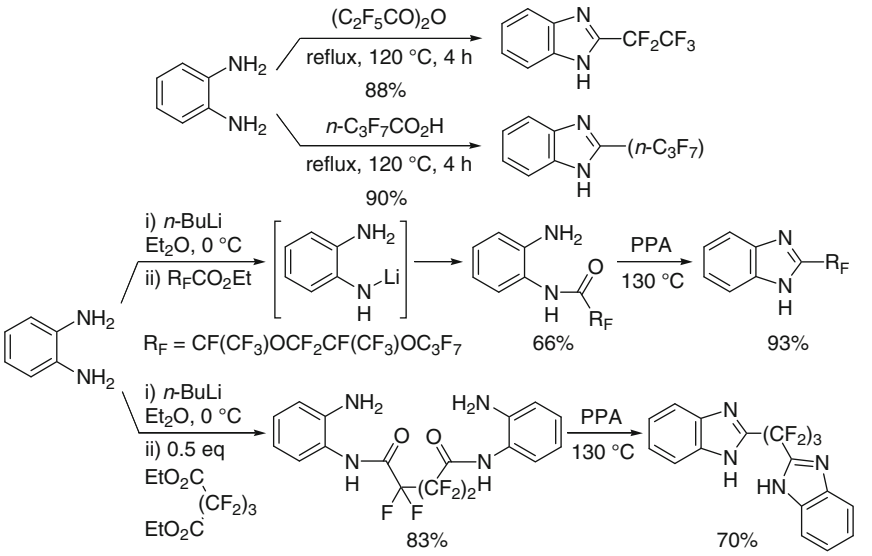
Scheme 15

Kazimierczuk and co-workers prepared several 2-(polyfluoroalkyl)benzimidazoles from *o*-phenylenediamines using the corresponding polyfluoroacetic acid (Scheme 16) [24]. Likewise, the reaction of *o*-phenylenediamine with difluoroacetic acid provided 2-(difluoromethyl)benzimidazole in 72 % yield [25]. Several other research groups utilized similar conditions to prepare the targeted 2-(trifluoromethyl)benzimidazoles [26].



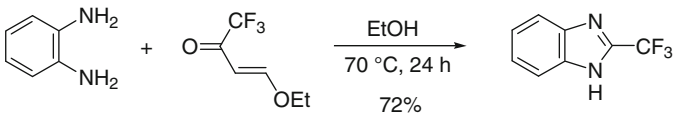
Scheme 16

Eapen and Tamborski prepared few 2-perfluoroalkylbenzimidazoles from *o*-phenylenediamine (Scheme 17) [27]. While 2-pentafluoroethyl- and 2-heptafluor opropylbenzimidazole were prepared by heating *o*-phenylenediamine with the corresponding acid anhydride and carboxylic acids, respectively, a benzimidazole bearing a perfluoroalkyl ether at C-2 was prepared in a two-step procedure via a *N*-monoacyl derivatives of *o*-phenylenediamine. Likewise, a bis(benzimidazole) was prepared by the condensation of o-phenylenediamine with 0.5 equivalent of diethyl 2,2,3,3,4,4-hexafluoropentanedioate.



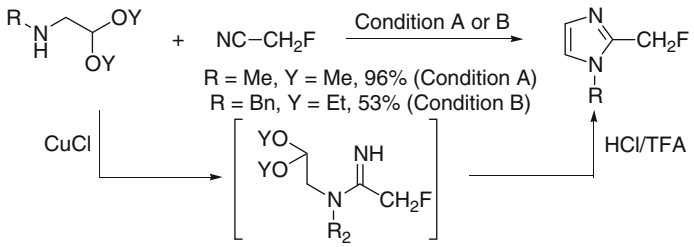
Scheme 17

A new strategy for the synthesis of 2-trifluoromethylbenzimidazole was reported by Zhu using the reaction of *o*-phenylenediamine and 4-ethoxy-1,1,1-trifluoro-3-butene-2-one (Scheme 18) [28]. The desired 2-trifluoromethylbenzimidazole was obtained in 72 % yield along with a small amount (5 %) of imidazole. A benzo[*b*][1, 4]diazepine intermediate was proposed for this transformation.



Scheme 18

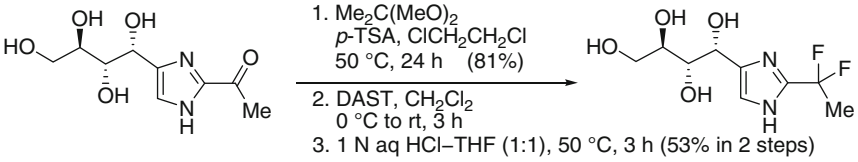
Frutos prepared 2-fluoromethylimidazoles via the cyclization of the amidines formed by the Cu(I)-promoted addition of α-amino acetals to fluoroacetonitrile (Scheme 19) [29]. The reactions were performed either stepwise or in a one-pot fashion (depending upon the removal of Cu salts before or after the cyclization) in which the amidine formation was carried out in the absence of any solvent followed by the cyclization using TFA or HCl–MeOH. Thus, the addition of (methylamino) acetaldehyde dimethyl acetal and (benzylamino)acetaldehyde diethyl acetal with fluoroacetonitrile followed by cyclization afforded the corresponding 2-(fluoromethyl)imidazoles in 96 % and 53 % yields, respectively.



Condition A (one-pot): i) CuCl, 85 °C, 8 h, ii) HCl, MeOH, rt to reflux, 4 h.
Condition B (stepwise): 1.CuCl, 85 °C, 12 h; 2. TFA, 75 °C, 1 h.

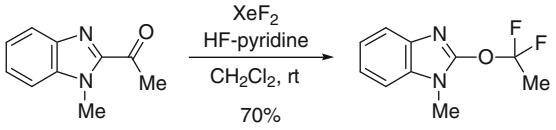
Scheme 19

During the synthesis of sphingosine-1-phosphate lyase (S1PL) inhibitor for the treatment of autoimmune disorders, Bagdanoff and co-workers prepared the α,α-difluoro analog of 2-acetyl-4(5)-[1(*R*),2(*S*),3(*R*),4-tetrahydroxybutyl]imidazole (Scheme 20) [30]. Ketalization of the diol using 2,2-dimethoxypropane followed by the treatment of bisketal with DAST and subsequent deprotection afforded the targeted 2-(1,1-difluoroethyl)imidazole derivative.



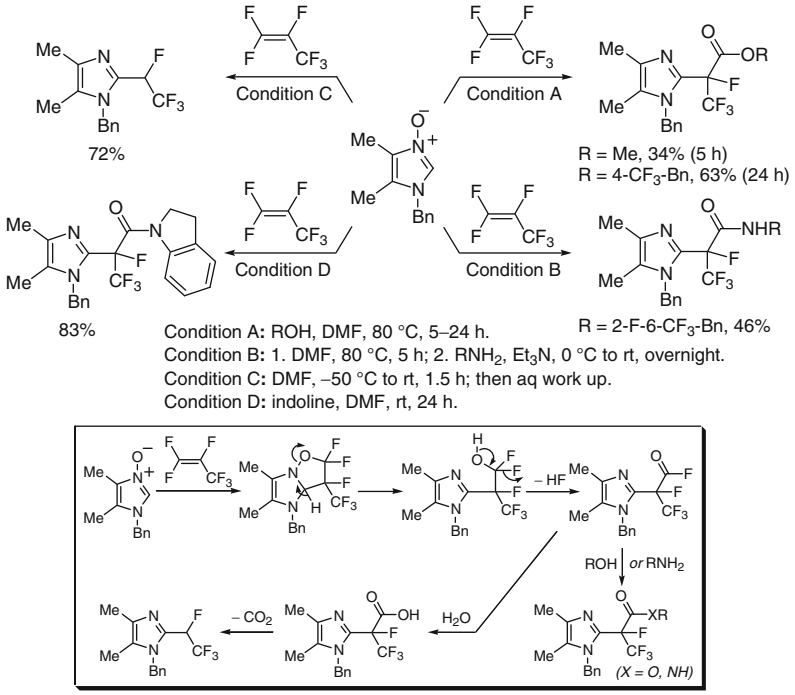
Scheme 20

Horne synthesized *N*-methyl-2-(1,1-difluoroethoxy)benzimidazole via the rearrangement of corresponding 2-acetylimidazole (Scheme 21) [31]. The reaction was carried out at room temperature in the presence of the mild fluorinating agents XeF_2 and HF-pyridine in dichloromethane. Undesired fluorination or the decomposition of the benzimidazole ring did not appear to be problematic under the applied conditions and the desired product was obtained in 70 % yield.



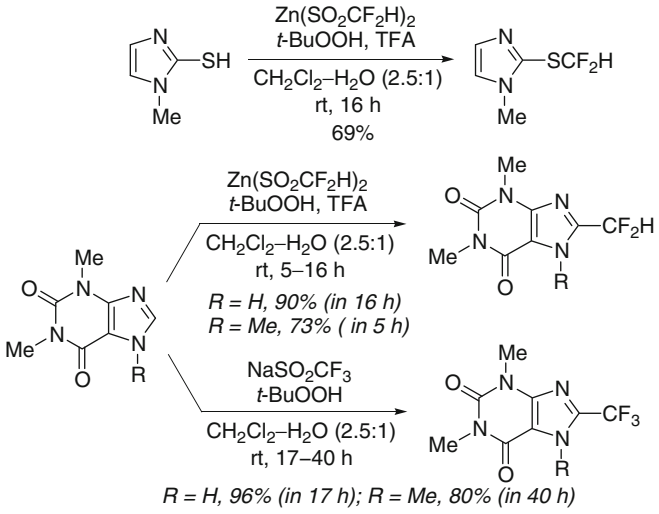
Scheme 21

Loska and Makosza observed that the reaction of 1-benzyl-4,5-dimethylimidazole-3-oxide with hexafluoropropene (HFP) afforded 2-(1,2,2,2-tetrafluoroethyl)imidazole (Scheme 22) [32]. However, 1-benzyl-4,5-dimethylimidazole-3-oxide with HFP in the presence of alcohol afforded the corresponding esters. Although the alcohols, in absence of strong bases, do not react with HFP, the reaction of HFP with primary amines is faster than the imidazole-*N*-oxide. Thus, to circumvent the problematic side-reactions of primary amines with HFP, the amide analogs were prepared in a two-step one-pot procedure. Indoline, an unreactive secondary amine, was used directly in the reaction in the presence of HFP to afford the corresponding amides in high yield. The reaction that was used for the preparation of these unique series of 2-(2-imidazolyl)propionic acid derivatives presumably proceeds via 1,3-dipolar cycloaddition to afford the isoxazolidine adduct. Re-aromatization drives N–O bond cleavage followed by elimination of HF gives the acyl fluoride in situ that undergoes nucleophilic attack by an alcohol or amine to provide the esters or amides. In contrast, the reaction of acyl fluoride with water produces the unstable carboxylic acid that undergoes spontaneous decarboxylation to provide the corresponding 1,2,2,2-tetrafluoroethanes.



Scheme 22

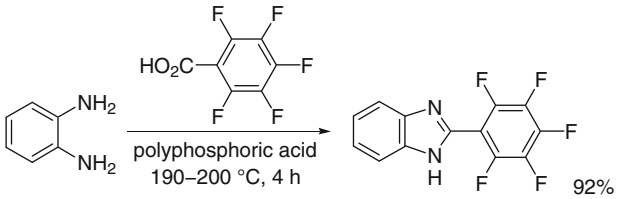
Baran reported the radical difluoromethylation of *N*-methylimidazole-2-thiol using zinc difluoromethanesulfinate [DFMS; Bis(((difluoromethyl)sulfinyl)oxy) zinc] to afford the corresponding difluoromethyl thioether (Scheme 23) [33].



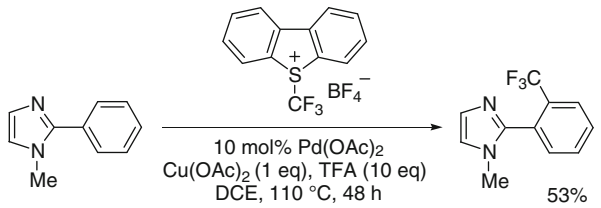
Scheme 23

3 Synthesis of 2-Perfluoroarylimidazoles and Benzimidazoles

Cohen reported the photochemical perfluoroarylation of imidazole with C_5F_5I to afford 2-perfluoroarylimidazole in 8 % yield along with the major 4-perfluoroarylimidazole as the major product (36 % yield) [34]. Eapen and Tamborski prepared 2-(pentafluorophenyl)benzimidazole by the condensation of *o*-phenylenediamine with pentafluorobenzoic acid in the presence of polyphosphoric acid (PPA) (Scheme 24) [27]. Yu reported a trifluoromethylation reaction via C–H activation where a trifluoromethyl group was successfully installed onto the *ortho*-position of the phenyl ring using the directing effect of imidazole (Scheme 25) [35].



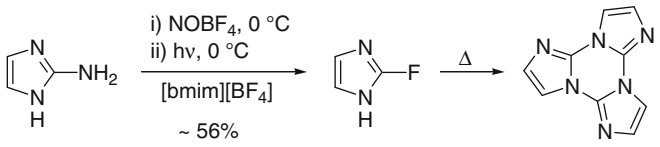
Scheme 24



Scheme 25

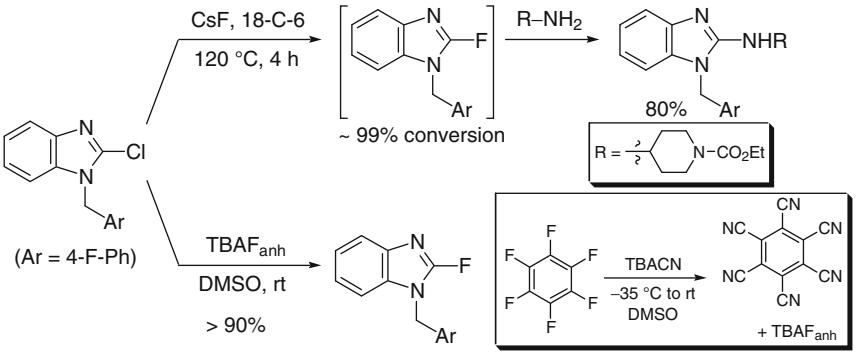
4 Synthesis of 2-Fluoroimidazoles and Benzimidazoles

The Balz–Schiemann reaction is one of the early methods that is still used for the generation of fluoroarenes from the corresponding aryl tetrafluoroborates and hexafluorophosphates [36]. However, the high temperature required for this reaction causes the decomposition of imidazole diazonium fluoroborates. To avoid the thermal decomposition, Kirk and Cohen used photochemical methods to prepare the 2-fluoroimidazoles by selectively activating the diazonium chromophore using UV irradiation that cleaved the C–N bond in diazonium salts [37]. In addition, the formation of the diazonium salt from 2-aminoimidazole and subsequent photochemical fluorodediazoniation can be done in a one-pot fashion without the isolation of the diazonium salts. However, the nucleophilicity of the solvent is detrimental to the aryl cation generated in situ during this process. In an attempt to increase the yield of 2-fluoroimidazole, Kirk used 1-butyl-3-methylimidazolium tetrafluoroborate (ionic liquid) as the solvent to avoid solvent-related side reactions and to stabilize the charged transition state during the de-diazoniation (Scheme 26) [38]. Furthermore, $NOBF_4$ was used for the diazotization reaction to completely eliminate the presence of water in the reaction medium. Notably, 2-fluoroimidazole slowly trimerizes at room temperature and even at 0 °C (stable at −80 °C); however, 2-fluorohistidine is stable at room temperature [37].



Scheme 26

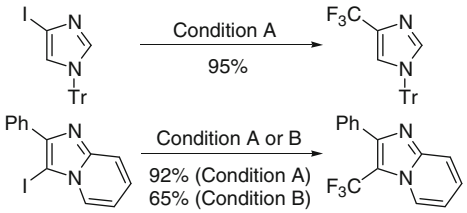
Senanayake used CsF to generate *N*-(4-fluorobenzyl)-2-fluorobenzimidazole in situ from the corresponding 2-chloroimidazole (Scheme 27) [39]. Almost quantitative conversion from chloride to fluoride was observed in 4 h at 120 °C, while TBAF with excess KF provided ~50 % conversion after heating the chloride at 120 °C for 24 h. The so-obtained fluoride was subsequently treated with an appropriate amine to furnish the desired product. Thus, fluoride efficiently promoted the conversion of 2-chlorobenzimidazole to 2-aminobenzimidazole via the highly reactive 2-fluorobenzimidazole intermediate. Although Senanayake noted low conversion for the Halex reaction of *N*-aryl-2-chlorobenzimidazole with TBAF or cyanuric fluoride in refluxing dioxane, Sun and DiMagno were able to obtain >90 % yield of the 2-fluorobenzimidazole in just 30 min after stirring the DMSO solution of *N*-(4-fluorobenzyl)-2-chlorobenzimidazole at room-temperature with $TBAF_{anh}$ [40a]. This "truly" anhydrous TBAF, capable of generating 2-fluorobenzimidazoles under mild conditions, was prepared in situ in polar aprotic solvents (e.g. DMSO, THF, MeCN) by the low-temperature nucleophilic aromatic substitution reaction of hexafluorobenzene with CN^- from tetrabutylammonium cyanide (TBACN) [40b].



Scheme 27

5 Synthesis of 4- and 5-Trifluoromethylimidazoles and Analogs

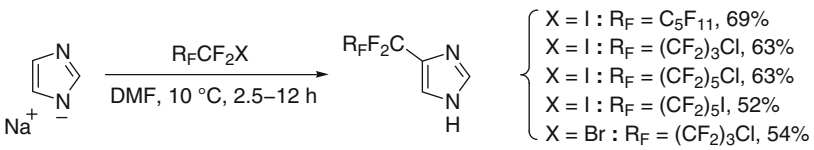
Using *S*-(trifluoromethyl)diphenyl iodonium triflate, Xiao converted *N*-trityl-4-iodobenzimidazole to the corresponding 4-(trifluoromethyl)imidazole (Scheme 28) [8]. These conditions were suitable for the conversion of 3-iodo-2-phenylimidazo[1,2-a]pyridine to its trifluoromethyl derivative, which was isolated in 92 % yield. In contrast, this product was previously produced in only 65 % yield under a $TMSCF_3$–KF–CuI protocol [41].



Condition A: Cu, $[Ph_2S\text{-}CF_3]^+[OTf]^-$, DMF, 60 °C, 9–11 h (iodide/triflate/Cu = 1:2:3).
Condition B: CuI, TMS-CF_3, KF, NMP, rt, 24 h.

Scheme 28

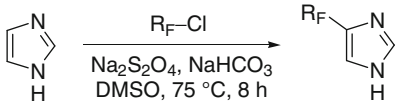
The reaction of sodium imidazolide with fluoroalkyl iodides and bromides afforded the corresponding 4-fluoroalkylimidazoles (Scheme 29) [42]. A decrease in conversion was observed by conducting the reaction in the dark (in comparison to visible light) as well as in the presence of 20 mol% of *p*-DNB or hydroquinone additive. An $S_{RN}1$ mechanism was suggested for these conversions due to the known difficulty in displacing the halides of perfluoroalkyl halides by S_N2 or S_N1 processes.



Scheme 29

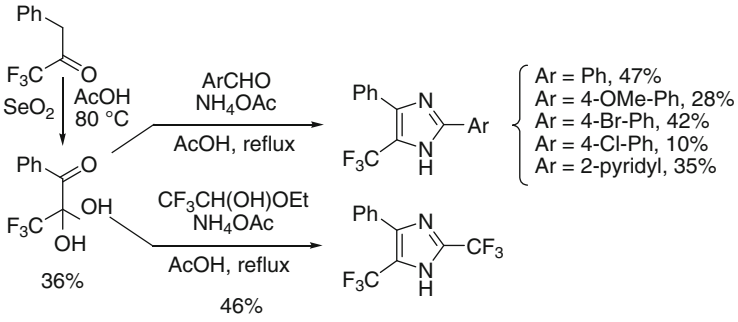
Reaction of imidazole with per(poly)fluoroalkyl chlorides in the presence of sodium dithionite in DMSO exclusively affords the 4(5)-fluoroalkylimidazoles (Scheme 30) [43]. In general, the electrophilic fluoroalkyl radical ($R_F^{\bullet}$) undergoes attachment to the relatively electron-rich position of the imidazole ring. No bis(fluoroalkylation) was observed, presumably due to the electron-density in the mono-fluoroalkylimidazoles.

Scheme 30



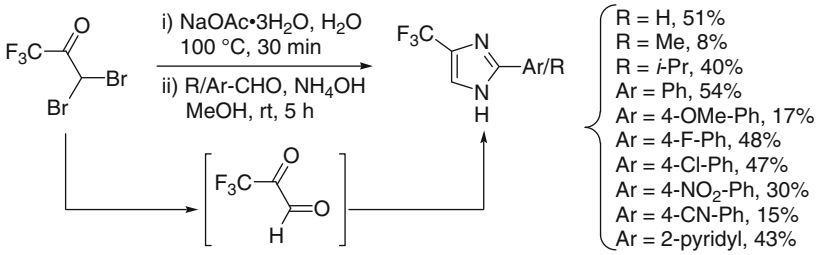
R_F = $(CF_2)_3CF_2H$, C_6F_{13}, C_8F_{17}: 63–67%

The condensation of 1-phenyl-3,3,3-trifluoro-1,2-propanedione monohydrate with various aldehydes in the presence of ammonium acetate afforded the corresponding 4-phenyl-5-trifluoromethylimidazoles (Scheme 31) [44]. For the preparation of 2,5-bis(trifluoromethyl)imidazoles, trifluoroacetaldehyde ethyl hemiacetal was used in excess instead of the aldehydes. The prerequisite diketone, that was isolated as its monohydrate, was prepared from the corresponding ketone using SeO_2.



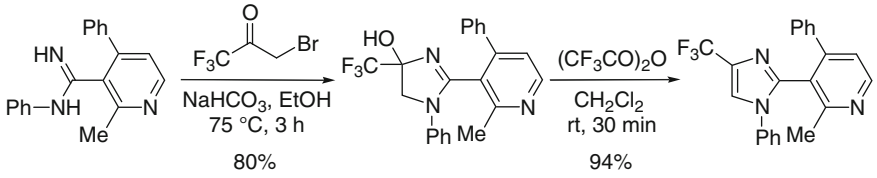
Scheme 31

Baldwin prepared a series of 4(5)-trifluoromethylimidazoles from 3,3-dibromo-1,1,1-trifluoroacetone (Scheme 32) [45]. Hydrolysis of 3,3-dibromo-1,1,1-trifluoroacetone, prepared by bromination of 1,1,1-trifluoroacetone, by aqueous sodium acetate afforded the corresponding glyoxals in situ, which underwent condensation with aldehydes in the presence of ammonia to produce the corresponding trifluoromethylated imidazoles. Matthews and co-workers used this protocol to prepare several 4-trifluoromethylimidazoles, containing an aryl group, such as 2-imidazolyl, 3-pyridyl, 2-thienyl, 3-thienyl, 2-furyl, 5-pyrazolyl, and 4-pyrazolyl, at the C-2 position [46a]. Notably, the treatment of these 4-trifluoromethylimidazoles with aqueous ammonium hydroxide afforded the corresponding nitriles in high yields [46b].



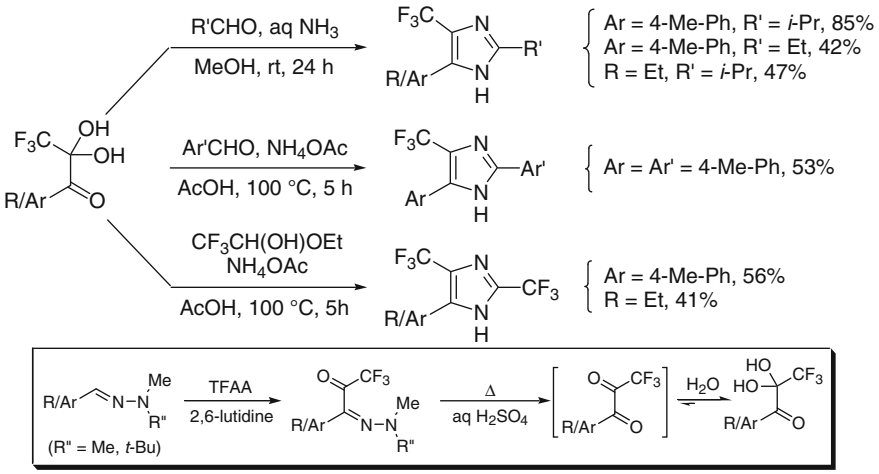
Scheme 32

Lukyanov prepared a 2-(3-pyridyl)-4-(trifluoromethyl)imidazole via the condensation of the corresponding aromatic amidine with 3-bromo-1,1,1-trifluoroacetone followed by TFAA-promoted dehydration (Scheme 33) [47].



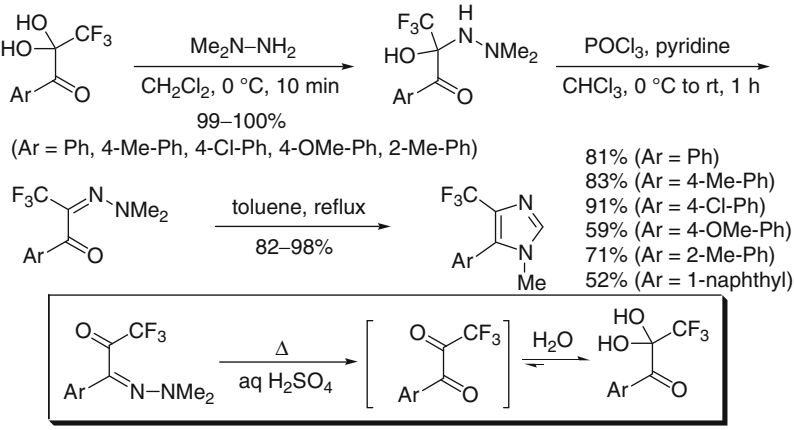
Scheme 33

Using 1,1,1-trifluoro-2,3-alkanediones, obtained as monohydrates from the acidic hydrolysis of 3-(dialkylhydrazino)-1,1,1-trifluoro-2-alkanones, Kamitori reported the synthesis of 4-(trifluoromethyl)imidazoles (Scheme 34) [48]. Two slightly different methods were used to construct the imidazole ring around the diketone skeleton. While the room-temperature reactions of diketones and aliphatic aldehydes in the presence of excess ammonia afforded the 4-(trifluoromethyl)imidazoles, the reactions of diketones with aromatic aldehydes were conducted in hot acetic acid in the presence of excess ammonium acetate. The later protocol was also used for the synthesis of a 2,4-bis(trifluoromethyl)imidazole.



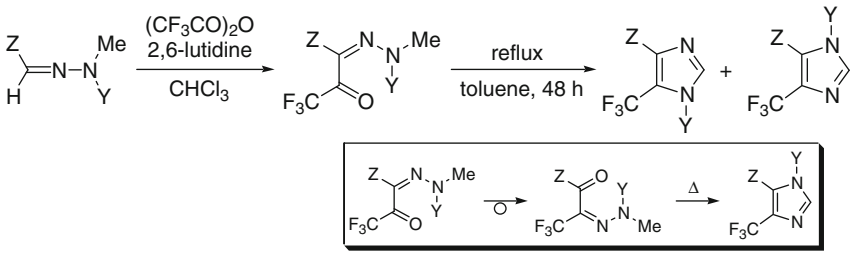
Scheme 34

Hojo reported a selective synthesis of 4-(trifluoromethyl)imidazoles (Scheme 35) [49]. The diketones, prepared from aldehyde dialkyl hydrazones via the hydrolysis of 3-(dialkylhydrazino)-1,1,1-trifluoro-2-alkanone intermediates, were treated with 1,1-dimethylhydrazine to afford the adduct. These adducts were generally unstable even at room temperature and, thus, were immediately dehydrated using $POCl_3$-pyridine to afford 3-aryl-1,1,1-trifluoropropane-2-,3-dione-2-dimethylhydrazone. Intramolecular cyclization of these hydrazones in refluxing toluene afforded the desired 4-(trifluoromethyl)imidazoles.



Scheme 35

A novel cyclization of trifluoroacetylated hydrazones, prepared by TFAA treatment of *N*,*N*′-dialkyl aldehyde hydrazones, was reported by Hojo for the synthesis of 5-trifluoromethylimidazoles (Scheme 36) [50]. Formation of the 4-(trifluoromethyl) isomers was observed in some cases along with the major 5-(trifluoromethyl)imidazole products, presumably due to isomerization of trifluoroacetylated hydrazones (Table 2). This isomerization is suggested to be enhanced in the presence of silica gel and the isomeric trifluoroacetylated hydrazones cyclized to give the 4-CF_3-imidazoles in refluxing toluene (*c.f.* Scheme 35).

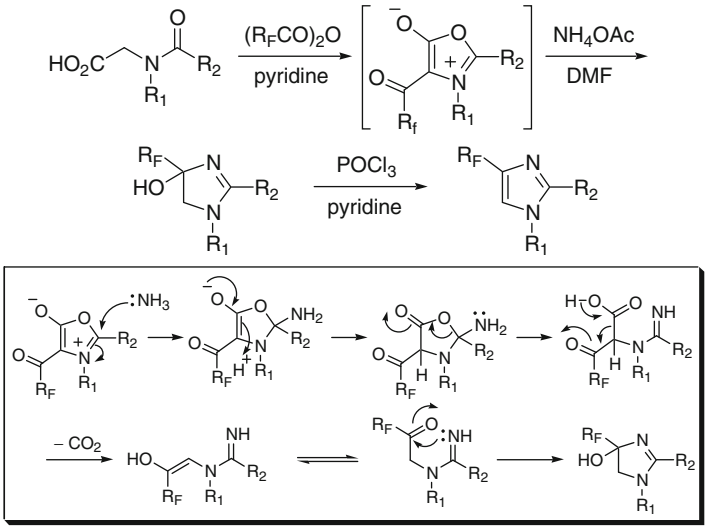


Scheme 36

Table 2 Synthesis of 5-trifluoromethylimidazoles via cyclization of hydrazones

Entry	Y	Z	5-CF_3/4-CF_3 ratio	Isolated yield of 5-CF_3
1	Me	Ph	93:7	52 %
2	Me	4-OMe-Ph	91:9	63 %
3	Me	4-Cl-Ph	81:19	65 %
4	Me	4-NO_2-Ph	75:25	58 %
5	*t*-Bu	Et	100:0	43 % (in 4 h)
6	*t*-Bu	*n*-Pr	100:0	81 % (in 16 h)
7	*t*-Bu	Bn	100:0	18 % (in 24 h)
8	*t*-Bu	4-Me-Ph	100:0	99 %
9	Ph	4-Me-Ph	100:0	88 %

Kawase prepared a series of 4-(perfluoroalkyl)imidazoles from the corresponding mesoionic 4-(perfluoroalkyl)-1,3-oxazolium-5-olates (Scheme 37, Table 3) [51]. These stable and isolable 1,3-oxazolium-5-olates can, in turn, be conveniently prepared from *N*-acyl-*N*-alkylglycines using the appropriate acid anhydrides (e.g., trifluoroacetic, pentafluoropropionic, heptafluorobutyric anhydrides). Thus, the preparation of 1,3-oxazolium-5-olates in situ from *N*-acyl-*N*-alkylglycines followed by the addition of ammonium acetate efficiently afforded the corresponding 4-(perfluoroalkyl)dihydroimidazoles in an one-pot fashion. The one-pot procedure also gave better yields than the step-wise synthesis of 4-(perfluoroalkyl)dihydroimidazoles from *N*-acyl-*N*-alkylglycines. Dehydration of these dihydroimidazoles by $POCl_3$-pyridine finally afforded the desired C-4 –perfluoroalkylated imidazoles. The reaction sequence is presumably initiated by nucleophilic attack of ammonia at C-2 of the 1,3-oxazolium-5-olate followed by ring opening due to the extrusion of CO_2 and subsequent intramolecular cyclization.



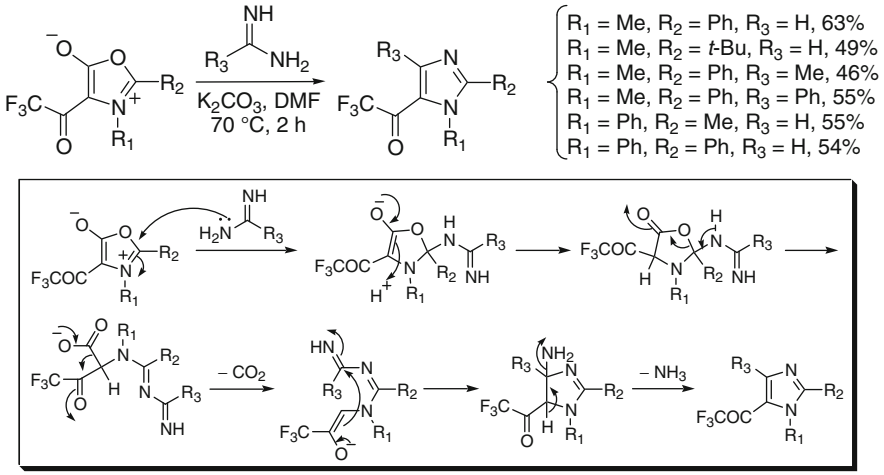
Scheme 37

Table 3 Synthesis of 4-(perfluoroalkyl)imidazoles from 1,3-oxazolium-5-olates

Entry	R_F	R_1, R_2	Dihydroimidazole[a] (%)	Imidazole (%)
1	CF_3	R_1=Me, R_2=Ph	92	88
2	CF_3	R_1=Me, R_2=Bn	98	91
3	CF_3	R_1=Me, R_2=*t*-Bu	78	88
4	CF_3	R_1=Ph, R_2=Ph	84	93
5	CF_3	R_1=Ph, R_2=Me	91	96
6	CF_3	R_1=Bn, R_2=Ph	89	99
7	CF_3	R_1=Bn, R_2=Me	85	94
8	C_2F_5	R_1=Me, R_2=Ph	93	99
9	C_3F_7	R_1=Me, R_2=Ph	87	93

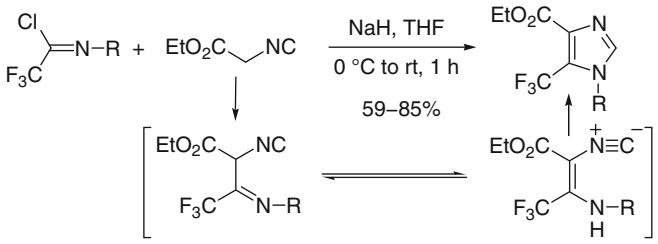
[a]Yield for one-pot procedure

Reaction of mesoionic 1,3-oxazolium-5-olates with amidines afforded 5-(trifluoroacetyl)imidazoles (Scheme 38) [52]. The mechanism for this novel ring transformation is presumably initiated by the nucleophilic attack of amidines onto C-2 of 1,3-oxazolium-5-olates. Subsequent ring fragmentation followed by decarboxylation and recyclization of the enolate ion with concomitant loss of ammonia afforded 5-trifluoroacetylated imidazoles. Reaction of *N*-benzoyl-*N*-methylglycine with pentafluoropropionic anhydride or heptafluorobutyric anhydride followed by the treatment of the resulting 1,3-oxazolium-5-olates with formamidine hydrochloride also afforded the corresponding 5-perfluoroacylimidazoles in an one-pot fashion.



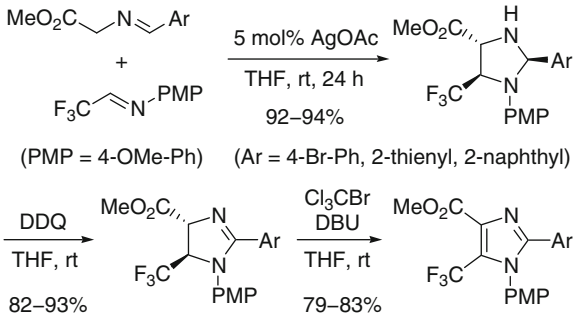
Scheme 38

Yuan described the synthesis of *N*-substituted 5-trifluoromethylimidazole-4-carboxylates via the base-induced cycloaddition of ethyl isocyanoacetates to trifluoroacetimidoyl chlorides followed by aromaticity-driven intramolecular cyclization via 1,1-addition of the amino group to the isocyano functionality (Scheme 39) [53]. A wide variety of 5-trifluoromethylimidazole-4-carboxylates, bearing an alkyl or aryl group at *N*-1, was prepared using this method. Moreover, the electronic nature of the aryl group did not significantly affect the course of reaction.



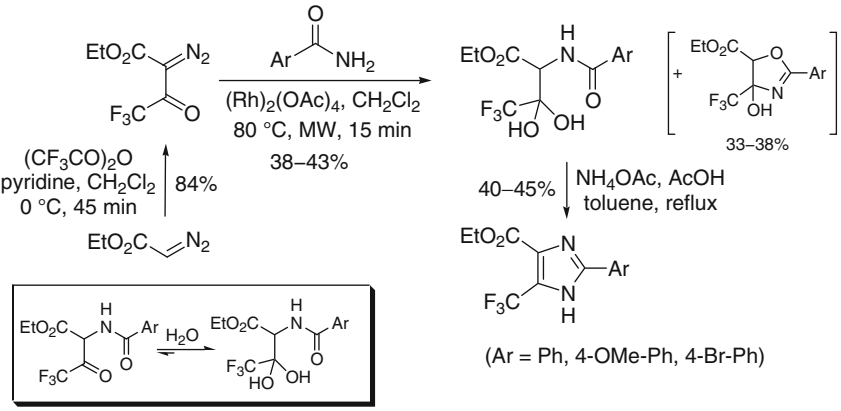
Scheme 39

The Ag(I)-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with trifluoromethylated imines afforded the corresponding 5-(trifluoromethyl)imidazole-4-carboxylates (Scheme 40) [54]. The tetrahydroimidazole cycloadducts were converted to dihydroimidazoles by DDQ oxidation, which in turn were treated with $BrCCl_3$ in the presence of DBU to afford the corresponding 2-aryl-5-trifluoromethylimidazoles. The azomethine ylides, bearing aryl and heteroaryl groups, successfully participated in this room-temperature cycloaddition, catalyzed by silver acetate.



Scheme 40

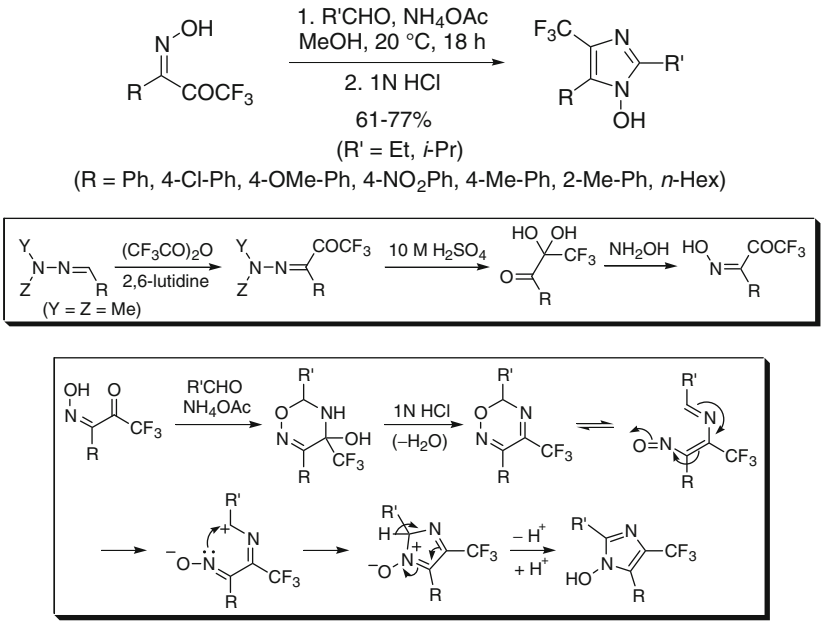
Moody reported the synthesis of 2-aryl-5-(trifluoromethyl)imidazole-4-carboxylate by the cyclization of the corresponding β-ketoamides in the presence of NH_4OH–AcOH in refluxing toluene (Scheme 41) [55]. The prerequisite β-ketoamides were prepared, in turn, by N–H insertion of rhodium carbenoids to aryl amides. These ketoamides was isolated as their hydrates due to increased electrophilicity of trifluoromethyl ketones. The carbene O–H insertion, followed by in situ cyclization, also produced the oxazolines as the by-products under these Rh-catalyzed conditions.



Scheme 41

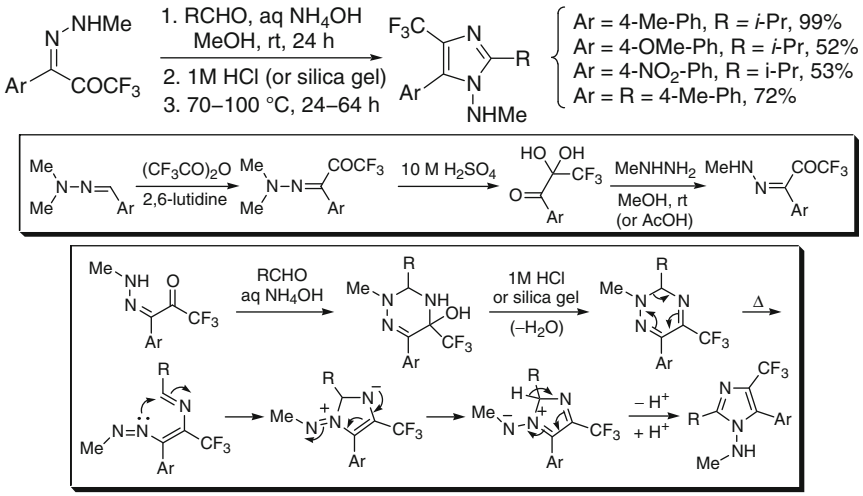
Reaction of 1,1,1-trifluoroalkane-2,3-dione 3-oximes with aldehydes in the presence of ammonium acetate and subsequent addition of 1N HCl afforded 4-trifluoromethylimidazol-1-ols (Scheme 42) [56]. The prerequisite 1,1,1-trifluoroalkane-2,3-dione 3-oximes were obtained from aldehyde dialkylhydrazones in three steps. Trifluoroacetylation of aldehyde dialkylhydrazones followed by hydrolysis

to afford 1,1,1-trifluoroalkane-2,3-diones as monohydrates. These monohydrates were subsequently treated with hydroxylamine hydrochloride in the presence of NaOAc to produce the oximes. The reaction presumably proceed by the dehydration of oxadiazine adduct, formed in the reaction of oxime and aldehyde in the presence of NH_4OAc, followed by electrocyclic ring opening. Subsequent recyclization followed by proton transfer provides the imidazol-1-ols.



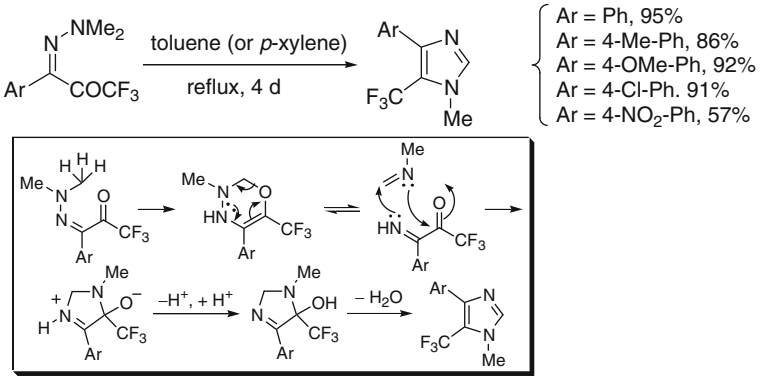
Scheme 42

Reaction of 1,1,1 -trifluoroalkane-2,3-diones with methylhydrazine with methylhydrazone in AcOH gave 1,1,1-trifluoro-3-methylhydrazonoalkan-2-ones (Scheme 43) [57]. Reaction of 1,1,1-trifluoro-3-methylhydrazonoalkan-2-ones with aldehydes in the presence of 28 % aqueous NH_4OH in MeOH followed by treatment with 1 M HCl afforded 5-trifluoromethyl-2,3-dihydro-1,2,4-triazines. Without the HCl treatment, 5-trifluoromethyl-2,3,4,5-tetrahydro-5-hydroxy-1,2,4-triazines were isolated as the major product, thus confirming the role of HCl in the dehydration of 5-trifluoromethyl-2,3,4,5-tetrahydro-5-hydroxy-1,2,4-triazines. Silica gel chromatography also sufficed for the efficient conversion of dihydrotriazines to tetrahydrotriazines. Finally, thermal rearrangement of 5-trifluoromethyl-2,3-dihydro-1,2,4-triazines afforded *N*-amino-4-trifluoromethylimidazoles via electrocyclic ring opening followed by recyclization and proton transfer.



Scheme 43

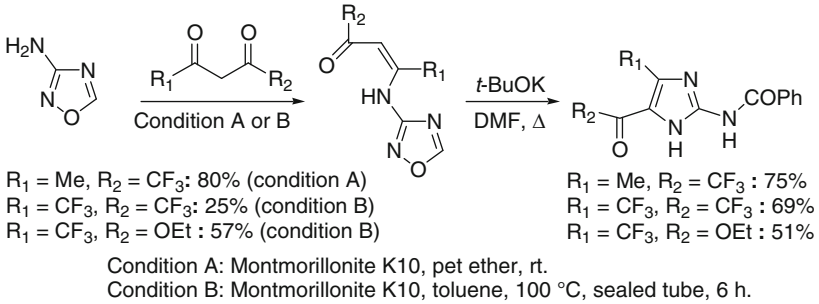
Refluxing 3-aryl-3-dimethylhydrazono- 1,1,1-trifluoro-2-propanones in toluene (or *p*-xylene) afforded 4-aryl-1-methyl-5-trifluoromethylimidazoles via 5-aryl-6-trifluoromethyl-3,6-dihydro-*2H*-[1,3,4]oxadiazine intermediates (Scheme 44) [58]. Retro Diels-Alder reaction of these oxadiazines afforded 3-imino-1,1,1-trifluoro-2-propanones and *N*-methyformimine that underwent cycloaddition to produced betaines. Proton transfer and subsequent dehydration gave the corresponding 5-trifluoromethylimidazoles.



Scheme 44

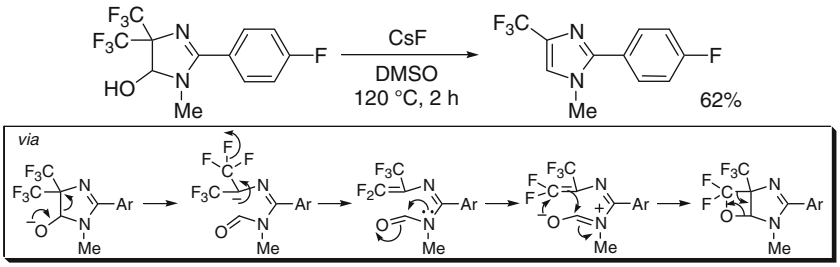
Buscemi prepared trifluoromethylated and trifluoroacetylated 2-(aminobenzoyl) imidazoles via ring rearrangement of 1,2,4-oxadiazole derivatives (Scheme 45) [59]. Condensation of 3-aminooxadiazole with acid anhydrides (or *β*-keto esters) in the presence of Montmorillonite K10 followed by treatment with potassium

tert-butoxide afforded the corresponding fluoro-functionalized (2-aminobenzyl) imidazoles. Hydrolysis of these (2-aminobenzyl)imidazoles provides the fluorinated 2-aminoimidazoles.

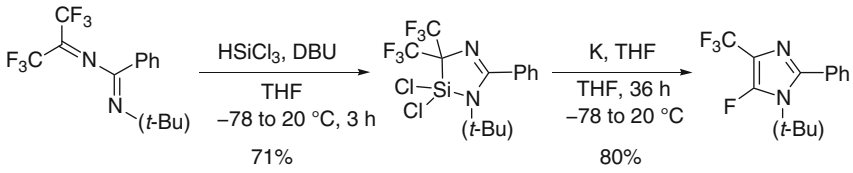


Scheme 45

Li and Boswell observed a base-promoted unusual de-trifluoromethylation of 4,4-bis(trifluoromethyl)-5-hydroxyimidazoline that afforded the corresponding 4-(trifluoromethyl)imidazole (Scheme 46) [60]. Karsch reported the formation of *N*-(*tert*-butyl)-5-fluoro-2-phenyl-4-trifluoromethylimidazole from a silaheterocycle under reductive conditions (Scheme 47) [61]. The silaheterocycle was prepared by [4 + 1]-cycloaddition of 1,3-diazabutadiene with $SiCl_3$ anion that was generated by the deprotonation of $HSiCl_3$ by DBU.

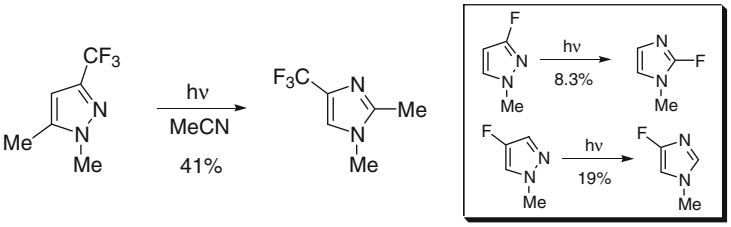


Scheme 46



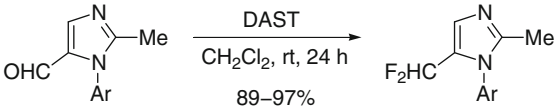
Scheme 47

Barltrop and Day observed that the irradiation of 1,5-dimethyl-3-(trifluoromethyl) pyrazole gave exclusively 1,2-dimethyl-4-(trifluoromethyl)imidazole in 41 % yield (Scheme 48) [62a]. Similar phototranspositions ("nitrogen walk") of *N*-methyl-3-fluoropyrazoles to *N*-methyl-2-fluoroimidazole and *N*-methyl-4-fluoropyrazoles to *N*-methyl-4-fluoroimidazole were also observed [62b]. A mixture of *N*-methyl-4-fluoroimidazole (23 %) and *N*-methyl-2-fluoroimidazole (~3 %) was obtained in the phototransposition chemistry of *N*-methyl-5-fluoropyrazole.



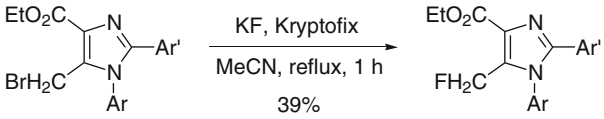
Scheme 48

Ferreira synthesized a series of 5-difluoromethylimidazoles by DAST-treatment of the corresponding 5-formylimidazoles (Scheme 49) [63]. The 5-formylimidazole precursors were obtained from *N*-aryl-amidines and 2-bromomalonaldehyde. Lange converted a 5-bromomethylimidazole to the corresponding 5-fluoromethylimidazole using KF in the presence of the cryptand Kryptofix in refluxing acetonitrile (Scheme 50) [64]. The addition of cryptands boosts the nucleophilicity of fluoride by complexing with the cation. Nevertheless, a low yield was obtained for this transformation.



Ar = Ph, 4-Cl-Ph, 4-Br-Ph, 4-F-Ph, 4-OMe-Ph, 4-NO_2-Ph, 4-CN-Ph, 2-Me-Ph, 2,6-di-F-Ph, 4-CF_3-Ph

Scheme 49

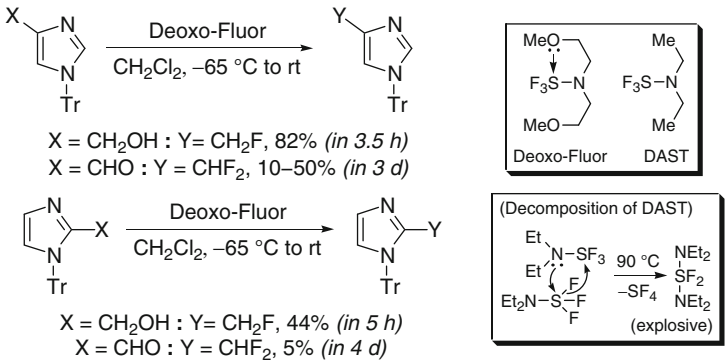


(Ar = 4-Cl-Ph, Ar' = 2,4-di-Cl-Ph)

Scheme 50

Dolensky and Kirk prepared trityl protected 2- and 4-fluoromethylimidazoles via the deoxyfluorination of the corresponding *N*-protected (hydroxymethyl)imidazoles using Deoxo-Fluor (Scheme 51) [65]. Deoxo-Fluor is a safer fluorinating

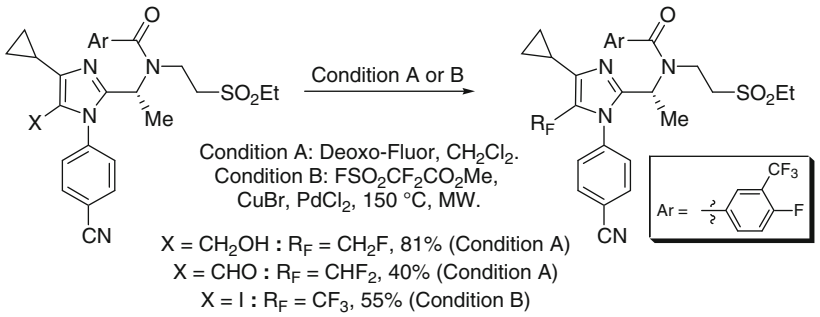
reagent than DAST due to stabilization by methoxy group coordination. While DAST decomposes at 90 °C within 3 h, Deoxo-Fluor decomposes at the same temperature over 25 h. Although 2- and 4-(fluoromethyl)imidazoles are stable compounds, a low yield of the 2-(fluoromethyl)imidazole was obtained due to higher lability of the trityl group in 2-(hydroxymethyl)- and 2-(fluoromethyl)imidazoles under these reaction conditions. However, deoxyfluorination of *N*-unprotected analogs was completely unsuccessful. Deoxyfluorination of 2- and 4-(formyl)imidazoles was also problematic. Inconsistent results were obtained for the deoxyfluorination of *N*-trityl-4-(formyl)imidazole with the yield of *N*-trityl-4-(difluoromethyl)imidazole ranging from 10–50 % along with 9–13 % of recovered aldehyde starting material. Extremely low yield (5 %) of *N*-trityl-2-(difluoromethyl) imidazole [along with 7 % yield of *N*-unprotected 2-(difluoromethyl)imidazole and ~6 % yield of a dimeric compound] from 2-(formyl)imidazole indicates the loss of trityl group under the reaction conditions. Indeed, the trityl groups can be easily removed by AcOH–aq HCl from the aforementioned fluorinated imidazoles, proving the corresponding *N*-unprotected imidazoles in 89–100 % yields.



Scheme 51

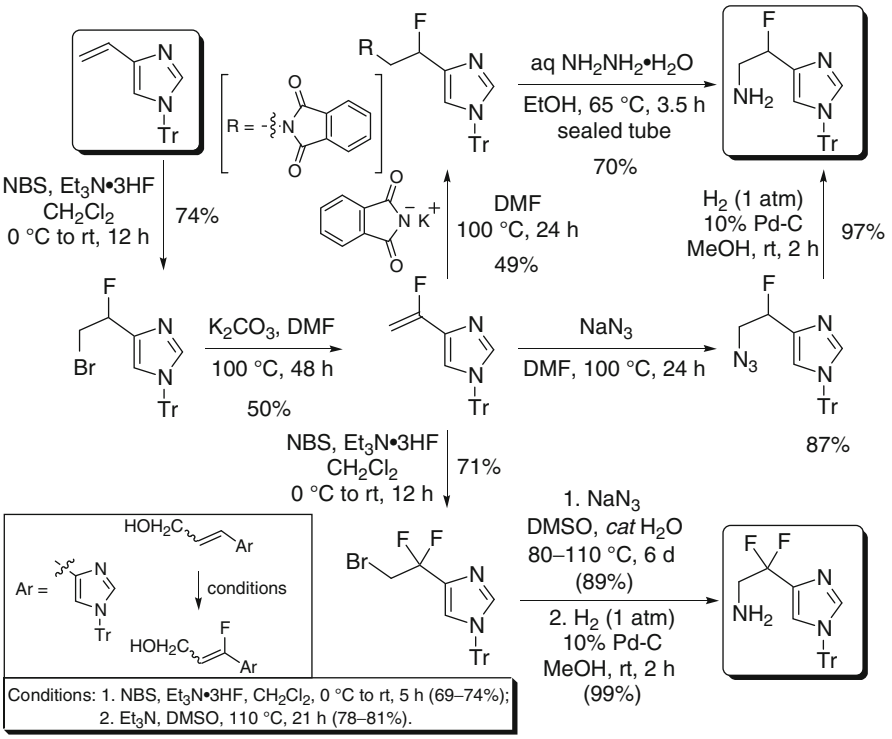
During the investigation of novel imidazole derivatives as potent CXCR3 antagonists, Medina and co-workers generated a short series of C-5 fluoroalkyl derivatives of the parent imidazole (Scheme 52) [66]. While Deoxo-Fluor was used for the preparation of fluoromethyl and difluoromethyl derivatives from the corresponding alcohol and aldehydes, respectively, 5-iodoimidazole was converted to its trifluoromethyl derivative via copper-catalyzed coupling using MFSDA (methyl fluorosulfonyldifluoroacetate).

Starting from *N*-trityl-4-vinylimidazole, Dolensky and Kirk made several fluorinated histamine analogs (Scheme 53) [67]. Bromofluorination of olefin, using an electrophilic Br^+ source (NBS) and nucleophilic F^- source ($Et_3N{\bullet}3HF$) gave the bromofluoro product. Elimination of HBr produced the corresponding 4-(1-fluorovinyl)imidazole which was converted to *β*-fluorohistamine by the treatment of sodium azide followed the reduction of azide to amine. Alternatively, addition of phthalimide to the fluoroolefin followed by deprotection using hydrazine



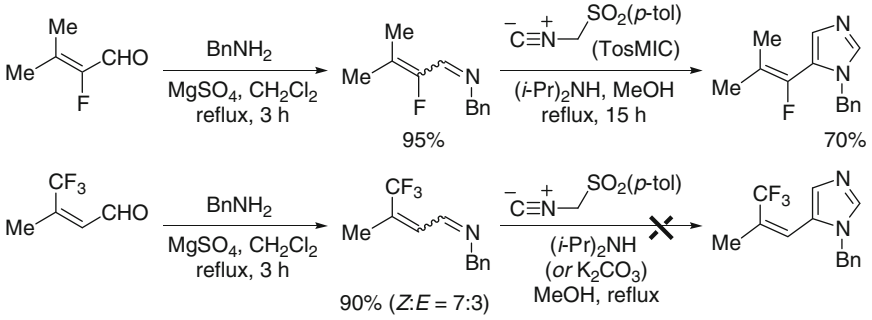
Scheme 52

also furnished the β-fluorohistamine. A second bromofluorination of 4-(1-fluorovinyl) imidazole gave the bromodifluoro adduct which was converted to the β,β-difluorohistamine by the displacement of bromide with sodium azide followed by the reduction using H_2-Pd/C. Likewise, the addition of an "FBr" equivalent to the double bond of 3-(*N*-trityl-4-imidazolyl)-prop-2-en-1-ol followed by the elimination of HBr gave the corresponding β-fluoro alcohol [68]. This compound was later conveniently converted to β-fluorourocanic acid.



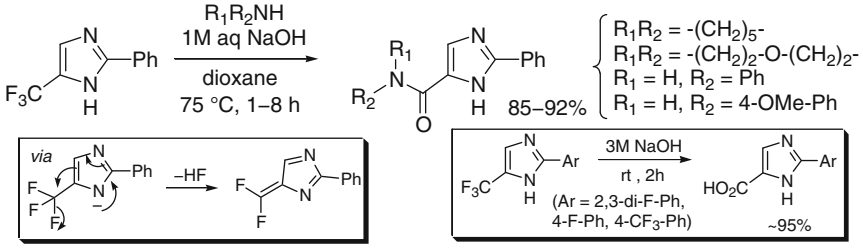
Scheme 53

The condensation of the imine, derived from 2-fluoro-3-methylbut-2-enal and benzylamine, with tosylmethyl isocyanide (TosMIC) produced *N*-benzyl-5-(1-fluoro-2-methylpropenyl)imidazole (Scheme 54) [69]. However, a similar condensation between the imine from 4,4,4-trifluoro-3-methyl-but-2-enal and benzylamine with TosMIC was ineffective, presumably due to the strong-electron withdrawing effect of the CF_3 group which caused unfavorable charge distribution in the α,β-unsaturated system of the imine. This prevents the initial TosMIC attack on the iminic C-position and leads to self-decomposition of TosMIC under the reaction conditions.

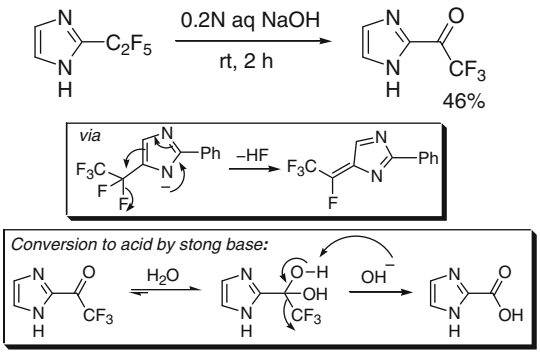


Scheme 54

Conducting the hydrolysis of 4(5)-(trifluoromethyl)imidazoles in the presence of secondary amine, O'Mahony and Pitts prepared the corresponding tertiary amides in the absence of any coupling agents (Scheme 55) [70]. The hydrolysis of both 2- and 4(5)-(trifluoromethyl)imidazoles by aqueous NaOH is known to proceed via electrophilic difluorodiazafulvenes that are produced in situ due to elimination of HF from the trifluoromethylimidazoles. Being much more reactive than the trifluoromethyl group (due to better stabilization of azafulvene by CF_3 than F), the pentafluoroethyl group at C-2 or C-4 of imidazole is converted to the corresponding trifluoroacetylimidazoles in almost quantitative yields (96–99 %). Reactions of 2- and 4(5)-(pentafluoroethyl)imidazole with methanolic KOH affords the corresponding ketals in excellent yields (94–99 %). Although treatment of 2-pentafluoroethylimidazole with 1N NaOH at room temperature affords the corresponding carboxylic acid, conducting the hydrolysis in a less basic media (0.2N aqueous NaOH at room temperature) produced 2-(trifluoroacetyl)imidazole in moderate (46 %) yield (Scheme 56).



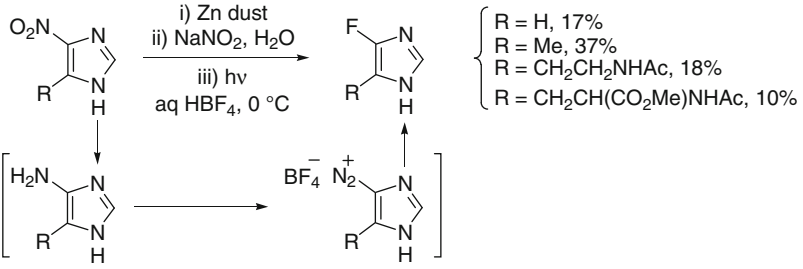
Scheme 55



Scheme 56

6 Synthesis of 4- and 5-Fluoroimidazoles

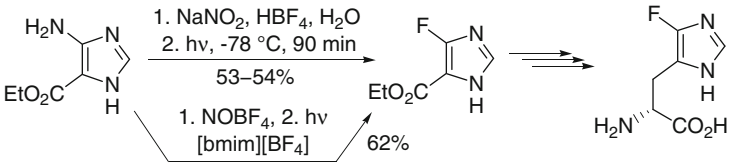
Kirk and Cohen reported the synthesis of 4(5)-fluorohistidine and related compounds from the corresponding 4-nitroimidazole via photolysis of the corresponding diazonium salts (Scheme 57) [71]. Due to the inherent instability of these 4-aminoimidazoles, the amine precursor for the diazonium salts was generated in situ by the reduction of the nitro group (4-aminoimidazoles can also be generated in situ by the acid-catalyzed deprotection of Boc-protected amines) and immediately diazotized to the corresponding diazonium salts. Thus, the reduction, diazotization, and the final photolysis of the diazonium salts were conveniently carried out in a one-pot fashion in aqueous tetrafluoroboric acid. The desired products were obtained in 10–37 % yields. Brown and co-workers utilized this method for the synthesis of 4-fluoroimidazole from 4-nitroimidazole in 30–40 % yield [72].



Scheme 57

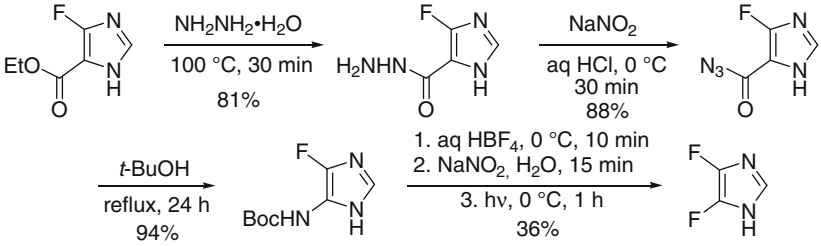
Using the aforementioned Balz-Schiemann reaction as the key step, Kirk reported an enantioselective synthesis of (*S*)-4-fluorohistidine (Scheme 58) [73]. The 4-aminoimidazoles, bearing an electron-withdrawing group (such as carboxylate) at C-5, are generally stable and isolable. Thus, using 4-aminoimidazole-5-carboxylate as the precursor for the diazotization and subsequent photolysis, the corresponding

4-fluoroimidazole was obtained in 53–54 % yield. However, carrying out this reaction sequence in an ionic liquid using $NOBF_4$ afforded a higher yield of the 4-fluoroimidazole-5-carboxylate [38]. The advantage of these protocols is the one-pot approach (diazotization and photolysis) to the 4(5)-fluoroimidazoles without the isolation of the diazonium salt intermediates. Notably, attempted thermal decomposition of stable diazonium tetrafluoroborate, prepared from ethyl 4-aminoimidazole-5 carboxylate, failed to produce the corresponding 4-fluoroimidazole.



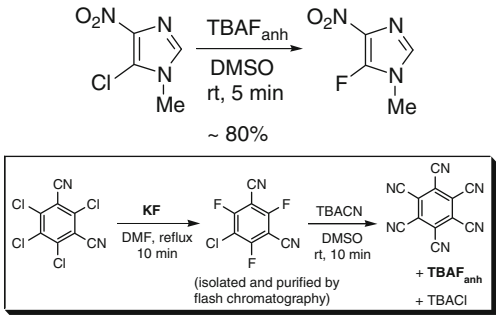
Scheme 58

The synthesis of 4,5-difluoroimidazole has also been described by Kirk using a photochemical Schiemann reaction (Scheme 59) [74]. Curtius rearrangement of the acyl azide, prepared in two steps from ethyl 4-fluoroimidazole-5-carboxylate via hydrazide, afforded the key intermediate Boc-protected 5-fluoroimidazol-4-carboxylate. In situ Boc deprotection followed by diazotization of the amine and photolysis of the diazonium tetrafluoroborate afforded 4,5-difluoroimidazole.



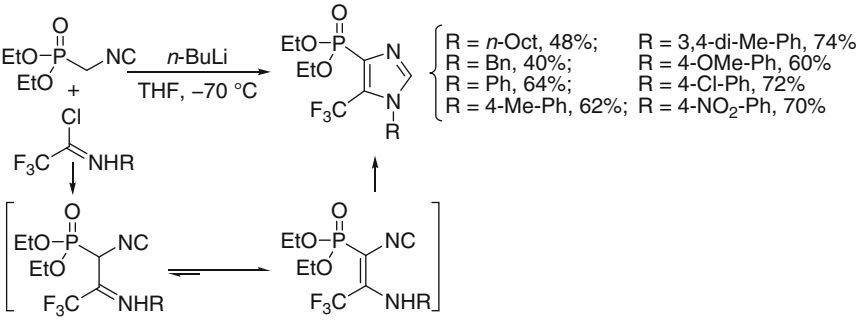
Scheme 59

Sun and DiMagno demonstrated the rapid generation of *N*-methyl-5-fluoro-4-nitroimidazole from the corresponding chloride using "anhydrous" TBAF that was generated in situ from KF by "fluoride relay" (Scheme 60) [75]. In fluoride relay, the reaction of KF with 2,6-dicyano-tetrachlorobenzene transfers the fluoride to the arene that finally produces the "activated" anhydrous tetrabutylammonium fluoride (TBAF) upon the addition of tetrabutylammonium cyanide (>60 % yield from KF). Other polar aprotic solvents, such as THF and acetonitrile, are also effective for this S_NAr fluorination reaction.



Scheme 60

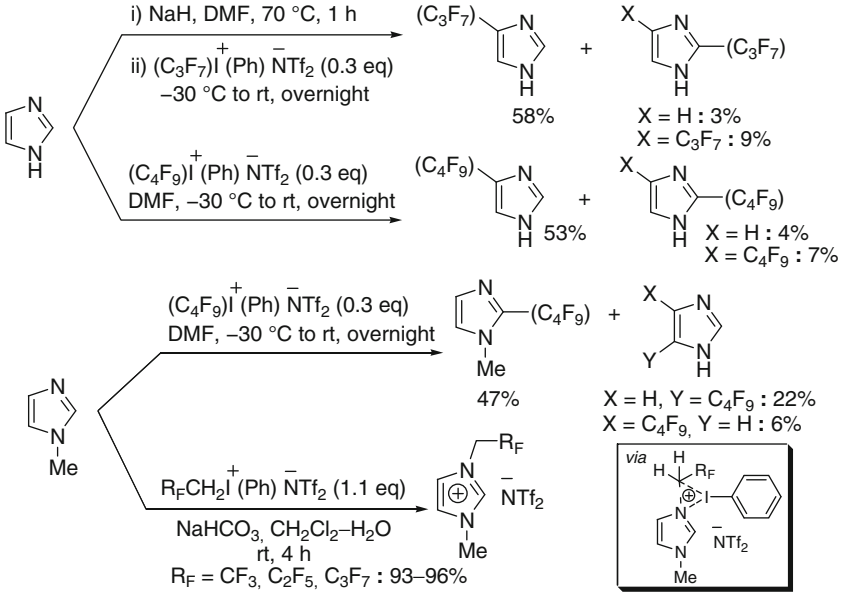
The synthesis of *N*-substituted 5-trifluoromethylimidazole-4-phosphonates was reported by Yuan (Scheme 61) [76]. Addition of lithiated species, derived from diethyl isocyanomethylphosphonate using *n*-BuLi, to *N*-substituted trifluoroacetimidoyl chloride gave an imine intermediate which underwent intramolecular cyclization to furnish regioselectively the 5-(trifluoromethyl)imidazole-4-phosphonate. The addition of an enamine to the isocyano carbon under these conditions, especially without any catalytic assistance, was driven by aromatization. However, replacement of *n*-BuLi with NaH was ineffective and produced an inseparable complex mixture.



Scheme 61

Using hypervalent iodonium salts, DesMarteau reported regioselective fluoroalkylation of imidazoles (Scheme 62) [77]. Thus, reaction of imidazolyl anion with heptafluoropropyliodonium salt gave the 4-(heptafluoropropyl)imidazole as the major product, presumably via a $S_{RN}1$ process. The initial addition of electrophile at C-4 or C-5 of the imidazolyl anion ultimately led to the same intermediate. The nonafluorobutylation of imidazole, even in absence of NaH, also afforded the 4-(nonafluorobutyl)imidazole as the major product. Although initial electrophilic addition at C-5 was favored over C-4 in this case due to resonance, tautomerization of the imidazole-*NH* finally afforded the C-4 substituted product. However, the nonafluorobutylation

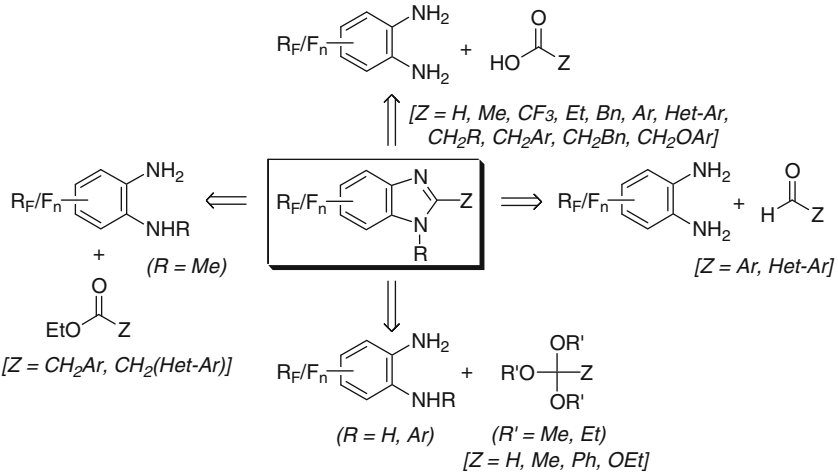
of *N*-methylimidazole under similar conditions (in absence of NaH), produced the corresponding C-2 perfluoroalkylimidazole as the major product. The C-5 substituted product was produced in higher yield than the C-4 substituted product due to the favorable electrophilic attack at C-5 over C-4 of imidazole. The methyl group at *N*-1 also increases the electron density at C-2 and C-5. However, C-2 is sterically less crowded than C-5 due to the presence of lone pair at the adjacent *N*-2 compared to the hydrogen present at C-4. In contrast, the reaction of *N*-methylimidazole with $[R_FCH_2I(Ph)]^+[NTf_2]^-$ promoted the *N′-1H*, *1H*-perfluoroalkylation presumably via a S_N2 pathway.



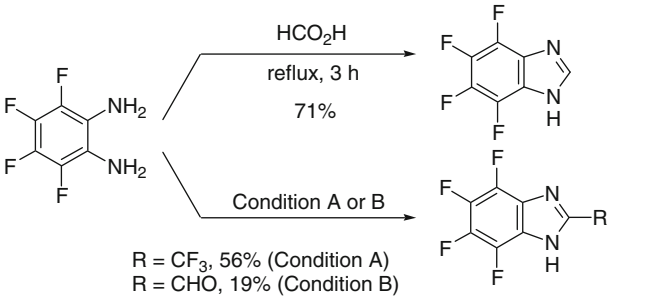
Scheme 62

7 Synthesis of 4,5,6,7-Tetrafluorobenzimidazoles

The common methods for the preparation of benzimidazoles containing fluorine(s) or fluoroalkyl group(s) in the benzenoid ring involve the condensation of predecorated 1,2-phenylenediamine with aldehyde, acid, ester or ortho-ester (Scheme 63) [2a]. Thus, condensation of 3,4,5,6-tetrafluoro-1,2-phenylenediamine with formic acid afforded 4,5,6,7-tetrafluoroimidazole in 71 % yield (Scheme 64) [78]. Refluxing the diamine in trifluoroacetic anhydride gave the *N,N′*-bis(trifluoroacetyl) derivative that was subsequently cyclized to the corresponding 2-(trifluoromethyl)imidazole. Likewise, condensation of a diamine with ethyl diethoxyacetate followed by acidic hydrolysis of the diethyl acetal afforded 2-formyl-tetrafluoroimidazole [79].



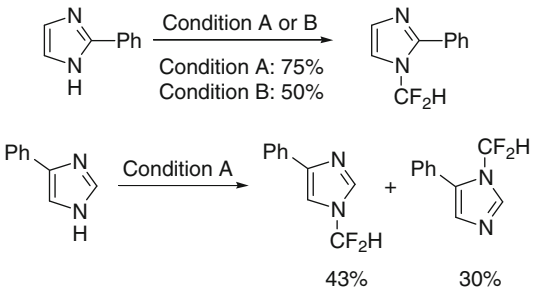
Scheme 63



Scheme 64

8 Synthesis of *N*-Fluoroalkylimidazoles and Benzimidazoles

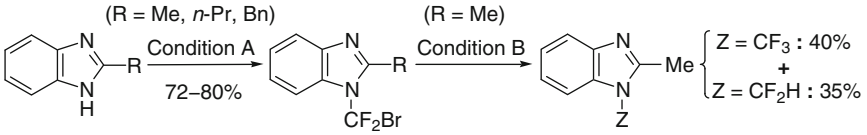
Lyga reported *N*-difluoromethylation of 2- and 4-phenylimidazoles (Scheme 65) [80]. While the treatment of 2-phenylimidazole with one-equivalent NaH followed the addition of $ClCF_2H$ afforded the corresponding *N*-difluoromethylated imidazole, the condensation of sodium salt of 4(5)-phenylimidazole with $ClCF_2H$ produced a mixture of two regioisomeric products under similar conditions. Alternatively, heating a mixture of 2-phenylimidazole with methyl chlorodifluoroacetate in the presence of KF also afforded *N*-difluoromethyl-2-phenylimidazole, albeit in a lower yield.



Condition A: i) NaH, THF, rt, 30 min, ii) $ClCF_2H$, rt, 1 h.
Condition B: KF, 18-crown-6, $ClCF_2CO_2Me$, diglyme, 85 °C, 16 h.

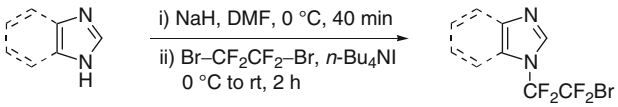
Scheme 65

Yagupolskii described the preparation of *N*-bromodifluoromethylated 2-alkylbenzimidazoles via the treatment of sodium salt of benzimidazoles with CF_2Br_2 (Scheme 66) [81]. The presence of Zn dust accelerates these reactions. Refluxing a mixture of *N*-bromodifluoromethyl-2-methylimidazole with tetramethylammonium fluoride afforded a mixture of *N*-trifluoromethylated and *N*-difluoromethylated benzimidazoles. Röschenthaler and Kolomeitsev also reported the room-temperature preparation of *N*-bromodifluoromethylated imidazole, 2-phenylimidazole and 2-methylbenzimidazole from the corresponding potassium salts (prepared by metalation of parent *NH*-azoles by *t*-BuOK in *t*-BuOH) using CF_2Br_2 (in DMF or THF) in 43 %, 71 % and 70 % yields, respectively [82]. Whereas the reaction of *N*-(bromodifluoromethyl)imidazole with SbF_3 (60 °C, 24 h) afforded *N*-trifluoromethylimidazole in 30 % yield; the reaction of *N*-(bromodifluoromethyl)imidazole with zinc in aqueous methanol (reflux, 24 h) gave *N*-difluoromethylimidazole 95 % yield. Likewise, *N*-(bromodifluoromethyl)-2-phenylimidazole and *N*-bromodifluoromethyl-2-methylbenzimidazole also afforded the corresponding *N*-difluoromethylated products in 95 % yields under similar conditions. The reactions of sodium salt of imidazole and benzimidazole with $BrCF_2CF_2Br$ in the presence of tetra-*n*-butylammonium iodide afforded the corresponding *N*-(2-bromotetrafluoroethyl)azoles (Scheme 67) [83].



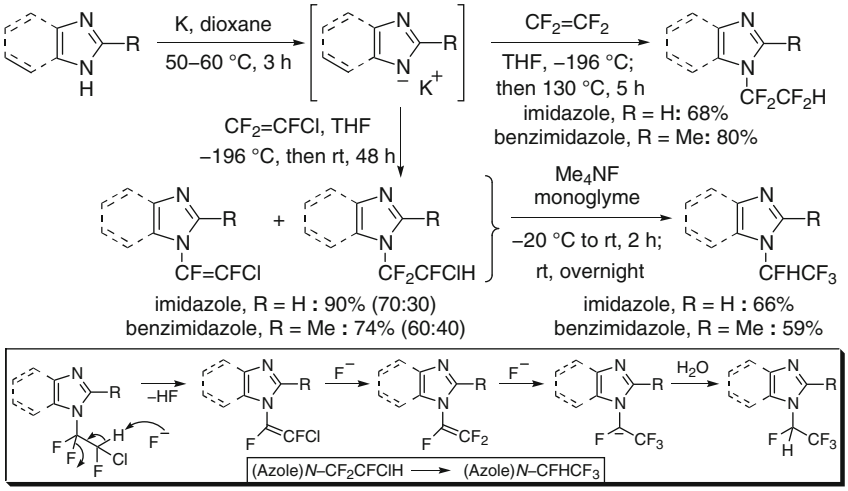
Condition A: i) NaH, Zn dust, MeCN, –15 °C, 3 h; ii) CF_2Br_2, -15 °C to rt, 16 h.
Condition B: Me_4NF, monoglyme, reflux, 5 h.

Scheme 66



Scheme 67

The addition of CF_2=CFCl to the potassium salt of imidazole and 2-methylbenzimidazole followed by warming to room temperature gave the mixture of corresponding *N*-(2-chloro-1,2-difluorovinyl)azoles and *N*-(2-chloro-1,1,2-trifluoroethyl)azoles (Scheme 68) [84]. In contrast, heating the potassium salt of imidazole and 2-methylbenzimidazole with chlorotrifluoroethylene (DMA, reflux, 3 h) afforded only the corresponding *N*-(2-chloro-1,2-difluorovinyl) derivatives in 15 % and 45 % yields, respectively. Treatment of the mixture of *N*-(2-chloro-1,2-difluorovinyl)azoles and *N*-(2-chloro-1,1,2-trifluoroethyl)azoles with tetramethylammonium fluoride afforded corresponding *N*-(1,2,2,2-tetrafluoroethyl)azoles in 66 % and 59 % yields, respectively. In contrast, addition of tetramethylammonium fluoride to *N*-(2-chloro-1,2-difluorovinyl)azoles under similar condition afforded the corresponding *N*-(1,2,2,2-tetrafluoroethyl)azoles in 35 % and 31 % yields, respectively. Likewise, reaction of potassium salt of imidazole and 2-methylbenzimidazole with tetrafluoroethylene afforded the corresponding *N*-(1,1,2,2-tetrafluoroethyl)azoles in 68 % and 80 % yields, respectively.



Scheme 68

In summary, the tactical approaches involved in the synthesis of various fluorinated/fluoroalkylated imidazoles and benzimidazole analogs are discussed in this chapter. A deeper understanding of these synthetic protocols may provide easier access to these molecules, as well as an impetus to the discovery of new fluorinated imidazoles and benzimidazoles in the pharmaceutical and agrochemical industries.

References

1. (a) Boiani M, Gonzalez M (2005) Imidazole and benzimidazole derivatives as chemotherapeutic Agents. Mini-Rev Med Chem 5:409–424; (b) De Luca L (2006) Naturally occurring and synthetic imidazoles: their chemistry and their biological activities. Curr Med Chem 13:1–23; (c) Bhattacharya S, Chaudhuri P (2008) Medical implications of benzimidazole derivatives as drugs designed for targeting DNA and DNA associated processes. Curr Med Chem 15:1762–1777
2. (a) Grimmett MR (1997) Imidazole and benzimidazole synthesis. Academic Press; (b) Xi N, Huang Q, Liu L (2008) Imidazoles. In: Comprehensive heterocyclic chemistry III, pp 143–364; (c) Kirk KL (2009) Fluorinated five-membered nitrogen containing heterocycles. In: Petrov VA (ed) Fluorinated heterocyclic compounds: synthesis, chemistry and applications. Wiley, Hoboken, pp 91–158; (d) Alford PE (2012) Lithiation-based and magnesation-based strategies for the functionalization of imidazole: 2001–2010. In: Gribble GW (ed) Metalation of azoles and related five-membered ring heterocycles. Springer, Berlin/Heidelberg, pp 77–102
3. (a) Müller K, Faeh C, Diederich F (2007) Fluorine in pharmaceuticals: looking beyond intuition. Science 317:1881–1886; (b) Purser S, Moore PR, Swallow S, Gouverneur V (2008) Fluorine in medicinal chemistry. Chem Soc Rev 37:320–330; (c) Hagmann WK (2008) The many roles for fluorine in medicinal chemistry. J Med Chem 51:4359–4369; (d) Roy S, Gregg BT, Gribble GW, Le V-D, Roy S (2011) Tetrahedron 67:2161–2195
4. (a) Park SB, Alper H (2003) Highly efficient, recyclable Pd(II) catalysts with bisimidazole ligands for the Heck reaction in ionic liquids. Org Lett 5:3209–3212; (b) Reddy KR, Krishna GG (2005) Palladium–imidazole derivatives as highly active catalysts for Heck reactions. Tetrahedron Lett 46:661–663; (c) Marion N, Díez-González S, Nolan SP (2007) *N*-Heterocyclic carbenes as organocatalysts. Angew Chem Int Ed 46:2988–3000; (d) Fortman GC, Nolan SP (2011) *N*-Heterocyclic carbene (NHC) ligands and palladium in homogeneous cross-coupling catalysis: a perfect union. Chem Soc Rev 40:5151–5169
5. (a) Green MD, Long TE (2009) Designing imidazole-based ionic liquids and ionic liquid monomers for emerging technologies. Polymer Rev 49:291–314; (b) Visser AE, Swatloski RP, Reichert WM, Mayton R, Sheff S, Wierzbicki A, Davis JH Jr, Rogers RD (2001) Task-specific ionic liquids for the extraction of metal ions from aqueous solutions. Chem Commun 135–136; (c) Xiao J-C, Shreeve JM (2005) Synthesis of 2,2′-biimidazolium-based ionic liquids: use as a new reaction medium and ligand for palladium-catalyzed Suzuki cross-coupling reactions. J Org Chem 70:3072–3078; (d) Deng W-Q, Molinero V, Goddard WA III (2004) Fluorinated imidazoles as proton carriers for water-free fuel cell membranes. J Am Chem Soc 126:15644–15645
6. (a) Niedzicki L, Żukowska GZ, Bukowska M, Szczeciński P, Grugeon S, Laruelle S, Armand M, Panero S, Scrosati B, Marcinek M, Wieczorek W (2010) New type of imidazole based salts designed specifically for lithium ion batteries. Electrochimica Acta 55:1450–1454; (b) Niedzicki L, Kasprzyk M, Kuziak K, Żukowska GZ, Armand M, Bukowska M, Marcinek M, Szczeciński P, Wieczorek W (2009) Modern generation of polymer electrolytes based on lithium conductive imidazole salts. J Power Source 192:612–617; (c) Niedzicki L, Kasprzyk M, Kuziak K, Żukowska GZ, Marcinek M, Wieczorek W, Armand M (2011) Liquid electrolytes based on new lithium conductive imidazole salts. J Power Source 196:1386–1391; (d) Zhou Q, Fitzgerald K, Boyle PD, Henderson WA (2010) Phase behavior and crystalline phases of ionic liquid-lithium salt mixtures with 1-alkyl-3-methylimidazolium salts. Chem Mater 22:1203–1208
7. (a) Hiyama T (2000) Organofluorine compounds: chemistry and applications, Springer, Berlin; (b) Kirsch P (2006) Modern fluoroorganic chemistry, Wiley, Weinheim; (c) Uneyama K (2006) Organofluorine chemistry, Blackwell, Oxford; (d) Chambers RD (2004) Fluorine in organic chemistry, CRC Press
8. Zhang C-P, Wang Z-L, Chen Q-Y, Zhang C-T, Gu Y-C, Xiao J-C (2011) Copper-mediated trifluoromethylation of heteroaromatic compounds by trifluoromethyl sulfonium salts. Angew Chem Int Ed 50:1896–1900
9. Mano T, Stevens RW, Ando K, Nakao K, Okumura Y, Sakakibara M, Okumura T, Tamura T, Miyamoto K (2003) Novel imidazole compounds as a new series of potent, orally active inhibitors of 5-lipoxygenase. Bioorg Med Chem 11:3879–3887

10. Owen MD, Plevey RG, Tatlow JC (1981) 2-Trifluoromethylimidazole, 2,4,5-tris (trifluoromethyl)imidazole and related compounds. J Fluor Chem 17:179–186
11. Kimoto H, Cohen LA (1979) Fluorine reactivity in 2-(trifluoromethyl)imidazoles. J Org Chem 44:2902–2906
12. Collman JP, Boulatov R, Sunderland CJ, Zhong M (2000) Fluorinated imidazoles as ^{19}F probes for biomimetic studies of heme a_3-Cu_b site in cytochrome c oxidase. J Fluor Chem 106:189–197
13. (a) Davidson D, Weiss M, Jelling M (1937) The action of ammonia on benzyl. J Org Chem 2:319–327; (b) Lombardino JG, Wiseman EH (1974) Preparation and antiinflammatory activity of some nonacidic trisubstituted imidazoles. J Med Chem 17:1182–1188
14. Duan G, Zhu N, Yam VW-W (2010) Syntheses and photochromic studies of dithienylethene-containing imidazolium derivatives and their reactivity towards nucleophiles. Chem Eur J 16:13199–13209
15. Li S, Li Z, Yuan Y, Peng D, Li Y, Zhang L, Wu Y (2012) Au(I)-catalyzed intramolecular hydroamination of the fluorinated *N′*-aryl-*N*-propargyl amidines: mild conditions for the synthesis of 2-fluoroalkyl imidazole derivatives. Org Lett 14:1130–1133
16. Dietrich J, Gokhale V, Wang X, Hurley LH, Flynn GA (2010) Application of a novel [3+2] cycloaddition reaction to prepare substituted imidazoles and their use in the design of potent DFG-out allosteric B-Raf inhibitors. Bioorg Med Chem 18:292–304
17. (a) Zou B, Yuan Q, Ma D (2007) Synthesis of 1,2-disubstituted benzimidazoles by a Cu-catalyzed cascade aryl amination/condensation process. Angew Chem Int Ed 46:2598–2601; (b) Cai Q, Zou B, Ma D (2006) Mild Ullmann-type biaryl ether formation reaction by combination of ortho-substituent and ligand effects. Angew Chem Int Ed 45:1276–1279
18. Zheng N, Buchwald SL (2007) Copper-catalyzed regiospecific synthesis of *N*-alkylbenzimidazoles. Org Lett 9:4749–4751
19. Chen M-W, Zhang X-G, Zhong P, Hu M-L (2009) Copper-catalyzed tandem C–N bond formation reaction: selective synthesis of 2-(trifluoromethyl)benzimidazoles. Synthesis 1431–1436
20. Zhu J, Xie H, Chen Z, Lia S, Wu Y (2009) Synthesis of 2-fluoroalkylbenzimidazoles via copper(I)-catalyzed tandem reactions. Chem Commun 2338–2340
21. Uneyama K (1999) Chemistries of trifluoroacetimidoyl halides: preparation, reactions, and applications for the synthesis of fluorinated heterocycles. J Fluor Chem 97:11–25
22. (a) Zhu J, Xie H, Chen Z, Li S, Wu Y (2009) Synthesis of *N*-substituted 2-fluoromethylbenzimidazoles via bis(trifluoroacetoxy)iodobenzene-mediated intramolecular cyclization of *N,N′*-disubstituted fluoroethanimidamides. Synlett 3299–3302; (b) Zhu J, Chen Z, Xie H, Li S, Wu Y (2012) An efficient method to access 2-fluoroalkylbenzimidazoles by PIDA oxidation of amidines. J Fluor Chem 133:134–138
23. Ge F, Wang Z, Wan W, Lu W, Hao J (2007) One-pot synthesis of 2-trifluoromethyl and 2-difluoromethyl substituted benzo-1,3-diazoles. Tetrahedron Lett 48:3251–3254
24. (a) Andrzejewska M, Yépez-Mulia L, Cedillo-Rivera R, Tapia A, Vilpo L, Vilpo J, Kazimierczuk Z (2002) Synthesis, antiprotozoal and anticancer activity of substituted 2-trifluoromethyl- and 2-pentafluoroethylbenzimidazoles. Eur J Med Chem 37:973–978; (b) Kazimierczuk Z, Andrzejewska M, Kaustova J, Klimešova V (2005) Synthesis and antimycobacterial activity of 2-substituted halogenobenzimidazoles. Eur J Med Chem 40:203–208
25. Rewcastle GW, Gamage SA, Flanagan JU, Frederick R, Denny WA, Baguley BC, Kestell P, Singh R, Kendall JD, Marshall ES, Lill CL, Lee W-J, Kolekar S, Buchanan CM, Jamieson SMF, Shepherd PR (2011) Synthesis and biological evaluation of novel analogues of the pan class I phosphatidylinositol 3-kinase (PI3K) inhibitor 2-(difluoromethyl)-1-[4,6-di(4-morpholinyl)-1,3,5-triazin-2-yl]-*1H*-benzimidazole (ZSTK474). J Med Chem 54:7105–7126
26. (a) Navarrete-Vázquez G, Rojano-Vilchis MM, Yépez-Mulia L, Meléndez V, Gerena L, Hernández-Campos A, Castillo R, Hernández-Luis F (2006) Synthesis and antiprotozoal activity of some 2-(trifluoromethyl)-*1H*-benzimidazole bioisosteres. Eur J Med Chem 41:135–141; (b) Navarrete-Vázquez G, Yépez L, Hernández-Campos A, Tapia A, Hernández-Luis F, Cedillo R, González J, Martínez-Fernández A, Martínez-Grueiro M, Castillo R (2003) Synthesis and antiparasitic activity of albendazole and mebendazole analogues. Bioorg Med Chem 11:4615–4622; (c) Hernández-Luis F, Hernández-Campos A, Castillo R, Navarrete-Vázquez G,

Soria-Arteche O, Hernández-Hernández M, Yépez-Mulia L (2010) Synthesis and biological activity of 2-(trifluoromethyl)-*1H*-benzimidazole derivatives against some protozoa and Trichinella spiralis. Eur J Med Chem 45:3135–3141
27. Eapen KC, Tamborski C (1981) Synthesis of some benzimidazoles containing 2-perfluoro substituents. J Fluor Chem 18:243–257
28. Zhu S, Chu Q, Wang Y (2000) A new route to 5-trifluoromethyl-2,3-dihydro-1,4-diazepine and 2-trifluoromethylbenzimidazole. Heteroat Chem 11:27–30
29. Frutos RP, Gallou I, Reeves D, Xu Y, Krishnamurthy D, Senanayake CH (2005) Expedient synthesis of substituted imidazoles from nitriles. Tetrahedron Lett 46:8369–8372
30. Bagdanoff JT, Donoviel MS, Nouraldeen A, Tarver J, Fu Q, Carlsen M, Jessop TC, Zhang H, Hazelwood J, Nguyen H, Baugh SDP, Gardyan M, Terranova KM, Barbosa J, Yan J, Bednarz M, Layek S, Courtney LF, Taylor J, Digeorge-Foushee AM, Gopinathan S, Bruce D, Smith T, Moran L, O'Neill E, Kramer J, Lai Z, Kimball SD, Liu Q, Sun W, Yu S, Swaffield J, Wilson A, Main A, Carson KG, Oravecz T, Augeri DJ (2009) Inhibition of sphingosine-1-phosphate lyase for the treatment of autoimmune disorders. J Med Chem 52:3941–3953
31. Horne DB, Bartberger MD, Kaller MR, Monenschein H, Zhong W, Hitchcock S (2009) Synthesis and conformational analysis of a, a-difluoroalkyl heteroaryl ethers. Tetrahedron Lett 50:5452–5455
32. (a) Loska R, Mąkosza M (2006) Simple method for the introduction of tetrafluoroethyl substituents into nitrogen heterocycles. Mendeleev Commun 16:161–163; (b) Loska R, Mąkosza M (2008) New synthesis of 2-heteroarylperfluoropropionic acids derivatives by reaction of azine *N*-oxides with hexafluoropropene. Chem Eur J 14:2577–2589
33. Ji Y, Brueckl T, Baxter RD, Fujiwara Y, Seiple IB, Su S, Blackmond DG, Baran PS (2011) Innate C-H trifluoromethylation of heterocycles. Proc Natl Acad Sci U S A 108:14411–14415
34. Kimoto H, Cohen LA (1982) Photochemical perfluoroalkylation of imidazoles. J Org Chem 47:2867–2872
35. Wang X, Truesdale L, Yu J-Q (2010) Pd(II)-catalyzed *ortho*-trifluoromethylation of arenes using TFA as a promoter. J Am Chem Soc 132:3648–3649
36. Laali KK, Gettwert VJ (2001) Fluorodediazoniation in ionic liquid solvents: new life for the Balz–Schiemann reaction. J Fluor Chem 107:31–34
37. (a) Cohen LA, Kirk KL (1971) Photochemical decomposition of diazonium fluoroborates. Application to the synthesis of ring-fluorinated imidazoles. J Am Chem Soc 93:3060–3061; (b) Kirk KL, Cohen LA (1973) Photochemistry of diazonium salts. I. Synthesis of 4-fluoroimidazoles, 4-fluorohistamine, and 4-fluorohistidine. J Am Chem Soc 95:4619–4624; (c) Kirk KL (2005) Selective fluorination of biologically important imidazoles and indoles. In: Soloshonok V (ed) Fluorine-containing synthons, ACS symposium series: 911, American Chemical Society, Washington, DC, pp 303–316
38. Heredia-Moya J, Kirk KL (2007) Photochemical Schiemann reaction in ionic liquids. J Fluor Chem 128:674–678
39. Senanayake CH, Hong Y, Xiang T, Wilkinson HS, Bakale RP, Jurgens AR, Pippert ME, Butler HT, Wald SA (1999) Properly tuned first fluoride-catalyzed TGME-mediated amination process for chloroimidazoles: inexpensive technology for antihistaminic norastemizole. Tetrahedron Lett 40:6875–6879
40. (a) Sun H, DiMagno SG (2006) Room-temperature nucleophilic aromatic fluorination: experimental and theoretical studies. Angew Chem Int Ed 45:2720–2725; (b) Sun H, DiMagno SG (2005) Anhydrous tetrabutylammonium fluoride. J Am Chem Soc 127:2050–2051
41. Takizawa S, Nishida J, Tsuzuki T, Tokito S, Yamashita Y (2007) Phosphorescent iridium complexes based on 2-phenylimidazo[1,2-a]pyridine ligands: tuning of emission color toward the blue region and application to polymer light-emitting devices. Inorg Chem 46:4308–4319
42. Chen Q-Y, Qiu Z-M (1987) Studies on fluoroalkylation and fluoroalkoxylation. Regioselective synthesis of fluoroalkylated imidazoles. Chem Commun 1240–1241
43. Huang X-T, Long Z-Y, Chen Q-Y (2001) Fluoroalkylation of aromatic compounds with per(poly)fluoroalkyl chlorides initiated by sodium dithionite in DMSO. J Fluor Chem 111:107–113
44. Lombardino JG (1973) Synthesis of 2-aryl-4-phenyl-5-trifluoromethylimidazoles. J Heterocycl Chem 10:697–698

45. Baldwin JJ, Kasinger PA, Novello FC, Sprague JM, Duggan DE (1975) 4-Trifluoromethylimidazoles and 5-(4-pyridyl)-1,2,4-triazoles, new classes of xanthine oxidase inhibitors. J Med Chem 18:895–900
46. (a) Matthews DP, McCarthy JR, Whitten JP, Kastner PR, Barney CL, Marshall FN, Ertel MA, Burkhard T, Shea PJ, Kariya T (1990) Synthesis and cardiotonic activity of novel biimidazoles. J Med Chem 33:317–327; (b) Matthews DP, Whitten JP, McCarthy JR (1986) A convenient procedure for the preparation of 4(5)-cyanoimidazoles. J Org Chem 51:3228–3231
47. Lukyanov SM, Bliznets IV, Shorshnev SV (2009) Synthesis of sterically hindered 3-(azolyl) pyridines. ARKIVOC iv:21–45
48. Kamitori Y (2001) A facile synthesis of fluorine-containing heterocycles – use of 1,1,1-trifluoro-2-alkanones as a convenient synthetic intermediate. J Heterocycl Chem 38:773–776
49. Kamitori Y, Hojo M, Masuda R, Kawamura Y, Fang X (1990) Convenient and selective synthesis of 4-trifluoromethylimidazoles. Heterocycles 31:2103–2106
50. Kamitori Y, Hojo M, Masuda R, Ohara S, Kawasaki K, Kawamura Y, Tanaka M (1990) 4- and 5-trifluoromethylimidazoles. Novel cyclization of trifluoroacetylated aldehyde dimethylhydrazones. J Heterocycl Chem 27:487–495
51. (a) Kawase M, Saito S, Kurihara T (1995) An efficient synthesis of 4-trifluoromethylated and 4-perfluoroalkylated imidazoles from mesoionic 1,3-oxazolium-5-olates. Heterocycles 41:1617–1620; (b) Kawase M, Saito S, Kurihara T (2001) Convenient synthesis of 4-trifluoromethyl-substituted imidazole derivatives. Chem Pharm Bull 49:461–464
52. Kawase M (1994) A novel ring transformation of mesoionic 1,3-oxazolium-5-olates into 5-trifluoroacetylated and 5-perfluoroacylated imidazoles by reaction with amidines. Chem Commun 2101–2102
53. Huang WS, Yuan CY, Wang ZQ (1995) Facile synthesis of 1-substituted 5-trifluoromethylimidazole-4-carboxylates. J Fluor Chem 74:279–282
54. Xie H, Zhu J, Chen Z, Li S, Wu Y (2010) Diastereoselective silver-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with fluorinated imine. J Org Chem 75:7468–7471
55. Honey MA, Pasceri R, Lewis W, Moody CJ (2012) Diverse trifluoromethyl heterocycles from a single precursor. J Org Chem 77:1396–1405
56. Kamitori Y (2000) A convenient synthesis of 4-trifluoromethylimidazol-1-ols. Heterocycles 53:107–113
57. Kamitori Y, Hojo M, Masuda R, Sukegawa M, Hayashi K, Kouzeki K (1994) A convenient and facile synthesis of 5-trifluoromethyl-1,2,4-triazine derivatives. Heterocycles 39:155–162
58. Kamitori Y, Sekiyama T, Okada E (2007) Thermal reaction of 5-aryl-6-trifluoromethyl-3,6-dihydro-2H-[1,3,4]oxadiazines accessing 5-trifluoromethylimidazols. Heterocycles 74:351–356
59. Piccionello AP, Pace A, Buscemi S, Vivona N, Pani M (2008) Synthesis of trifluoromethylated 2-benzoyl- and 2-aminoimidazoles from ring rearrangement of 1,2,4-oxadiazole derivatives. Tetrahedron 64:4004–4010
60. Li H-Y, DeLucca I, Drummond S, Boswell GA (1997) An unusual trifluoromethyl elimination reaction from the 4,4-bis(trifluoromethyl)-5-hydroxyimidazoline ring system. J Org Chem 62:2550–2554
61. Karsch HH, Bienlein F, Sladek A, Heckel M, Burger K (1995) New method for the synthesis of silaheterocycles and the first pentacoordinate silanol. J Am Chem Soc 117:5160–5161
62. (a) Barltrop JA, Day AC, Mack AG, Shahrisa A, Wakamatsu S (1981) Competing pathways in the phototransposition of pyrazoles. Chem Commun 604–606; (b) Pavlik JW, Kurzweil EM (1991) Phototransposition chemistry of 1-methylpyrazole. Deuterium, methyl, and fluorine substitution. J Org Chem 56:6313–6320
63. Ferreira SB, Costa MS, Boechat N, Bezerra RJS, Genestra MS, Canto-Cavalheiro MM, Kover WB, Ferreira VF (2007) Synthesis and evaluation of new difluoromethyl azoles as antileishmanial agents. Eur J Med Chem 42:1388–1395
64. Lange JHM, van Stuivenberg HH, Coolen HKAC, Adolfs TJP, McCreary AC, Keizer HG, Wals HC, Veerman W, Borst AJM, de Looff W, Verveer PC, Kruse CG (2005) Bioisosteric replacements of the pyrazole moiety of rimonabant: synthesis, biological properties, and

molecular modeling investigations of thiazoles, triazoles, and imidazoles as potent and selective CB1 cannabinoid receptor antagonists. J Med Chem 48:1823–1838
65. Dolensky B, Kirk KL (2002) Preparation of (fluoromethyl)- and (difluoromethyl)imidazoles. Collect Czech Chem Commun 67:1335–1344
66. Du X, Chen X, Mihalic JT, Deignan J, Duquette J, Li AR, Lemon B, Ma J, Miao S, Ebsworth K, Sullivan TJ, Tonn G, Collins TL, Medina JC (2008) Design and optimization of imidazole derivatives as potent CXCR3 antagonists. Bioorg Med Chem Lett 18:608–613
67. Dolensky B, Kirk KL (2001) New building blocks for fluorinated imidazole derivatives: preparation of β-fluoro- and β, β-difluorohistamine. J Org Chem 66:4687–4691
68. Dolensky B, Kirk KL (2002) New building blocks for fluorinated bioimidazole derivatives II: preparation of *β*-fluorourocanic acids. J Org Chem 67:3468–3473
69. Arbonés C, Sánchez FJ, Marco MP, Camps F, Messeguer A (1990) Fluorinated analogues of the imidazole insect growth regulator KK42. Heterocycles 31:67–78
70. O'Mahony G, Pitts AK (2010) Synthesis of tertiary amides from anionically activated aromatic trifluoromethyl groups. Org Lett 12:2024–2027
71. Kirk KL, Cohen LA (1973) Photochemistry of diazonium salts. III. A new and facile synthesis of 4-fluoroimidazoles. J Org Chem 38:3647–3648
72. Chandra T, Zou X, Valente EJ, Brown KL (2006) Regio- and stereoselective glycosylation: synthesis of 5-haloimidazole *α*-ribonucleosides. J Org Chem 71:5000–5003
73. Hajduch J, Cramer JC, Kirk KL (2008) An enantioselective synthesis of (S)-4-fluorohistidine. J Fluor Chem 129:807–810
74. Dolensky B, Takeuchi Y, Cohen LA, Kirk KL (2001) Synthesis of 4,5-difluoroimidazole. J Fluor Chem 107:147–148
75. Sun H, DiMagno SG (2007) Fluoride relay: a new concept for the rapid preparation of anhydrous nucleophilic fluoride salts from KF. Chem Commun 528–529
76. Huang W, Yuan C (1996) Studies on organophosphorus compounds 92: a facile synthesis of 1-substituted 5-trifluoromethylimidazole-4-phosphonates. Synthesis 511–513
77. Lu C, VanDerveer D, DesMarteau DD (2008) Fluoroalkylation of imidazoles by hypervalent iodonium salts. Org Lett 10:5565–5568
78. Heaton A, Hill M, Drakesmith F (1997) Polyhalogenonitrobenzenes and derived compounds. Part 5. Improved preparations of 1,2,3,4-tetrafluoro-5,6-dinitrobenzene and 3,4,5,6-tetrafluoro-1,2-phenylenediamine, and the use of the latter for the synthesis of tetrafluorobenzheterocycles. J Fluor Chem 81:133–138
79. Murata H, Miyazaki Y, Inaba A, Paduan-Filho A, Bindilatti V, Oliveira NF Jr, Delen Z, Lahti PM (2008) 2-(4,5,6,7-Tetrafluorobenzimidazol-2-yl)-4,4,5,5-tetramethyl-4,5-dihydro-*1H-imidazole*-3-oxide-1-oxyl, a hydrogen-bonded organic quasi-1D ferromagnet. J Am Chem Soc 130:186–194
80. Lyga JW, Patera RM (1998) *N*-difluoromethylation of phenylazoles. J Fluor Chem 92:141–145
81. (a) Yagupolskii LM, Fedyuk DV, Petko KI, Troitskaya VI, Rudyk VI, Rudyu VV (2000) *N*-Trihalomethyl derivatives of benzimidazole, benzotriazole and indazole. J Fluorine Chem 106:181–187; (b) Yagupolskii LM, Fedyuk DV (2000) 2-Alkyl-1-(2-aryl-1,1-difluoro-2-hydroxyethyl)benzimidazoles: potential angiotensin II receptor antagonists. Tetrahedron Lett 41:2265–2267
82. Bissky G, Röschenthaler G-V, Lork E, Barten J, Médebielle M, Staninets V, Kolomeitsev AA (2001) Generation of heteroarylium-N-difluoromethylides and heteroaryl-*N*-difluoromethyl anions and their reactions with electrophiles: heteroaryl- and heteroarylium-*N*-difluoromethyl trimethylsilanes and a new heteroaryl-*N*-trifluoromethane. J Fluor Chem 109:173–181
83. Petko KI, Sokolenko TM, Bezdudny AV, Yagupolskii LM (2005) *N*-(2-bromotetrafluoroethyl) derivatives of five-membered nitrogen-containing heterocycles. J Fluor Chem 126:1342–1346
84. Rudyuk VV, Fedyuk DV, Yagupolskii LM (2004) *N*-polyfluoroethyl and *N*-2-chlorodifluorovinyl derivatives of azoles. J Fluor Chem 125:1465–1471

Chemistry of Fluorinated Oxadiazoles and Thiadiazoles

Andrea Pace, Antonio Palumbo Piccionello, Ivana Pibiri, Silvestre Buscemi, and Nicolò Vivona

Contents

A. Pace (✉) • A. Palumbo Piccionello • I. Pibiri • S. Buscemi • N. Vivona
Dipartimento di Scienze e Tecnologie Biologiche Chimiche e Farmaceutiche, Università degli Studi di Palermo, Viale delle Scienze Ed. 17, 90128 Palermo, Italy
e-mail: andrea.pace.unipa@gmail.com

V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_9,

Abstract A literature survey of the chemistry of fluorinated oxadiazoles and thiadiazoles is presented. The core part on synthetic procedures is given by type of heterocycle and includes recent developments up to the end of 2012. Reactivity is discussed when induced by the presence of the fluorinated moiety. Selected examples of bioactive compounds and applications are illustrated.

Keywords Fluorinated azoles • Oxadiazoles • Thiadiazoles • Fluorinated bioactive azoles • Fluorinated materials

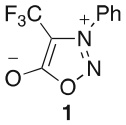
1 Introduction

Oxadiazoles and thiadiazoles are a subset of heteroaromatic compounds which are widely applied in many fields, and their chemical and physicochemical properties can be appropriately tuned by the introduction of fluorine or fluorinated groups. This is one of the main reasons of the increasing development of synthetic methodologies leading to targeted fluorinated heterocycles. Additionally, the presence of the fluorinated moiety opens the way to new *fluorine-induced* reactivity with respect to corresponding non-fluorinated systems [1]. Target fluorinated oxadiazoles and thiadiazoles find applications in materials and fluoropolymer science and, in the case of biologically active compounds, their use as agrochemicals or pharmaceuticals is also common. Four types of compounds can be considered under the general classification "fluorinated heterocycles" in this chapter: (i) compounds where the fluorine atom is directly linked to the heterocyclic core; (ii) compounds where the heterocycle is substituted with a mono-, poly- or perfluoroalkyl group; (iii) compounds where the heterocycle is substituted with a mono-, poly- or perfluoroaryl group; (iv) compounds where the fluorine substituent is far from the heterocyclic core. Although the latter category may seem too generally applicable, in several cases the presence of a fluorinated group not directly linked to the heterocyclic core can strongly affect the heterocyclic moiety chemical behaviour. Most of the literature refers to (per)fluoroalkyl and (per)fluoroaryl derivatives and reported examples have been selected on the basis of general interest or major breakthrough. Our efforts have been devoted to present an update until the end of 2012, mainly considering publications appeared in the last two decades. Previous papers have been cited when of general interest for the synthetic approach.

2 Synthetic Routes to Fluorinated Oxadiazoles and Thiadiazoles

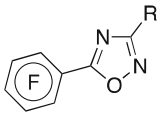
2.1 1,2,3-Oxadiazoles

With the exception of mesoionic compounds such as sydnone **1** (Fig. 1) [2], fluorinated 1,2,3-oxadiazole systems are rare and often included as structures in patent's Markush, without sufficient experimental details [3].

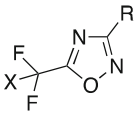


1

Fig. 1 A reported example of fluorinated 1,2,3-oxadiazole system



2



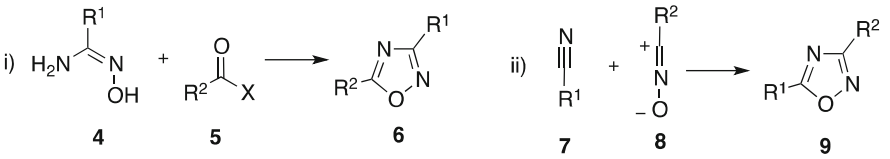
3

Fig. 2 Examples of 1,2,4-oxadiazole reagents

2.2 1,2,4-Oxadiazoles

Fluorinated 1,2,4-oxadiazoles find their application in both the pharmaceutical industry and materials science. Recently, 3-substituted 5-pentafluorophenyl-1,2,4-oxadiazoles **2** (Fig. 2) have been used as fluorinated oxadiazole arylating reagents (FOXARs) for the attachment of fluorinated moieties to nucleophilic pendants of polymers [4] and macromolecules [5]. Fluorinated 1,2,4-oxadiazoles **3** (Fig. 2) have been employed as reagents to introduce the difluoromethylene moiety into organic compounds [6]. To date, despite the fact that 3- (or 5-) chloro- or bromo- derivatives are known, there is still no literature on the synthesis of 1,2,4-oxadiazoles bearing a fluorine atom directly linked to the oxadiazole ring.

The synthesis of fluorinated oxadiazoles can be achieved from open-chain fluorinated precursors through conventional heterocyclization reactions such as the *amidoxime route* (i in Scheme 1) and the *cycloaddition route* (ii in Scheme 1), both necessitating of a nitrile precursor [7].

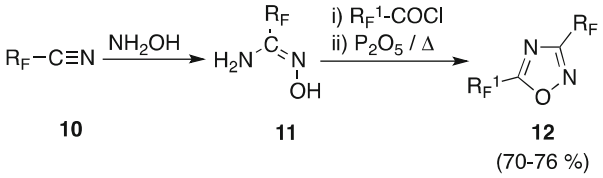


4 5 6 7 8 9

Scheme 1 1,2,4-oxadiazole synthesis by (i) the amidoxime route; (ii) the cycloaddition route

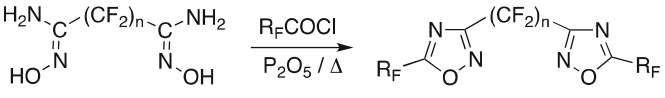
2.2.1 The Amidoxime Route

The historical *amidoxime route* towards 1,2,4-oxadiazoles is still the most represented in the literature also for fluorinated structures. Oxadiazoles **12**, bearing fluorinated groups at both the C(3) and C(5) can be obtained from the appropriate perfluoroalkyl amidoxime **11** and a fluorinated acylating reagent (Scheme 2). Similarly, from suitably fluorinated reagents, one can obtain oxadiazoles bearing the fluorinated group either at the C(3) or at C(5), respectively.



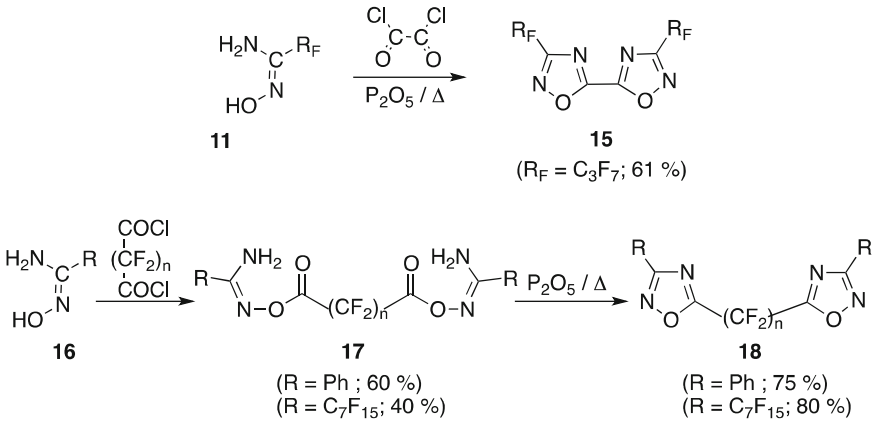
Scheme 2 Synthesis of 1,2,4-oxadiazoles bearing fluorinated groups at both the C(3) and C(5) by the amidoxime route

Pioneering work on this subject [8] reported the preparation of various perfluoro-alkylamidoximes **11** (R_F=CF_3, C_2F_5, C_3F_7, C_7F_{15}) and their acylation with perfluoro-acylchlorides (R_F^1COCl) followed by cyclodehydration to produce 3,5-bis(perfluoroalkyl)-1,2,4-oxadiazoles **12** either symmetrically (R_F=R_F^1) or unsymmetrically substituted. By following the same methodology, bis-oxadiazoles **14** (n=3) could be obtained (Scheme 3) [8, 9].



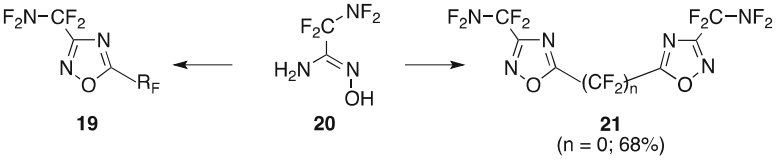
Scheme 3 Synthesis of perfluoroalkylated bis-oxadiazoles **14** by the amidoxime route

Perfluoroalkyl substituted oxadiazoles joined by the annular 5,5′- positions can be obtained by using the appropriate diacyl chloride. For instance, in the reaction of amidoxime **11** with oxalyl chloride, the 5,5′-bis(1,2,4- oxadiazolyl) compound **15** is produced (Scheme 4) [8]. Furthermore, the corresponding O,O′-hexafluoroglutaryl diamidoxime **17** (n=3) was isolated in acceptable yields by the reaction of amidoxime **16** and hexafluoroglutaryl chloride [10]. Subsequent dehydration by heating with phosphorus pentoxide gave the corresponding bis-oxadiazole **18** in good yields (Scheme 4).



Scheme 4 Bis-oxadiazoles **15** and **18** obtained by the amidoxime route followed by dehydration step with P_2O_5

Various 5-perfluoroalkyl-3-phenyloxadiazoles have been obtained from the direct reaction of benzamidoxime **16** (R=Ph) with perfluoroacylating reagents [10, 11]. Difluoromalonyl chloride and benzamidoxime directly gave the bis-oxadiazolyl-difluoromethane **18** (n = 1). Similarly, the reaction of difluoroaminodifluoroacetamidoxime **20** with perfluoroalkanoyl chlorides followed by dehydration of the resulting *O*-perfluoroacylamidoximes with P_2O_5 leads to 5-perfluoroalkyl-oxadiazoles **19**. When heating amidoxime **20** with perfluorosuccinic acid and phosphorus pentoxide, the bis-oxadiazole **21** (n = 2) is obtained [12]. The same amidoxime **20** with oxalyl chloride will yield bis-oxadiazole **21** (n = 0) (Scheme 5) [13].



Scheme 5 Synthesis of perfluoroalkyl 1,2,4-oxadiazole **19** and bis-oxadiazole **21**

5-Pentafluorophenyl-oxadiazoles of general formula **22** (Fig. 3) can be obtained directly from the reaction of the corresponding amidoximes and pentafluorobenzoyl chloride in refluxing toluene in the presence of pyridine [14].

Similarly, 3-benzoyl- **24** (R=Ph) [15] and 3-carboxyethyl-5-perfluoroalkyl-oxadiazole **24** (R=OEt) are prepared from amidoximes (**23**; R=Ph, OEt respectively) and the corresponding perfluoroalkanoyl chlorides (or anhydrides) (Scheme 6).

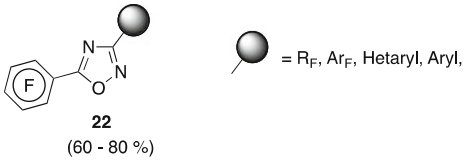
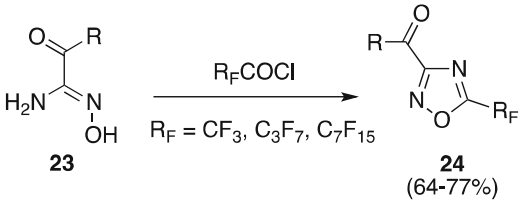
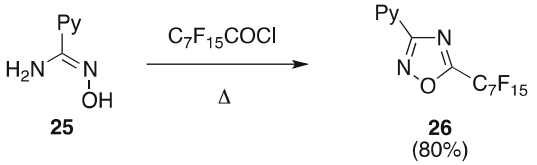


Fig. 3 Examples of synthetically available FOXARs



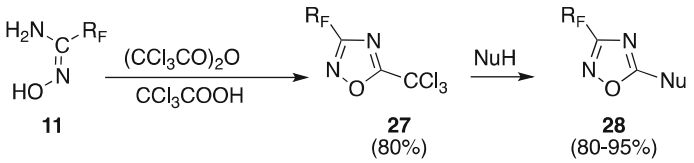
Scheme 6 Synthesis of 5-perfluoroalkyl 1,2,4-oxadiazole **24**

4-(5-Perfluoroheptyl-1,2,4-oxadiazol-3-yl)pyridine or 3-(5-perfluoroheptyl-1,2,4- oxadiazole-3-yl)pyridine **26,** have been obtained directly (in 90 and 70 % yields, respectively) from the acylation reaction of the corresponding nicotyl amidoxime and isonicotyl amidoxime (Scheme 7) [16]. From these derivatives, the corresponding *N*-methyl-pyridinium salts have been prepared for possible applications as *S*elf-*O*rganized *F*unctional *O*rganic *S*alts (SOFOS) [16].



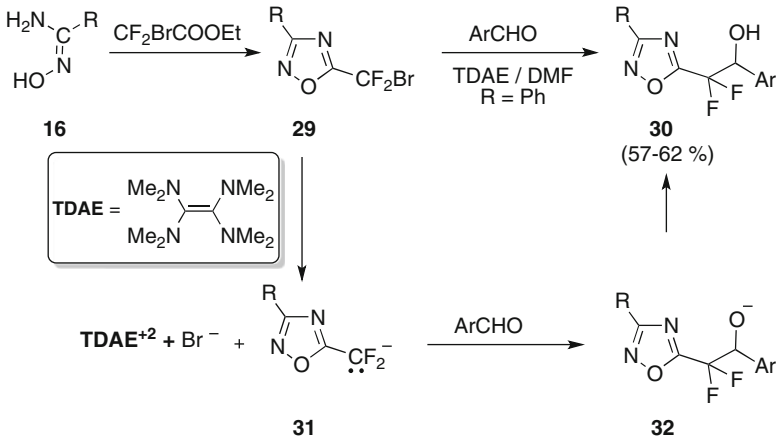
Scheme 7 Synthesis of 3- and 4-(5-perfluoroheptyl-1,2,4-oxadiazol-3-yl)pyridine **26**

The *amidoxime route* has been used for the synthesis of derivatives differently functionalized at C(5). Amidoxime **11** treated with trichloroacetic anhydride in hot trichloroacetic acid, lead to the corresponding 5-trichloromethyl- 1,2,4-oxadiazole **27.** The latter, in the presence of nitrogen nucleophiles (ammonia, primary or secondary amines), undergoes an aminolysis reaction leading to **28** (Scheme 8) [17].



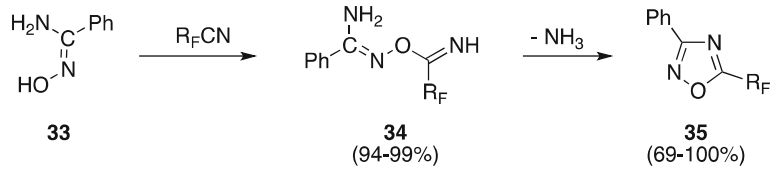
Scheme 8 Synthesis of 5-trichloromethyl- 1,2,4-oxadiazole **27** and its aminolysis leading to **28**

Amidoximes also react with ethyl bromodifluoroacetate to give 5-(bromodifluoromethyl)oxadiazoles **29** [18]. A series of difluoro alcohols such as **30** were obtained by an electron transfer process in the presence of aromatic aldehydes starting from compounds **29** (Scheme 9). The reactions occurs through an initial formation of a red colored charge-transfer complex between TDAE (donor) and bromo derivative **29** (acceptor). A temperature increase from −20 °C to rt allows to complete an electron transfer process producing difluoromethylene anion **31**, which is stable enough to react with aromatic aldehydes, finally leading to the corresponding alcohols **30** [19].



Scheme 9 Synthesis of 5-(bromodifluoro-methyl)oxadiazoles **29** and difluoro alcohols **30**

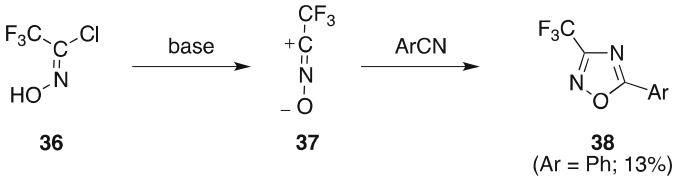
Nitriles themselves can be also used as acylating reagent for amidoximes in some cases. Subsequent heterocyclization involves loss of ammonia in the final step (Scheme 10). For this purpose, the reaction is carried out in the presence of an ammonia acceptor reagent (e. *g.* the perfluorocarboxylic acid, or an excess of the nitrile). For example, from the reaction of benzamidoxime with perfluoroalkylnitriles, a series of 5-perfluoroalkyl-1,2,4-oxadiazoles **35** can be obtained [20].



Scheme 10 Synthesis of 5-perfluoroalkyl-1,2,4-oxadiazoles **35**

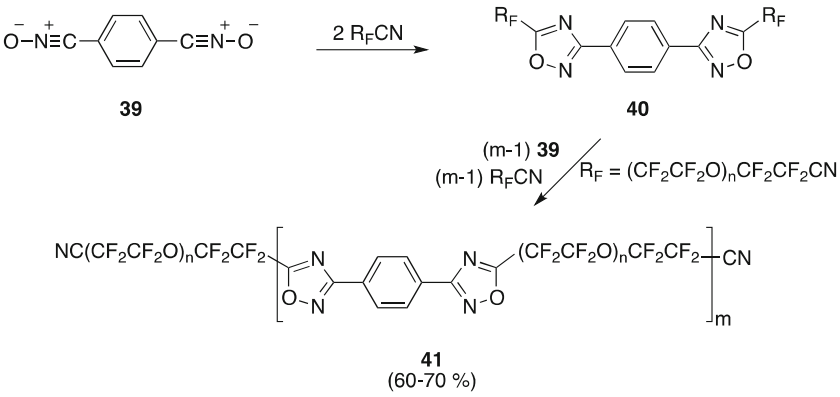
2.2.2 The Cycloaddition Route

Another general approach to the synthesis of fluorinated 1,2,4-oxadiazoles is based on the [3+2] cycloaddition between nitriles and nitrile oxides (each component of the reaction can contain the fluorinated moiety). Cycloaddition of the trifluoroacetonitrile oxide **37** produced the 3-trifluoromethyl-5-phenyl derivative **38** (Ar=Ph) (Scheme 11) [21]. Unfortunately, aliphatic nitriles such as the butyronitrile do not undergo cycloaddition into the oxadiazole derivative [21].



Scheme 11 Synthesis of 3-trifluoromethyl-5-phenyl derivative **38** by the Cycloaddition Route

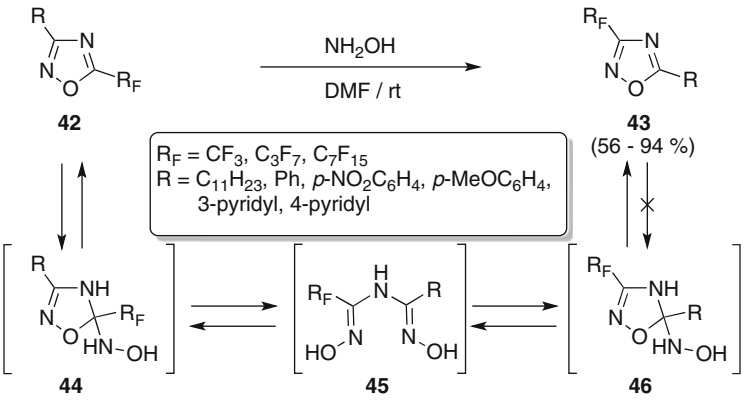
The method involving cycloaddition between nitriles and nitrile oxides has also been employed for the synthesis of complex systems precursors of polymeric materials. For example, terephthaldinitrile oxide **39** was reacted with R_FCN (Scheme 12) to give representative oxadiazole **40**. In the case of R_F=nitrile-terminated polyperfluoroalkylether chain, the presence of several nitrile pendants as curing sites can lead to further functionalized oligomers **41** [22].



Scheme 12 Synthesis of functionalized oligomers **41**

2.2.3 The Ring-Rearrangement Route

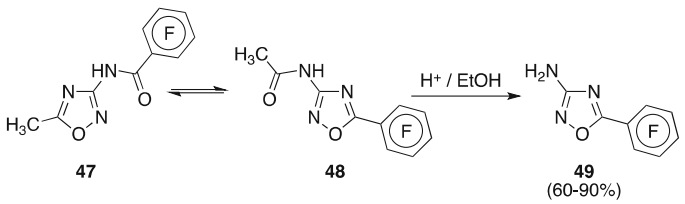
More than a decade from our laboratories demonstrated how heterocyclic rearrangements can be fruitfully implemented for the synthesis of fluorinated heterocycles. ANRORC-like reactions, which consists of the **Addition** of a **Nucleophile** to a electron deficient heterocycle, followed by **Ring-Opening** and **Ring- Closure** steps [23], represent a valuable strategy to transform an easily accessible fluorinated heterocycle into a different one containing the heteroatoms originally belonging to the nucleophilic reagent. The reaction of 5-perfluoroalkyl-1,2,4-oxadiazoles **42** with hydroxylamine in DMF at room temperature gave excellent yields of 3-perfluoroalkyl-1,2,4-oxadiazoles **43,** resulting in a virtual C(5)-C(3) annular switch (Scheme 13) [24].



Scheme 13 ANRORC-like reactions: the C(5)-C(3) annular switch

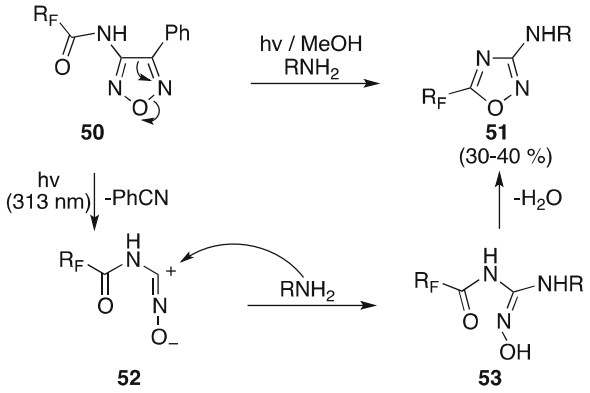
The ring-degenerate ANRORC rearrangement has been successfully applied also for the synthesis of perfluoroalkylated 1,2,4-oxadiazolyl-pyridines **43** (R_F=C_7F_{15}; R=3- or 4-pyridyl), suitable precursors of the corresponding *N*-methylated salts [16].

The ring-rearrangement approach is an efficient methodology also for the synthesis of 3-amino-5-polyfluoroaryl-1,2,4-oxadiazoles. Following the Boulton-Katritzky rearrangement pattern, the ring-degenerate thermal equilibration of **47** (easily accessible from the reaction of 3-amino-5-methyl-1,2,4-oxadiazole with pentafluorobenzoyl chloride) gave a mixture of both the ring degenerate isomers **47** and **48** in a 80:20 ratio as a result of the electron-withdrawing character of the pentafluorophenyl moiety (Scheme 14) [25]. Interestingly, acidic hydrolysis of this thermally equilibrated mixture gave the expected 3-amino compound **49** in about 60 % yield because of the acid induced shift of the ring-degenerate equilibrium. By the same procedure, different 3-amino-5-polyfluorophenyl-1,2,4-oxadiazoles have also been prepared [25]. These results appear of some significance, since attempts to synthesize the same fluorinated oxadiazoles by conventional procedures (e. g., by the acylcyanamide method) were reported to be unsuccessful.



Scheme 14 The Boulton-Katritzky ring-degenerate thermal equilibration of **47**

Unfortunately, because of the structure-dependent reactivity of 3-acylamino oxadiazoles towards ring- degenerate interconversions, this procedure is not applicable to the synthesis of 5-perfluoroalkyl derivatives [25]. Nevertheless, these compounds can be obtained through photo-induced rearrangements of O-N bond containing azoles [26] involving the photo-fragmentation of 3-perfluoroalkanoylamino furazans **50** at λ = 313 nm in methanol and in the presence of ammonia or primary aliphatic amines giving the corresponding 3-amino- or 3-N-alkylamino-5- perfluoroalkyl-1,2,4-oxadiazoles **51** as a result of the involvement of the added amine in the reaction of photofragmented intermediates (Scheme 15) [27].



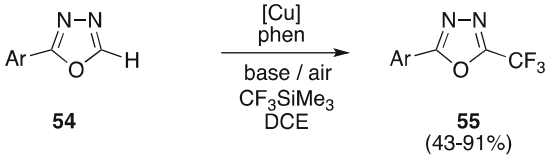
Scheme 15 Synthesis of 3-N-alkylamino-5- perfluoroalkyl-1,2,4-oxadiazoles **51** by photo-fragmentation of 3-perfluoroalkanoylamino furazans **50**

In order to maximize yields, the irradiated solution needs to stand in the dark overnight, to complete the final cyclization step of **53** into **51**. Although yields are not optimal due to the subsequent photoreactivity of compounds **51** at the used irradiation wavelength (see Sect. 2.3.3), this route appears to be the most accessible synthetic method for the synthesis of 3-(alkyl) amino-5-perfluoroalkyl-1,2,4-oxadiazoles.

2.3 1,3,4-Oxadiazoles

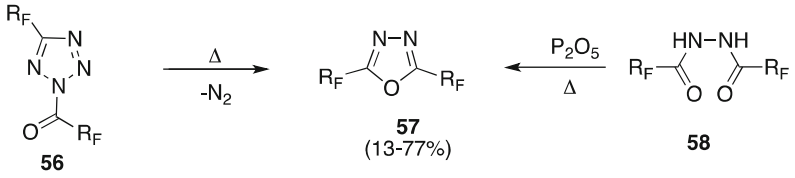
There are several reports in the literature concerning 1,3,4-oxadiazoles bearing a fluorinated group at either or both positions 2 and 5 of the ring. Some trifluoromethyl-1,3,4-oxadiazoles are also commercially available. As for oxadiazoles with a fluorine atom directly bond to the ring, although some patents actually claim such derivatives [28], no description of experimental detail has been reported.

Recently, the direct trifluoromethylation of 1,3,4-oxadiazoles has been achieved by reaction with trifluoromethyltrimethylsilane through direct C-H activation of oxadiazole **54** using copper acetate as catalyst under oxidative conditions (Scheme 16) [29].



Scheme 16 Synthesis of trifluoromethyl-1,3,4-oxadiazole **55** by copper acetate catalysis

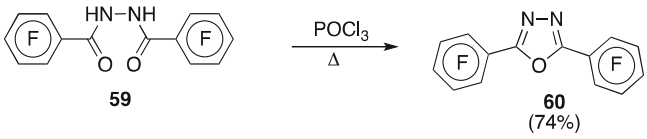
Beside this direct approach, the most widely used methodologies to obtain fluorinated 1,3,4-oxadiazole derivatives are: (i) the cyclodehydration of fluorinated diacylhydrazines **58** (Scheme 17); (ii) the ring-transformation of fluorinated 2-acyltetrazoles **56** (Huisgen reaction) [30] involving the loss of a nitrogen molecule of the acylated tetrazole ring leading to a nitrilimine intermediate which will finally produce 1,3,4-oxadiazoles **57** (Scheme 17). Besides these general methodologies, some syntheses of particular 1,3,4-oxadiazoles through photoinduced ring-rearrangements have been reported as well (see Scheme 26 in Sect. 2.3.3).



Scheme 17 Synthesis of perfluoroalkylated 1,3,4-oxadiazoles **57** by cyclodehydration of fluorinated diacylhydrazines **58** and Huisgen reaction of fluorinated 2-acyltetrazoles **56**

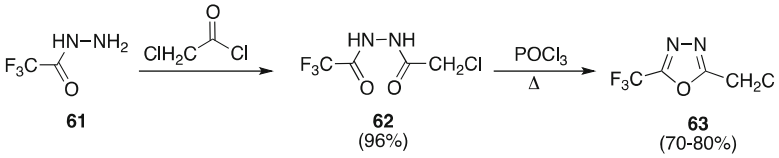
2.3.1 The Diacylhydrazine Route

Historical examples of syntheses by cyclodehydration of bis-perfluoro-acylhydrazines with P_2O_5 were reported by Brown et al. [31] as well as by Chambers and Coffman [32]. By using the same approach, a series of symmetrically and asymmetrically substituted 2,5-bis(polyfluoroaryl)-1,3,4-oxadiazoles **60** can be prepared in excellent yields (Scheme 18) [33].



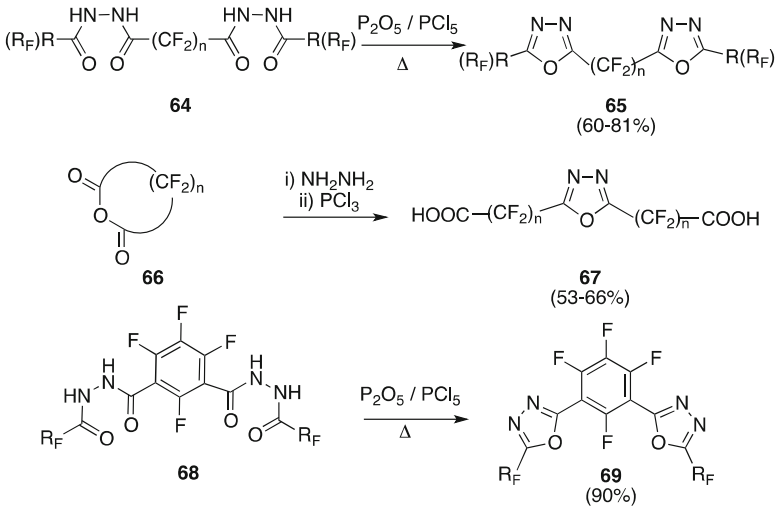
Scheme 18 Synthesis of 2,5-bis(polyfluoroaryl)-1,3,4-oxadiazoles **60** by cyclodehydration of bis-perfluoro-acylhydrazines with P_2O_5

Chloromethyl derivative **63**, a useful precursor for other trifluoromethylated heterocycles [34] can be obtained by reaction of **61** with chloroacetylchloride followed by cyclization of the resulting diacylhydrazide with phosphorus oxychloride **62** (Scheme 19) [35].



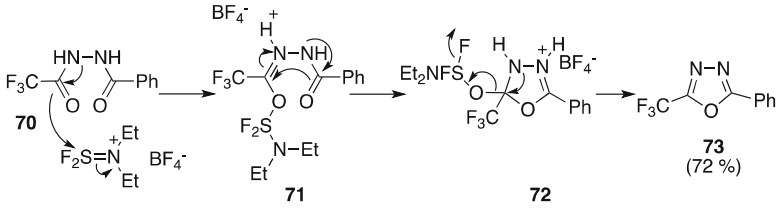
Scheme 19 Synthesis of chloromethyl derivative **63**

An interesting application of the cyclodehydration approach is the synthesis of bis-oxadiazoles **65** by dehydration of bis-diacylhydrazines **64** [36, 37]. Similarly, reaction of perfluoroanhydride **66** leading to **67** is also reported [38]. Bis-oxadiazoles **69**, which have a good thermal stability, are prepared by cyclodehydration of the corresponding tetrafluoroisophthaloyl bis(perfluoroacyl-hydrazines) **68** (Scheme 20) [39].



Scheme 20 Synthesis of bisoxadiazoles **65** and **69** and oxadiazoles **67** by the cyclodehydration approach

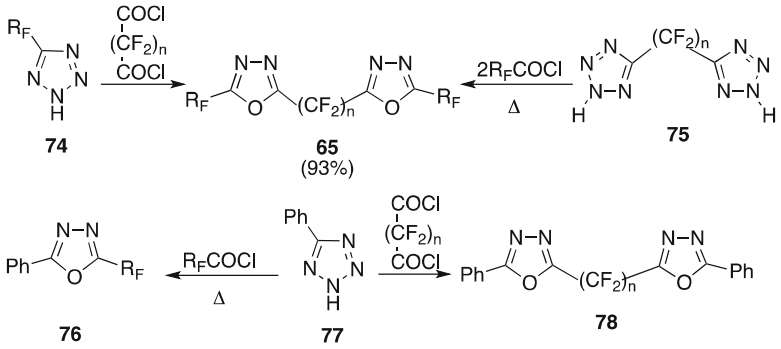
More recently, the synthesis of 1,3,4-oxadiazoles **73**, including fluorinated derivatives, from 1,2-diacylhydrazines was reported by using $[Et_2NSF_2]BF_4$ as a convenient cyclodehydration agent (Scheme 21) [40].



Scheme 21 Synthesis of 1,3,4-oxadiazoles **73** by using $[Et_2NSF_2]BF_4$ as a cyclodehydration agent

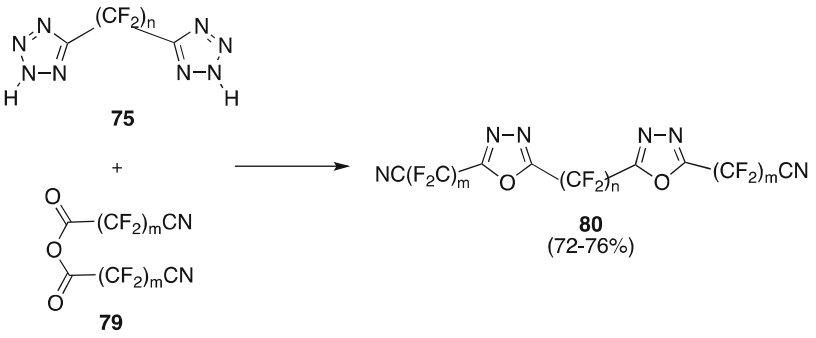
2.3.2 The Acyl-Tetrazole Rearrangement Route

Some of the previously illustrated fluorinated 1,3,4-oxadiazoles, such as **57** (R_F=CF_3, C_3F_7) and **65** (R=C_3F_7; n = 3), can be alternatively obtained by the Huisgen reaction approach [41]. Both 5-perfluoroalkyl-2-phenyl-1,3,4-oxadiazoles **76** and the diheterocyclic compound 1,3-bis(2-phenyl-1,3,4-oxadiazol-5- yl)hexafluoropropane **78** (n = 3) can be obtained by reaction of 5-phenyltetrazole **77** with perfluoroacyl chloride or perfluoroglutaryl chloride respectively (Scheme 22) [10].



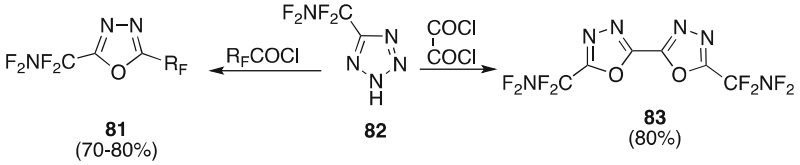
Scheme 22 The Acyl-Tetrazole Rearrangement Route in the synthesis of fluorinated 1,3,4-oxadiazoles **65**, 5-perfluoroalkyl-2-phenyl-1,3,4-oxadiazoles **76** and 1,3-bis(2-phenyl-1,3,4-oxadiazol-5- yl)hexafluoropropane **78**

Bifunctional reagents have been considered for the construction of polymeric structures. The reaction of α,ω-bis(tetrazol-5-yl)perfluoroalkane **75** with ω-cyanoperfluoroanhydrides **79** (at 150 °C) produces bis-oxadiazoles **80** from which further functionalization may be added on the two terminal nitriles (Scheme 23) [42, 43].



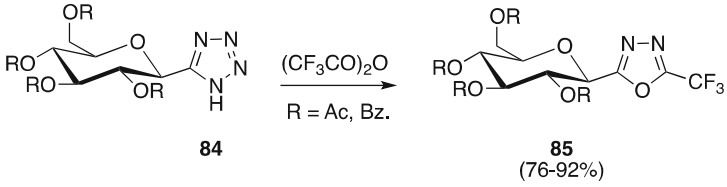
Scheme 23 Bifunctional reagents in the construction of polymeric structures

By the use of the same methodology, the *N,N-difluoroaminodifluoromethyl-tetrazole* **82** reacts with perfluoroacyl chlorides or oxalyl chloride leading to the corresponding oxadiazoles **81** or bis-oxadiazole **83**, respectively (Scheme 24) [13].



Scheme 24 Synthesis of perfluoroalkyl oxadiazoles **81** and bis-oxadiazole **83**

Overall, the *tetrazole transformation* methodology is a quite general approach. Almost any nitrile can be transformed into the corresponding tetrazole precursor which can lead to a perfluoroalkyl-1,3,4-oxadiazole. One example is represented in Scheme 25 for sugar-linked system **85** obtained from the corresponding D-glucose tetrazole derivative (Scheme 25) [44].

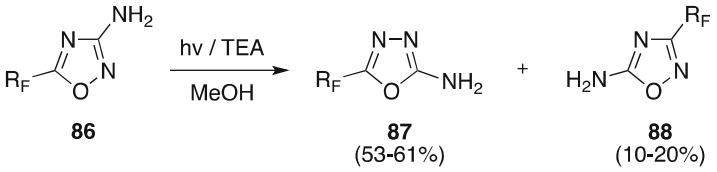


Scheme 25 Sugar-linked system **85** obtained by the *tetrazole transformation* methodology

2.3.3 The Photoinduced Ring-Rearrangement

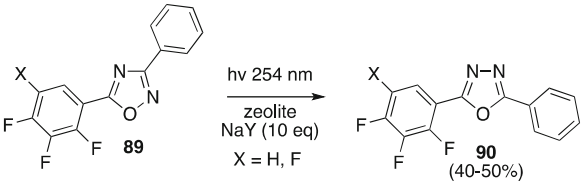
Although simple derivatives such as the 2-amino-5-trifluoromethyl-1,3,4-oxadiazole **87** (R_F=CF_3) can be prepared by reaction of trifluoroacetylhydrazine with BrCN, an interesting alternative is represented by the photorearrangement of the corresponding 1,2,4-oxadiazoles [26, 45].

As far as functional groups are concerned, in solution this approach is restricted to 1,2,4-oxadiazoles bearing a tautomerizable group at C(3) [7]. For instance, 3-amino-5-pefluoroalkyl-1,2,4-oxadiazoles **86** produced the corresponding 2-amino-5- perfluoroalkyl-1,3,4-oxadiazoles **87** (53–61% of yields) upon UV irradiation at 313 nm in methanol and in the presence of triethylamine (TEA). The reaction followed the typical ring contraction-ring expansion route [46]. In the same reaction, amounts of 5-amino-1,2,4-oxadiazole derivatives **88** are formed also through a competing process following the internal cyclization-isomerization route (Scheme 26) [46].



Scheme 26 Competing photoinduced ring-rearrangement: the ring contraction-ring expansion route and the internal cyclization-isomerization route

Very recent unpublished studies from our laboratories showed also the possibility to exploit the intrazeolite photorearrangement of 1,2,4-oxadiazoles [45] for the preparation of fluorinated diaryl-1,3,4-oxadiazole derivatives **90** (Scheme 27).

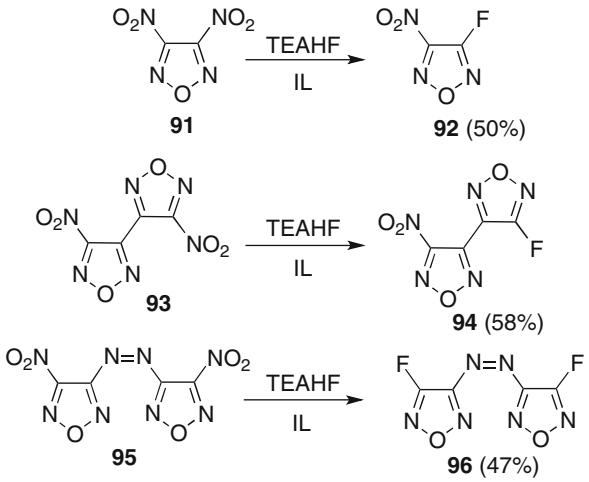


Scheme 27 Intrazeolite photorearrangement of 1,2,4-oxadiazoles

2.4 1,2,5-Oxadiazoles

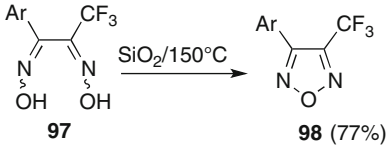
There are not many examples regarding the synthesis of fluorinated 1,2,5-oxadiazole (furazan) systems in the literature. Furazans bearing fluoro atoms were easily obtained by nucleophilic displacement of a nitro group at the furazan ring by using

a fluoride source and a ionic liquid (IL) as a medium [47]. Treatment of dinitro derivatives **91** and **93** with triethylamine hydrofluoride (TEAHF), by using butylmethylimidazolium salts (IL) as solvent, gave monofluorinated furazans **92** and **94** in 50–58 % yields (Scheme 28). Unfortunately, formation of the corresponding difluoro derivatives was observed in traces, with the double substitution of the nitro groups, just obtained in the case of diazo-derivative **96** (47 % yield) from the corresponding dinitro derivative **95**.



Scheme 28 Synthesis of furazans bearing fluoro atoms by nucleophilic displacement in ionic liquids

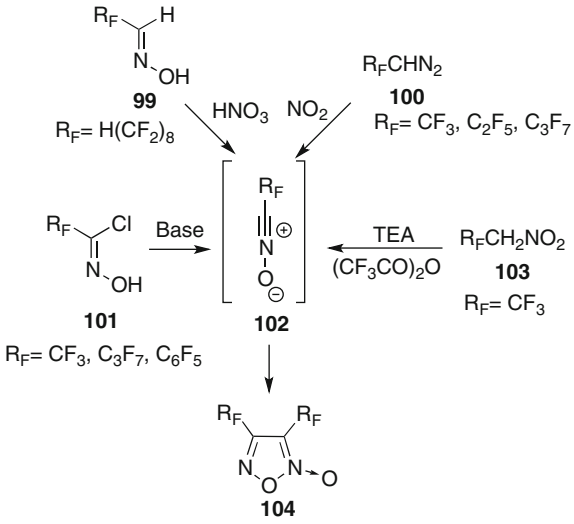
The synthesis of trifluoromethyl furazans **98** was described by Kamitori through the dehydration of dioximes **97** in the presence of silica (Scheme 29) [48]. Since the presence of silica is fundamental for this process, the author suggests that an interaction between the substrate and the silanol groups assists the cyclization reaction. The final products were obtained in higher yields (77 %) in presence of electron-withdrawing *p*-nitrophenyl group which facilitated reaction more effectively than the *p*-tolyl group in favoring the cyclization step.



Scheme 29 Synthesis of trifluoromethyl furazans **98** through the dehydration of dioximes **97** in the presence of silica

Furazan-*N*-oxides (furoxanes) **104** (Scheme 30) are isolated as a result of the nitrile oxide dimerization when chloro-oximes **101** are treated with bases in the absence of dipolarophiles [21, 49, 50]. Oxidation of aldoxime **99** with nitric acid gives furoxan **104** [R_F=H$(CF_2)_8$] in 50 % yield [51]. Similarly, furoxane **104** (R_F=C_6F_5)

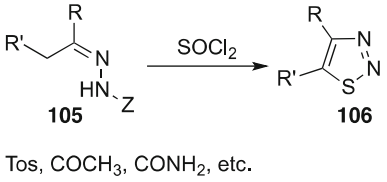
can be also formed from lead tetraacetate oxidation of the pentafluorobenzaldehyde oxime [49]. The involvement of nitrile oxide dimerization has been also suggested in the formation of furoxanes **104** by reaction of perfluoroalkyldiazomethanes **100** (R_F=CF_3, C_2F_5, C_3F_7) with nitrogen dioxide [52], and in the formation of the 3,4-*bis*(trifluoromethyl) derivative **104** (R_F=CF_3) from the dehydration reaction of trifluoromethylnitromethane **103** with trifluoroacetic anhydride (Scheme 30) [53]. More recently, the unstable trifluoroacetonitrile *N*-oxide molecule, CF_3CNO, has been generated in high yield in the gas phase from the corresponding bromo-oxime [54]. Cold trapping of this molecule followed by slow warming forms the stable bis (trifluoromethyl)furoxan **104** (R_F=CF_3), and the mechanism of the dimerization process to the furoxan ring was studied with density functional theory.



Scheme 30 Synthesis of the 3,4-*bis*(trifluoromethyl) furoxan **104**

2.5 1,2,3-Thiadiazoles

The synthesis of fluorinated 1,2,3-thiadiazole was not widely investigated and is essentially related to the general scheme of the Hurd-Mori reaction [55], i.e. the treatment of hydrazone derivatives with thionyl chloride (Scheme 31).



Scheme 31 Hurd-Mori reaction to 1,2,3-thiadiazole

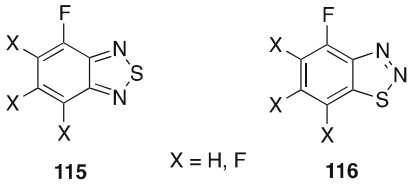
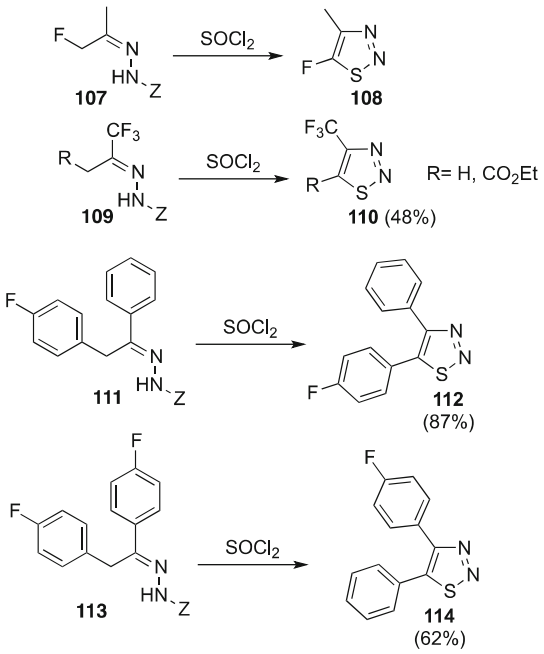


Fig. 4 Structure of fluorinated benzothiadiazoles

By applying this method some representative fluorinated 1,2,3-thiadiazoles were obtained from the corresponding hydrazone derivatives (Scheme 32) [56].

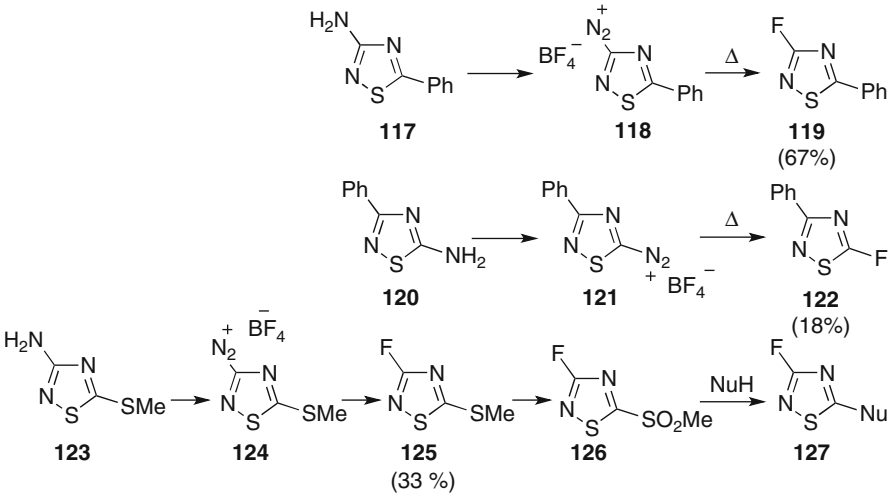


Scheme 32 Synthesis of fluorinated 1,2,3-thiadiazole by the Hurd-Mori reaction

Concerning benzocondensated derivatives, despite the largely cited use of fluorinated 2,1,3-benzothiadiazoles **115** in electronic devices [57], due also to the redox properties and anion stability of 2,1,3-benzothiadiazole systems such as **115** (Fig. 4) [58], the preparation of fluorinated 1,2,3-benzothiadiazoles such as **116** (Fig. 4), used for application as agrochemical, are rarely reported [59].

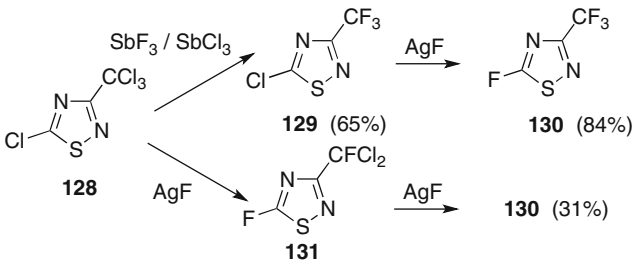
2.6 1,2,4-Thiadiazoles

When aminoderivatives such as **117** or **120** are available, the introduction of a fluorine atom directly bonded to the ring can be achieved by the generally applied decomposition of diazoniumtetrafluoroborates **118** and **121** leading to 3-fluoro-5-phenyl- **119** (67 %) or the regioisomer 5-fluoro-3-phenylthiadiazole **122** (18 %), respectively [60] (Scheme 33). The same methodology has been utilized for the preparation of 3-fluoro-5-methylthiothiadiazole **125** which can be obtained in a 33 % yield [61]. In turn, this 5-methylthio derivative **125** can be oxidized to the 5-sulfonylthiadiazole **126** which is a precursor of a series of compounds of industrial interest (of the general type **127**) obtained through nucleophilic substitution reactions with appropriate reagents (NuH in the Scheme 33).



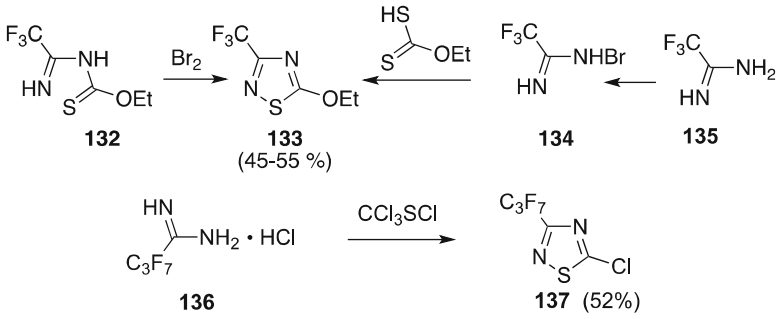
Scheme 33 Introduction of a fluorine atom directly bonded to the 1,2,4-thiadiazole ring

The introduction of fluorine has also been described through nucleophilic substitutions or fluorination of functional groups already bonded to the ring. For instance, 5-chloro-3-trichloromethylthiadiazole **128** can be fluorinated with different reagents (Scheme 34) [62]. By the use of the $SbF_3/SbCl_3$ fluorinating mixture, only the trichloromethyl group is fluorinated to yield the trifluoromethyl derivative **129**. The annular 5-chloro moiety undergoes substitution and partial fluorination of the 3-trichloromethyl moiety is also observed with AgF. Further reactions of derivatives **129** and **131** with AgF lead to perfluorinated compound **130**.



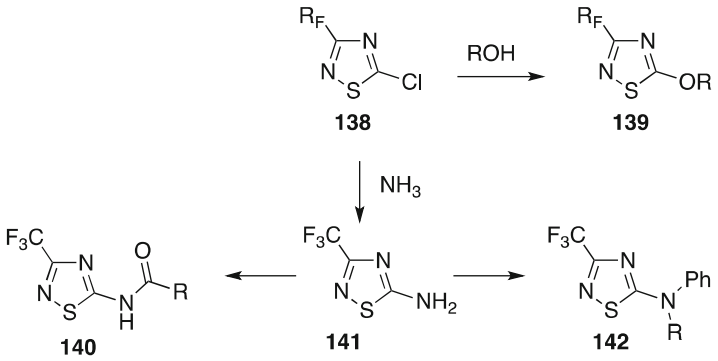
Scheme 34 Introduction of fluorine in 1,2,4-thiadiazole systems through nucleophilic substitution or fluorination of functional groups already bonded to the ring

With regard to the syntheses from fluorinated acyclic precursors, an approach to fluorinated 1,2,4-thiadiazoles utilized the oxidative heterocyclization of fluorinated thioacyl-amidines. For example, trifluoroacetamidine and ethyl chlorothiocarbonate will form the open-chain intermediate **132** which, upon oxidation with bromine, leads to 5-ethoxy-3-trifluoromethyl-1,2,4-thiadiazole **133** (Scheme 35) [63]. A direct heterocyclization into the thiadiazole **137** takes places from the reaction of the fluorinated *N*-bromotrifluoroacetamidine **134**, prepared by selective bromination of the corresponding trifluoroacetamidine **135**, with ethyl xanthate [64]. In addition, the 3-perfluoropropyl-5-chlorothiadiazole **137** is obtained in 52 % yield from the reaction of heptafluorobutyramidine hydrochloride **136** with trichloromethylsulfenyl chloride in the presence of a base (Scheme 35) [62].



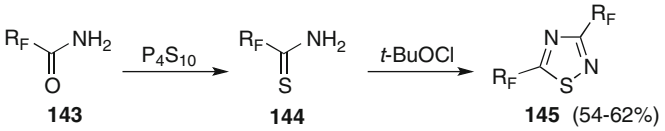
Scheme 35 Synthesis of fluorinated 1,2,4-thiadiazole from fluorinated acyclic precursors

Due to their reactivity towards both O- and N- nucleophiles, 5-chlorothiadiazole derivatives **138** are used as precursors for the synthesis of various compounds such as **139** [65]. Further reactions of 5-amino-3-trifluoromethyl-1,2,4-thiadiazole **141** into target compounds **140** and **142** are also patented (Scheme 36) [66].



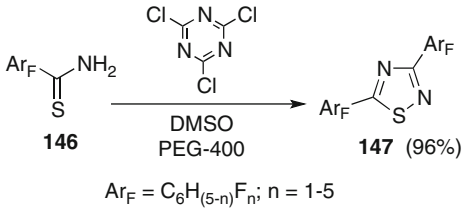
Scheme 36 5-chlorothiadiazole derivatives **138** as precursors for the synthesis of fluorinated 1,2,4-thiadiazoles

Reaction of polyfluoroalkylthioamide **144**, prepared by sulfur insertion on the appropriate polyfluoroalkylcarboxamide, give rise to 1,2,4-thiadiazoles **145** in 54–62% yields (Scheme 37) [67, 68].



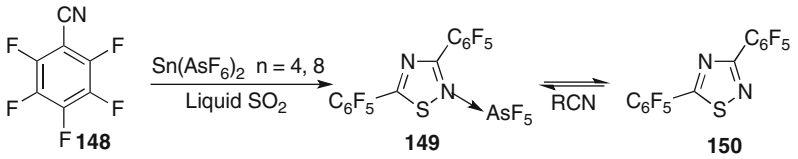
Scheme 37 Synthesis of 3,5-perfluoroalkyl-1,2,4-thiadiazoles **145**

Another convenient strategy for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles is the oxidative dimerization of arylthioamides by using 2,4,6-trichloro-1,3,5-triazine and dimethylsulfoxide in polyethylene glycol 400 (PEG-400) as solvent at ambient temperature. This methodology can be applied to various fluoroarylated systems (Ar_F=mono-, poly-, or perfluorophenyl). The reaction give rise to 4-fluoro substituted derivatives **147** during 8 min in yields of 96 % (Scheme 38) [69]. The same reaction has been recently reported by using 1-butyl-3-methylimidazolium tetrafluoroborate as eco-friendly reaction medium at room temperature [70].



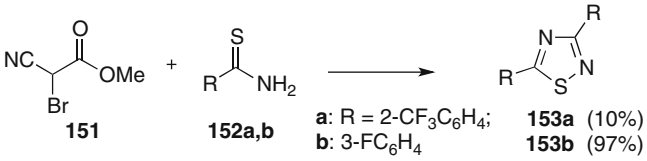
Scheme 38 Synthesis of 3,5-diaryl-1,2,4-thiadiazoles **147** by oxidative dimerization of arylthioamides

Concerning perfluoroaryl-1,2,4-thiadiazoles synthesis, C_6F_5CN reacts with $Sn(AsF_6)_2$ (n=4,8) in liquid SO_2 to give 3,5-bis(perfluorophenyl)-1,2,4-thiadiazole **150** in mixture with its precursor **149** (Scheme 39) [71].



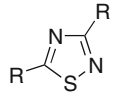
Scheme 39 Synthesis of 3,5-diaryl-1,2,4-thiadiazoles **150** by oxidative dimerization of arylnitriles

A new and efficient method for the synthesis of the 3,5-diaryl-1,2,4-thiadiazole system including fluorophenyl and trifluoromethylphenyl derivatives was investigated. The appropriate aryl thioamide **152a, b**, undergo a very rapid condensation in the presence of methyl bromocyanoacetate **151** in methanol to provide the corresponding fluorinated 3,5-diaryl-1,2,4-thiadiazoles **153a, b** with yields from low to quantitative (Scheme 40) [72].



Scheme 40 Synthesis of fluorinated 3,5-diaryl-1,2,4-thiadiazoles **153a, b** by condensation of the aryl thioamide

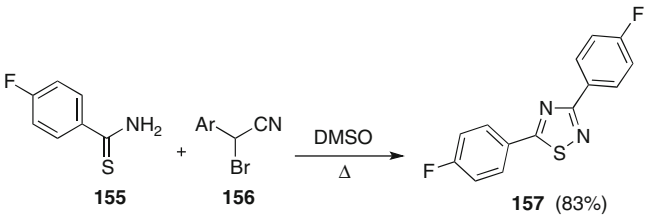
A similar approach has been exploited by Cushman and coworkers to obtain a series of thiadiazole **154**, for pharmaceutical applications as analogues of resveratrol, in quantitative yields (Fig. 5) [73].



154
(95-100%)
R = 2-FC_6H_4, 3-FC_6H_4, 4-F-C_6H_4, 2-$CF_3C_6H_4$, 4-$CF_3C_6H_4$.

Fig. 5 Fluorinated thiadiazoles used as pharmaceutical analogues of resveratrol

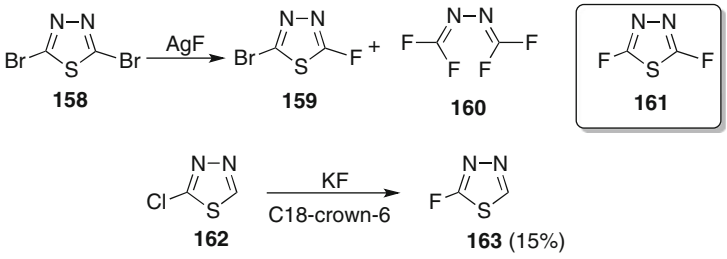
Alternatively, a simple and fast route reported for the preparation of 3,5-bis(fluoroaryl)-1,2,4-thiadiazoles **157**, consists in the reaction of benzothioamides **155** and 2-bromo-2-phenylacetamide derivatives **156** at 60 °C in DMSO (Scheme 41) [74].



Scheme 41 Synthesis of 3,5-bis(fluoroaryl)-1,2,4-thiadiazoles **157**

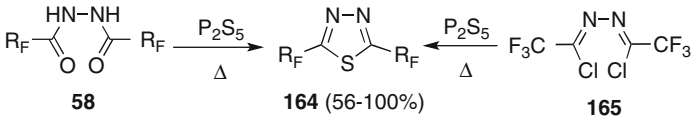
2.7 1,3,4-Thiadiazoles

In the case of 1,3,4-thiadiazoles, a fluorine atom can be directly introduced on the ring through nucleophilic substitution of other halogens. An example of this approach is represented by the reaction of the 2,5-dibromo derivative **158** with AgF, leading to the monofluorinated compound **159** (although in low yield; 16 %) and the perfluorinated open-chain compound **160**. The latter probably originated from the ring-cleavage of the unisolated **161** (Scheme 42) [62], although any attempts to obtain the difluoro derivative **161** through the diazotization of the 2,5-diaminothiadiazole were unsuccessful. A relatively recent Japanese patent reports the synthesis of a series of derivatives, having the fluorine atom bonded to an annular carbon, through substitution reactions. *Inter alia*, the reaction of 2-chloro-1,3,4-thiadiazole **162** with KF (in the presence of 18-crown-6 ether at 150 °C) leading to the 2-fluoro derivative **163** (15 %) is claimed [75].



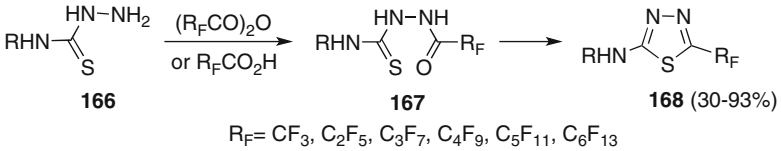
Scheme 42 Introduction of a fluorine atom on the 1,3,4-thiadiazole ring through nucleophilic substitution

In analogy to what was observed in the case of 1,3,4-oxadiazoles, the sulfuration of *N,N′*-diacylhydrazines **58** with P_2S_5 represent a general methodology for the synthesis of 2,5-*bis*(perfluoroalkyl)-1,3,4-thiadiazoles **164** which, in the reported examples, are obtained in 56–75 % yields depending on the nature of R_F (Scheme 43) [32]. Quantitative yields were observed in the synthesis of 2,5-*bis*(trifluoromethyl)-1,3,4-thiadiazoles **164** (R_F=CF_3) by the reaction of dichloroazine **165** with P_2S_5 (Scheme 43) [76]. More recently, Lawesson's reagent has been also employed for the obtainment of 2-phenyl-5-trifluoromethyl-1,3,4-thiadiazole in moderate yield (54 %) [77].



Scheme 43 Synthesis of 2,5-*bis*(perfluoroalkyl)-1,3,4-thiadiazoles **164** by sulfuration with P_2S_5

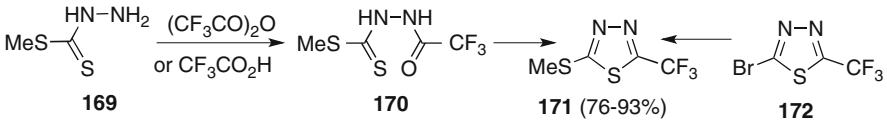
Particular importance has been payed to fluorinated thiadiazoles which contain functionalities such as amino or methylthio groups due to their industrial production. The synthesis of aminothiadiazoles **168** is based on the heterocyclization of acylthiosemicarbazides **167** with yields depending on experimental conditions (Scheme 44). In some cases the heterocyclization into the thiadiazole derivative occurs directly during the acylation reaction. In this manner, the reaction of thiosemicarbazide with trifluoroacetic anhydride lead to the formation of 2-amino-5-trifluoromethylthiadiazole **168** (R_F=CF_3, R=H) in a 30 % yield [78]. However, reaction carried out in the presence of $POCl_3$ permitted to obtain the yield increased to 93% [79]. Reactions between thiosemicarbazides **166** and trifluoroacetic acid or anhydride in the presence of PPA were also used for the synthesis of 2-amino and 2-methylamino derivatives **168** (R_F=CF_3) [80].



Scheme 44 Synthesis of aminothiadiazoles **168** by heterocyclization of acylthiosemicarbazides **167**

Several patents report the synthesis (or in some cases just a purification methodology) of 2-methylthio-5-trifluoromethyl-1,3,4-thiadiazole **171** which can be prepared through the reaction of **169** with trifluoroacetic acid or anhydride

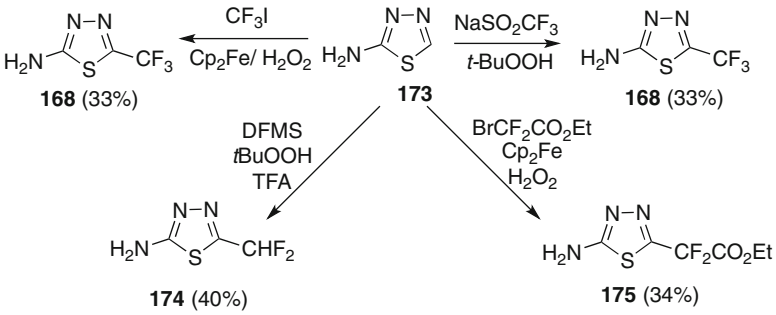
(Scheme 45) [81]. The same compound **171** can also be obtained from the 2-bromo derivative **172** [82].



169 **170** **171** (76-93%) **172**

Scheme 45 Synthesis of 2-methylthio-5-trifluoromethyl-1,3,4-thiadiazole **171**

Very recently, direct trifluoromethylation of the pre-formed 1,3,4-thiadiazole ring has been reported. In all the cases the trifluoromethyl radical is involved as electrophilic species attacking the ring. Generation of the reactive radical could be achieved from CF_3I in the presence of ferrocene (Cp_2Fe) and hydrogen peroxide [83] or by using CF_3SO_2Na (Langlois reagent) in the presence of *t*-BuOOH [84]. This quite interesting reactivity was just evidenced for the obtainment of 2-amino-5-tryfluoromethyl-1,3,4-thiadiazole **168** from the corresponding 2-amino derivative **173** and unfortunately in low yields. Similarly, radical fluoroalkylation of amine **173** was also achieved by using the new difluoromethylating agent $Zn(SO_2CF_2H)_2$ (DFMS) [85] or $BrCF_2CO_2Et$ [86] as CF_2R radical sources (Scheme 46).



168 (33%) **173** **168** (33%)

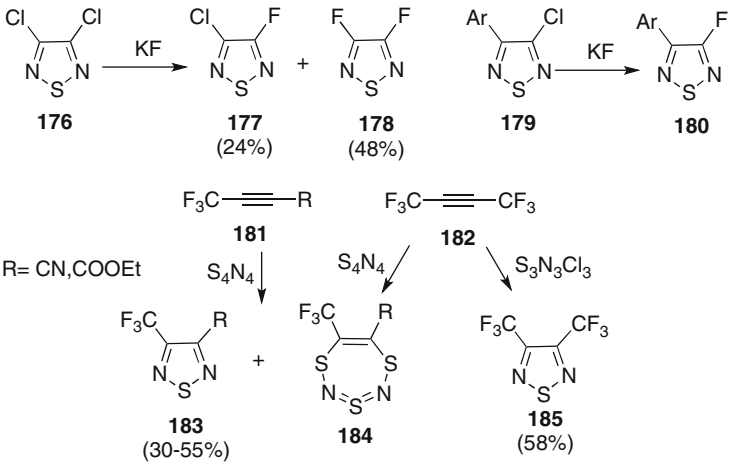
174 (40%) **175** (34%)

Scheme 46 Synthesis of fluorinated 1,3,4-thiadiazoles by radical fluoroalkylation of amine **173**

2.8 1,2,5-Thiadiazoles

Similarly to other thiadiazoles, the direct introduction of fluorine on the 1,2,5-thiadiazole can be achieved *via* substitution reactions on the corresponding chloro derivatives. Thus, reaction of the commercially available 4,5-dichloro-thiadiazole **176** with KF in sulfolane at 180ºC allow to obtain both the monofluoro compound **177** (24%) and difluorothiadiazole **178** (48%) (Scheme 47) [87].

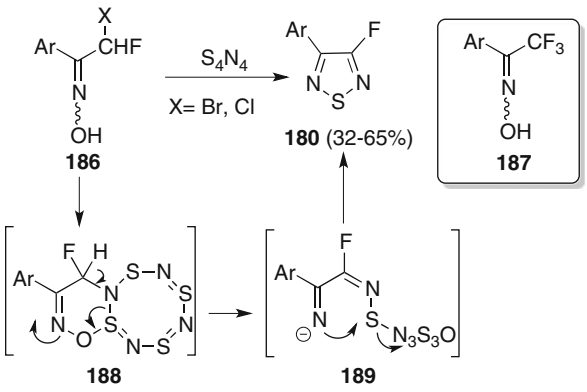
Similarly, 3-aryl-4-fluoro-1,2,5-thiadiazoles **180** have been prepared by treating the corresponding 4-chloro derivatives **179** with KF at high temperatures (Scheme 47) [88]. A synthesis of fluorinated 1,2,5-thiadiazoles from acyclic precursors utilizes the reaction of particular fluorinated substrates with tetrasulfur tetranitride (S_4N_4) in a (3 + 2) synthetic pattern. For instance, trifluorobutynonitrile **181** (R=CN) and ethyl 4,4,4-trifluoro-2-butynoate **181** (R=COOEt) treated with S_4N_4 in dichloromethane at 150ºC produced trifluoromethyl substituted thiadiazoles **183** (30–55 %) (Scheme 47)[89]. Interestingly, the reaction was accompanied by the formation of trithiadiazepine **184**. In the case of the reaction with hexafluorobutyne **182**, only the corresponding trithiadiazepine derivative **184** (R=CF_3) was isolated, although the authors assumed that the *bis*(trifluoromethyl)thiadiazole **185** was formed also and lost during the reaction work-up because of its volatility. The formation of **185** was claimed in 58 % yield from the reaction of hexafluorobutyne **182** with the more electrophilic trithiazyl trichloride ($S_3N_3Cl_3$) reagent.[90] In this case, the addition of two NSCl moieties to the triple bond and the loss of SCl_2 during the hetero-cyclization is suggested. The same *bis*(trifluoromethyl) derivative **185** had been suggested to be involved in the reaction of **182** with thiazyl fluoride (NSF) [91]. Bis(trifluoromethyl)thiadiazole **185** was also obtained from the photochemical decomposition of bis(trifluoromethyl)-1,3,2-dithiazol-2-yl radical [92].



Scheme 47 Synthesis of fluorinated 1,2,5-thiadiazole by direct introduction of fluorine on the ring through nucleophilic substitution or starting from fluorinated acyclic precursors

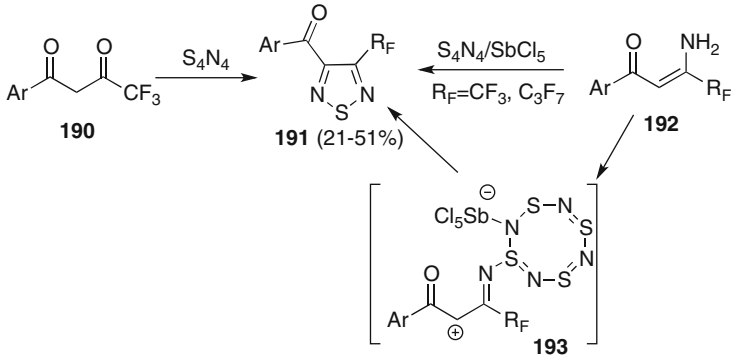
Cyclization with tetrasulfur tetranitride has been employed with the 1-aryl-2,2-dihaloethanone oximes **186**. From the reaction carried out in refluxing dioxane, 3-aryl-4-fluorothiadiazoles **180** have been obtained in fair yields (32–65%) and

the mechanistic aspects which involve the species **188** have been discussed (Scheme 48) [93]. It has to be noted that the same reaction performed on 1-aryl-2,2,2-trifluoroethanone oximes **187** does not result in cyclization to thiadiazole [94].



Scheme 48 Mechanistic aspects of the synthesis of fluorinated 1,2,5-thiadiazole by cyclization with tetrasulfur tetranitride

The reaction of benzyl ketones with tetrasulfur tetranitride provided a method for the synthesis of 3,4-diaryl- and 3-alkyl-4-aryl-1,2,5-thiadiazoles [95]. Similarly, in the case of fluorinated substrates, 3-aroyl-4-trifluoromethylthiadiazoles **191** have been obtained in 40–50 % yields from the reaction of aroyltrifluoroacetylmethanes **190** with S_4N_4 in refluxing toluene [96]. Enaminones **192** have also been utilized as suitable substrates for the cyclization into 1,2,5-thiadiazoles **191** (21–51 %) [97]. The reaction has been realized using $S_4N_4/SbCl_5$ complex in toluene at 100 °C and **193** as a key intermediate has been suggested (Scheme 49).

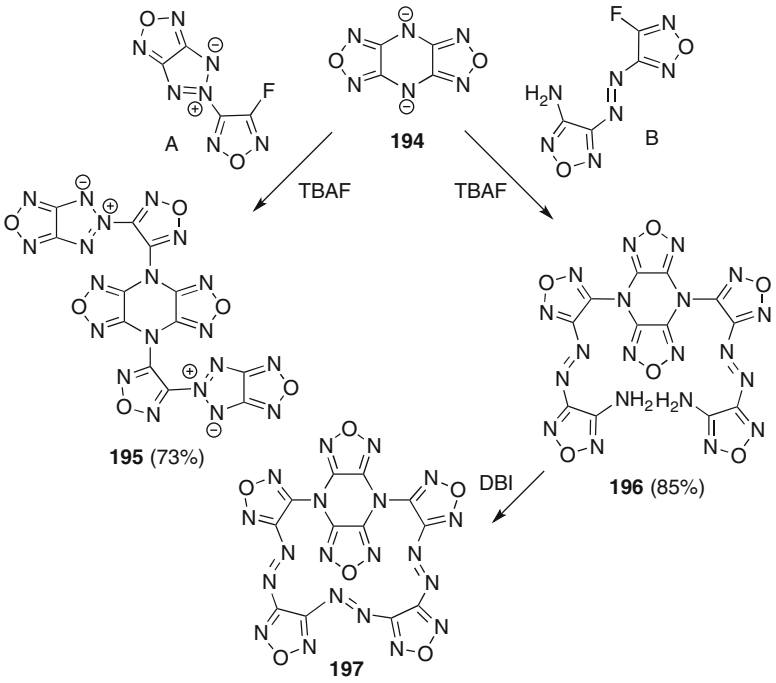


Scheme 49 Synthesis of 3-aroyl-4-trifluoromethylthiadiazoles **191**

3 Fluorine-Induced Reactivity of Fluorinated Oxadiazoles and Thiadiazoles

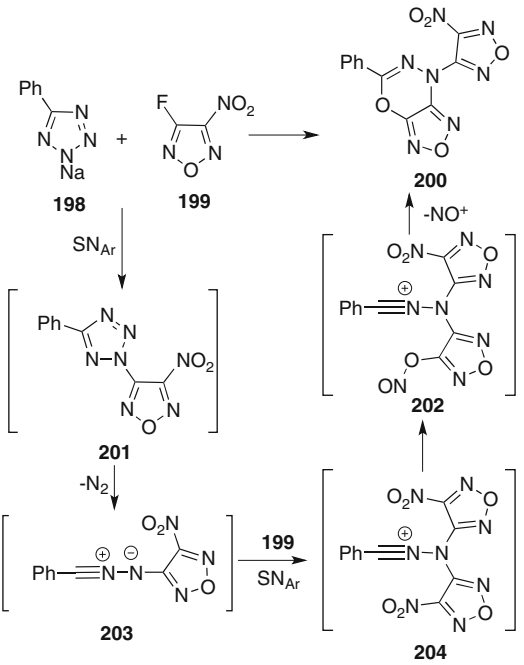
3.1 Ring-Fluorinated Derivatives

Few examples are reported in the literature regarding the reactivity of fluorinated 1,2,5-oxadiazoles. As for many azoles, the nucleophilic substitution of a fluorine atom is relatively easy and provided high yields. Fluorofurazans **A** react with bisfurazanopyrazine dianion **194** yielding a disubstituted compound **195** (73 %) containing two tris (furazanyl)-amino moieties [98]. The same reaction performed on fluoroderivative **B** gave compound **196** (85 %), the precursor of macrocycle **197** synthesised by oxidative cyclization with dibromoisocyanurate (DBI) (Scheme 50).



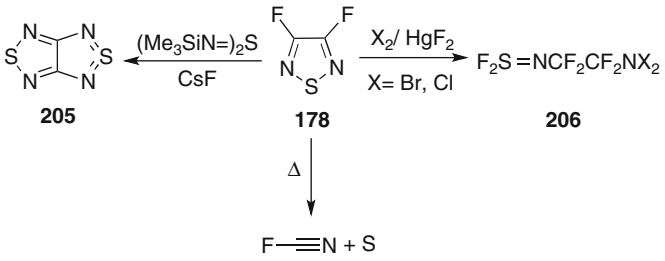
Scheme 50 Reactivity of fluorinated 1,2,5-oxadiazoles: the nucleophilic substitution of a fluorine atom

Displacement of fluoride from furazan **199** is the initial step of a new ring cleavage/ring closure reactions of tetrazole which provides a route to the new furazano[3,4-e]-1-oxa-3,4-diazine system **200** [99]. Interestingly, the nucleophilic substitution on a second molecule of fluorinated furazan **199** is one of the key steps of the suggested mechanism outlined in Scheme 51.



Scheme 51 Suggested mechanism for a route to furazano[3,4-e]-1-oxa-3,4-diazine system **200**

Concerning the reactivity of fluorinated 1,2,5-thiadiazoles, the only reported examples are related to the 3,4-difluoro-1,2,5-thiadiazole **178**. This compound show nucleophilic displacement by fluoride ion-induced condensation with $(Me_3SiN=)_2S$, giving [1, 2, 5]thiadiazolo[3,4-c][1, 2, 5]thiadiazole **205** in 62 % yield [100]. Electrochemical generation of **205** radical anion might be of interest to materials science as a building block for molecular ion-based conductors and/or magnets. Ring-opening reactions of **178** were performed with molecular chlorine and/or bromine in the presence of HgF_2 giving open-chain compounds $F_2S{=}NCF_2CF_2NX_2$ **206** (X=Cl, Br) (Scheme 52) [101].

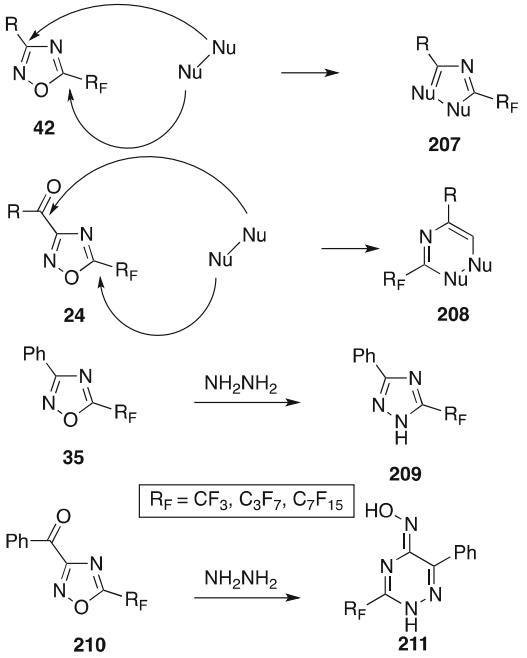


Scheme 52 Ring-opening reactions of **178**

The gas-phase generation and spectroscopic identification of nitrile sulfides by thermolysis of 1,2,5-thiadiazole precursors was attempted, but in all cases the thiadiazoles were found to produce sulfur and the corresponding nitrile [102]. Interestingly, compound **178** was indicated as the most stable derivative, giving not decomposition up to 900 °C.

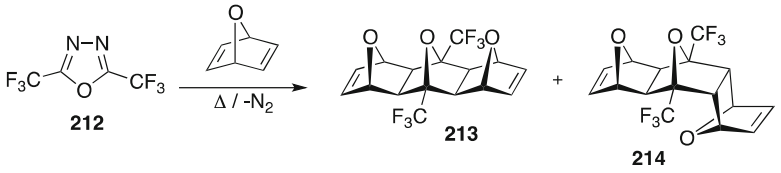
3.2 Ring-Fluoroalkylated Derivatives

The C(5) position is the most electrophilic site of the heterocycle in perfluoroalkyl-1,2,4-oxadiazoles due to the electron- withdrawing effect of both O(1) and N(4) [7]. In the presence of a perfluoroalkyl group linked at the C(5) of the oxadiazole the first step of the addition of a nucleophile–ring opening–ring closure (ANRORC) reaction of 5-perfluoroalkyl-1,2,4-oxadiazoles is strongly favoured (Scheme 53). Depending on the nature of the 3-substituent, the cyclization step of the open-chain intermediate can involve either the C(3) or an electrophilic site of the original C(3)-linked side-chain, leading to other five- **207** or six-membered ring **208** heterocycles, respectively [15, 16, 24, 103, 104]. Besides ring-degenerate rearrangement leading to regioisomeric 1,2,4-oxadiazoles (Scheme 13 in Sect. 2.2.3), this ANRORC reactivity has been exploited for the synthesis of fluorinated triazoles **209** and triazines **211** (Scheme 53) [103].



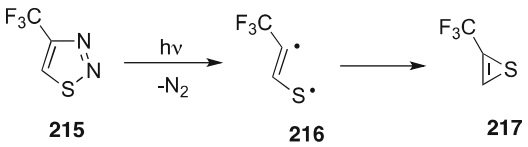
Scheme 53 The ANRORC reactivity in the synthesis of fluorinated triazoles **209** and triazines **211**

The reaction of the 2,5-bis-trifluoromethyl-1,3,4-oxadiazole **212** with oxanorbornene derivatives has been recently re-evaluated for its stereoselectivity aspects, through a combination of experimental and computational studies [105]. In particular, the theoretical model was able to explain the origin of stereoselectivity towards the bent product **214** caused by repulsive lone pair interactions between oxygen bridges in the transition state of the 1,3-dipolar addition (Scheme 54).



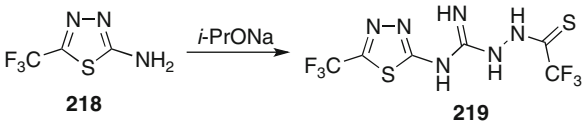
Scheme 54 Stereoselectivity towards the bent product **214** in the reaction of the 2,5-bis-trifluoromethyl-1,3,4-oxadiazole **212** with oxanorbornene derivatives

An interesting photochemical ring contraction has been reported for trifluoromethylated 1,2,3-thiadiazoles. Thiirene **217** was obtained by the argon matrix photolysis at 265 nm of 1,2,3-thiadiazoles **215** at 8 K. Interestingly, trifluoromethyl group exert a stabilizing effect on the highly unstable 4π-electron ring system (Scheme 55) [56b].



Scheme 55 Thiirene **217** by photochemical ring contraction of trifluoromethylated 1,2,3-thiadiazoles

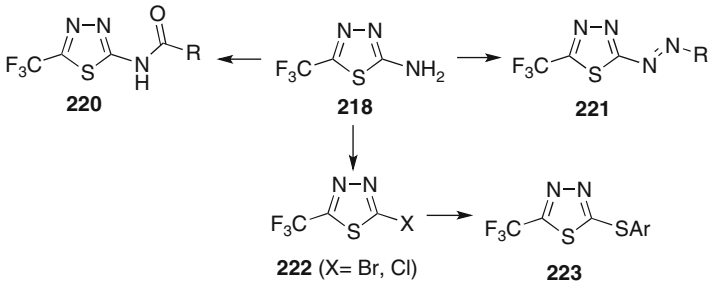
Regarding the reactivity of fluorinated 1,3,4-thiadiazoles, rare examples of peculiar reaction due to the presence of fluorinated moieties are reported in the literature, and all involve the thiadiazole ring-opening. Beside the above discussed obtainment of perfluorinated open-chain compound **160**[62] the only example is related to the treatment 2-amino-5-trifluoromethyl-1,3,4-thiadiazole **218** with an alcoholate, causing dimerization with opening of a thiadiazole ring and formation of **219** in 34 % yield (Scheme 56) [106].



Scheme 56 Reactivity of fluorinated 1,3,4-thiadiazoles: dimerization with opening of a thiadiazole ring and formation of **219**

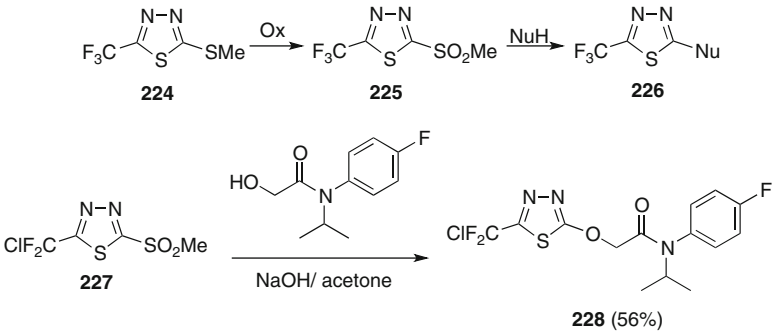
On the other hand, reactivity of other functionalities linked to the thiadiazole ring is not affected by the presence of fluorinated moieties, therefore fluorinated 1,3,4-thiadiazoles behave as unfluorinated congeners. Also in this case, particular attention to fluorinated thiadiazoles which contain amino or methylthio groups has been given, due to their the industrial importance.

It is worth noting that 2-amino-5-trifluoromethylthiadiazole **218** is a commercial product which is widely employed to link the fluorinated thiadiazole to several targets through its amino group by means, for example, of an acylation reaction, as in the case of **220**. Several patents on the synthesis of pharmaceuticals and agrochemicals take advantage of this of type of reaction [107]. In some cases, the amino group is involved in a diazotation reaction followed by a coupling reaction (leading to **221**) [108] or a nucleophilic substitution [109]. For example, 2-halo derivatives **222** can be prepared *via* diazonium salts from 2-amino-5-trifluoromethylthiadiazole **218** (Scheme 57) [109]. Also 2-arylthio derivatives **223** are obtained through a nucleophilic substitution reaction [110].



Scheme 57 Reactivity of fluorinated thiadiazoles which contain amino groups

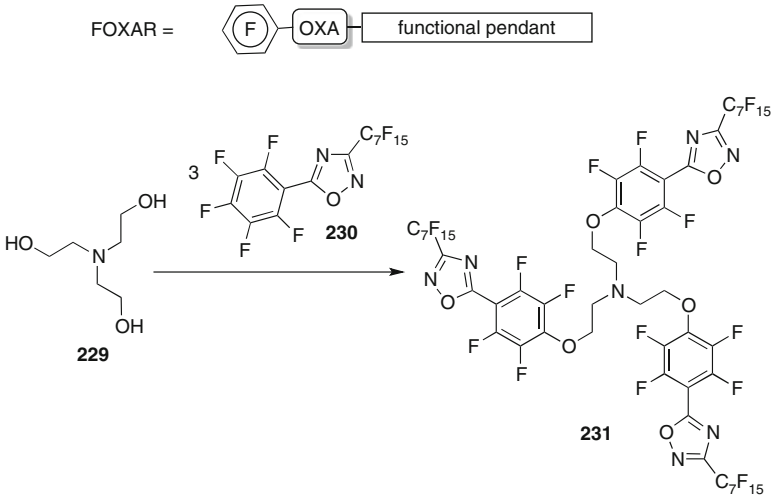
The methylthiothiadiazole **224** can be oxidized easily to the corresponding sulfonyl derivative **225** (Scheme 58). Some patents have also focused on the optimization of this oxidation which usually is carried out with hydrogen peroxide in acetic acid and in the presence of different catalytic species (boric acid, metal salts, etc.) [111]. The importance of this oxidation is related to the possibility to obtain the sulfonyl derivative system, due the ability of such a group to undergo nucleophilic substitution with several nucleophiles (NuH in the Scheme 58). In this way, it is possible to introduce the trifluoromethylthiadiazole moiety into target compounds for potential industrial applications [112]. Similar reactions are reported for the chlorodifluoromethyl derivative **227**, which is used as a precursor for the preparation of herbicides such as **228** [113]. The latter showed very strong preemergent and strong postemergent herbicidal activity.



Scheme 58 Reactivity of fluorinated methylthiothiadiazoles

3.3 Ring-Fluoroarylated Derivatives

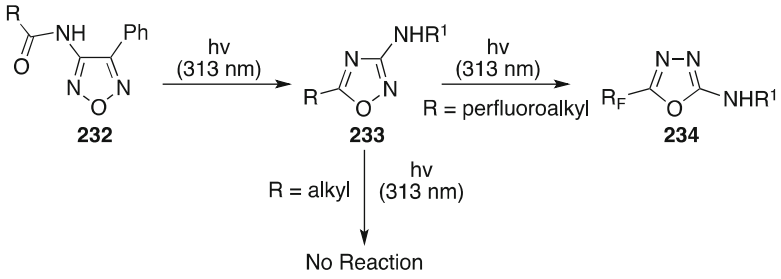
As mentioned above, the 1,2,4-oxadiazole is one of the most electron-withdrawing azole having a very activated C(5) position. In turn, when the electronic demand can be distributed over conjugated aromatic rings, the 1,2,4-oxadiazoles can activate the nucleophilic aromatic substitution. Indeed, 5-fluoroaryl-1,2,4-oxadiazoles are ideal examples for this concept. Due to the electron deficient character of the oxadiazole [which is more evident at the C(5) position], the *p*-fluoro moiety of the pentafluorophenyl ring is activated towards aromatic nucleophilic substitution by nucleophiles such as amines or alkoxides. Such a reactivity has great potential for the development of other synthetic applications and for the functionalization of macromolecules with nucleophilic pendants (Scheme 59) [5, 7]. In fact, a series of variously substituted 5-pentafluorophenyl-1,2,4-oxadiazoles have been used for the arylation of polymers, calixarenes, and tripodal ligands such as highly fluorinated system **231** [5b].



Scheme 59 Fluoroaryl 1,2,4-oxadiazoles in the functionalization of macromolecules with nucleophilic pendants

3.4 Systems Containing Fluorine Far from the Heterocyclic Core

Due to the presence of labile O-N bonds, the furazan system possess also an interesting photochemical reactivity. As discussed previously (Scheme 15 in Sect. 2.2.3 and Scheme 26 in Sect. 2.3.3), 3-perfluoroacylamino-1,2,5-oxadiazoles **50** are useful precursor for the obtainment of fluorinated 3-amino-1,2,4-oxadiazoles [27]. However, differently from non-fluorinated analogues **233** (R=alkyl) which are stable at the irradiation wavelength, perfluoroalkylated 1,2,4-oxadiazoles can undergo a subsequent photorearrangement into the corresponding 1,3,4-oxadiazole system [46]. Due to this peculiar reactivity of fluorinated derivatives, synthesis of fluorinated heterocycles involving photochemical steps must be carefully monitored in order to avoid unwanted reactivity not evidenced in unfluorinated substrates (Scheme 60).



Scheme 60 Photorearrangements in the perfluoroalkylated oxadiazole series

4 Biological Activity of Fluorinated Oxadiazoles and Thiadiazoles

A series of 5-trifluoromethyl-1,2,4-oxadiazoles are patented as potential pesticides [114] and tested for biological activity [115]. More recently, trifluoromethyl-1,2,4-oxadiazole derivatives such as **235** have been evaluated as cannabinoid antagonists [116] Besides these recent reports, one of the major debated bioactivity concerning fluorinated azoles is the efficiency of PTC124, also known with the name of *Ataluren* **236**, which was claimed to promote the readthrough of nonsense premature stop codons (Fig. 6) [117, 118].

Fluorinated 1,2,5-oxadiazoles have also been considered as important fragments in the field of medicinal chemistry, but only very recently compounds with considerable activity have been discovered. Some fluoroaryl substituted furoxans derivatives (Fig. 7), developed in the frame of SAR studies on *Furoxan*, were reported as inhibitors of thioredoxin glutathione reductase (TGR), with nitric oxide (NO) donor ability, acting as efficacious antischistosomal agents [119]. In particular, compounds **238** and **239** displayed an inhibition activity comparable to that of lead compound,

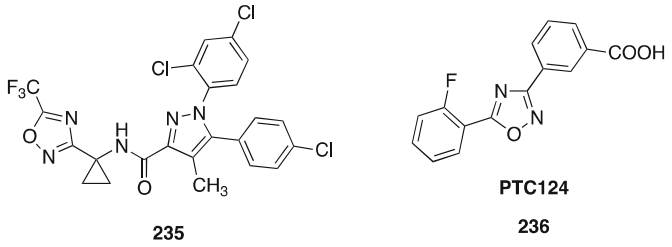


Fig. 6 Examples of fluorinated biologically active 1,2,4-oxadiazoles

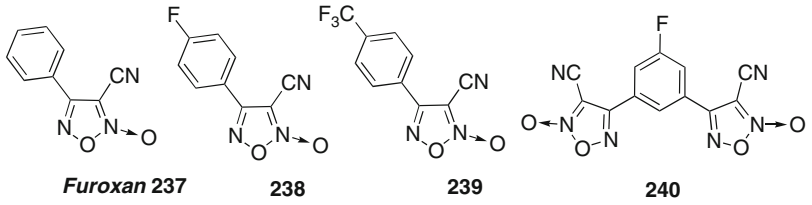
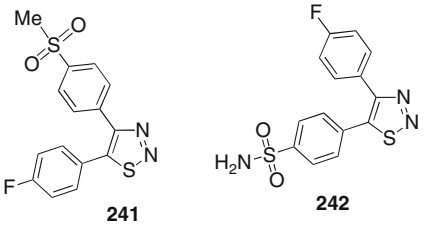


Fig. 7 Examples of fluorinated biologically active 1,2,5-oxadiazoles

Fig. 8 Examples of fluorophenyl thiadiazoles as potential COX-2 inhibitors



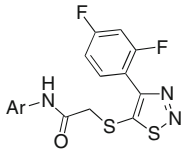
while fluorinated bis-furoxan **240** is a better TGR inhibitor than *Furoxan* **237** (IC_{50} = 0.48 μM vs 6.3 μM) with improved NO donation and ADME (solubility, Caco-2 permeability) properties.

Fluorinated 4,5-diaryl thiadiazoles **241** and **242** were evaluated as cyclooxygenase-2 (COX-2) inhibitors (Fig. 8). They showed good cell viability but poor inhibitor activity [120].

Difluorophenyl derivatives **243** were synthesized and tested in the frame of a SAR study on 1,2,3-Thiadiazole thioacetanilides as HIV non-nucleoside reverse transcriptase inhibitors. They showed the ability to protect MT-4 cells from viral cytopathogenicity in the low-micromolar range, but resulted less active than the chlorinated analogues to be further considered (Fig. 9) [121].

During the discovery of a series of pyrrolidine-2,4-dicarboxylic acid amides, which have 1-(sulfur-containing hetero-aryl)piperazin-4-yl carbonyl as a substituent of the L-prolyl moiety, and are novel and stable DPP-IV inhibitors, the 1,2,4-thiadiazole **244** (Fig. 10) was found to be acceptable in the desired enzyme pocket, but its

Fig. 9 Example of an anti-HIV fluoroarylated thiadiazole



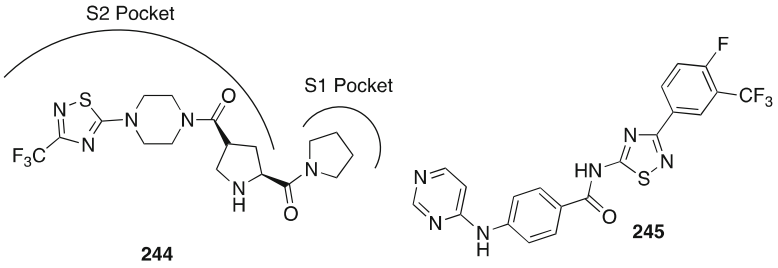


Fig. 10 Examples of fluorinated biologically active 1,2,4-thiadiazoles

inhibitory activity in plasma decreased along with an increase of lipophilicity [122]. In a series of pyrimidine benzamide-based thrombopoietin receptor agonists [123], in which the lead molecule contains a 2-amino-5-unsubstituted thiazole (a group that has been associated with idiosyncratic toxicity), the potential for metabolic oxidation at C-5 of the thiazole, the likely source of toxic metabolites, was removed by substitution at C-5 or by replacing the thiazole with a thiadiazole. In particular, the 4-F-3-CF_3 analog **245** (Fig. 10) is active and only slightly less potent than the corresponding 2-amino-4-arylthiazole lead.

Recently, several fluorinated 1,3,4-thiadiazoles have been considered as Drugs. Through a highthroughput biochemical screening of more than 340,000 synthetic compounds, the thiadiazole derivative **XCT790** (**246** in Fig. 11) has been identified as an estrogen-related receptor α (ERRα)–specific inverse agonist, validating ERRα as a promising therapeutic target in the treatment of metabolic disorders, including diabetes and obesity [124]. This compound could also be used in pathologies such as breast cancer [125], enhancing the efficacy of Fulvestrant **247** – an estrogen receptor antagonist with no agonist effects, already clinically used for the treatment of metastatic breast cancer in postmenopausal women [126]. Moreover, **XCT790** itself is a perspective drug for the treatment of hormone-related tumors such as prostate and breast cancer [127].

A patent from *Janssen Pharmaceutica* disclosed compound **248**, and other trifluoromethyl-1,3,4-thiadiazole derivatives, as fast dissociating dopamine 2 receptor antagonists with a pIC_{50} value > 5.0 when tested for *in vitro* binding affinity for human D2L receptor [128]. Compound **248** should be useful for treating or

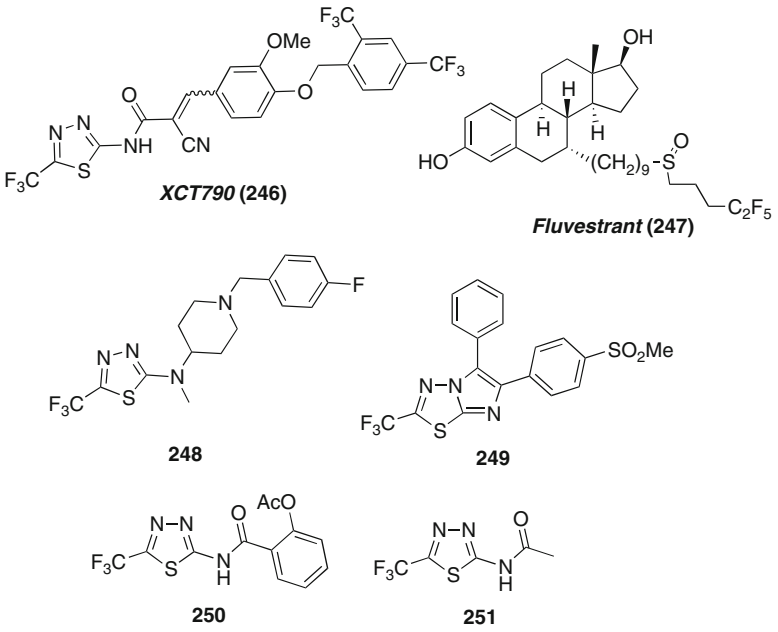


Fig. 11 Examples of fluorinated biologically active 1,3,4-thiadiazoles

preventing central nervous system disorders, for example schizophrenia, by exerting an antipsychotic effect without motor side effects. Also in the field of non-steroidal anti-inflammatory drugs (NSAIDs) fluorinated thiadiazoles appear. Compound **249** showed appreciable cyclooxygenase-2 (COX-2) selective inhibitory activity [129]. This compound also exhibited significant *in vivo* anti-inflammatory activity, comparable to that of the reference compound *Celecoxib*. 5-Trifluoromethyl-1,3,4-thiadiazolyl-amide **250** has been considered for anti-parasitic activity against *Sarcocystis neurona* [130], an obligate intracellular parasite that causes equine protozoal myeloencephalitis (EPM), and *Cryptosporidium parvum* [131], responsible for diarrhea in immunocompetent children and adults (cryptosporidiosis). Compound **250** is more active than reference compound nitazoxanide (NTZ) and seems promising for the treatment of both threats. In the field of anti-fungal compound, derivative **251** has been recently highlighted as a chitinase inhibitor for the fungal pathogen *Aspergillus fumigates* [132]. Despite the weak inhibitory activity, it could represent an interesting lead for future inhibitor development.

Regarding biological applications of fluorinated 1,2,5-thiadiazoles, compounds **180** were investigated for their nematocidal activity [88], while compound **252** was highlighted as antiviral agent, showing an EC_{50} of 0.008 μg/mL *in vitro*, protecting HIV-infected MT-4 cells from death [133] (Fig. 12).

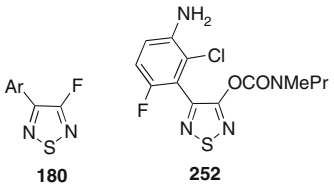


Fig. 12 Examples of fluorinated biologically active 1,2,5-thiadiazoles

5 Applications of Fluorinated Oxadiazoles and Thiadiazoles

Potential artificial oxygen carriers, based on new water-soluble fluorinated polymers, were obtained by using FOXARs (see also Scheme 59 in Sect. 3.3) to introduce fluorinated pendants in the α,β-poly(N-2-hydroxyethyl)-DL-aspartamide (PHEA) and polyethylenglycol–PHEA (PHEA– PEG) biocompatible polymers. The introduction of the fluorinated moiety increased the polymer's oxygen-dissolving ability without compromising its biocompatibility which was checked by an in vitro viability assay[4].

Fluorinated ionic liquid crystals (ILC) were synthesized by quaternization of pyridyl-1,2,4-oxadiazoles with CH_3I [134]. Interestingly, replacing the rigid perfluoroalkyl moiety with a more disordered alkyl chain resulted in a dramatic change of the salt's physico-chemical properties. In the field of supramolecular interactions involving fluorinated heterocyclic systems, a very recent study was performed on a series of perfluoroalkyl-1,2,4-oxadiazolyl-pyridines as H-bond acceptors in protic ionic liquids [135]. Interestingly, self-assembling capability of 1,3,4-oxadiazoles **256** (Fig. 13) allowed the obtainment of tubular crystals of size controllable through sublimation protocols [136].

Other examples regarding applications of fluorinated oxadiazoles in the field of sensoring and optoelectronics are illustrated in Fig. 13. In some cases the luminescent properties of a system can be designed to be a function of a measure such as the concentration of a given species in solution. For example, the fluorescence of the star-shaped molecule similar to **253** (Fig. 13) is self-quenched by the tertiary amino moiety of its core and is strongly dependant on the medium's acidity [5b] Additionally, the derivative **253** has been recently developed as fluorescent sensor for mercuric ion in aqueous media [137]. Starburst oxadiazole **254** is a precursor of dendritic emitter [138]. Finally, compound **255** represents the simplest oligomer of highly fluorinated polyarylene systems with fluoride anion sensing ability [139].

The application of fluorinated furazan is rather limited for synthesis and reactivity. Most studied derivative is 3-amino-4-trifluoromethyl-1,2,5-oxadiazole, which is commercially available. Nevertheless, in recent years, some perspective applications have been envisaged. In the agrochemical field a large library (more than 300 derivatives) of *N*-(4-trifluoromethyl-1,2,5-oxadiazol-3-yl)benzamides **257** has been prepared and considered for herbicidal activity [140], while 1-(4-fluoro-1,2,5-oxadiazol-3-yl)pyrazole derivatives **258** were claimed as herbicides and plant growth regulators (Fig. 14) [141].

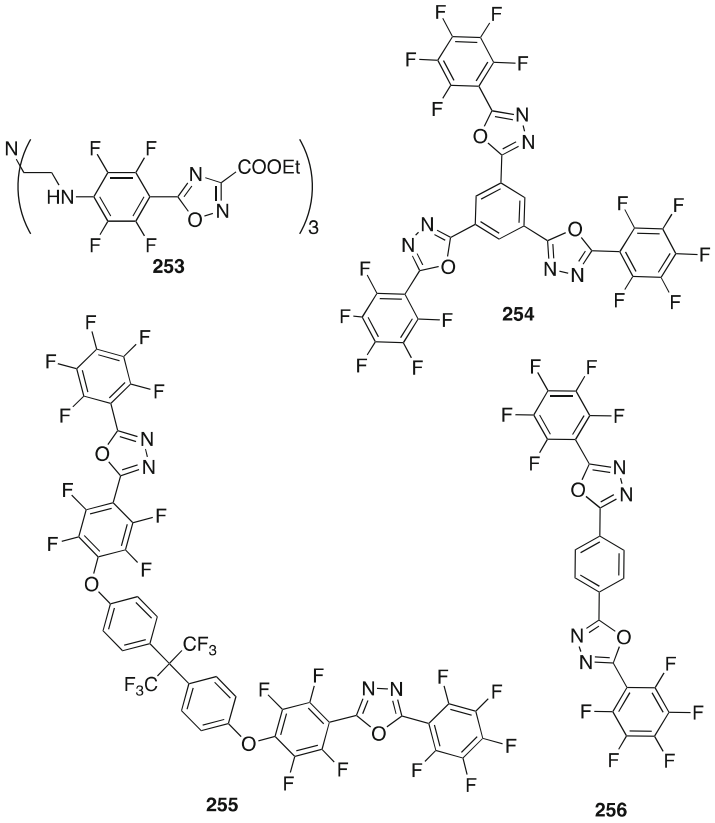
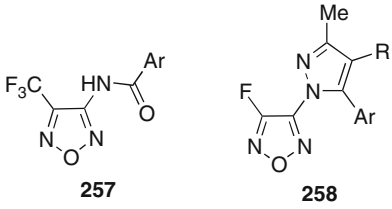


Fig. 13 Examples of fluorinated oxadiazoles for sensoring and optoelectronics

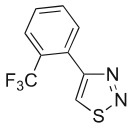
Fig. 14 Examples of fluorinated 1,2,5-oxadiazoles agrochemicals



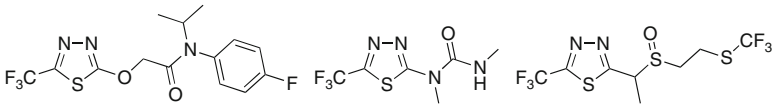
Many fluorinated thiadiazoles have been applied as agrochemicals. For instance, thiadiazole **259** is an antidote for acetanilide herbicides, protecting sorghum and wheat against phytotoxicity without affecting green foxtail control by these herbicides (Fig. 15) [142].

As outlined above, fluorinated 1,3,4-thiadiazoles are widespread applied in many fields as agrochemicals, drugs and materials. It is noteworthy that in the agrochemical field some 1,3,4-thiadiazole derivatives have reached the market, in particular, *Flufenacet* **260** and *Thiazafluron* **261** (Fig. 16).

Fig. 15 A fluorinated 1,2,3-thiadiazole herbicide

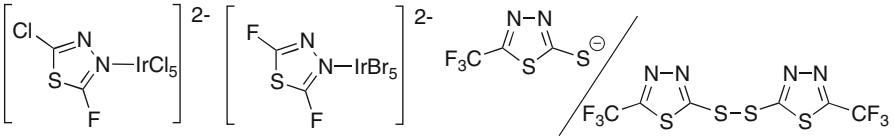


259



***Flufenacet* (260)** ***Thiazafluron* (261)** **262**

Fig. 16 Examples of commercial fluorinated 1,3,4-thiadiazole agrochemicals



263 **264** **265**

Fig. 17 Examples of fluorinated 1,3,4-thiadiazoles applied in materials science

Flufenacet (brand names: Artist®, Axiom®, Cadou®, Define®, Liberator®, Radius®, Tiara®, Terano®) was introduced by Bayer AG and is an oxyacetanilide herbicide applied before crops have emerged [143]. Is an inhibitor of cell division acting on very-long-chain-fatty-acid (VLCFA) synthesis. Applied for crop protection (Corn, Rice, Wheat, Potatoes, Soybeans) presents a spectrum of activity on infesting annual grasses like *Alopecurus myosuroides, Apera spica-venti, Digitaria spp., Echinochloa crus-galli, Poa annua, Setaria spp*.

Thiazafluron (other names: Erbotan® GS 29696, Thiazfluron) is an herbicide introduced by Ciba-Geigy AG [144]. *Thiazafluron* is believed to be obsolete for use as pesticides is one of 320 pesticides to be withdrawn in July 2003. Recently, other trifluoromethyl-1,3,4-thiadiazole derivatives such as **262** (Fig. 16) have been claimed useful for fighting or controlling invertebrate pests in agricultural as well as veterinary applications [145].

In the field of materials for photography, metal complexes containing fluorothiadiazoles as monodentate ligand have been used. Emulsion layer contains Ag halide and the iridium complex **263** provides high-speed development method with high-quality images free from pressure-derived fogs [146], while the emulsion containing the iridium complex **264** showed high sensitivity and contrast, preventing reciprocity law failure in broader exposure range (Fig. 17) [147].

Also in the field of reagents for materials characterization fluorinated 1,3,4-thiadiazoles have found some applications. In fact, the couple 5-trifluoromethyl-2-mercapto-1,3,4-thiadiazolate/5,5′-bis(2-trifluoromethyl-1,3,4-thiadiazole) disulfide **265** was employed as organic redox couple in nonaqueous media to perform capacitance measurements through Electrochemical Impedance Spectroscopy (EIS) on semiconductive materials (Fig. 17) [148].

6 Concluding Remarks

Due to the peculiar features introduced by fluorinated moieties, the synthesis, the reactivity, and the application of fluorinated oxadiazoles and thiadiazoles still are challenging research topics. Therefore, the updated synthetic guidelines reported in this chapter will represent a useful tool for both the experienced synthetic chemists and those willing to embrace the study of fluorinated azoles. For this reason, it is the authors' opinion that synthetic information organized by kind of heterocycle is better approached by the reader for faster consultation. On the other hand, reactivity has been presented by focusing on the type and position of the fluorinated moiety, in the attempt to provide general concepts transferable also to other heterocyclic systems. Finally, examples of fluorinated oxadiazoles and thiadiazoles used in materials chemistry or as bioactive compounds have been briefly illustrated to suggest the potential application of newly synthesized compounds.

Acknowledgments Financial support from the Università degli Studi di Palermo: Project 2012-ATE-0291, and from the Italian MIUR within the "FIRB-Futuro in Ricerca 2008" Program – Project RBFR08A9V1, and the "FIRB-Futuro in Ricerca 2012" Program – Project RBFR12SIPT is gratefully acknowledged.

References

1. Pace A, Buscemi S, Vivona N (2005) The synthesis of fluorinated heteroaromatic compounds. Part 1. Five-membered rings with more than two heteroatoms. A review. Org Prep Proc Int 37:447–506
2. Foster RS, Jakobi H, Harrity JPA (2012) A general and regioselective synthesis of 5-trifluoromethyl-pyrazoles. Org Lett 14:4858–4861
3. Rheinheimer J, Vogelbacher UJ, Baumann E, Koenig H, Gerber M, Westphalen KO, Walter H (1995) Ger Offen DE 4337321
4. (a) Mandracchia D, Palumbo Piccionello A, Pitarresi G, Pace A, Buscemi S, Giammona G (2007) Fluoropolymer based on a polyaspartamide containing 1,2,4-oxadiazole units: a potential artificial oxygen (O_2) carrier. Macromol Biosci 7:836–845. (b) Pitarresi G, Palumbo Piccionello A, Calabrese R, Pace A, Buscemi S, Giammona G (2008) Fluorinated derivatives of a polyaspartamide bearing polyethylene glycol chains as oxygen carriers. J Fluor Chem 129:1096–1103
5. (a) Buscemi S, Pace A, Palumbo Piccionello A, Pappalardo S, Garozzo D, Pilati T, Gattuso G, Pappalardo A, Pisagatti I, Parisi MF (2006) Lower rim arylation of calix[n]arenes with extended perfluorinated domains. Tetrahedron Lett 47:9049–9052. (b) Buscemi S, Pace A,

Palumbo Piccionello A, Vivona N (2006) Synthesis of fluorinated first generation starburst molecules containing a triethanolamine core and 1,2,4-oxadiazoles. J Fluor Chem 127:1601–1605
6. Yang X, Wang Z, Fang X, Yang X, Wu F, Shen Y (2007) Synthesis of difluoromethylene-containing 1,2,4-oxadiazole compounds via the reaction of 5-(difluoroiodomethyl)-3-phenyl-1,2,4-oxadiazole with unsaturated compounds initiated by sodium dithionite. Synthesis 2007:1768–1778
7. Pace A, Pierro P (2009) The new era of 1,2,4-oxadiazoles. Org Biomol Chem 7:4337–4348
8. Brown HC, Wetzel CR (1965) Reactions of perfluoroalkyl nitriles. VII. Perfluoroacyl amidoximes and 3,5-bis(perfluoroalkyl)-1,2,4-oxadiazoles. J Org Chem 30:3734–3738
9. Knunyants IL, Krasuskaya MP, Del'tsova DP (1966) Di (1,2,4-oxadiazolyl)polydifluoromethylenes. Izv Akad Nauk Ser Khim 577–579
10. Critchley JP, Pippett JS (1973) The synthesis and stability of some perfluoroalkyl- and perfluoroalkylene-1,2,4- and 1,3,4-oxadiazoles. J Fluor Chem 2:137–156
11. Critchley JP, Fear EJP, Pippett JS (1964) Interaction of benzamidoxime with fluoroacetyl chlorides. Some novel 1,2,4-oxadiazoles. Chem Ind 806–807
12. Critchley JP, Pippett JS (1973) 1,2,4-oxadialazolyl perfluoro-olefins. J Fluor Chem 2:157–165
13. John EO, Kirchmeier RL, Shreeve JM (1990) Oxadiazoles with NF_2-containing substituents. J Fluor Chem 47:333–343
14. Buscemi S, Pace A, Palumbo Piccionello A, Pibiri I, Vivona N (2004) Fluorinated heterocyclic compounds. A photochemical approach to a synthesis of fluorinated quinazolin-4-ones. Heterocycles 63:1619–1628
15. Buscemi S, Pace A, Palumbo Piccionello A, Macaluso G, Vivona N, Spinelli D, Giorgi G (2005) Fluorinated heterocyclic compounds. An effective strategy for the synthesis of fluorinated Z-oximes of 3-perfluoroalkyl-6-phenyl-2H-1,2,4-triazin-5-ones via a ring-enlargement reaction of 3-benzoyl-5-perfluoroalkyl-1,2,4-oxadiazoles and hydrazine. J Org Chem 70:3288–3291
16. Pibiri I, Pace A, Buscemi S, Vivona N, Malpezzi L (2006) Designing fluorous domains. Synthesis of a series of pyridinium salts bearing a perfluoroalkylated azole moiety. Heterocycles 68:307–321
17. Buscemi S, Pace A, Pibiri I, Vivona N (2002) Fluorinated heterocyclic compounds. Synthesis of 5-amino-, 5-N-alkylamino-, and 5-N, N-dialkylamino-3-perfluoroheptyl-1,2,4-oxadiazoles. Heterocycles 57:1891–1896
18. Dolbier WR Jr, Burkholder CR, Médebielle M (1999) Syntheses of 2-(bromodifluoromethyl) benzoxazole and 5-(bromodifluoromethyl)-1,2,4-oxadiazoles. J Fluor Chem 95:127–130
19. Burkholder C, Dolbier WR Jr, Médebielle M (1998) Tetrakis(dimethylamino)ethylene as a useful reductant of some bromodifluoromethyl heterocycles. Application to the synthesis of new gem-difluorinated heteroarylated compounds. J Org Chem 63:5385–5394
20. Kabakchi EV, Il'in VV, Ignatenko AV, Ponomarenko VA (1992) Synthesis of mixed 1,2,4-oxadiazoles by reaction of perfluorinated nitriles with benz- and terephthalamidoximes. Izv Akad Nauk SSSR Ser Khim 1863–1870
21. Middleton WJ (1984) Trifluoroacetonitrile oxide. J Org Chem 49:919–922
22. (a) Cochov RE (1976) Poly(perfluoroether) oxadiazole elastomer system cured with terephthalonitrile oxide. J Appl Polym Sci 20:1035–1047. (b) Cochov RE (1975) US Patent 553701
23. Van der Plas HC (1999) Degenerate ring transformations of heterocyclic compounds. Adv Heterocycl Chem 74:1–253
24. Buscemi S, Pace A, Pibiri I, Vivona N, Lanza CZ, Spinelli D (2004) Fluorinated heterocyclic compounds. The first example of an irreversible ring-degenerate rearrangement on five-membered heterocycles by attack of an external bidentate nucleophile. Eur J Org Chem 2004:974–980

25. Buscemi S, Pace A, Frenna V, Vivona N (2002) A generalized synthesis of 3-amino-5-aryl-, 3-amino-5-polyfluorophenyl-, and 3-amino-5-alkyl-1,2,4-oxadiazoles through ring-degenerate rearrangements. Heterocycles 57:811–823
26. Pace A, Pibiri I, Buscemi S, Vivona N (2004) Molecular rearrangements of 1-Oxa-2-azoles as an expedient route to fluorinated heterocyclic compounds. Heterocycles 63:2627–2648
27. Buscemi S, Pace A, Vivona N (2000) Fluoro heterocycles. A photochemical methodology for the synthesis of 3-amino- and 3-(N-alkylamino)-5-perfluoroalkyl-1,2,4-oxadiazoles. Tetrahedron Lett 41:7977–7981
28. (a) Yamamoto S (1993) JP Patent 05124948. (b) Fujiyama T, Sekiguchi M, Michiru A (2004) JP Patent 2004018434
29. Chu L, Qing FL (2012) Copper-catalyzed direct C-H oxidative trifluoromethylation of heteroarenes. J Am Chem Soc 134:1298–1304
30. (a) Huisgen R, Sauer J, Sturm HJ (1958) Acylierung 5-substitutierter tetrazole zu 1.3.4-oxdiazolen. Angew Chem 70:272–273. (b) Huisgen R, Sauer J, Sturm HJ, Markgraf JH (1960) Ringöffnungen der Azole, II. Die Bildung von 1.3.4-Oxdiazolen bei der Acylierung 5-substituierter Tetrazole. Chem Ber 93:2106–2124. (c) Sauer J, Huisgen R, Sturm HJ (1960) Zur acylierung von 5-aryl-tetrazolen; ein duplikationsverfahren zur darstellung von polyarylen. Tetrahedron 11:241–251. (d) Herbst RM (1961) The degradative benzoylation of 5-phenyltetrazole. J Org Chem 26:2372–2373
31. Brown HC, Cheng MT, Parcell LJ, Pilipovich D (1961) Synthesis of 2,5 Bis(perfluoroalkyl)-1,3,4-oxadiazoles. J Org Chem 26:4407–4409
32. For fluoroalkyl derivatives see: (a) Chambers WJ, Coffman DD (1961) Synthesis of 2,5-Bis(polyfluoroalkyl)-1,3,4-oxadiazoles and –thiadiazoles. J Org Chem 26:4410–4412. (b) Chambers WJ, Coffman DD (1961) US Patent, 2,992,226. For bis-pentafluorophenyl derivatives see: (c) Prudchenko AT, Vereshchagina SA, Barkhash VA, Vorozhtsov NN Jr (1967) Hydrazide of pentafluorobenzoic acid. Zhur Obsh Khim 37:2195–2197. (d) Lynch ER, Cummings W (1967) GB Patent 1096600
33. Zheng X, Li Z, Wang Y, Chen W, Huang Q, Liu C, Song G (2003) Syntheses and insecticidal activities of novel 2,5-disubstituted 1,3,4-oxadiazoles. J Fluor Chem 123:163–169
34. Balsells J, Liu J (2004) PCT Int. 2004080958
35. Kristinsson H, Winkler T, Mollenkropf M (1986) Reaktionen von 3-substituiertem 5-trifluormethyl-1,3,4-oxadiazol-2(3H)-on mit nucleophilen. Helv Chim Acta 69:333–339
36. Krasuskaya MP, Del'tsova DP, Knunyants IL (1965) Perfluoroalkylenebis(1,3,4-oxadiazoles). Izv Akad Nauk SSSR Ser Khim 2039–2042
37. Mazalova ZI, Lopyrev VA, Sokolov SV (1972) Reactions of perfluoro acid hydrazides. IV. Reaction of perfluorocarboxylic acid hydrazides with perfluorodicarboxylic acid anhydrides. Zh Org Khim 8:531–537
38. Mazalova ZI, Lopyrev VA, Sokolov SV, Ryazanova RM (1975) Reactions of hydrazides of perfluoro acids. VI. Reaction of cyclic anhydrides of perfluoro acids with hydrazine and hydrazides of perfluoro acids. Zh Org Khim 11:62–67
39. Lynch ER, Cummings W (1967) GB Patent 1097098
40. Pouliot MF, Angers L, Hamel JD, Paquin JF (2012) Synthesis of 1,3,4-oxadiazoles from 1,2-diacylhydrazines using $[Et_2NSF_2]BF_4$ as a practical cyclodehydration agent. Org Biomol Chem 10:988–993
41. Brown HC, Kassal RJ (1967) 5-Perfluoroalkyltetrazoles. I. Ring-opening reactions. J Org Chem 32:1871–1873
42. Mazolova ZI, Lopyrev VA, Sokolov SV, Fedorova GB (1976) SU Patent 502889
43. EI du Pont de Nemours and Co. (1965) GB Patent 988119
44. Hadady Z, Toth M, Somsak L (2004) C-(β-D-Glucopyranosyl) heterocycles as potential glycogen phosphorylase inhibitors. ARKIVOC vii:140–149
45. Pace A, Buscemi S, Vivona N (2005) Heterocyclic rearrangements in constrained media. A zeolite-directed photorearrangement of 1,2,4-oxadiazoles. J Org Chem 70:2322–2324

46. Buscemi S, Pace A, Pibiri I, Vivona N, Caronna T (2004) Fluorinated heterocyclic compounds: an assay on the photochemistry of some fluorinated 1-oxa-2-azoles: an expedient route to fluorinated heterocycles. J Fluor Chem 125:165–173
47. Sheremetev AB, Aleksandrova NS, Dmitriev DE (2006) Synthesis of fluorofurazans. Mendeleev Comm 16:163–165
48. Kamitori Y (1999) A convenient and facile synthesis of 3-(trifluoromethyl)-1,2,5-oxadiazoles with the use of silica gel as an effective catalyst. Heterocycles 51:627–630
49. Wakefield BJ, Wright DJ (1970) Polyhaloaromatic compounds. XII. Synthesis and cycloaddition reactions of pentafluoro-nd pentachlorobenzonitrile N-oxide. J Chem Soc (C) 1165–1168
50. Kissinger LW, McQuistion WE, Schwartz M (1963) Reactions of perfluoroalkyldiazomethanes. II. Nitrosyl chloride and nitryl chloride. Tetrahedron 19(Suppl 1):137–141
51. Scribner RM (1964) Reactions of nitrogen dioxide with organic halogen compounds. I. Synthesis of fluoro aldehydrols and fluoro ketols from fluoro alcohols. J Org Chem 29:279–283
52. Kissinger LW, McQuistion WE, Schwartz M (1963) Reactions of perfluoroalkyldiazomethanes. I. Nitrogen dioxide. Tetrahedron 19(Suppl 1):131–135
53. Krzhizhevskii AM, Mirzubekyants NS, Cheburkov YA, Knunyants IL (1974) Reactions of polyfluoronitroalkanes containing an active hydrogen atom. Izv Akad Nauk SSSR, Ser Khim 2513–2517
54. Havasi B, Pasinszki T, Westwood NPC (2005) Gas-phase infrared and *ab initio* study of the unstable CF_3CNO molecule and its stable furoxan ring dimer. J Phys Chem A 109:3864–3874
55. Hurd CD, Mori RI (1955) On acylhydrazones and 1,2,3-thiadiazoles. J Am Chem Soc 77:5359–5364
56. (a) Fujita M, Kobori T, Hiyama T, Kondo K (1993) Regioselectivity in the Hurd-Mori reaction. Heterocycles 36:33–36. (b) Torres M, Clement A, Bertie JE, Gunning HE, Strausz OP (1978) Low-temperature matrix isolation of thiirenes. J Org Chem 43:2490–2493. (c) Sambasiva Rao P, Kurumurthy C, Veeraswamy B, Santhosh Kumar G, Narsaiah B, Pranay Kumar K, Murthy USN, Karnewar S, Kotamraju S (2012) Synthesis, antimicrobial and cytotoxic activities of novel 4-trifluoromethyl-(1,2,3)-thiadiazolo-5-carboxylic acid hydrazide Schiff's bases. Med Chem Res. doi:10.1007/s00044-012-0168-x. (d) Karimi L, Navidpour L, Amini M, Shafiee A (2005) Syntheses of 4,5-Diaryl-1,2,3-thiadiazoles. Phosphorus, sulfur and silicon and the related elements. 180:1593–1600. (e) Meier H, Trickes G, Laping E, Merkle U (1980) Reaction of substituted hydrazones with thionyl chloride and sulfuryl chloride. Chem Ber 113:183–192
57. (a) Albrecht S, Janietz S, Schindler W, Frisch J, Kurpiers J, Kniepert J, Inal S, Pingel P, Fostiropoulos K, Koch N, Neher D (2012) Fluorinated copolymer PCPDTBT with enhanced open-circuit voltage and reduced recombination for highly efficient polymer solar cells. J Am Chem Soc 134:14932–14944; (b) Zhang Y, Zou J, Cheuh C-C, Yip H-L, Jen AK-Y (2012) Significant improved performance of photovoltaic cells made from a partially fluorinated cyclopentadithiophene/benzothiadiazole conjugated polymer macromol 45:5427–5435; (c) Zhang Y, Chien S-C, Chen K-S, Yip H-L, Sun Y, Davies JA, Chen F-C, Jen AK-Y (2011) Increased open circuit voltage in fluorinated benzothiadiazole-based alternating conjugated polymers. Chem Comm 47:11026–11028; (d) Zhou H, Yang L, Stuart AC, Price SC, Liu S, You W (2011) Development of fluorinated benzothiadiazole as a structural unit for a polymer solar cell of 7 % efficiency. Angew Chem Int Ed 50:2995–2998; (e) Fong HH, Lee J-K, Lim Y-F, Zakhidov AA, Wong WWH, Holmes AB, Ober CK, Malliaras, GG (2011) Orthogonal processing and patterning enabled by highly fluorinated light-emitting polymers. Adv Mater 23:735–739
58. Vasilieva NV, Irtegova IG, Gritsan NP, Lonchakov AV, Makarov AY, Shundrin LA, Zibarev AV (2010) Redox properties and radical anions of fluorinated 2,1,3-benzothia(selena)diazoles and related compounds. J Phys Org Chem 23:536–543

59. (a) Wilkins DJ, Bradley PA (2004) Product class 9: 1,2,3-thiadiazoles Sci Synth 13:253–275; (b) Kunz W, Schurter R (1992) Eur Pat Appl EP 502473; (c) Gil DL, Wilkinson CF (1977) Structure-activity relationships of 1,2,3-benzothiadiazole insecticide synergists as inhibitors of microsomal oxidation. Pestic Biochem Physiol 7:183–193
60. Ginsberg A, Goerdeler J (1961) Über 1.2.4-thiodiazole, XIV. Thiodiazol-3- und 5-diazoniumsalze. Chem Ber 94:2043–2060
61. Foerster H, Bertsch A, Boehm S, Diehr HJ, Kysela E, Dollinger M, Santel HJ (1996) Ger Patent 19509044
62. Schroeder H, Ratz R, Schnabel W, Ulrich H, Kober E, Grundmann C (1962) Synthesis of polyfluorinated heterocycles by indirect fluorination with silver fluorides. IV. Fluorothiadiazoles. J Org Chem 27:2589–2592
63. Olien Mathieson Chemical Corp (1967) NL Patent 6610627
64. Rothgery EF, Schroeder HJA (1979) US Patent 4143044
65. Foerster H, Klauke E, Eue L, Schmidt RR, Luerssen K (1984) Ger Patent 3228147
66. (a) Gay WA (1980) US Patent 4207089; (b) Gay WA (1982) US Patent 4337081; (c) Moser H, Vogel C (1974) US Patent 3822280; (d) Moser H, Vogel C (1971) Ger Offen 2113033
67. El-Wassimi MTM, Jorgensen KA, Lawesson SO (1983) The reaction of t-butyl hypochlorite with thiocarbonyl compound – a convenient method for the C=S to C=O transformation. Tetrahedron 39:1729–1734
68. Timoshenko VM, Rudnichenko AV, Tkachenko AV, Shermolovic YG (2005) 1,1-dichloropol yfluoroalkanesulfenamides and their dehydrochlorination effected by triethylamine. Russ J Org Chem 41:268–271
69. Khosropour AR, Noei J (2010) A convenient strategy for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles: oxidative dimerization of arylthioamides using CC–DMSO in PEG-400. Monatsh Chem 141:649–651
70. Khosropour AR, Noei J (2011) TCT-DMSO/[bmim]BF_4: a novel promoter system for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles at ambient temperature. J Heterocycl Chem 48:226–229
71. Cameron TS, Decken A, Fang M, Parsons S, Passmore J, Wood DJ (1999) Oxidation of methyl groups in the reaction of sulfur homopolyatomic cations with acetonitrile: formation and crystal structure of the novel trithietanylium ring. Chem Comm 1801–1802
72. Mayhoub AS, Kiselev E, Cushman M (2011) An unexpected synthesis of 3,5-diaryl-1,2,4-thiadiazoles from thiobenzamides and methyl bromocyanoacetate. Tetrahedron Lett 52:4941–4943
73. Mayhoub AS, Marler L, Kondratyuk TP, Park EJ, Pezzuto JM, Cushman M (2012) Optimizing thiadiazole analogues of resveratrol versus three chemopreventive targets. Bioorg Med Chem 20:510–520
74. Boeini HZ, Mobin M (2011) You have full text access to this content. An unexpected result of the reaction of benzothioamide derivatives with 2-aryl-2-bromoacetonitriles. Helv Chim Acta 94:2039–2044
75. Takasaki M, Inaba T, Matsuno T, Yamada K (2003) JP Patent 2003176279
76. Eltoum AOA, O'Reilly NJ, Tipping AE (1993) 2,4-diene with halide ion and oxygen- and sulphur-centred nucleophiles and of its 2,5-di-iodo analogue with reducing agents and certain nucleophiles. J Fluor Chem 65:101–110
77. Gierczyk B, Zalas M (2005) Synthesis of substituted 1,3,4-thiadiazoles using Lawesson's reagent. Org Prep Proced Int 37:213–222
78. Lalezari I, Sharghi N (1966) Synthesis of 1,3,4-thiadiazoles containing the trifluoromethyl group. J Heterocycl Chem 3:336–337
79. Eremin KI, Krutikov VI, Golovanov AV, Lavrent'ee AN (1995) Cyclization of thiosemicarbazide using phosphorus trichloride. Zhur Obsh Khim 65:1576
80. (a) Hoegerle K, Cellarius HJ, Rathgeb P, Rumpf J (1987) US Patent 4,686,294; (b) Hoegerle K, Rathgeb P, Cellarius HJ, Rumpf J (1969) Ger Patent 1816696

81. See, for example: (a) Prasad VA, Schmidt T, Newallis PE (2000) US Patent 6,034,245; (b) Prasad VA, Noack A (1999) US Patent 5,898,074; (c) Desai VC, Newallis PE, Prasad VA, Seifert H (1999) US Patent 5,905,157; (d) Newman H, Tomcufcik AS (1971) US Patent 3,562,284
82. Reisdorff H, Haberkorn A, Plempel M, Stendel W (1977) Ger Patent 2533605
83. Kino T, Nagase Y, Ohtsuka Y, Yamamoto K, Uraguchi D, Tokuhisa K, Yamakawa T (2010) Trifluoromethylation of various aromatic compounds by CF_3I in the presence of Fe(II) compound, H_2O_2 and dimethylsulfoxide. J Fluor Chem 131:98–105
84. Ji Y, Brueckl T, Baxter RD, Fujiwara Y, Seiple IB, Su S, Blackmond DG, Baran PS (2011) Innate C-H trifluoromethylation of heterocycles. Proc Natl Acad Sci U S A 108:14411–14415
85. Fujiwara Y, Dixon JA, Rodriguez RA, Baxter RD, Dixon DD, Collins MR, Blackmond DG, Baran PS (2012) A new reagent for direct difluoromethylation. J Am Chem Soc 134:1494–1497
86. Ohtsuka Y, Yamakawa T (2011) Direct ethoxycarbonyl difluoromethylation of aromatic compounds using Fenton reagent. Tetrahedron 67:2323–2331
87. Geisel M, Mews R (1982) Fluorination reactions on 3,4-dichloro-1,2,5-thiadiazole. Chem Ber 115:2135–2140
88. Engel JF, Puglis JM (1985) US Patent 4,555,521
89. (a) Dunn PJ, Rees CW (1987) Organic heterocyclothiazenes. Part 5. Cycloaddition reactions of tetrasulfur tetranitride with highly electron-deficient alkynes. J Chem Soc, Perkin Trans 1 1579–1584. (b) Dunn PJ, Rees CW (1987) Organic heterocyclothiazenes. Part 6. Improved synthesis of trithiadiazepines from tetrasulfur tetranitride and alkynes. J Chem Soc Perkin Trans 1: 1585–1591
90. Lork A, Gard G, Hare M, Mews R, Stohrer WD, Winter R (1992) N-(chlorosulfenyl)aziridines. J Chem Soc Chem Commun 1992:898–899
91. Bludssus W, Mews R (1979) 1λ4,2-Thiazacyclohexa-1,4-dienes. J Chem Soc Chem Commun 35–36.
92. Brownridge S, Du H, Fairhurst SA, Haddon RC, Oberhammer H, Parsons S, Passmore J, Schriver MJ, Sutcliffe LH, Westwood NPC (2000) The isolation, characterization, gas phase electron diffraction and crystal structure of the thermally stable radical [CF3CSNSCCF3]. J Chem Soc Dalton Trans 19:3365–3382
93. Yoon SC, Cho J, Kim K (1998) Reactions of 1-aryl-2,2-dihaloethanone oximes with tetrasulfur tetranitride (S_4N_4): a general method for the synthesis of 3-aryl-4-halogeno-1,2,5-thiadiazoles. J Chem Soc Perkin Trans 1:109–116
94. Kim K-J, Lee H-S, Kim K (1996) Reactions of 1-aryl-2,2,2-trifluoroethanone oximes with tetrasulfur tetranitride: novel synthesis of 5-aryl-5-trifluoromethyl-*4H*-1,3,2,4,6-dithiatriazines and 1-aryl-2,2,2-trifluoro-ethanonylidenaminosulfenamides. J Heterocycl Chem 33:295–302
95. Mataka S, Hosoki A, Takahashi K, Tashiro M (1980) Sulfur nitride in organic chemistry. 9. The reaction of tetrasulfur tetranitride with benzyl ketones. Preparation of 3,4-disubstituted-1,2,5-thiadiazoles. J Heterocycl Chem 17:1681–1685
96. Mataka S, Hosoki A, Takahashi K, Tashiro M (1982) Preparation of 4-substituted 3-aroyl-1,2,5-thiadiazoles by the reaction of tetranitrogen tetrasulfide with diaroylmethanes and aroylacetones. Synthesis 976
97. Bae S-H, Kim K, Park YJ (2000) Reactions of tetrasulfur tetranitride antimony pentachloride complex (S_4N_4 $SbCl_5$) with primary β-enaminones and β-enamino esters: synthesis of 4-substituted 3-aroyl- and 3-ethoxycarbonyl-1,2,5-thiadiazoles. Heterocycles 53:159–172
98. Sheremetev AB, Kulagina VO, Yudin IL, Kuzmina NE (2001) Synthesis of trisfurazanylamine derivatives. Mendeleev Commun 11:112–113
99. Sheremetev AB, Aleksandrova NS, Suponitsky KY, Antipin MY (2009) New ring-transformation reaction: the conversion of a tetrazole ring into a 1-oxa-3,4-diazine ring. Mendeleev Commun 19:89–91
100. Makarov AY, Irtegova IG, Vasilieva NV, Bagryanskaya IY, Borrmann T, Gatilov YV, Lork E, Mews R, Stohrer W-D, Zibarev AV (2005) [1,2,5]thiadiazolo[3,4-c][1,2,5]thiadiazolidyl: a long-lived radical anion and its stable salts. Inorg Chem 44:7194–7199

101. Geisel M, Mews R (1986) Chloro- and bromofluorination of acyclic and cyclic C-N multiple bond systems. Chem Ber 119:107–115
102. Pasinszki T, Karpati T, Westwood NPC (2001) Structure and stability of small nitrile sulfides and their attempted generation from 1,2,5-thiadiazoles. J Phys Chem A 105:6258–6265
103. (a) Buscemi S, Pace A, Pibiri I, Vivona N, Spinelli D (2003) Fluorinated heterocyclic compounds. An expedient route to 5-Perfluoroalkyl-1,2,4-triazoles via an unusual hydrazinolysis of 5-perfluoroalkyl-1,2,4-oxadiazoles: first examples of an ANRORC-Like reaction in 1,2,4-Oxadiazole derivatives. J Org Chem 68:605–608. (b) Buscemi S, Pace A, Palumbo Piccionello A, Pibiri I, Vivona N, Giorgi G, Mazzanti A, Spinelli D (2006) Five-to-six membered ring-rearrangements in the reaction of 5-perfluoroalkyl-1,2,4-oxadiazoles with hydrazine and methylhydrazine. J Org Chem 71:8106–8113. (c) Palumbo Piccionello A, Pace A, Buscemi S, Vivona N (2009) An ANRORC approach to the synthesis of perfluoroalkylated 1,2,4-triazole-carboxamides. ARKIVOC vi:235–244
104. Palumbo Piccionello A, Pace A, Buscemi S, Vivona N, Giorgi G (2009) Synthesis of fluorinated 1,2,4-oxadiazin-6-ones through ANRORC rearrangement of 1,2,4-oxadiazoles. Tetrahedron Lett 50:1472–1474
105. Margetic D, Eckert-Maksic M, Troselj P, Marinic Z (2010) Reaction of 2,5-bis-trifluoromethyl-1,3,4-oxadiazole with 7-oxanorbornenes revisited: experimental and quantum-chemical study of reaction stereoselectivity. J Fluor Chem 131:408–416
106. Kim DG, Il'inykh ES (2010) Unusual dimerization of 2-amino-5-trifluoromethyl-1,3,4-thiadiazole. Chem Heterocycl Compd 46:1154–1155
107. Among the plethora of Patents regarding the use of this compound see for example: (a) Konishi S, Yamazaki Y, Honda T, Fujii K, Mori Y (1981) JP Patent 56158703. (b) Nakao H, Matsuzaki Y, Tohnishi M, Morimoto M, Fujioka S, Takemoto T, Mamezuka K (2001) JP Patent 143322. (c) Driscoll PR (1979) US Patent 4,175,081. (d) Krenzer J, Olesch DH (1975) Ger Offen 2330453. (e) Okada I, Shiga Y, Fukuchi T (2002) JP Patent 2002155065. (f) Okada I, Shiga Y, Fukuchi T (2001) JP Patent 2001172271. (g) Okada I, Fukuchi T (2000) JP Patent 2000226389
108. See for example: (a) Hirata N, Hashimoto K, Murata A (1982) JP Patent 57095381. (b) Dawson JF, Jackson MS, Bramham K, Pitt AW (1982) GB Patent 2079303
109. Modarai B, Ghandehari MH, Massoumi H, Shafiee A, Lalezari I, Badali A (1974) Kinetic studies of nucleophilic substitution of various halothiadiazoles with methoxide ion. J Heterocycl Chem 11:343–345
110. Reisdorff JH, Haberkorn A, Plempel M, Stendel W (1977) Ger Patent 2533605
111. See for example: (a) Prasad VA, Newallis PE (2002) US Patent 6,437,189; (b) Prasad VA, Jelich K, Hanson JJ (2000) US Patent 6,031,108; (c) Prasad VA, Hanson JJ, Jelich K (1999) US Patent 5,965,737; (d) Prasad VA, Applegate JM, Jelich K, Noack A (1999) US Patent 5,856,499. (e) Desai VC, Erdman DT, Applegate JM, Jelich K, Noack A (1999) Eur Patent 926143
112. See, for example: (a) Prasad VA, Applegate JM, Wasleski DM, Jelich K (1998) US Patent 5,792,872; (b) Prasad VA, Newallis PE, Wasleski DM, Applegate JM, Jelich K (1999) US Patent 5,895,818; (c) Foerster H, Diehr HJ, Santel HJ, Dollinger M (1995) Ger Patent 4420337; (d) Foerster H, Andree R, Santel HJ, Schmidt RR, Strang H (1989) Ger Patent 3821600
113. Riebel H-J, Foerster H, Drewes MW, Dahmen P, Feucht D, Pontzen R (2001) Ger Patent 19935964
114. Ciba-Geigy AG Switz (1988) JP Patent 63162680
115. Nicolaides DN, Fylaktakidou KC, Litinas KE, Hadjipavlou-Litina D (1998) Synthesis and biological evaluation of several coumarin-4-carboxamidoxime and 3-(coumarin-4-yl)-1,2,4-oxadiazole derivatives. Eur J Med Chem 33:715–724
116. Sasmal PK, Talwar R, Swetha J, Balasubrahmanyam D, Venkatesham B, Rawoof KA, Neelima Devi B, Jadhav VP, Khan SK, Mohan P, Srinivasa Reddy D, Nyavanandi DK, Nanduri S, Shiva Kumar K, Kannan M, Srinivas P, Nadipalli P, Chaudhury H, Sebastian VJ (2011) Structure-activity relationship studies of novel pyrazole and imidazole carboxamides as cannabinoid-1 (CB1) antagonists. Bioorg Med Chem Lett 21:4913–4918

117. Wilton S (2007) PTC124, nonsense mutations and Duchenne muscular dystrophy. Neuromuscul Disord 17:719–720
118. Pichavant C, Aartsma-Rus A, Clemens PR, Davies KE, Dickson G, Takeda S, Wilton SD, Wolff JA, Wooddell CI, Xiao X, Tremblay JP (2011) Current status of pharmaceutical and genetic therapeutic approaches to treat DMD. Mol Ther 19:830–840
119. Rai G, Sayed AA, Lea WA, Luecke HF, Chakrapani H, Prast-Nielsen S, Jadhav A, Leister W, Shen M, Inglese J, Austin CP, Keefer L, Arnér ESJ, Simeonov A, Maloney DJ, Williams DL, Thomas CJ (2009) Structure mechanism insights and the role of nitric oxide donation guide the development of oxadiazole-2-oxides as therapeutic agents against schistosomiasis. J Med Chem 52:6474–6483
120. Ostad SN, Amini M, Haghipour Z, Karimi L, Navidpour L, Ghahremani MH, Shafiee A (2005) Inhibitory activities of new series of 4,5-diaryl thiadiazoles derivatives on lipopolysaccharide-induced COX-2 expression. Int J Pharm 1:79–84
121. Zhan P, Liu X, Cao Y, Wang Y, Pannecouque C, De Clercq E (2008) 1,2,3-thiadiazole thioacetanilides as a novel class of potent HIV-1 non-nucleoside reverse transcriptase inhibitors. Bioorg Med Chem Lett 18:5368–5371
122. Kondo T, Nekado T, Sugimoto I, Ochi K, Takai S, Kinoshita A, Hatayama A, Yamamoto S, Kishikawa K, Nakai H, Toda M (2008) Design and synthesis of DPP-IV inhibitors lacking the electrophilic nitrile group. Bioorg Med Chem 16:1613–1631
123. Reiter LA, Subramanyam C, Mangual EJ, Jones CS, Smeets MI, Brissette WH, McCurdy SP, Lira PD, Linde RG, Li Q, Zhang F, Antipas AS, Blumberg LC, Doty JL, Driscoll JP, Munchhof MJ, Ripp SL, Shavnya A, Shepard RM, Sperger D, Thomasco LM, Trevena KA, Wolf-Gouveia LA, Zhang L (2007) Pyrimidine benzamide-based thrombopoietin receptor agonists. Bioorg Med Chem Lett 17:5447–5454
124. Willy PJ, Murray IR, Qian J, Busch BB, Stevens WC Jr, Martin R, Mohan R, Zhou S, Ordentlich P, Wei P, Sapp DW, Horlick RA, Heyman RA, Schulman IG (2004) Regulation of PPARγ coactivator 1α (PGC-1α)signaling by an estrogen-related receptor α (ERRα) ligand. Proc Natl Acad Sci U S A 101:8912–8917
125. Lanvin O, Bianco S, Kersual N, Chalbos D, Vanacker JM (2007) Potentiation of ICI182,780 (fulvestrant)-induced estrogen receptor-α degradation by the estrogen receptor-related receptor-α inverse agonist XCT790. J Biol Chem 282:28328–28334
126. Kansra S, Yamagata S, Sneade L, Foster L, Ben-Jonathan N (2005) Differential effects of estrogen receptor antagonists on pituitary lactotroph proliferation and prolactin release. Mol Cell Endocrinol 239:27–36
127. (a) Teyssier C, Bianco S, Lanvin O, Vanacker JM (2008) The orphan receptor ERRa interferes with steroid signaling. Nucleic Acids Res 36:5350–5361; (b) Bianco S, Lanvin O, Tribollet V, Macari C, North S, Vanacker JM (2009) Modulating estrogen receptor-related receptor-α activity inhibits cell proliferation. J Biol Chem 284:23286–23292
128. Macdonald GJ, Bartolome-Nebreda JM, Van Gool MLM (2008) WO 2008128996
129. Gadad AK, Palkar MB, Anand K, Noolvi MN, Boreddy TS, Wagwade J (2008) Synthesis and biological evaluation of 2-trifluoromethyl/sulfonamido-5,6-diaryl substituted imidazo[2,1-b]-1,3,4-thiadiazoles: a novel class of cyclooxygenase-2 inhibitors. Bioorg Med Chem 16:276–283
130. Gargala G, Le Goff L, Ballet JJ, Favennec L, Stachulski AV, Rossignol JF (2009) In vitro efficacy of nitro- and halogeno-thiazolide/thiadiazolide derivatives against *Sarcocystis neurona*. Vet Parasitol 162:230–235
131. Gargala G, Le Goff L, Ballet JJ, Favennec L, Stachulski AV, Rossignol JF (2010) Evaluation of new thiazolide/thiadiazolide derivatives reveals nitro group-independent efficacy against *In vitro* development of *Cryptosporidium parvum*. Antimicrob Agents Chemother 54:1315–1318
132. Schüttelkopf AW, Gros L, Blair DE, Frearson JA, van Aalten DMF, Gilbert IH (2010) Acetazolamide-based fungal chitinase inhibitors. Bioorg Med Chem 18:8334–8340

133. Ijichi K, Shigeta S, Baba M, Fujiwara M, Yokota T, Takayama H, Sakai S, Hanasaki Y, Ide T (1996) PCT International Application WO 9609296
134. Lo Celso F, Pibiri I, Triolo A, Triolo R, Pace A, Buscemi S, Vivona N (2007) Study on the thermotropic properties of highly fluorinated 1,2,4-oxadiazolylpyridinium salts and their perspective applications as ionic liquid crystals. J Mater Chem 17:1201–1208
135. Pibiri I, Pace A, Buscemi S, Causin V, Rastrelli F, Saielli G (2012) Oxadiazolyl-pyridines and perfluoroalkyl-carboxylic acids as building blocks for protic ionic liquids: crossing the thin line between ionic and hydrogen bonded materials. PCCP 14:14306–14314
136. Tang H, Gao JP, Xiong Y, Wang ZY (2006) Self-assembled, discrete organic tubular crystals with controllable sizes by simple sublimation. Crystal Growth Design 6:1559–1562
137. Pibiri I, Palumbo Piccionello A, Calabrese A, Buscemi S, Vivona N, Pace A (2010) Fluorescent Hg2+ sensors: synthesis and evaluation of a tren-based starburst molecule containing fluorinated 1,2,4-oxadiazoles. Eur J Org Chem 4549–4553
138. Zhao ZH, Jin H, Zhang YX, Shen Z (2011) Synthesis and properties of dendritic emitters with a fluorinated starburst oxadiazole core and twisted carbazole dendrons. Macromolecules 44:1405–1413
139. Ding J, Day M (2006) Novel highly fluorinated poly(arylene ether-1,3,4-oxadiazole)s, their preparation, and sensory properties to fluoride anion. Macromolecules 39:6054–6062
140. Koehn A, Tiebes J, Van Almsick A, Ahrens H, Heinemann I, Braun R, Schmitt MH, Willms L, Feucht D, Rosinger CH, Haeuser-Hahn I, Drewes M, Doerner-Rieping S, Dittgen J, Adamczewski M (2011) PCT International Application WO 2011035874
141. Jakobi H, Martelletti A, Dittgen J, Feucht D, Haeuser-Hahn I, Rosinger CH (2011) PCT International Application WO 2011073098
142. Kloek JA (1981) Substituted-1,2,3-thiadiazole safening agents. US Patent 4253864A
143. Foerster H, Andree R, Santel H-J, Schmidt RR, Strang H (1990) US Patent 4,968,342
144. Driscoll PR (1979) US Patent 4,175,081
145. Soergel S, Paulini R, Gross S, Beyer C, Pohlman M, Bastiaans HMM, Rack M, Culbertson DL, Anspaugh DD, Thompson S, Salgado V (2011) PCT International Application WO 2011061110
146. Nakahira S, Yoshida K (2004) JP Patent 2004054026
147. Inaba T, Matsuno T, Sato T (2002) JP Patent 2002357879
148. (a) Hammami A, Marsan B, Armand M, Hersant G (2007) WO 2007109907; (b) Courtel FM, Paynter RW, Marsan B, Morin M (2009) Synthesis, characterization, and growth mechanism of n-Type $CuInS_2$ colloidal particles. Chem Mater 21:3752–3762; (c) Courtel FM, Hammami A, Imbeault R, Hersant G, Paynter RW, Marsan B, Morin M (2010) Synthesis of n-type $CuInS_2$ particles using *N*-methylimidazole, characterization and growth mechanism. Chem Mater 22:3752–3761

Fluorinated Oxazoles, Thiazoles and Selenazoles

M.A. Yurovskaya

Contents

Abstract This chapter provides information about the methods of synthesis, chemical properties and applications of fluorine-containing oxazoles, thiazoles and selenazoles and their benzo analogues.

M.A. Yurovskaya (✉)
Department of Chemistry, Moscow State University,
Leninskie Gory, Moscow 119992, Russian Federation
e-mail: yumar@org.chem.msu.ru

V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_10,

Keywords Fluoro- and fluoroalkyl-oxazoles • -benzoxazoles • -thiazoles • -selenazoles • -benzothiazoles

1 Fluorinated Oxazoles and Benzoxazoles

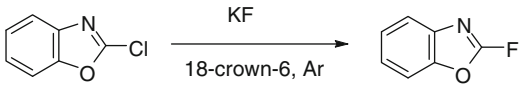
1.1 Methods of Synthesis

The methods for preparation of oxazoles and benzoxazoles may be subdivided into two synthetic approaches:

1. Incorporation of fluorine atom or fluoroalkyl groups.
2. Synthesis from fluorine-containing acyclic fragments.

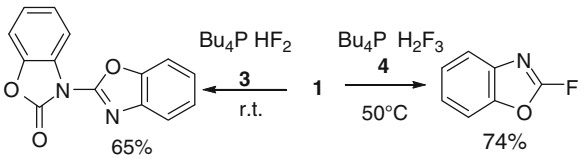
1.1.1 Incorporation of Fluorine Atom and Fluoroalkyl Groups into Heterocycle

Only two examples of the fluorine atom incorporation into position 2 of benzoxazole *via* nucleophilic substitution of the chlorine atom are known. Thus, the reaction of 2-chlorobenzoxazole (**1**) with KF in the presence of catalytic amounts of 18-crown-6 (15–25 h at 110–120 °C) gave 2-fluorobenzoxazole (**2**) in 45–65 % yield [1].

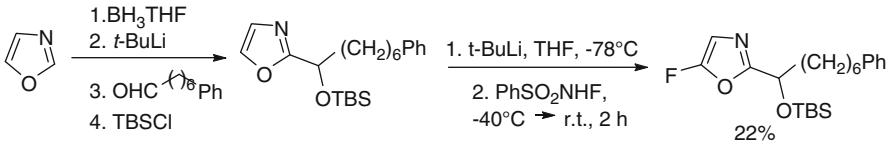


1 **2**

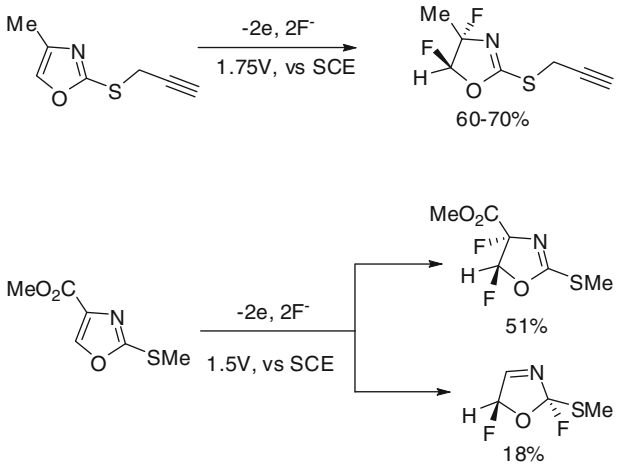
Fluorination of various chlorinated N-heterocycles with tetrabutylphosphonium hydrogendifluoride (**3**) or dihydrogentrifluoride (**4**) proceeded readily to give 2-fluorobenzoxazole (**2**) in high yields under mild conditions. Treatment of 2-chlorobenzoxazole (**1**) with **3** at 50 °C gave the 2-fluoro derivative, but a run at room temperature resulted in the formation of 1-(2-benzoxazolyl)benzoxazolone. It appears that 2-chlorobenzoxazole was partly converted to the 2-fluoro derivative that promptly underwent hydrolysis and homocoupling or reacted with the starting substrate during working-up [2].



Fluorine atom can be incorporated into oxazole core *via* the selective C(5) lithiation of 2-substituted oxazole followed by treatment of electrophile, – N-fluorobenzenesulfonimide [3, 4]:

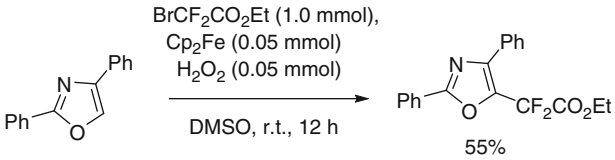


Electrochemical fluorination of 4-methyl-2-(propargylthio)oxazoles has been successfully carried out using $Et_4NF \cdot nHF$ (n = 4, 5) as the supporting electrolyte and fluoride source to provide the corresponding 4,5-difluoro-4-methyl-2-propargylthio-2-oxazolines, and fluorination did not take place at the sulfur atom. In the case of electrochemical fluorination of 4-methoxycarbonyl-2-(methylthio)oxazole, 2,5-difluoro-3-oxazoline derivative was formed in addition to a 4,5-difluoro-2-oxazoline [5].

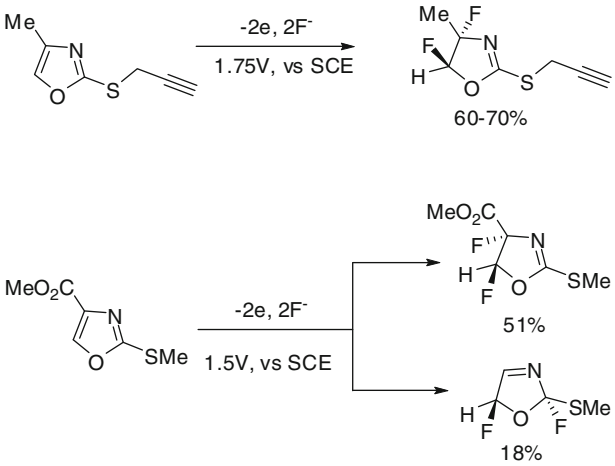


It is known that the radical trifluoromethylation of various benzene derivatives and five- and six-membered heteroaromatic compounds by CF_3I was successfully achieved using the Fenton reagent comprising of $FeSO_4$ or ferrocene (Cp_2Fe) and H_2O_2 as a catalyst in dimethylsulfoxide (DMSO) [6, 7]. The Fenton reagent generates an electrophilic ethoxycarbonyldifluoromethyl radical from $BrCF_2CO_2Et$ in DMSO. As a result efficient direct ethoxycarbonyldifluoromethylation of various aromatic compounds takes place. An electrophilic character of this radical is owing to the electron-withdrawing nature of fluorine atom and ethoxycarbonyl group. Thus, 2,4-diphenyloxazole gave selectively in this reaction ethyl (2,4-diphenyloxazol-5-yl)difluoroacetate despite the presence of the

phenyl group at the 4-position. This orientation can be explained in terms of the trend of the electrophilic substitution of oxazoles [8]. The mechanism of this process is represented below [8].

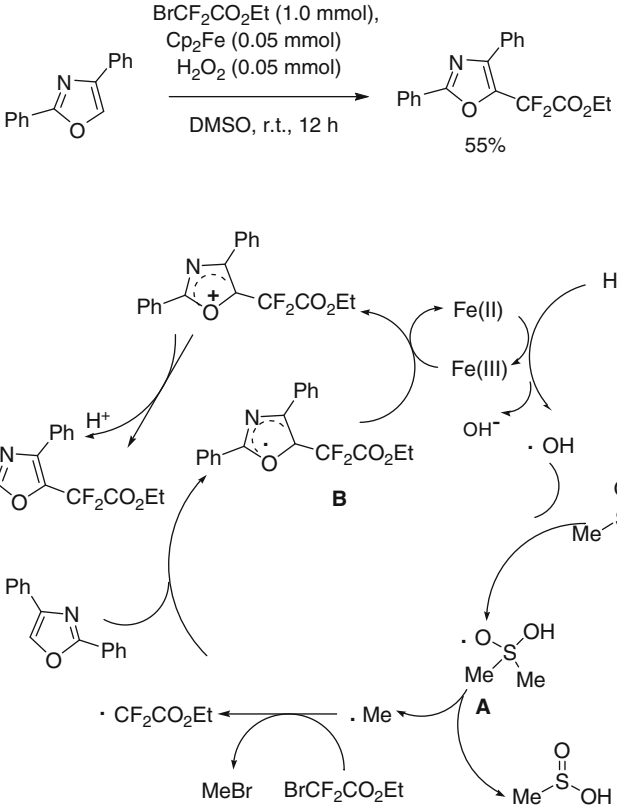


Electrochemical fluorination of 4-methyl-2-(propargylthio)oxazoles has been successfully carried out using $Et_4NF \cdot nHF$ (n = 4, 5) as the supporting electrolyte and fluoride source to provide the corresponding 4,5-difluoro-4-methyl-2-propargylthio-2-oxazolines, and fluorination did not take place at the sulfur atom. In the case of electrochemical fluorination of 4-methoxycarbonyl-2-(methylthio)oxazole, 2,5-difluoro-3-oxazoline derivative was formed in addition to a 4,5-difluoro-2-oxazoline [5].

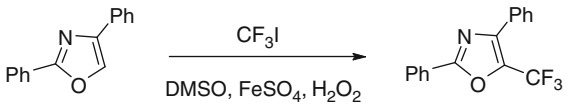


It is known that the radical trifluoromethylation of various benzene derivatives and five- and six-membered heteroaromatic compounds by CF_3I was successfully achieved using the Fenton reagent comprising of $FeSO_4$ or ferrocene (Cp_2Fe) and H_2O_2 as a catalyst in dimethylsulfoxide (DMSO) [6, 7]. The Fenton reagent generates an electrophilic ethoxycarbonyldifluoromethyl radical from $BrCF_2CO_2Et$ in DMSO. As a result efficient direct ethoxycarbonyldifluoromethylation of various aromatic compounds takes place. An electrophilic character of this radical is owing to the electron-withdrawing nature of fluorine atom and ethoxycarbonyl group. Thus, 2,4-diphenyloxazole gave selectively in this reaction ethyl (2,4-diphenyloxazol-5-yl) difluoroacetate despite the presence of the phenyl group at the 4-position. This

orientation can be explained in terms of the trend of the electrophilic substitution of oxazoles [8]. The mechanism of this process is represented below [8].

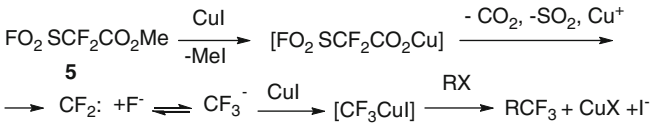


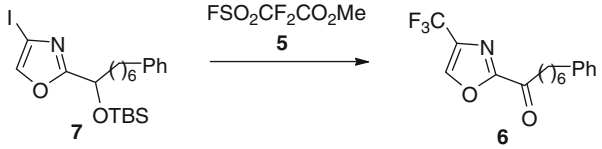
CF_3I behaves in similar manner under these conditions by generating the electrophilic trifluoromethyl radical [7]. Therefore, direct trifluoromethylation is simple and promising approach to be used as an industrial process.



Another reagent, methyl fluorosulphonyldifluoroacetate (**5**), is used as the source of trifluoromethyl group and replaces the halogen in aryl, alkenyl, and alkyl halides in the presence of copper(I) iodide [9]. Compound **5** is easy to handle liquid and can be readily obtained from the corresponding acid fluoride, which is a starting material for producing the commercial ion-exchange resins, Nafion H®. Treatment of **5** with aryl, alkenyl, and alkyl halide in DMF in the presence of catalytic amounts of copper(I) iodide (12 mol %) at 60–80 °C during 2–6 h gave

the corresponding trifluoromethyl derivatives in good yields with simultaneous elimination of SO_2, CO_2, and methyl halide. The possible mechanism of the reaction is shown below. The trifluoromethyl derivative **6** was prepared from iodide **7** using this method [4, 10, 11].

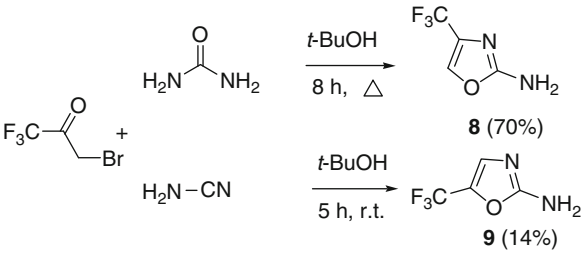




1.1.2 Synthesis of Fluoroalkyloxazoles and Fluoroalkylbenzoxazoles from Fluorine-Containing Acyclic Fragments

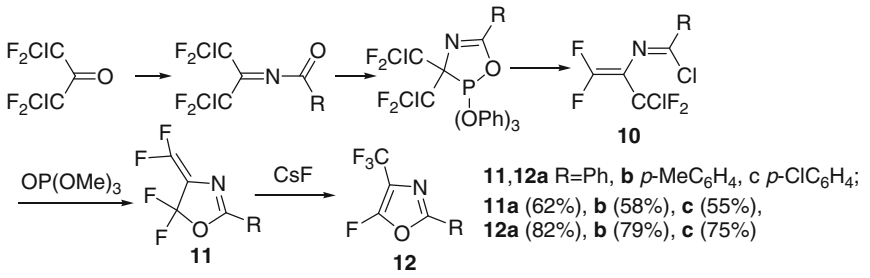
1.1.2.1 Synthesis of Fluoroalkyloxazoles

Condensation with the appropriate components is widely represented in literature approach to fluoroalkyl derivatives of oxazole. Fluoroalkyloxazoles are of interest due to their application as surface modifiers of hydrophilic polymers, polymeric films for second-order non-linear optics, effective herbicides, body-membrane penetration enhancers, and intermediates for the synthesis of unnatural α-amino acids [12]. Thus, the syntheses of the trifluoromethylated 2-aminooxazoles **8** and **9** were performed by reacting commercially available trifluorobromoacetone with five equivalents of urea or cyanamide in refluxing *tert*-butanol to afford the corresponding 4- and 5-trifluoromethyl-2-aminooxazoles in 70 % and 14 % yields, respectively [13, 14].

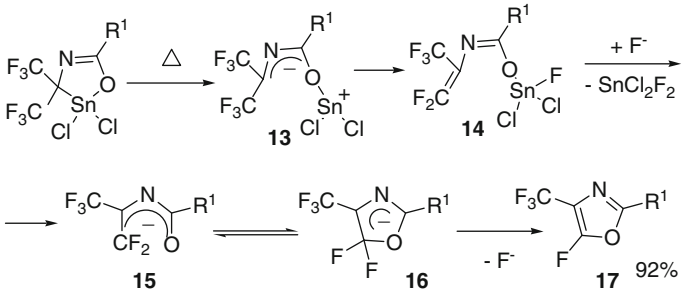


An interesting example of application of 1,3-dichloro-1,1,3,3-tetrafluoroacetone was given in the work [15]. Using this compound *N*-(l-chlorodifluoromethy)l-2,

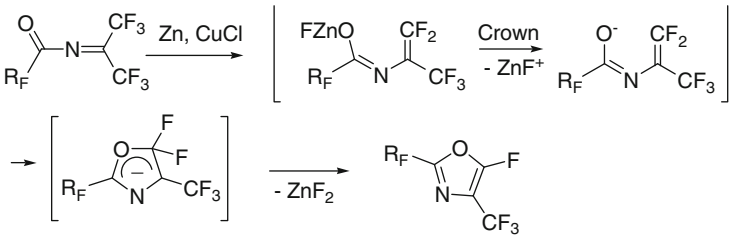
2-difluorovinyl]imidoyl chlorides **10** were prepared. Heating of **10** with trimethyl phosphate yields 5,5-difluoro-4-difluoromethyliden-2-oxazolines **11.** In the presence of cesium fluoride the latter rearranged to 5-fluoro-4-trifluoromethyl-oxazoles **12**.



Similarly, heterodienes of [$(CF_3)_2$=N-C(R^1)=O] type react with tin(II) compounds [tin(II) chloride, stannocene etc.] to give [4+1] cycloadducts. The cycloaddition process causes an "umpolung" at the carbon atom which two trifluoromethyl groups are attached to. This is the precondition for the controlled, stepwise elimination of fluoride from one of trifluoromethyl groups. Therefore, trifluoromethyl-substituted tin heterocycles are useful building blocks for the synthesis of fluoro- and trifluoromethyl-substituted compounds [16–21]. The reaction sequence starts from heterocycle opening with formation of zwitter-ion **13**. The second stage is the migration of fluorine atom to tin (**13** → **14**). The splitting of the Sn-X bond (**14** → **15**) induced by fluoride ion allows the formation of heteropentadienide anion which undergoes electrocyclization and fluoride ion elimination leading to the aromatization.

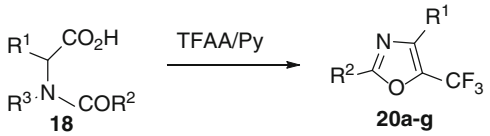


5-Fluoro-2-perfluoroalkyl-4-(trifluoromethyl)oxazoles were formed by reduction of perfluoroacylimines with some metals. The reaction is promoted by catalytic amounts of CuI salts and crown ethers. Among the metals (magnesium, tin, aluminum, and zinc) only zinc and tin exerted as a defluorinating effect. The best yields of oxazoles were attained in the presence of zinc [22, 23]. A similar single electron transfer mechanism was described for cyclization of other hexafluoroacetone imines with metals. The role of crown ether is apparently reduced to the assistance in the elimination of ZnF^+ with formation of O-anion, which results in the intramolecular cyclization to oxazoles.



R_F=CF_3 (62%), C_2F_5 (51%), C_3F_7 (30%)

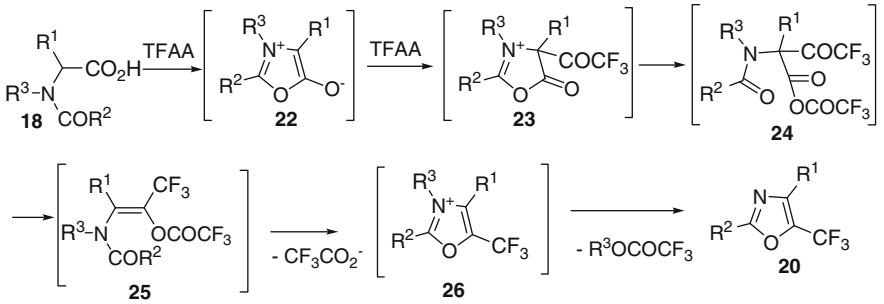
Perfluoroalkanoic anhydrides can be used as another source of fluoroalkyl substituents in the formed oxazole nucleus. For example, the reaction of *N*-acyl-*N*-alkyl-α-amino acids (**18**) or *N*-acylprolines (**19**) with trifluoroacetic anhydride in the presence of pyridine (under Dakin-West reaction conditions) [24] affords 5-trifluoromethyloxazoles (**20** or **21**) in good yields [25, 26] (best yields are observed for R^3=Bn).



18 **20a-g**

a R^1=Bn, R^2=Ph, R^3=Me (88%); **b** R^1=Bn, R^2=Ph, R^3=Ph (83%);
c R^1=Bn ,R^2=-Ph, R^3=*i*-Pr (61%); **d** R^1=Bn, R^2=Ph, R^3=Bn (92%);
e R^1=Bn, R^2=*t*-Bu, R^3 =Bn (88%); **f** R^1=Bn, R^2=PhCH=CMe,
R^3=Bn (46%); **g** R^1=Ph, R^2=Ph, R^3=Bn (92%)

The proposed reaction mechanism involves formation of mesoionic 1,3-oxazolium-5-olate **22** through the cyclodehydration of **18** by TFAA. The intermediate **22** undergoes trifluoroacetylation followed by decarboxylation to give enol trifluoroacetate (**25**). Cyclization of **25** leads to oxazolinium salt (**26**). If the R^3 group of **25** is easily removable, the reaction could proceed efficiently. This is the reason why *N*-benzyl derivatives are the best substrates for this transformation.

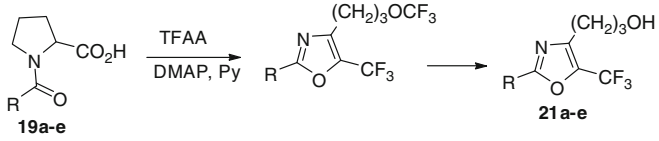


18 **22** **23** **24** **25** **26** **20**

R^1=Bn, Ph, Me, s-Bu; R^2=Ph,*t*-Bu, PhCH=CMe, 2-Thienyl, R_3=Me, Et, *i*-Bu [13-20%, Bn 80-90%]

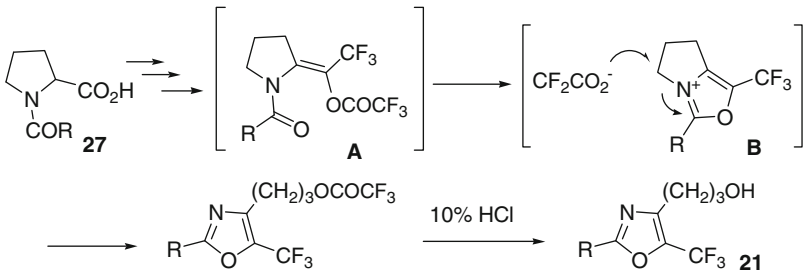
2,4-Diphenyl-5-pentafluoroethyl- and 5-heptafluoropropyloxazoles were obtained in high yields (92 % and 98 %, correspondingly) when pentafluoropropionic and heptafluorobutyric anhydride were used instead of TFAA. Similar reaction

of *N*-acylprolines **19** with TFAA in the presence of pyridine resulted in the formation of 5-trifluoromethyloxazoles **21a-e** in good yields.

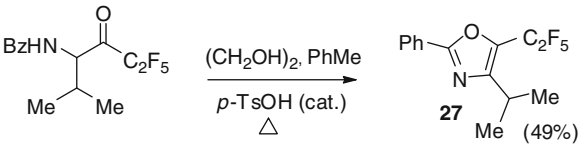


21a R=*t*-Bu (87%), **b** Ph (61%), **c** 4-MeOC$_6$H$_4$ (81%), **d** 4-ClC$_6$H$_4$ (46%), **e** PhCH=CMe (65%)

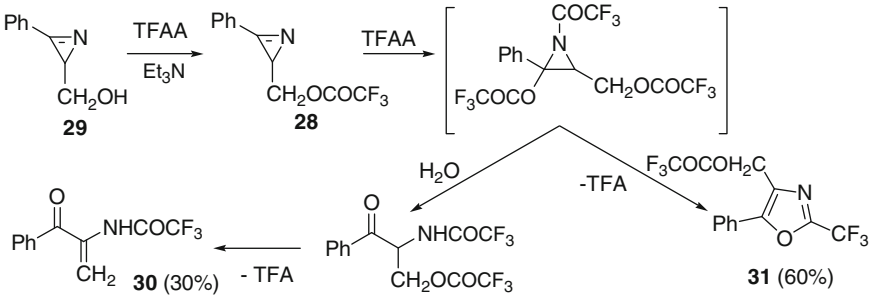
In case of *N*-acylprolines **19**, the key intermediate of reaction (**A**) was isolated. A similar mechanism has been postulated in the Dakin-West reaction. The cleavage of N-C bond of the intermediate (**B**) readily occurs upon the attack of the trifluoroacetate anion because of the hindered 5-5 bicyclic system.



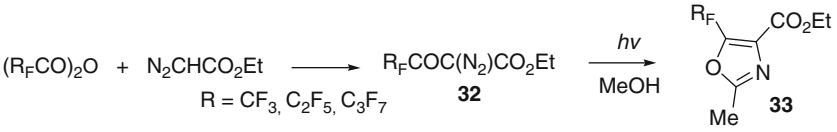
The Dakin-West reaction was successfully implemented for preparation of pentafluoroethyloxazole in the presence of *p*-TsOH [27].



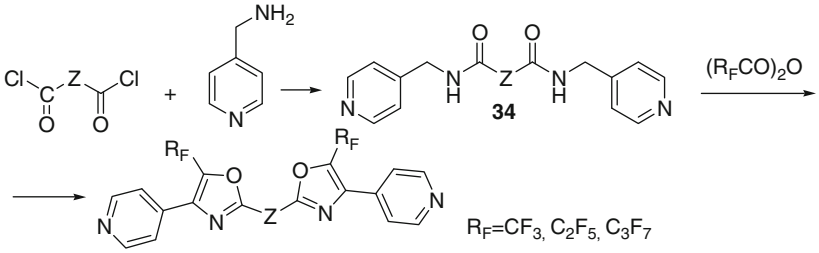
Attempts to prepare 3-phenyl-2H-azirine-2-methanol trifluoroacetate **(28)** by treating hydroxymethyl derivative **29** with TFAA and triethylamine produced 1-phenyl-2-(trifluoroacetylamino)prop-2-en-1-one (**30,** 30 %) and 2-trifluoromethyl-4-trifluoroacetoxymethyl-5-phenyloxazole **(31,** 60 %*)* [28].



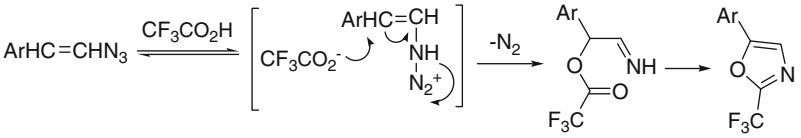
Perfluoroacylated diazoacetic esters **32** were generated by acylation of ethyl diazoacetate with perfluorinated acid anhydrides. These intermediates were cyclized into ethyl 2-methyl-5-perfluoroalkyloxazole-4-carboxylates **33** in 60–70 % yield during irradiation (Hanau TQ 81, 70 W) [29].



A series of bispyridinium compounds containing the 5-perfluoroakyl-substituted oxazole fragment were synthesized by a short sequence of reactions from symmetric diamides. All compounds were tested for their antiproliferative activity against HT-29, a cell line derived from a human colon adenocarcinoma, and their inhibitory activity against choline kinase (ChoK), a novel anticancer molecular target already in clinical trials. Most of the analyzed compounds showed good antiproliferative activities in the micromolar range with the identification of promising lead molecules as a new family of potential inhibitors of ChoK. The treatment of symmetric diamides **34** (easily prepared from the corresponding dicarboxylic acid chloride) with perfluoroalkyl anhydrides (bearing three, five, or seven fluorine) in dry toluene in the presence of pyridine provided 5,5′-bisperfluoroalkyl-2,2′-bisoxazoles in low (41 %) to excellent (94 %) yields. Three different linkers Z (*p*-biphenylene, *p*-$C_6H_4C(CF_3)_2C_6H_4$-*p*, *p*-phenylene) were used [30, 31].



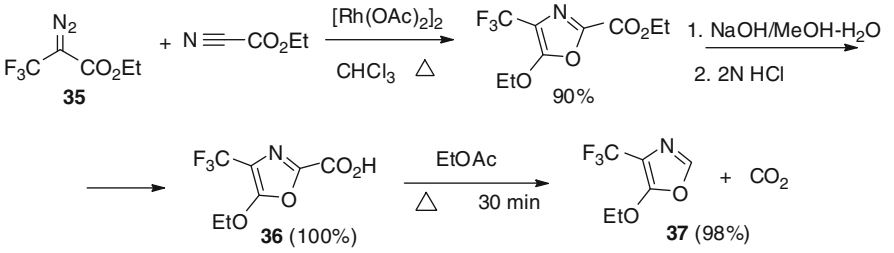
The reaction of ß-azidostyrene with trifluoroacetic acid gave 5-phenyl-2-(trifluoromethyl)oxazole *via* attack of halogenoacetate anion on a benzylic carbocation or a conjugate acid of the azide [32].



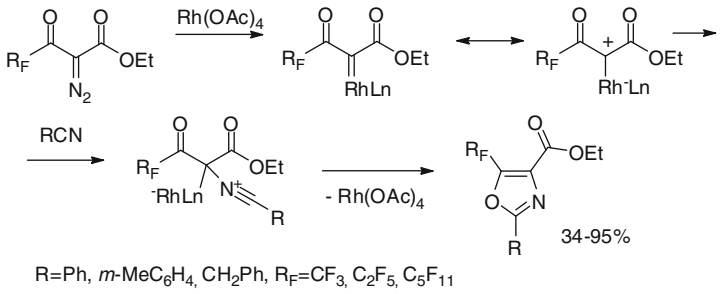
Ar=Ph (48%), 4-MeC$_6$H$_4$ (45%)

Although the electronic properties of the cyano group of ethyl cyanoformate might have been considerably altered by its direct connection to the ethoxycarbonyl

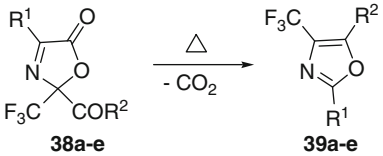
group, the rhodium catalyzed reaction of the CF_3-containing diazo compound **35** with ethyl cyanoformate proceeded readily and afforded the expected oxazole product in good yield. Under these conditions ethyl 2-diazoacetoacetate (obtained by the reaction of ethyl fluoroalkylacetoacetate with perfluoroalkanesulfonyl azide or tosyl azide) reacted readily also with other nitriles to give a series of 5-fluoroalkyl substituted 1,3-oxazoles in fair to good yields [33–36].



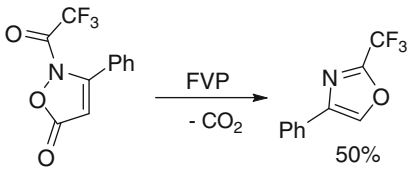
To account for formation of the desired 5-fluoroalkyl oxazoles, the more nucleophilic fluoroalkylated carbonyl group should participate in cyclization rather than the ester group. The mechanism of this reaction is outlined below. As a key intermediate rhodium carbenoid is formed [34].



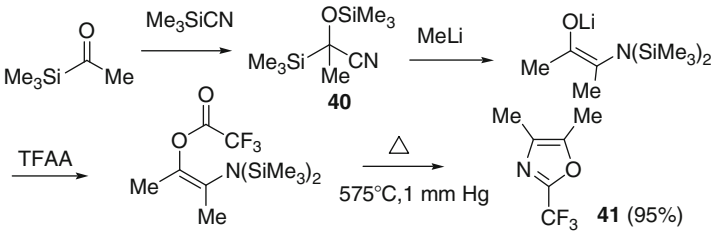
The original method for the synthesis of trifluoromethyl-substituted oxazoles is based on the transformation of acyloxazolin-5-ones. Thus, 2-acyl-2-trifluoromethyl-Δ^3-oxazolin-5-ones **38** undergo cycloelimination of CO_2 on heating at 200–230 °C to yield trisubstituted oxazoles **39**. In this case substituents at positions 2 and 4 of the oxazole ring are formally interchanged [37]. Flash vacuum pyrolysis (540–600 °C/0.01 mm Hg) of N-trifluoroacetylisoxazole-5-one also leads to 2-trifluoromethyloxazole [38].



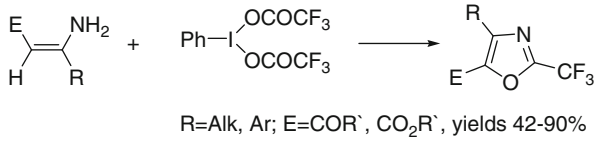
a R^1=R^2=Me (94%); **b** R^1=Ph, R^2=OMe (47%); **c** R^1=CH_2CHMe_2, R^2=OMe (51%);
d R^1=CH_2CHMe_2, R^2=OMe (51%); **e** R^1=Me, R^2=*p*-$NO_2C_6H_4$(61%)



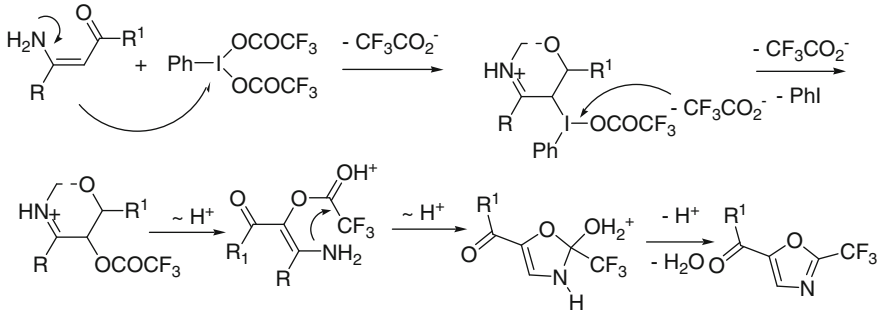
Sequential addition of methyl lithium and trifluoroacetic anhydride to O-trimethylsilyl acetyltrimethylsilane cyanohydrin (**40**) affords ß-trifluorioacyloxy-N,N-bis(trimethylsilyl)enamines which cyclize to 2-trifluoromethyl-4,5-dimethyloxazole (**41**) under thermolysis [39, 40].



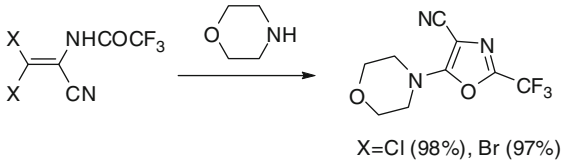
Treatment of β-monosubstituted enamines with phenyliodyl bis(trifluoroacetate) (PIFA) was found to give a variety of 4,5-disubstituted 2-(trifluoromethyl)oxazoles in good yields [41]. This approach allows the incorporation of the trifluoromethyl moiety of PIFA into the final products, which presumably takes place via the oxidative β-trifluoroacetoxylation of the enamine substrates followed by subsequent intramolecular cyclization.



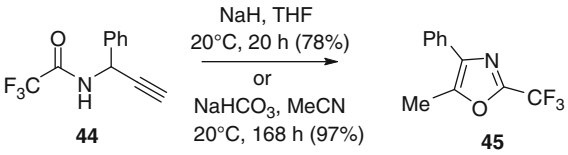
R=Alk, Ar; E=COR`, $CO_2R$`, yields 42-90%



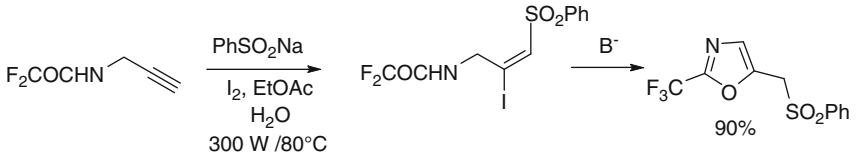
Reaction of 2-trifluoroacetylamino-3,3-dihaloacrilonitrylonitriles with morpholine gave 2-trifluoromethyl-5-morpholinooxazole 4-carbonitiles in almost quantitative yields under mild conditions [42]:



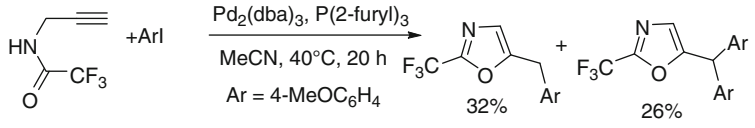
Base-induced cyclization of 2,2,2-trifluoro-N-(1-phenylprop-2-ynyl) acetamide (**44**) in the presence of NaH or $NaHCO_3$ gives the corresponding 2-trifluoromethyloxazole **45** in 78 % and 97 % yields, correspondingly [43].



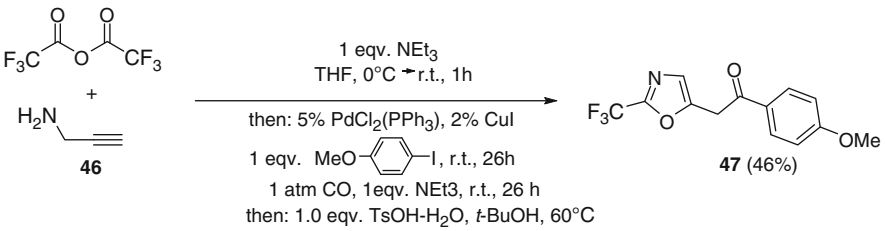
Other methods of converting propargylamides to oxazoles are also known. Thus, N-trifluoroacetylpropargylamines have been regioselectively converted to (*E*)-iodo(vinyl)sulfones which, in turn, were converted to 2-trifluoromethyl-5-substituted oxazoles by the base treatment [44].



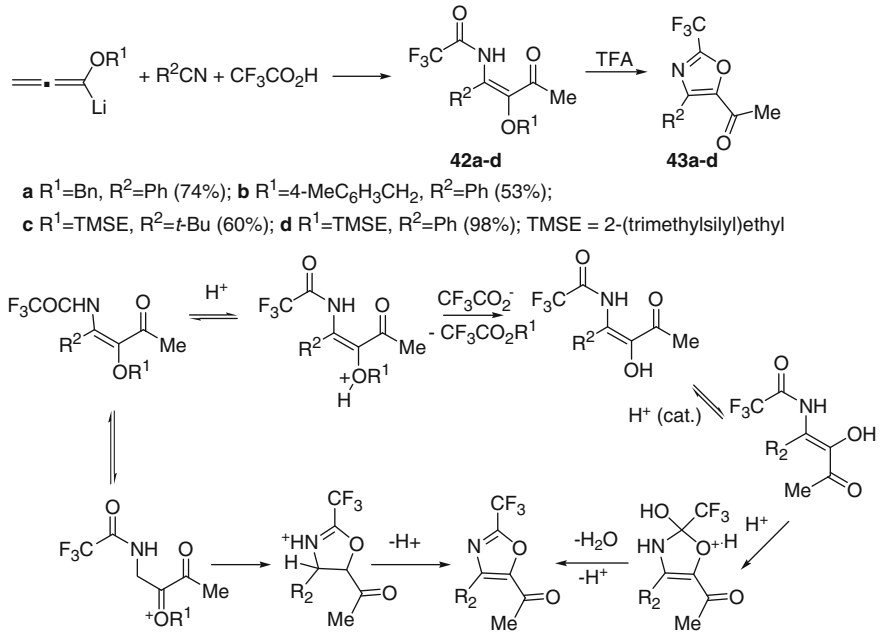
2,5-Disubstituted oxazoles have been prepared also through the reaction of *N*-propargylamides with aryl iodides in the presence of $Pd_2(dba)_3$, tri(2-furyl) phosphine, and NaOBu^t. The reaction appears to proceed through a palladium-catalyzed coupling step followed by the *in situ* cyclization of the resultant coupling product [45].



Acylation of propargylamine (**46**) with trifluoroacetic anhydride followed by carbonylative alkynylation of *p*-iodoanisole and subsequent TsOH-catalyzed cycloisomerization gave rise to the formation of the oxazole derivative **47** in moderate yield, yet in one-pot fashion [46].



Lithiated alkoxyallenes, nitriles, and TFA have been employed as precursors in a three-component reaction leading to highly substituted enamides **42a–d**. Upon treatment with trifluoroacetic acid, these enamides could be easily cyclized to 2-trifluoromethyl-5-acetyloxazole derivatives **43a–d** [47]. Two most probable pathways for oxazole formation from enamides were proposed.

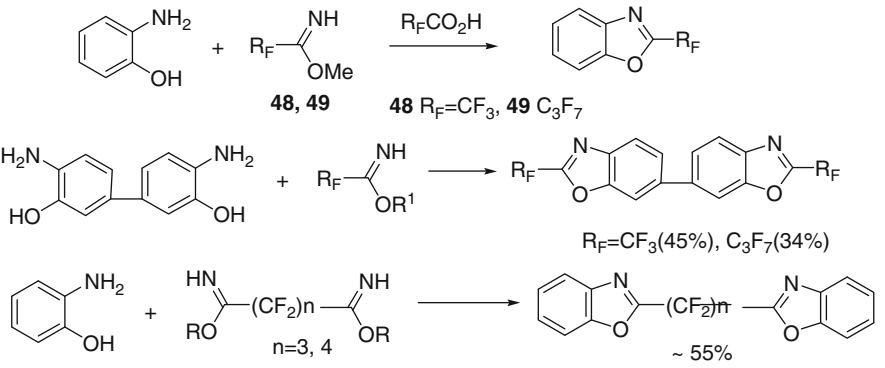


a R^1=Bn, R^2=Ph (74%); **b** R^1=4-Me$C_6H_3CH_2$, R^2=Ph (53%);
c R^1=TMSE, R^2=*t*-Bu (60%); **d** R^1=TMSE, R^2=Ph (98%); TMSE = 2-(trimethylsilyl)ethyl

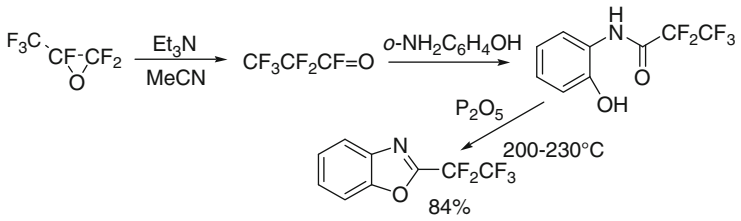
1.1.2.2 Synthesis of Fluoroalkyl Benzoxazoles

Almost all syntheses of fluoroalkylated benzoxazoles are based on the use of *ortho-aminophenols*. Thus, condensation of perfluoroalkanoic acid imidates with *o-aminophenol* is a convenient method for preparation of 2-perfluoroalkyl-substituted benzoxazoles. 2-Trifluoromethyl- and 2-(perfluoropropyl)benzoxazoles can be synthesized by heating at 100 °C in dry dioxane, but the yield of benzoxazoles does not exceed 35–40 %. The best results are obtained by reaction of *o*-aminophenol with

the imidates **48** and **49** in the presence of equimolecular quantity of trifluoroacetic or perfluorobutyric acids, respectively, at room temperature [48]. Bisaminophenol gave similarly the corresponding 6,6′-di-(2-perfluoroalkyl)benzoxazole. Imidates of perfluorinated dicarboxylic acids permit preparation of α,ω-di(benzoxazole-2-yl) perfluoroalkanes [49].

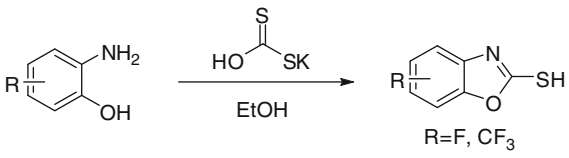


Utilizing the high reactivity of hexafluoro-1,2-epoxypropane (HFPO, hexafluoropropylene oxide), several new benzoannulated compounds containing CF_3 and C_2F_5 groups were prepared. For example, treating of 2-aminophenol with HFPO/Et_3N followed by dehydration gave 2-(pentafluoroethyl)benzoxazole in high yield [50].

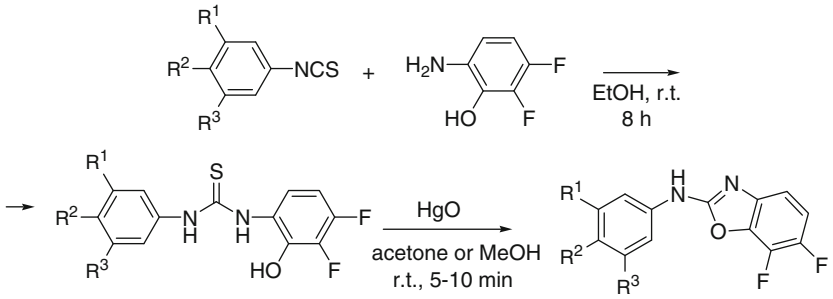


1.1.2.3 Synthesis of Benzoxazoles with Fluorinated Benzene Ring

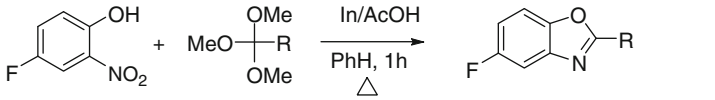
Fluorine-containing *ortho*-aminophenols or their precursors are commonly used for the preparation of fluorinated benzoxazoles. For example, F- and CF_3-containing *ortho*-aminophenols were cyclized by potassium xanthogenate to give 2-mercaptobenzoxazoles [51].



Difluoro-*ortho*-aminophenols in reaction with aryl isothiocyanates gave the corresponding difluoro-substituted 2-(phenylamino)benzoxazoles [52].

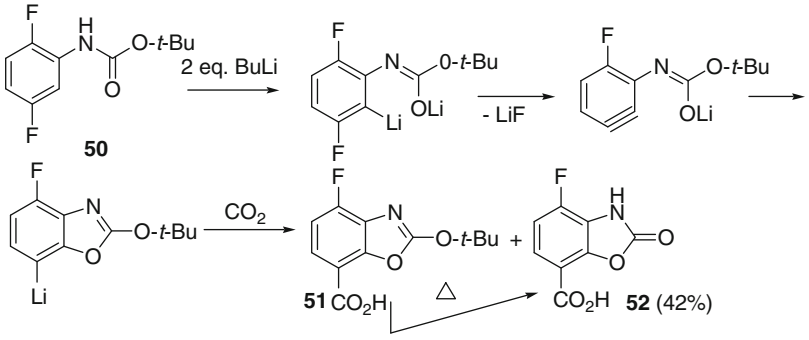


O*rtho*-nitrophenols can be used instead of *ortho*-aminophenols [53]. One-pot reduction-triggered heterocyclizations of 2-nitrophenols leads to benzoxazoles. For example, 2-nitrophenols reacted with orthoesters using indium/AcOH system in benzene at reflux to give the corresponding benzoxazoles in excellent yields within 1 h.



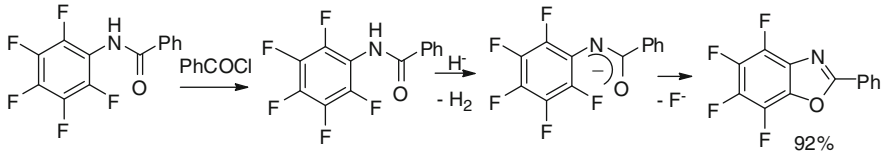
R=H (50%), Me (70%), Ph (92%)

Original method of benzoxazole synthesis starting from 2,5-difluoroaniline is based on the aryne mechanism [54]. Boc-protected difluoroaniline **50** undergoes base-induced aryne formation via *ortho* directed lithiation. Subsequent intramolecular cyclization produced a mixture of benzoxazole derivatives **51** and **52**, which could be converted into **52** exclusively by heating.

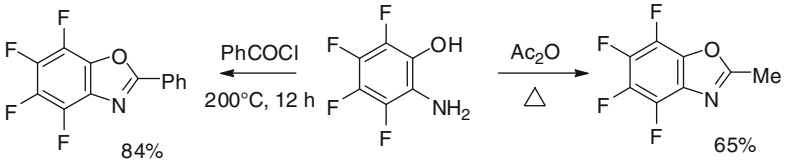


The use of perfluoroanilines for the synthesis of benzoxazoles having fully fluorinated benzene ring was demonstrated [55]. Pentafluoroaniline has amine nitrogen

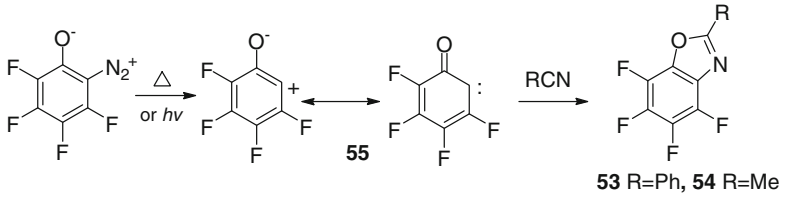
atom much less nucleophilic than ordinary anilines. Nevertheless, corresponding amides can be prepared by acylation with various acyl halides in the presence of pyridine or aqueous alkali generally in a good yield. The carbonyl oxygen of these amides acts as internal nucleophile at the cyclization step. Upon reflux in the presence of sodium hydride in DMF such benzamide gave strongly fluorescent 4,5,6,7-tetrafluoro-2-phenylbenzoxazole, presumably by the nucleophilic substitution of the *ortho*-fluorine.



Tetrafluorobenzoxazoles may also be obtained from 2-aminotetrafluorophenol and benzoyl chloride or acetic anhydride [55].



Thermal decomposition of 2-diazotetrafluorobenzene 1-oxide in benzonitrile or acetonitrile yields the corresponding 4,5,6,7-tetrafluorobenzoxazoles **53, 54**. The formation of the intermediate **55** under thermal conditions is confirmed by decomposition of the diazooxide in the presence of dipolarophiles [56].

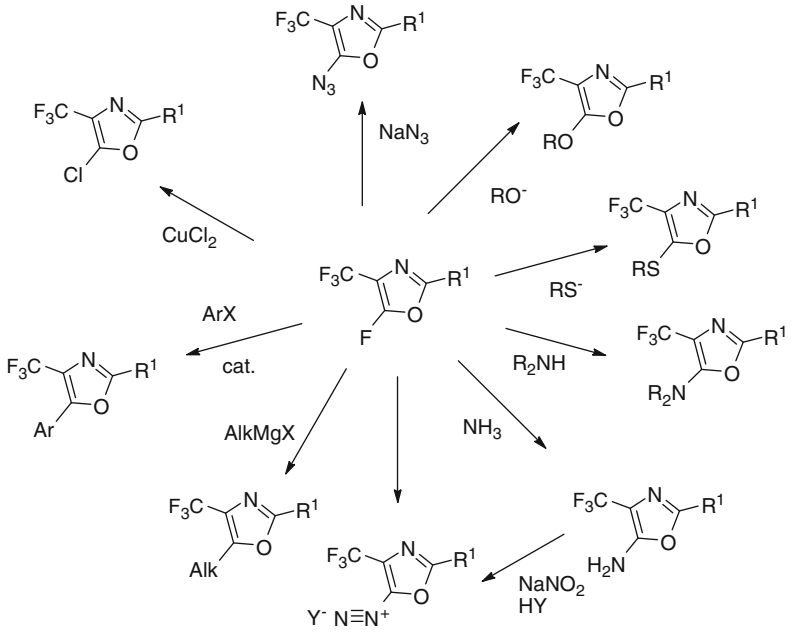


1.2 Chemical Properties

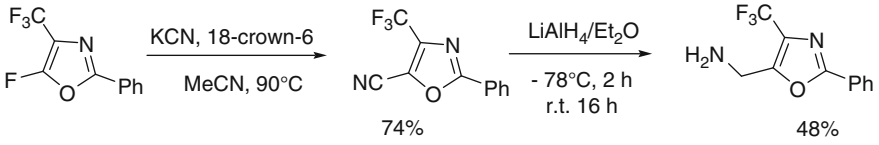
1.2.1 Chemical Properties of Fluorinated Oxazoles and Benzoxazoles

The 5-fluoro-4-(trifluoromethyl)oxazoles are able to participate in nucleophilic substitution of fluorine by a wide range of various nucleophiles. CF_3 group being electron-withdrawing substituent facilitates nucleophilic substitution in position 5

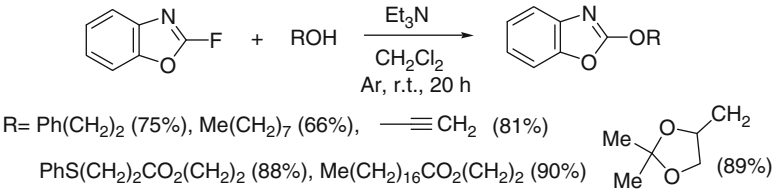
whereas usually nucleophilic substitution proceeds more easily in position 2 of 1,3-azoles [16, 17].



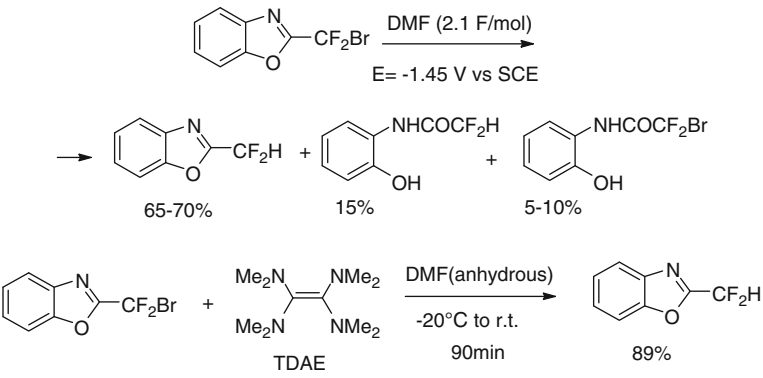
5-Aminomethyl-4-trifluoromethyl-2-phenyloxazole was obtained by reaction of 5-fluoro-4-(trifluoromethyl)oxazole with cyanide anion followed by reduction with $LiAlH_4$ [57].



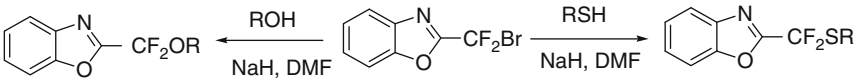
It was also found that 2-fluorobenzoxazole reacted readily with various primary alcohols in the presence of triethylamine to give the corresponding 2-alkyloxybenzoxazoles in good yields. This reaction provides a convenient method for the preparation of 2-alkyloxybenzoxazoles under mild conditions [1].

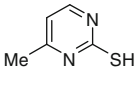
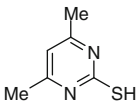
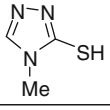
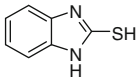


The electrochemical reduction of a series of bromodifluoromethyl benzoxazoles was used to prepare new fluorine-containing compounds which are active against HIV [58]. Tetrakis(dimethylamino)ethylene was also found to be an efficient reductant for this aim [59].



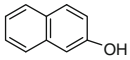
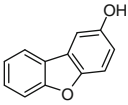
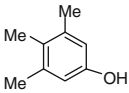
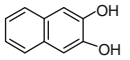
The displacement of bromine atom of the CF_2Br group does not occur by a simple S_N2 mechanism due to the presence of the alpha fluorine atoms. Instead, it proceeds by $S_{RN}1$ mechanism involving a SET chain process. Thus, the reaction of the CF_2Br group is limited to nucleophiles that can react by such $S_{RN}1$ mechanism, for example, substitution with thiols gave the corresponding sulfides. It was found that sodium phenolate reacts with CF_2Br much more slowly than sodium benzenethiolate; however, after 24 h at room temperature, the reaction was complete, and the desired product was isolated in 70 % yield.



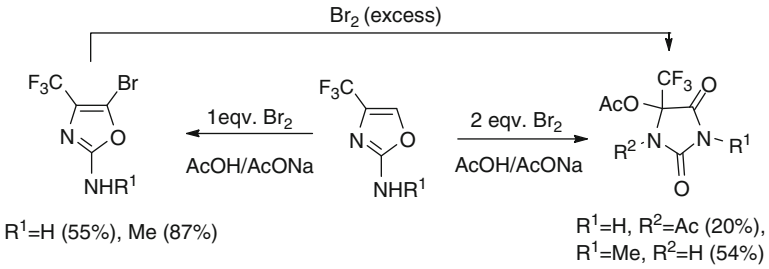
RXH	Yield, %	RXH	Yield, %	RXH	Yield, %
	84		62		76
	82		74		65
	51		72		59

(continued)

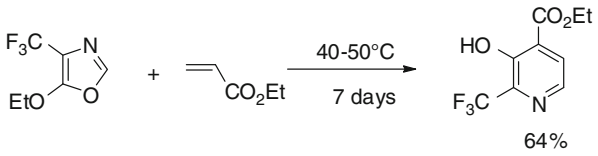
(continued)

RXH	Yield, %	RXH	Yield, %	RXH	Yield, %
PhSH	86	PhOH	70		42
	44		47		28

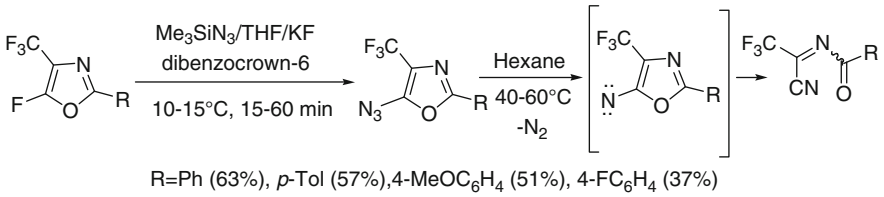
All the transformations of fluorinated oxazoles and benzoxazoles presented above were connected with the nucleophilic substitution of fluoride or halide. However it is a whole series of changes stipulated by substitution, opening, transformation and recyclyzation reactions of heterocyclic ring. Thus, bromination of 2-amino-4-trifluoromethyloxazoles in acetic acid gave initially 5-bromooxazoles, which were further transformed to 5-acetoxyhydantoines. The rearrangement took place mainly during 5-halogenation of the oxazoles when one equivalent bromine was used and proceeded in high yield with two equivalent bromine [60].



The use of the CF_3-substituted oxazole as an aza-diene for a Diels-Alder reaction was briefly examined. Thus, prolonged heating of the mixture of 5-ethoxy-4-trifluoromethyloxazole and an excess of acrylic acid afforded the CF_3-substituted pyridine derivative in reasonable yield [61]. However, cycloaddition with other olefins, such as ethyl acrylate, N-phenylmaleimide, 2,5-dihydrofuran, maleic anhydride, and 2-buten-4-olide did not take place to any appreciable extent presumably because of the deactivation of the oxazole ring by a strongly electron-withdrawing CF_3 group.

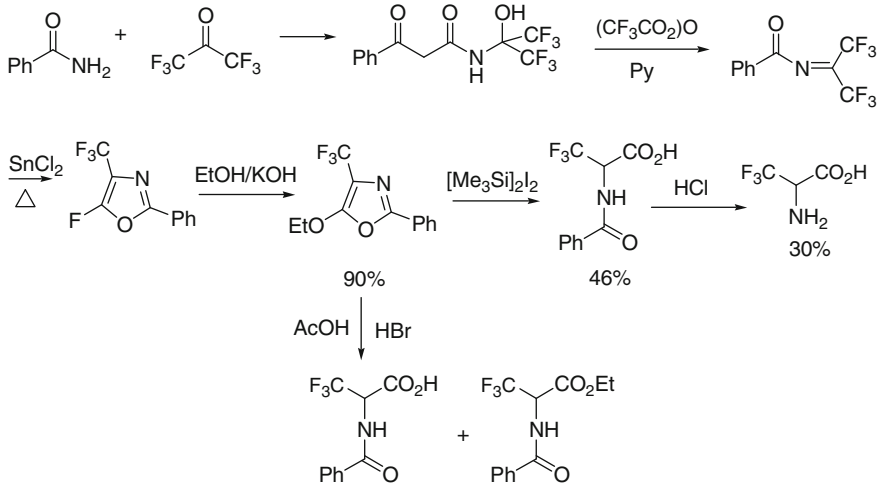


5-Azido-4-trifluoromethyloxazoles are thermolabile molecules and decomposed already at room temperature to give 4-cyano-4-trifluoromethyl-1-oxa-3-azabuta-1,3-diene [18, 62].



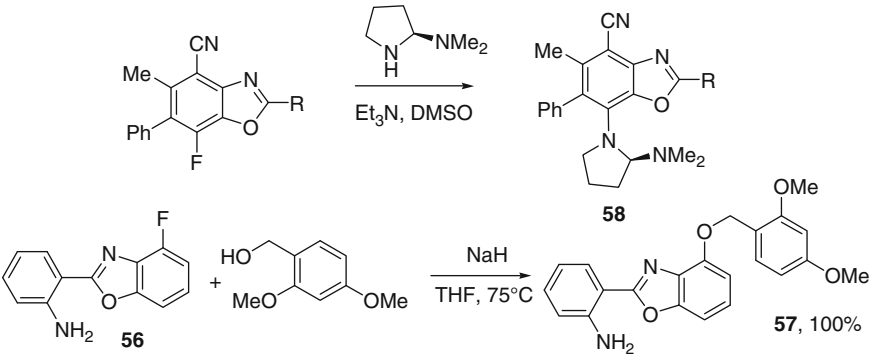
R=Ph (63%), *p*-Tol (57%),4-MeOC$_6$H$_4$ (51%), 4-FC$_6$H$_4$ (37%)

The opening of the fluorine-substituted oxazoles may be used for the synthesis of some important fluorinated compounds. Thus, a new synthesis of 3,3,3-trifluoroalanine starting from hexafluoroacetone is described.



1.2.2 Chemical Properties of Fluorinated Benzoxazoles

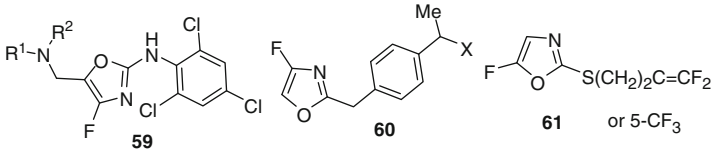
Direct S_NAr substitution using non-activated aryl fluorides can be viewed as an acceptable strategy affording from moderate to excellent yields of the substituted product [63]. However, there are no earlier data of direct S_NAr on benzoxazoles with any substitution at any position of the benzene ring, probably because of the fact that benzoxazoles can by readily undergo ring-opening under basic conditions to afford the corresponding amidophenol precursors [64]. However, recently several examples of nucleophilic fluorine substitution in the benzene ring of fluorobenzoxazoles were found. Thus, the interaction of 4-fluorobenzoxazole **58** with 2,4-dimethoxybenzylalcohol in the presence of NaH gave the product of substitution **57** in quantitative yield [65]. Nucleophilic substitution was used also for the synthesis of potent inhibitor of *Candida* species **57** [66, 67].



1.3 Applications

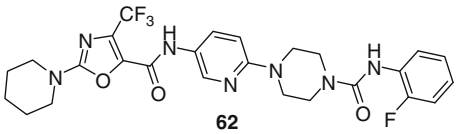
Some of 4-fluorooxazole derivatives exhibited high biological activity and represented as potent drug. Thus, the pharmaceutical compositions containing 2-amino-4-fluorooxazoles derivatives (for example, **59**) are antagonists of the corticotrophin releasing factor receptor ("CRF receptor") and are used for the treatment of depression, anxiety, affective disorders, feeding disorders, post-traumatic stress disorder, headache, drug addiction, inflammatory disorders, drug or alcohol withdrawal symptoms and other conditions the treatment of which can be effected by the antagonism of CRF-1 receptor [68].

(4-Fluorooxazol-2-yl)phenyethyl derivatives (**60**) are useful in the treatment of pathologies depending on the chemotactic activation of neutrophils and monocytes induced by the fraction C5a of the complement. In particular, the compounds of the invention are useful in the treatment of autoimmune hemolytic anemia, psoriasis, bullous pemphigoid, rheumatoid arthritis, ulcerative colitis, acute respiratory distress syndrome, idiopathic fibrosis, glomerulonephritis, and in prevention and treatment of injury caused by ischemia and reperfusion [69]. The 5-fluoro(trifluoromethyl)-2-mercaptooxazole derivatives (**61**) and compositions containing them have nematicidal, insecticidal and acaricidal activity [70].



Oxazole derivative **62** and its pharmaceutical compositions are a novel diacylglycerol acetyltransferase ("DGAT") inhibitors which are used for treating or

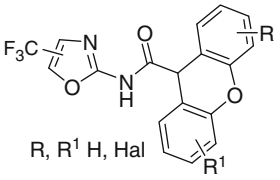
preventing a cardiovascular disease, a metabolic disorder, obesity-related disorder, diabetes, dyslipidemia, a diabetic complication, impaired glucose tolerance or impaired fasting glucose [71].

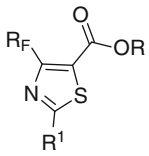


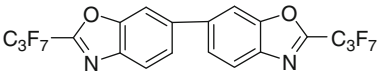
62

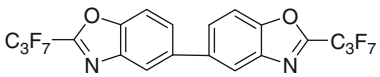
Fluorinated 9*H*-xanthene-9-carboxylic acid oxazol-2-ylamides have been used as pharmacological tools for the study of the physiological roles mediated by mGlu1 receptors [13] and for treating a disease or a condition selected from the group of Alzheimer's disease, hereditary cerebral hemorrhage with amyloidosis, cerebral amyloid angiopathy, a prion-meditated disease, inclusion body myositis, stroke, multiple sclerosis and Down's Syndrome [72]

Derivatives of 2-substituted perfluoroalkyl-5-oxazolecarboxylic acid have been found effective in reducing herbicidal injury to crop plants caused by thiocarbamate and acetanilide herbicides, and especially in reducing herbicidal injury to rice, sorghum or wheat corps, especially rice and sorghum, caused by triallate, alachlor and butachlor herbicides [73]. 2,2′-Bis(heptafluoropro pyl)-5,5′- [74] and −6,6′-bibenzoxazoles [75] are suitable for use as antiplasticizers.

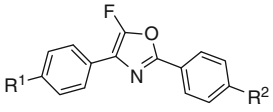


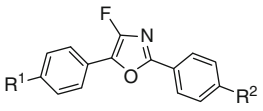






The 4- and 5-fluorooxazole derivatives have also the potential technical application. Thus, it has been found that some fluorinated oxazoles, even when admixed in small amount, have a favorable effect on the properties of liquid-crystalline mixtures [76].





2 Fluoro-, Fluoroalkylthiazoles, selenazoles, and benzothiazoles

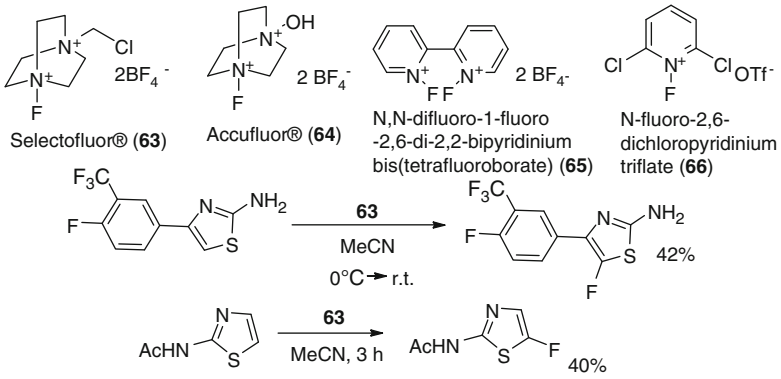
2.1 Method of Synthesis Fluoro- and Fluoro-alkylthiazoles and Selenazoles

Similarly to synthesis of fluorinated oxazoles the methods of preparation of fluorine-containing thiazoles may be subdivided into two synthetic approaches: incorporation of fluorine atom or fluoroalkyl groups in thiazole structure, and the synthesis based on fluorinated building blocks.

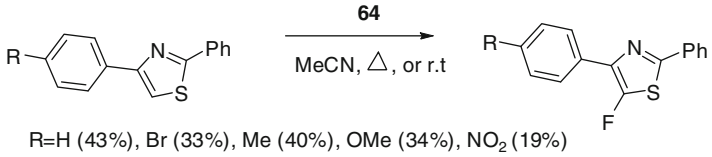
2.1.1 The Synthesis of Fluorinated Thiazoles and -Selenazoles

2.1.1.1 Incorporation of Fluorine Groyps into Thiazoles and Selenazoles

Direct electrophilic introduction of fluorine atom into the thiazole ring is a widely used approach. Various commercially available fluorinating agents can be used for this aim [77]. Thus, the fluorination with the Selectofluor® (**63**) of 3-amino-4-aryl- [78] and 2-acetylaminothiazoles [79] proceeds in 5-positions in the moderate yields.

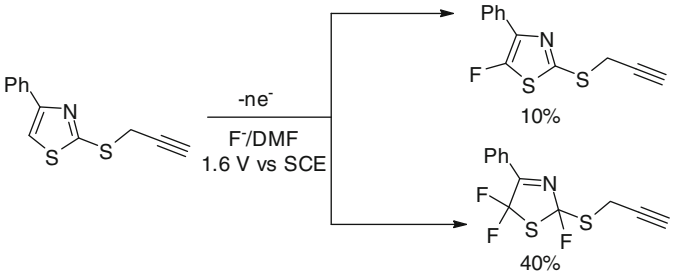


However, Selectfluor® was not as effective as Accufluor® (**64**) for the fluorination of 2,4-diarylthiazoles since it gave admixture of the 5-chlorothiazole that was difficult to remove [77]. Fluorination of this diaryl system with **64** occurred selectively at the 5-position of the thiazole; however, as the reaction could not be driven to completion, the yields were low to moderate (19–43 %) [77]. Other N–F reagents were also examined to improve the effectiveness of fluorination reaction and eliminate the formation of the chlorinated byproducts. Compared to **63**, only a small amount of fluorination occurred when diarylthiazole was reacted under similar conditions with N,N-difluoro-2,2-bipyridinium bis(tetrafluoroborate) (**65**) or with 1-fluoro-2,6-dichloropyridinium triflate (**66**) [77].

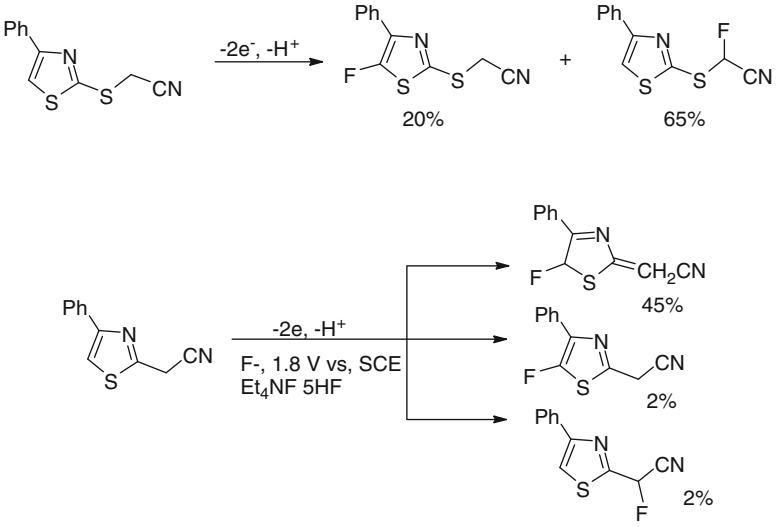


R=H (43%), Br (33%), Me (40%), OMe (34%), NO_2 (19%)

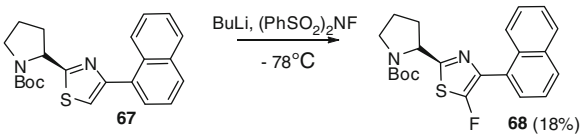
The anodic fluorination of 2-thiazolyl sulfides was successfully carried out to provide the corresponding 5-fluorothiazole and 2,5,5-trifluorothiazoline derivatives [80].



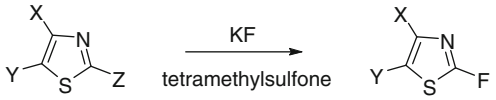
The selectivity of anodic fluorination changed in case of electron-withdrawing substituents. For example, 2-thiazolylcyanomethyl sulfide afforded 5-fluorothiazole and the product of fluorination on methylene group. Electrochemical fluorination of (4-arylthiazol-2-yl)acetonitriles afforded the corresponding (4-aryl-5-fluoro-5*H*-thiazol-2-ylidene)acetonitriles as main products in addition to (4-aryl-5-fluorothiazol-2-yl)acetonitriles and (4-arylthiazol-2-yl)fluoroacetonitriles [81].



Deprotonation of naphthyl thiazole **67** with BuLi followed by treatment with $(PhSO_2)_2NF$ yielded the fluorinated derivative **68** in low yield [82]:

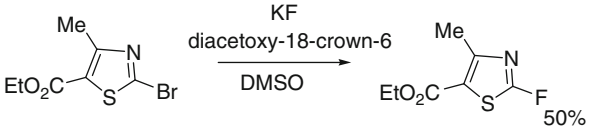


Nucleophilic substitution is an alternative method of fluorine atom incorporation into the thiazole ring. Thus, displacement of the 2-halogen atoms in polyhalogenated thiazoles by fluorine was accomplished utilizing dry potassium fluoride in tetrametylenesulfone at 130 °C to yield 2-fluoro derivatives [83]:

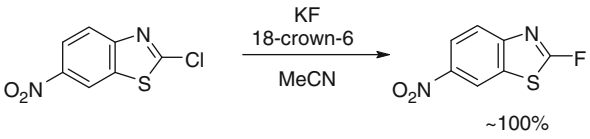


X=Y=Z=Cl (57%); X=Y=Z=Br (18%); X=Cl, Y=Z=Br (35%)

In case of reaction of ethyl 2-bromo-4-methylthiazole-5-carboxylates with potassium fluoride the substitution was facilitated by crown ether [84].

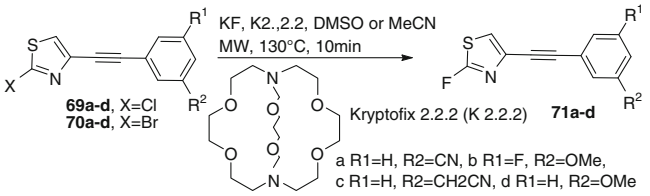


2-Fluoro-6-nitrobenzothiazole was prepared in almost quantitative yield by reaction of 2-chloro compound with anhydrous potassium fluoride in MeCN in the presence of 18-crown-6 [85].

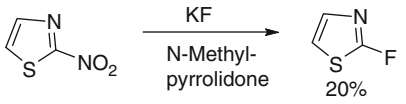


By treating bromides **70a–d** with a potassium fluoride-Kryptofix 2.2.2 (K 2.2.2) complex in DMSO under microwave irradiation (30 W, 130 °C, 8–15 min), the respective 2-fluoro compounds **71a–d** were obtained in 24–43 % yield. When the 2-chloro precursors **69a–d** were treated similarly, the yields of fluorination products were dramatically improved, reaching 78 % in the case of **71c**. By contrast, only negligible product amount (yield < 5 %) was detected when the iodo precursor was submitted to nucleophilic fluorination [86, 87]. These results confirmed

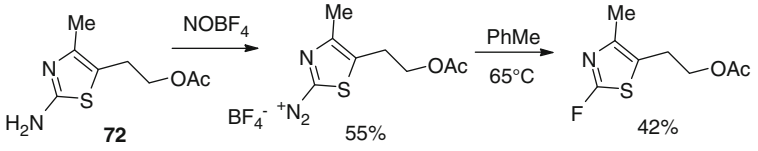
previous observations on leaving group ability in the nucleophilic fluorination of simpler 2-halothiazoles [87].

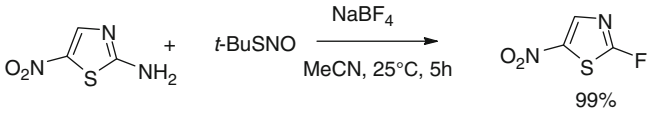


Nitro group can be also used as leaving group, thus, 2-fluorothiazole has been synthesized from the corresponding nitro derivatives by treatment with fluoride ion in N-methyl-2-pyrrolidone, however, the yield was only 20 % [88]:

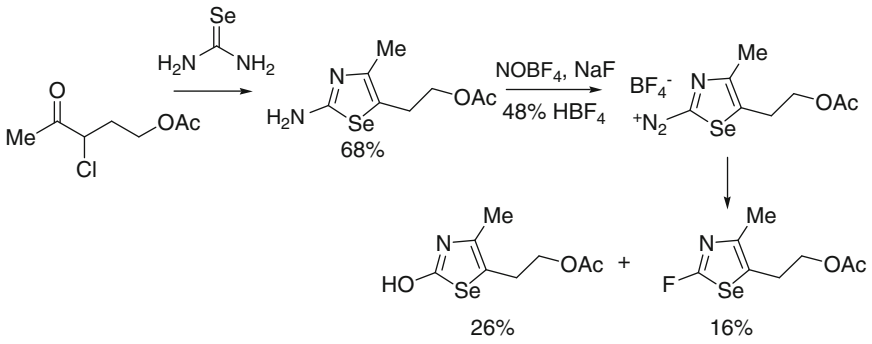


Diazotization of 2-aminothiazole **72** with $NOBF_4$ followed by pyrolysis of diazonium tetrafluoroborate gave 5-acetoxy-2-fluoro-4-methylthiazole [89] in 42 % yield. Similarly, 2-amino-5-nitrothiazole reacted readily with *t*-butyl thionitrite or *t*-butyl thionitrate in the presence of sodium tetrafluoroborate to afford the corresponding fluorine derivative in good yield [90, 91].



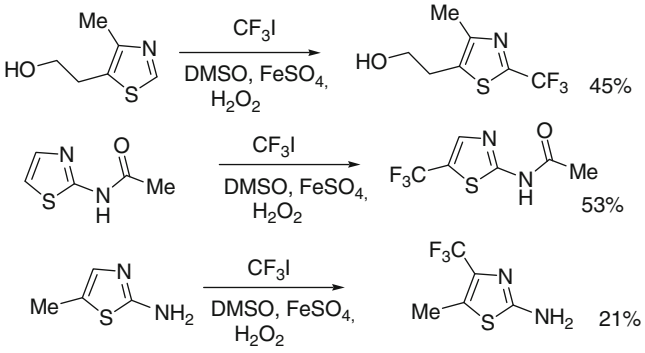


In contrast to oxazoles and thiazoles the information about fluoroselenazoles is almost absent. There is only one publication dealing with these compounds [92]. Diazotization of 5-(acetoxyethyl)-2-amino-4-methylselenazole with nitrosonium borofluoride in the presence of NaF in HF solution furnishes the corresponding diazoselenazole and the 2-hydroxycompound. Despite low yields, this was the first example of Schiemann reaction used successfully for 2-aminoselenazoles. Earlier it was reported [93] that Schiemann reaction of 2-aminoselenazoles had failed completely, elemental selenium being obtained as only isolatable product.

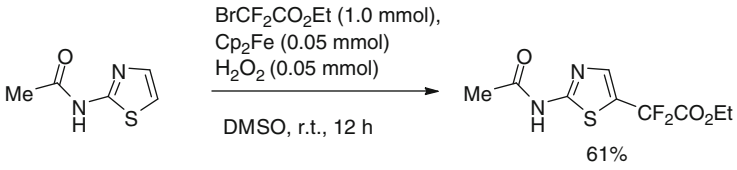


2.1.1.2 Syntheses of Fluoroalkylated Thiazoles

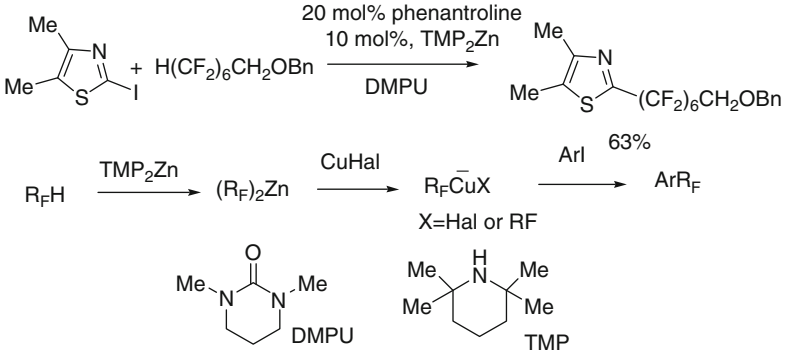
A radical trifluoromethylation is widely used for incorporation of CF_3 group into thiazole ring. This is simple and therefore promising procedure as an industrial process. Trifluoromethyl radical has electrophilic nature and can be readily generated from various sources. For example, the reaction of thiazoles with CF_3I is carried out in the presence of Fe (II), H_2O_2 and DMSO under mild conditions [7]. In this case usual orientation of electrophilic substitution was observed.



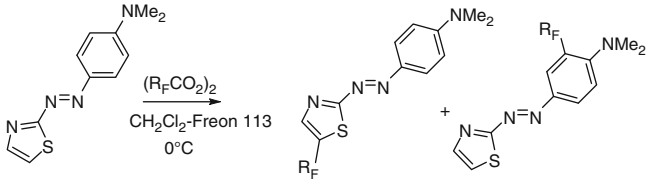
Ethoxycarbonyldifluoromethyl radical generated from $BrCF_2CO_2Et$ using the Fenton reagent in DMSO efficiently reacted with various aromatic compounds including thiazoles [8].



Readily available 1*H*-perfluoroalkanes can also be used for radical alkylation. This method employs, for example, thiazolyl iodide and 1*H*-perfluoroalkane reagents, DMPU solvent, TMP_2Zn base, and a copper chloride/phenanthroline catalyst [8]. The reaction mechanism includes deprotonation of 1H-perfluoroalkanes with TMP_2Zn to afford bis(perfluoroalkyl)zinc species. Subsequent transmetallation with copper halide produces a mixture of anionic Cu species that reacts with aryl iodides (including thiazoles), either directly or via a neutral perfluoroalkyl compound, to give the coupling product.



Perfluoroalkylated thiazole azo compounds were prepared by the reaction with bis(perfluoroalkanoyl)peroxides. Thus, the reaction of 4-(2-thiazolylazo)-*N*,*N*-dimethylaniline with bis(trifluoroacetyl)peroxide gave an inseparable mixture of 5-trifluoromethyl- and 2-trifluoromethyl-substituted products in 6:4 ratio in 9 % yield [94].

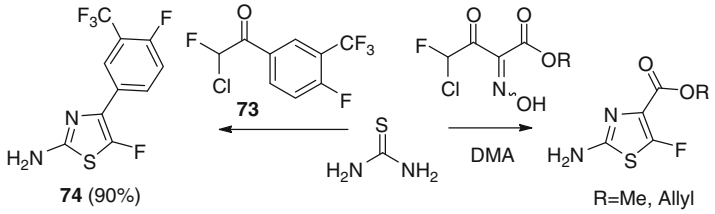


2.1.2 Syntheses of Fluorinated Thiazoles and Benzothiazoles Using Fluorinated Building Blocks

2.1.2.1 Syntheses of the Fluorothiazoles

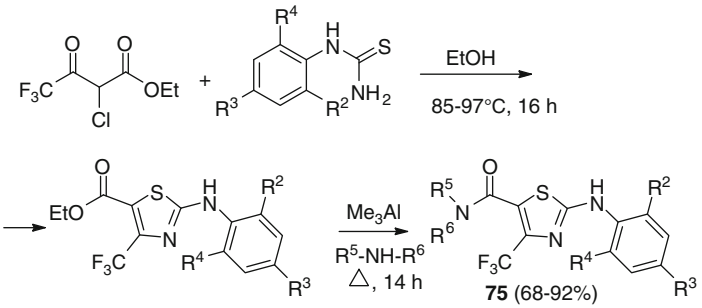
Condensation of α-fluoro-α-chlorocarbonyl compounds with thiourea is the only known approach to the synthesis of 2-amino-5-fluorothiazole derivatives [82, 95, 96]. This methodology was used for the synthesis of the precursors of cephalosporin derivatives containing the fluorothiazole fragment [95, 96]. Analogously the

interaction of the ketone **73** with thiourea gives 4-aryl-substituted 5-fluorothiazole **74** in high yield [82].

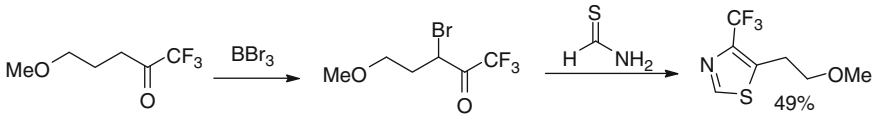


2.1.2.2 Syntheses of the Fluoroalkyl-thiazoles and -benzothiazoles

The fluoroalkylthiazoles and -benzothiazoles generally are synthesized from fluorine-containing acyclic fragments. 2-Arylamino-5-(N,N-dialkylcarbamoyl)-4-(trifluoromethyl)thiazoles **75** represent a novel class of high-affinity corticotrophin releasing factor-1 receptor (CRF_1R) antagonists which are prepared in three steps from commercially available starting materials in good overall yields. The corresponding aminothiazole was assembled by condensation of ethyl 2-chloro-4,4,4-trifluoro-3-oxobutyrates with aryl thioureas [97].

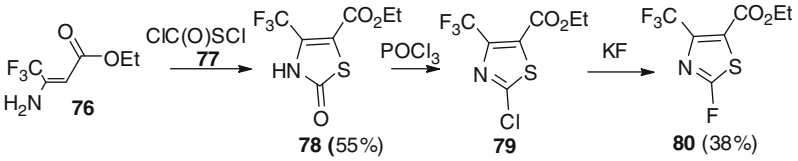


Thioformamide is utilized for the synthesis of 2-unsubstituted 5-trifluoromethylthiazoles. Thus, 5-methoxy-1,1,1-trifluoro-2-pentanone gave 5-(methoxyethyl)-4-trifluoromethylthiazole in reasonable total yield on bromination with BBr_3 followed by treatment with thioformamide [89].

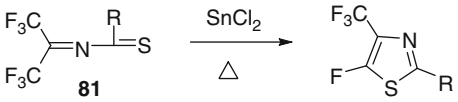


The reaction of ethyl 3-amino-4,4,4-trifluoroacrylate (**76**) with chlorocarbonylsulfenyl chloride (**77**) afforded 2,3-dihydro-2-oxo-3-trifluoromethyl-5-thiazolecarboxylate (**78**). The 2-chloro derivative **79** was obtained by treatment of

78 with $POCl_3$. Nucleophilic displacement of chlorine with KF gives ethyl 2-fluoro-4-(trifluoromethyl)-5-thiazolecarboxylate (**80**) in moderate yield [98].

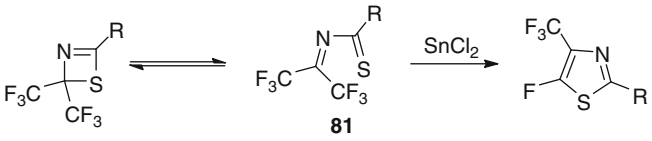


The methods allowing to synthesize the thiazoles containing simultaneously fluorine atom and the trifluoromethyl group are known. Thus, heterodienes of type [$(CF_3)_2$=N-C(R^1)=S] (**81**) react with tin(II) compounds [$SnCl_2$, stannocene etc.] to give [4 + 1] cycloadducts and finally to give, by thermolysis, the corresponding thiazoles under the mechanism described above for the oxazole [17, 21].

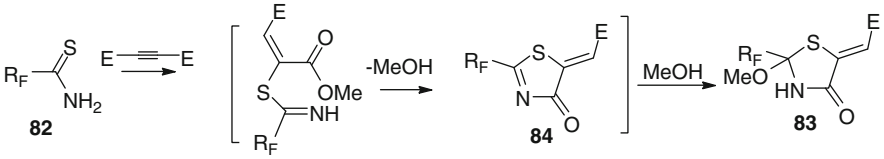


X=S R=Ph (51%), *p*-Me-C_6H_4 (60%)

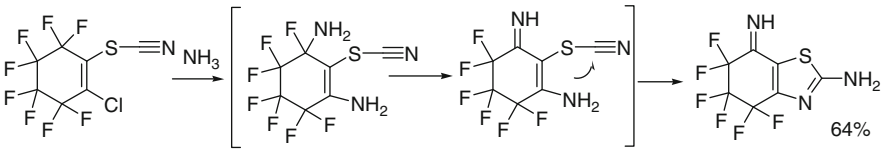
4,4-Bis(trifluoromethyl)-2*H*-1,3-thiazete undergoes tautomerization into 4,4-bis(trifluoromethyl)-1-thia-3-aza-1,3-butadiene **81** at 80 °C. In presence of equimolecular amount of anhydrous $SnCl_2$ **81** gave 2-aryl-5-fluoro-4-trifluoromethylthiazole by formal removal of F_2 [16].



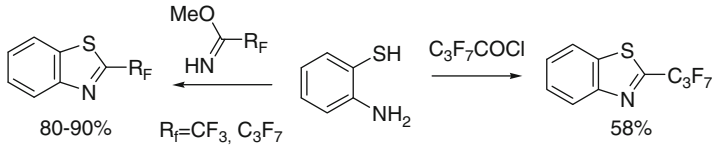
Primary thioamides (**82**) easily react with dimethyl acetylenedicarboxylate (DMAD) to give 2-methoxy-5-methoxycarbonylmethylene-2-polyfluoroalkyl-1,3-thiazolidin-4-ones (**83**). The formation of these compounds is a result of methanol addition to the C=N bond of intermediates **84**. The increasing activity of the C=N bond in compounds **84** is induced by polyfluoroalkyl substituent [99].



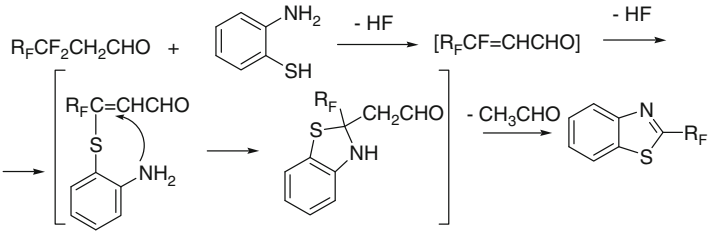
The reaction of ammonia with 2-chloroperfluoro-1-cyclohexene-1-thiocyante leads to 2-amino-7-iminoperfluoro-4,5,6-dihydrobenzo-1,3-thiazole due to intramolecular Thorpe type heterocyclization [100].



2-Perfluoroalkylbenzothiazoles can be synthesized from *ortho-aminothiophenols* and various perfluoroalkyl-containing carboxylic acid derivatives such as chlorides, anhydrides, and imidates [101]. For example, S-copper salt of *ortho-aminobenzenethiol* reacted with perfluorobutyryl chloride in benzene to afford 58 % yield of 2-perfluoropropylbenzothiazole [101].

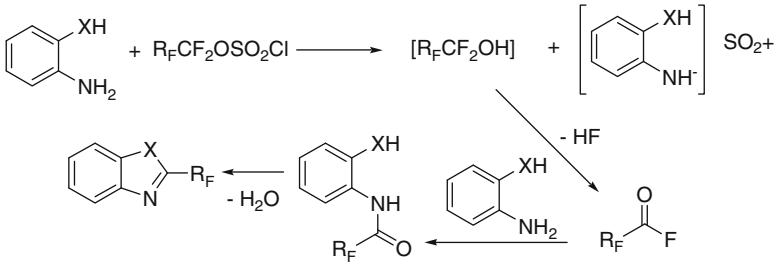


The original method for the preparation of 2-perfluoroalkyl benzothiazoles by reaction of α-perfluoroalkyl aldehydes with 2-aminobenzenethiole includes dehydrofluorination, Michael addition-cyclization followed by elimination of acetaldehyde [102].



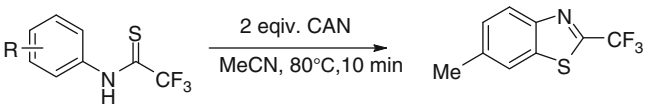
CF_3 (48%), CF_2Cl (50%), CF_2Br (46%), $Cl(CF_2)_3$ (52%), $CF_3(CF_2)_4$ (53%)

Perfluoroalkylated chlorosulfates react readily with the appropriate 2-mercaptoanilines at ambient temperatures. A mixture of heterocyclic compound and its precursor, anilide, is formed as the reaction products [103].

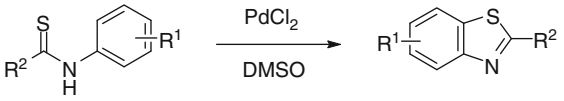


R_F=C_7F_{15} (68%), $(CF_2)_5OCF_2(CF_3)$ (46%)

Trifluoromethylated thiobenzanilides are converted efficiently to 2-trifluoromethylbenzothiazoles *via* intramolecular oxidative cyclization under CAN/$NaHCO_3$ oxidation [104]. The optimized reaction conditions were also evaluated for a range of substituted precursors in the presence of 5 mol % $PdCl_2$ [57].

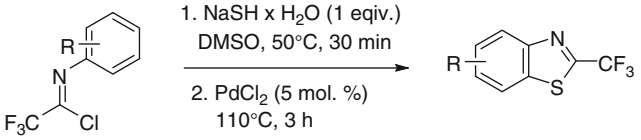


R=H (73%), *p*-F (83%), *p*-Cl (76%), *p*-CF_3 (65%), *p*-CO_2Et (66%), *p*-NO_2 (35%), *p*-CN (62%), 2-naphtyl (86%), *o*-Me (78%), R=HCF_2Cl instead of CF_3 (81%), R=HCF_2CF_2 instead of CF_3 (74%)



R^2=CF_3, R^1=*p*-I (83%), *p*-CO_2Et (70%), *p*-CN (60%), *p*-NO_2 (55%), *o*-OMe (78%), *m*-CF_3 (R=5-CF_3) (61%), R_1=H, R^2=C_2F_5 (61%), R^2=CF_2Cl (16%)

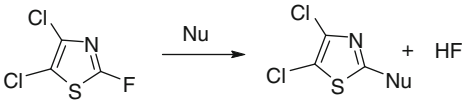
An efficient one-pot method for the synthesis of 2-trifluoromethylbenzothiazoles by the treatment of trifluoromethylimidoyl chlorides with sodium hydrosulfide using $PdCl_2$ as the catalyst is described. The reaction proceeds in DMSO via thiolation/C-H bond functionalization/C-S bond formation in moderate to high yields with good functional group tolerance [57].



R=H (72%), *p*-OMe (82%), *p*-Me (71%), *p*-NMe_2 (66%), *p*-F (69%), *p*-Cl (77%), *p*-Br (67%), *p*-I (43%), *p*-CO_2Et (51%), *o*-F (65%), *o*-Cl (65%), *o*-Br (60%), *o*-I (62%), *o*-OMe (74%), naphthyl (69%), *m*-OMe (R=5-OMe) (78%), *m*-Me (R=5-Me) (74%), *m*-Cl (R=5-Cl) (66%)

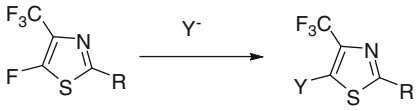
2.2 *Chemical Properties*

Chemical properties of fluorine-containing thiazoles are represented only by reactions of nucleophilic substitution. Thus, nucleophilic displacement of fluoride ion in 4,5-dichloro-2-fluorothiazole by cyano, hydroxy and methoxy anions as well as by diethylamine produced the respective 2-substituted dichlorothiazoles [83].



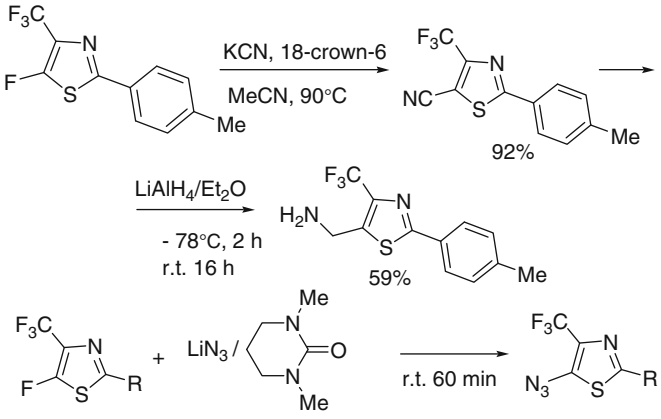
Nu = OH^- (69%), OMe^- (85%), CN^- (27%), $HNEt_2$ (80%)

2-Substituted thiazoles generally are more active toward nucleophilic substitution than 5-substituted derivatives. However, the presence of electron-withdrawing substituent near them in 4-trifluoromethyl-5-fluorothiazoles facilitates the process of nucleophilic substitution of fluorine atom [21].



Y=H (70%), CN (90%), SEt (82%), NEt_2 (79%)

5-Aminomethyl-2-*p*-tolyl-4-trifluoromethylthiazole was obtained from the corresponding 5-fluoro-4-trifluoromethylthiazole by the reaction with potassium cyanide followed by the $LiAlH_4$ reduction [105]. 5-Azido-4-trifluoromethylthiazoles are obtained from 5-fluoro-4-trifluoromethylthiazoles [105].

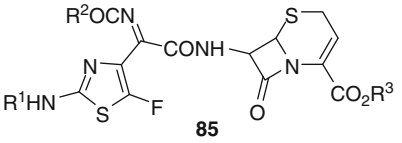


R= Ph (74%), *p*-Tol (97%), 4-ClC_6H_4 (92%), 2-Furyl (80%), 2-Thienyl (64%)

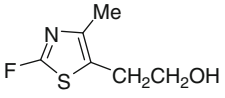
2.3 *Applications*

The fluoro- and fluoroalkyl-substituted thiazoles and their derivatives can be used as potent agents in the various fields of medicine, biology, and agriculture. Thus, the [^{18}F] 2-fluoro-1,3-thiazolyl moiety constitutes a new and easily-labeled structural motif for prospective molecular imaging radiotracers [86]. This novel ^{18}F-labeled thiazole

derivative (see compound **71**) is useful for imaging of metabotrophic glutamate subtype 5 receptors (mGlu5) in living mammalian brain [105]. 3-Cephem derivatives **85** containing 5-fluorothizole fragments are active remedies against Gram-negative bacterium (*Escherichia coli, Klebsiella, Proteus vulgaris*) [19, 20, 34]. The less complex compound **86** also showed antibacterial action against two strains of *Escherichia coli* [89].

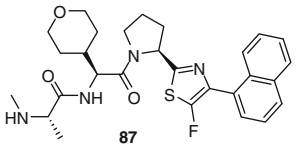


85

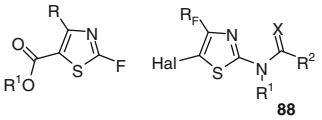


86

2-Amino-5-fluorothiazole represents the activator glucokinase which increases the metabolism of glucose and is used for treatment diabetes II [105]. In addition 5-fluoro substitution of an aminothiazole moiety within a series of thrombopoietin receptor agonists leads to potent agents with an improved hepatic safety profile in rodent toxicology studies [78]. A series of inhibitor of apoptosis antagonists is based on thiazole amide isosteres. These compounds were tested for binding to the XIAP-BIR3 and ML-IAP BIR using a fluorescence polarization assay. These compounds **87** containing the 5-fluorothiazole fragment are the most potent [82]. 2,4-Disubstituted thiazole-5-carboxylic acids have been found to reduce herbicidal injury of corn, rice and sorghum plants due to the application thereto of acetamide herbicides [106]. The 4-perfluoroalkylthiazole derivatives **88** have insecticidal and acaricidal activity [107].

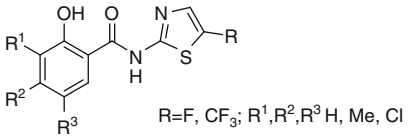


87



88

According to QSAR study of the wide range of compounds, 5-fluoro- and trifluoromethylthiazole derivatives are active against hepatitis B virus replication [3].



References

1. Watanabe Y, Mukaiyama T (1978) An efficient phosphorylation method by the activation of alcohol. Chem Lett 349–352
2. Uchibori Y, Umeno M, Yoshiokat H (1992) Nucleophilic fluorination of chlorinated N-heterocycles with tetrabutylphosphonium hydrogen fluoride and dihydrogen trifluoride. Heterocycles 34:1507–1509

3. Romero FA, Hwang I, Boger DL (2006) Delineation of a fundamental α-ketoheterocycle substituent effect for use in the design of enzyme inhibitors. J Am Chem Soc 128:14004–14006
4. Romero FA, Du W, Hwang I, Rayl TJ, Kimball FS, Leung D, Hoover HS, Apodaca RL, Breitenbucher JG, Cravatt BF, Boger DL (2007) Potent and selective α-ketoheterocycle-based inhibitors of the anandamide and oleamide catabolizing enzyme, fatty acid amide hydrolase. J Med Chem 50:1058–1068
5. Riyadh SM, Ishii H, Fuchigami T (2002) Electrolytic partial fluorination of organic compounds. Part 65: regioselective anodic difluorination of oxazolyl sulfides. Tetrahedron 58:9273–9278
6. Uraguchi D, Yamamoto K, Otsuka Y, Tokuhisa K, Yamakawa T (2008) Catalytic trifluoromethylation of uracil to 5-trifluoromethyluracil by use of CF_3I and its industrial applications. Appl Catal A 342:137–143
7. Kino T, Nagase Y, Uraguchi D, Yamamoto K, Otsuka Y, Tokuhisa T, Yamakawa T (2010) Trifluoromethylation of various aromatic compounds by CF_3I in the presence of Fe(II) compound, H_2O_2 and dimethylsulfoxide. J Fluorine Chem 131:98–105
8. Ohtsuka Y, Yamakawa T (2011) Direct ethoxycarbonyldifluoromethylation of aromatic compounds using Fenton reagent. Tetrahedron 67:2323–2331
9. Chen Q-Y, Wu S-W (1989) Methyl fluorosulphonyldifluoroacetate; a new trifluoromethylating agent. J Chem Soc Chem Commun 1989:705–706
10. DeMartino JK, Garfunkle J, Hochstatter DG, Cravatt BF, Boger DL (2008) Exploration of a fundamental substituent effect of α-ketoheterocycle enzyme inhibitors: potent and selective inhibitors of fatty acid amide hydrolase. Bioorg Med Chem Lett 18:5842–5846
11. Romero FA, Hwang I, Boger DL (2006) Delineation of a fundamental α-ketoheterocycle substituent effect for use in the design of enzyme inhibitors. J Am Chem Soc 128:14004–14005
12. Elguero J, Fruchier A, Jagerovic N, Werner A (1995) Trifluoromethyl and perfluoroalkyl derivatives of azoles. A review. Org Prep Proc Int 27:33–74 and references cited therein
13. Crank G, Foulis MJ (1971) Derivatives of 2-aminooxazoles showing antiinflammatory activity. J Med Chem 14:1075–1077
14. Vieira E, Huwyler J, Jolidon S, Knoflach F, Mutel V, Wichmann J (2009) Fluorinated 9H-xanthene-9-carboxylic acid oxazol-2-yl-amides as potent, orally available mGlu1 receptor enhancers. Bioorg Med Chem Lett 19:1666–1669
15. Burger K, Goth H (1981) Selektive Einfűrung von Fluor und Trifluormethyl Gruppen in Heterocyclische Systeme.1. Syntheses von 5-Fluor-4-trifluormethyl Oxazolen. J Fluorine Chem 17:585–589
16. Burger K, Geith K, Sewald N (1990) Űber das Synthese Potential Trifluormethyl-Substituirter Zinnheterocyclen. J Fluorine Chem 46:105–122
17. Burger K, Ottlinger R, Goth H, Firl J (1982) Zum Reaktionsverhalten von Trifluormethyl-Gruppen Synthese von 1,3-Azolen aus Trifluormethyl-substituierten Hetero-l,3-dienen. Chem Ber 115:2492–2507
18. Burger K, Hübl D, Gertitschke P (1985) Synthese von 3,3,3-trifluoralanin aus hexafluoraceton. J Fluorine Chem 27:327–332
19. Burger K, Geits K, Hübl D (1998) Über eine neue Methode zur positionsselektiven Einführung von Trifluormethyl-Gruppen in Heteroaromaten. 1. Synthesis von Trifluormethyl-substiuiierten 1,3-Azollen (Oxazole, Thiazole, Imidazole). Synthesis 189–194
20. Burger K, Geits K, Hübl D (1998) Über eine neue Methode zur positionsselektiven Einführung von Trifluormethyl-Gruppen in Heteroaromaten. 3. Lineare and angulare Verknűpfung von Ringsystemen sowi Herstellung anellierten trifluormethyl-substituierter Fűnfring-Heterocyclen. Synthesis 199–203
21. Ottlinger R, Burger K, Goth H (1978) Eine neue Strategie zur Synthese partiell fluorierter 1,3-Azole. Tetrahedron 50:5003–5006
22. Koshelev VM, Barsukov IN, Vasil'ev NA, Gontar AF (1989) Synthesis of perfluorinated oxazoles. Chem Heterocycl Compd 25(12):1418

23. Koshelev VM, Truskanova TD, Cherstkov VF, Romanov DV, Vasilirev NV (2005) Synthesis and properties of polyfluorinated oxazoles. Russ Chem Bull 54:1675–1679
24. Buchanan GL (1988) The Dakin–West reaction. Chem Soc Rev 17:91–109
25. Kawake M, Miyamae H, Kurihara T (1998) A general method for the preparation of 5-trifluoromrthyl oxazoles from α-amino acids. Chem Pharm Bull 46:749–756
26. Kawake M (1993) A facile one-pot synthesis of 5-trifluorumethyl oxazoles from N-alkyl-N-acylamino acids. Heterocycles 36:2441–2444
27. Cunan TT (1995) Implementation of the Dakin-West reaction for the preparation of a α-amino-pentafluoroethyl ketone. J Fluorine Chem 74:107–112
28. Padwa A, Carlsen PHJ, Tremper A (1978) Photochemical transformations of small-ring heterocyclic compounds. 99. 1,4-Substituent shifts in the photorearrangement of 2-hydroxymethyl-2H-azirine derivatives to N-vinylimjnes. J Am Chem Soc 100:4481–4490
29. Takeuchi H, Kitamura Y, Hayakawa S, Kikuhiko K (1989) Reactions of ß-azidostyrenes with halogenoacetic acids. A novel formation of oxazoles. J Chem Soc Chem Commun 1414–1415
30. Martín-Cantalejo Y, Sáez B, Soto J, Villa MJ, Brañab MF (2003) A new convergent synthesis of 4,4′-bispyridyl-5,5′-disubstituted-2,2-bisoxazoles and -bisthiazoles. Synthesis 2003:2211–2215
31. Martín-Cantalejo Y, Sáez B, Monterde MI, Murillo MT, Braña MF (2011) Synthesis and biological activity of new bispyridinium salts of 4,4′-bispyridyl-5, 5′-perfluoroalkyl-2,2′-bisoxazoles. Eur J Med Chem 46:5662–5667
32. Steglich W, Heininger H-U, Dworschak H, Weygand F (1967) Allgemeine Methode zur Darstellung von P-Perfluoralkyl-alaninen. Angew Chem 79:822
33. Shi G, Xu Y, Xu M (1991) A convenient synthesis of 5-ethoxy-4-(trifluoromethyl)-2-oxazolecarbonic acid and related trifluoromethyl substituted heterocyclic compounds. J Fluorine Chem 52:149–157
34. Wang Y, Zhu S (2000) A rhodium-catalyzed heterocycloaddition route to 5-fluoroalkyl substituted 1,3-oxazoles. J Fluorine Chem 103:139–144
35. Shi G, Xu Y, Xu M (1991) A convenient synthesis of 5-ethoxy-4-(trifluoromethyl)-2-oxazolecarbonic acid and related trifluoromethyl substituted heterocyclic compounds. J Fluorine Chem 52:149–152
36. Shi G, Xu Y (1989) Ethyl 3-trifluoro-2-diazo-propionate as a potentially useful CF_3-containing building block: preparation and $[Rh(OAc)_2]_2$-catalysed reaction with nitriles. J Chem Soc Chem Commun 1989:607–608
37. Höfle G, Steglich W (1971) Umwandlung von 4-Acyl-Δ^2- und 2-Acyl-Δ^3-oxazolonen-(5) in trisubstituierte Oxazole. Ein einfacher Zugang zu 3.3.3-Trifluor-alanin und 3.3.3-Trifluor-2-amino-propionyl-Derivaten. Chem Ber 104:1408–1419
38. Ang KH, Prager RH, Smith JA, Weber B, Williams CM (1995) The synthesis of oxazoles by thermolysis or photolysis of 2-acylisoxazol-5-ones. Tetrahedron Lett 37:675–678
39. Cunico RF, Kuan CP (1990) Oxazoles from ß-acyoxy-N, N-bis(trimethylsilyl)enamines. Tetrahedron Lett 31:1945–1948
40. Cunico RF, Kuan CP (1991) Synthesis of oxazoles from O-trimethylsilyl acyltrimethylsilane cyanohydrines. J Org Chem 57:3331–3336
41. Zhao F, Liu X, Qi R, Zhang-Negrerie D, Huang J, Du Y, Zhao K (2011) Synthesis of 2-(trifluoromethyl)oxazoles from β-monosubstituted enamines via $PhI(OCOCF_3)$ 2-mediated trifluoroacetoxylation and cyclization. J Org Chem 76:10338–10344
42. Matsumura K, Saraie T, Hashimoto N (1976) Studies of nitriles. VIII. Reactinn of N-acylderivatives of 2-amino-3,3-dihalogenacrylonitriles (ADAN) with amines (1). A new synthesis of 2-substituted-5-(substituted amine)oxazole-4-carbonitriles. Chem Pharm Bull 24:924–940
43. Nilson BM, Hacksell U (1988) Base-catalyzed cyclization of N-propargilamides to oxazoles. J Heterocycl Chem 26:269–275
44. Short KM, Zieger CB Jr (1993) An addition-elimination strategy for synthesis of oxazoles. Tetrahedron Lett 34:71–74

45. Arcadi A, Cacchi S, Cascia L, Fabrizi G, Marinelli F (2001) Preparation of 2,5-disubstituted oxazoles from *N*-propargylamides. Org Lett 3:2501–2504
46. Merkul E, Müller TJJ (2006) A new consecutive three-component oxazole synthesis by an amidation–coupling–cycloisomerization (ACCI) sequence. Chem Commun 2006:4817–4819
47. Lechel T, Gerhard M, Trawny D, Brusilowskij B, Schefzig L, Zimmer R, Rabe JP, Lentz D, Schalley CA, Reissig H-U (2011) Synthesis of 5-acetyloxazoles and 1,2-diketones from ß-alkoxy-ß-ketoenamides and their subsequent transformations. Chem Eur J 17:7480–7491
48. Braz GI, Myasnikova GV, Yakubovich AY, Bazov VP, Kardash LE, Kardash LE, Pravednikov AN (1967) Synthesis of benzoxazoles from imino esters. Chem Heterocycl Compd 3:215–219
49. Gitina RM, Braz GI, Bazov VP, Yakubovich AY (1966) 2,2′-Dialkyl(aryl)-substituted 6,6′-dibenzoxazoles and polybenzoxazoles. Polymer 8:1691–1695
50. Ishikawa N, Sasaki S (1977) Preparation of perfluoroalkylated benzoheterocyclic compounds using hexafluoro-1,2-epoxypropan. Bull Chem Soc Jpn 50:2164–2167
51. Yamazaki Y, Abe K, Toma T et al (2007) Design and synthesis of highly potent and selective human peroxisome proliferator-activated receptor a agonists. Bioorg Med Chem Lett 17:4689–4693
52. Qiana X, Xub X, Lib Z, Songb G (2004) Syntheses, structures and bioactivities of fluorine-containing phenylimino-thia(oxa)zolidine derivatives as agricultural bioregulators. J Fluorine Chem 125:1609–1620
53. Lee JJ, Kim J, Jun YM, Lee BM, Kim BH (2009) Indium-mediated one-pot synthesis of benzoxazoles or oxazoles from 2-nitrophenols or 1-aryl-2-nitroethanones. Tetrahedron 65:8821–8831
54. Reavill DR, Richardson SK (1990) Synthesis of polysubstituted aromatic acids using an intramolecular benzene cyclisation. Synth Commun 20:1423–1436
55. Inukai Y, Oono Y, Sonoda T, Kobayashi H (1979) *Ortho*-disubstituted *F*-benzenes. I. Preparation of (*F*-benzo)heterocyclic compounds from *F*-aniline and reaction of some intermediate (*F*-phenyl)amino compounds. Bull Chem Soc Jpn 52:516–520
56. Birchall JM, Haszeldine RN, Nikokavouras J, Wilks ES (1971) Polyfluoroarenes. Part XV. Diazo-oxides and related compounds. J Chem Soc C 1971:562–566
57. Burger K, Höß E, Geith K (1990) 5-amino-4-trifluoromethylthyazole und 5-4-trifluoromethyl-1,3-azole: Nüzliche Ausgangssubstanzen für Wirkstoff-Synthesen. Synthesis 360–365
58. Tozer MJ, Herpin T (1996) Method for the of synthesis *gem*-difluorinated compounds. Tetrahedron 52:8619–8683
59. Burkholder R, Dolbier WR Jr, Médebielle M (2001) Synthesis and reactivity of halogeno-difluoromethyl aromatics and heterocycles. Application to the synthesis of gem-difluorinated bioactive compounds. J Fluorine Chem 109:39–48
60. Lawson JP, VanSant KA (1999) Rearrangement of 2-amino-4-(trifluoromethyl)oxazoles to hydantoins. J Heterocycl Chem 36:283–285
61. Shi G, Xu Y, Xu M (1991) A convenient synthesis of 5-ethoxy-4-(trifluoromrthyl)-2-oxazolecarbonic acid and related trifluoromethyl substituted heterocyclic compounds. J Fluorine Chem 52:149–157
62. Burger K, Geith K, Höß E (1990) Synthese und Reactionsverhalten von 5-zido-4-trifluoromrthyl-1,3-azolen. Synthesis 1990:352–356
63. Amii H, Uneyama K (2009) C-F bond activation in organic chemistry. Chem Rev 109:2119–2183
64. Brunner H, Olschewski G, Nuber B (1999) Enantioselective catalyses; 126: axially chiral N,N-ligands with binaphthyl/bipyridyl structure. Synthesis 429–434
65. Germain H, Harris CS, Vautier M, Warin N (2010) Facile preparation of alkoxybenzoxazoles *via* direct S_NAr on the benzoxazole ring. Tetrahedron Lett 51:554–556
66. Kuroyanagi J-I, Kanai K, Sugimoto Y et al (2010) 1,3-benzoxazole-4-carbonitrile as a novel antifungal scaffold of ß-1,6-glucan synthesis inhibitors. Bioorg Med Chem 18:7593–76065
67. Kuroyanagi J-I, Kanai K, Horiuchi T et al (2011) Structure–activity relationships of 1,3-benzoxazole-4-carbonitriles as novel antifungal agents with potent *in vivo* efficacy. Chem Pharm Bull 59:341–352

68. Dubowchik GM, Zuev DS (2001) Substituted azole derivatives as inhibitor of corticotrophin releasing factor. US Patent 2002161019, 17 Sept 2001
69. Moriconi A, Armani A (2007) (*R*)-4-(Heteroaryl)phenyethyl derivatives and pharmaceutical compositions containing them. WO 2008050258037, 18 Oct 2007
70. Turnbull MD, Smith AM, Salmon R (1998) Oxazoles and their agricultural compositions. US Patent 5,705,516, 6 Jan 1998
71. Ting PC, Aslanian R, Caplen MA, Cao J, Kim D et al (2011) Inhibitors of diacylglycerol acetyltransferase. US Patent 20110224136, 15 Sept 2011
72. Huwyler J, Knoflach F, Vieira E, Wichmann J (2004) Oxazolesw as mGluR1 enhancer. WO 2004050814, 8 Jul 2004
73. Howe RK, Lee LF (1979) 2-substituted-4-alkyl or trifluoroalkyl-5-oxazoltcarboxilic acids as safeting agents. US 4,303,439, 1 Oct 1979
74. Burton CD, Madison NL (1968) 2,2′-bis(heptofluoropropyl)-5,5′-bibenzoxazole. US Patent 3,564,003, 5 Feb 1968
75. Burton CD, Madison NL (1968) 2,2′-bis(heptofluoropropyl)-6,6′-bibenzoxazole. US Patent 3,565,908, 5 Feb 1968
76. Wingen R, Hornung B, Ogawea A, Schmidt W (2001) Fluorinated azoles, and their use in liquid-crystalline mixtures. US Patent 6,231,786, 15 May 2001
77. Campbell TF, Stephens CE (2006) Nuclear fluorination of 2,4-diarylthiazoles with Accufluor®. J Fluorine Chem 127:1591–1594
78. Antipas AS, Blumberg LC, Brissette WH et al (2010) Structure–activity relationships and hepatic safety risks of thiazole agonists of the thrombopoietin receptor. Bioorg Med Chem Lett 20:4069–4077
79. Stachulski AV, Pidathala C, Row EC et al (2011) Thiazolides as novel antiviral agents. 1. Inhibition of hepatitis B virus replication. J Med Chem 54:4119–4132
80. Riyadh SM, Fuchigami T (2002) Electrolytic partial fluorination of organic compounds. 64. Anodic mono- and difluorination of thiazolyl sulfides. J Org Chem 67:9379–9383
81. Riyadh SM, Fuchigami T (2003) Electrolytic partial fluorinated of organic compounds. 66. Anodic fluorination of (thiazol-2-yl)acetonitriles. Heterocycles 60:15–20
82. Cohen F, Koehler MFT, Bergeron P et al (2010) Antagonists of inhibitor of apoptosis proteins based on thiazole amide isosteres. Bioorg Med Chem Lett 20:2229–2233
83. Herkes FF, Blazer TA (1976) Perhalogenated thiazoles, their synthesis, reaction and mass spectra. J Heterocycl Chem 13:1297–1304
84. Barton A (nee Beer), Breukelman SP, Kaye PT, Meakins GD, Morgan DJ (1982) The preparation of thiazole-4- and -5-carboxylates, and an infrared study of their rotational isomers. J Chem Soc Perkin Trans 1, 159–164
85. Gallagher PT, Iddon B, Suschitzky H (1980) Synthesis and reactions of azido-benzothiazoles and -benzo[*b*]thiophens; novel thiazalo[4,5-*g*] benzoxazoles and dihydrothieno[3,2-*g*]-benzoxazoles. J Chem Soc Perkin Trans 1:2358–2361
86. Simeon FG, Wendahl MT, Pike VW (2010) The $[^{18}F]_2$-fluoro-1,3-thiazolyl moiety – an easily-accessible structural motif for prospective molecular imaging radiotracers. Tetrahedron Lett 51:6034–6036
87. Simeon FG, Wendahl MT, Pike VW (2011) Syntheses of 2-amino and 2-halothiazole derivatives as high-affinity metabotropic glutamate receptor subtype 5 ligands and potential radioligands for *in vivo* imaging. J Med Chem 54:901–908
88. Bartoli G, Latrofa A, Naso F, Todesco PE (1972) Fluorodenitration of some mildly activated nitro-compounds. J Chem Soc Perkin Trans 1:2671
89. Archerx S, Perianayagam C (1979) An attempt to apply lethal synthesis to the design of chemotherapeutic agents. Fluorinated 50-(hydroxyethyl)-4-methylthiazoles. J Med Chem 22:306–309
90. Kim YH (1900) Organic synthesis using organosulfur – nitrites and nitrates. Phosphorus Sulfur Silicon Relat Elem 74:249–260
91. Kim YH, Lee CH, Chang KY (1900) Facile direct conversion of amino-heterocycles to fluoro-heterocycles using *t*-butylthionitrite or *t*-butylthionitrate with sodium tetrafluoroborate. Tetrahedron Lett 31:3019–3022

92. Archer S, McGarry R (1982) Diazotation of 2-amino-1,3-selenazole. J Heterocycl Chem 19:1245–1246
93. Haiginiwa J (1948) Polarization of aromatic heterocyclic compounds. LXXIV. Chemical properties of 2-amino-4-methylselenazole. Yakugaku Zasshi 68:197–200
94. Matsui M, Kawamura S, Shibata K, Muramatsu H (1992) Perfluoroalkylation of azo compounds. J Fluorine Chem 57:209–217
95. Yamawaki K, Nomura T, Yasukata T et al (2007) A novel series of parenteral cephalosporins exhibiting potent activities against *Pseudomonas aeruginosa* and other gram-negative pathogens: synthesis and structure–activity relationships. Bioorg Med Chem 15:6716–6732
96. Yamamoto H, Eikyu Y, Okuda S, Kawabaa K et al (2002) Orally active cephalosporins. Part 4: synthesis, structure–activity relationships and oral absorption of novel 3-(4-pyrazolylmethylthio) cephalosporins with various C-7 side chains. Bioorg Med Chem 10:1535–1545
97. Dubowchik GM, Michne JA, Zuev D et al (2003) 2-arylaminothiazoles as high-affinity corticotropin-releasing factor 1 receptor (CRF_1R) antagonists: synthesis, binding studies and behavioral efficacy, bioorganic. Med Chem Lett 13:3997–4000
98. Lee LF, Schleppniuk FM, Howe RK (1985) Synthesis and reactions of 2-halo-5-thiazolecarboxylates. J Heterocycl Chem 22:1621–1630
99. Rudnichenko AV, Timoshenko VM, Chernega AN et al (2004) Addition reactions of 2-polyfluoroalkyl substituted 1,3-thiazolin-4-one derivatives. J Fluorine Chem 125:1351–1356
100. Popkova VY, Vinogradova LE, Leites LA, Osmanov VK (1991) Intramolecular heterocyclization with accompanying exoiminization in the reaction of ammonia with 2-chloroperfluoro-1-cyclohexene-1-thiocyanate. Russ Chem Bull 10:2075–2078
101. Wang Q-F, Mao Y-Y, Zhu S-Z, Hu C-M (1999) A novel synthesis of per(poly)fluoroalky-1H-benzimidazoles or per(poly)fluoroalky-1*H*-benzthyazoles. J Fluorine Chem 95:141–143
102. Chen LS, Eapen KC (1990) Perfluoroalkyl and perfluoroalkylether chlorosulfates in the synthesis of substituted benzazoles. J Fluorine Chem 49:197–206
103. Zhu J, Xie H, Li S, Chen Z, Wua Y (2011) Switching reaction pathways of trifluoromethylated thiobenzanilides by choice of different oxidative systems. J Fluorine Chem 132:306–309
104. Zhu J, Chen Z, Xie H, Li S, Wu Y (2010) A general and straightforward method for the synthesis of 2-trifluoromethylbenzothiazoles. Org Lett 12:2434–2436
105. Pike VW, Simeon FG (2009) 2-fluorothiazole derivatives useful as imaging agents; methods of synthesis, and methods of use. US Patent 2011098326, 26 Oct 2009
106. Fyff MCT, Naud F (2004) Fluorination process of protected aminothiazole. WO 2006016174, 12 Aug 2004
107. Howe RK, Lee LI (1981) 2,4-disubstituted-5-thiazole-carboxylic acids and derivatives. US Patent 4,437,876, 22 Apr 1981

Fluorinated Triazoles and Tetrazoles

Vladimir A. Ostrovskii and Rostislav E. Trifonov

Contents

V.A. Ostrovskii (✉)
Department of Chemistry and Technology of Nitrogen Organic Compounds,
St.-Petersburg State Institute of Technology (Technical University),
Moskovskii av. 26, St.-Petersburg 190013, Russian Federation
e-mail: va_ostrovskii@mail.ru

R.E. Trifonov
Department of Natural Compounds Chemistry, Chemical Faculty,
St.-Petersburg State University, Universitetskii pr. 26,
Petrodvorets 198504, Russian Federation

V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_11,

Abstract The chapter encompasses the synthesis, chemical transformations, properties, and applications of fluorinated monocyclic 1,2,3-, 1,2,4-triazoles and tetrazoles as well as their fused analogs. The heterocycles directly bonded with a fluorine atom (N-F or C-F isomers) as well as trifluoromethyl, perfluoroalkyl, perfluoroaryl, SF_5, NF_2 groups and some other fluorinated fragments were considered.

Keywords Fluorine • Triazole • Tetrazoles • Heterocycle • Synthesis • Application • Biological activity

1 Introduction

Fluorinated polynitrogen heterocycles like 1,2,3-triazoles, 1,2,4-triazoles and tetrazoles differ considerably from the other related heterocyclic systems in the preparation methods and some characteristics. Heterocycles containing three or four endocyclic nitrogen atoms, including one, two, or three N-N bonds combined with a powerful electron-acceptor and energy-consuming substituent like a fluorine atom or perfluoroalkyl groups possess a relatively high enthalpy of formation and notably differ from the other azoles by their chemical properties. Some fluorinated tri- and tetrazoles are well known and find versatile applications [1]. These compounds are widely used in medicine, agriculture, and in material sciences. Thus, several commercially important drugs as well as a lot of bioactive compounds with different types of activity have in their composition fluorinated triazolyl or tetrazolyl groups. Among them there are well-known antidiabetic DPP-IV inhibitors, NK1 receptor antagonist, antifungal agents, herbicides, and some other compounds with useful properties [1–5]. On the other hand these compounds possess a number of unique properties providing a possibility to utilize them in quite different fields of technology. For instance, these compounds are efficient corrosion inhibitors, they can be used as components of energy-rich compounds, ionic liquids, semiconductors, etc. [1, 6]. The applications of fluorinated tri- and tetrazoles will be discussed in more detail in Sect. 6 of this chapter.

Fluorinated derivatives of azoles are known since over half century, the chemical methods of their synthesis and their certain chemical properties are described in many reviews and monographs [1, 6–15]. In general two different ways to incorporate fluorine or perfluoroalkyl groups into a heterocyclic system may be considered:

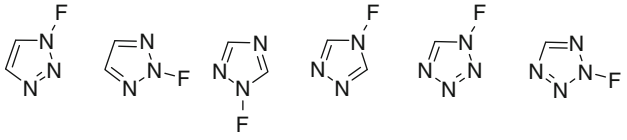
The heterocyclization of fluorine-containing acyclic systems many various types of which are known, or direct introduction of fluorine or a perfluoroalkyl group into existing heterocyclic system [1, 7–15]. So far the problems of the synthesis of highly nitrogenated cyclic systems, especially of 1,2,3-triazoles and tetrazoles have been poorly understood. It should be noted that quite a big number of original publications has appeared in this field within the last decade.

Taking into account the essential difference in the properties and the preparation procedures we consider further in succession compounds having a fluorine atom directly bound to the heterocycle and another fluorine-containing substances, perfluoroalkyl and perfluoroaryl derivatives of 1,2,3-, 1,2,4-triazoles and tetrazoles. The research on the synthesis and the reactivity of tri- and tetrazoles containing as substituents at the endocyclic carbon atom CF_3 or the other perfluoroalkyl groups have been developed since the 1960s. The last decade has been marked with a significant progress in this direction due to some of these compounds have important practical applications. Tri- and tetrazoles containing as substituents perfluoroaryl fragments, SF_5 and NF_2 groups, and also heterocycles involved into fluorobenzofused systems are considered separately.

2 Compounds Having Fluorine Bonded Directly to Endocyclic Atoms

2.1 N-F Derivatives

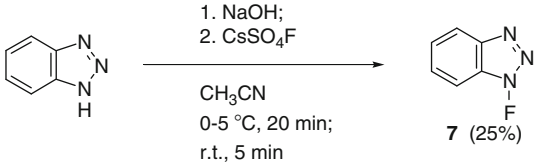
In the case of unsubstituted triazoles and tetrazoles the existence of two isomers is possible for each heterocyclic system. Such derivatives are very different in thermodynamic stability: 1H- and 2H-1,2,3-triazoles and tetrazoles, and also 1H- and 4H-1,2,4-triazoles. By now all parent N-F heterocycles **1**–**6** remain hypothetical. Among substituted derivatives all known N-F heterocycles are only 1H-isomers.



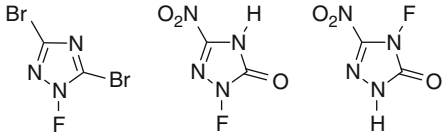
1 **2** **3** **4** **5** **6**

In general the information on the synthesis and properties of the N-fluorinated derivatives of 1,2,3- and 1,2,4-triazoles is very scanty [6]. The data about N-fluorotetrazoles are totally absent today. We discuss below the results of the few publications considering the synthesis of N-fluoro-1,2,3- and 1,2,4-triazoles. This desultory information is difficult to classify since the most of these papers lack any experimental details on the synthesis of the compounds of this type and the proofs confirming the structure.

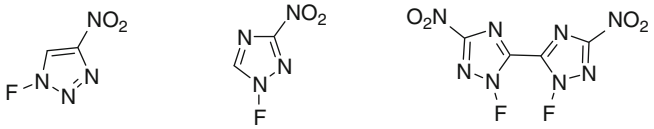
By now the synthesis of 1-fluoro-benzotriazole **7** is well established fact [16]. Gakh et al. carried out a direct replacement of the hydrogen attached to the nitrogen atom of the "pyrrole" type of benzotriazole by the fluorine. For this aim benzotriazole anion was fluorinated with cesium fluorooxysulfate (CEOX). The cesium fluorooxysulfate discovered by Appelman in 1979 is one of the soft and regioselective reagents for anions fluorination. It requires however a cautious handling for it is prone to spontaneous instant decomposition [8, 9].



An example of synthesis of N-fluoro-1,2,4-triazole was described in the patent of Strazdina and Grinstein [6, 17]. Here 1-fluoro-3,5-dibromo-1,2,4-triazole **8** was obtained by treating the heterocyclic substrate with the hypohalous acid or its derivatives at −40 to +50 °C in water or an organic solvent in the presence of bases. Langlet and Ostmark in a patent [18] have described the application of isomeric fluoro-triazolones **9, 10** as components of explosive compositions, but the data on the synthesis of these substances have been not reported.



Miroshnichenko et al. [19] published results on calorimetric investigation of N-F derivatives of various nitroazoles, in particular, of some N-fluoro derivatives of 1,2,3- and 1,2,4-triazoles **11**–**13** (the values of standard enthalpy of formation ΔH_f^o, kJ/mol are given in parentheses). Regretfully, the methods of the synthesis of N-F triazoles and the data confirming their structure and individuality were not reported in this article.

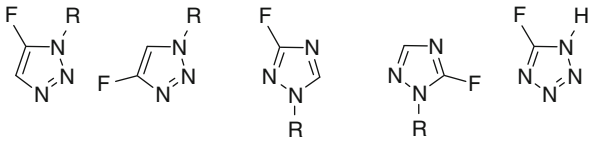


According to theoretical calculations the N-F bond in the molecules of N-fluoro-1,2,4-triazoles is rather strong, in contrast to N-Cl (Br, I) bonds [20]. Therefore, it remains possible to prepare a wide range of thermodynamically stable N-fluoro derivatives of 1,2,4-triazole which may be of a practical importance. Thus, using

ab initio quantum-chemical methods, the structure of salts was investigated that were formed with N-F-1,2,4-triazolium cation and dinitramide anion which might be used for the preparation of exotic energy-rich ionic liquids [21].

2.2 C-F Derivatives

Taking into account that 1,2,3- and 1,2,4-triazole rings contain two carbon atoms, and the tetrazole cycle only a single one, the fluorine atom can be located in two different positions in the isomeric C-F triazoles with nonequivalent substituents **14**–**17** and in a single position in 5-fluorotetrazole **18**. All types of these derivatives are known.

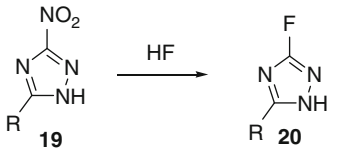


14 **15** **16** **17** **18**

The direct incorporation of a fluorine atom in the ring essentially affects versatile physicochemical and chemical characteristics of the heterocyclic system, in particular, its tautomerism, dipole moment, and the acid-base properties. For instance, tautomeric equilibria involving NH-unsubstituted fluoro derivatives of 1,2,3-triazoles [22, 23], 1,2,4-triazoles [24], and tetrazoles [25–28] were explored in a series of theoretical studies. The acid-base properties of these heterocycles (in particular, the CH-acidity of some among them) were also studied [28–30]. These investigations showed that the fluorine atom attached to the heterocyclic system changed significantly the character of the electron density distribution and consequently the polarity of the heterocycle, strongly increased its acidity and decreased its basicity.

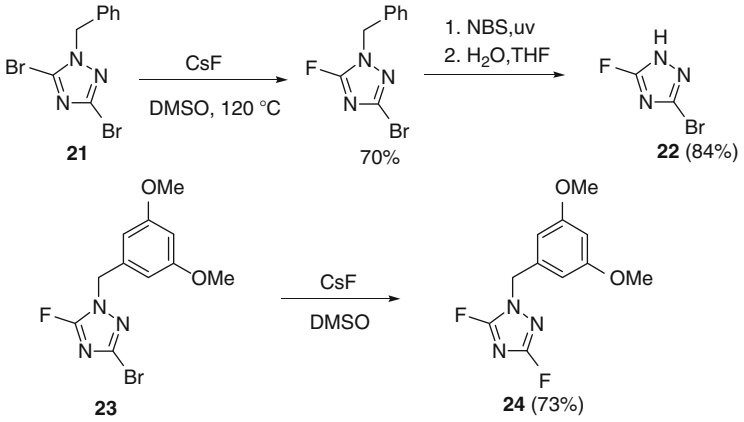
The synthetic procedures for the preparation of C-F derivatives of tri- and tetrazoles are more developed compared to the synthesis of the derivatives with the N-F bond. The preparation methods of C-F derivatives are known not only for 1,2,3- and 1,2,4-triazoles, but also for tetrazoles. The C-F bond is successfully formed by the replacement of hydrogen atom or various "leaving" groups under the action of the fluorination reagents. Along with the above methods diverse versions are applied of 1,3-dipolar cycloaddition of azides to dipolarophiles containing fluorine. Also very useful approach is oxidative cyclization of molecules with the linear structure containing a C-F bond.

The first report on the preparation of 1,2,4-triazoles fluorinated at the carbon atom of the ring appeared as early as 1973 [31]. In this study the corresponding 3-fluoro-1,2,4-triazoles **20** were obtained in good yields by treatment of 5-R-3-nitro-1,2,4-triazoles **19** with hydrogen fluoride. Nitro group substitution by fluorine under these conditions required a prolonged time (20–48 h) and heating at high temperature (100–150 °C).

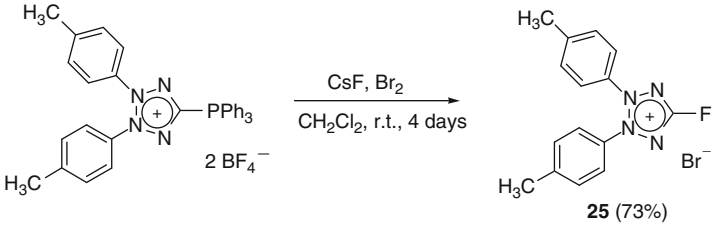


R	Temperature,°C	Time, h	Yield, %
H	150	48	80
Br	100	36	98
CO_2Me	100	20	70
OH	100	36	21

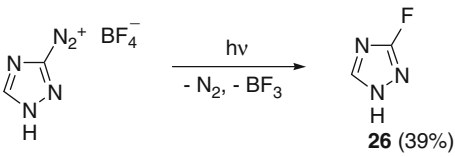
The nucleophilic exchange of one bromine atom in 1-benzyl-3,5-dibromo-1,2,4-triazole **21** with fluorine under the action of CsF followed by the photoinitiated elimination of the benzyl protective group led to the formation of 3-bromo-5-fluoro-1H-1,2,4-triazole **22** in 59 % overall yield. The alkylation of this substrate gave 1-alkyl-3-fluoro-1,2,4-triazoles for the first time. Both bromine atoms were substituted to provide the corresponding difluoro derivative **24** under the same reaction conditions, but using 1-(3,5-dimethoxybenzyl)-3,5-dibromo-1,2,4-triazole **23** as substrate for fluorination [32].



Cesium fluoride was also used in the synthesis of 2,3-di(*p*-tolyl)-5-fluorotetrazolium bromide **25** from the corresponding 5-triphenylphosphoniotetrazolium salt [33].

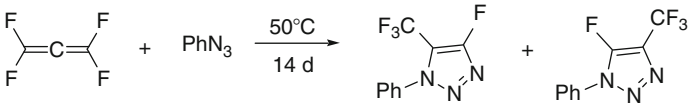


Another example of the direct introduction of the fluorine atom into a heterocycle was demonstrated in [34]. Here 3-fluoro-1,2,4-triazole **26** was obtained by the photochemical decomposition of hetaryldiazonium tetrafluoroborate in solution oversaturated with $NaBF_4$.

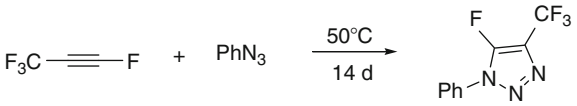


26 (39%)

A widely used method of the preparation of versatile 1,2,3-triazoles and tetrazoles consists in the reaction of azides with fluorine-containing compounds with multiple bonds. For example, this approach afforded N-substituted 4(5)-fluoro-1,2,3-triazoles **27, 28** by the 1,3-dipolar cycloaddition of perfluoropropadiene to phenyl azide [35]. In the course of the reaction a mixture of regioisomeric 1,2,3-triazoles was formed; 1-phenyl-4-fluoro-5-trifluoromethyl-1,2,3-triazole **27** was considerably prevailed. On the contrary, the reaction of phenyl azide with the perfluoropropyne resulted in predominantly the isomer that was minor in the previous scheme.

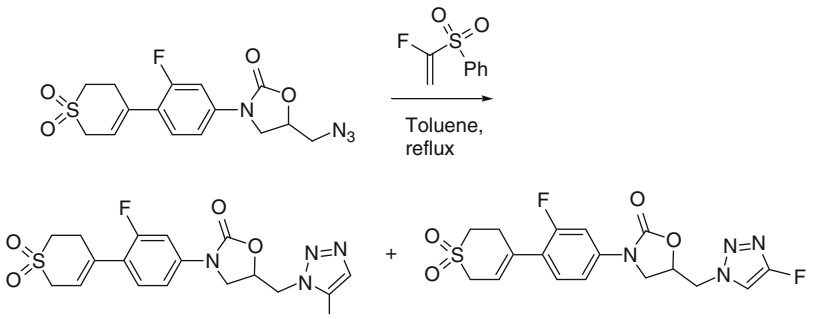


27 (25%) **28** (3%)



28 (32%)

Reck et al. demonstrated that phenylsulfinic acid was eliminated in course of 1,3-dipolar cycloaddition involving 1-fluoro-1-(phenylsulfonyl)ethylene and (5R)-3-[4-(1,1-dioxo-3,6-dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-5-(azidomethyl)oxazolidin-2-one. As a result a mixture of regioisomeric 4- and 5-fluoro-1,2,3-triazoles **29, 30** in 7:1 ratio was formed in 28 % overall yield. Compounds **29, 30** may be regarded as effective antimicrobial agents [36].



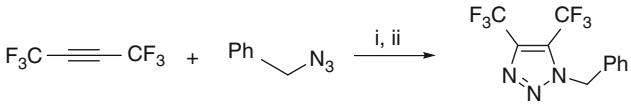
29 (major) **30** (minor)

Apparently the simplest 5-fluorotetrazole **18** and its derivatives can be synthesized by the reaction of 2 + 3 dipolar cycloaddition of azides to cyanogen fluoride or by some other method. Yet we failed to find the mention of such synthesis in available publications. The possibility of this reaction and its mechanism were assessed theoretically [37]. Publications are known where compound **18** is used as a component of the energy-rich compositions [38].

3 Trifluoromethyl and Perfluoroalkyl Derivatives

3.1 1,2,3-Triazoles

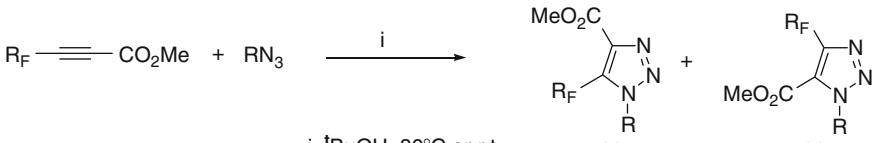
The most common synthetic procedure for the preparation of perfluoroalkylated 1,2,3-triazole derivatives is 1,3-dipolar cycloaddition of azides to diverse unsaturated dipolarophiles containing perfluoroalkyl substituents. Thus, in 1966 Carpenter et al. carried out the cycloaddition of benzyl azide to perfluoroalkyl substituted acetylene derivatives leading to the formation of trifluoromethyl-1,2,3-triazolines and 1,2,3-triazoles [39]. In this paper a synthesis of l-benzyl-4,5-bistrifluoromethyl-l,2,3-triazole **31** from hexafluoro-2-butyne was described.



i, test tube chilled to -70 °C
ii, 2 days, r.t.

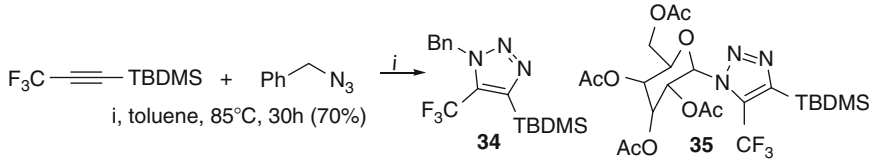
31 (5%)

The regioselectivity of 1,3-cycloaddition of benzyl azide to unsymmetrical acetylenes containing CF_3 substituent at one carbon atom of the fragment C ≡ C and CO_2Et group at the other carbon was analyzed [40]. The formation of regioisomeric mixtures of 1,2,3-triazoles **32, 33** was observed. This study was further developed recently. Zhang et al. published the results of a research on the 1,3-dipolar cycloaddition of benzyl azide and some other aryl azides to methyl perfluoroalkylalkynoate. It was shown that the ratio of regioisomers is governed by two factors: the orbital control (the role of the frontier orbitals was established) and also spatial interaction of the perfluoroalkyl and aryl (or benzyl) groups [41].

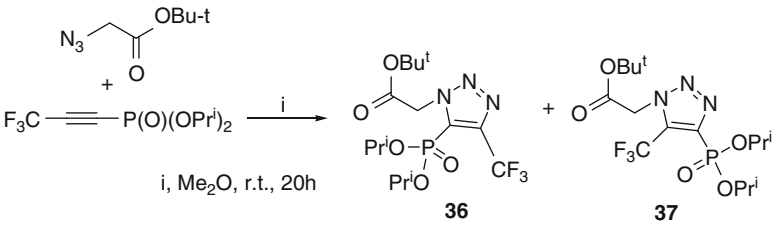


R_F	R	ratio **32:33**	Yield,%
CF_3	$C_6H_5CH_2$	1:0.7	91
C_2F_5	*p*-$MeOC_6H_4CH_2$	1:0.9	82
C_3H_7	*p*-$MeOC_6H_4CH_2$	1:1.2	83
CF_3	C_6H_5	1:2.1	85

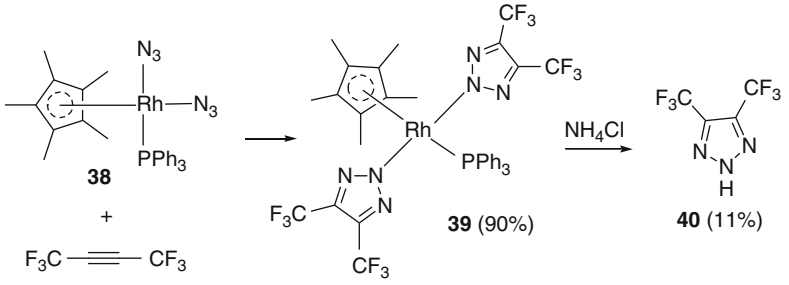
The influence of the steric effects on the regioselectivity of the cycloaddition was studied in detail by an example of the 1,3-dipolar cycloaddition of benzyl azide to trifluoromethylacetylene containing a TBDMS (*tert*-butyldimethylsilyl) protecting group. The regioselective formation in this case of the single isomer of 1,2,3-triazole **34** was explained by the presence in the structure of dipolarophile of a bulky substituent (TBDMS) [42]. Such an approach made it possible to perform a regioselective synthesis of nucleosides analogs containing in their molecular structure a trifluoromethyl-1,2,3-triazolyl fragment **35** [42].



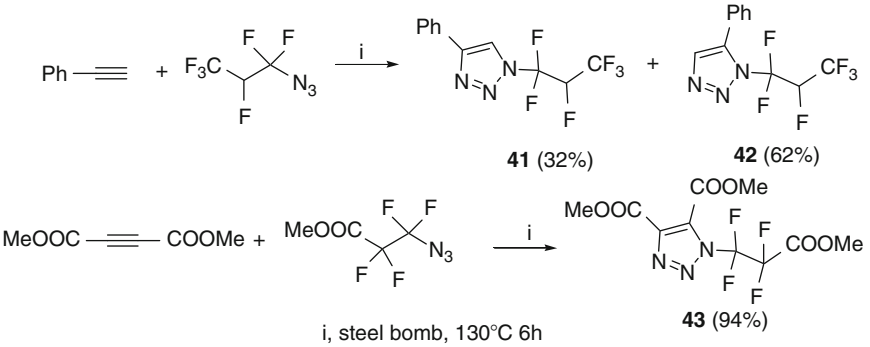
The reaction of *tert*-butyl azidoacetate with diisopropyl-3,3,3-trifluoroprop-1-ynylphosphonate gave regioisomeric diisopropyl(1-*tert*-butoxycarbonylmethyl-4-trifluoromethyl-1H-l,2,3-triazol-5-yl)phosphonate **36** and disopropyl(l-*tert*-but oxycarbonylmethyl-5-fluoromethyl-lH-l,2,3-triazol-4-yl)phosphonate **37** in 75:25 ratio (90 % overall yield) [43].



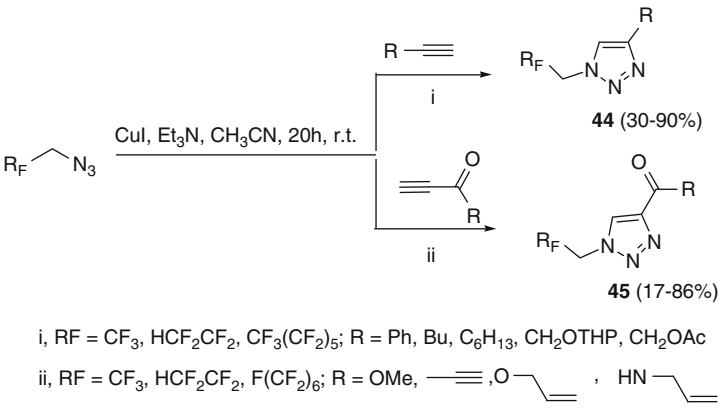
Pentamethylcyclopentadienylrhodium (or iridium) azido complexes **38** react with ditrifluoromethylacetylene to give the corresponding 1,2,3-triazole rhodium complex **39**. Subsequent treatment with NH_4Cl opened the route to free NH-triazole **40** [44].



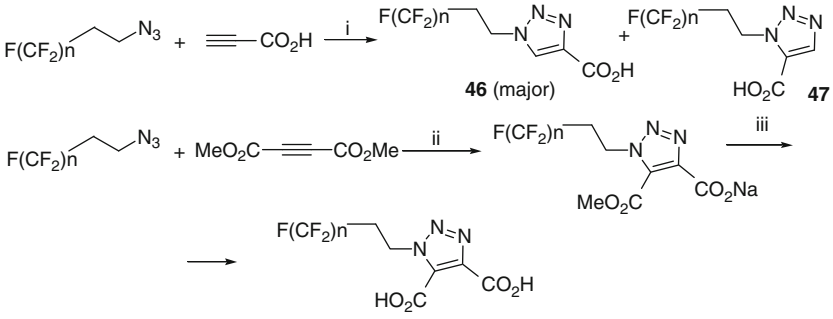
Lermontov et al. reported some successful reactions of two α,α-difluoroazides, namely, 2-hydroperfluoropropyl azide and the methyl ester of 3-azidoperfluoropropanoic acid, with various acetylene compounds, and described some properties of the resulting products [45]. Thus, phenylacetylene reacts with 2-hydroperfluoropropyl azide to give the corresponding 4-phenyl-1-(2H-perfluoropropyl)-1,2,3-triazole **41** and 5-phenyl-1-(2H-perfluoropropyl)-1,2,3-triazole **42** in 1/2 ratio. Disubstituted acetylenes also react with these azides to give the corresponding 1H-1,2,3-triazoles [45]. Thus in the case of triazole **43** the yield is close to the quantitative.



In the paper [46] of Wu, Chen et al. a method for the preparation of the fluoroalkylated 1,4-disubstituted-1,2,3-triazoles by the 1,3-dipolar cycloaddition of fluoroalkylated azides to terminal alkynes in the presence of Cu(I) salt as catalyst at room temperature was described. All these reactions were highly regioselective giving 1,4-disubstituted **44, 45**, no 1,5-disubstituted products. The structure of key compounds was confirmed both by the NOSEY spectra and an X-ray diffraction study.

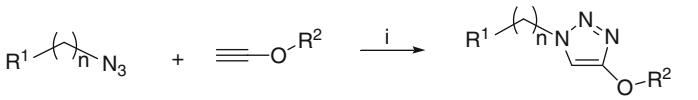


A series of fluoroalkylated amphiphilic 1,2,3-triazoles **46**, **47**, **48** was synthesized by efficient 1,3-dipolar cycloaddition of 2-perfluoroalkylethyl azides and acetylenic acids or esters [47].



Recently Yi et al. also utilized 2-perfluoroalkylethyl azides as 1,3-dipoles in the 1,3-dipolar cycloaddition to phenyl- or butylacetylenes [48]. As a result in the presence of copper(I) salt the corresponding 1-fluoroalkyl-4-substituted 1,2,3-triazoles were obtained in about 60 % yield. Note that in this case only anti- isomers were obtained: 1-fluoroalkyl-4-aryl- or 1-fluoroalkyl-4-butyl-1,2,3-triazoles. The authors do not explain the high selectivity of the process, although it may be attributed to the steric effect of the bulky substituents (aryl, butyl). Yi et al. note the relatively high efficiency of the fluoroalkyl 1,4-disubstituted-1,2,3-triazoles as catalysts of aldol condensation which may be easily recovered and reused [48]. Read et al. [49] virtually simultaneously with [48] published the results of their proper exploration of the copper salts catalyzed 1,3-dipolar cycloaddition of fluorinated alkyl azides to acetylenes. This research extended the methodology

formerly suggested by Wu et al. [46] who were among the first to apply the catalytic system based on Cu(I). It was shown that practically for the generation of the Huisgen-Meldal catalyst the system $CuSO_4$ $5H_2O$ – sodium ascorbate was preferable. Just under these reaction conditions a wide range of 1,2,3-triazoles **49** was obtained having the perfluoroalkyl groups at the atoms in the positions *1* and *4* [49]. It was also shown that the higher rate of the process and the higher yield of cycloaddition products were achieved both in the presence of copper salts and at the microwave acceleration.



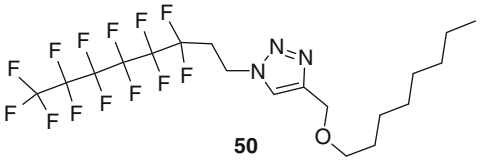
49 (50-97%)

i, $CuSO_4$ $5H_2O$, Na ascorbate, DMSO, heat

$R^1 = C_4F_9, C_6F_{13}, C_8F_1$; n = 2; $R^2 = C_8H_{17}$; etc.

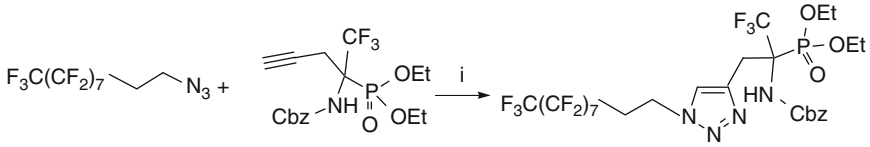
$R^1 = C_4H_9, C_6H_{13}, C_8H_{17}, C_9H_{19}, CH_2Ph$; n=0; $R^2 = CH_2CH_2C_6F_{13}$, etc.

1,3-Dipolar cycloaddition of fluoroalkyl azides to acetylenes in the version of the click-chemistry involving the above mentioned catalytic system ($CuSO_4$ $5H_2O$ – sodium ascorbate) essentially extended the set of the known fluoroalkyl derivatives of 1,2,3-triazole; some 1,2,3-triazole derivatives previously regarded as exotic became relatively accessible. Read et al. recently reported on the results of research of the effect on the *m*-xylene surface tension of the additives of exotic surfactants based on fluoroalkyl derivatives of 1,2,3-triazoles, e.g., compound **50** [50]. The synthesis of fluoroalkyl-1,2,3-triazoles using the above mentioned procedure was also described in the earlier publication of the same team [51].



50

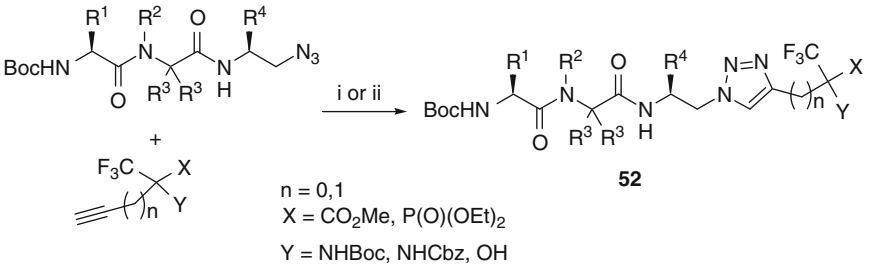
A convenient method for the preparation of 1,2,3-triazole-containing CF_3-α-aminophosphonates **51** via copper-catalyzed (3+2)-cycloaddition of α-CF_3-α-aminophosphonates bearing an alkynyl group at the α-carbon atom to different organic azides has been described [52].



i, *t*-BuOH - H_2O, r.t., 8h, yield 92%

51

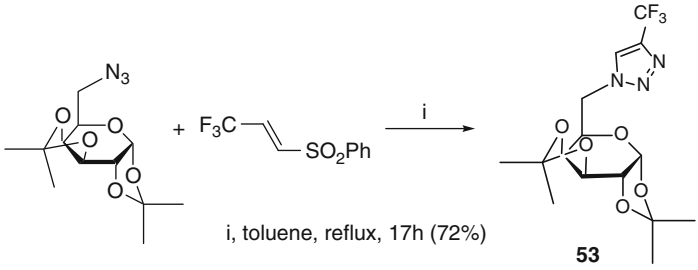
A convenient and simple method for the synthesis based on copper-catalyzed 1,3-dipolar cycloaddition of azidopeptides to acetylenes of tetrapeptide surrogates containing CF_3-alkyl-1,2,3-triazolyl moiety **52** having ester of phosphonates functionalities or have been developed by Nenajdenko et al. [53, 54].



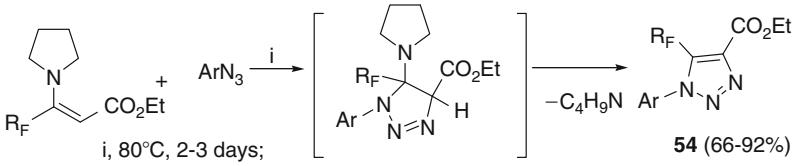
i, sodium ascorbate (40%), $CuSO_4$ $5H_2O$ (10%), CH_2Cl_2/H_2O (10:1), 40°C, 3-5 h (70-97%)

ii, sodium ascorbate (30%), $CuSO_4$ $5H_2O$ (5%), *t*-BuOH/H_2O (1:1), r.t. or 90°C, 2 h (57-96%)

Some approaches to the synthesis of trifluoromethyl-1,2,3-triazoles by the azidation of compounds containing not a triple but a double C=C bond were described. In this case apparently a functional group elimination occurs *in situ* to provide the formation of an additional carbon-carbon bond. For instance, Miethchen et al. described a synthesis of 4-trifluoromethyl-1,2,3-triazole **53** linked to the C^6-atom of D-galactose and D-altrose. 1,3-Dipolar cycloaddition using the monosaccharide azides and the perfluoroalkyl- substituted phenylvinylsulfones was performed [55, 56].

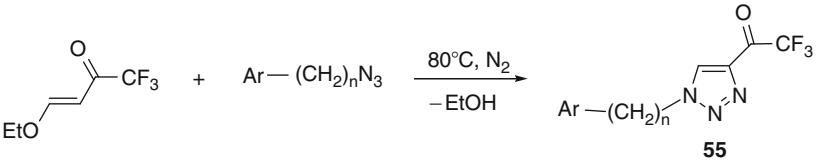


A number of 5-fluoroalkylated 1H-1,2,3-triazoles **54** was synthesized in good yield by the 100 % regioselective 1,3-dipolar cycloaddition of (*Z*)-ethyl-3-fluoroalkyl-3-pyrrolidino-acrylates with aryl or benzyl azides [57].



R_F = $ClCF_2$, $BrCF_2$, CF_3, $Cl(CF_2)_3$; Ar = Ph, 4-$CH_3OC_6H_4$,4-$NO_2C_6H_4$

1,3-Dipolar cycloaddition of aryl (or benzyl) azides to 1,1,1-trifluoro-4-ethoxy-3-butene-2-one proceeded smoothly by heating without solvent. As a result 1-substituted 4-trifluoroacetyl-1*H*-1,2,3-triazoles **55** were formed regioselectively in good yield [58]. These compounds were readily hydrated at air exposure.



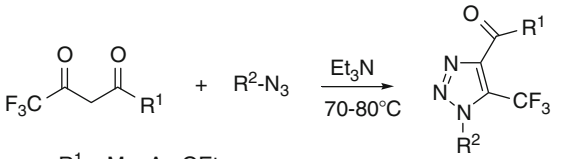
55

n=0; Ar = C_6H_5, 66h, yield 51%; 4-MeC_6H_4, 48h, yield 80%,

4-$NO_2C_6H_4$, 66h, yield 78%, 4-ClC_6H_4, 44h, yield 73%,2-$CH_3C_6H_4$, 144h, yield 68%.

n=1; Ar= C_6H_5, 35h, yield 69%, Ar=4-OMe, 24h, yield 79%; Ar=4-NO_2, 72h, yield 88%.

Recently Nenaidenko et al. carried out reactions of a variety alkyl and aryl azides with 1-trifluoromethylated 1,3-dicarbonyl compounds what lead 100 % regioselectively to a single 4-acyl-5-trifluoromethyl-1,2,3-triazoles **56** isomer in good yields [59]. The reaction represents a general and highly selective method for the synthesis of 1,2,3-triazoles otherwise difficulty available. The observed regioselectivity can be explained by selective enolization of trifluoromethyl ketone fragment to form enolate with double bond conjugated to the CF_3 group.

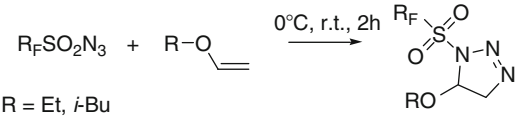


R^1 = Me, Ar, OEt

R^2 = Alk, Ar

56 (up to 92%)

Fluoroalkanesulfonyl azides in reactions with alkenes are more reactive than alkyl azides because of strong electron-acceptor properties of the sulfonyl group. Thus, Zhu, He et al. shown that the reaction of vinyl ethers with 1-fluoroalkanesulfonyl azides proceeded in mild conditions to afford 1-fluoroalkanesulfonyl-5-alkoxy-1,2,3-triazolines in good yields (≈70 %) [60, 61]. The authors point out that the cycloaddition is extremely regioselective. Only the 5-alkoxy derivative of 1,2,3-triazoline **57** has been obtained, whereas the corresponding 1,4-isomer has not been detected.



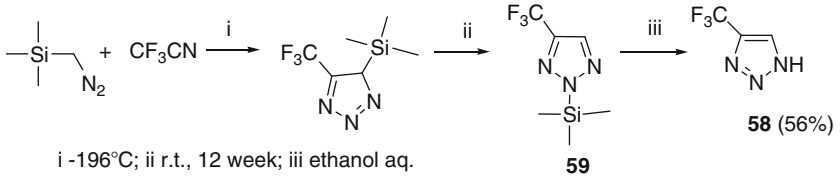
57

R = Et, *i*-Bu

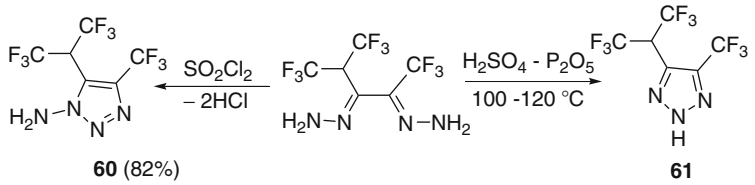
R_F = $ICF_2CF_2OCF_2CF_2$, $ClCF_2CF_2OCF_2CF_2$, $Me_2CHO_2CCF_2$, C_4H_9

According to Shreeve et al., 4-trifluoromethyl-1,2,3-triazole **58** may be synthesized as a result of 1,3-dipolar cycloaddition of $TMSN_3$ to trifluoropropyne in the presence of Cu(I) [62]. The synthesis of perfluoroalkyl-1,2,3-triazoles was also described in the earlier cited paper of Taylor et al. [35]. In this study the reaction was investigated between perfluoropropadiene with phenyl azide resulting in regioisomeric 1,2,3-triazole containing at the endocyclic carbon atoms both the fluorine atom and the CF_3-group.

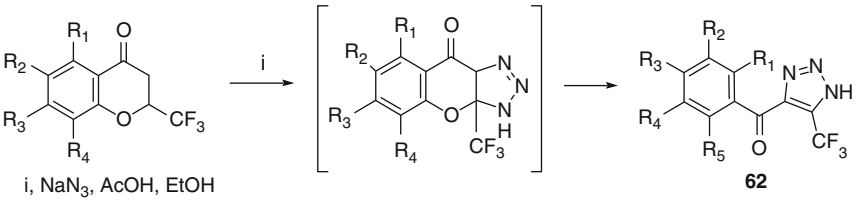
Below we described some other, less wide spread methods as compared to 1,3-dipolar cycloaddition used in the preparation of perfluoroalkyl derivatives of 1,2,3-triazoles. For instance, Haszeldine et al. [63] developed an original method of the synthesis of trifluoromethyl-1,2,3-triazole about 40 years ago. The reaction of diazomethyltrimethylsilane with trifluoroacetonitrile led to the formation of an intermediate adduct rearranged into 2-trimethylsilyl-4-trifluoromethyl-1,2,3-triazole **59**. This compound being treated with aqueous ethanol liberated the trimethylsilane to yield 4-trifluoromethyl-1,2,3-triazole **58**.



Bargamov and Bargamova reported on new polyfluorinated 1-amino-1,2,3-triazoles **60** which were obtained by oxidation of the bis-hydrazones of aliphatic polyfluorinated α-dicarbonyl compounds with sulfuryl chloride, bromine, or selenium dioxide in an aprotic solvent [64, 65]. In a later article these authors described an oxidation of a dihydrazone of 1,1,1,5,5,5-hexafluoro-4-trifluoromethylpentane-2,3-dione in the presence of the H_2SO_4 – P_2O_5 mixture (molar ratio 3:1) to 4-(1,1,1,3,3,3-hexafluoroisopropyl)-5-trifluoromethyl-2*H*-1,2,3-triazole **61** (no yield was given) [66].



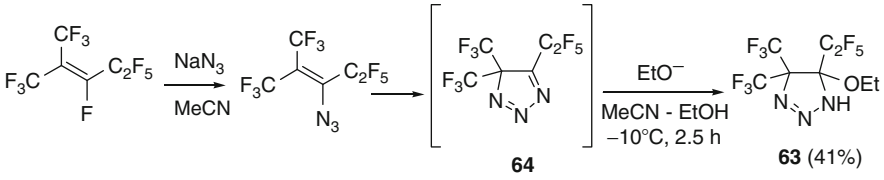
The reactions of 2-trifluoromethylchromones and 2-trifluoromethyl-4H-chromen-4-imines with sodium azide in the presence of acetic acid gave ketone (or imine) derivatives of 5(4)-trifluoromethyl-1,2,3-triazole **62** in high yields [67].



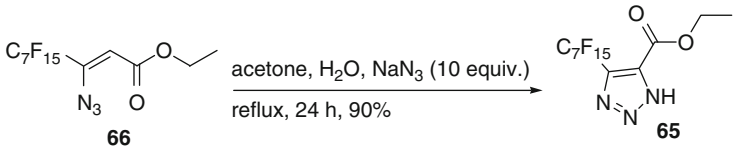
$R^1 = R^3 = R^4 = H$, $R^2 = NO_2$ (86%) $R^1 = R^3 = H$, $R^2 = R^4 = Br$ (50%)

$R^1 = R^3 = R^4 = H$, $R^2 = Cl$ (68%) $R^1 = R^3 = Me$, $R^2 = R^4 = NO_2$ (66%)

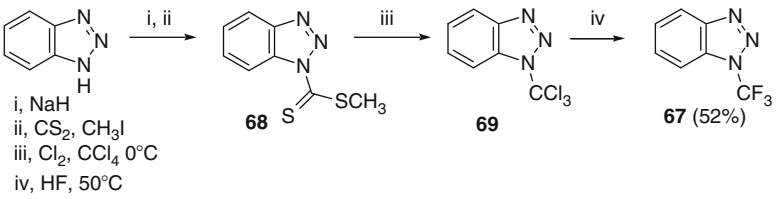
Furin et al. (2001) published a method for the synthesis of 4,4-bis(trifluoromethyl)-5-ethoxy-5-pentafluoroethyl-1,2,3-triazoline **63** based on the electrocyclic cyclization of linear vinyl azide as a precursor [68]. In the first stage of this process the perfluoro-2-methyl-2-pentene reacted with sodium azide in acetonitrile–ethanol mixture at −20 °C furnishing the vinyl azide, which at −10 °C underwent an intramolecular cyclization into an unstable intermediate **64**. In the presence of ethanol a nucleophilic attack of ethoxy anion on C=N bond of intermediate **63** occurs to form a stable product **64** [68].



Bozkurt et al. demonstrated that 5-(perfluoroheptyl)-3H-1,2,3-triazole-4-carboxylate **65** is formed in a high yield by the intramolecular cyclization of ethyl 3-azido-3-(perfluorheptyl)propenoate **66** in presence of a significant excess of sodium azide [69].

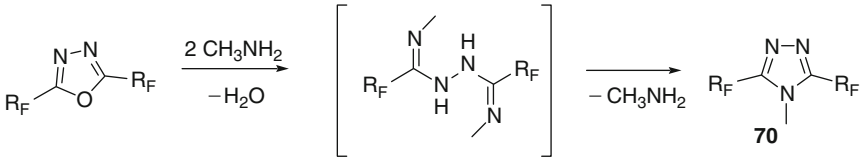


An example of the "direct" incorporation of a perfluoroalkyl group into the structure of an already formed 1,2,3-triazole was given [70]. In this paper a method of synthesis of 1-trifuoromethyl-substituted benzotriazole **67** is described by the chlorination of the corresponding methyl 1-azoledithiocarboxylates **68** followed by the fluorination of the resulting 1-trichloromethyl derivatives **69** using anhydrous HF [70].



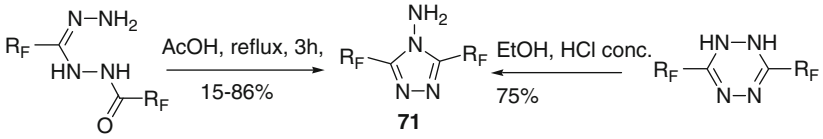
3.2 1,2,4-Triazoles

Perfluoroalkyl-1,2,4-triazoles are often formed by rearrangement of other heterocycles or by cyclization of carboxylic acid hydrazides or their analogues. In 1962 Brown and Cheng described for the first time the synthesis of 3,5-bis(perfluoroalky1)-1,2,4-triazoles **70** by treatment of bis(perfluoroalkyl)-1,3,4-oxadiazoles with methylamine [71]. The method for the synthesis of NH-unsubstituted 3,4-bis(perfluoropropyl)-l,2,4-triazole by the action of P_2O_5 on the corresponding hydrazine was also reported in this paper. Thirty years later Threadgill et al. [72] prepared 3,5-bis(trifluoromethyl)-4-(3-benzyloxypropyl)-4H-l,2,4-triazole by the reaction of 2,5-bis(trifluoromethyl)-l,3,4-oxadiazole with 3-benzyloxypropylamine in methanol (reflux, 9 days).

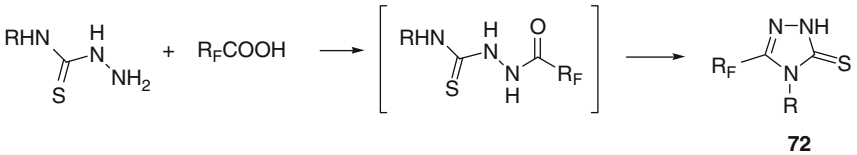


R_F = CF_3 (93%), C_2F_5 (94%), C_3F_7 (68%)

Brown et al. also suggested a version of the synthesis of 3,5-bis(perfluoroalkyl)-4H-1,2,4-triazoles **71** from perfluoroalkylhydrazides and from bis-(perfluoroalkyl)-1,2-dihydro-1,2,4,5-tetrazines [73].



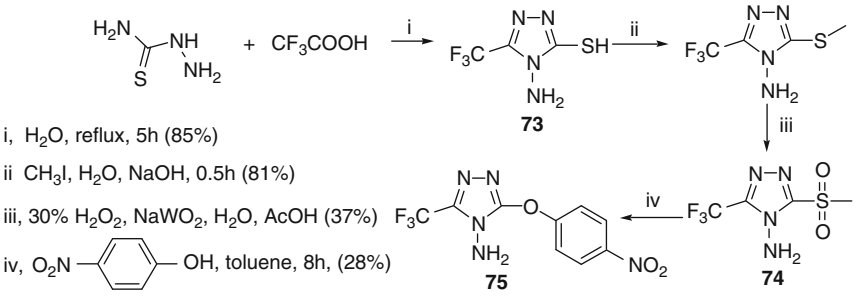
Charushin et al. demonstrated that 4-substituted thiosemicarbazides react with di- and trifluoroacetic acids to give the corresponding 3-fluoroalkyl-4,5-dihydro-1,2,4-triazole-5(1H)-thiones **72** [74].



72

R_F	R	Yield, %	R_F	R	Yield, %
CHF_2	1-pyrrolidino	36	CF_3	4-$CH_3C_6H_4$	55
CHF_2	Ph	45	CF_3	4-FC_6H_4	88
CF_3	piperidino	50	CF_3	Ph	70
CHF_2	3,4-$(MeO)_2C_6H_3$	35			

It should be noted that in 1998 El-Sayed and Khodairy recognized that thiones **72** are versatile substrates for the synthesis of fused and spiroheterocyclic systems [75]. Recently Chen et al. synthesized 4-amino-5-(trifluoromethyl)-4H-1,2,4-triazole-3-thiol **73** from thiocarbohydrazide [76]. The latter compound in its turn served as a reagent for the preparation of new functional triazole derivatives **74** and **75** [76].



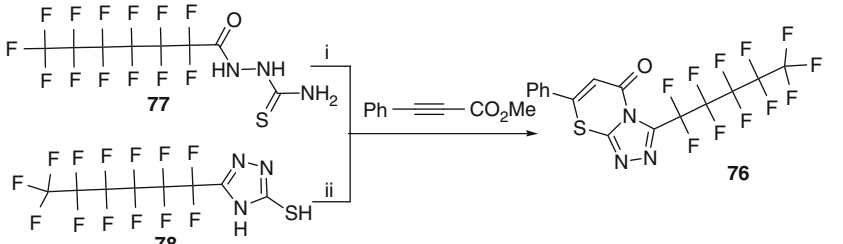
i, H_2O, reflux, 5h (85%)

ii CH_3I, H_2O, NaOH, 0.5h (81%)

iii, 30% H_2O_2, $NaWO_2$, H_2O, AcOH (37%)

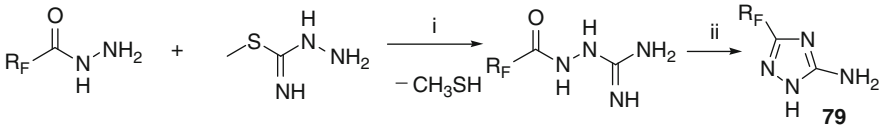
iv, O_2N–C$_6$H$_4$–OH, toluene, 8h, (28%)

Ivin et al. obtained 3-(perfluorohexyl)-7-phenyl-5H-[1, 2, 4]triazolo[3,4-b][1,3] thiazin-5-one **76** as a result of a reaction of methyl phenylpropynoate with a linear 1-(perfluoroheptanoyl)thiosemicarbazide **77** or a cyclic 5-(perfluorohexyl)triazole-3-thiol **78**. In both cases the reaction conditions were practically identical, and the yields of compounds containing the trifluorohexyl group in the position *3* of the 1,2,4-triazole ring were comparable [77].



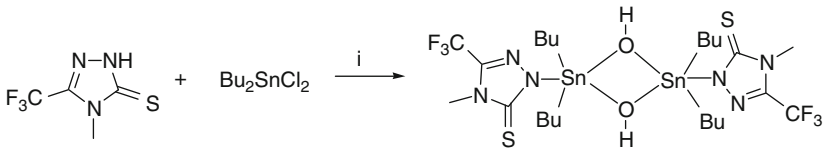
i, AcOH, reflux, 5 h, yield, 68%; ii, the same conditions, yield, 72%

Lopyrev et al. developed an original method for the synthesis of 3-perfluoroalkyl-5-amino-1,2,4-triazoles **79** in nearly quantitative yields based on the cyclization of perfluoroacylaminoguanidines that in their turn were obtained in good yields (60–81 %) from hydrazides of perfluorocarboxylic acids and S-methylisothiourea [78].



R_F = CF_3, C_2F_5, C_3F_7, $CF_3OCF_2CF_2$ i, 0.1 N NaOH, r.t., 72h; ii, 170°C, 30 min

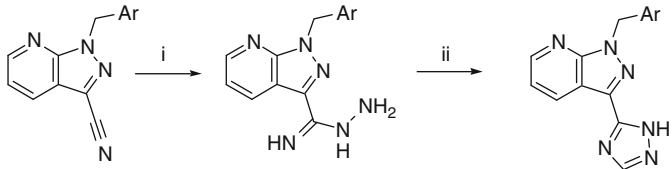
New organotin(IV) compounds with 4-methyl-5-trifluoromethyl-4H-1,2,4-triazoline-3(2H)-thione fragments **80** have been synthesized and characterized [79]. The central tin atoms of complexes is five-coordinated with distorted trigonal bipyramidal geometry.



i, EtONa, benzene, 12h, 40°C

80 (85%)

The synthesis of potentially biologically active substances whose structure contained a fragment of 5-trifluoromethyl-1,2,4-triazole linked to pyrazolo- or imidazolopyridine core **81** were presented in the article of Roberts et al. [80]. One of the typical schemes of the synthesis of such compounds includes a hydrazinolysis of the cyano group. Subsequent acylation with trifluoroacetic anhydride (TFAA) followed by the closure of the triazole ring afforded **81** (yields unknown).

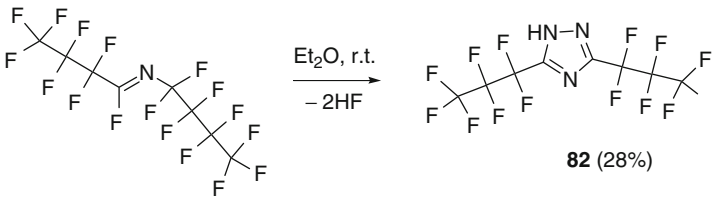


i, NH_2NH_2 H_2O, MeOH, r.t.

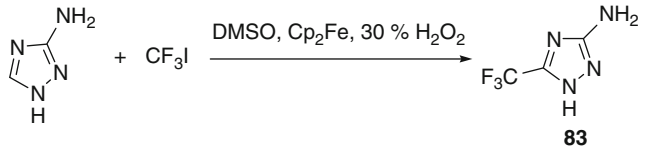
ii, TFAA, r.t.

81

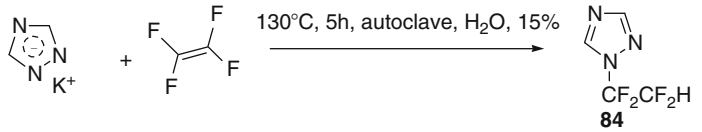
Siedle et al. established that the hydrazinolysis of corresponding fluoroimine occurred via particular mechanism “nucleophilic addition – HF elimination” leading to the formation of 3,5-bis(heptafluoropropyl)-1,2,4-triazole **82** [81].



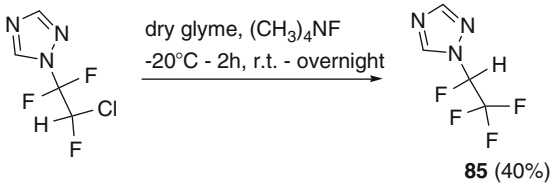
An original procedure of a "direct" incorporation of a trifluoromethyl group into molecules of heteroaromatic substrates was developed by Jamakawa et al. Using this procedure 3-amino-1,2,4-triazole was trifluoromethylated by trifluoromethyl iodide in DMSO in presence of hydrogen peroxide-ferrocene system [82] to obtain 3-amino-5-trifluoromethyl-1,2,4-triazole **83**.



Yagupolskii et al. developed various versions of the alkylation of 1,2,4-triazolate anion with fluoroethylene [83] to form 1-(1,1,2,2-tetrafluoroethyl)-1,2,4-triazole **84** in a low yield.

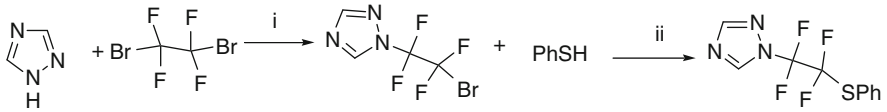


The same authors developed an original method of the synthesis of 1-(1,2,2,2-tetrafluoroethyl)-1,2,4-triazole **85** by treatment of N-(2-chloro-1,1,2-trifluoro)-1,2,4-triazole with tetramethylammonium fluoride [83]. The assumed reaction mechanism consist of several steps. In the first stage elimination of HF and the formation of 2-chloro-1,2-difluoroethylene derivative takes place. Further chlorine atom is replaced by fluorine with the formation of 1,2,2-trifluoroethylene-1,2.4-triazole. Finally addition of HF gave the final product **85**.



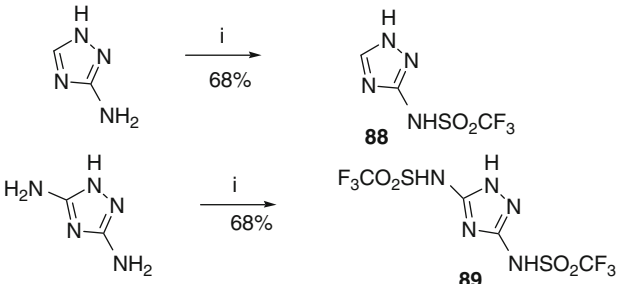
In extension of this study the sodium salt of 1,2,4-triazole was alkylated with 1,2-dibromotetrafluoroethane (Freon 114B2) to obtain N-(2-bromotetrafluoroethyl)-1,2,4-triazole **86**. This compound was then subjected to photoinduced (UV-irradiation)

reaction with thiophenol in liquid ammonia. Selective nucleophilic substitution of bromine with thiophenol residue was achieved under these conditions. As a result N-(2-phenylthiotetrafluoroethyl)-1,2,4-triazole **87** was obtained in a high yield [84, 85].



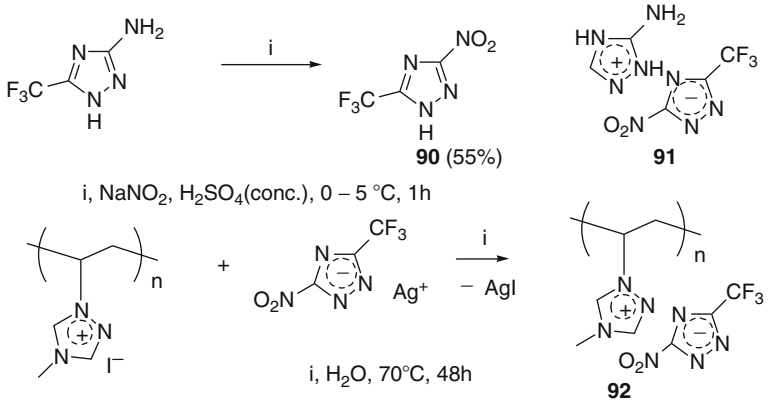
i, DMF, NaH, Bu_4NI, 2h, 55°C, 63% **86** ii, NH_3, hv, (Hg, 950w), 86% **87**

Lately Garg and Shreeve suggested a simple synthesis of trifluoromethanesulfonamide derivatives of 3-amino- and 3,5-diamino-1,2,4-triazoles **88, 89** from the corresponding aminoazoles and trifluoromethanesulfonyl fluoride [86].

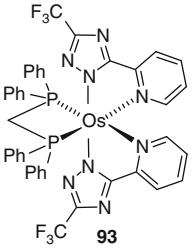


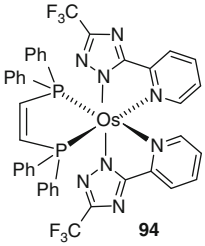
i, CF_3SO_2F, MeCN, Et_3N, r.t., 10-12 h

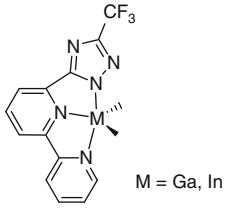
New energetic materials were prepared from by perfluoroalkyl-1,2,4-triazoles. For instance, Shreeve et al. obtained 3-nitro-5-trifluoromethyl-1,2,4-triazole **90** by the diazotization of 3-amino-5-trifluoromethyl-1,2,4-triazole in the concentrated sulfuric acid [87]. In its turn 3-amino-1,2,4-triazole and 3-nitro-5-trifluoromethyl-1,2,4-triazole were used in the preparation of energetic 3-amino-1,2,4-triazolium 3-nitro-5-trifluoromethyl-1,2,4-triazolate **91**. Energetic polymeric material **92** was synthesized containing in the monomer unit ions of 3-nitro-5-trifluoromethyl-1,2,4-triazolate. The yield of polymer is unknown [88].



The perfluoro-1,2,4-triazoles are known to be effective ligands. For instance, a number of charge neutral Os(II) pyridyl-1,2,4-triazolate complexes with either bis(diphenylphosphino)methane **93** or *cis*-1,2-bis(diphenylphosphino)ethene **94** chelates were synthesized, and their structural, electrochemical, photophysical properties and thermodynamic relationships were established [89, 90]. Chi, Carty et al. synthesized 6-(3-trifluoromethyl-1,2,4-triazolyl)-2,2'-bipyridine and built up on this basis tridentate 6-azolyl-2,2′-bipyridine chelate complex compounds of Ga and In **95** [91].



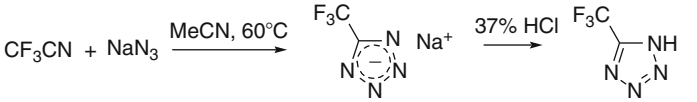




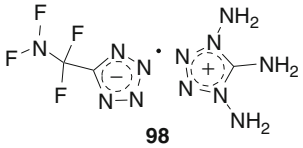
Among trifluoromethyl-derivatives of 1,2,4-triazole, an efficient inhibitors of dipeptidyl peptidaze IV (sitagliptin and its derivatives) have been found (see Sect. 6.1).

3.3 *Tetrazoles*

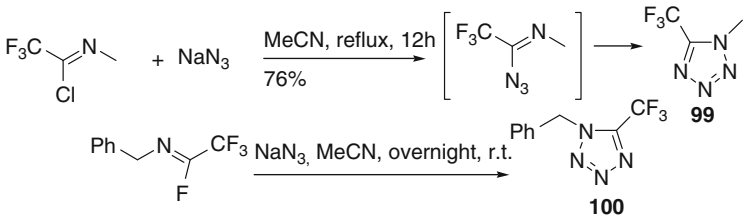
5-Trifluoromethyltetrazole **96** – the simplest of tetrazoles containing a perfluoroalkyl substituent – was prepared for the first time by Norris in 1962 by the cycloaddition of the azide-anion to the trifluoroacetonitrile [92]. This reaction occurred with a considerable heat evolution. The conversion of corresponding anion **97** into the neutral form required the use of concentrated mineral acids due to the relatively high NH-acidity of tetrazole **96** (pK_{BH+} 1.1) [28, 93]. It was shown later that the 5-trifluoromethyltetrazole **96** could be obtained reacting CF_3CN with coordinated azides similarly to the synthesis of 4,5-bistrifluoromethyl-1,2,3-triazole **40** [44].



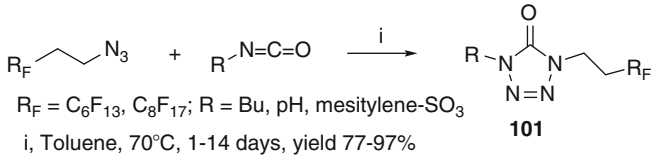
To explore the properties of some energetic salts **98**, in a series of publications Shreeve et al. described the procedure of the synthesis of NH-5-difluoroaminodifluoro methyltetrazole by same manner for which F_2NCF_2CN was used as a precursor [94].



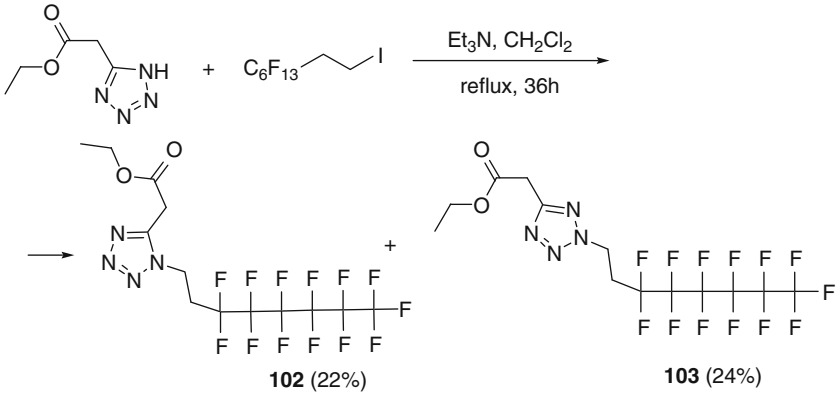
The 1-substituted 5-trifluoromethyltetrazoles may be also obtained by the azidation of imidoyl halides. For instance, the nucleophilic substitution of the chlorine for the azide group in the N-methylimidoyl chloride provided the corresponding imidoyl azide (azidoazomethine), which suffered a cyclization into 1-methyl-5-trifluoromethyltetrazole **99** [95]. Carpenter et al. synthesized 1-benzyl-5-trifluoromethyltetrazole **100** by replacing the fluorine atom in N-benzyltrifluoroacetimidoyl fluoride by an azide group followed by electrocyclic cyclization of the intermediate imidoyl azide (azidoazomethine). The yield of purified product **100** is unknown [39].



1,3-Dipolar cycloaddition of perfluoroalkylethyl azides to isocyanates afforded 1-perfluoroalkyl-4-(*n*-Bu, phenyl or mesitylsulfonyl) tetrazol-5-ones **101** in good yields [96].

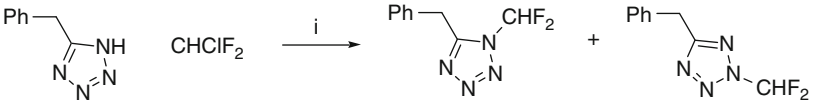


The synthesis of surfactants in the series of fluoroalkyltetrazoles **102**, **103** and the study of their effect on the surface tension of *m*-xylene was described by Read et al. [50, 97].



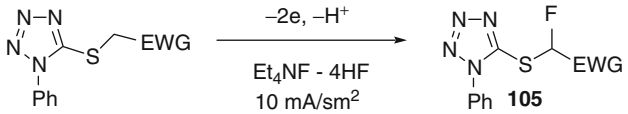
The synthesis of N-fluoroalkyltetrazoles may be carried out also by the alkylation of the corresponding NH-unsubstituted tetrazoles. Jończyk et al. showed that 5-benzyl-1H-tetrazole reacted with chlorodifluoromethane in the presence of

concentrated aqueous sodium hydroxide and a catalyst, benzyltriethylammonium chloride (TEBAC), in THF with the formation of regioisomeric N-difluoromethyl substituted derivatives **104, 105** [98].



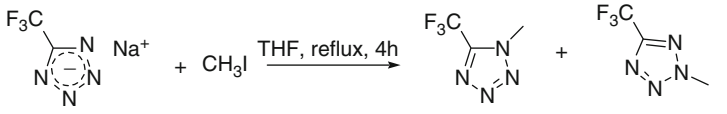
i, 50% aq NaOH, TEBAC, THF, CH_2Cl_2 **104** (23%) **105**(15%)

An interesting approach to the synthesis of tetrazoles with fluorine atoms in the side chain was suggested by Fuchigami et al. who performed an anodic monofluorination of 1-substituted 5-tetrazolyl sulfides containing an α-electron-withdrawing group (EWG) leading to the formation of the corresponding C-F derivatives **105** [99].



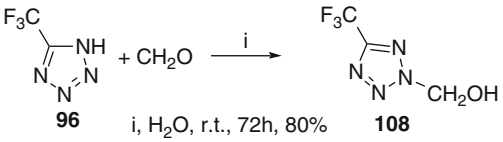
EWG, Solvent, Yield, %: Ph, DME, 38; CO_2Et, MeCN, 46; CN, MeCN, 20

Norris in his pioneering article described also some chemical transformations of 5-trifluoromethyltetrazole **96** [92]. For instance, the alkylation of anion **97** with methyl iodide resulted in regioisomeric N-methyl-5-trifluoromethyltetrazoles **106**, **107** with 2-methyl isomer **107** prevailing. Also a direct halogenation was performed of the 5-trifluoromethyltetrazole sodium salt with the molecular chlorine furnishing the N-chloroderivative of 5-trifluoromethyltetrazole that was found an explosive extremely dangerous at handling [92].

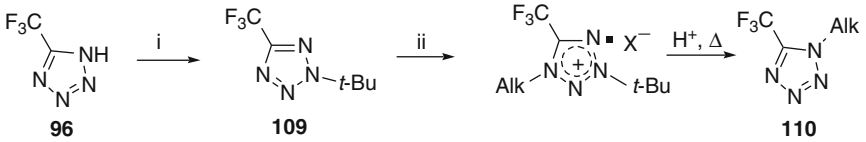


97 **106** (9.8%) **107** (55%)

The high regioselectivity of tetrazolate **97** alkylation in the environment of aqueous acetone giving predominantly the 2H-isomer was later noted also by Spear et al. [100]. 5-Trifluoromethyltetrazole **96** slowly reacts with formaldehyde in water solution at pH 5 giving 2-hydroxymethyl-5-trifluoromethyltetrazole **108** [101]. Later the role of the electronic effects of the substituents at the endocyclic carbon of the tetrazole, and also the influence of the solvation effects on the alkylation regioselectivity of tetrazoles was treated in detail in quite a number of theoretic and experimental publications [28, 102].



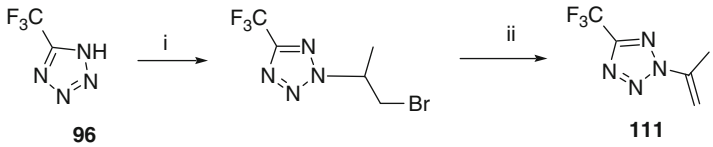
Uncompromising regioselectivity of exhaustive alkylation of 2-substituted 5-trifluoromethyltetrazoles was exploited in a recently developed elegant procedure for the synthesis of 1-alkyltetrazoles starting from *N*-unsubstituted ones. This three-step reaction sequence utilizing an N^2-regioselective *t*-butylation (the product is compound **109**) in the first step, was reported to provide isomerically pure products **110** in high to nearly quantitative yields [103, 104].



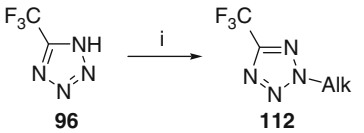
i, *t*-BuOH, 96% H_2SO_4, r.t., 40 min, 92%

ii, AlkX, Alk = Me, Et, *n*-Bu; X = OSO_2OMe, OSO_2Ph, TsO, OEt_2 BF_3

2-(1-Methylvinyl)-5-trifluoromethyltetrazole **111** was obtained by the regioselective alkylation of 5-trifluoromethyltetrazole with 3-bromopropene in sulfuric acid followed by dehydrohalogenation of the intermediate products [105].

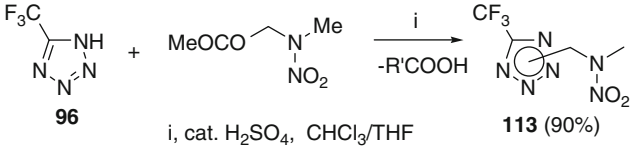


Generally, alcohols, readily generating carbenium cations in the presence of acidic catalysts, were found to react with *NH*-unsubstituted 5-trifluoromethyltetrazole **96** yielding N^2-alkylated products **112** [28, 103]. The reaction can be carried out in neutral organic solvents (chloroform, dichloromethane, acetonitrile, nitromethane) in the presence of catalytic amounts of sulfuric or *p*-toluenesulfonic acids as well as Lewis acids like boron trifluoride etherate or zinc triflate.



i, *t*-BuOH, $CHCl_3$, H_2SO_4 cat., yield 85%

Alkylation of 5-trifluoromethyltetrazole **96** with esters of 2-nitro-2-azapropanol in the presence of catalytic amounts of sulfuric acid was described [106]. Here the regioselectivity of the process was not assessed and a mixture of 1- and 2-alkyltetrazoles **113** (the ratio is unknown) was obtained.

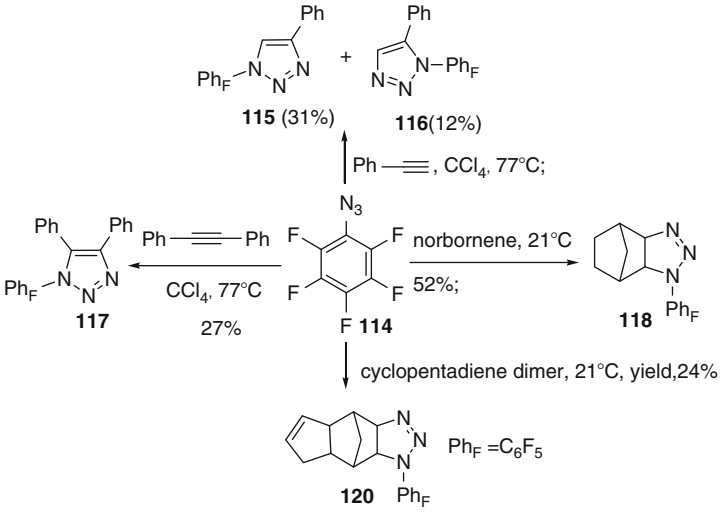


Gaponik et al. found that the NH-unsubstituted 5-trifluoromethyltetrazole in the systems containing transition metal salts formed water-soluble polymeric complexes [107].

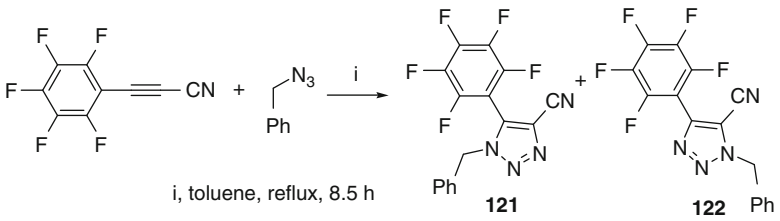
4 Perfluoroaryl and Fluorobenzo-Fused Heterocycles

4.1 1,2,3-Triazoles

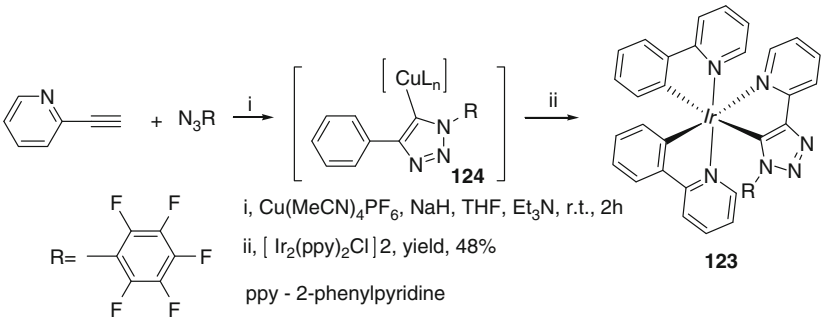
Banks and Prakash were first to demonstrate the wide opportunities of the 1,3-dipolar cycloaddition of 1-azido-2,3,4,5,6-pentafluobenzene **114** to acetylenes as the general method of the synthesis of 1,2,3-triazoles **115**–**120** containing a perfluorophenyl group at the endocyclic nitrogen atom [108].



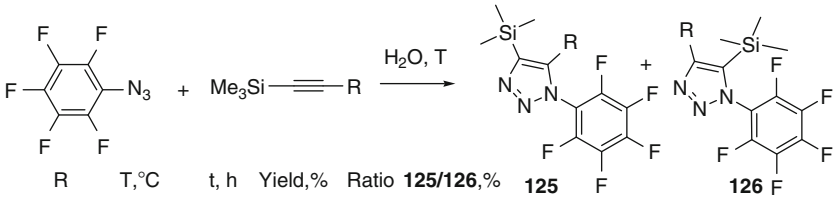
1,3-Dipolar cycloaddition of benzyl azide to 3-(2,3,4,5,6-pentafluorophenyl) propynenitrile resulted in the formation of isomeric 1,2,3-triazoles **121, 122** in 17 and 61 % yield respectively [109].



Swager et al. synthesized various Ir(III) complexes **123**, among them complexes containing a perfluoroaryl substituent [110]. The method of building up these structures is underlain by the "click-reaction" leading to the formation of the corresponding Cu(I)-triazolide intermediate **124**.

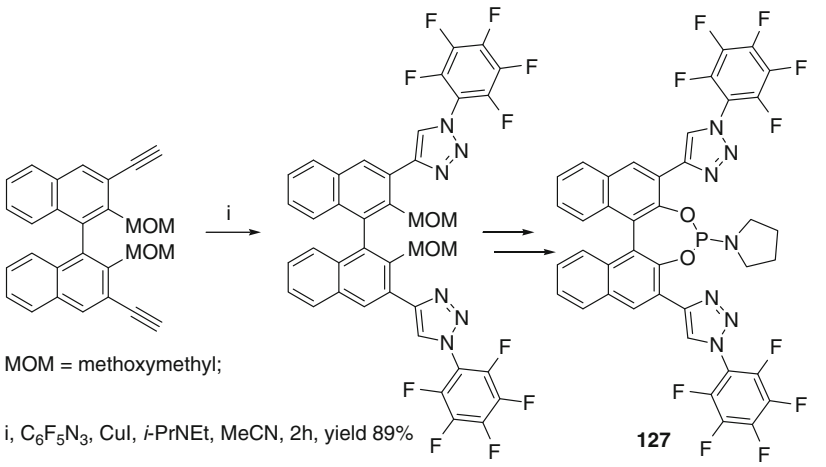


Schubert et al. subjected to a systematical examination reactions of 1,3-[3+2]-cycloaddition of substituted aromatic azides to trimethylsilylacetylenes in water affording regioisomeric 1,2,3-triazoles, in particular, those containing a perfluoroaryl substituent at endocyclic atoms of the heterocycle **125, 126** [111].

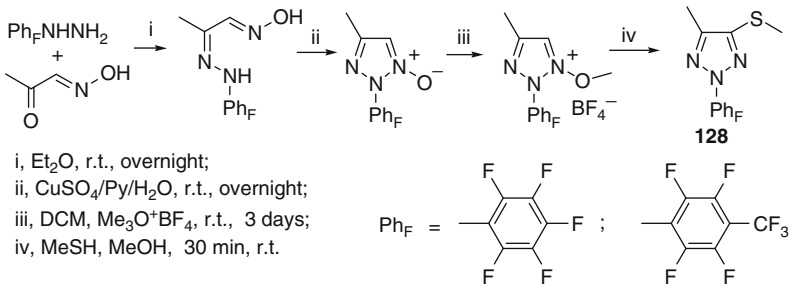


R	T,°C	t, h	Yield,%	Ratio **125/126**,%
Mesityl	110	30	61	>91
p-$NO_2C_6H_4$	110	17	28	87
CO_2Et	85	5	92	22

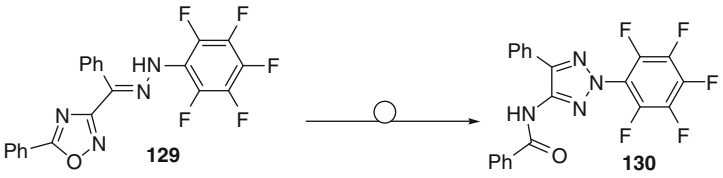
Recently, a number of chiral phosphoramidite ligands **127** containing 1,2,3-triazole ring at the 3,3′-positions of the binol scaffold were synthesized by McErlean et al. [112].



O'Mahony et al. [113] advanced an alternative version of cyclization resulting in perfluoroaryl-1,2,3-triazoles. These authors demonstrated that 2-(2,3,4,5,6-pen tafluorophenyl)-4-methyl-5-methylthio-1,2,3-triazole **128** obtained by this procedure (yield is unknown) possessed considerable pesticide activity.

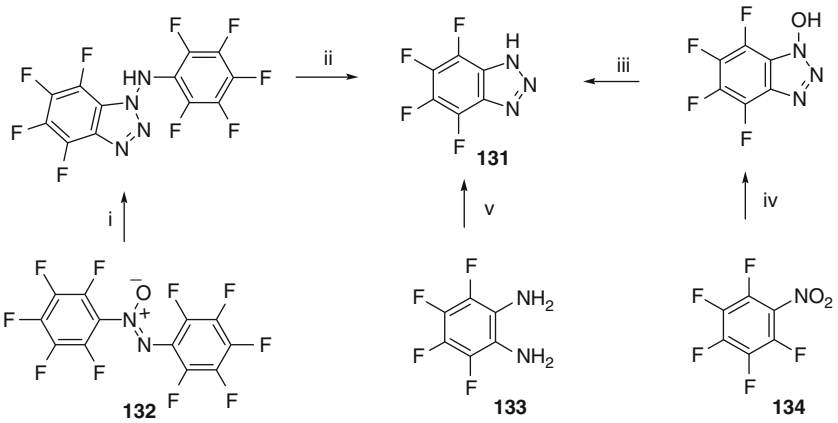


The paper of Frenna, Spinelli et al. contained data on the kinetics of the rearrangement of 3-benzoyl-5-phenyl-1,2,4-oxadiazole **129** into the corresponding 2-aryltriazoles **130** (Boulton–Katritzky reaction) [114].



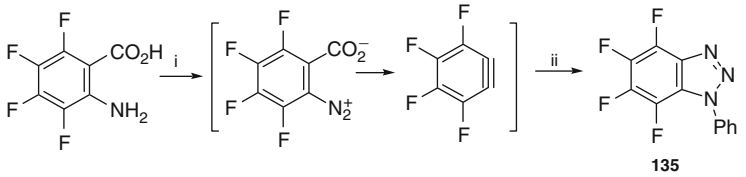
Haszeldine in 1970 developed several routes for the synthesis of perfluorobenzofused 1,2,3-triazole **131** from decafluoroazoxybenzene **132**, tetrafluoro-o-phenylenediamine **133**, and 2,3,4,5,6-pentafluoronitrobenzene **134** [115]. More than a quarter of a century later Heaton et al. suggested a similar version of the synthesis

of tetrafluorobenzotriazole **131** from 1,2,3,4-tetrafluoro-5,6-dinitrobenzene and 3,4,5,6-tetrafluoro-1,2-phenylenediamine that were regarded as versatile semiproducts in the synthesis of various tetrafluorobenzoheterocycles [116].



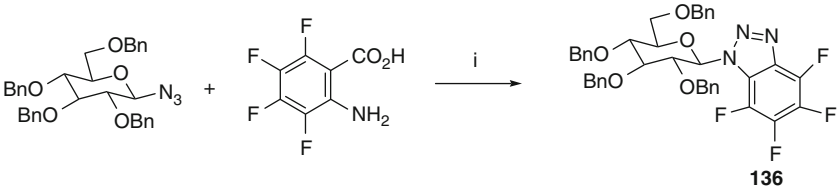
i, NH_2NH_2 H_2O, EtOH, yield, 28%; ii, HI, yield, 22%; iii, HI, almost 100%; iv, $NH_2NH_2H_2O$, EtOH, yield,14%; v, HNO_2, yield, 84%

The synthesis of 1-phenyl-4,5,6,7-tetrafluorobenzotriazole **135** from tetrafluoroanthranilic acid through tetrafluorodehydrobenzene as intermediate is described by Yakobson et al. in 1967 [117].



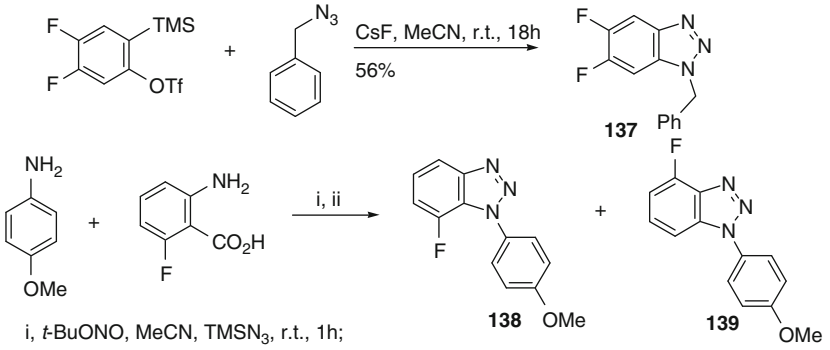
i, BuONO, CH_2Cl_2,2h, reflux ii, $C_6H_5N_3$, acetone, yield 35%

Williams et al. reports that 1-(2,3,4,5-tetra-O-benzyl-β-*D*-glucosyl)-3,4,5,6-tetrafluoro-1–H-benzo[d][1,2,3]-triazole **136** can be prepared from available anomeric azide and 2-amino-3,4,5,6-tetrafluorobenzoic acid through "click" methodology [118].



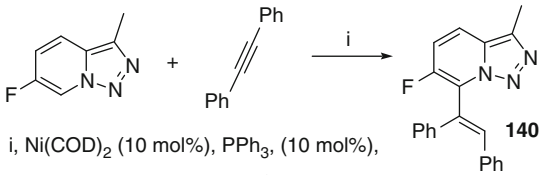
i, 1 equiv. azide, 3 equiv. of anthranilic acid, dioxane, 5 equiv. isoamil nitrite (CH_2Cl_2), 30 min, reflux under N_2, yield 42%

Recently "click-chemistry" approach to the preparation of fluorobenzo-fused 1,2,3-triazole **137** was demonstrated in the paper of Larock et al. [119]. Zhang and Moses developed a special version of one-pot "click-chemistry" for the preparation of monofluoro derivatives of benzotriazole **138**, **139** from *p*-methoxyaniline and *o*-fluoroanthranilic acid with two *in situ* generated intermediates: *p*-methoxyphenyl azide and fluorobenzyne [120].



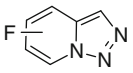
i, *t*-BuONO, MeCN, $TMSN_3$, r.t., 1h;
ii, *o*-fluoroanthranilic acid, *t*-BuONO, MeCN, reflux, 15h, yield, 36%, **138/139** =1:1

Driver et al. explored the Ni-catalyzed C7-alkenylation of 6-fluorotriazolopyridine with diphenylacetylene applying bis-(1,5-cyclooctadiene)nickel(0) ($Ni(COD)_2$) leading to the formation of fluorobenzotriazole **140** [121]. It was underlined in the article that the crucial importance for the high conversion of the reagents and the sufficient yields of the alkenylation products had the selection of the Lewis acid which was $AlMe_3$ in this study.



i, $Ni(COD)_2$ (10 mol%), PPh_3, (10 mol%),
$AlMe_3$ (1.2 eq), toluene, 70°C, yield, 71%

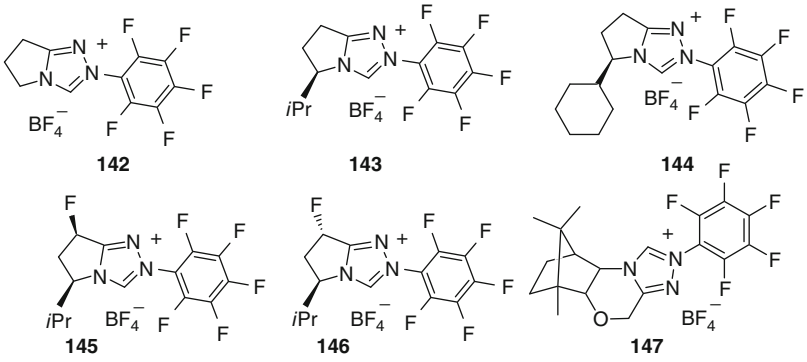
Some isomers of fluorobenzotriazoles are capable of ring-chain rearrangements with the opening of the triazole ring. Elguero, Alkorta et al. performed a quantum-chemical investigation of the ring-chain isomerization of fluoro derivatives of 1,2,3-triazolopyridines **141** [122].



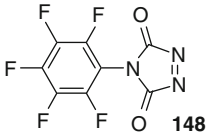
141

4.2 1,2,4-Triazoles

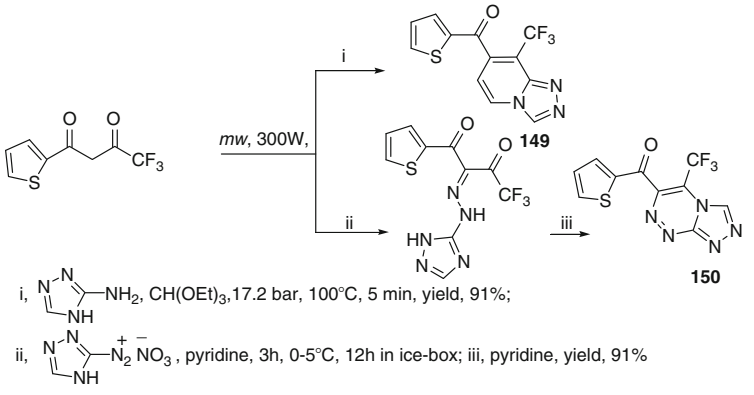
Efficient enantioselective catalysts of various organic reactions were found among pentafluoroaryl-1,2,4-triazoles. Tetrafluoroborates of 2-(2,3,4,5,6-pentafluorophenyl)-1,2,4-triazolium **142–147** are practically useful compounds. The synthesis and application examples of these catalysts are presented in the series of publications [123–129].



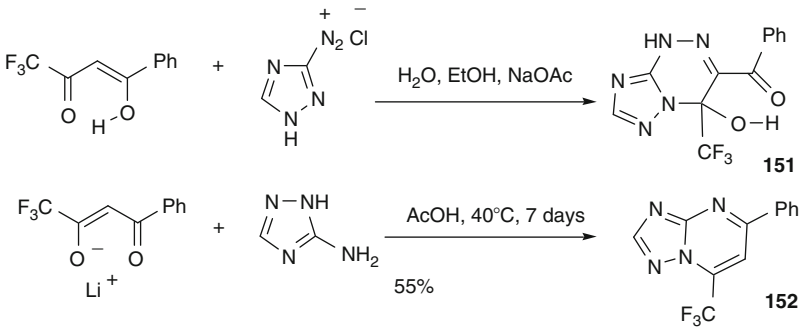
As it was shown by Golding et al., 4-(2,3,4,5,6-pentafluorophenyl)-1,2,4-triazoline-3,5-dione **148** belonging to perfluoroaryl-1,2,4-triazoles is an efficient reagent for trapping volatile organic compounds (VOCs) included in the list of the most important environmental pollutants [130].



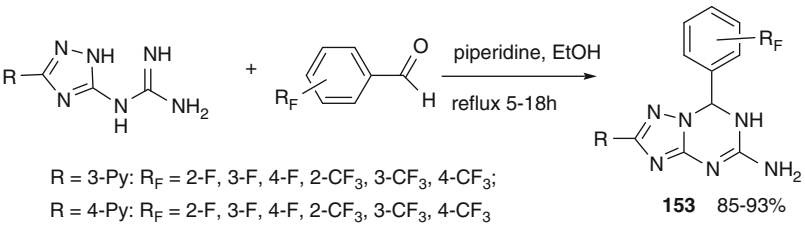
Shaaban showed the possibility to obtain under the microwave irradiation fused systems, 1,2,4-triazolo[1,5-a]pyrimidine **149** and 1,2,4-triazolo[3,4-c][1, 2, 4]triazine **150**, containing a trifluoromethyl group as a substituent in the six-membered ring [131].



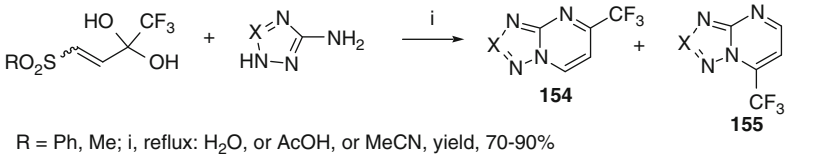
Saloutin, Chupakhin et al. applied a related condensation involving 1,2,4-triazolyldiazonium resulting in the formation of 6-benzoyl-7-hydroxy-7-trifluoromethyl-4,7-dihydro[1,2,4]triazolo[5,1-c][1,2,4]triazine **151** (59 %) [132]. Rusinov et al. reported on another successful example of this reaction involving lithium β-diketonates and 3-amino-1,2,4-triazole and affording 7-fluoromethyl-1,2,4-triazolo[1,5-a]pyrimidine **152** [133].



Dolzhenko et al. synthesized 12 new fluorinated 7-aryl-2-pyridyl-6,7-dihydro[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-amines **153** via three-step procedure starting from (iso)nicotinic hydrazides [134].



Nenajdenko et al. obtained regioisomeric 5-CF_3 or 7-CF_3 triazolopyrimidines **154**, **155** by the reaction of 1,1,1-trifluoro-4-sulfonyl-but-3-ene-2,2-diol with 3-amino-1,2,4-triazole [135].

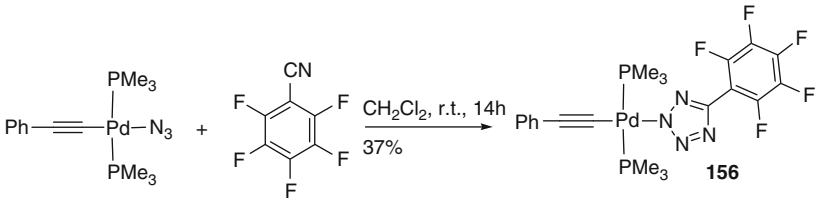


R = Ph, Me; i, reflux: H_2O, or AcOH, or MeCN, yield, 70-90%

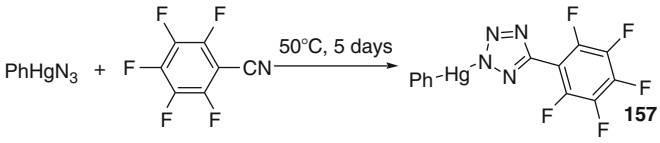
X = HC, MeC, CF_3C, (1-Ad)C, *t*-BuC, PhC, 4-$MeOC_6H_4C$, 4-ClC_6H_4C, 2-BrC_6H_4C, MeO_2CC

4.3 Tetrazoles

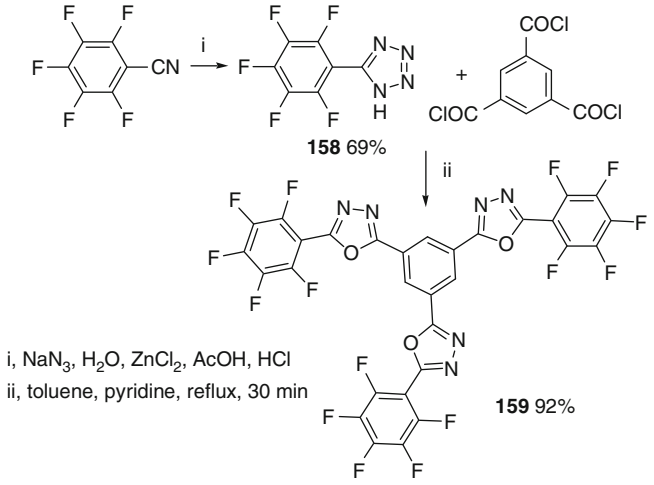
Kim et al. showed that 1,3-dipolar cycloaddition of alkynyl Pd(II) azido complexes to perfluorobenzonitrile proceeded at room temperature affording the corresponding N-coordinated tetrazolato compound (*trans*-[Pd(C≡CPh)(N_4C-C_6F_5)(PMe_3)$_2$]) **156** [136].



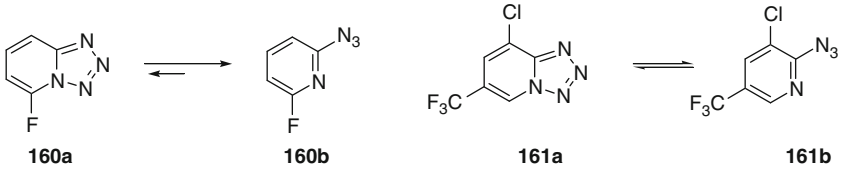
Klapötke et al. obtained recently by the intermolecular 1,3-dipolar cycloaddition of organomercury(II) azide to pentafluorocyanobenzene the corresponding (5-pentafluorophenyl-2H-tetrazol-2-yl)phenylmercury **157** (yield is unknown) [137].



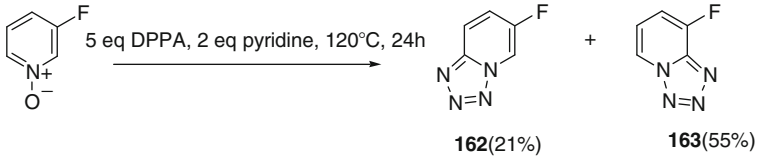
The synthetic methods and photoluminescent properties of new dendrimers with an electron-deficient fluorinated starburst oxadiazole core were discussed in the publication of Chen, Fan et al. [138]. Here in the first, key stage the 1,3-dipolar cycloaddition occurred of 2,3,4,5,6-pentafluorobenzonitrile to NaN_3 along the known procedure (Demko-Sharpless) giving 5-(perfluorophenyl)-1H-tetrazole **158**. In the next stage 5-(perfluorophenyl)-1H-tetrazole was acylated by benzene-1,3,5-tricarbonyl trichloride to obtain 1,3,5-(5-perfluorophenyl-1,3,4-oxadiazol-2-yl)benzene **159**.



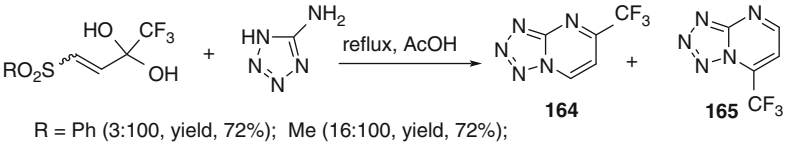
The fused tetrazoles are prone to ring-chain isomerism. Cmoch and Korczak investigated the azido-tetrazole equilibrium between two fluorine-containing tetrazoles: 6-fluorotetrazolopyridine **160** and 6-trifluoromethyl-8-chlorotetrazolopyridine **161** [139]. It turned out that the equilibrium in the case of compound **160** is completely shifted to the side of azide **160b**, whereas for compound **161** the NMR spectra showed the presence of both tetrazole **161a** and azide **161b** forms.



Keith (2006) developed an original one-stage solvent-free method of preparation of fluorine-containing tetrazolo[1,5-a]pyridines **162**, **163** forming in a plausible yield from the corresponding pyridine N-oxide and activated diphenylphosphorazidate (DPPA) in the presence of pyridine [140]. In this case the azido-tetrazole equilibrium is virtually totally shifted to the ring form.



In the above cited paper [135] it was also reported that the reaction of 1,1,1-trifluoro-4-sulfonylbut-3-ene-2,2-diol with 5-aminotetrazole furnished regioisomeric 5-CF_3 or 7-CF_3 tetrazolopyrimidines **164**, **165**. It was also shown that the ratio of the regioisomers (at equal overall yield of the products) was governed by the nature of the substituent R in the 1,1,1-trifluoro-4- sulfonylbut-3-ene-2,2-diol.



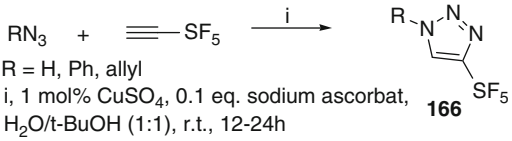
R = Ph (3:100, yield, 72%); Me (16:100, yield, 72%);

5 Other Types of Perfluorinated Substituents

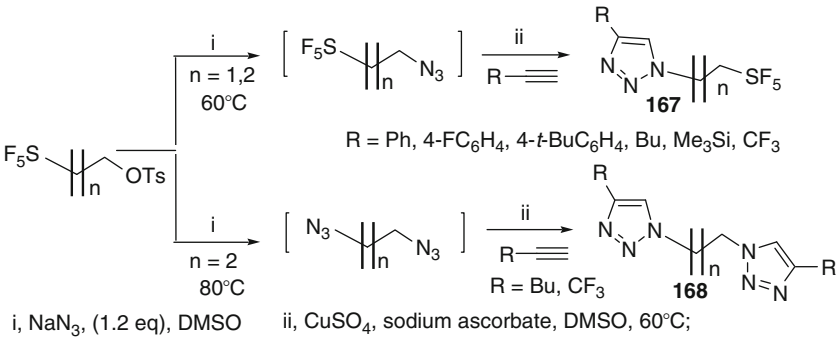
5.1 SF_5 Derivatives

Pentafluorosulfanyl (SF_5) group is interesting as a stable moiety bearing simultaneously five fluorine atoms. In recent reviews [141, 142] it was stressed that this group is now widely applied in the organic synthesis and in industry. 1,2,3-Triazoles

containing the SF_5 group attached to the endocyclic carbon atoms became recently more accessible. A number of publications describes the acceleration of the 1,3-dipolar cycloaddition with the use of the catalytic system based on Cu(I) generated *in situ* from $CuSO_4$ and sodium ascorbate. This procedure made it possible to obtain in relatively mild conditions a series of 1-R-4-pentafluorosulfanyl-1,2,3-triazoles **166** in "good yield" [62, 143].



It should be noted that the recent advances in the chemistry of trifluoromethyl- and pentafluorosulfanyl derivatives of tri- and tetrazole favor the applied studies of these unique objects of the chemistry of the fluoro-containing heterocycles. Thus a significant attention is paid to 1,2,3-triazoles and tetrazoles containing a pentafluorosulfanyl group. The introduction of this group into the heterocycle provides a possibility to prepare energetic compounds of high density [142]. Shreeve et al. investigated the 1,3-dipolar cycloaddition of alkyl azides containing a terminal pentafluorosulfanyl group to substituted acetylenes [144].

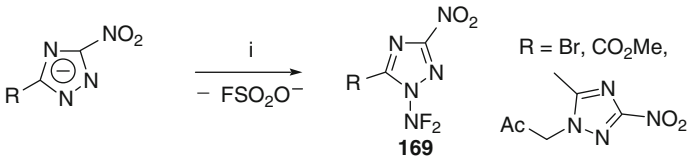


In this case the yield of pentafluorosulfanylalkyl-4-R-1,2,3-triazoles **167** crucially depends on the ratio of the initial reagents and on the reaction temperature. At the excess of the sodium azide and at a high temperature the replacing azidation occurs of both the tosyl and the pentafluorosulfanyl groups giving the corresponding diazide and further bis-1,2,3-triazoles **168** in good yields [144].

5.2 NF_2 Derivatives

Tri- and tetrazoles containing an NF_2 group at the endocyclic nitrogen or carbon atoms belong to an exotic group of highly energetic compounds. The combination in the same molecule of the polynitrogen heterocyclic ring and the electron-acceptor

difluoroamine group enhanced the energy potential of these molecules. The prospect of application of the difluoroamino derivatives of 1,2,4-triazole as components of energetic ionic liquids was estimated by the *ab initio* quantum-chemical calculations [21]. In the evaluation of the application prospects of the N-difluoroazoles their high sensitivity to explosive decomposition caused by various effects (impact, friction, electric discharge, fire beam) should be taken into consideration [94, 145, 146]. In an original article Shevelev et al. [147] reported on the preparation of NF_2 derivatives of 3-nitro-1,2,4-triazole **169** by the action of O-fluorosulfonyl-N,N-difluorohydroxylamine (F2NOSO2F) on NH-form of the corresponding 1,2,4-triazoles.



i, F_2NOSO_2F, PTC: polyester PEG-400, $NaHCO_3$ aq, yield, 22-50%

6 Applications

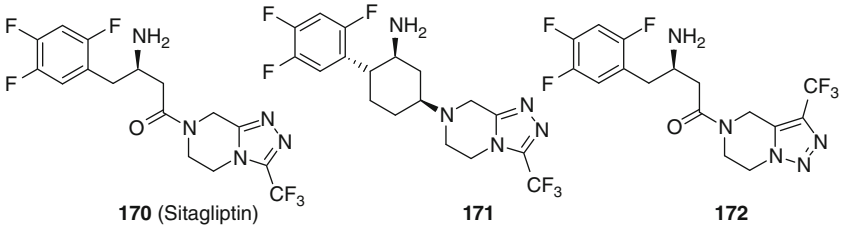
6.1 Medicine and Medicinal Chemistry

The medicinal applications of fluorinated tri- and tetrazoles grow steadily [148]. Some compounds containing in their molecular structure these heterocycles are included in the list of highly efficient modern drugs [149]. Many among fluorinated tri-and tetrazoles are regarded as promising antidiabetic, cardiological, fungicidal, antibacterial, and antiviral pharmaceuticals, drugs for the treatment of the central nervous system, etc. We give below some examples of these compounds exhibiting versatile kinds of biological activity.

6.1.1 Antidiabetics

Sitagliptin **170**, the first inhibitor of dipeptidyl peptidase IV (DPP-4) approved by the FDA for the treatment of type 2 diabetes, has a trifluorophenyl group linked to a β-amino butanoyl moiety coupled to a triazolopiperazine [150, 151]. Many publications appeared treating the problem of the synthesis of this compound and its derivatives. For instance, a scheme of asymmetric synthesis of the sitagliptin phosphate from the precursor, α,β-enamine amide, is given in [152]. A wide search for effective antidiabetic agents was performed among the homologues of this compound; therewith the varied structural parameter was the substituent in the phenyl ring [153] and also the substituents in the piperazine fragment [154]. Biftu et al. based on the data of XRD analysis and computer simulation proposed a structure and

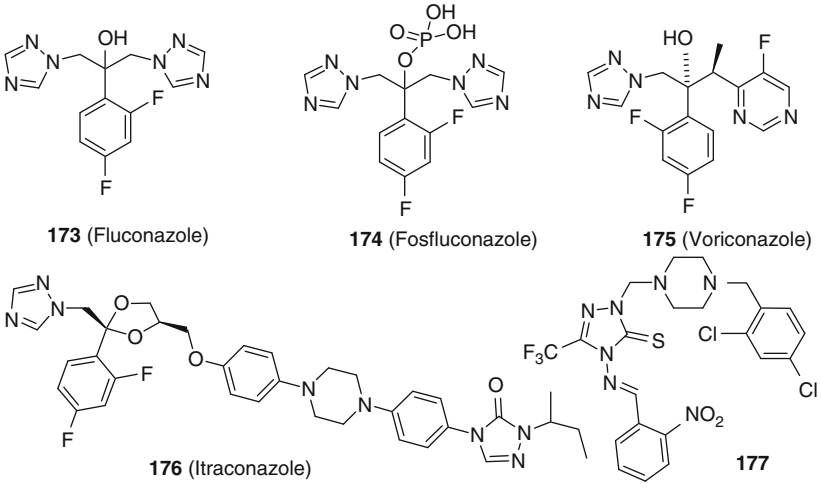
synthesized a new analogous compound **171** that also proved to be an efficient inhibitor of DPP-4 (IC50 = 21 nM), showed high activity *in vivo* and possessed a feasible pharmacokinetic profile [155]. Note an interesting study of Chen et al. who synthesized and tested the biological activity of a series of Sitagliptin analogs in whose molecules the fragment of 3-trifluoromethyl-1,2,4-triazolopiperidine was replaced by 4R-1,2,3-triazolopiperidine moiety. The highest biological activity was found in compound **172** [156].



170 (Sitagliptin) **171** **172**

6.1.2 Fungicides

The following fluoroaryl derivatives of 1,2,4-triazole belong to the third generation fungicides: Fluconazole **173**, Fosfluconazole (prodrug) **174**, Voriconazole (UK 109496) **175**, Itraconazole **176** [4]. All these compounds are the inhibitors of the fungal cytochrome P450 enzyme 14α-demethylase. Recently results were published of the investigation of the fungicidal activity of the derivatives of 3-trifluoromethyl-1,2,4-triazole-5-thione: one among these substances, **177,** exhibited a high activity [157]. At present the research is carried out on the preparation of active pharmaceutical ingredients of new fungicides, Fluconazole analogs, containing alongside the 1,2,4-triazole ring fluoropyrimidine, tetrazole, and also the other heterocyclic fragments [158].



173 (Fluconazole) **174** (Fosfluconazole) **175** (Voriconazole)

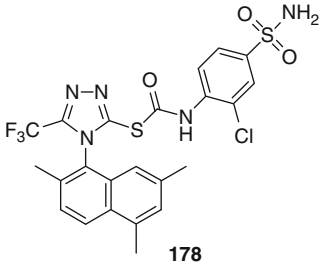
176 (Itraconazole) **177**

6.1.3 Antibacterials

Faidallah et al. showed that the derivatives of 3,5-di(trifluoromethyl)-1,2,4-triazolesulfonyl urea and thiourea exhibited a pronounced antimicrobial action [159]. McGeary et al. established a considerable inhibitory activity of 4-methyl-5-(trifluoromethyl)-4H-1,2,4-triazole-3-thiol and its derivatives with respect to β-lactamases [160].

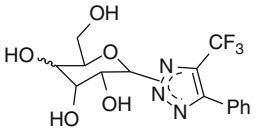
6.1.4 Antiviral Agents

Girardet et al. synthesized and investigated the anti-HIV-1 activity of the derivatives of 3-trifluoromethyl-1,2,4-triazole-5-thiol **178** [161]. The anti-HIV action of compound **178** proved to be comparable with that of the efficient protease inhibitor Efavirenz. The authors of the article noted that the compound exhibited single-digit nanomolar activity against the Y188L mutant, with no cytotoxicity.

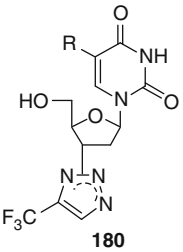


178

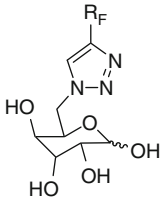
Known publications were cited in [162] concerning the structures of 1,2,3-triazole analogs of nucleosides containing a polyfluoroalkyl substituent in the heterocyclic core **179**–**181**.



179

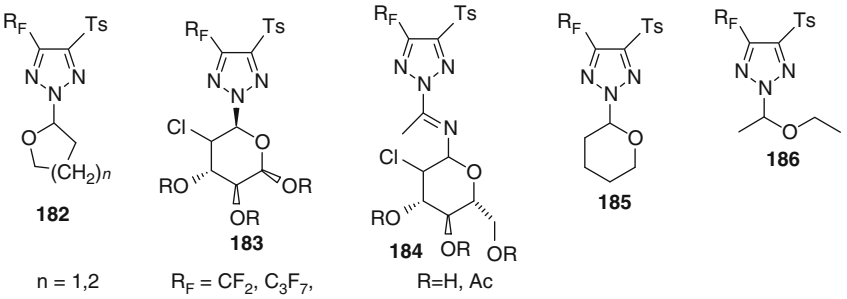


180



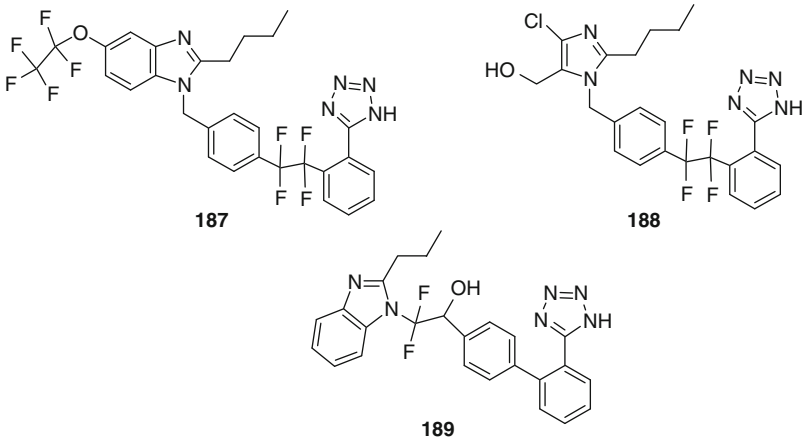
181

Nucleoside mimetics, N^2-substituted derivatives of 4-tosyl-5-polyfluoroalkyl-1,2,3-triazoles containing fragments of 3-chlorotetrahydrofuran, 3-chloro-tetrahydropyran, tetrahydropyran, dihydrofuran, dihydropyran, or acyclic substituents, were also studied **182**–**186** [162]. It was demonstrated that some among the studied compounds exhibit a pronounced anti-Epstein-Barr virus (EBV) activity.



6.1.5 Hypotensive Drugs

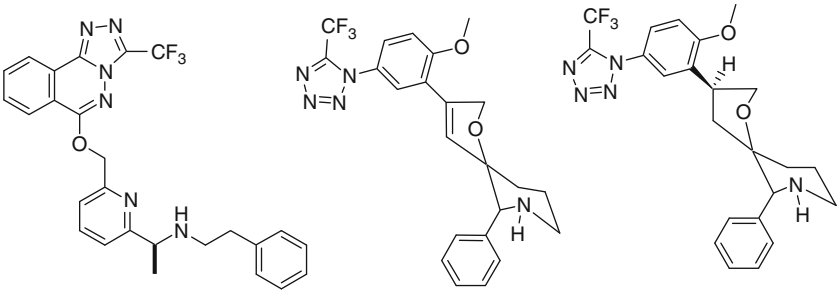
Angiotensin II receptor antagonist like Losartan and its analogs retain strong positions on the pharmaceutical market of the hypotensive drugs [158]. Yagupolskii et al. have synthesized two fluorine-containing Losartan analogs with fluoroalkyl substituents **187**–**189**, whose pharmacological activity is expected to be high [163].



6.1.6 CNS Therapy

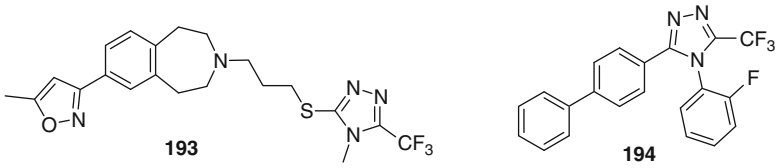
Lebsack et al. produced a series of 1,2,3-triazolo[3,4-a]phthalazine derivatives, in particular, containing a trifluoromethyl substituent in the fused 1,2,4-triazole ring **190**, as high-affinity ligands to the $\alpha_2\delta$-1 subunit of voltage gated calcium channel [164]. These compounds are interesting as anticonvulsant drugs. The work of Williams et al. [165] consisted in the synthesis and the study of the biological activity of new antidepressants, 3-styryl[4.5]-spiroether and [4.5]-spiroether neurokinin-1 (NK1) antagonists **191**, **192**, containing in the molecular structure

trifluoromethyltetrazol-1-yl fragment. The research concerning the pursuit of promising neurokinin-1 (NK1) antagonists, containing fluorinated tri- and tetrazoles is continued [166].



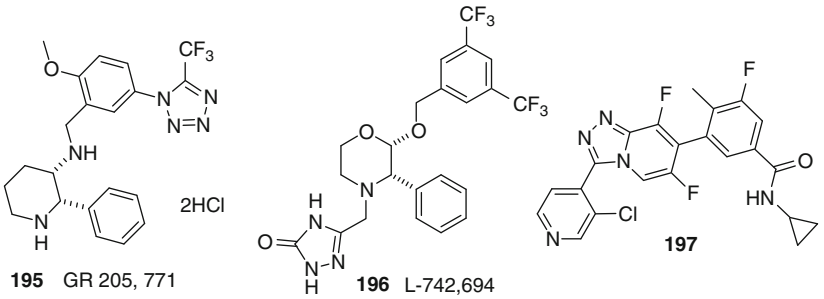
190 **191** **192**

1,2,4-Triazol-3-yl-thiopropyl-tetrahydrobenzazepine **193** whose structure includes a nonfused 1,2,4-triazole-3-trifluoromethyl-5-thiol fragment separated by an alkyl bridge from the benzazepine framework was found to be a potent and selective dopamine D_3 receptor antagonist [167]. Sugane et al. established the high biological activity *in vitro* of new glycine transporter 1 (GlyT1) inhibitors 3-biphenyl-4-yl-4-(2-fluorophenyl)-5-R-4H-1,2,4-triazole, in particular, of compound **194** [168].



193 **194**

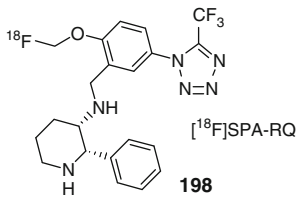
Below two structural formulas of potent, orally active, long-acting morpholine acetal human NK-1 receptor antagonists **195**, **196**, are given. These compounds are tested as efficient drugs for the treatment of the Alzheimer disease [169]. The fluorine-containing biaryl-triazolopyridine **197** is tried as a potent and selective p38α inhibitor for stress relief [170].



195 GR 205, 771 **196** L-742,694 **197**

6.1.7 Imaging Agents

One of the modern ways of CNS disorders diagnostics depends on the development of new radiolabeled NK1 receptor antagonists. Some examples of fluorine-18 labeling compounds are known [171, 172], effective radioligands for imaging brain neurokinin type-1 (NK1) receptors in clinical research and drug discovery with positron emission tomography, like [^{18}F]SPA-RQ **198**.



[^{18}F]SPA-RQ

198

6.2 Light-Emitting Diodes

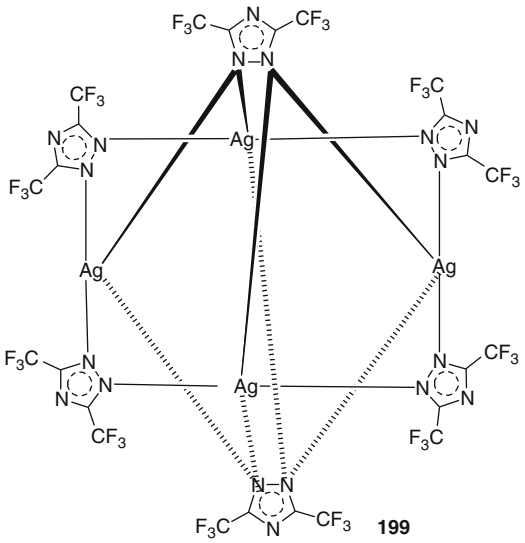
Some complex compounds of fluorinated tri- and tetrazoles possess interesting photo- and electroluminescent properties. We have given above formulas of **93**, **94,** representatives of a new series of charge neutral Os (II) pyridyl 3-trifluoromethyl- 1,2,4-triazolate complexes with either bis(diphenylphosphino)methane or cis-1,2-bis(diphenylphosphino)ethene chelates. Their structural, electrochemical, photophysical properties and thermodynamic relationship were established [89, 90]. It was demonstrated that such coordination compounds can be used in the production of highly efficient white [173], blue [174], orange, and red organic light-emitting diodes (LEDs) [175].

The photo- and electroluminescence properties of a series of novel, heteroleptic, *mer*-cyclometallated iridium complexes have been fine-tuned from green to blue by changing the substituents on the 3-trifluoromethyl-1,2,4-triazolylpyridyl ring of the ligand [176, 177]. Chi, Chou, Wu et al. synthesized Ir(III) emissive complexes with 5-pyridyl-3-trifluoromethyl-1,2,4-triazole ligand which might be used in white OLEDs technologies [178].

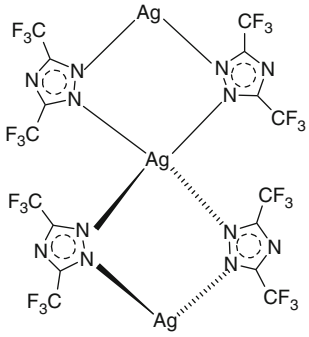
6.3 Sorbents, Ion Liquids, and Surfactants

Omary et al. have demonstrated that fluorous metallorganic frameworks (FMOFs) **199**, **200** are highly hydrophobic porous materials with a high capacity and affinity to C_6-C_8 hydrocarbons of oil components [179]. FMOFs exhibits reversible adsorption with a high capacity for *n*-hexane, cyclohexane, benzene, toluene, and *p*-xylene, with no detectable water adsorption even at near 100 % relative humidity drastically outperforming activated carbon and zeolite porous materials. The results suggest

great promise for FMOFs in applications like removal of organic pollutants from oil spills or ambient humid air, hydrocarbon storage and transportation, water purification, *etc.* under practical working conditions



199



200

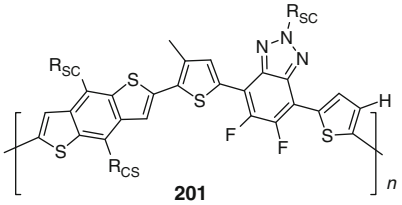
Read et al. synthesized surface-active derivatives of 1,2,3-triazole **49**, **50** containing at the nitrogen atom perfluoroalkyl (lipophilic) substituents, and at the carbon atom perfluoroalkoxy or alkoxy (hydrophilic) groups. It is significant that the surfactant properties of these compounds can be purposefully regulated varying the length of the fluoroalkyl chain [49, 50].

The ionic liquids formed by the 1,2,4-triazolium cation and dinitramide anion as well as charge-diffuse tetrazolium cation with a variety of substituents coupled with various (usually oxygen containing) anions have been studied by *ab initio* quantum chemistry calculations [21, 180].

6.4 Ion and Electron Conductors

We cited above the study of Boskurt et al. who synthesized 5-(perfluoroheptyl)-3H-1,2,3-triazole-4-carboxylate **65** [69]. They also reported on the effect of the proton conductivity observed in the solutions of organic electrolytes with the additives of this fluoroalkylated 1,2,3-triazole. Recent research advances on conjugated polymers for photovoltaic devices have focused on creating low band gap materials, but a suitable band gap is only one of many performance criteria required for a successful conjugated polymer [181]. This work focuses on the design of two medium band gap copolymers for the use in photovoltaic cells which are designed to possess a high hole mobility, low highest occupied molecular orbital and lowest

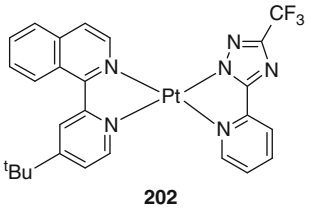
unoccupied molecular orbital energy levels. The resulting fluorinated polymer **201** is a viable candidate for the use in highly efficient tandem cells. It also highlights other performance criteria which contribute to high photovoltaic efficiency, besides a low band gap.



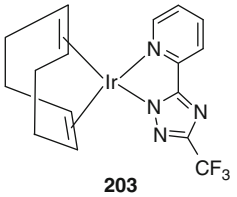
201

6.5 Ligands

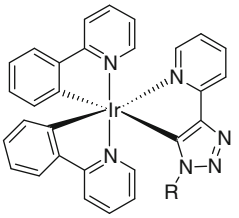
Some fluorine-containing tri- and tetrazoles behave as polidentate ligands and form stable complex compounds with various metal ions. The coordination compounds of Os(II), Ir(III), Ga(III), In(III), Ag(I), Sn(IV) with 5-pyridyl-2-yl-3-trifluoromethyl-1,2,4-triazole ligands we have already mentioned.



202

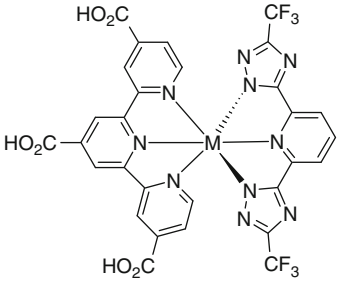


203



R = C_6F_5

204



M = Os(II), Ru(II)

205

Let us cite some other characteristic examples. Thus, based on 5-(6-methylpyridin-2-yl)-3-trifluoromethyl-1,2,4-triazole ligand platinum(II) complexes **202** were synthesized with spatially encumbered chelates, and their photophysical properties were also studied [182]. Compound **202** was found to be weakly emissive in both

Table 1 1,2,4-triazolium salts as catalysts of enantioselective reactions

Catalysts	Reaction (synthesis)	References
142	Macrocyclization of α,γ-dialdehydes	[123]
	Nucleophilic carbyne-catalyzed redox azidation of epoxyaldehydes	[124]
144	Synthesis of *trans*-γ-lactams; the most efficient *trans*-γ-lactam synthesis has been achieved using cyclohexyl-substituted carbyne precursor	[129]
145	The asymmetric intermolecular Stetter reaction was investigated	[125]
147	Enantioselective N-heterocyclic carbene-catalyzed Michael addition reactions to α,β-unsaturated aldehydes by redox oxidation	[126]
	Asymmetric intramolecular Stetter reaction	[127]

fluid and solid states at room temperature. Exotic coordination compounds are also known prepared from the mentioned bidentate ligands and the isoelectronic system Ir(I) **203** with distorted square-planar geometry [183]. Here the lowest absorption band consists of increased triplet $d\pi \rightarrow \pi$ transitions of Ir (I) atom. Later Swager et al. obtained heteroleptic tris-cyclometallated Ir(III) complexes **204** based on 2-(1-perfluorophenyl-1,2,3-triazol-4-yl)pyridine [110]. Complex compounds **205** formed by two tridentate ligands coordinated to Os(II) or Ru(II) interesting as components of dye-sensitized solar cells (DSCs), were recently prepared by Chou et al. [184].

6.6 Organic Catalysis

Chiral N-pentafluorophenyl 1,2,4-triazolium salts (triazolium bicyclic catalysts) had been found to significantly influence reaction yields and enantiomeric ratios. The examples of the application of triazolium bicyclic catalysts **142, 144, 145, 147** whose structures we have already mentioned are listed in Table 1.

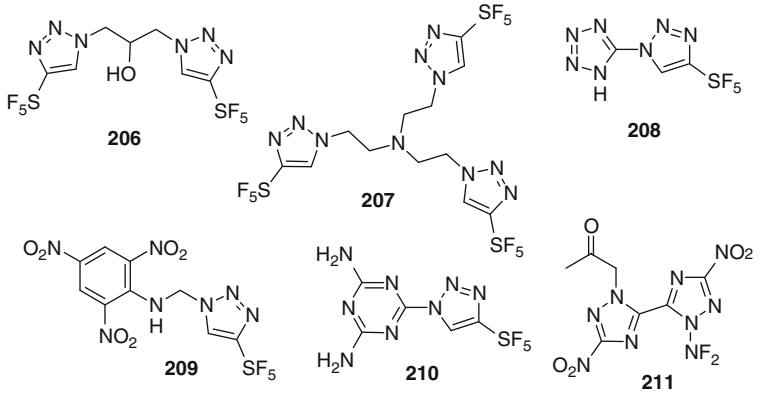
6.7 Energetic Compounds

The burning of the energetic compositions containing organofluorine derivatives affords products with relatively small molecular mass which favors the operating characteristics. Owing to these and many other useful properties the fluorine-containing heterocyclic compounds, first of all tri- and tetrazoles, are traditionally attractive energetic substances.

Klapotke et al. described the energetic properties of sodium 5-trifluoromethyltetrazolate, sodium 5-pentafluoroethyltetrazolate, and sodium 5-heptafluoropropyltetrazolate [185]. Based on DSC-thermograms the authors concluded that the 5-perfluoroalkyltetrazole salts are thermally and thermodynamically stable energy-rich substances. It was also indicated that the sodium salts of 5-perfluoroalkyltetrazoles showed

relatively low sensitivity to impact and friction. The other publications of this scientific team reported on the calcium salts of 5-perfluoroalkylated tetrazoles as components of ternary mixtures with magnesium and Viton [186], and also on pyrolants containing magnesium and guanidinium 5-(perfluoropropyl)-5H-tetrazolate and ammonium 5-(perfluoropropyl)-H-tetrazolate [187] The subject of the energy-rich salts formed from nitro-1,2,4-triazol-5-one, 5-nitroaminotetrazole, and other nitro-substituted azoles, among them energetic polymer salts from 1-vinyl-1,2,4-triazole derivatives, was treated in a series of Shreeve et al. publications that we cited before [62, 86–88, 94]. The data on enthalpy of formation, density, detonation velocity (calculated value), and on the other parameters were published making it possible to regard these salts as interesting components of explosive compositions. As promising components of explosive compositions trifluoromethyl- or pentafluorosulfanyl-substituted poly-1,2,3-triazole compounds should be mentioned. Below are given the formulas of some representative of pentafluorosulfanyl derivatives of tri- and tetrazoles **206–210**. It is noteworthy that the introduction of the SF_5 group into the 1,2,3-triazole ring results in energetic compounds of high density (1.83–1.90 g/cm^3) [142, 188], the most important quality for the energy-rich compounds and materials.

Let us turn again to the pioneering publication of Shevelev et al. [147] that has announced the synthesis of N-difluoroazoles, the representatives of the new series of N-substituted azole. Focusing our attention on NF_2 derivative of 3-nitro-1,2,3-triazole containing the NF_2 group **211**, it may be stated that this extraordinary molecule may be regarded as a precursor of the hypothetic substance possessing exclusively high detonation parameters. Presumably, due to the high sensitivity to the mechanical treatment (impact, friction) similar compounds are very dangerous in handling.



7 Conclusions

The analysis of the literature published within the last decade easily demonstrates the essential intensification of applied research in the field of fluorinated derivatives of tri- and tetrazoles. The especially intensive development is observed in the

directions of creating new biologically active substances based on the mentioned compounds, light-emitting diodes, polymer materials, sorbents, catalysts of chemical processes. The appearance of original and refinement of the known approaches to the synthesis of fluorine-containing tri- and tetrazoles is a natural response to these demands. It is easy to forecast in the near future a significant success in this field of the chemistry of fluorine-containing heterocyclic compounds.

References

1. Kirk KL (2009) Fluorinated five-membered nitrogen-containing heterocycles. In: Petrov VA (ed) Fluorinated heterocyclic compounds. Synthesis, chemistry and applications. Wiley, New York
2. Uneyama K, Sasaki K (2009) Pharmaceuticals containing fluorinated heterocyclic compounds. In: Petrov VA (ed) Fluorinated heterocyclic compounds. Synthesis, chemistry and applications. Wiley, New York
3. Hong W (2009) Agricultural products based on fluorinated heterocyclic compounds. In: Petrov VA (ed) Fluorinated heterocyclic compounds. Synthesis, chemistry and applications. Wiley, New York
4. Kirk KL (2006) Fluorine in medicinal chemistry: recent therapeutic applications of fluorinated small molecules. J Fluorine Chem 127:1013–1029. doi:10.1016/j.jfluchem.2006.06.007
5. Gakh AA, Kirk KL (2009) Fluorinated heterocycles, ACS symposium series. American Chemical Society, Washington, DC. doi:10.1021/bk-2009-1003.ch001
6. Pevzner MS (2000) Aromatic N-haloazoles. Adv Heterocycl Chem 75:1–77
7. Burger K, Wucherpfennig U, Brunner E (1994) Fluoro heterocycles with five-membered rings. Adv Heterocycl Chem 60:1–64
8. Furin GG, Fainzilberg AA (2000) Modern methods for fluorination of organic compounds. Nauka, Moscow
9. Furin GG, Chi K-W (2001) Synthesis methods for fluoroorganic compounds. University of Ulsan Press, Ulsan
10. Furin GG (2004) Fluorine-containing heterocycles. Part I. Synthesis by intramolecular cyclization. Adv Heterocycl Chem 86:129–224
11. Furin GG (2004) Fluorine-containing heterocycles. Part II. Synthesis of perfluoroalkyl heterocycles from carbonyl compounds. Adv Heterocycl Chem 87:273–383
12. Furin GG (2005) Fluorine-containing heterocycles. Part III: synthesis of perfluoroalkyl heterocycles using perfluoroolefins containing a reactive group at the double bond. Adv Heterocycl Chem 88:231–310
13. Pace A, Buscemi S, Vivona N (2005) The synthesis of fluorinated heteroaromatic compounds. Part 1. Five-membered rings with more than two heteroatoms. Org Prep Proced Int 37:447–506. doi:10.1080/00304940509354978
14. Dawood KM (2004) Electrolytic fluorination of organic compounds. Tetrahedron 60:1435–1451. doi:10.1016/j.tet.2003.11.017
15. Nenajdenko VG, Balenkova ES (2011) Preparation of unsaturated trifluoromethylketones and their application in the synthesis of heterocycles. Arkivoc 2011(1):246–328
16. Gakh AA, Romanko SV, Urgak BI, Fainzilberg AA (1991) N-fluorination with cesium fluoroxysulfate. Tetrahedron 47:7447–7458
17. Strazdina A, Grinsteins V (1968) Preparation of N-halogen derivatives of 1,2,4-triazole. SU203693
18. Langlet A, Ostmark H (1994) Explosive body. WO 94/024434
19. Miroshnichenko EA, Lebedev VP, Kostikova LM, Vorob'eva VP, Vorob'ev AB, Inozemtcev JO (2003) Book of Abstr Int Ann Conf ICT34. 122/1-122/7

20. Pevzner MS, Trifonov RE (1998) Theoretical study of the structure of N-halo-1,2,4-triazoles. Russ J Org Chem 34:742–743
21. Schmidt MW, Gordon MS, Boatz JA (2005) Triazolium-based energetic ionic liquids. J Phys Chem A 109:7285–7295
22. Oziminski WP, Dobrowolski JC, Mazurek AP (2003) DFT studies on tautomerism of C5-substituted 1,2,3-triazoles. J Mol Struct 651–653:697–704
23. Dabbagh HA, Rasti E, Chermahini AN (2010) Theoretical studies on tautomerism of triazole derivatives in the gas phase and solution. J Mol Struct (Theochem) 947:92–100
24. Oziminski WP, Dobrowolski JC, Mazurek AP (2004) DFT studies on tautomerism of C5-substituted 1,2,4-triazoles. J Mol Struct (Theochem) 680:107–115
25. Chermahini AN, Dabbagh HA, Teimouri A (2007) Relation between the substituent effect and aromaticity in tetrazoles, protonated tetrazoles and tetrazolate derivatives. J Mol Struct (Theochem) 822:33–37
26. Sadlej-Sosnowska N (2001) Application of natural bond orbital analysis to delocalization and aromaticity in C-substituted tetrazoles. J Org Chem 66:8737–8743
27. Chermahini AN, Nasr-Esfahani M, Dalirnasab Z, Dabbagh HA, Teimouri A (2007) Theoretical studies on tautomerism of tetrazole derivatives by polarisable continuum method (PCM). J Mol Struct (Theochem) 820:7–11
28. Ostrovskii VA, Koldobskii GI, Trifonov RE (2008) Tetrazoles. In: Katritzky AR, Ramsden CA, Scriven EFV, Taylor RJK (eds) Comprehensive heterocyclic chemistry III, vol 6. Elsevier, Oxford, pp 257–424
29. Murlowska K, Sadlej-Sosnowska N (2005) Absolute calculations of acidity of C-substituted tetrazoles in solutions. J Phys Chem A 109:5590–5595
30. Halauko YS, Matulis VE, Ivashkevich OA, Grigoriev YV, Gaponik PN (2010) DFT calculations of CH acidity of substituted triazoles and experimental study of their ability to undergo mercuration. Tetrahedron 66:3415–3420
31. Naik SR, Witkowski JT, Robins RK (1973) A novel route to 3(5)-fluoro-1,2,4-triazoles and 8-fluoropurines by displacement of the nitro group. J Org Chem 38:4353–4354
32. Zumbrunn A (1998) The first versatile synthesis of 1-alkyl-3-fluoro-1H-[1,2,4]-triazoles. Synthesis 1357–1361
33. Lowack RN, Weiss R (1990) In situ generation of 2,3-diaryltetrazolinylidenes: trapping experiments and ring opening to 1-cyanoazimines. J Am Chem Soc 112:333–338
34. Vilarrasa J, Galvez C, Calafell M (1975) Synthesis de Fluoroazoles. An Quim 71:631–632
35. Blackwell GB, Haszeldine RN, Taylor DR (1982) Polyhalogeno-allenes and -acetylenes. Part 15. Dipolar cycloadditions of N-phenylsydnone and aryl azides to perfluoropropadiene and perfluoropropyne. J Chem Soc, Perkin Trans 1: 2207–2210
36. Reck F, Zhou F, Girardot M, Kern G, Eyermann CJ, Hales NJ, Ramsay RR, Gravestock MB (2005) Identification of 4-substituted 1,2,3-trriazoles as novel oxazolidinone antibacterial agents with reduced activity against monoamine oxidase-a. J Med Chem 48:499–506
37. Himo F, Demko ZP, Noodleman L, Sharpless KB (2002) Mechanisms of tetrazole formation by addition of azide to nitriles. J Am Chem Soc 124:12210–12216
38. Lee LA, Baroody EE (1974) Carbon dioxide laser fuels. US Patent Appl US 530260 A0 19741206
39. Carpenter W, Haymaker A, Moore DW (1966) Fluorinated 1,2,3-triazolines. J Org Chem 31:789–792
40. Coats SI, Link JS, Gauthier D, Hlasta DJ (2005) Trimethylsilyl-directed 1,3-dipolar cycloaddition reactions in the solid-phase synthesis of 1,2,3-triazoles. Org Lett 7:1469–1472
41. Wei J, Chen J, Xu J, Cao L, Deng H, Sheng W, Zhang H, Cao W (2012) Scope and regioselectivity of the 1,3-dipolar cycloaddition of azides with methyl 2-perfluoroalkynoates for an easy, metal-free route to perfluoroalkylated 1,2,3-triazoles. J Fluorine Chem 133:146–154
42. Xiong Z, Qiu X-L, Huang Y, Qing F-L (2011) Regioselectivity synthesis of 5-trifluoromethyl-1,2,3-triazole nucleoside analogues via TBS-directed 1,3-dipolar cycloaddition reaction. J Fluorine Chem 132:166–174

43. Shen Y, Zheng J, Xin Y, Lin Y, Qi M (1995) Synthesis of perfluoroalkylated heterocyclic phosphonates. J Chem Soc Perkin Trans 1 997–999
44. Rigby W, Bailey PM, McCleverty JA, Maitlis PM (1979) Pentamethylcyclopentadienyl-rhodium and -iridium complexes 19. Preparation and reactions of azido-, cyanato-, thiocyanato-, nitrito-, and nitrato-rhodium complexes. J Chem Soc Dalton Trans 371–381
45. Lermontov SA, Shkavrov SV, Pushin AN (2000) The reaction of α, α-difluoroazides with acetylenic compounds. J Fluorine Chem 105:141–147
46. Wu Y-M, Deng J, Fang X, Chen Q-Y (2004) Regioselective synthesis of fluoroalkylated-1,2,3-triazoles by Huisgen cycloaddition. J Fluorine Chem 125:1415–1423
47. Mayot E, Gèrardin-Charbonnier C, Selve C (2005) Highly fluoroalkylated amphiphilic triazoles: regioselective synthesis and evaluation of physicochemical properties. J Fluorine Chem 126:715–720
48. Zhu Y-W, Yi W-B, Cai C (2011) A recyclable fluoroalkylated 1,4-disubstituted-1,2,3-triazole organocatalyst for aldol condensation of aldehydes and ketones. J Fluorine Chem 132:71–74
49. Francis DV, Miles DH, Mohammed AI, Read RW, Wang X (2011) Towards functional fluorous surfactants. Synthesis of hydrophilic fluorous 1,2,3-triazolylmethyl ethers and di(1,2,3-triazolylmethyl)ethers. J Fluorine Chem 132:898–906
50. Read RW, Wang X (2012) A structure–function study of the surface tension changes of m-xylene in the presence of fluorous 1H-1,2,3-triazoles and tetrazoles. J Fluorine Chem 135:25–32
51. Read RW, Wang X (2009) A conceptual design of fluorous surfactants based on a heterocyclic core, put into practice through synthesis of fluorous 1,2,3-triazoles. East-West J Math 36:247–257
52. Vorobyeva DV, Karimova NM, Vasilyeva TP, Osipov SN, Shchetnikov GT, Odinets IL, Röschenthaler G-V (2010) Synthesis of functionalized α-CF3-α-aminophosphonates via Cu(I)-catalyzed 1,3-dipolar cycloaddition. J Fluorine Chem 131:378–383
53. Vorobyeva DV, Sokolova NV, Nenajdenko VG, Peregudov AS, Osipov SN (2012) Synthesis of CF3-containing tetrapeptide surrogates via Ugi reaction/dipolar cycloaddition sequence. Tetrahedron 68:872–877
54. Sokolova NV, Vorobyeva DV, Osipov SN, Vasilyeva TP, Nenajdenko VG (2012) Synthesis of a-CF3-a-hydroxy acid-peptide conjugates via click chemistry. Synthesis 44:130–136
55. Hager C, Miethchen R, Reinke H (2000) Organofluorine compounds and fluorinating agents, part 26 New reversed nucleosides – perfluoroalkyl substituted 1,2,3-triazoles linked to D-galactose and D-altrose. J Fluorine Chem 104:135–142
56. Hager C, Miethchen R, Reinke H (2000) New trifluoromethyl substituted 1,2, 3-triazoles linked to D-galactose and D-gulose. J Prakt Chem 342:414–420
57. Peng W, Zhu S (2003) Efficient synthesis of 5-fluoroalkylated 1H-1,2,3-triazoles and application of the bromodifluoromethylated triazole to the synthesis of novel bicyclic gem-difluorinated 1H-pyrano[3,4-d][1,2,3]-triazol-4-one compounds. Tetrahedron 59:4395–4404
58. Peng W, Zhu S-Z (2002) 1,3-Dipolar cycloaddition of β-alkoxyvinyl trifluoromethylketones with aryl (or benzyl) azides. Synthesis of 4-trifluoroacetylated 1H-1,2,3-triazoles. J Fluorine Chem 116:81–86
59. Rozin YA, Leban J, Dehaen W, Nenaidenko VG, Muzalevskiy VM, Eltsov OS, Bakulev VA (2012) Regioselective synthesis of 5-trifluoromethyl-1,2,3-triazoles via CF3- directed cyclization of 1-trifluoromethyl-1,3-dicarbonyl compounds with azides. Tetrahedron 68:614–618
60. Zhu S-Z, He P, Zhao J-W, Cai X (2004) Reactions of fluoroalkanesulfonyl azides with vinyl ether and tetrakis(dimethylamino)ethylene. J Fluorine Chem 125:445–450
61. He P, Zhu S-Z (2005) Study on the reactions of fluoroalkanesulfonyl azides with indole derivatives. J Fluorine Chem 126:825–830
62. Ye C, Gard GL, Winter RW, Syvret RG, Twamley B, Shreeve JM (2007) Synthesis of pentafluorosulfanylpyrazole and pentafluorosulfanyl-1,2,3-triazole and their derivatives as energetic materials by click chemistry. Org Lett 9:3841–3844

63. Crossman JM, Haszeldine RN, Tipping AE (1973) Organosilicon chemistry. X. The reaction of and cyanogen halides to give triazoles. J Chem Soc (Dalton) 483–486
64. Bargamov GG, Bargamova MD (1994) Formation of 1-amino-1,2,3-triazole by the oxidation of 1,1,1,5,5,5-hexafluoro-4-(trifluoromethyl)pentane-2,3-dione dihydrazone. Izv Akad Nauk Ser Khim 1838–1839
65. Bargamov GG, Bargamova MD (1996) Polyfluoroalkyl- substituted 1-amino-1,2,3-triazoles. J Fluorine Chem 79:45–47
66. Bargamov GG, Bargamova MD (1998) Formation of 4- (1,1,1,3,3,3-hexafluo roisopropyl) – 5 – trifluoromethyl-2H–1,2,3-triazole by the oxidation of dihydrazone of 1,1,1,5,5,5 – hexa-fluoro- 4- trifluoromethylpentane – 2,3- dione. Russ Chem Bull 47:192
67. Sosnovskikh VY, Usachev BI (2002) A convenient synthesis of 4(5)-(2-hydroxyaroyl)-5(4)-trifluoromethyl-1,2,3-triazoles from 2-trifluoromethylchromones and chromen-4-imines. Mendeleev Commun 12:75–76
68. Furin GG, Gatilov YV, Bagryanskay IY, Zhurhgov EL (2001) Synthesis and transformations of perfluoro-2-methyl-3-azido-2-pentene. J Fluorine Chem 110:21–24
69. Coşgun S, Celik Ü̈, Özden S, Tüysüz S, Bozkurt A, Gèrardin-Charbonnier C (2010) Proton conductivity properties of acid doped fluoroalkylated 1,2,3-triazole. J Fluorine Chem 131:776–779
70. Yagupolskii LM, Fedyuk DV, Petko KI, Troitskaya VI, Rudyk VI, Rudyuk VV (2000) N-Trihalomethyl derivatives of benzimidazole, benzotriazole and indazole. J Fluorine Chem 106:181–187
71. Brown HC, Cheng MT (1962) Nucleophilic attack on the 2,5-bis(perfluoroalkyl)-1,3,4-oxadiazoles. I. Synthesis of 3,5-bis(perfluoroalky1)-1,2,4-triazoles and 4-methyl-1,2,4-triazoles. J Org Chem 27:3240–3241
72. Jones BG, Branch SK, Thompson AS, Brian GJ, Branch SK, Thompson AS, Threadgill MD (1996) Synthesis of a series of trifluoromethylazoles and determination of pK, of acidic and basic trifluoromethyl heterocycles by I9F NMR spectroscopy. J Chem Soc Trans 1 2685–2691
73. Brown HC, Gisler HJ, Cheng MT Jr (1966) Nucleophilic attack on the 2,5-bis(perfluoroalkyl)-1,3,4-oxadiazoles, II. Synthesis of perfluoroalkyl-substituted 1,2,4,5-tetrazines, 1,2-dihydro-1,2,4,5-tetrazines, and 4-amino-1,2,4-triazoles. J Org Chem 31:781–783
74. Vasil'eva EB, Filyakova VI, Sidorova LP, Filatov IE, Charushin VN (2005) Ambident properties of 4-substituted thiosemicarbazides in condensations with fluoroacetic acids. Russ J Org Chem 41:1522–1525
75. El-Sayed AM, Khodairy A (1998) Synthesis of new fused and spiroheterocycles derived from 4-amino-5-mercapto-3-trifluoromethyl-1,2,4-triazole. Phosphorus Sulfur Silicon 132:41–52
76. Chen M, Wang X-F, Wang S-S, Feng Y-X, Chen F, Yang C-L (2012) Synthesis, characterization and fungicidal activities of novel fluorinated 3,5-disubstituted-4H-1,2,4-triazol-4-amines. J Fluorine Chem 135:323–329
77. Danilkina NA, Vershilov SV, Ganina MB, Mikhailov LE, Ivin BA (2004) Synthesis of perfluoroalkyl[1,2,4]triazolo[1,3]thiazinones. Russ J Gen Chem 74:472–474
78. Lopyrev VA, Sidorova LP, Netsetskaya OA, Grinblat MP (1969) Reactions of hydrazides of perfluoro acids. I. Preparation of perfluoroacylamidoguanidines and their cyclization. Zh Obshch Khim 39:2525–2528
79. Ma C, Li J, Zhang R, Qiu L (2007) Organotin(IV) derivatives of a triazoline thione ligand. Dimeric and self-assembled supramolecular helical structures. J Mol Struct 830:1–7
80. Roberts R, Bradley PA, Bunnage ME, England KS, Fairman D, Fobian YM, Fox DNA, Gymer GE, Heasley SE, Molette J, Smith GL, Schmidt MA, Tones MA, Dack KN (2011) Acidic triazoles as soluble guanylate cyclase stimulators. Bioorg Med Chem Lett 21:6515–6518
81. Siedle AR, Webb RJ, Newmark RA, Brostrom M, Weil DA, Erickson K, Behr FE, Young VG Jr (2003) Solvolyis reactions of perfluoro-5-aza-4-nonene, C3F7–CF=N–C4F9. J Fluorine Chem 122:175–182

82. Kino T, Nagase Y, Ohtsuka Y, Yamamoto K, Uraguchi D, Tokuhisa K, Yamakawa T (2010) Trifluoromethylation of various aromatic compounds by CF3I in the presence of Fe(II) compound, H2O2 and dimethylsulfoxide. J Fluorine Chem 131:98–105
83. Rudyuk VV, Fedyuk DV, Yagupolskii LM (2004) N-Polyfluoroethyl and N-2-chlorodifluorovinyl derivatives of azoles. J Fluorine Chem 125:1465–1471
84. Petko KI, Sokolenko TM, Bezdudny AV, Yagupolskii LM (2005) N-(2-bromotetrafluoroethyl) derivatives of five-membered nitrogen-containing heterocycles. J Fluorine Chem 126:1342–1346
85. Dmowski W (2012) 1,2-Dibromotetrafluoroethane (Freon 114B2) as a building block for fluorine compounds. J Fluorine Chem 142:6–13
86. Garg S, Shreeve JM (2011) Trifluoromethanesulfonamide derivatives of azoles. J Fluorine Chem 132:241–243
87. Xue H, Gao H, Twamley B, Shreeve JM (2007) Energetic salts of 3-nitro-1,2,4-triazole-5-one, 5-nitroaminotetrazole, and other nitro-substituted azoles. Chem Mater 19:1731–1739
88. Xue H, Gao H, Shreeve JM (2008) Energetic polymer salts from 1-vinyl-1,2,4-triazole derivatives. J Polym Sci (A) 46:2414–2421
89. Tung Y-L, Lee S-W, Chi Y, Tao Y-T, Chien C-H, Cheng Y-M, Chou P-T, Peng S-M, Liu C-S (2005) Organic light-emitting diodes based on charge-neutral Os(II) emitters: generation of saturated red emission with very high external quantum efficiency. J Mater Chem 15:460–464
90. Cheng Y-M, Lee G-H, Chou P-T, Chen L-S, Chi Y, Yang C-H, Song Y-H, Chang S-Y, Shih P-I, Shu C-F (2008) Rational design of chelating phosphine functionalized Os(II) emitters and fabrication of orange polymer light-emitting diodes using solution process. Adv Funct Mater 18:183–194
91. Song Y-H, Chiu Y-C, Chi Y, Chou P-T, Cheng Y-M, Lin C-W, Lee G-H, Carty AJ (2008) Synthesis, characterization, and photophysical properties of luminescent gallium and indium complexes constructed using tridentate 6-azolyl-2,2′-bipyridine chelates. Organometallics 27:80–87
92. Norris WP (1962) 5-Trifluoromethyltetrazole and its derivatives. J Org Chem 27:3248–3251
93. Trifonov RE, Ostrovskii VA (2006) Protolytic equilibria in tetrazoles. Russ J Org Chem 42:1585–1605
94. Ye C, Gao H, Shreeve JM (2007) Synthesis and thermochemical properties of NF2-containing energetic salts. J Fluorine Chem 128:1410–1415
95. Uneyama K (1999) Chemistries of trifluoroacetimidoyl halides: preparation, reactions, and applications for the synthesis of fluorinated heterocycles. J Fluorine Chem 97:11–25
96. Mekni N, Baklouti A (2008) Synthesis of new 1-substituted 4-perfluoroalkyl tetrazol-5-ones. J Fluorine Chem 129:1073–1075
97. Huang Y, Read RW, Wang X (2010) Efficient alkylation methods for the synthesis of hybrid fluorocarbon-hydrocarbon tetrazoles as potential fluorinated surfactants. Aust J Chem 63:802–807
98. Jończyk A, Nawrot E, Kisielewski M (2005) Reactions of some nitrogen heterocycles with chlorodifluoromethane under conditions of phase-transfer catalysis. J Fluorine Chem 126:1587–1591
99. Zagipa B, Nagura H, Fuchigami T (2007) Electrolytic partial fluorination of organic compounds 89: regioselective anodic fluorination of tetrazolyl sulfides. J Fluorine Chem 128:1168–1173
100. Spear RJ (1984) Positional selectivity of the methylation of 5-substituted tetrazolate anions. Aust J Chem 37:2453–2568
101. Tselinskii IV, Mel'nikov AA, Varyagina LG, Zhigadlova IG (1983) Synthesis of N-oxymethylderivatives for 5-substituted tetrazoles. Chem Heterocycl Compd 19:341–344
102. Trifonov RE, Alkorta I, Ostrovskii VA, Elguero J (2004) A theoretical study of the tautomerism and ionization of 5-substituted NH-tetrazoles. J Mol Struct (Theochem) 668:123–132
103. Koren AO, Gaponik PN (1990) Regioselective of tetrazole and 5-substituted tetrazoles N2 alkylation by alcohols. Chem Heterocycl Compd 26:1366–1370

104. Koren AO, Gaponik PN, Ivashkevich OA, Kovalyova TB (1995) A new route to 1-alkyltetrazoles: via 2-tert-butyltetrazoles. Mendeleev Commun 5:10–11
105. Voitekhovich SV, Gaponik PN, Koren AO (1997) Selective synthesis of 2-(1-methylvinyl) tetrazoles. Mendeleev Commun 7:41–42
106. Gareev GA, Kirillova LP, Shulgina VM, Buzilova SR, Vologdina LV, Vereshchagin LI (1988) Reaction of some derivatives of 2-nitro-2-azapropanol with azoles. Russ J Org Chem 24:2221–2226
107. Gaponik PN, Ivashkevich OA, Krasitskii VA, Tuzik AA, Lesnikovich AI (2002) Water-soluble polymeric complexes of cobalt(II) and nickel(II) with azolate anions. Russ J Gen Chem 72:1457–1462
108. Banks RE, Prakash A (1974) Studies in azide chemistry. Part VI. Some reactions of perfluoro-azidobenzene and perfluoro-4-azidotoluene. J Chem Soc Perkin Trans 1 1365–1371
109. Rama Rao VVVNS, Lingaiah BPV, Yadla R, Shanthan Rao P, Ravikumar K, Swamy GYSK, Narsimuluc K (2006) Synthesis of fluorine containing N-benzyl-1,2,3-triazoles and N-methyl-pyrazoles from conjugated alkynes. J Heterocycl Chem 43:673–679
110. Liu S, Müller P, Takase MK, Swager TM (2011) "Click" synthesis of heteroleptic tris-cyclometalated iridium(III) complexes: Cu(I) triazolide intermediates as transmetalating. Inorg Chem 50:7598–7609
111. Kloss F, Köhn U, Jahn BO, Hager MD, Görls H, Schubert US (2011) Metal-free 1,5-regioselective azide–alkyne [3+2]-cycloaddition. Chem Asian J 6:2816–2824
112. Recsei C, McErlean CSP (2012) Synthesis of modified binol-phosphoramidites. Tetrahedron 68:464–480
113. Boddy IK, Briggs GG, Harrison RP, Jones TH, O'Mahony MJ, Marlow ID, Roberts BG, Willis RJ, Bardsley R, Reid J (1996) The synthesis and insecticidal activity of a series of 2-aryl- l,2,3-triazoles. Pest Sci 48:189–196
114. D'Anna F, Ferroni F, Frenna V, Guernelli S, Lanza CZ, Macaluso G, Pace V, Petrillo G, Spinelli D, Spisani R (2005) On the application of the extended Fujita–Nishioka equation to polysubstituted systems. A kinetic study of the rearrangement of several poly-substituted Z-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole into 2-aryl-4-benzoylamino-5-phenyl-1,2,3-triazoles in dioxane/water. Tetrahedron 61:167–178
115. Birchall JM, Haszeldine RN, Kemp JEG (1970) Polyfluoroarenes. XII. Some azoxy-compounds and benzotriazoles. J Chem Soc (C) 1519–1523
116. Heaton A, Hill M, Drakesmith F (1997) Polyhalogenonitrobenzenes and derived compounds. 5. Improved preparations of 1,2,3,4-tetrafluoro-5,6-dinitrobenzene and 3,4,5,6-tetrafluoro-1,2-phenylenediamine, and the use of the latter for the synthesis of tetrafluorobenzheterocycles. J Fluorine Chem 81:133–138
117. Petrova TD, Savchenko TI, Yakobson GG (1967) Formation of tetrafluorodehydrobenzene from tetrafluoroanthranilic acid. Zhurn Obshch Khim 37:1170
118. Watt JA, Gannon CT, Loft KJ, Dinev Z, Williams SJ (2008) Click' Preparation of carbohydrate 1-benzotriazoles, 1,4-disubstituted, and 1,4,5-trisubstituted triazoles and their utility as glycosyl donors. Aust J Chem 61:837–846
119. Shi F, Waldo JP, Chen Y, Larock RC (2008) Benzyne click chemistry: synthesis of benzotriazoles from benzynes and azides. Org Lett 10:2409–2412
120. Zhang F, Moses JE (2009) Benzyne click chemistry with in situ generated aromatic azides. Org Lett 11:1587–1590
121. Liu S, Sawicki J, Driver TG (2012) Ni-Catalyzed alkenylation of triazolopyridines: synthesis of 2,6-disubstituted pyridines. Org Lett 14:3744–3747
122. Blanco F, Alkorta I, Elguero J, Cruz V, Abarca B, Ballesteros R (2008) [1,2,3]triazolo[1,5-a]pyridines. A theoretical (DFT) study of the ring–chain isomerization. Tetrahedron 64:11150–11158
123. Mennen SM, Miller SJ (2007) Development of a bio-inspired acyl-anion equivalent macrocyclization and synthesis of a trans-resorcylide precursor. J Org Chem 72:5260–5269
124. Vora HU, Moncecchi JR, Epstein O, Rovis T (2008) Nucleophilic carbene catalyzed synthesis of 1,2 amino alcohols via azidation of epoxy aldehydes. J Org Chem 73:9727–9731

125. Joann MU, DiRocco DA, Noey EL, Rovis T, Houk KN (2011) Quantum mechanical investigation of the effect of catalyst fluorination in the intermolecular asymmetric stetter reaction. J Am Chem Soc 133:11249–11254
126. Rong Z-Q, Jia M-Q, You S-L (2011) Enantioselective N-heterocyclic carbene-catalyzed Michael addition to α, β-unsaturated aldehydes by redox oxidation. Org Lett 13:4080–4083
127. Rong Z-Q, Li Y, Yang G-Q, You S-L (2011) D-Camphor-derived triazolium salts for enantioselective intramolecular stetter reactions D-camphor-derived triazolium salts for stetter reactions. Synlett 1033–1037
128. Jia M-Q, You S-L (2012) Desymmetrization of cyclohexadienones via D-camphor-derived triazolium salt catalyzed intramolecular Stetter reaction. Chem Commun 6363–6365
129. De Vreese R, D'hooghe M (2012) N-Heterocyclic carbene/brønsted acid cooperative catalysis as a powerful tool in organic synthesis. Beilstein J Org Chem 8:398–402
130. Henderson AP, Mutlu E, Leclercq A, Bleasdale C, Clegg W, Henderson RA, Golding BT (2002) Trapping of benzene oxide-oxepin and methyl-substituted derivatives with 4-phenyl- and 4-pentafluorophenyl-1,2,4-triazoline-3,5-dione. Chem Commun 1956–1957
131. Shaaban MR (2008) Microwave-assisted synthesis of fused heterocycles incorporating trifluoromethyl moiety. J Fluorine Chem 129:1156–1161
132. Khudina OG, Shchegol'kov EV, Burgart YV, Kodess MI, Kazheva ON, Chekhlov AN, Shilov GV, Dyachenko OA, Saloutin VI, Chupakhin ON (2005) Synthesis and the reactions of trifluoromethylated 1,2,3-triketones 2-(het)arylhydrazones and 4,7-dihydroazolo[5,1-c]triazines. J Fluorine Chem 126:1230–1238
133. Kuznetsova OA, Filyakova VI, Pashkevich KI, Ulomskii EN, Plekhanov PV, Rusinov GL, Kodess MI, Rusinov VL (2003) Fluoroalkyl containing lithium β-diketonates in the synthesis of 1,2,4-triazolo[1,5-a]pyrimidines. Russ Chem Bull Int Ed 52:1190–1194
134. Dolzhenko AV, Tan BJ, Dolzhenko AV, Chiu GNC, Chui WK (2008) Synthesis and biological activity of fluorinated 7-aryl-2-pyridyl-6,7-dihydro[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-amines. J Fluorine Chem 129:429–434
135. Krasovsky AL, Moiseev AM, Nenajdenko VG, Balenkova ES (2002) Synthesis of new fluorine-containing triazolo- and tetrazolopyrimidines. Synthesis 901–905
136. Kim Y-J, Lee S-H, Lee S-H, Jeon SI, Lim MS, Lee SW (2005) Reactivity of alkynyl Pd(II) azido complexes toward organic isocyanides, isothiocyanates, and nitriles. Inorg Chim Acta 358:650–658
137. Klapцtke TM, Krumm B, Moll R (2011) Convenient room-temperature, mercury-assisted synthesis of tetrazoles by1,3-dipolar cycloaddition. Eur J Inorg Chem 422–428
138. Zhao Z-H, Jin H, Zhang Y-X, Shen Z, Zou D-C, Fan X-H (2011) Synthesis and properties of dendritic emitters with a fluorinated starburst oxadiazole core and twisted carbazole dendrons. Macromolecules 44:1405–1413
139. Cmoch P, Korczak H, Stefaniak L, Webb GA (1999) 1H, 13C and ^{15}N NMR and IR studies of halogen-substituted tetrazolo[1,5-a]pyridines. J Phys Org Chem 12:470–478
140. Keith JM (2006) One-step conversion of pyridine N-oxides to tetrazolo[1,5-a]pyridines. J Org Chem 71:9540–9543
141. Altomonte S, Zanda M (2012) Synthetic chemistry and biological activity of pentafluorosulphanyl (SF5) organic molecules. J Fluorine Chem 143:57–93
142. Martinez H, Zheng Z, Dolbier WR Jr (2012) Energetic materials containing fluorine. Design, synthesis and testing of furazan-containing energetic materials bearing a pentafluorosulfanyl group. J Fluorine Chem 143:112–122
143. Rostovtsev VV, Green LG, Fokin VV, Sharpless KB (2002) A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective ligation of azides and terminal alkynes. Angew Chem Int Ed 41:2596–2599
144. Huang Y, Gard GL, Shreeve JM (2010) One-pot syntheses of 1,2,3-triazoles containing a pentafluorosulfanylalkyl group via click chemistry. Tetrahedron Lett 51:6951–6954
145. Politzer P, Lane P (1997) Computational studies of structures and properties of energetic difluoramines. Adv Mol Struct 3:269–285

146. Ostrovskii VA, Pevzner MS, Kofman TP, Shcherbinin MB, Tselinskii IV (1999) Energetic 1,2,4-triazoles and tetrazoles. Targets Heterocycl Syst 3:467–526
147. Dalinger IL, Vinogradov VM, Shevelev SA, Kuz'min VS (1996) N-(Difluoroamino)azoles – a new class of N-substituted azoles. Mendeleev Commun 6:13–15
148. Hagmann WK (2008) The many roles for fluorine in medicinal chemistry. J Med Chem 51:4359–4369
149. Ismail FMD (2002) Important fluorinated drugs in experimental and clinical use. J Fluorine Chem 118:7–33
150. Lyseng-Williamson KA (2007) Sitagliptin. Drugs 67:587–597
151. Desai AA (2011) Sitagliptin manufacture: a compelling tale of green chemistry, process intensification, and industrial asymmetric catalysis. Angew Chem Int Ed 50:1974–1976
152. Clausen AM, Dziadul B, Cappuccio KL, Kaba M, Starbuck C, Hsiao Y, Dowling TM (2006) Identification of ammonium chloride as an effective promoter of the asymmetric hydrogenation of α, β-enamine amide. Org Proc Res Dev 10:723–726
153. Kim D, Kowalchick JE, Edmondson SD, Mastracchio A, Xu J, Eiermann GJ, Leiting B, Wu JK, Pryor KD, Patel RA, He H, Lyons KA, Thornberry NA, Weber AE (2007) Triazolopiperazine-amides as dipeptidyl peptidase IV inhibitors: close analogs of JANUVIATM (sitagliptin phosphate). Bioorg Med Chem Lett 17:3373–3377
154. Kim D, Kowalchick JE, Brockunier LL, Parmee ER, Eiermann GJ, Fisher MH, He H, Leiting B, Lyons K, Scapin G, Patel SB, Petrov A, Pryor K-AD, Roy RS, Wu JK, Zhang X, Wyvrat MJ, Zhang BB, Zhu L, Thornberry NA, Weber AE (2008) Discovery of potent and selective dipeptidyl peptidase IV inhibitors derived from β-aminoamides bearing substituted triazolopiperazines. J Med Chem 51:589–602
155. Biftu T, Scapin G, Singh S, Feng D, Becker JW, Eiermann G, Huaibing H, Lyons K, Patel S, Petrov A, Sinha-Roy R, Zhang B, Wu J, Zhang X, Doss GA, Thornberry NA, Weber AE (2007) Rational design of a novel, potent, and orally bioavailable cyclohexylamine DPP-4 inhibitor by application of molecular modeling and X-ray crystallography of sitagliptin. Bioorg Med Chem Lett 17:3384–3387
156. Shan Z, Peng M, Fan H, Lu Q, Lu P, Zhao C, Chen Y (2011) Discovery of potent dipeptidyl peptidase IV inhibitors derived from β-aminoamides bearing substituted [1,2,3]-triazolopiperidines for the treatment of type 2 diabetes. Bioorg Med Chem Lett 21:1731–1735
157. Wang B-L, Liu X-H, Zhang X-L, Zhang J-F, Song H-B, Li Z-M (2011) Synthesis, structure and biological activity of novel 1,2,4-triazole mannich bases containing a substituted benzylpiperazine moiety. Chem Biol Drug Des 78:42–49
158. Ostrovskii VA, Trifonov RE, Popova EA (2012) Medicinal chemistry of tetrazoles. Russ Chem Bull Int Ed 61:768–780
159. Faidallah HM, Khan KA, Asiri AM (2011) Synthesis and biological evaluation of new 3,5-di(trifluoromethyl)-1,2,4-triazolesulfonyl urea and thiourea derivatives as antidiabetic and antimicrobial agents. J Fluorine Chem 132:870–877
160. Faridoon, Hussein WM, Vella P, Islam NU, Ollis DL, Schenk G, McGeary RP (2012) 3-mercapto-1,2,4-triazoles and N-acylated thiosemicarbazidesas metallo-β-lactamase inhibitors. Bioorg Med Chem Lett 22:380–386
161. De La Rosa M, Kim HW, Gunic E, Jenket C, Boyle U, Koh Y, Korboukh I, Allan M, Zhang W, Chen H, Xu W, Nilar S, Yao N, Hamatake R, Lang SA, Hong Z, Zhang Z, Girardet J-L (2006) Tri-substituted triazoles as potent non-nucleoside inhibitors of the HIV-1 reverse transcriptase. Bioorg Med Chem Lett 16:4444–4449
162. Kanishchev OS, Gudz GP, Shermolovich YG, Nesterova NV, Zagorodnya SD, Golovan AV (2011) Synthesis and biological activity of the nucleoside analogs based on polyfluoroalkyl-substituted 1,2,3-triazoles. Nucleosides Nucleotides Nucleic Acids 30:768–783
163. Yagupolskii LM, Maletina II, Petko KI, Fedyuk DV, Handrock R, Shavaran SS, Klebanov BM, Herzig S (2001) New fluorine-containing hypotensive preparations. J Fluorine Chem 109:87–94

164. Lebsack AD, Gunzner J, Wang B, Pracitto R, Schaffhauser H, Santini A, Aiyar J, Bezverkov R, Munoz B, Liuc W, Venkatramana S (2004) Identification and synthesis of [1,2,4] triazolo[3,4-a]phthalazine derivatives as high-affinity ligands to the α2δ-1 subunit of voltage gated calcium channel. Bioorg Med Chem Lett 14:2463–2467
165. Williams BJ, Cascieri MA, Chicchi GG, Andrew TH, Owens P, Owen SN, Rupniak NMJ, Tattersall DF, Williams A, Swain CJ (2002) Spirocyclic NK1 antagonists II: [4.5]-spiro-ethers. Bioorg Med Chem Lett 12:2719–2722
166. Shirai J, Yoshikawa T, Yamashita M, Yamamoto Y, Kawamoto M, Tarui N, Kamo I, Hashimoto T, Ikeura Y (2011) Design, structure–activity relationship, and highly efficient asymmetric synthesis of 3-phenyl-4-benzylaminopiperidine derivatives as novel neurokinin-1 receptor antagonists. Bioorg Med Chem 19:6430–6446
167. Micheli F, Bonanomi G, Blaney FE, Braggio S, Capelli AM, Checchia A, Curcuruto O, Damiani F, Di Fabio R, Donati D, Gentile G, Gribble A, Hamprecht D, Tedesco G, Terreni S, Tarsi L, Lightfoot A, Stemp G, MacDonald G, Smith A, Pecoraro M, Petrone M, Perini O, Piner J, Rossi T, Worby A, Pilla M, Valerio E, Griffante C, Mugnaini M, Wood M, Scott C, Andreoli M, Lacroix L, Schwarz A, Gozzi A, Bifone A, Ashby CR Jr, Hagan JJ, Heidbreder C (2007) 1,2,4-triazol-3-yl-thiopropyl-tetrahydrobenzazepines: a series of potent and selective dopamine D3 receptor antagonists. J Med Chem 50:5076–5089
168. Sugane T, Tobe T, Hamaguchi W, Shimada I, Maeno K, Miyata J, Suzuki T, Kohara A, Kimizuka T, Morita T, Doihara H, Saita K, Aota M, Furutani M, Shimada Y, Hamada N, Sakamoto S, Tsukamoto S-I (2011) Synthesis and biological evaluation of 3-biphenyl-4-yl-4-phenyl-4H-1,2,4-triazoles as novel glycine transporter 1 inhibitors. J Med Chem 54:387–391
169. Hale JJ, Mills SG, MacCoss M, Finke PE, Cascieri MA, Sadowski S, Ber E, Chicchi GG, Kurtz M, Metzger J, Eiermann G, Tsou NN, Tattersall FD, Rupniak NMJ, Williams AR, Rycroft W, Hargreaves R, MacIntyre DE (1998) Structural optimization affording 2-(R)-(1-(R)-3,5-bis(trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine, a potent, orally active, long-acting morpholine acetal human NK-1 receptor antagonist. J Med Chem 41:4607–4614
170. Aiguadé J, Balagué C, Carranco I, Caturla F, Dominguez M, Eastwood P, Esteve C, González J, Lumeras W, Orellana A, Preciado S, Roca R, Vidal L, Vidal B (2012) Novel triazolopyridylbenzamides as potent and selective p38a inhibitors. Bioorg Med Chem Lett 22:3431–3436
171. Hamill TG, Burns HD (2004) The synthesis of tritium labelled neurokinin-1 receptor ligands. J Label Compd Radiopharm 47:099–106
172. Chin FT, Morse CL, Shetty HU, Pike VW (2006) Automated radiosynthesis of [18 F] SPA-RQ for imaging human brain NK1 receptors with PET. J Label Compd Radiopharm 49:17–31
173. Zhang Y, Huang F, Chi Y, Jen AKY (2008) Highly efficient white polymer light-emitting diodes based on nanometer-scale control of the electron injection layer morphology through solvent processing. Adv Mater 20:1565–1570
174. Cheng Y-M, Li EY, Lee G-H, Chou P-T, Lin S-Y, Shu C-F (2007) Strategic design and synthesis of osmium(II) complexes bearing a single pyridyl azolate π-chromophore: achieving high-efficiency blue phosphorescence by localized excitation. Inorg Chem 46:10276–10286
175. Chien C-H, Hsu F-M, Shu C-F, Chi Y (2009) Efficient red electrophosphorescence from a fluorene-based bipolar host material. Org Electron 10:871–876
176. Mak CSK, Hayer A, Pascu SI, Watkins SE, Holmes AB, Kцhler A, Friend RH (2005) Blueto-Green electrophosphorescence of iridium-based cyclometallated materials. Chem Commun 4708–4710
177. Yang C-H, Li S-W, Chi Y, Cheng Y-M, Yeh Y-S, Chou P-T, Lee G-H, Wang C-H, Shu C-F (2005) Heteroleptic cyclometalated iridium(III) complexes display blue phosphorescence in solution and solid state at room temperature. Inorg Chem 44:7770–77780

178. Hung J-Y, Lin C-H, Chi Y, Chung M-W, Chen Y-J, Lee G-H, Chou P-T, Chen C-C, Wu C-C (2010) Phosphorescent Ir(III) complexes bearing double benzyldiphenylphosphine cyclometalates; strategic synthesis, fundamental and integration for white OLED fabrication. J Mater Chem 20:7682–7693
179. Yang C, Kaipa U, Mather QZ, Wang X, Nesterov V, Venero AF, Omary MA (2011) Fluorous metal organic frameworks with superior adsorption and hydrophobic properties toward oil spill cleanup and hydrocarbon storage. J Am Chem Soc 133:18094–18097
180. Zorn DD, Boatz JA, Gordon MS (2006) Electronic structure studies of tetrazolium-based ionic liquids. J Phys Chem B 110B:11110–11119
181. Price SC, Stuart AC, Yang L, Zhou H, You W (2011) Fluorine substituted conjugated polymer of medium band gap yields 7 % efficiency in polymer-fullerene solar cells. J Am Chem Soc 133:4625–4631
182. Hsieh H-Y, Lin C-H, Tu G-M, Chi Y, Lee G-H (2009) Platinum(II) complexes with spatially encumbered chelates, syntheses, structure and photophysics. Inorg Chim Acta 362:4734–4739
183. Fang C-H, Chen Y-L, Yang C-H, Chi Y, Yeh Y-S, Li EY, Cheng Y-M, Hsu C-J, Chou P-T, Chen C-T (2007) Iridium(I) pyridyl azolate complexes with saturated Red metal-to-ligand charge transfer phosphorescence; fundamental and potential applications in organic light-emitting diodes. Chem Eur J 13:2686–2694
184. Wu K-L, Ho S-T, Chou C-C, Chang Y-C, Pan H-A, Chi Y, Chou P-T (2012) Engineering of osmium(II)-based light absorbers for dye-sensitized solar cells. Angew Chem Int Ed 51:5642–5646
185. Crawford M-J, Klapotke TM, Radies H (2008) Synthesis and characterization of perfluorinated nitriles and the corresponding sodium 5-perfluoroalkyltetrazolate salts. J Fluorine Chem 129:1199–1205
186. Koch E-C, Klapotke TM, Radies H, Lux K, Hahma A (2011) Metal-forocarbon prolants. XII: Calcium salts of 5-prfluoroalkylated tetrazoles –synthesis, characterization and performance evaluation as oxidizers in ternary mixtures with magnesium and Viton. Z Naturforsch 66b:378–386
187. Koch E-C, Hahma A, Klapotke TM, Radies H (2010) Metal – fluorocarbon pyrolants: XI. Radiometric performance of pyrolants based on magnesium, perfluorinated tetrazolates, and Viton A. Propell Explos Pyrotech 35:248–253
188. Garg S, Shreeve JM (2011) Trifluoromethyl- or pentafluorosulfanyl-substituted poly-1,2,3-triazole compounds as dense stable energetic materials. J Mater Chem 21:4787–4795

1,2-Bis(Hetaryl)Perfluorocyclopentenes as Unique Thermally Irreversible Photochromes. Synthesis and Structural Singularities

M.M. Krayushkin and M.A. Kalik

Contents

Abstract The review considers the synthesis and structures of photochromic products, in which hetaryl substituents are separated by the central 1,2-perfluorocyclopentene moiety. It was also briefly presented main methods for synthesis of octafluorocyclopentene and its reactivity. Among methods used for the synthesis of the photochromes, the reactions of lithium derivatives of thiophene, benzothiophene, and other heterocyclic compounds with octafluorocyclopentene, 1,2-dichlorohexafluorocyclopentene, and their analogues are described. Another general method for the synthesis of dihetarylethenes, considered in the review, is based on the McMurry reaction involving the initial

M.M. Krayushkin (✉) • M.A. Kalik
Laboratory of Heterocyclic Compounds, N.D. Zelinsky
Institute of Organic Chemistry, Russian Academy of Sciences,
119991, Moscow, Leninsky prospect 47, Russia
e-mail: mkray@ioc.ac.ru; orgchem@mail.ru

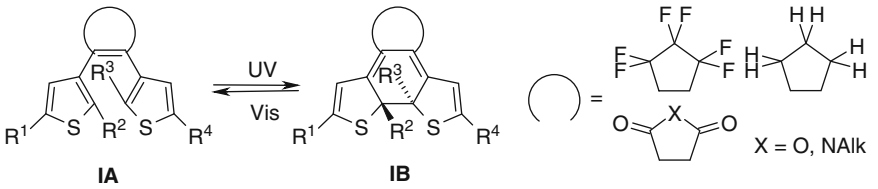
V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_12,

synthesis of 1,5-diketone by acylation of the corresponding heterocyclic compound with perfluoroglutaryl dichloride followed by the cyclization of the diketone in the presence of metallic titanium or its salts. The review also summarizes the results of X-ray diffraction studies of some 1,2-dihetarylperfluorocyclopentenes.

Keywords Octafluorocyclopentene • Dihetarylethenes • Dithienylethenes • Photochromes • Synthesis • X-ray-structures

1 Introduction

As revealed in the late 1980s, photochromic dihetarylethenes (DHE) **I** (often named in literature as diarylethenes) have a unique property, namely, in the absence of photoirradiation, their initial **IA** and cyclized **IB** forms are stable, in the most part of cases, up to decomposition temperatures [1–4].



This singularity certainly attracted attention of researchers in the field of nonlinear optics and optical switchers and resulted in a burst of publications related to problems of information recording and storage [5–13]. Permanent interest in photochromes **I** stirred up by prospects of developing multilayer optical discs [14–18] is retained nowadays.

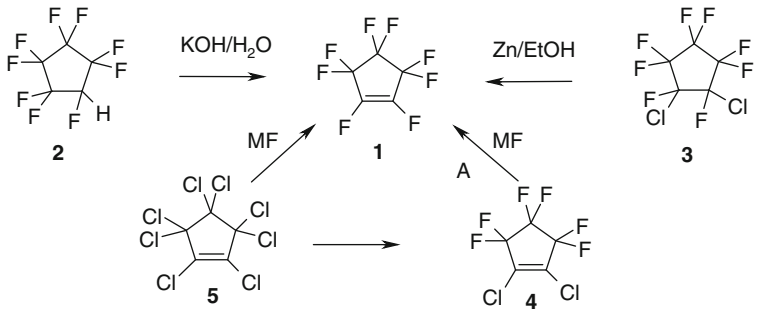
It is important to emphasize that many representatives of these photochromes also possess high fatigue resistance. Among such compounds, organic molecules containing a perfluorocyclopentene backbone have recently been recognized as one of the most attractive units for the applications to optoelectronic devices due to a successful combination of such exploitation properties as chemical stability, solubility in organic solvents, compatibility with polymers for the preparation of registration media, a substantial difference in positions of absorption bands of the initial and cyclic forms, a possibility of non-destructive information reading using photoluminescence of one of the forms [19, 20], etc.

The synthesis and structures of the photochromic products in which the hetaryl substituents are separated by the central 1, 2-perfluorocyclopentene fragment are described in the present review. The first section briefly presents the main methods for the synthesis of perfluorocyclopentene and its reactivity that predetermines methods for the synthesis of photochromic dihetarylethenes. The second section directly deals with the methods for the synthesis of these photochromes, and specific features of their structures are described in the third section. The photochromic properties of the products, for minor exceptions, are not considered.

2 Synthesis and Chemical Properties of Octafluorocyclopentene (OFCP)

2.1 Synthesis of Octafluorocyclopentene

At present 1,2,3,3,4,4,5,5-octafluorocyclopentene (OFCP, **1**) is a commercially available product, which is mainly prepared by the dehydrofluorination of nanofluorocyclopentane **2** in water in the presence of solid KOH [21], dechlorination of 1,2-dichlorooctafluorocyclopentane **3** with zinc in boiling EtOH (i-PrOH-AcOH) [21, 22], and fluorination of 1,2-dichlorohexafluorocyclopentene **4** or perchlorocyclopentene **5** with alkaline metal fluorides (KF, CsF) in various solvents (DMF, N-methylpyrrolidone, alkyl sulfoxides, sulfolanes, etc.) [23–25] (Scheme 1). The improved variant [26, 27] of the most popular method A in Scheme 1 produces OFCP of high purity (up to 99.99 %) in high yields (90.4 %) [28] from various fluorochlorosubstituted cyclopentenes or their mixtures. A series of Japanese reviews [29–31] is devoted to problems of improvement of the technology of its production, further use, and influence on the environment.

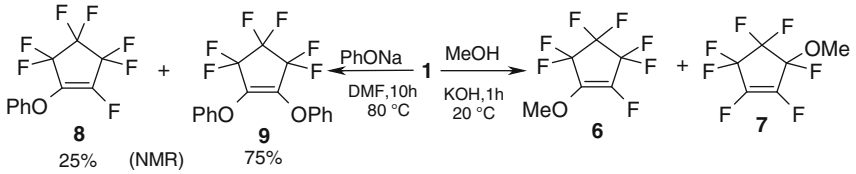


Scheme 1

2.2 Reactivity of Perfluorocyclopentene

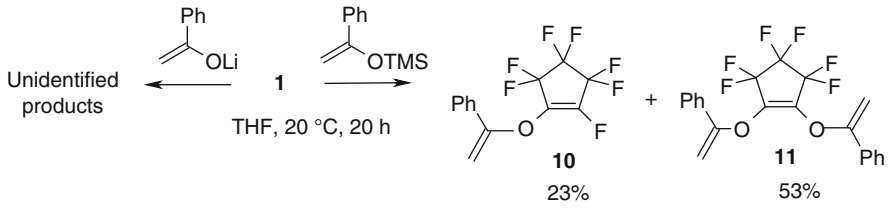
Some characteristic reactions of OFCP, including those used for the synthesis of photochromic DHE, are considered below. Octafluorocyclopentene, like the most part of other fluorinated olefins, is a pronounced electrophile characterized by the interaction with various nucleophiles according to the addition–elimination type reactions. For selected reports on the reaction of perfluorocyclopentene **1** or the 1, 2-dichloroanalog with O,N,S,P-nucleophiles, see [32, p. 4222 and references cited therein].

The reactions of cyclene **1** with alcohols or alkoxides leading, as a rule, to products with substituents at the double bond are studied most completely. However, there are described examples where the fluorine atoms in the allyl positions of cyclopentene were involved in the S_N2 type reaction [33, 34]. For instance, OFCP reacts with methanol (1 equiv) in the presence of KOH to form 1-methoxy-substituted isomer **6** as the major product and 4 % of heptafluoro-3-methoxycyclopentene **7** [33] (Scheme 2). The process can be directed towards the formation of bis(vicinal)-substituted compounds along with the monoalkoxy products by the variation of conditions [35, 36]. For example, OFCP and sodium phenoxide generate both **8** and **9** in a ratio of 1:3 [36]. The reaction of OFCP with bisphenols in the presence of NEt_3 gave the whole class of polyethers containing both aromatic and perfluorocyclopentene rings [36].



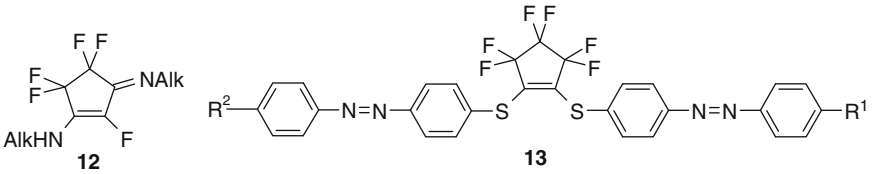
Scheme 2

The reaction of **1** with the lithium derivative of acetophenone affords unidentified products, whereas the reaction with trimethylsilyl enol gave the expected subtances **10** and **11** in an approximate ratio of 1:2 [37] (Scheme 3).

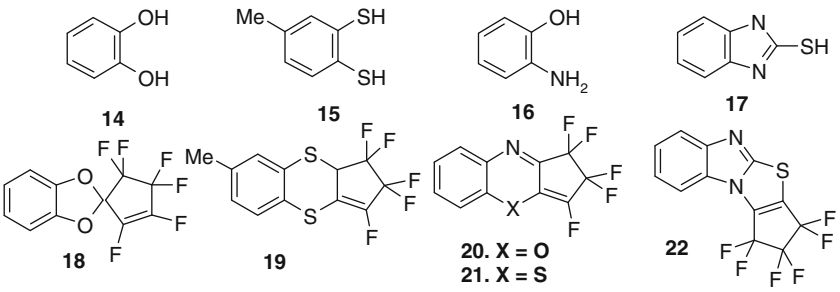


Scheme 3

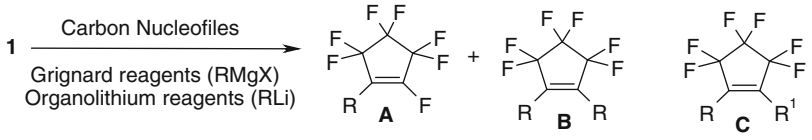
The reactions of OFCP with methylamine and ethylamine include both the addition–elimination reactions at the double bond and the simultaneous formation of products **12** with the imine fragments (100 % yield for Alk=Me and 72 % for Alk=Et) [38]. The formation of azochromophores **13** with the perfluorocyclopentene bridge, including the reaction of substance 4 with thiols as the first stage, was described in [39].



This direction is reasonably continued by the studies that described the reactions of OFCP with difunctional nucleophiles **14–17**. Under mild conditions, these reactions were found to give a range of heterocycles with the perfluorocyclopentene fragment **18–22**, respectively, generally in good yields [40].



Naturally, the reactions of OFCP accompanied by the formation of C-C bonds are most similar to the methods of preparation of photochromes described in Sect. 3. The treatment of **1** with organolithium reagents gave the corresponding symmetrical **disubstituted** perfluorocyclopentenes **B** (Scheme 4) in good to high yields.

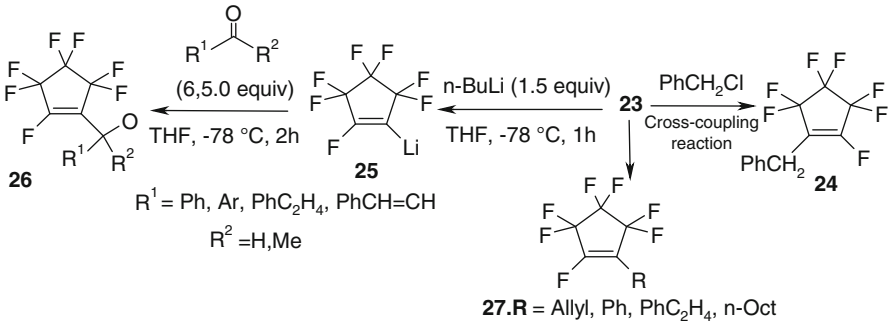


Scheme 4

The reaction with the Grignard reagents led to the **monosubstituted** perfluorocyclopentenes **A**, which were subjected to the further nucleophilic substitution reaction using another Grignard or aryllithium reagents to obtain unsymmetrical disubstituted perfluorocyclopentenes **C** in high yields [41].

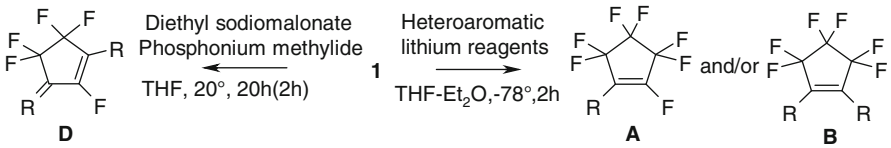
The preparation of perfluorocyclopentenylmetal species and their cross-coupling reaction with **electrophiles** as remarkable accesses to versatile perfluorocyclopentene derivatives are described in [32]. The authors demonstrated that the treatment of perfluorocyclopentene with bis(tributylstannyl)cyanocuprate in THF at −78 °C for 1 h gave perfluorocyclopentenylstannane **23** in good yield. The product successfully enters the cross-coupling reaction with benzyl chloride to give the benzyl derivative **24** in good yield.

The reaction of fluorinated vinylstannane **23** with n-BuLi in THF at −78 °C for 1 h followed by the addition of carbonyl compounds afforded the corresponding allyl alcohols **26** in good yields (Scheme 5). On the other hand, the Pd(0)-catalyzed cross-coupling reaction of perfluorocyclopentenylstannane **23** with benzyl chloroformate in THF at reflux for 2 h proceeded smoothly to form the decarbonylated coupling product **27** in high yield.



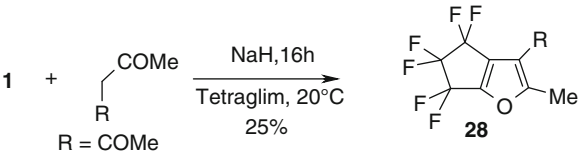
Scheme 5

The reactions of perfluorocyclopentene with various carbon nucleophiles, namely, heteroaromatic lithium reagents, enolate and phosphonium ylide, leading to the C-C-addition products are described in [37]. It was shown that the addition of the heteroaromatic lithium reagents to a THF solution of perfluorocyclopentene **1** provided preferentially the corresponding monosubstituted products **A**, while an opposite order of addition efficiently gave the 1, 2-disubstituted products **B** in good to excellent yields. Both mono- (**A**) and disubstituted (**B**) products were obtained in yields from moderate (20–30 %) to quantitative depending on the nature of HetLi-reactant, -{Het-2(3)-furyl, 2(3)-thienyl, 1-methylpyrryl, benzofuryl, benzothienyl, 1-methylindolyl}, ratio of reagents and reaction conditions [37]. The reaction of **1** with an excess (4,4–6,6 equiv.) of sodium malonate at 20 °C or phosphonium ylide also proceeded smoothly to form the 1, 3-disubstituted product **D** in high yield (81 %) (Scheme 6).



Scheme 6

Note that, as shown in [42], the reactions of OFCP with enolate anions, being acetylacetone and ethyl acetoacetate derivatives that can be considered as dinucleophiles, afford furans **28** (Scheme 7).



Scheme 7

On the whole, the materials of this brief section indicate that octafluorocyclopentene is an accessible (for at least research purposes) product, whose reactivity was studied in rather detail. The variation of the reaction conditions makes it possible to obtain the diverse mono- and disubstituted derivatives of this product containing substituents both at the double bond of cyclene and in the allyl positions.

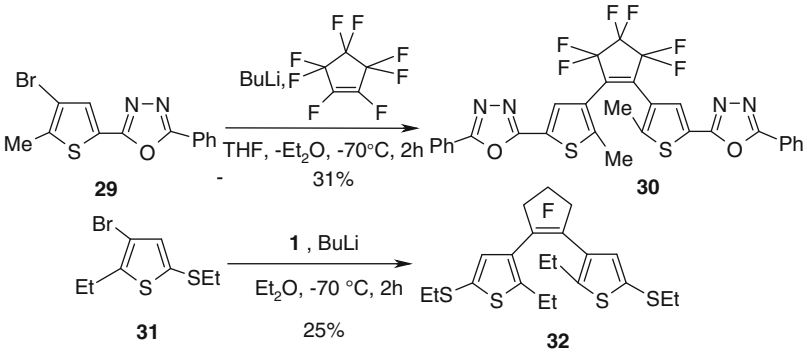
3 Synthesis of Dihetarylethenes with Perfluorocyclopentene Bridge

3.1 Reactions of Lithium Derivatives of Thiophene with Octafluorocyclopentene

The main method for the preparation of perfluorocyclopentene DHE used in the majority of studies is the reaction of the lithium derivatives of thiophene with octafluorocyclopentene [43–45, 41]. The photochromic products are thus "assembled" from the components indifferent to butyllithium or the molecule backbone is formed for further functionalization. This approach allows one to synthesize both symmetrical and unsymmetrical photochromes.

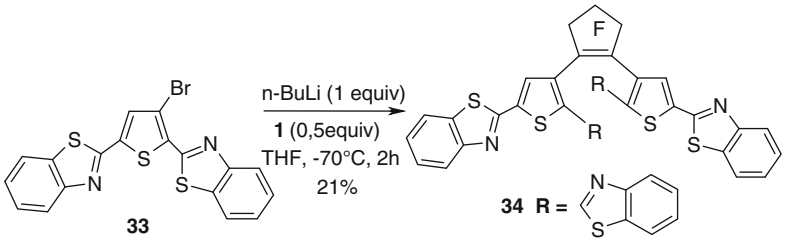
3.1.1 Symmetrical and Unsymmetrical DTE

Typical syntheses of the symmetrical products are demonstrated in Scheme 8. The treatment of bromides **29** and **31** with butyllithium, under standard conditions, in the presence of perfluorocyclopentene affords photochromes **30** [46] and **32** [44].



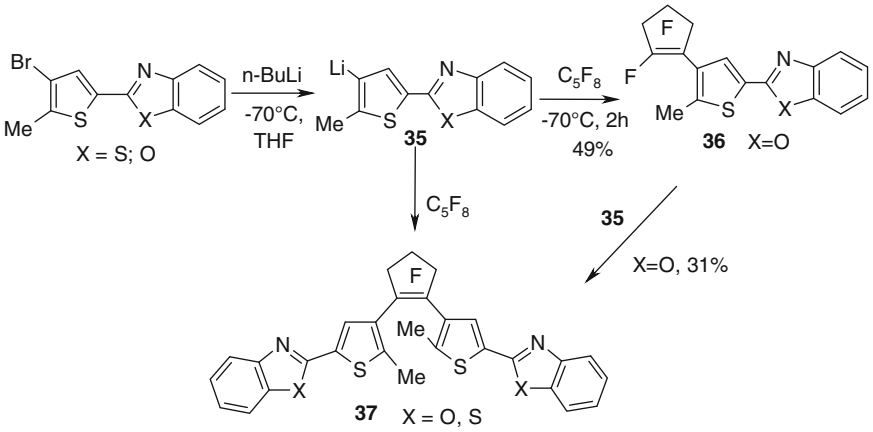
Scheme 8

Even thienyl bromide **33** with the electron-withdrawing and fairly bulky benzothiazole fragments enters the reaction to form the photochromic product **34** (Scheme 9) [47]. As a rule, the yields of the symmetrical photochromes are 30–50 %.



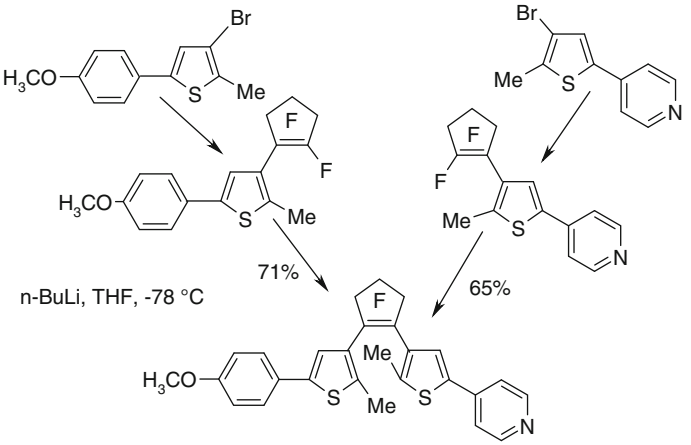
Scheme 9

The reaction of the lithium derivatives of thiophene with **1** can be accompanied by the formation of the products of substitution of only one fluorine atom at the double bond of cyclene. For example, photochrome **37** was synthesized (Scheme 10) either in one stage with a twofold excess of the lithium derivative **35** over perfluorocyclopentene or in two stages with the preliminary isolation of monofluoride **36** [46].



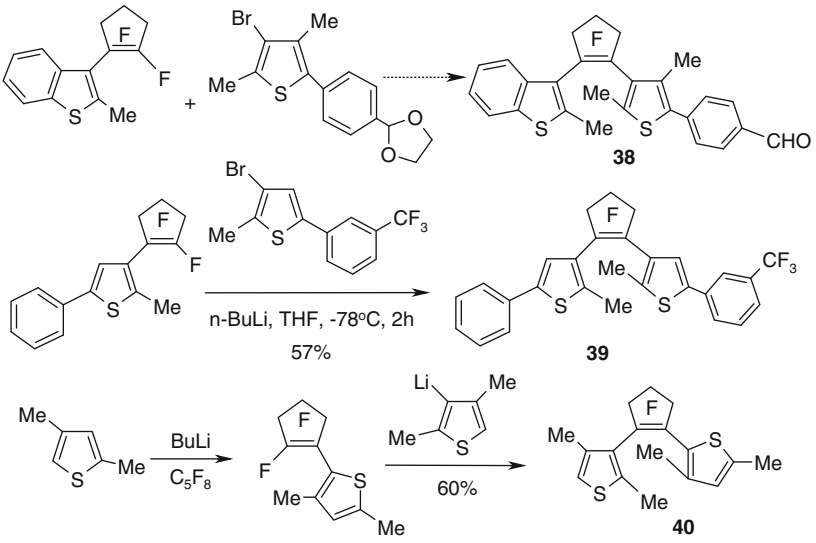
Scheme 10

It is noteworthy that the monosubstitution products can be isolated and involved in further transformations leading to photochromes of unsymmetrical structure as it shown on Scheme 11 [48].



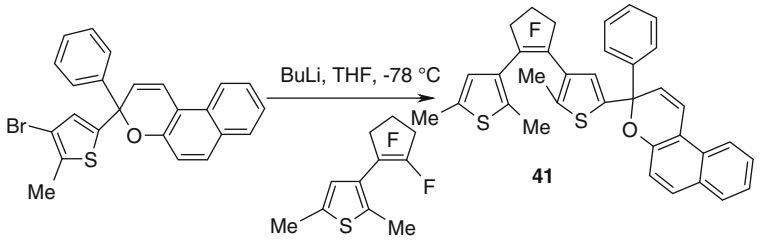
Scheme 11

Characteristic examples of this approach are also the syntheses of unsymmetrical compounds **38** [49], **39** [50], and **40** (Scheme 12). In the latter case, perfluorocyclopentene is bound to different positions of the thiophene rings [51, 52].



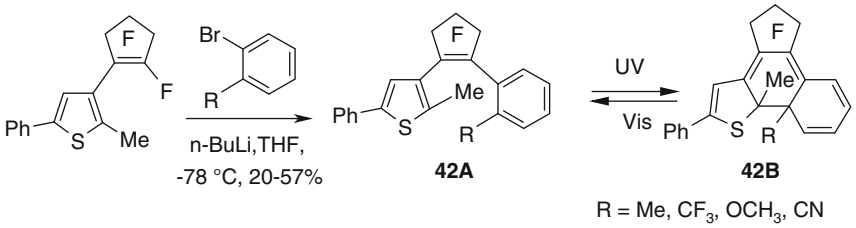
Scheme 12

The "dyad," viz., biphotochromic product **41** in which the dihetarylethene fragment is directly linked with the chromene moiety, was obtained by this method in 52 % yield [53] (Scheme 13).



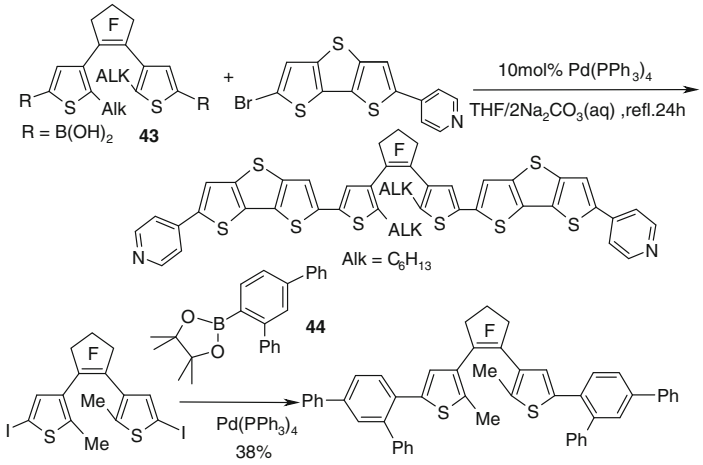
Scheme 13

A non-traditional type of photochromic dihetarylethenes bearing a six-membered aryl unit was developed in [54]. Compounds **42** were prepared from 2-methyl-5-phenyl-3-thienylperfluorocyclopentene in the one-step coupling reactions with 2-bromoanisole,2-bromotoluene,2-bromobenzonitrile,and2-bromobenzotrifluoride, respectively (Scheme 14).



Scheme 14

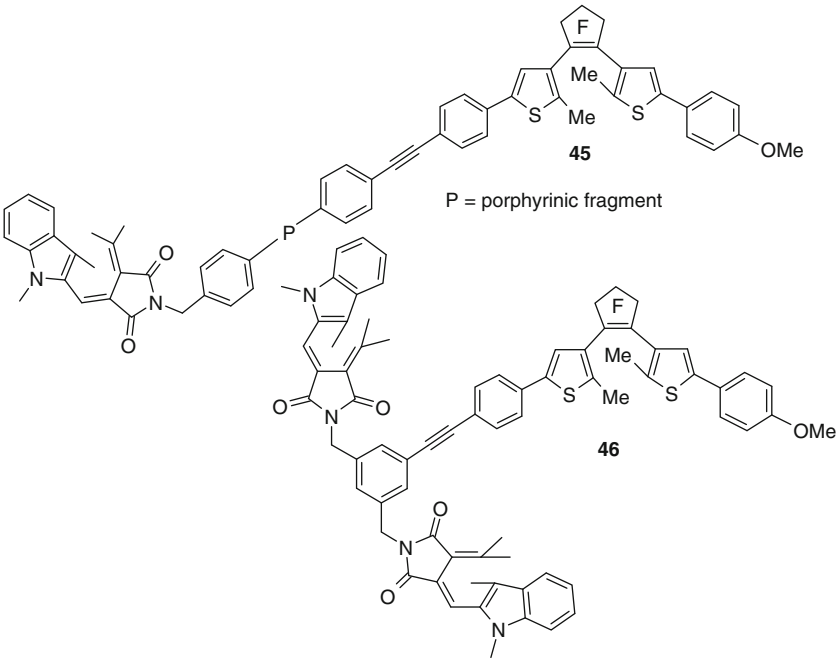
The examples of the further functionalization of the universal "preparations" formed by the reactions of the lithium derivatives with PFCP are presented in Scheme 15.



Scheme 15

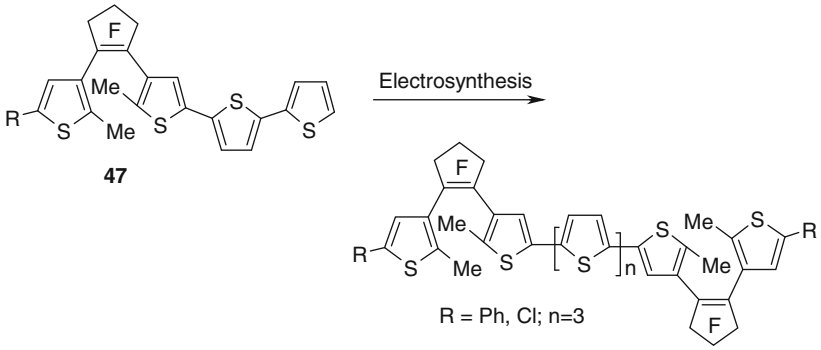
In both cases, the Suzuki reaction is an efficient method for chain growing. In the former case, photochrome **43** [55] was the boron substrate, whereas in the second case, this was terphenyl **44** [56].

The cross-coupling reactions were also actively used for the synthesis of "dyad" **45** and "triad" **46** including the dithienylperfluorocyclopentene and fulgimide moieties [57–59] (Scheme 16).



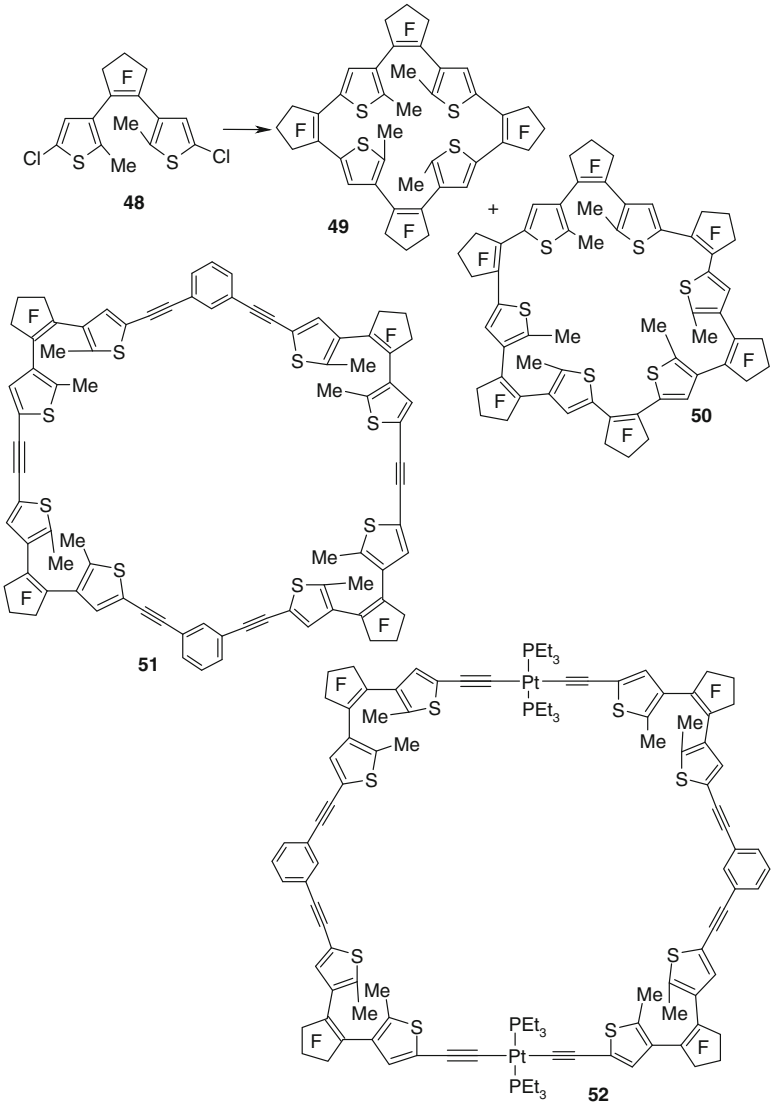
Scheme 16

An example for the electrochemical dimerization of photochrome **47** is given below (Scheme 17) [60].



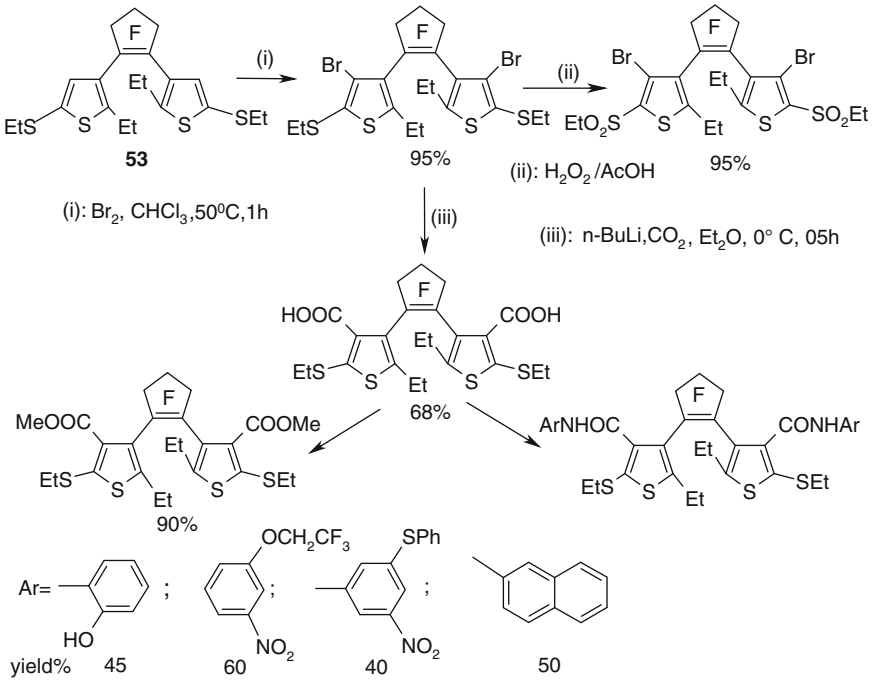
Scheme 17

The reaction of photochromic dichloride **48** with *n*-butyllithium and OFCP in ether at −78° yielded macrocyclic compounds **49** (8.4 %) and **50** (2.6 %) [61] (Scheme 18). The authors mentioned that the former substance exhibited no photochromic properties, because its cyclized form is conformationally unfavorable due to the formation of the strained 20-membered ring, whereas the 30-membered macrocycle **50** is a typical photochrome. The syntheses of the macromolecules **51** and **52** from 1, 2-bis(2-methyl-5-bromo-3-thienyl)perfluorocyclo-pentene using the Sonogashira coupling are described in paper [62].



Scheme 18

Scheme 19 demonstrates the functionalization of photochrome **53** by the introduction of the substituents into positions 4 and 4′ of the thiophene rings [63].

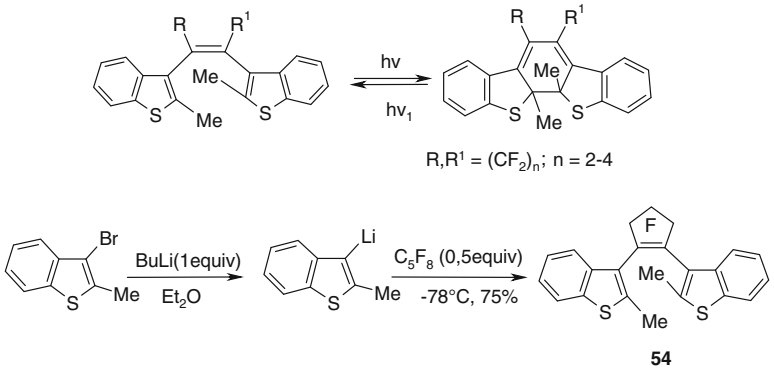


Scheme 19

3.1.2 DHE Based on Fused Thiophenes and Other Heterocycles

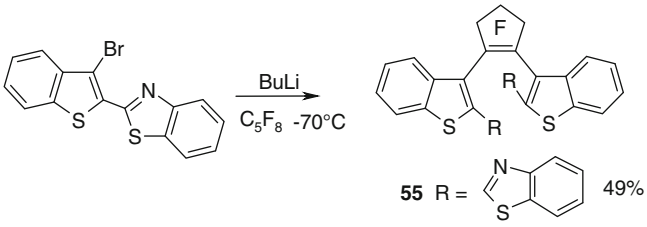
3.1.2.1 Benzo-, Thieno-, and Dithienothiophenes

A family of photochromic products in which the benzothiophene cycle is linked with perfluorocyclenes (Scheme 20) was described in [64]. Researchers are interested in these substances, because the latter are characterized, as a rule, by higher cyclicity than the thienyl derivatives [65]. The method for their synthesis is almost the same as that described above for DTE and is highly regioselective.



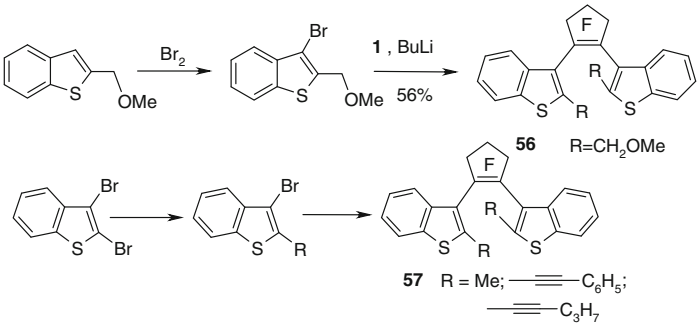
Scheme 20

It has already (see Scheme 9) been mentioned that the presence of the benzothiazole cycles in positions 2 and 2′ of the thienyl rings of compound **34** does not prevent exhibiting the photochromic properties. Under similar conditions, substance **55** was synthesized and its photochromic properties were demonstrated [47] (Scheme 21).



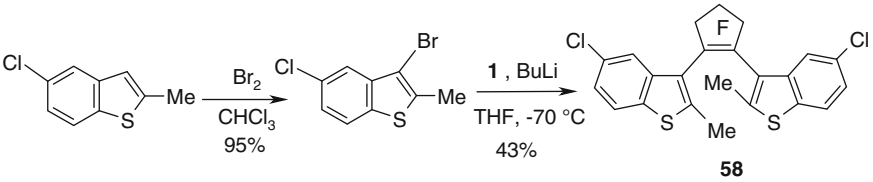
Scheme 21

The same algorithm of synthesis was proposed for the preparation of photochromic dihetarylethenes **56** and **57** bearing the methoxymethyl [66], phenylethinyl, and 1-pentinyl groups [67] at the reactive carbon atom (Scheme 22).



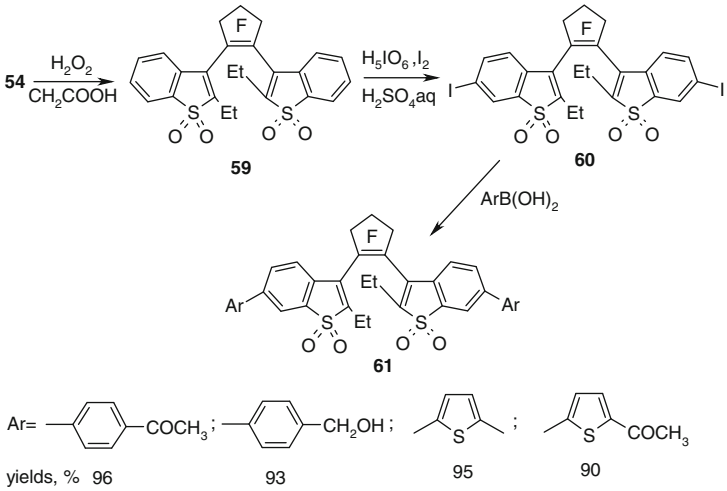
Scheme 22

A considerably greater easiness of formation of the lithium derivative using position 3 of the thiophene ring compared to halogen substitution in the benzene ring made it possible to accomplish the scheme for the synthesis of photochrome **58** with retention of the chlorine atom preliminarily introduced into the benzene ring [68] (Scheme 23).



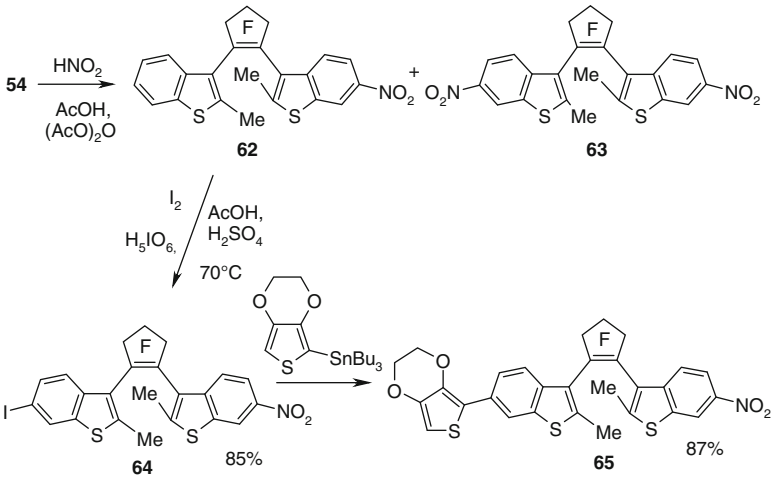
Scheme 23

The further modification of the benzothiophene photochromes can proceed involving both the thiophene and benzene rings. For example, Scheme 24 shows the oxidation products of the sulfur atoms (**59**) in dihetarylethenes and the iodination products (**60**), as well the Suzuki reaction leading to a set of compounds **61**, where R are substituted aryls or thienyls [69]. The oxidation of the sulfur atoms in dihetarylethenes was also described in works [70–73].



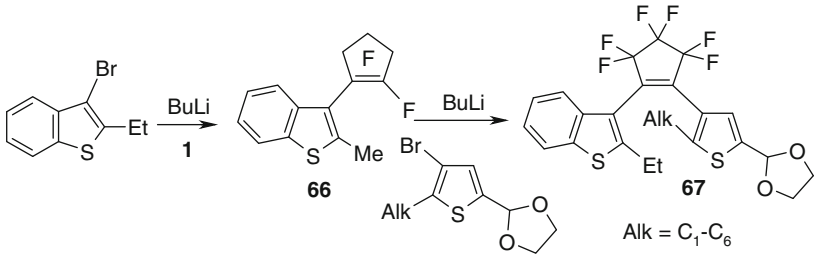
Scheme 24

In several cases, at an equimolar ratio of the reactants, the reaction can be directed to the predominant formation of the mono- or disubstituted products. The nitration of photochrome **54** gave the monosubstitution product **62** in 75 % yield, which allowed the authors to synthesize unsymmetrical photochromes **64** and **65** [74] (Scheme 25).



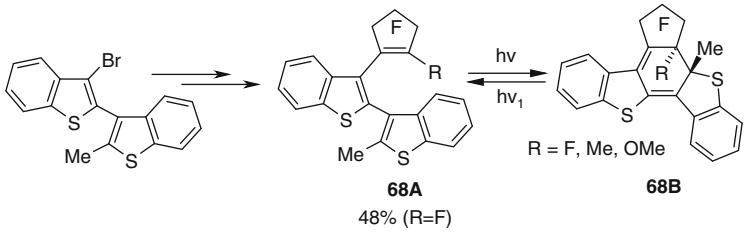
Scheme 25

The synthesis of novel photochromic diarylethenes **67** including the intermediate formation of the monosubstitution product **66** was elaborated [75] (Scheme 26).



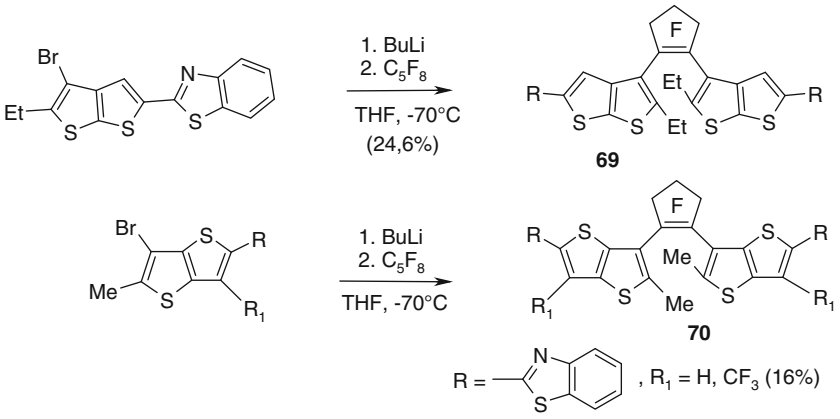
Scheme 26

The monosubstitution products **68** were also assumed as photochromic 6-π-conjugated systems with the bis(2,3′-benzothienyl) fragment of a non-traditional structure, where the fluorine atom or the methyl or methoxy group instead of the heterocycle is adjacent to the benzothienyl substituent in the vicinal position of perfluorocyclopentene [52] (Scheme 27).



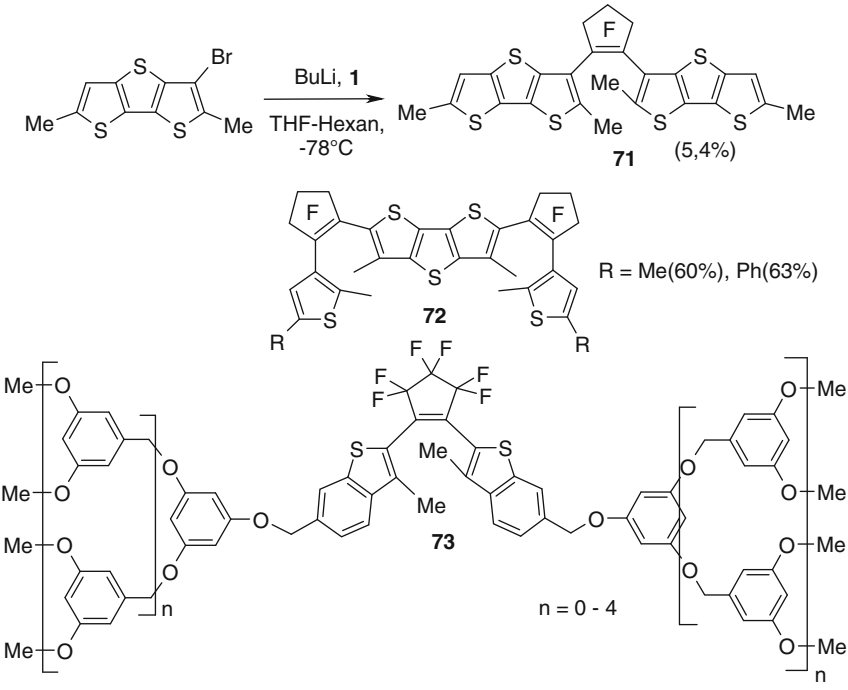
Scheme 27

Perfluorosubstituted derivatives with the thienothiophene substituents were synthesized in a series of works. For instance, the synthesis of compound **69** was proposed in [76a], and its isomeric analogs **70** were synthesized in [76b] (Scheme 28).



Scheme 28

Examples for the synthesis of photochromic perfluorocyclopentenes **71** and **72** with the dithienothiophene substituents (Scheme 29) are given in works [77a–c].

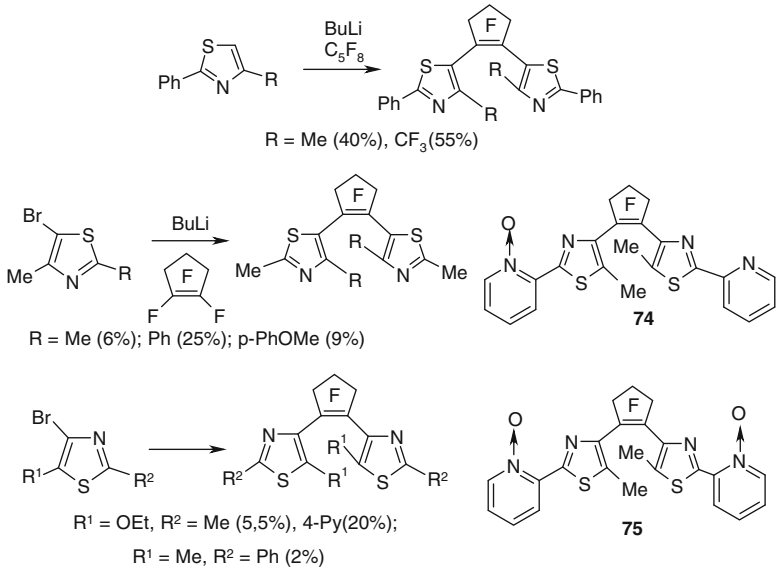


Scheme 29

In the first example, the perfluorocyclopentene bridge was bound to positions 3 and 3′ of the thienyl groups, whereas in the product **72** the fluorinated fragment was linked with positions 2,2′ and 3,3′ of dithienothiophene and thiophenes, respectively. The photochromic polymeric dendrimers **73** in which the multiple bond of the bridge was also connected with positions 2,2′ of the benzothienyl rings were described in [78].

3.1.2.2 Other Heterocycles and "Hybrids"

Not only lithium derivatives of thiophene and also of other heterocycles, particularly, thiazole (Scheme 30), react with perfluorocyclopentene to form photochromes. As a rule, the yields of the thiazole derivatives are significantly inferior to those for the thienyl derivatives [79–82].

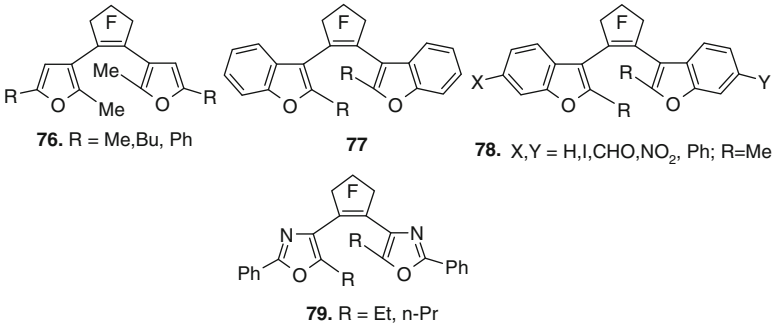


Scheme 30

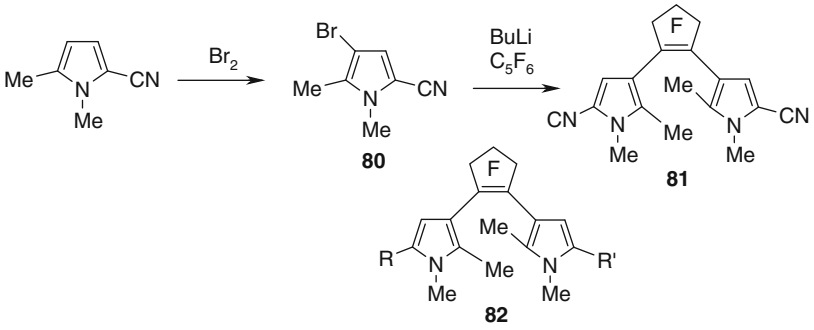
The oxidation of 1,2-bis[5′-methyl-2′-(2″-pyridyl)thiazolyl]perfluorocyclo-pentene with *m*-CPBA involves only the nitrogen atoms of the pyridine cycle and affords the corresponding photochromic mono- **74** and bis-N-oxides **75** exhibiting photochromism both in solution and in the crystalline state [83].

The reactions of 2,5-disubstituted 3-furyl bromides with butyllithium and OFCP in anhydrous THF at −78° afforded bisfurylethenes **76** [84]. Photochrome **77** [85, 86] (29–46 % yield) and a series of its derivatives **78** (55–65 % yield) with various substituents in position 6 of the benzofuran ring [87] were obtained from 3-bromo-2-methyl-1-benzofuran. 1,2-Bis(5-*n*-alkyl-2-phenyloxazol-4-yl)perfluorocyclopent-enes

79 were synthesized and their photochromic properties were examined in a hexane solution as well as in the single-crystal phase [88].



1,2-Dihetarylethene **81** with two pyrrole cycles was obtained by the consecutive interaction of the corresponding bromide **80** with BuLi and C_5F_8 in THF in 11 % yield [89] (Scheme 31). Later French authors [90] succeeded in optimizing the reaction conditions, increasing the yield to 74 %, and synthesizing the whole range of symmetrical and unsymmetrical 5,5′-disubstituted derivatives **82**.

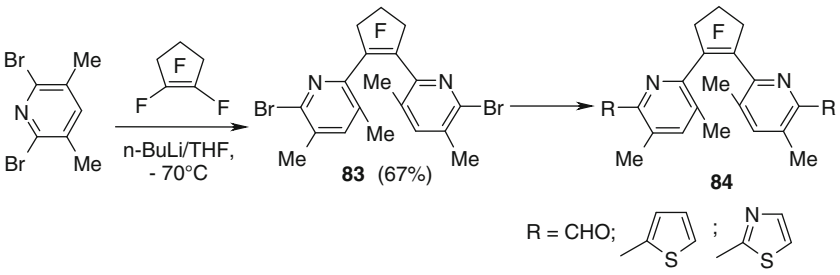


Scheme 31

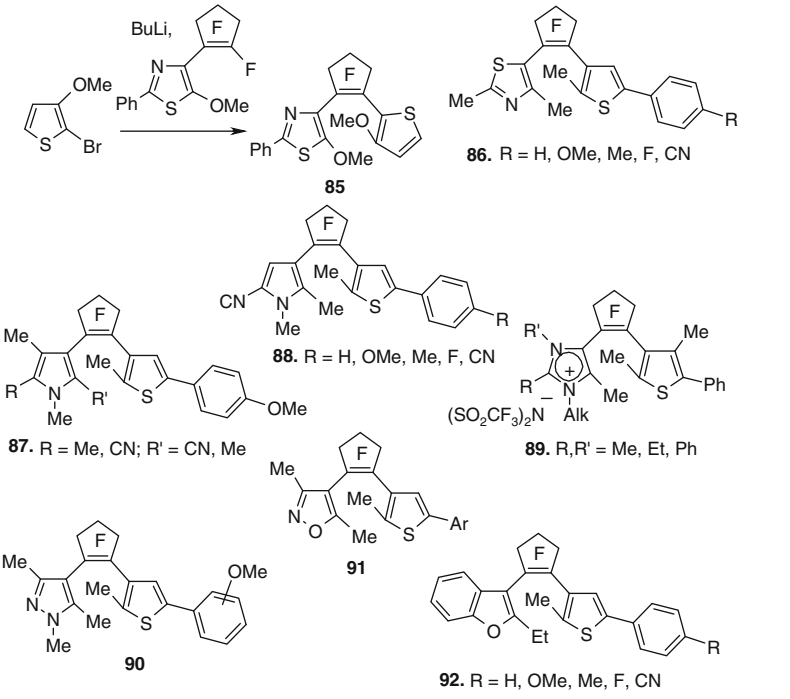
Dibromosubstituted dipyridylethene **83** was prepared in 67 % yield from the known 2,6-dibromo-3,5-dimethylpyridine. This compound can be converted very conveniently into a variety of derivatives **84** through the halogen-metal exchange and the consequent reaction with electrophiles or through one of many cross-coupling reactions involving aryl halides [91] (Scheme 32).

Unique peculiar **"**hybrid" 1-hetaryl-2-thienylperfluorocyclopentenes (Scheme 33) including the thiazole (**85**, **86**) [92a, b] pyrrole (**87**, **88**) [93–95], imidazole (**89**) [96], pyrazole (**90**) [97], isoxazole (**91**) [98], and benzofuran (**92**) [99] cycles were described.

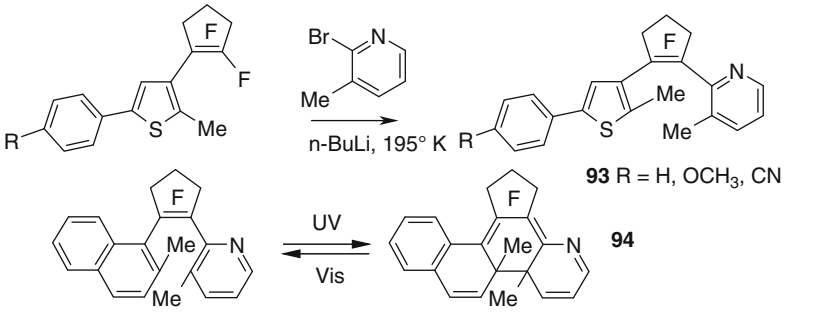
Compounds **93** containing the pyridine and thiophene cycle [100], as well as the pyridine and naphthalene moieties (**94**) [101], have been synthesized for the first time (Scheme 34).



Scheme 32

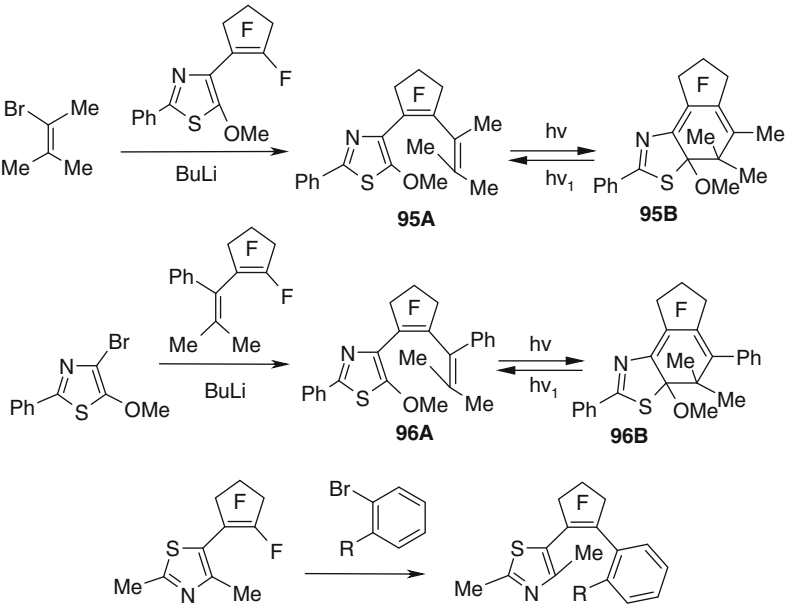


Scheme 33



Scheme 34

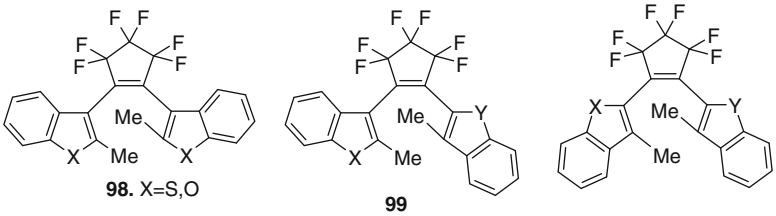
Non-traditional photochromes **95** and **96** were synthesized by the reactions of 2-bromo-3-methyl-2-butene and 4-bromo-5-methyl-2-phenylthiazole with BuLi and the corresponding monofluorides [102] (Scheme 35) and new photochromic di-arlethenes **97** bearing both the thiazole and benzene moieties that exhibit fluorescence in solution and in the PMMA film [103] are worth mentioning.



97. R = Me, OMe, CF3, CN

Scheme 35

A similar principle for the formation of molecules was used for the synthesis of the photochromic compounds containing combinations of benzothiophene (benzofuran) and indene **98** [104], pyrazole [105], or benzofuran cycles **99** and **100** [106, 107].

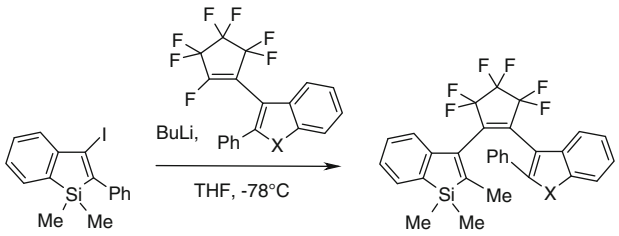


98. X=S,O

99

100. X,Y = S or O

The novel diarylethene derivatives **101** having the benzo[b]silole group together with benzofuran or benzothiophene fragment were synthesized in paper [108] (Scheme 36).



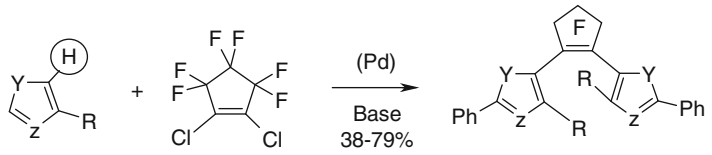
101. X=S(12%),O(13%)

Scheme 36

An efficient method for the synthesis of photochromic diarylethenes through the generation of heteroaryllithiums and the subsequent reaction with octafluorocyclopentene was developed by using integrated flow microreactor systems [109]. The reactions can be conducted without using cryogenic conditions by virtue of efficient temperature and residence time control, although much lower temperatures (<78 °C) are needed for the batch macroreactions. The authors assert that this integrated flow microreactor method serves as a practical way for synthesizing various photochromic diarylethene derivatives [110].

To conclude, we should mention the work similar, in essence, in which thienylboronic acids or pinacol esters react with 1,2-dichlorohexafluorocyclopentene via the Suzuki–Miyaura coupling [111]. A doubtless advantage of the method is its applicability to various substrates bearing reactive functionalities such as cyano and ester moieties, which cannot be compatible under the conventional diarylethene synthesis conditions using organolithium reagents.

A novel and efficient palladium-catalyzed direct diheteroarylation of 1,2-dichlorop erfluorocyclopentene with a variety of heteroarenes has recently been reported, giving rise to 1,2-di(hetaryl)perfluorocyclopentene photochromic compounds **102**. The reaction occurs with thiazoles, thiophenes, or furan derivatives and tolerates various substituents [112] (Scheme 37).



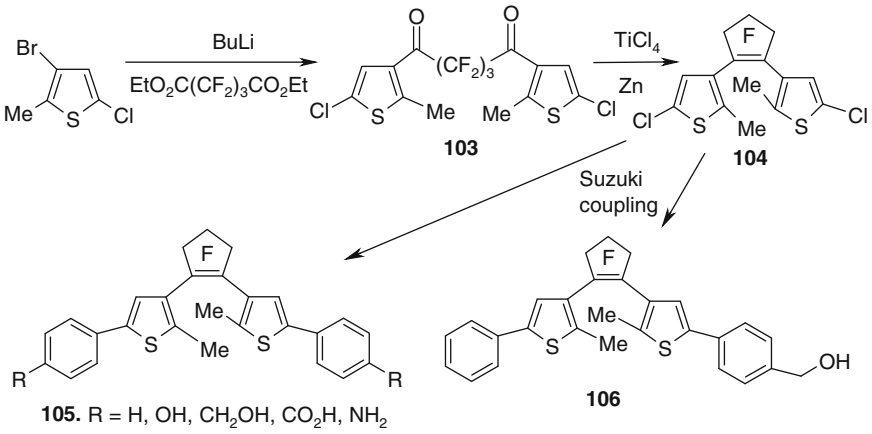
102. Y = O,S; Z = CH, N

Scheme 37

3.2 McMurry Reaction

As a whole, we can speak about accessibility of thermally irreversible photochromes based on perfluorocyclopentene. However, its relatively high cost and certain inconveniences in the work related to its high volatility (b.p. 26–28 °C) [113], as well as low (in many cases) yield of the final products, stimulate a search for new approaches to

photochromes with the hexafluorocyclopentene fragment. For example, B.L. Feringa and coworkers proposed a very promising method for the synthesis of symmetrical derivatives of 1, 2-dithienylperfluorocyclopentene based on the use of diethyl hexafluoroglutarate as the starting compound (Scheme 38) [114, 115]. The authors assert that the formation of dithienyl ketone **103** and cyclization to the final product **104** (McMurry reaction) occurs in 70 and 55 % yields, respectively (Scheme 38).



Scheme 38

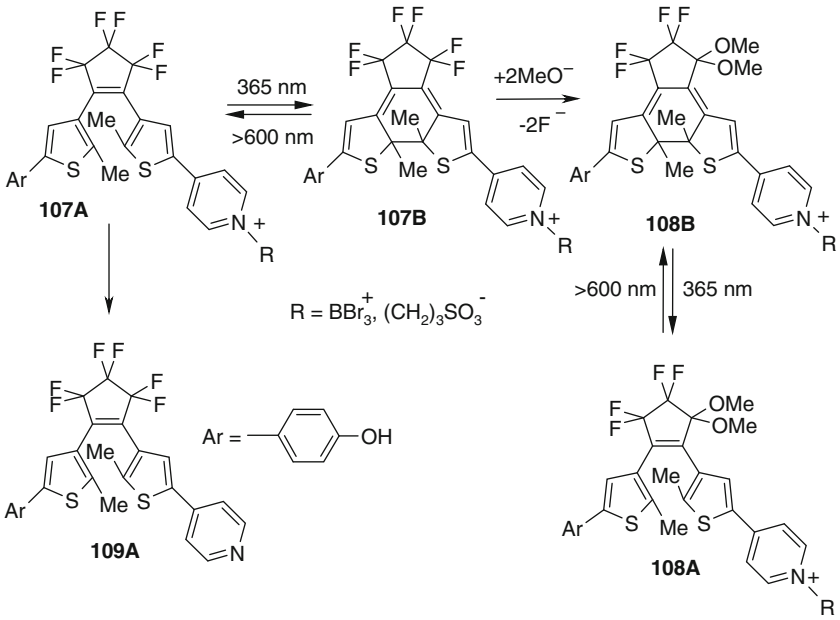
The product **104** is a convenient starting compound for the subsequent modification of photochromes. In particular, publication [116] described an efficient route for the synthesis of both symmetrical (**105**) and unsymmetrical (**106**) phenyl-substituted dihetarylethenes bearing amino, hydroxyl, or carboxyl groups from this dichloride and commercially available substituted boronic acids (or their pinacol esters) via the Suzuki reaction in a DME-H_2O (4:1) mixture under reflux (24 h). The yields attain 85–95 % for the symmetrical products and 60 % for the unsymmetrical products. It should be noted however, the McMurry reaction mainly found application in the synthesis of the perhydrocyclopentene analogs of dithienylperfluorocyclopentenes [117].

3.3 Dithienylethenes, Substituted in Perfluorocyclopentene Bridge

All data presented above concern the methods for the synthesis of DTE with unsubstituted hexafluorocyclopentene bridge. In our opinion, particular and so far rare examples of synthesis of DTE containing other substituents along with F atoms in the bridge are worth of special mentioning [48, 118].

When studying the photochemical behavior of alcohol **107A** in an aqueous-alcohol medium under basic conditions the methoxide ions displaced the fluorine atoms of one of the allylic CF_2 groups to yield **108B** and two isolated products were **108B** and **108A** (Sheme 39).

A surprising aspect of the allylic substitution reaction was that it only took place for the **cyclized** form **107B** of the photochrome. Transformation of **107B** to **108B** was extremely rapid; the former species was never observed. In marked contrast, the open isomer **107A** proved to be stable in methoxide solutions for prolonged periods of time (no detectable change after over **12 h** of standing at ambient temperature). It is noteworthy that such a transformation did not occur during the conversion of **107A** (R = BBr_3) to **109A** (open forms), which required very strongly basic conditions (Scheme 39).

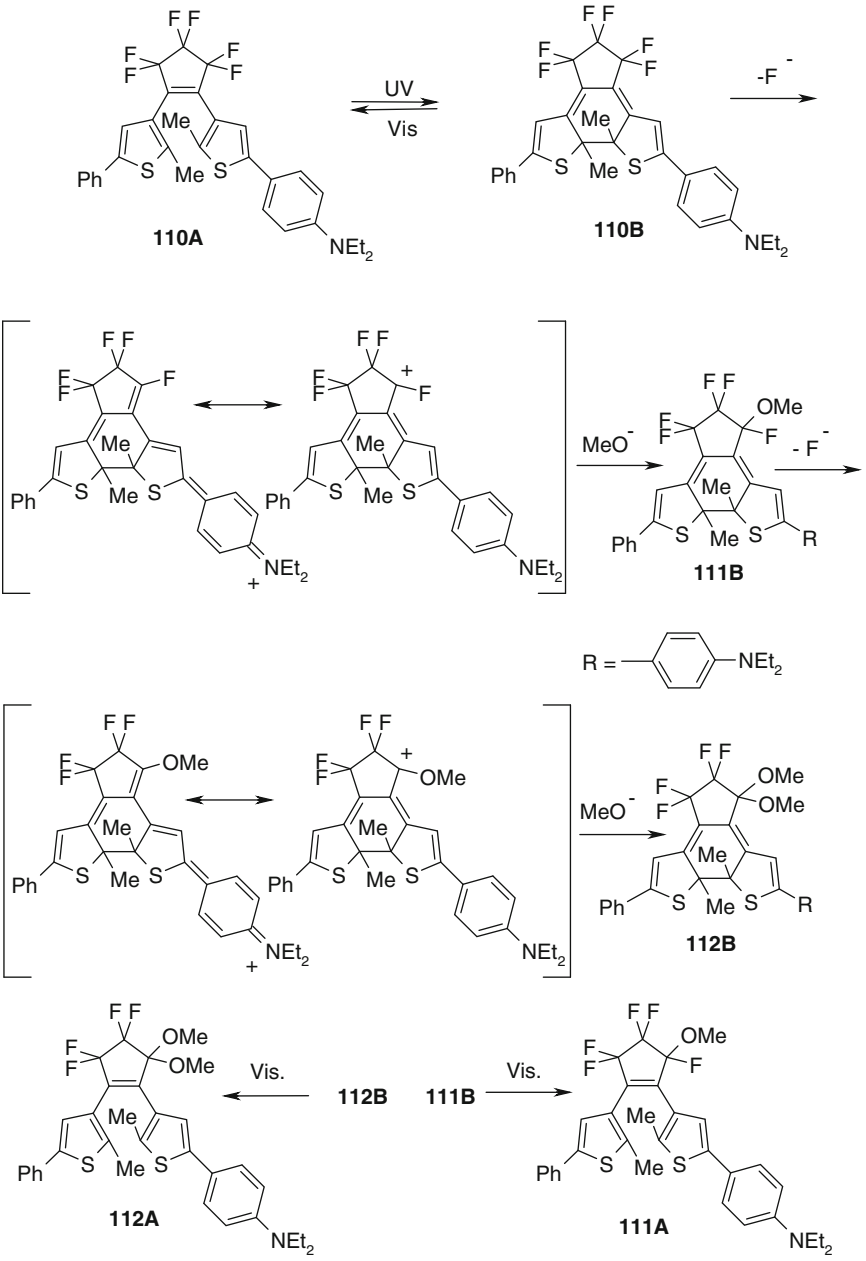


Scheme 39

The examination of models showed that for the open isomers of these photochromes, in which the thiophene rings were rotated far out of the plane of the central fluorinated cycle, attack by a nucleophile on the allylic carbons of the central fluorinated ring was strongly hindered. On the other hand, these centers were accessible once the system was closed and essentially planar. The flatness of the **cyclized** form also allowed the electron-withdrawing pyridinium group to activate the allylic center towards attack by the alkoxide nucleophile. Authors have also observed the analogous substitution reactions when the closed photochrome **107B** was treated with ethoxide, ammonia or methylamine [48].

A similar phenomenon of substitution for fluorine atoms by methoxy groups was also observed in a later publication [118] Thus, DTE **110A** upon irradiation at 365 nm was reacted in methanol for 40 h at room temperature. After the solution was irradiated with visible light to return to the colorless open-ring isomers, the products were separated to result in the isolation of two products -**111A** and **112A** (Scheme 40). The structures of the products were identified by ^{1}H NMR, mass spectrometry, and X-ray crystallographic analysis. When ethylene glycol was employed as the reacting agent

the corresponding cyclic product was also obtained. The reaction of diarylethene **110B** with isopropyl alcohol did not occur. This result indicates that only primary alcohols can react with diarylethene closed-ring isomer. The proposed mechanism of the formation of these products was shown in Scheme 40.



Scheme 40

It is important to note that this type of transformation may be of practical significance in that it provides a ready means of covalently attaching fluorinated diarylethenes of this type to polymers or other materials which bear pendant nucleophilic groups.

4 Structures of 1,2-Dihetarylhexafluorocyclopentenes

Dihetarylethenes with the perfluorocyclopentene "bridge" (**F** cycle) belong to a not numerous class of the so-called thermally irreversible photochromes in which the initial and cyclized forms do not transform into each other in the absence of irradiation. They are stable up to decomposition temperatures both in solutions and in the crystalline phase. It should be noted that the most part of photochromes, in particular, most widely abundant spiropyrans and spirooxazines, are characterized by the reversibility of the cyclized form even in the dark. The thermal irreversibility of DTE is determined, roughly speaking, by a small difference in energies of the initial cyclized forms caused by a change in the aromaticity of the thiophene cycles on going from one form to another. In the above mentioned spiropyrans and spirooxazines, the aromaticity of the benzene rings is lost on going from one form to another, and recovery of the aromaticity is a powerful driving force for the reversibility process. Similar discussions of this and other factors determining photochromism of DTE and the theoretical background of the photochromic reactions, color changes of the derivatives in solution as well as in the single crystalline phase are presented in review [12].

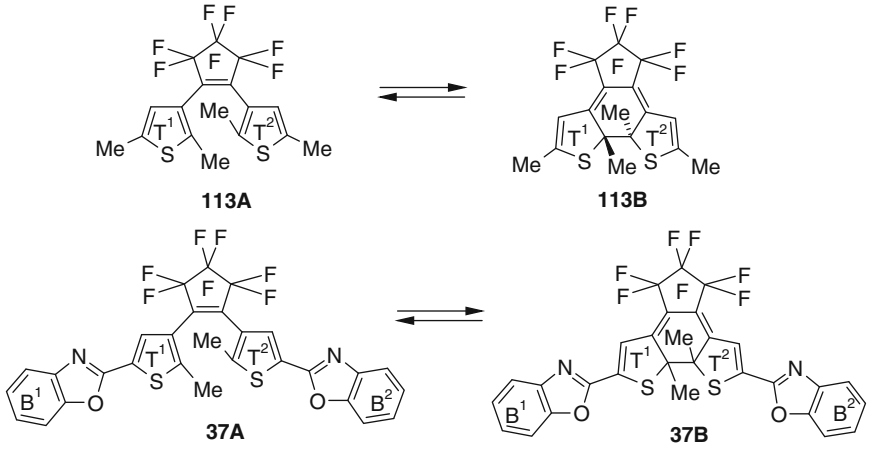
The efficiency of the cyclization of UV-irradiated photochromic hexafluorocyclopentenes and the backward transformation is determined, to a considerable extent, by their structures. A large material on the X-ray diffraction studies of the photochromes in the crystalline state has been obtained to present time [119–122]. Several typical examples throwing light on the peculiarities of the fine structure of DTE in the solid state are given below. The structures of the initial forms **A** of dihetarylethenes were studied in most detail, whereas the isolation and study of their cyclized isomers are much more difficult and labor-consuming.

4.1 Open Forms of Dihetarylethenes

Let us begin from the consideration of the structures of photochromic DTE **113A** and **37A** with substituents in positions $2,2^1$ and $5,5^1$. The numbering of atoms in the heterocycle is shown in Scheme 41; perfluorocyclopentene is denoted as **F**; thiophene cycles are **T1** and **T2**; benzoxazole is designated as **B**.

The structure of 1,2-bis(2,5-dimethyl-3-thienyl)hexafluorocyclopentene (**113A**) is rather simple (Fig. 1) [123, 124].

The dihedral angles **T1/F**, **T2/F**, and **T1/T2** in **113A** are equal to 46.78, 46.77, and 62.25°, respectively. The peculiarity of this compound is the ability of a single crystal to undergo repeated ($>10^4$ times) photochromic transition **A** ↔ **B** without the



Scheme 41

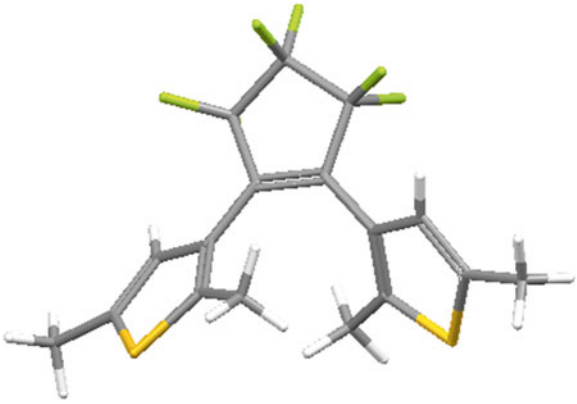
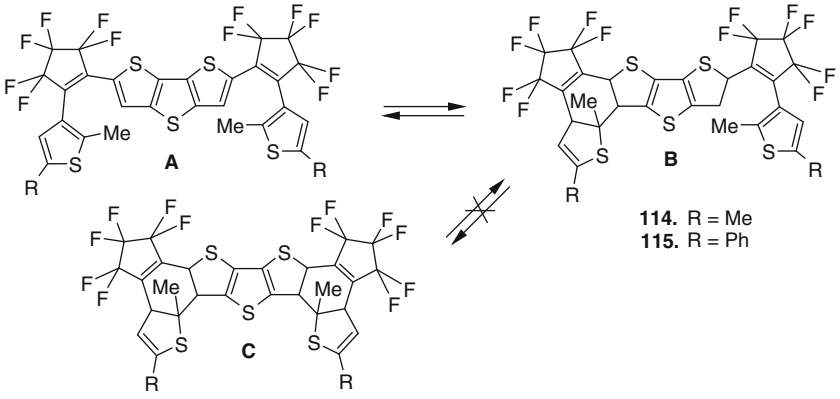


Fig. 1 Molecular structure of open form **A** of photochrome **113** (Cambridge Structural Database System CCDC; FAWFOY03) [123, 124]

destruction of the crystal structure: colorless crystals of **113A** after the UV irradiation ($\lambda = 366$ nm) are transformed into the red-colored form **113B**. The latter is stable in the dark up to 100 °C and transforms back into form **A** by the action of the visible light. Photochromism of the compound is also retained in solution; particularly, the spectral characteristics in a hexane solution indicate the full photoreversibility of the reaction.

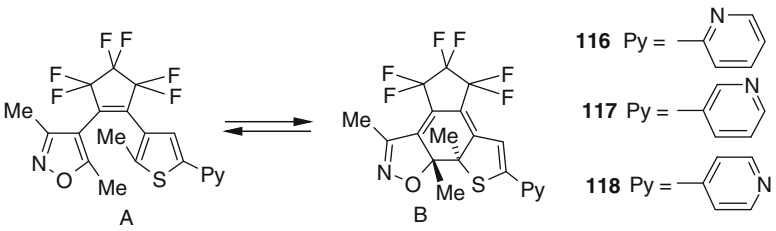
The full photoreversibility of the isomers upon the irradiation of an ethanolic solution of form **37A** with the light of $\lambda = 313$ nm and of form **37B** with the light of $\lambda = 578$ nm is common for 1,2-bis[5-(benzoxazol-2-yl)-2-methylthien-3-yl]perfluorocyclopentene (**37**) [47] (Scheme 41). The structure is built up of two crystallographically independent molecules that slightly differ only by the deflection angles of the benzoxazole fragments (**B**) relative to the thiophene cycles and by the torsion angles in the **F** cycle [125].

Contrary to structure **113A**, the **F** cycle in this compound has a shape of an envelope with a vertex opposite to the double bond. Another peculiarity of the compound is the formation of a planar spatially elongated conjugated system thiophene–benzoxazole. The deflection angle of the benzoxazole fragments relative to cycles **T** does not exceed 2–3°. The conjugation in the planar system is also confirmed by an appreciable shortening of the C−C bonds between the thiophene and benzoxazole cycles down to 1.442 Å in comparison to the standard value of this bond (1.48 Å). Thus, two planar conjugated thiophene–benzoxazole systems are turned relative to each other at 55–60° in molecule **37A**. There is no conjugation between these systems. Each of them is rotated relative to the **F** cycle at ~53.6°. The intramolecular distance C*(2)*···C′*(2)* equal to 3.59 Å, as well as that in **113A**, corresponds to the normal van der Waals contact (Scheme 42).



Scheme 42

For the diarylethene "dimer", in the most cases, the intramolecular excited energy transfer from the open-form unit to one of the closed forms prohibits the formation of two closed-ring dimers. Crystals **114A** and **115A** could only take place at one of the diarylethene units even upon prolonged irradiation [77b]. Upon irradiation with the 380-nm light, the pale yellow crystals of both photochromes turned orange quickly as a result of the formation of closed-ring isomers **114B** and **115B** (not **C**!). Alternatively, the orange color of the crystals turned to pale yellow and reproduced initial forms **A** upon irradiation with the visible light (>500 nm). It can be observed that compounds **114A** and **115A** adopted the photoactive antiparallel conformation in the crystalline phase. For **114A**, there are two independent molecules (I and II) in the unsymmetrical unit, and all of them are in the photoactive antiparallel conformation. The distance between the photoactive carbon atoms is one of the most important parameters for the photochromism of dihetarylethenes. In this case, the distances between the photoactive carbons were 3.464 and 3.593 Å in molecule **114A**-I and 3.550 and 3.535 Å in molecule **114A**-II. For the second diarylethene, the distances between the photoactive carbons were 3.616 and 3.616 Å, respectively [126]. Similar results were obtained for crystals of the open forms of photochromes **116–118** [127] (Scheme 43).



Scheme 43

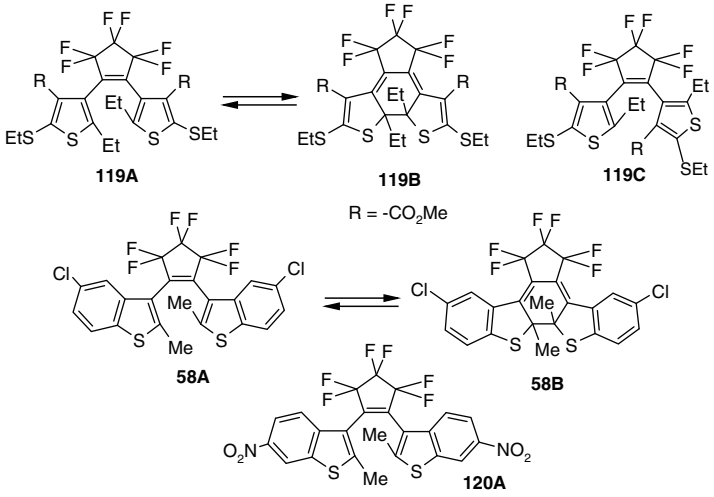
The intermolecular distances between two photoactive C*(2)*···C′*(2)* atoms in these photochromes were 3.5, 3.6, and 3.6 Å, respectively, which were close enough to perform the cyclization reactions [128, 129]. The dihedral angles between the hexafluorocyclopentene ring and two adjacent heteroaryl rings were 48.3° for O1/N1/C16-C18 and 51.3° for S1/C6-C9, whereas that between the thiophene ring and the linked pyridine ring was 19.5°. From these data it could be concluded that all molecules of crystals **116–118** were fixed in the antiparallel mode in the crystalline phase, and the distances of two reactive C atoms were shorter than 4.2 Å. So, they could be expected to undergo photochromism in the single crystalline phase. As a matter of fact, the crystals of **116–118** underwent excellent photochromism in accordance with the expected ring closure upon UV irradiation.

Note, however, that in several cases, the photochrome molecules are packed during crystallization in such a way that their conformations with elongated distances between the photoactive C–C atoms prevent photocyclization.

So, 1,2-bis-(4-methoxycarbonyl-2-ethyl-5-ethylthiothien-3-yl)hexafluorocyclopentene (**119A**) in which all hydrogen atoms of the heterocycles are substituted, whose synthesis is described in Scheme 19, did not isomeriize to isomer **119B** upon the UV irradiation [130]. As shown by X-ray diffraction analysis, the conformation of molecule **119A** has some peculiarities in comparison with the previously considered structures. First, the **F** cycle is considerably compressed: the deviation of the envelope vertex from the cycle plane is equal to 0.12 Å only. The dihedral angles **T1/F**, **T2/F**, and **T1/T2** are close to 90° (−84.7°, 86.7°, and 79.00°, respectively). They are considerably larger than similar angles in the compounds with two functional groups (**37A**, **113A**). Second, the thienyl fragments are unfolded in opposite directions relative to the **F** cycle (structure **119C** in Scheme 44, Fig. 2). As a result, the distance between the atoms C*(2)*···C*(2′)* (4.45 Å) is much longer than the normal van der Waals contact and, therefore, is geometrically unfavorable for cyclization. In fact, compound **119** in the crystalline state does not change its color upon UV irradiation.

The X-ray diffraction analysis also elucidated the reasons for the absence of photochromism of product **58** in the solid state (Fig. 3) [68].

The product showed no photochromism in the crystalline phase as compared with similarly structured 1,2-bis(2-methyl-6-nitro-1-benzothiophen-3-yl)perfluorocyclopentene **120** [131]. The unit cell of a crystal of **58A** includes two symmetrically independent



Scheme 44

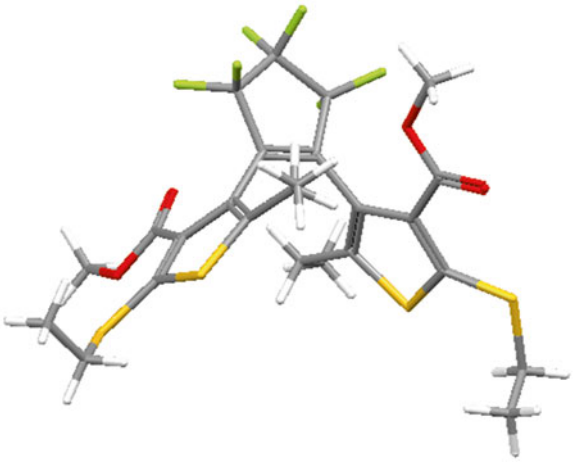


Fig. 2 Molecular structure of **DTE 119C** (CCDC; code: QEQVEN) [130]

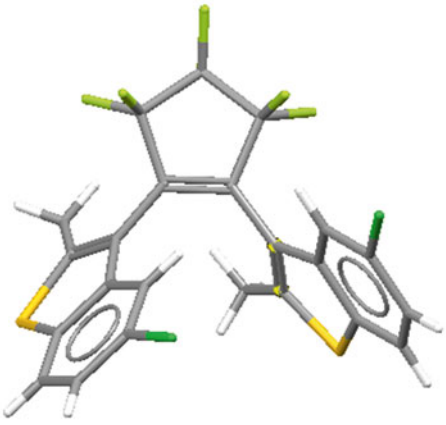


Fig. 3 Molecular structure of **DTE 58A** (CCDC; code: XIDJOK) [68]

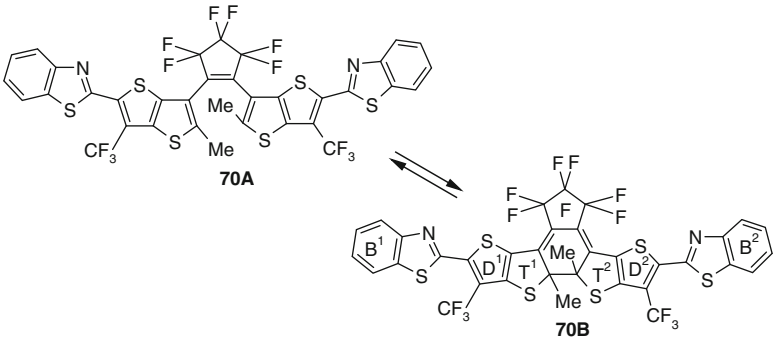
molecules (**a** and **b**). The comparison of the geometrical and conformational parameters of **a** and **b** did not reveal any critical differences (the average values are given below). All bond lengths and bond angles correspond to the standard values.

The perfluorocyclopentene fragment adopts an envelope conformation with the C4 atom deviated from the plane of other four cyclopentene carbons by 0.408 Å. The dihedral angles between the perfluorocyclopentene plane and each benzothiophene ring are 65.8° and 68.0°, respectively, while two benzothiophene planes form a dihedral angle of 72.7°. At this conformation, the distance between the carbon atoms in positions 2 and 2′ turned out to be 4.25 Å, *i.e.*, significantly exceeding the van der Waals radius. That is why, compound **58** in the crystalline state remains to be photochemically inactive. It should be repeated that an analogous observation was reported for crystals of **120**.

It is important to emphasize that photochromes **58**, **119**, and **120** differ drastically in behavior in the crystalline state and in solutions. The unfavorable crystalline conformations prevent the photocyclization of these compounds, while in solutions, where the fragments can freely rotate about the C–C bonds to form conformations necessary for cyclization, they manifest the typical photochromic properties.

4.2 Cyclized Forms of Photochromes

Spatial structures of forms **B** of the photochromes are poorly studied because of the difficulties in the production of single crystals suitable for X-ray diffraction and separation. Let us consider the structure of the cyclized form using considerably structurally different isomers **70B** and **113B** as examples (Schemes 41 and 45).



Scheme 45

The **F** cycle in **70B** looks like an envelope with a vertex, which is deflected from the base by 0.38 Å [46]. The cycles $\mathbf{T^1}$ and $\mathbf{T^2}$ in the thieno[3,2-b]thienyl fragments have also the envelope conformations, that is, the aromaticity in the thienyl cycles bonded with ring **F** is broken. Other seven atoms of thieno[3,2:b]thienyl form planar systems in each of the molecules ($\mathbf{D^1}$, $\mathbf{D^2}$). These systems and fragments **F** and **B** make up the

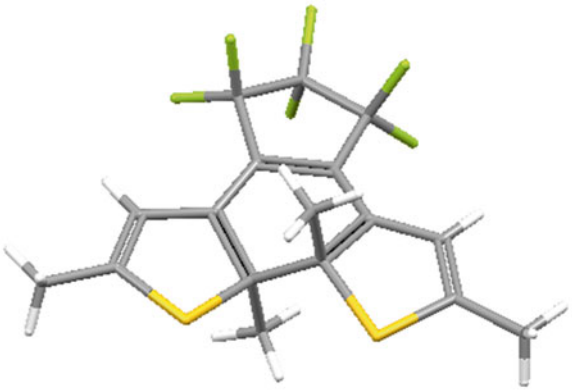


Fig. 4 Molecular structure of cyclized form **B** of photochrome **113** (CCDC; code: FAWKIX) [123, 124]

flattened skeleton of the molecule (except for fluorine atoms), since the dihedral angles **D/F**, $\mathbf{D^2/F}$, $\mathbf{D^1/D^2}$, and $\mathbf{B^1/T^1}$ are small (0.32, 2.97, 3.27, and 1.39°, respectively). The angle $\mathbf{B^2/T^2}$ is slightly larger (11.45°) and is evidently caused by the action of the crystal lattice field. The alternation of C−C bond lengths by different multiplicity factors in the flattened fragment of the molecule indicates the formation of a new conjugated system of the polyene type. The six-membered cycle formed as a result of the cyclization acquires the conformation of "twisted sofa" with methyl substituents in positions 2,2′ trans-oriented relative to the plane of the molecule.

Molecule **113B** (Fig. 4) [119, 123] has a similar structure: the cycles **F**, $\mathbf{T^1}$, and $\mathbf{T^1}$ have the envelope conformation, and the six-membered cycle takes the conformation of "twisted sofa".

The values of dihedral angles $\mathbf{T^1/F}$ (−12.14), $\mathbf{T^2/F}$ (11.62), and $\mathbf{T^1/T^2}$ (177.17°) indicate the flattened structure of the molecule (except for the F and H atoms of the methyl groups). The new system of conjugated bonds can be separated out in the planar fragment of the molecule, as well as in **70B**. Thus, forms **B** of the photochromes with the perfluorocyclopentene bridges are characterized by the following analysis and enantiomeric features: (a) the skeleton of the molecule is practically planar, (b) all five-membered rings have envelope conformations, (c) the thienyl cycles lose aromaticity, and (d) a new system of conjugated bonds is formed.

Acknowledgement The authors are grateful to Dr. Ludmila Vorontsova who has partly contributed in the work described herein.

References

1. Irie M, Mohri M (1988) Thermally irreversible photochromic systems. Reversible photocyclization of diarylethene derivatives. J Org Chem 53:803–808. doi:10.1021/jo00239a022
2. Irie M (1989) Advances in photochromic materials for optical data storage media. Jpn J Appl Phys 28(Suppl 28–3):215–219

3. Irie M (1994) Photo-reactive materials for ultrahigh density optical memory. Elsevier, Amsterdam
4. Irie M (2000) Diarylethenes for memories and switches. Chem Rev 100:1685–1716. doi:10.1021/cr980069d
5. Krayushkin MM (2001) Synthesis of photochromic dihetarylethenes. Khim Geterotsikl Soedin 19–40
6. Kobatake S, Irie M (2003) Photochromism. Annu Rep Prog Chem Sect C 99:277–313. doi:10.1039/b208508a
7. Tian H, Yang S (2004) Recent progresses on diarylethene based photochromic switches. Chem Soc Rev 33:85–97. doi:10.1039/b302356g
8. Krayushkin MM, Barachevsky VA, Irie M (2007) Synthesis of thienyl-containing photochromes (dithienylethenes, fulgides, fulgimides, and spirocompounds). Heteroatom Chem 18:557–567. doi:10.1002/hc.20334
9. Irie M (2008) Photochromism and molecular mechanical devices. Bull Chem Soc Jpn 81:917–926. doi:10.1246/bcsj.81.917
10. Barachevsky VA, Krayushkin MM (2008) Photochromic organic compounds for optical memory. Russ Chem Bull Int Ed Engl 57:867–875
11. Cusido J, Deniz E, Raymo FM (2009) Fluorescent switches based on photochromic compounds. Eur J Org Chem 2009:2031–2045. doi:10.1002/ejoc.200801244
12. Irie M (2010) Photochromism of diarylethene molecules and crystals. Proc Jpn Acad Ser B 86:472–483. doi:10.2183/pjab.86.472
13. Bertarelli C, Bianco A, Castagna R, Pariani G (2011) Photochromism into optics: opportunities to develop a light-triggered optical elements. J Photochem Photobiol C: Photochem Rev 12:106–125. doi:10.1016/j.jphotochemrev. 2011.05.003
14. Parthenopoulos DA, Rentzepis PM (1989) Three-dimensional optical storage memory. Science 245:843. doi:10.1126/science.245.4920.843
15. Irie M, Matsuda K (2001) Memories. In: Balzani V (ed) Electron transfer in chemistry. Springer, Berlin, pp 215–242
16. Irie M (2001) Photoswitchable molecular systems based on diarylethenes. In: Feringa BL (ed) Molecular switches. Wiley, Weinheim, pp 37–62
17. Bianco A, Bertarelli C, Dassa G, Toso G, Zerbi G (2008) Realization of photochromic polymeric films for optical applications. Adv Sci Technol 55:1–6
18. Corns SN, Partington SM, Towns AD (2009) Industrial organic photochromic dyes. Color Technol 125:249–261. doi:10.1111/j.1478-4408.2009.00204.x
19. Han M, Lee S, Jung J, Park KM, Kwon SK, Ko J, Lee PH, Kanga Y (2006) Effect of a perfluorocyclopentene core unit on the structures and photoluminescence of fluorene- and anthracene-based compounds. Tetrahedron 62:9769–9777. doi:10.1016/j.tet.2006.07.065
20. Berberich M, Natali M, Spenst P, Chiorboli C, Scandola F, Würthner F (2012) Nondestructive photoluminescence read-out by intramolecular electron transfer in a perylene bisimide-diarylethene dyad. Chem Eur J 18:13651–13664. doi:10.1002/chem.201201484
21. Heitzman RJ, Patrick CR, Stephens R, Tatlow JC (1963) 45. Fluorocyclopentanes. Part I. The 1H,2H- and 1H,3H-octafuorocyclopentanes, and 1H,3H/2H-heptafluorocyclopentane. J Chem Soc 1963:281–289. doi:10.1039/JR9630000281
22. Henne AL, Latif KA (1954) Perfluorinated alkene, alkyne and cycloalkene. J Am Chem Soc 76:610–612. doi:10.1021/ja01631a089
23. Maynard JT (1963) The synthesis of highly fluorinated compounds by use of potassium fluoride in polar solvents. J Org Chem 28:112–115. doi:10.1021/jo01036a025
24. Henne AL (1962) Replacing vinylic halogens with fluorine. US 3024290, CA 56:15333i
25. Sekiya A, Yamada T, Watanabe K (1998) Process for producing fluorinated alkene and fluorinated alkane. US 005847243A
26. Ji HS, Cho OJ, Ryu JG, Yang JY, Ahn YH, Kim BS, Kim DH (2007) Octafluorocyclopentene as dry etching gas for semiconductor devices manufacturing. DE 102006049156
27. Mase T, Kim YN, Yamada T (2001) Preparation of 1,2,3,3,4,4,5,5- octafluorocyclopentene. JP 2001247493A

28. Ozol SI, Vinogradov DV, Mikhailov IN, Zaitsev S, Barabanov VG (2008) Process for preparation of octafluorocyclopentene by fluorination of mixed chloro- and fluoro-containing cyclopentenes with potassium fluoride in DMF containing a small amount of water. RU 2318793
29. Otsuki N (2005) Environmentally friendly new five-member-ring fluoro compound manufacture and their practical application. Petrotech 28:489–493
30. Yamada T, Otsuki N, Sugimoto T, Tanaka K, Sekiya A (2003) Preparation technology and properties of environmentally friendly five-membered cyclic fluoro compounds. Fain Kemikaru 32:13–20
31. Yamada T, Sekiya A (1998) Development of next-generation fluorine compounds. Eco Industry 3:31–39
32. Yamada S, Ishii E, Konno T, Ishihara T (2008) Preparation of perfluorocyclopentenylmetal species and their cross-coupling reaction with electrophiles – remarkable accesses to versatile perfluorocyclopentene derivatives. Tetrahedron 64: 4215–4223 (p 4222 and references cited therein). doi:10.1016/j.tet.2008.02.089
33. Clayton AB, Roylance J, Sayers DR, Stephens R, Tatlow JC (1965) Polyfuorocycloalkenes. Part III. Reactions with alcohols under ionic conditions to give ethers. J Chem Soc 7358–7367. doi:10.1039/JR9650007358
34. Lindner PE, Lemal DM (1996) Highly fluorinated cyclopentanones and their enols. J Org Chem 61:5109–5115. doi:10.1021/jo9602940
35. Stockel RF, Beachem MT, Megson FH (1964) The reaction of methoxide ion with perfluorocyclopentene. Can J Chem 42:2880–2883. doi:10.1139/v64-425
36. Cracowski JM, Sharma B, Brown DK, Christensen K, Lund B, Smith DW Jr (2012) Perfluorocyclopentenyl (PFCP) aryl ether polymers via polycondensation of octafluorocyclopentene with bisphenols. Macromolecules 45:766–771. doi:org/10.1021/ma2024599
37. Yamada S, Ishii E, Konno T, Ishihara T (2007) Reaction of perfluorocyclopentene with various carbon nucleophiles – heteroaromatic lithium reagents, enolate and phosphonium ylide. Org Biomol Chem 5:1442–1449. doi:10.1039/B701702B
38. McBee ET, Turner JJ, Morton CJ, Stefani AP (1965) Reaction of amines with cyclic fluorinated olefins. J Org Chem 30:3698–3705. doi:10.1021/jo01022a025
39. Mir Q, Shreeve JM (1994) Reactions of 1, 2-dichlorotetrafluorocyclobut-1-ene and 1, 2-dichlorohexafluorocyclopent-1-ene with 2-mercaptoethanol and ethanedithiol and of their products. J Fluorine Chem 68:269–272. doi:10.1016/0022-1139(93)05006-M
40. Bayliff AE, Bryce MR, Chambers RD (1987) Polyhalogenoheterocyclic compounds. Part 38 reactions of fluorinated alkenes and cycloalkenes with difunctional nucleophiles. J Chem Soc Perkin I 763–767. doi:10.1039/P19870000763
41. Yamada S, Konno T, Ishihara T, Yamanaka H (2005) Reaction of octafluorocyclopentene with various carbon nucleophiles. J Fluorine Chem 126:125–133. doi:10.1016/j.jfluchem.2004.10.047
42. Chambers RD, Kirk JR, Powell RL (1983) Polyhalogenoheterocyclic compounds. Part 35. Reactions of fluorinated alkenes and cycloalkenes with enolate anions. J Chem Soc Perkin I 1983:1239–1242. doi:10.1039/P19830001239
43. Krayushkin MM, Kalik MA, Dzhavadov DL (1998) Synthesis, structure and some reactions of 1,2-bis(2-alkylthio-3-thienyl) perfluorocyclopentene. Khim Geterotsikl Soedin 927–933
44. Krayushkin MM, Kalik MA, Dzhavadov DL, Martynkin AYu, Firsov AV, Uzhinov BM (1999) Photochromic diarylethenes. 2. Synthesis and photochromic properties of 5,5′ alkylthio (alkylsulfonyl)-substituted 1,2-bis(2-alkylthien-3-yl) perfluorocyclopentenes. Izv Acad Nauk Ser Khim 979–982
45. Krayushkin MM, Uzhinov BM, Martynkin AY, Dzhavadov DL, Kalik MA, Ivanov VL, Stoyanovich FM, Uzhinova LD, Zolotarskaya OY (1999) Thermally irreversible photochromic diarylethenes. Int J Photoenergy 1:183–190
46. Krayushkin MM, Stoyanovich FM, Zolotarskaya OYu, Martynkin AYu, Ivanov VL, Uzhinov BM (1999) Photochromic dihetarylethenes. 3. Synthesis and photochromic properties of 1, 2-bis[2-methyl-(5-benzoxazol-2-yl)thien-3-yl] hexafluorocyclopentene. Izv Acad Nauk Ser Khim 1011–1013

47. Krayushkin MM, Stoyanovich FM, Zolotarskaya OY, Murav'ev IV, Martynkin AY, Uzhinov BM (2001) Photochromic dihetarylethenes.10 Photochromic 1,2-bis[2-benzothiazol-2-yl-3-thienyl] and 1,2-bis[2-benzothiazol-2-yl)benzothiophen-3-yl]ethenes. Russ Chem Bull Int Ed Engl 50:2420–2423
48. Kawai SH, Gilat SL, Lehn J-M (1999) Photochemical p*K*a-modulation and gated photochromic properties of a novel diarylethene switch. Eur J Org Chem 1999:2359–2366. doi:10.1002/(SICI)1099-0690(199909)1999:9<2359
49. Takeshita M, Irie M (1998) Reversible fluorescence intensity change of a diarylethene. Chem Lett: 1123–1124
50. Yang T, Pu S, Fan C, Liu G (2008) Synthesis, crystal structure and optoelectronic properties of a new unsymmetrical photochromic diarylethene. Spectrochim Acta Part A 70:1065–1072. doi:org/10.1016/j.saa.2007.10.026
51. Uchida K, Irie M (1995) A photochromic dithienylethene that turns yellow by UV irradiation. Chem Lett 969–970. doi:org/10.1246/cl.1995.969
52. Yamaguchi T, Fujita Y, Irie M (2004) Photochromism of a novel 6π conjugate system having a bis(2,3′-benzothienyl) unit. Chem Commun 1010–1011. doi:10.1039/B401207K
53. Frigoli M, Mehl H (2005) Multiple addressing in a hybrid biphotochromic system. Angew Chem Int Ed Engl 44:5048–5052. doi:10.1002/anie.200462575
54. Pu S, Fan C, Miao W, Liu G (2008) New photochromic diarylethenes with a six-membered aryl unit. Tetrahedron 64:9464–9470
55. Tsivgoulis GM, Lehn J-M (1996) Photoswitched and functionalized oligothiophenes: synthesis and photochemical and electrochemical properties. Chem Eur J 2:1399–1406. doi:10.1002/chem.19960021112
56. Takami S, Irie M (2007) Photochromic properties of diarylethenes having 2, 4-diphenylphenylsubstituents in the amorphous and PMMA films. J Photochem Photobiol A: Chem 187:202–208. doi:10.1016/j.jphotochem.2006.10.024
57. Andre'asson J, Straight SD, Moore TA, Moore AL, Gust D (2008) Molecular all-photonic encoder-decoder. J Am Chem Soc 130:11122–11128. doi:10.1021/ja802845z
58. Andre'asson J, Pischel U, Straight SD, Moore TA, Moore AL, Gust D (2011) All-photonic multifunctional molecular logic device. J Am Chem Soc 133:11641–11648. doi:org/10.1021/ja203456h
59. Straight SD, Liddell PA, Moore TA, Terazono Y, Moore AL, Gust D (2007) All-photonic molecular XOR and NOR logic gates based on photochemical control of fluorescence in a fulgimide–porphyrin–dithienylethene triad. Adv Funct Mater 17:777–785. doi:10.1002/adfm.200600802
60. Areephong J, Hurenkamp JH, Milder MTW, Meetsma A, Herek JL, Browne WR, Feringa BL (2009) Photoswitchable sexithiophene-based molecular wires. Org Lett 11:721–724. doi:10.1021/ol8028059
61. Yin J, Lin Y, Cao X, Yu G-A, Liu SH (2008) Novel photochromic macrocycles composed of thiophene and ethylene building blocks: synthesis, structure, and photochromic property. Tetrahedron Lett 49:1582–1585
62. Jung I, Choi H, Kim E, Lee C-H, Kang SO, Ko J (2005) Synthesis and photochromic reactivity of macromolecules incorporating four dithienylethene units. Tetrahedron 61:12256–12263. doi:10.1016/j.tet.2005.09.099
63. Krayushkin MM, Kalik MA, Dzhavadov DL, Vorontsova LG, Starikova ZA, Martynkin AYu, Ivanov VL, Uzhinov BM (2000) Photochromic dihetarylethenes 5 synthesis, structure andphotochromic properties of 4,4′-disubstituted 1,2-bis[2-ethyl-5-ethylthio(etrhylsulfonyl)-3-thienyl] perfluorcyclopentenes. Izv Acad Nauk Ser Khim 1778–1784
64. Hanazawa M, Sumiya R, Horikawa Y, Irie M (1992) Thermally irreversible photochromic systems. Reversible photocyclization of 1, 2-bis (2-methylbenzo[*b*]thiophen-3-yl)perfluorocyclocoalkene derivatives. J Chem Soc Chem Commun 206–207. doi:10.1039/C39920000206
65. Irie M, Uchida K (1998) Synthesis and properties of photochromic diarylethenes with heterocyclic aryl groups. Bull Chem Soc Jpn 71:985–996

66. Yarovenko VN, Es'kov AA, Semenov SL, Zavarzin IV, Kadentsev VI, Kalik MA, Krayushkin MM, Strokach YP, Valova TM, Golotiuk ZO, Barachevsky VA (2005) Photochromic 1,2-dihetarylethenes with perfluorocyclopentene bridge: synthesis and spectral and kinetic study. Russ Chem Bull Int Ed 54:2790–2794
67. Morimitsu K, Kobatake S, Irie M (2004) Large geometrical structure changes of photochromic diarylethenes upon photoirradiation. Tetrahedron Lett 45:1155–1158. doi:10.1016/j.tetlet.2003.12.005
68. Krayushkin MM, Migulin VA, Yarovenko VN, Barachevskii VA, Vorontsova LG, Starikova ZA, Zavarzin IV, Bulgakova VN (2007) Synthesis and characterisation of 1, 2-dihetarylethenes containing chlorobenzothiophene moieties. Mendeleev Commun 17:125–127. doi:10.1016/j.mencom.2007.03.025
69. Uno K, Niikura H, Morimoto M, Ishibashi Y, Miyasaka H, Irie M (2011) In situ preparation of highly fluorescent dyes upon photoirradiation. J Am Chem Soc 133:13558–13564. doi:org/10.1021/ja204583e
70. Jeong YC, Yang SI, Kim E, Ahn KH (2006) Development of highly fluorescent photochromic material with high fatigue resistance. Tetrahedron 62:5855–5861. doi:10.1016/j.tet.2006.04.029
71. Jeong YC, Han JP, Kim Y, Kim E, Yang SI, Ahn KH (2007) Characterization and photophysical properties of sulfur-oxidized diarylethenes. Tetrahedron 63:3173–3182. doi:10.1016/j.tet.2007.02.007
72. Yeo KM, Gao CJ, Ahn KH, Lee IS (2008) Superparamagnetic iron oxide nanoparticles with photoswitchable fluorescence. Chem Commun 4622–4624. doi:10.1039/B807462C
73. Jeong YC, Park DG, Lee IS, Yang SI, Ahn KH (2009) Highly fluorescent photochromic diarylethene with an excellent fatigue property. J Mater Chem 19:97–103. doi:10.1039/b814040e
74. Kim E, Kim M, Kim K (2006) Diarylethenes with intramolecular donor–acceptor structures for photoinduced electrochemical change. Tetrahedron 62:6814–6821. doi:10.1016/j.tet.2006.04.089
75. Wang T, Liu G, Liu W, Cui S (2012) Synthesis of a novel photochromic diarylethene for polarization optical recording. Adv Mater Res 396–398: 2357–2360. doi:10.4028/www.scientific.net/AMR.396-398.2357
76. (a) Krayushkin MM, Kalik MA, Kozhinov DV, Martynkin Au, Strokach YP, Barachevskii VA (2005) Synthesis and photochemical properties of 1, 2-bis{2-ethyl-5-(benzothiazol-2-yl) thieno[2,3-b]thiophene-3-yl}hexafluorocyclopentene. Khim Geterotsikl Soedin 360–364; (b) Krayushkin MM, Stoyanovich FM, Zolotarskaya OY, Murav'ev IV, Martynkin Ayu, Vorontsova LG, Starikova ZA, Ivanov VL, Uzhinov BM (2001) Russ Chem Bull Int Ed Engl 50:110–115
77. (a) Krayushkin MM, Stoyanovich FM, Zolotarskaya OYu, Yarovenko VN, Bulgakova VN, Zavarzin IV, Martynkin AYu (2002). Photochromic dihetarylethenes. 18. New approach to the synthesis of dithienothiophene and preparation of its photochromic derivative. Russ Chem Bull 51:2097–2099. doi:10.1023/A:1021676313508; (b) Wang H, Xu W, Zhu D (2012) Synthesis and photochromic reactivity of a new class of photochromic diarylethene dimer containing dithieno[3,2-*b*:2′3′-*d*]thiophene. Tetrahedron 68: 8719–8723. http://dx.doi.org/10.1016/j.tet.2012.08.026; (c) Wang H, Xu W, Zhu D (2013) Photochromism of diarylethenes containing dithieno[3,2-b:2′,3′-d]thiophene. Dyes Pigments 97:303–310. doi:10.1016/j.dyepig.2013.01.011
78. Fujimoto Y, Ubukata T, Yokoyama Y (2008) Dendrimer diarylethenes: the memory effect of conformation in polymer matrices. Chem Commun 5755–5757. doi:10.1039/b812503a
79. Iwato S, Ishihara Y, Qian CP, Tanaka K (1992) Thermal stability of photochromic bis[(trifluoromethyl)thiazolyl]ethene derivatives. J Org Chem 57:3726–3727. doi:10.1021/jo00039a040
80. Uchida K, Ishikawa T, Takeshita M, Irie M (1998) Thermally irreversible photochromic systems. Reversible photocyclization of 1,2-bis(thiazolyl)per-fluorocyclopentenes). Tetrahedron 54:6627–6638. doi:10.1016/S0040-4020(98)00330-5
81. Giraud M, Le'austic A, Guillot R, Yu P, Lacroix PG, Nakatani K, Pansuc R, Maurel F (2007) Dithiazolylethene-based molecular switches for nonlinear optical properties and fluorescence: synthesis, crystal structure and ligating properties. J Mater Chem 17:4414–4425. doi:10.1039/B704806H

82. Léaustic A, Anxolabéhère-Mallart E, Maurel F, Midelton S, Guillot R, Métivier R, Nakatani K, Yu P (2011) Photochromic and reductive electrochemical switching of a dithiazolylethene with large redox modulation. Chem Eur J 17:2246–2255. doi:10.1002/chem.201002451
83. Giraud M, Leaustic A, Guillot R, Yu P, Maurel F, Nakatani K (2009) Easy and efficient tuning of the photochromic properties of 1,2-bis[5′-methyl-2′-(2″-pyridyl)thiazolyl]perfluorocyclopentene). Tetrahedron Lett 50:1485–1489. doi:10.1016/j.tetlet.2009.01.078
84. Yamaguchi T, Irie M (2006) Photochromic and fluorescent properties of bisfurylethene derivatives. J Mater Chem 16:4690–4694. doi:10.1039/B611294C
85. Yamaguchi T, Irie M (2005) Photochromism of bis(2-alkyl-1-benzofuran-3-yl)perfluorocyclopentene derivatives. J Org Chem 70:10323–10328. doi:10.1021/jo051372z
86. Yamaguchi T, Irie M (2006) Photochromism of 1, 2-bis(2-alkyl-1-benzofuran-3-yl)perfluorocyclopentene derivatives. Eur J Org Chem 3105–3111. doi:10.1002/ejoc.200600011
87. Yamaguchi T, Takami S, Irie M (2008) Photochromic properties of 1,2-bis(6-substitute-2-methyl-1-benzofuran-3-yl)ethene derivatives. J Photochem Photobiol A: Chem 193:146–152. doi:10.1016/j.jphotochem.2007.06.019
88. Yamaguchi T, Taniguchi W, Kagawa T, Kamihashi Y, Ozeki T, Morimoto M, Irie M (2011) Photochromism of 1, 2-bis(5-n-alkyl-2-phenyloxazol-4-yl)perfluorocyclopentene derivatives in single-crystalline phase. Chem Lett 40:635–637. doi:10.1246/cl.2011.635
89. Uchida K, Matsuoka T, Sayo K, Iwamoto M, Hayashi S, Irie M (1999) Thermally reversible photochromic systems. Photochromism of a dipyrrolylperfluorocyclopentene. Chem Lett 28:835–836
90. Heynderickx A, Kaou AM, Moustrou C, Samat A, Guglielmetti R (2003) Synthesis and photochromic behaviour of new dipyrrolylperfluorocyclopentenes. New J Chem 27:1425–1432. doi:10.1039/B302623J
91. Walko M, Feringa BL (2005) Synthesis and properties of dipyridylcyclopentenes. Mol Cryst Liq Cryst 431:549–553. doi:10.1080/15421400590947379
92. (a) Takami S, Irie M (2004) Synthesis and photochromic properties of novel yellow developing photochromic compounds. Tetrahedron 60:6155–6161. doi:10.1016/j.tet.2004.05.029; (b) Liu G, Pu S, Wang X (2010) Photochromism of new 3,5-position hybrid diarylethene derivatives bearing both thiophene and thiazole moieties. Tetrahedron 66:8862–8871. doi:10.1016/j.tet.2010.09.066
93. Pu S, Liu G, Shen L, Xu J (2007) Efficient synthesis and properties of isomeric photochromic diarylethenes having a pyrrole unit. Org Lett 9:2139–2142. doi:10.1021/ol070622q
94. Liu G, Pu S, Wang X, Liu W, Yang T (2011) Effects of substitution on the optoelectronic properties of photochromic diarylethenes bearing a pyrrole moiety. Dyes Pigments 90:71–81. doi:10.1016/j.dyepig.2010.11.001
95. Liu G, Pu S, Wang X (2010) Synthesis and the effect of substituent position upon unsymmetrical isomeric diarylethenes earing a pyrrole unit. J Photochem Photobiol A: Chem 214:230–240. doi:10.1016/j.jphotochem.2010.07.001
96. Nakashima T, Miyamura K, Sakai T, Kawai T (2009) Photo-, solvent-, and ion-controlled multichromism of imidazolium-substituted diarylethenes. Chem Eur J 15:1977–1984. doi:10.1002/chem.200801192
97. Pu S, Yang T, Xu J, Chen B (2006) Syntheses and properties of new photochromic diarylethene derivatives having a pyrazole unit. Tetrahedron Lett 47:6473–6477. doi:10.1016/j.tetlet.2006.06.073
98. Tong Z, Pu S, Cui S (2012) Synthesis and properties of a new photochromic compound bearing isoxazol moiety. Adv Mater Res 399–401: 1119–1122. doi:10.4028/www.scientific.net/AMR.399-401.1119
99. Pu S, Wang R, Liu G, Liu W, Cui S, Yan P (2012) Photochromism of new unsymmetrical diarylethene derivatives bearing both benzofuran and thiophene moieties. Dyes Pigments 94:195–206. doi:10.1016/j.dyepig.2012.01.003
100. Pu S, Yan P, Liu G, Liu W, Miao W (2011) New photochromic diarylethenes bearing a pyridine moiety. Tetrahedron Lett 52:143–147. doi:10.1016/j.tetlet.2010.11.011

101. Wang R, Pu S, Liu G, Cui S, Liu W (2012) New photochromic 1, 2-diarylperfluorocyclopentenes bearing unsymmetrical six-membered aryl units. Tetrahedron Lett 53:320–324. doi:10.1016/j.tetlet.2011.11.035
102. Takami S, Irie M (2005) Photochemically stable novel yellow developing photochromic compounds having a thiazole group. Mol Cryst Liq Cryst 431:467–471. doi:10.1080/15421400590947144
103. Pu S, Li H, Liu G, Liu W (2010) Photochromism of new diarylethenes bearing both thiazole and benzene moieties. Tetrahedron Lett 51:3575–3579. doi:10.1016/j.tetlet.2010.05.004
104. Yamaguchi T, Irie M (2006) Photochromism of diarylethene derivatives having an indene unit. Tetrahedron Lett 47:1267–1269. doi:10.1016/j.tetlet.2005.12.074
105. Liu W, Wang W, Fan C, Liu G (2012) Synthesis and properties of a photochromic switch Adv Mater Res 396–398: 2431–2433. doi:10.4028/www.scientific.net/AMR.396-398.2431
106. Yamaguchi T, Irie M (2006) Photochromism of diarylethene derivatives having n-alkylbenzothiophene and n-alkylbenzofuran units. Bull Chem Soc Jpn 79:1100–1105. doi:10.1246/bcsj.79.1100
107. Yamaguchi T, Uchida K, Irie M (2008) Properties of diarylethene derivatives having benzofuran and benzothiophene rings based on regioisomers. Bull Chem Soc Jpn 81:644–652. doi:10.1246/bcsj.81.644
108. Yamaguchi T, Hosaka M, Ozeki T, Morimoto M, Irie M (2011) Photochromism of diarylethene derivatives bearing a benzo[b]silole unit. Tetrahedron Lett 52:5601–5604. doi:10.1016/j.tetlet.2011.08.063
109. Ushiogi Y, Hase T, Iinuma Y, Takata A, Yoshida J (2007) Synthesis of photochromic diarylethenes using a microflow system. Chem Commun 43:2947–2949. doi:10.1039/b702277h
110. Asai T, Takata A, Nagaki A, Yoshida J (2012) Practical synthesis of photochromic diarylethenes in integrated flow microreactor systems. ChemSusChem 5:339–350. doi:10.1002/cssc.201100376
111. Hiroto S, Suzuki K, Kamiya H, Shinokubo H (2011) Synthetic protocol for diarylethenes through Suzuki–Miyaura coupling. Chem Commun 47:7149–7151. doi:10.1039/c1cc12020d
112. Beydoun K, Roger J, Boixel J, Le Bozec H, Guerchais V, Doucet H (2012) A straightforward access to photochromic diarylethene derivatives *via* palladium-catalysed direct heteroarylation of 1,2-dichloroperfluorocyclopentene. Chem Commun 48:11951–11953 [117] (112). doi:10.1039/C2CC37046H
113. Chambers RD, Edwards AR (1997) Perfluorocarbon fluids as solvent replacements. J Chem Soc Perkin Trans 1:3623–3628. doi:10.1039/A704823H
114. Lucas LN, van Esch JH, Kellogg RM, Feringa BL (1999) A new synthetic route to symmetrical photochromic diarylperfluorocyclopenthenes. Tetrahedron Lett 40:1775–1778. doi:10.1016/S0040-4039(98)02688-4
115. Lucas LN, de Jong JJD, van Esch JH, Kellog RM, Feringa BL (2003) Syntheses of dithienylcyclopentene optical molecular switches. Eur J Org Chem 155–166. doi:10.100 2/1099-0690(200301)2003:1<155
116. Hermes S, Dassa G, Toso G, Bianco A, Bertarelli C, Zerbi G (2009) New fast synthesis route for symmetric and asymmetric phenyl substituted photochromic dithienylethenes bearing functional groups such as alcohols, carboxylic acids, or amines. Tetrahedron Lett 50:1614–1617. doi:10.1016/j.tetlet.2009.01.102
117. Krayushkin MM, Kalik MA, Migulin VA (2009) McMurry reaction in the synthesis of photochromic dihetarylethenes. Russ Chem Rev 78:329–336. doi:10.1070/RC2009v078n04ABEH004018
118. Kobatake S, Imao S, Yamashiro Y, Terakawa Y (2011) Photoswitching of an alcohol-sensitive photochromic diarylethene. Tetrahedron Lett 52:1905–1908. doi:10.1016/j.tetlet.2011.02.039
119. Kobatake S, Irie M (2004) Single-crystalline photochromism of diarylethenes. Bull Chem Soc Jpn 77:195–210
120. Morimoto M, Kobatake S, Irie M (2004) Crystal engineering of photochromic diarylethene single crystals. Chem Rec 4:23–38
121. Kuroki L, Takami S, Yoza K, Morimoto M, Irie M (2010) Photoinduced shape changes of diarylethene single crystals: correlation between shape changes and molecular packing. Photochem Photobiol Sci 9:221–225

122. Kobatake S, Hasegawa H, Miyamura K (2011) High-convertible photochromism of a diarylethene single crystal accompanying the crystal shape deformation. Cryst Growth Des 11:1223–1229. dx.doi.org/10.1021/cg101448m
123. Kobatake S, Yamada T, Uchida K, Kato N, Irie M (1999) Photochromism of 1,2-Bis (2,5-dimethyl-3-thienyl)perfluorocyclopentene in a single crystalline phase. J Am Chem Soc 121:2380–2386
124. Yamada T, Kobatake S, Irie M (2000) X-Ray crystallographic study on single-crystalline photochromism of 1,2-Bis(2,5-dimethyl-3-thienyl) perfluorocyclopentene. Bull Chem Soc Jpn 73:2179–2184
125. Vorontsova LG, Krayushkin MM, Starikova ZA, Kalik MA, Stoyanovich FM, Zolotarskaya OYu, Dzhavadov DL (2000) Molecular and crystal structure of 1, 2-bis(2-ethyl-5-ethylsulfonylthien-3-yl) perfluorocyclopentene and 1,2-bis[5-(benzoxazol-2-yl)-2-methylthien-3-yl]perfluorocyclopentene. Izv Akad Nauk Ser Khim 74–76
126. Kobatake S, Uchida K, Tsuchida E, Irie M (2002) . Single-crystalline photochromism of diarylethenes: reactivity–structure relationship. Chem Commun 2804–2805. doi:10.1039/b208419h
127. Liu G, Liu M, Pu S, Fan C, Cui S (2012) Photochromism of new unsymmetrical isomeric diarylethenes bearing a pyridine group. Tetrahedron 68:2267–2275
128. Morimoto M, Irie M (2005) Photochromism of diarylethene single crystals: crystal structures and photochromic performance. Chem Commun 3895–3905. doi:10.1039/B505256D
129. (a) Ramamurthy V, Venkatesan K (1987) Photochemical reactions of organic crystals. Chem Rev 87 433–481 doi:10.1021/cr00078a009; (b) Morimoto M, Irie M (2006) Photochromic reactions of diarylethenes in single crystals with intermolecular OH···N hydrogen-Bonding networks. Chem Eur J 12:4275–4282
130. Krayushkin MM, Vorontsova LG, Uzhinov BM (2001) The structure and characteristics of photochromic dithienylethenes. Int J Photoenergy 3:25–32
131. Kobatake S, Yamada M, Yamada T, Irie M (1999) Photochromism of 1,2-bis(2-methyl-6-nitro-1-benzothiophen-3-yl)-perfluorocyclopentene in a single-crystalline phase: dichroism of the closed-ring form isomer. J Am Chem Soc 121:8450–8456. doi:10.1021/ja991013

Chemistry of α-Fluorinated Ethers- and Thioethers-Containing Heterocycles

Gerd-Volker Röschenthaler and Olesya Kazakova

Contents

Abstract The present chapter points out the importance of α-fluorinated ethers and sulfides, discloses synthetic routes and possible applications.

α-Fluorinated ethers show applications as analgesics, anaesthetics and cardiovascular, respiratory, psychopharmacologic, neurological, gastrointestinal drugs and anti-infective therapeutics. The number of molecules containing an CF_3O-group has quadrupled between 2008 and 2012, nevertheless CF_3O-containing heterocycles are still quite rare. Several examples show the efficiency of either CF_3O-compounds but also OFC_2H-containing substances.

G.-V. Röschenthaler (✉) • O. Kazakova
School of Engineering and Science, Jacobs University Bremen gGmbH,
Campus Ring 1, 28759 Bremen, Germany
e-mail: g.roeschenthaler@jacobs-university.de

V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_13,

α-Fluorinated sulphides show similarity to the corresponding ethers with respect to the pK_a value. But regarding the stereo-electronic effects there is a huge difference. Amongst others, substances containing a SCF_3- or SCF_2H-group find applications in medicinal chemistry, e.g. against anorexia nervosa, as anti-inflammatory agent or as antibiotics.

Keywords Fluorine • Trifluoromethoxy group • Trifluoromethylthio group • Synthesis • Fluorinated heterocycles

1 Introduction

Nowadays, fluorine, the most electronegative element, plays a key role in pharmaceutical, agrochemical and material sciences. About 20 % of all pharmaceuticals and about 30 % of agrochemicals under development or recently introduced on the market contain fluorine. Although mainly single fluorine atoms or a trifluoromethyl group have been introduced in various molecules, the introduction of (difluoromethoxy)- or (trifluoromethoxy) aryl fragments into crop production products was also realized [1].

Numerous CF_3O containing compounds have been prepared, clinically evaluated and in many cases marketed as drugs with enhanced effectiveness, often coupled with diminished side-effects [2]. Between 2008 and 2012 the number of structures bearing an CF_3O-substituent has more than quadrupled (SciFinder). Mainly all of the documents are patents, but there are also numerous research articles. Whereas for trifluoromethoxy substituted heterocycles is found almost exclusively in patent applications [3].

Of the currently employed fluorinated moieties, the α-fluorinated ethers and thioethers are becoming more and more important in both agrochemical research and pharmaceuticals chemistry [1–3]. However, examples of trifluoromethyl ethers in pharmaceutical chemistry are still quite rare [2, 3]. They were rapidly used as volatile, non-toxic, non-explosive and fast-acting inhalation anaesthetics and anti-inflammatory agents. Numerous new α-fluorine containing compounds have been prepared, marketed as drugs with enhanced effectiveness often coupled with diminished side-effects. Today, significant application areas for α-fluorinated ether are analgesics, anaesthetics, cardiovascular drugs, respiratory drugs, psychopharmacologic drugs, neurological drugs, gastrointestinal drugs and anti-infective therapeutics.

Heterocyclic compounds bearing the trifluoromethoxy group [4], are of special interest, some of which showed remarkable biological activity and have been applied as neurologic agents such as Riluzole [5], a CF_3-substituted 2-amino-benzothiazole, is the first drug approved for treatment of amyotropic lateral sclerosis, to treat schizophrenia and other neurological diseases. (-)-Pantoprazole [6], an irreversible proton pump inhibitor, reached its first market worldwide for acute treatment of gastric and duodenal ulcers and gastroesophageal reflux disease (Fig. 1).

The α-fluorinated thioethers like Triflumidate [7], bearing a CF_3SO_2- moiety, are used for their anti-inflammatory activity (Fig. 2).

The successful use of α-fluorinated ethers and thioethers in active ingredients for modern agrochemicals is witnessed by various commercial products like

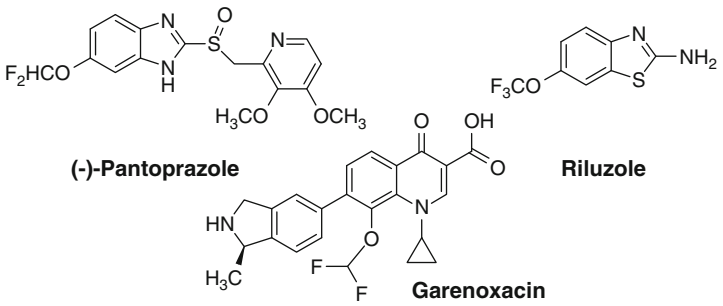
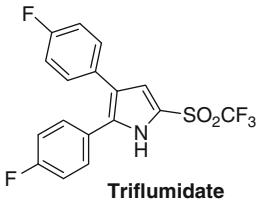


Fig. 1 Fluorinated ethers as pharmaceuticals

Fig. 2 Triflumidate as an example of *S*-perfluoroalkyl substituted pharmaceutical



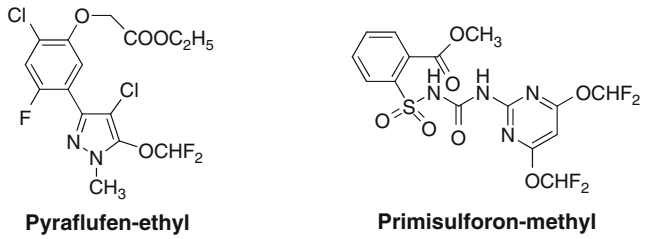
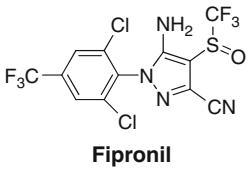


Fig. 3 CHF_2O-containing agrochemicals

insecticides, fungicides, plant growth regulators, and herbicides. According to the 14th (2006) edition of the pesticide manual [8a], only five pesticides containing CF_3O-groups were registered so far. In 15th edition (2011) there are already 23 compounds [8b]. However, the CF_3O-group is mainly located on the aromatic ring. The proinsecticide Indoxacarb [9], the insect growth regulant (IGR) Triflumuron [10], the plant growth regulator Flurprimidol [11], the inhibitor of the respiratory chain and succinate dehydrogenase (SD) Thifluzamide [12] as well as the inhibitor of acetolactate synthase (ALS) Flucarbazone-sodium [13] are some of them. Primisulfuron-methyl [14], a selective fluorosulfonylurea herbicide bears two difluoromethoxy subunits. Pyraflufen-ethyl [15] is CHF_2O-containing pyrazole, a contact herbicide for the control of broadleaf weeds (Fig. 3).

The trifluoromethyl sulfoxide-containing arylaminopyrazole Fipronil [16] (Fig. 4), launched in 1993 by Rhone-Poulenc, is one of the most important non-competitive GABA antagonist in insects.



Fipronil

Fig. 4 Fipronil as an example of a *S*-perfluoroalkyl substituted agrochemical

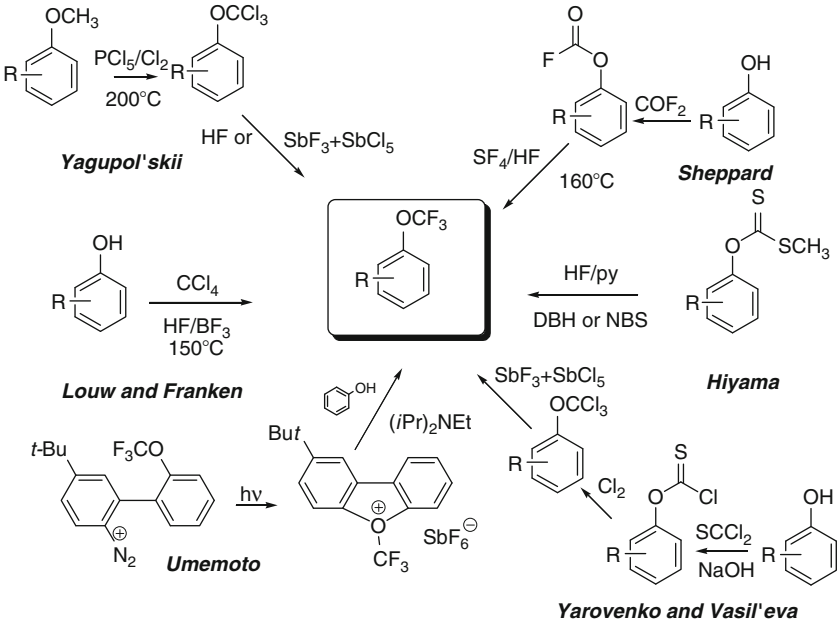


Fig. 5 Trifluoromethoxylation of aromatic compounds

Various reviews have been published about this topic. Jeschke and Leroux [2] published about the medical application of α-fluorinated ethers. Leroux and Pazenok [1] wrote about the synthesis and the properties of trifluoromethyl ethers. Leroux, Jeschke and Schlosser [3b] reviewed the properties of α-fluorinated ethers, thioethers and amines. The work of Boiko [4a] is dedicated to aromatic and heterocyclic perfluoralkyl sulfides. Vovk and Gakh [4b] gave a detailed review about trifluoromethoxy containing azoles and azines. This review summarized the literature data on synthesis and biological activity of trifluoromethoxy, difluoromethoxy and α-fluorinated sulfides derivatives of five and six membered heterocycles.

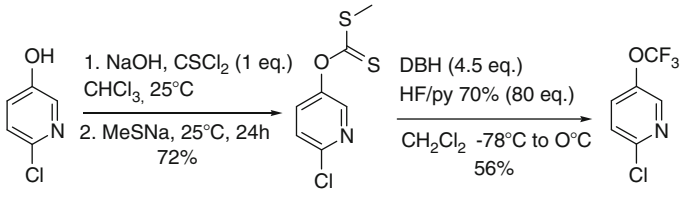
2 Preparation of α-Fluorinated Ethers

2.1 α-Trifluoromethyl Ethers

The trifluoromethoxy group in aryl cannot be formed analogously to the methoxy group, by simple treatment of trifluorohalomethanes with alkoxides, so it has to be introduced or constructed by one of the following approaches (Fig. 5):

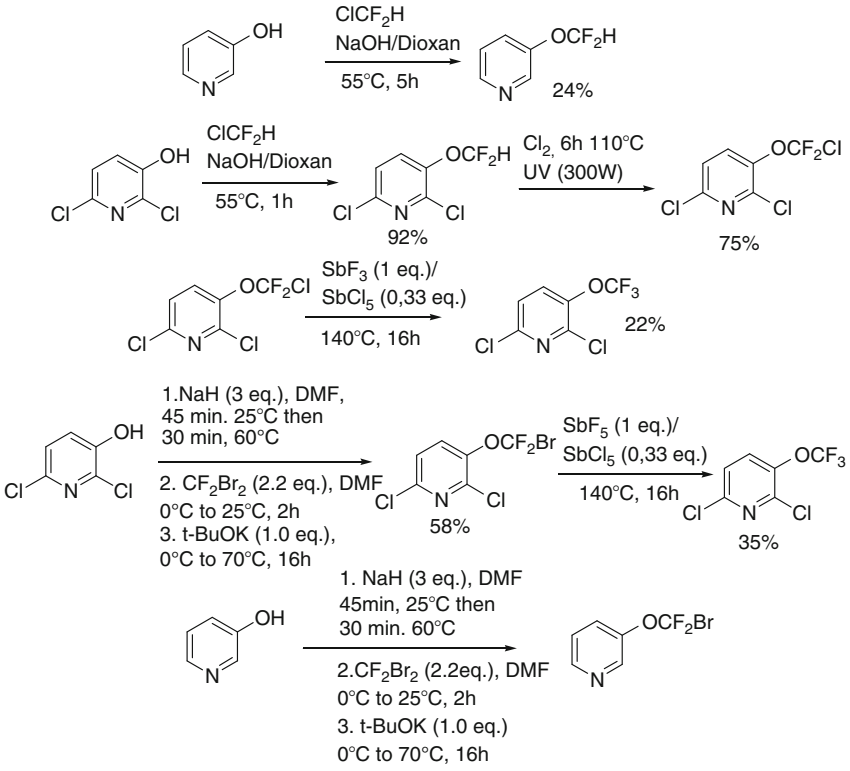
– L. Yagupol'skii [17] prepared the first aryl trifluoromethyl ethers from substituted anisols. The substitution of chlorine by fluorine was realized using anhydrous hydrogen fluoride or with antimony trifluoride (Swart's reagent) in the presence of antimony pentachloride.
– Louw and Franken [18] could convert anisole into trichloromethyl anisole by photochlorination with elemental chlorine in refluxing tetrachloromethane. Feiring [19] could show more recently, that the trichloromethyl aryl ethers can be *in situ* converted into the final trifluoromethyl aryl ethers by treatment with HF.
– Yarovenko and Vasil'eva [20] developed an approach based on aryl chlorothionoformates. They can be cleanly converted by chlorination into trichloromethyl aryl ethers. This step is then followed by fluorination using antimony trifluoride and a catalytic amount of antimony pentachloride.
– Sheppard [21] described the syntheses of aryl trifluoromethylethers by reaction of SF_4 with aryl fluoroformates.
– Hiyama [22] et al. developed the oxidative desulfurization–fluorination of dithiocarbonates (xanthogenates) by treatment with 1,3-dibromo-5,5-dimethylhydantoin (DBH) or N-bromosuccinimide (NBS) and a huge excess of 70 % hydrogen fluoride-pyridine (Olah's reagent, up to 80 equivalents). The corresponding trifluoromethyl ethers are formed in moderate to excellent yields.
– Umemoto [23] reported the preparation of *O*-(trifluoromethyl)-dibenzofuranium salts and their use as CF_3-transfer agents based on studies of L. Yagupol'skii [24]. The direct *O*- and *N*-trifluoromethylation of alcohols, phenols, amines, anilines and pyridines under mild conditions was described.

As expected, the introduction of the OCF_3 group in the pyridine ring is associated with certain difficulties. Leroux et al. [25] investigated the introduction of trifluoromethoxy substituents on various heterocycles by classical approaches. Hiyama's oxidative desulfurization/fluorination [22], developed for aromatic and aliphatic series, already required careful optimization of the reaction conditions in the synthesis of the required xanthogenates, due to the low nucleophilicity of the hydroxy group. Dithiocarbamates were finally obtained, but their conversion into the corresponding (trifluoromethoxy) pyridines failed. After several fruitless attempts the needs for chlorine atoms on the pyridine ring if the desired outcome of the oxidative desulfurization/fluorination was to be achieved. 2-Chloro-5-(*S*-methyl)dithiocarbamate pyridine (Scheme 1), prepared from 2-chloro-5-hydroxypyridine, sodium methanethiolate, and thiophosgene [26], reacted with excess (80 equiv.) HF/pyridine and 1,3-dibromo-5,5-dimethylhydantoine (DBH, 4.5 equiv.) to afford the desired 2-chloro-5-(trifluoromethoxy)pyridine in 56 % yield. Although it was shown that the oxidative desulfurization/fluorination of a pyridine xanthogenate was only possible in the presence of ring chlorine atoms.



Scheme 1 Preparation of the 3-(trifluoromethoxy)pyridine

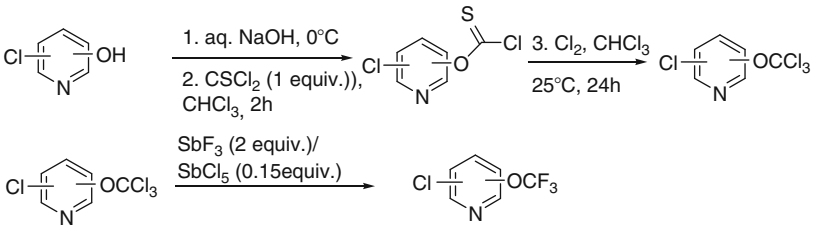
Another standard route to aromatic trifluoromethyl ethers is based on the treatment of phenolates with chlorodifluoromethane (CHF_2Cl) [27] or dibromodifluoromethane (CF_2Br_2) [27, 28] in the presence of a base, with subsequent introduction of the third fluorine atom. Leroux [25] et al. studied this approach for the synthesis of pyridine trifluoromethyl ethers. In this case the reactivity at the pyridine ring was also influenced by chlorine. When 3-hydroxypyridine and 2,6-dichloro-3-hydroxypyridine were treated with chlorodifluoromethane in a biphasic mixture of aqueous sodium hydroxide and dioxane, the difluoromethoxypyridine and 2,6-dichloro difluoromethoxypyridine were obtained in 24 and 92 % yield (Scheme 2). The photochlorination of 2,6-dichloro difluoromethoxypyridine gave 2,6-dichloro-3-(chlorodifluoromethoxy) pyridine but required a large amount of elemental chlorine and worked only on small scale. In an analogous manner, the treatment of 2,6-dichloro-3-hydroxypyridine with CF_2Br_2 afforded 2,6-dichloro-3-(bromodifluoromethoxy)pyridine in 58 % yield. Both 2,6-dichloro-3-(halodifluoromethoxy)pyridines were subjected to fluorination with antimony trifluoride (SbF_3, Swart's reagent) in the presence of catalytic amounts of $SbCl_5$, which afforded 2,6-dichloro-3-(trifluoromethoxy) pyridine in 22 and 35 % yields, respectively (Scheme 2). In contrast, 3-hydroxypyridine afforded only a 7 % yield of 3-(bromodifluoromethoxy)pyridine [25].



Scheme 2 (Trifluoromethoxy)pyridine synthesis through alkylation of hydroxypyridines with difluorocyrbene

Although it was shown that CF_3O-substituted pyridines are accessible through alkylation of hydroxypyridines with CF_2Br_2 and subsequent nucleophilic substitution with SbF_3, two main drawbacks still remained: (a) the optimized overall yields of these two-step syntheses were low (about 15 %), and (b) the alkylating reagents (CF_2Br_2 or CF_2BrCl) are no longer commercially available because they are now classified as ozone-depleting substances (ODSs) [25].

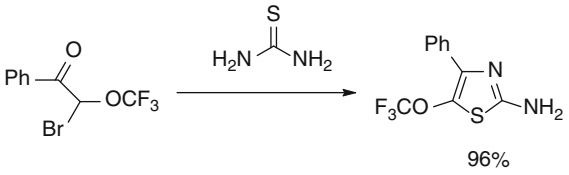
The approach of Yarovenko and Vasil'eva [20] was also applied by Leroux [25]. The chlorothionoformiates were obtained by treatment of the hydroxypyridines with thiophosgene in aqueous sodium hydroxide at 0 °C and directly subjected to chlorination without isolation. The crude Cl_3CO-pyridines were then used for the fluorination step without further purification (Scheme 3). The advantage of this approach is that no large amounts of chlorine gas are required, as is often the case for radical chlorination of methoxy groups. The conversion of (trichloromethoxy) pyridines into (trifluoromethoxy)pyridines with antimony trifluoride (SbF_3) and catalytic antimony pentachloride ($SbCl_5$) was successful. The chlorine/fluorine exchange proceeds rapidly to the OCF_2Cl intermediate [29]. However, the final Cl/F exchange is the rate-determining step, as had previously been observed in the aromatic series for the conversion of -CCl_3 into -CF_3. Heating with $SbCl_5$ (0.15 equiv.) and SbF_3 (2 equiv.) for 6 h at 150 °C was required for complete conversion under optimized reaction conditions [25]. The influence of the chlorine position in the pyridine ring with respect to the results of chlorination/fluorination sequence was discussed [25].



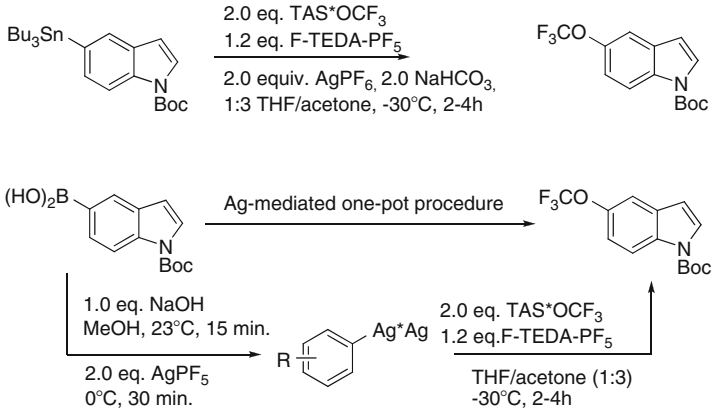
Scheme 3 Synthesis of (trifluoromethoxy)pyridines

Vovk and Gakh [4] reported in their review on trifluoromethoxy containing azoles and azines, wherein the CF_3O-group is located at aromatic ring. Y. Yagupolskii presented an efficient synthesis of 5′-fluoroalkoxythiazoles via α-bromo-α-fluoroalkoxyacetophenones Hantzsch type cyclization with thioureas or thioamides. Bromoacetophenones are convenient and widely used building blocks for various types of heterocyclization and for the Hantzsch's thiazole synthesis in particular. The α-bromo-α-fluoroalkoxyacetophenones readily react with thiourea in aqueous dioxane at room temperature giving the desired 2-aminothiazole with almost quantitative yield (Scheme 4) [30]. This approach cannot be applied for wide range of heterocycles due to the dominance of the keto-form over the hydroxy one in their structures [31]. The direct *O*-perfluoroalkylation in contrast to standard well known *O*-alkylations is still a real challenge [3].

Scheme 4 Hantzsch-type thiazole synthesis

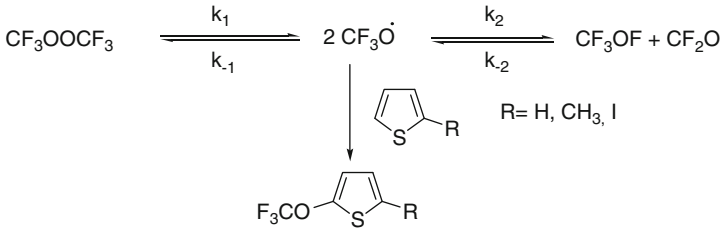


Ritter et al. [32a] developed a silver-mediated cross-coupling of trifluoromethoxide (Tris(dimethylamino)sulfonium trifluoromethoxide (TAS·OCF_3) [32b] with aryl stannanes and arylboronic acids to give aryl trifluoromethyl ethers. This is the first report of a transition-metal-mediated C_{aryl}-OCF_3 bond formation (Scheme 5).



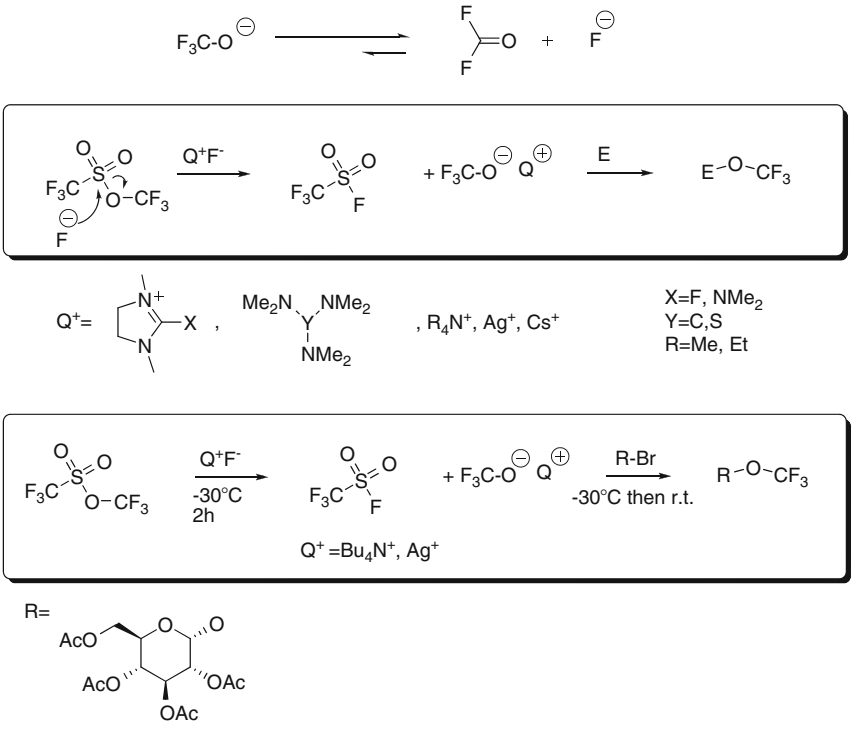
Scheme 5 Trifluoromethoxylation of stannanes and heteroarylboronic acid

A new 'green' process to obtain trifluoromethoxylated compounds by a gas-phase method was presented by Argüello [33]. In this work, we present the direct synthesis of 2-substituted-5-(trifluoromethoxy)thiophenes by a co-thermolysis between bistrifluoromethyl peroxide CF_3OOCF_3 (BTMP) and 2-substituted-thiophenes (Scheme 6). Through it, new 2-substituted-5-(trifluoromethoxy)thiophenes have been obtained in moderate to good yields.



Scheme 6 Scavenge of CF_3O radicals by co-thermolysis with thiophenes

Marrec et al. [34] used trifluoromethyl triflate (TFMT) as a generator of trifluoromethoxy anion when activated by fluoride anions. Commercially available fluorides (silver fluoride and n-tetrabutylammonium triphenyldifluorosilicate), combined with TFMT, allow a simple generation, *in situ*, of silver and n-tetrabutylammonium trifluoromethoxides which were able to react with electrophilic substrates. Silver trifluoromethoxide, which is usually more efficient than n-tetrabutylammonium trifluoromethoxide, converts, under mild conditions, primary aliphatic bromides and iodides as well as primary and secondary benzylic or allylic bromides. Several trifluoromethyl ethers, which could be valuable building-blocks, were prepared in such a way (Scheme 7).

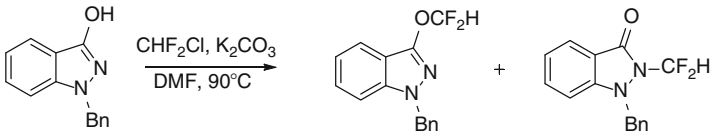


Scheme 7 Generation of trifluoromethoxide from TFMT and trifluoromethoxylation of alkyl bromides with nBuNOCF$_3$ or AgOCF$_3$

2.2 α,α -Difluoromethyl Ethers

α,α-Difluoromethyl aryl ethers are most conveniently prepared by reaction of the appropriate phenolate with chlorodifluoromethane in the presence of a base such as sodium hydroxide which generates an intermediate difluorocarbene n-tetrabutylammonium trifluoromethoxide [27, 35c].

T. Sokolenko and L. Yagupolskii [36] have studied the difluoroalkylation 1-benzyl-1*H*-indazol-3-ol with chlorodifluoromethane. The selection of such a subject for investigation was caused by the fact that indazole derivatives possess a broad spectrum of biological activity. It is known that 1-substituted indazol-3-ols with alkyl sulfates, alkyl halides, or diazomethane give a mixture of products of *O-and N*-alkylation, with 3-dimethylaminopropylbenzene sulfonate only the product of *O*-alkylation, and with acrylonitrile and ethyl acrylate the product of addition at the nitrogen atom [37]. The reaction of 1-benzylindazol-3-ol with difluorocarbene, generated from chlorodifluoromethane, proceeds unselectively, although in high overall yield (~80 %), and a mixture is formed of the products of *O*- and *N*-alkylation in a ratio of 5:4 (Scheme 8). Compounds *O*- and *N*-alkylated compounds differ substantially in physical properties and may be separated by column chromatography.



Scheme 8 Synthesis of difluoromethoxy imidazolol derivatives

3 Preparation of α-Fluorinated Thioethers

3.1 α-Trifluoromethyl Thioethers

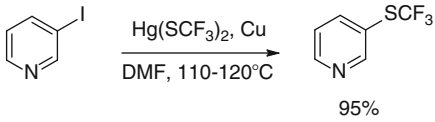
Trifluoromethylthio group canto be incorporated or constructed by one of the following approaches:

- The introduction of R_FS-moieties into aromatic compounds by both electrophilic and nucleophilic reagents.
- The halogenation of alkyl S-derivatives with subsequent replacement of the halogen atoms by fluorine.
- Various modes of perfluoroalkylation of organosulfur compounds including cationic, anionic, radical and ionradical variants.

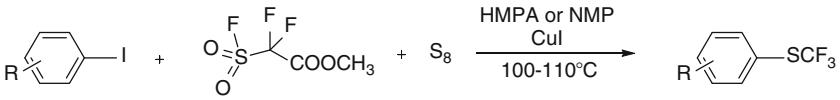
3.1.1 Nucleophilic Substitution

L. Yagupolskii [38] developed a method for trifluoromethylsulfanylation of aromatic and heterocyclic compounds using trifluoromethylthiocopper. Remy [39] suggested carrying out the synthesis of aryltrifluoromethyl sulfides by generation $CuSCF_3$ (from trifluoromethylthio mercury and -copper) *in situ* with the aryl halides. This not only reduces the number of steps but also increases the overall efficiency (Scheme 9).

Scheme 9 Reactions with in situ generated $CuSCF_3$

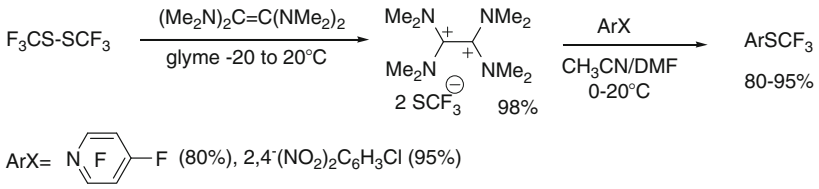


As described previously for trifluoromethyl ethers, Umemoto [23c] reported on the trifluoromethylation of thiols with *S*-(trifluoromethyl) dibenzothiophenium triflate affording the corresponding trifluoromethyl thioethers in medium to good yield. Otherwise, trifluoromethyl phenyl thioethers and ring-substituted analogs are readily made from iodo- or bromoarenes, methyl difluoro(fluorosulfonyl)acetate and elemental sulphur in the presence of cuprous iodide in hexamethylphosphoric triamide (HMPA) or *N*-methylpyrrolidone (NMP) (Scheme 10).



Scheme 10 Synthesis of trifluoromethyl phenyl thioethers

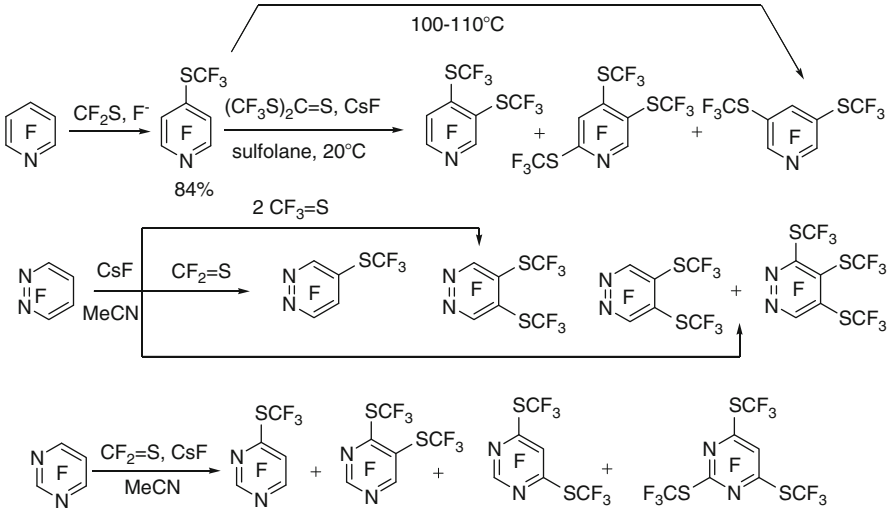
Kolomeitsev and Röschenthaler [40] produced tetrakis(dimethylamino)ethylene dication stabilized perfluoroalkyl thiolates via reduction of bis(perfluoroalkyl)disulfides with tetrakis(dimethylamino) ethylene. The ionic character of this salt was proven by reactions with activated fluoroaromatics halides, which lead to near quantitative formation of the corresponding trifluoromethylthio derivatives (Scheme 11).



Scheme 11 Tetrakis(dimethylamino)ethylene dication trifluoromethyl thiolate as a stable reagent for substitution of aromatic halides

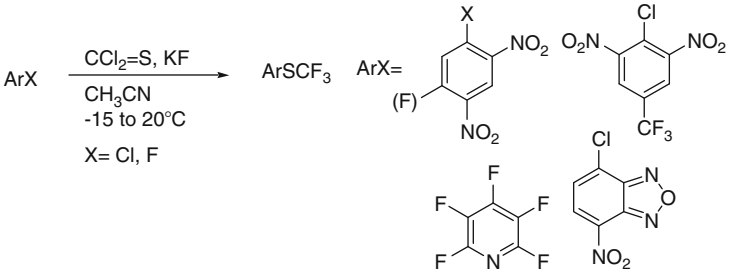
Dmowski and Haas [41] used the reaction of thiocarbonyl difluoride with metal fluorides, to generate the trifluoromethylthiolate anion for introduction into activated perfluoroheterocyclic compounds. Thus, reaction of CF_2S/CsF with pentafluoropyridine under mild conditions gave the 4-substituted product. However, for the subsequent introduction of additional SCF_3 groups this system is not suitable due to effective selfcondensation of thiocarbonyl difluoride (CF_2=S) at higher concentrations. For this purpose the trimer of thiocarbonyl difluoride, bis(trifluoromethyl)trithiocarbonate $(CF_3S)_2C$=S, is more stable and reacts with CsF in sulfolane to generate

CF_3S^- anions. However, the use of this reagent leads to mixtures of products. Whilst reaction of $CsF/CF_2{=}S$ (or its trimer) with tetrafluoropyridazine allows for the selective formation of mono-, di- and tri- (SCF_3) substituted products, the analogous reaction with tetrafluoropyrimidine results in a mixture of polyfluoropyrimidine derivatives (Scheme 12).



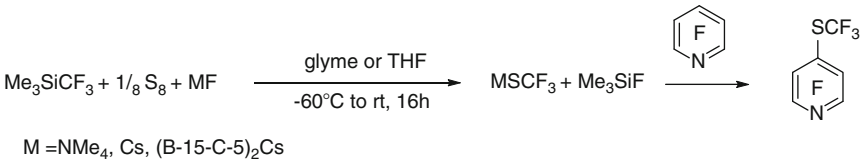
Scheme 12 The use of $CF_2{=}S/CsF$ or $(CF_3S)_2C{=}S/CsF$ for the introduction of CF_3S groups into fluorinated heterocycles

A considerable improvement of this method was developed by Clark et al. [42]: No preliminary preparation of difluorothiophosgene or its trimer is necessary, the required reagents being generated in situ (from thiophosgene and KF). The reaction with activated aromatic compounds is shown in Scheme 13.



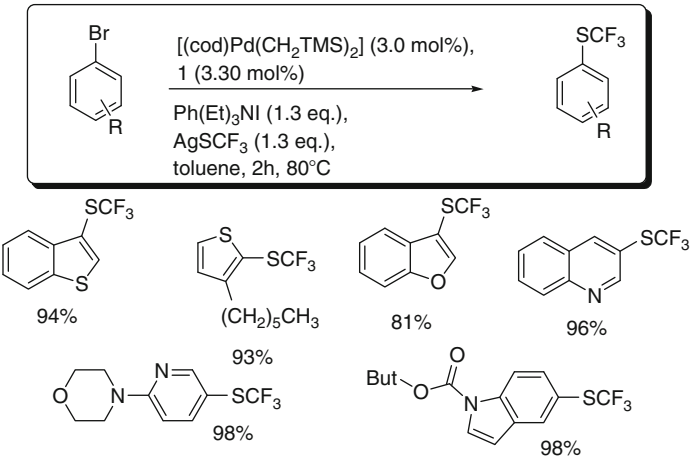
Scheme 13 One-pot synthesis of $ArSCF_3$ from ArX, $CCl_2{=}S$ and KF

Tyrra and Naumann [43] reported on the synthesis of $[NMe_4]SCF_3$, $CsSCF_3$ and $[(B\text{-}15\text{-}C\text{-}5)_2Cs]SCF_3$ (B-15-C-5: benzo-15-crown-5) from reactions of the corresponding fluorides, trimethyl(trifluoromethyl) silane, Me_3SiCF_3, and elemental sulphur. The salts obtained by this method are considerably more thermally stable. They can be treated with boiling ether or CS_2 to remove excess sulfur and readily react at room temperature with inorganic, aliphatic and activated aromatic halides with the formation of trifluoromethyl sulfides (Scheme 14).



Scheme 14 Nucleophilic thiotrifluoromethylation

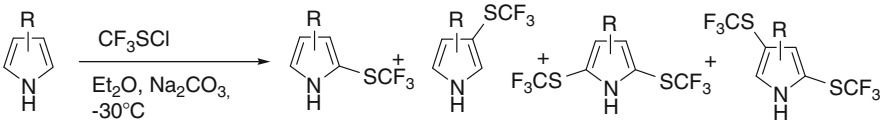
Buchwald et al. [44a] developed a general method for the Pd-catalyzed HetAr-SCF3 bond-forming reaction. Using this method, a wide range of heterocyclic aryl bromides were converted into their corresponding heteroaryl trifluoromethyl sulfides (Scheme 15). Clark and Adams'[44b] work on the use of $(Bu)_4NI$ and $AgSCF_3$ [44c] for S_NAr reactions with aryl halides indicated to us that the addition of a quaternary ammonium salt might be beneficial. Base on this work it is presumed that the iodide anion binds to $AgSCF_3$ to generate an anionic "ate" complex. Presumably a large diffuse cation further aids in the solubility of this complex.



Scheme 15 Pd-catalyzed formation of heteroaryl-SCF_3 compounds

3.1.2 Electrophilic Substitution

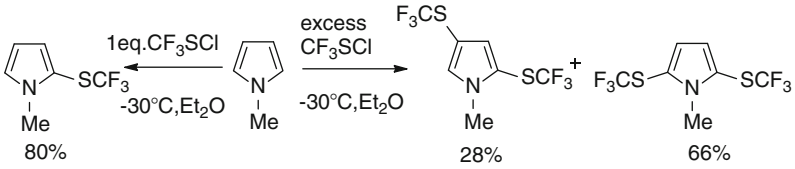
Haas and coworkers performed a series of studies on the reactivity of the perfluoroalkyl sulfenyl chlorides with electron rich heterocyclic compounds, to give CF_3S derivatives. Pyrroles are good substrates for reaction with trifluoromethyl sulfenyl chloride due to higher nucleophilicity compared to benzene [45]. An excess of reagent gives bis-(CF_3S) pyrrole derivatives as shown in Scheme 16.



R= H, 2-COOH, 2-COMe, 2,4- and 2,5 Me_2

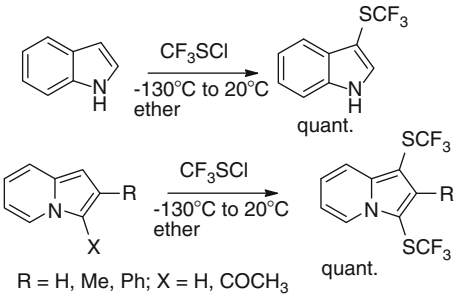
Scheme 16 Reactions of pyrroles with CF_3SCl

N-Methylpyrrole can be variously substituted depending on the conditions as illustrated in Scheme 17 [45, 47].



Scheme 17 Reactions of *N*-methylpyrrole with CF_3SCl

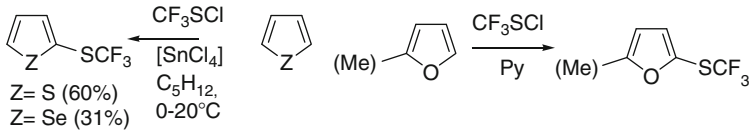
Condensed pyrroles also react readily with CF_3SCl. Indole undergoes substitution, as expected, at the 3-position [42], while indolizine and some of its derivatives give 1,3-bis (CF_3S)-substituted products, in some cases, in quantitative yield [46]. It is interesting to note that not only hydrogen, but also an acetyl group in the 1-position can be substituted (Scheme 18).



R = H, Me, Ph; X = H, $COCH_3$

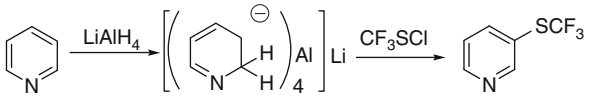
Scheme 18 Trifluoromethylsulfanylation of indole and indolizines

Unlike pyrroles, furan, thiophene and selenophene react with CF_3SCl only in the presence of catalysts. $SnCl_4$ is sufficiently active for the reaction with selenophene [47] and thiophenes [48], whilst furans require more forcing conditions usually involving prolonged heating (20 h at 60 °C) and presence of pyridine for additional activation (Scheme 19).



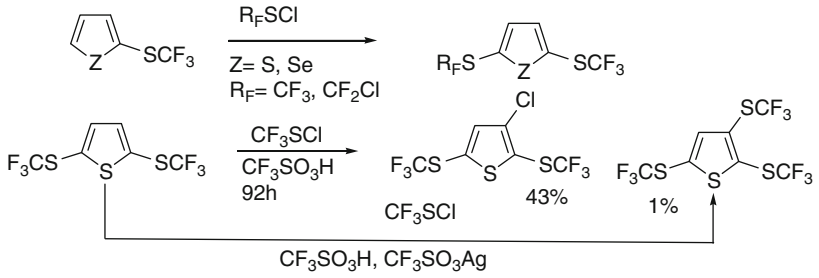
Scheme 19 Reactions of furan, thiophene and selenophene with CF_3SCl

Pyridine is too deactivated for trifluoromethylsulfanylation under classical conditions. To achieve the substitution it is first of all necessary to convert pyridine to an anionic hydride σ-complex by reduction with $LiAlH_4$ [49]. The reaction with CF_3SCl then proceeds with difficulty and mono-substituted 3-trifluoromethylsulfanyl pyridine is formed in low yield along with small amounts of the 3,5-bis(CF_3S) derivative (~1 %) (Scheme 20).



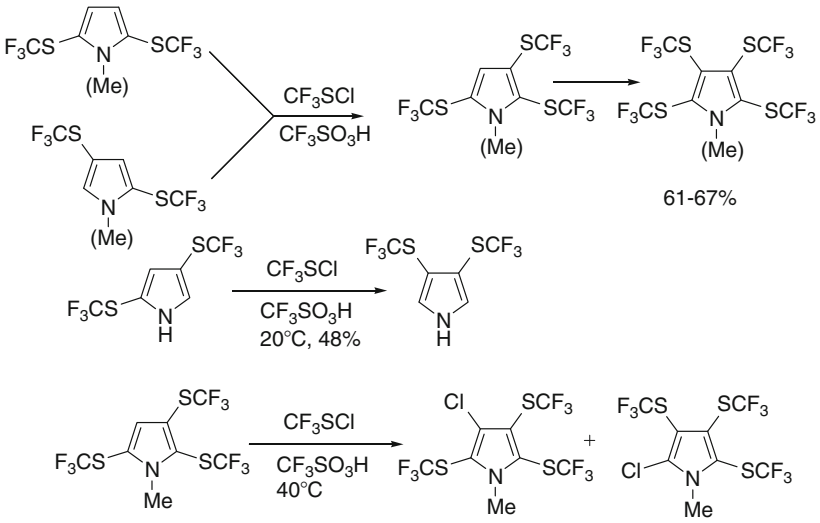
Scheme 20 Trifluoromethylsulfanylation of pyridine requires initial hydride reduction

Introduction of additional CF_3S-groups into heterocyclic compounds (except for pyrrole and its derivatives) occurs in the presence of perfluoroalkanesulfonic acids as an activator. Incorporation of the second fluoroalkylsulfanyl group into thiophenes [47] and selenophene [48] is possible in the presence of CF_3SO_3H. However, reaction of CF_3SCl with 2,5-bis(CF_3S) thiophene in presence of CF_3SO_3H gives the 3-chloro-derivative as the major product. 2,3,5-Tris(CF_3S) thiophene is accessible if silver triflate is added [50] (Scheme 21).



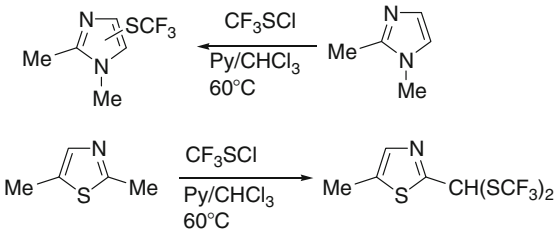
Scheme 21 Introduction of additional R_FS-groups into heterocyclic compounds in the presence of CF_3SO_3H

Such reactions can also be successfully carried out with pyrroles (Scheme 22) [47, 51]. Prolonged reaction times lead to chlorinated products as well as products that arise from migration of the CF_3S-groups [47].



Scheme 22 Introduction of additional R_FS-groups into pyrroles

Interestingly, unlike 1,2-dimethylimidazole, the sulfanylation of 2,4-dimethylthiazole under the same conditions occurs not to imidazole ring but attack twice the methyl group in 2-position to form bis-trifluoromethylsulfanylated derivative (Scheme 23) [52].

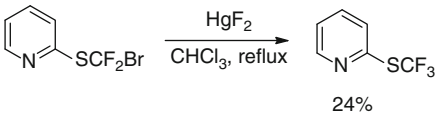


Scheme 23 Trifluoromethylsulfanylation of imidazole and thiazole derivatives

3.1.3 Substitution of Halogen Atoms by Fluorine

The Cl- and Br-substituents can then be replaced by fluorine by mercury fluoride without use of HF or SbF_3 [53] (Scheme 24).

Scheme 24 Conversion of CF_2BrS group to CF_3S

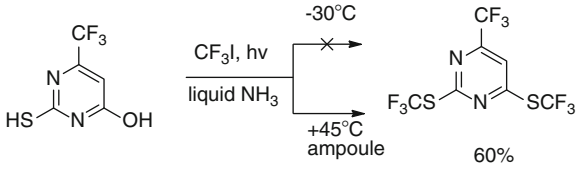


3.1.4 Radical Ion Perfluoroalkylation

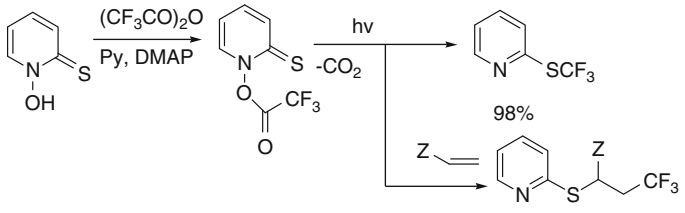
The $S_{RN}1$ reaction of aryl thiolates with trifluoromethyl iodide or bromide was the first synthesis of trifluoromethyl sulphides. This method, first reported by L. Yagupolskii [54] using CF_3I and UV irradiation, and by Wakselman and Tordeux [55] using CF_3Br. The other popular method involves the reaction of trifluoromethyl anion (generated *in situ* by various methods) with aryl and alkyl disulphides [56]. Heterocyclic thiols form *S*-perfluoroalkyl derivatives when irradiated in liquid ammonia in the presence of iodoperfluoroalkanes. The type of heterocyclic ring and the position of the thiol group influences the reaction. More electron-deficient heterocycles require longer irradiation times.

It appears that 4-hydroxypyrimidine-2-thiol does not react with CF_3I under standard conditions. Similar to the reaction of 4-nitrothiophenol noted above [57], this reaction requires more forcing conditions. Other 4-hydroxypyrimidine-2-thiols behave similarly. The irradiation of an ammonia solution of 2-mercapto-4-oxy-6-trifluoromethylyrimidine with CF_3I must be conducted in a Pyrex ampoule at 30–45 °C to produce the *S*-trifluoromethyl derivative (Scheme 25). Apparently, the reaction of these hydroxymercapto heterocyclic derivatives is complicated by stabilization of sulfur centred radicals.

Scheme 25 Trifluoromethylation of 2-mercapto-4-hydroxy-6-trifluoromethylpyrimidene



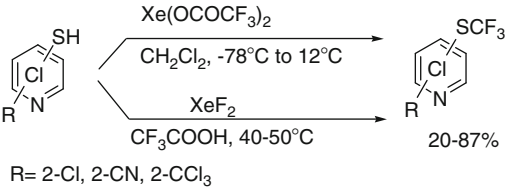
Barton [58] has shown that the irradiation of thiohydroxamic esters of perfluorocarboxylic acids generates $R_F^{\cdot}$ radicals which in the presence of olefins give addition products. However, in the absence of radical traps they attack the sulfur to yield, for example, *S*-trifluoromethyl derivatives of pyridine (Scheme 26).



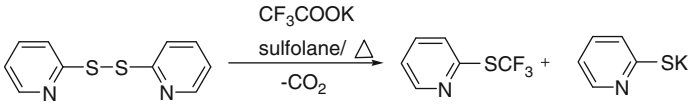
Scheme 26 Barton's *S*-perfluoroalkylation reactions

Xenon difluoride has been used to initiate oxidative decarboxylation of perfluorocarboxylic acids for $R_F^{\cdot}$ generation and with aromatic and heterocyclic compounds the perfluoroalkyl groups can also become incorporated into the aromatic ring [59]. On the other hand, Sipyagin et al. [60] have employed this method for the perfluoroalkylation of thiols such as polychloropyridine thiols. Two different methods were used: the action of preformed xenon carboxylates or treatment of a pyridinethiol solution in R_FCOOH directly with xenon difluoride. A range of isomeric perfluoroalkyl sulfides was obtained (Scheme 27).

Scheme 27 Perfluoroalkylation of polychloropyridine thiols with xenon perfluorocarboxylates or XeF_2

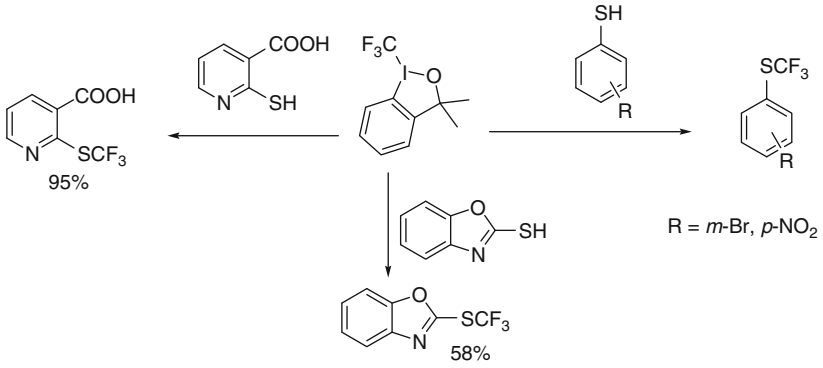


A simple method for the generation of metal derivatives of perfluoroalkyl carbanions by the decarboxylation of alkali salts of perfluorocarboxylic acids, has also been used. For example, heating potassium perfluoroalkyl carboxylates in the presence of dipyridine disulfides in DMF or sulfolane leads to the formation of the corresponding pyridine perfluoroalkyl sulfides [61] (Scheme 28).



Scheme 28 Thermal reaction of CF_3CO_2K with pyridine disulfides

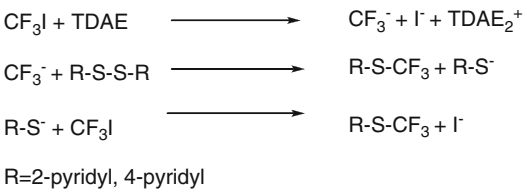
Togni [62] found that both aromatic and aliphatic thiols undergo selectively and smoothly *S*-trifluoromethylation in the presence of 1.1 equivalent of hypervalent CF_3-iodine(III) reagents to afford the products of trifluoromethylation in good to excellent yields (Scheme 29).



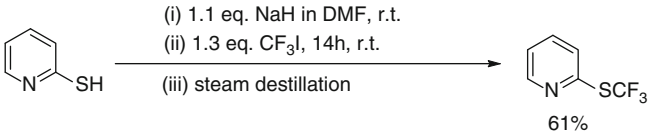
Scheme 29 Trifluoromethylation of thiols using iodine (III) reagent

A new procedure for preparation of trifluoromethyl thioethers was reported by Dolbier [63], wherein now both halves of aryl- and alkyldisulphides are able to be utilized with high efficiency, the so called "Tandem CF_3I process". When alkyl or aryl disulphides are reduced by the organic reducing agent tetrakis-(dimethylamino) ethylene (TDAE), the CF_3I forms a reagent anion that converts disulphides into their trifluoromethyl thioethers (Scheme 30).

Scheme 30 Tandem CF_3I process

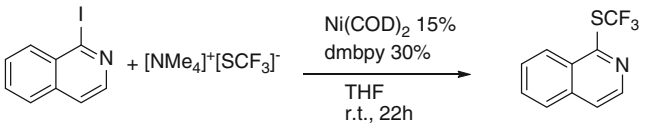


2011 Harsanyi et al. [64] improved and combined the efficiency and applicability of the classic $S_{RN}1$ type methods for *S*-trifluoromethylation (Scheme 31). This method is simplified compared to the previously reported ones as neither UV irradiation or pressure safe equipment is needed. It is somewhat similar to the second part of the "Tandem CF_3I process", which has been introduced by Dolbier [63] and coworkers. In the case of other acidic group containing thiols such as 2-mercaptobenzimidazole the inhibition of the radical chain reaction was observed.



Scheme 31 Preparation of trifluoromethyl sulfides

A novel method for the synthesis of aryl at RT has been proposed by Vicic [65]. Inexpensive nickel-bipyridine (bis(cyclooctadiene)nickel(0) ($Ni(COD)_2$) and 4,4′-dimethoxyl-2,2′-bipyridine (dmbpy)) complexes were found to be active for the trifluoromethylthiolation of heteroaryl iodides at room temperature using the convenient $[NMe_4][SCF_3]$ reagent (Scheme 32).



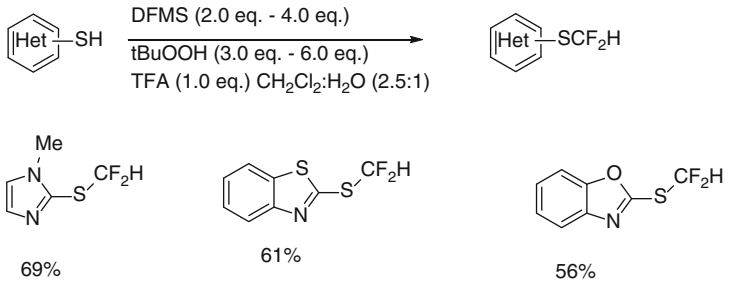
Scheme 32 Nickel-catalyzed synthesis of isochinoline trifluoromethyl sulfides

3.2 α,α -Difluoromethyl Thioethers

As phenols, thiophenols react in the presence of sodium hydroxide with chlorodifluoromethane to give difluoromethyl aryl sulphides, via the intermediate formation of chlorodifluoromethylsodium and difluorocarbene [27c]. α,α-Difluoroalkyl alkyl thioethers have also been obtained by the fluorodesulfuration with DEOXO-FLUOR of the corresponding thionothioesters as described previously for *O*-nucleophiles [66].

Trifluoromethyl zinc bromide was also used for the preparation of *S*-difluoromethylethers [67]. The first electrophilic (phenylsulfonyl)difluoromethylation with a hypervalent iodine(III)-CF_2SO_2Ph reagent was very recently reported by Hu [68].

Baran et al. [69] developed new reagent ($Zn(SO_2CF_2H)_2$, DFMS, synthesized from n dust and Difluoromethanesulfonyl chloride) the innate difluoromethylation of organic substrates via a radical process. This mild, operationally simple, chemoselective, and scalable difluoromethylation method is compatible with a range of nitrogen-containing heteroarene substrates of varying complexity as well as select classes of conjugated π-systems and thiols. Aromatic thiols exhibit unexpected reactivity toward the CF_2H radical, leading to the generation of difluoromethyl thioethers (Scheme 33). Radical difluoromethylation was also successful in the context of other electron-deficient π-systems such as α,β-unsaturated enones.



Scheme 33 Scope of C–H difluoromethylation of heteroarene substrates

4 Properties

What makes the introduction of CF_3O into pharmaceutically relevant compounds particularly intriguing is their unique electron distribution. The geminal combination of an alkoxy or aryloxy group with a fluorine atom offers the possibility of bonding/non-bonding resonance which can be formally expressed by the superposition of a covalent and an ionic limiting structure (Fig. 6).

On the basis of its electronic properties, which are close to those of a chlorine or a fluorine atom [70], the trifluoromethoxy group has been referred to as a super- [71] or a pseudo-halogen [72]. The advantage of incorporating a trifluoromethoxy group into a molecule can be described in terms of its properties. The trifluoromethoxy group is

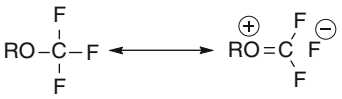


Fig. 6 Mesomeric structure of the CF_3O-group

Table 1 Electronic and hydrophobic parameters for various substituents

Atom/group	Pauling electronegativity	Hydrophobicity π
H	2.1	0.00
F	4.0	0.14
Cl	3.0	0.71
Br	2.8	0.86
I	2.5	1.12
CH_3	2.3	0.56
$C(CH_3)_3$	2.3	1.98
CF_3	3.5	0.88
OCH_3	2.7	–0.02
OCF_3	3.7	1.03
SCF_3	–	1.44
C_6H_5	–	1.96
SF_5	3.65	1.23

both more electron withdrawing and lipophilic than its methoxy analogue. The fluorinated carbon adjacent to an oxygen atom increases lipophilicity as shown by the high value of the OCF_3 hydrophobic substituent parameter. While both trifluoromethyl and trifluoromethoxy substituents invariably boost the lipophilicity [3], single fluorine atoms may alter this parameter in either direction. If the halogen occupies a vicinal or homovicinal position with respect to a hydroxy, alkoxy or carbonyl oxygen atom, it enhances the solvation energy in water more than in organic solvents and hence lowers the lipophilicity [73]. It appears that the OCF_3 substituent is far more lipophilic ($\pi = +1.04$) than the halogens and lies between a CF_3 ($\pi = +0.88$) and a SCF_3 ($\pi = +1.44$) group. It may thus replace advantageously a fluorine atom ($\pi = +0.14$) in most molecules with the benefit of increased lipid solubility [3] (Table 1).

The trifluoromethoxy group is at the same time a strong electron-withdrawing substituent due to the three fluorine atoms and a π-donating substituent due to the oxygen lone pairs. Yagupol'skii [74] and Sheppard [21, 75] provided detailed data on the pK_a-values of benzoic acids and phenols which reveal that the trifluoromethoxy group is a moderately electron-withdrawing moiety which resembles a chlorine atom. The pK_a values are lowered by the trifluoromethoxy group by 0.5–1.0 units [76].

The CF_3O group is thermally and chemically resistant to attack by acids, bases, organometallic reagents and oxidizing/reducing agents [21, 77]. When substituted on an aromatic ring, the trifluoromethoxy group exhibits similar electron withdrawing behavior to the alkoxy group but also acts to deactivate the aromatic ring system [72].

α-Fluoroalkyl sulfides are very similar to the corresponding ethers. For example, the pK_a values of benzoic acids are almost identical when CF_3O or CF_3S serves as a *meta*- or *para*-substituent. On the other hand, the stereoelectronics of (trifluoromethoxy) benzene and (trifluoromethylthio)benzene differ markedly. More-over, the two series

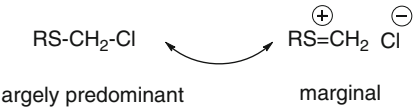


Fig. 7 Structure of α-haloalkyl sulfides

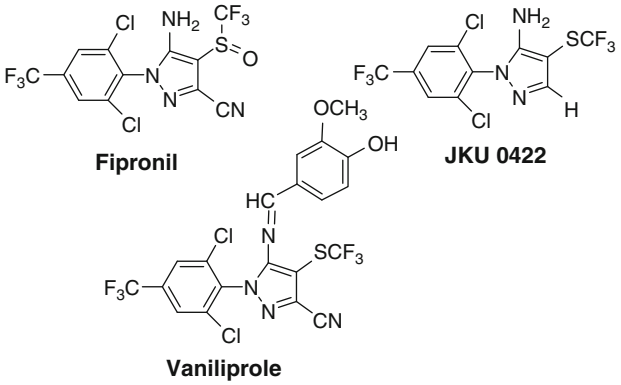


Fig. 8 Insecticides Fipronil, JKU 0422 and vaniliprole

distinguish themselves as far as anomeric effects are concerned, which are only marginally sustained by sulfur compounds. The relatively long bond distance between the second row element and carbon weakens of course double bonds as the one present in the charged limiting structure of α-haloalkyl sulfides (Fig. 7) [3b].

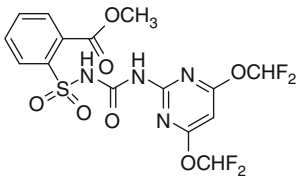
To some extent at least, electron density can nevertheless flow from a neutral sulfur to a positively charged carbon atom. This anomeric bonding/nonbonding resonance (n-σ^* interaction) explains why the S_N1 solvolysis rate of chloromethyl methyl sulphide is increased by many powers of ten when compared with that of 1-chlorobutane, which, moreover, appears to follow a solvent-S_N2 rather than a genuine S_N1 process [3b].

5 Application

5.1 Agrochemicals

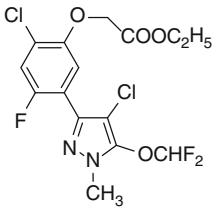
Inhibitors of the γ-aminobutyric acid (GABA) receptor/chloride ionophore complex, which has been the focus of intense interest as a target of insecticidal action and its role in resistance as well. The GABA-gated chloride channels are located in the insect central nervous system (CNS) and also in peripheral nerves where they mediate the proper integration of neuronal activity and muscle relaxation by inhibitory actions [78]. Azomethine formation with the phenylpyrazole amino group leads to vaniliprole, the derivative of the Finpronil [79]. The trifluoromethylsulfoxide group is a remarkable trigger for insecticidal activity (*"indication shift"*). This is shown for the arylaminopyrazole (JKU 0422) [80] (Fig. 8).

Fig. 9 Promisulfiron-methyl



Primisulforon-methyl

Fig. 10 Pyraflufen-ethyl



Pyraflufen-ethyl

Primisulfuron-methyl [14], a selective fluorosulfonylurea herbicide bears two difluoromethoxy subunits (Fig. 9).

Primisulfuron-methyl is a selective herbicide for the control of grasses in maize. Comparison [81] with its unfluorinated triazine counterpart methsulfuron-methyl indicates that crop safety for maize is achieved by the replacement of the triazine methoxy and methyl substituents with two difluoromethoxy groups. It has been shown that primisulfuron-methyl is deactivated in maize by hydroxylation of the phenyl and pyrimidyl moieties followed by hydrolysis or conjugation [82].

Pyraflufen-ethyl [15] is CHF_2O-containing phenylpyrazole (Fig. 10). This compound is a post-emergence contact herbicide for the control of broadleaf weeds, including cleavers (*Galium aparine*), in cereals and cotton, which also shows excellent crop selectivity for wheat and barley. It is rapidly absorbed by the foliage of broadleaf weeds, resulting in necrosis and desiccation.

Pyriprole, pyrafluprole and Flufiprole [83] are experimental insecticides introduces by Nihon Nohyaku and related, both in chemistry and action to the highly successful insecticide Fipronil. Fipronil acts at the GABA receptor [83a] (Fig. 11).

5.2 Pharmaceuticals

Riluzole (Rilutek) [5] a CF_3O-substituted 2-aminobenzothiazole, is known to affect motor neurons by at least three mechanisms, including inhibition of glutamate release, inhibition of postsynaptic events following glutamate receptor stimulation, and stabilization of *vgSChs*. It is the first drug approved for treatment of amyotropic lateral sclerosis (Fig. 12).

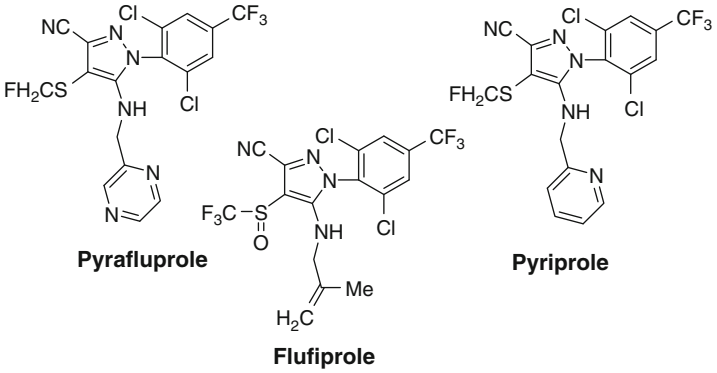


Fig. 11 Pyrafluprole, Pyriprole and Flufiprole

Fig. 12 Riluzole

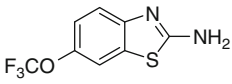
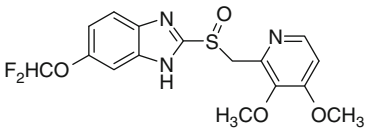


Fig. 13 Pantoprazole

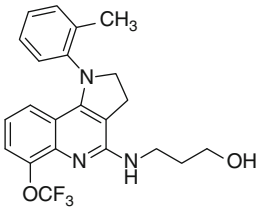


Substituted benzimidazoles such as omeprazole, lansoprasole, rabeprazole (all non-α-fluorinated ethers) and the pH-selective (-)-pantoprazole (pantoprazole sodium, Rifun, Pantozol, Pantec) [6] are known as gastric proton pump inhibitors (PPIs) (Fig. 13). All PPIs accumulate in the acidic space of the secreting parietal cell, where their active forms create disulfide bonds with key cysteines of the H^+, K^+-ATPase. (-)-Pantoprazole, an irreversible proton pump inhibitor, reached its first market worldwide for acute treatment of gastric and duodenal ulcers and gastro-esophageal reflux disease. This profile is different to other PPIs and is likely related to the unique binding of (-)-pantoprazole to cysteine 882, a binding site that is buried deep within the membrane domain of the pump and may therefore be inaccessible to reducing agents. Thus, (-)-pantoprazole is a valuable alternative to other PPIs in the treatment of acid related disorders. Furthermore, the PPIs were found to have in vitro activity against three different isolates of *Plasmodium falciparum* [6d].

Recently, the effect of novel quinoline derivatives such as (AU-006, Fig. 14) was described [84]. Its protective effect against gastric lesions was not affected by an NO synthase inhibitor.

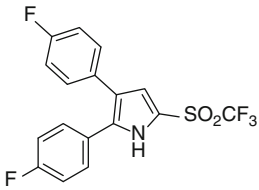
A series of 4,5-diaryl-2-(substituted thio)-1*H*-imidazoles, such as the 1,1,2,2-tetrafluoro-ethyl-sulfonylcontaining triflamizole (EN-350), was described

Fig. 14 AU-006



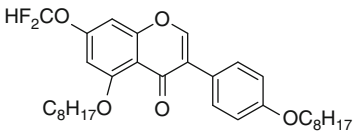
AU-006

Fig. 15 Triflumidate



Triflumidate

Fig. 16 7-Difluoromethoxyl-5,4′-di-n-octylgenistein (DFOG)



DFOG

as antiinflammatory and analgesic agents (e.g., antirheumatic) [7]. On the other hand, for the F_3CSO_2 derivate lethal effects of arachidonate induced platelet aggregation were reported (Fig. 15).

Cao et al. [85] examined the antitumor effects of 7-difluoromethoxyl-5,4′-di-n-octylgenistein (DFOG), a novel synthetic genistein derivative, on human ovarian cancer cells as well as the molecular mechanism (Fig. 16).

The anti-HIV-1 activities and pharmacokinetics of a series of arylpiperazinyl fluoroquinolones are reported [86]. The SAR study revealed that the substituent at the C-8 position of arylpiperazinyl fluoroquinolones plays an important role in anti-HIV-1 activities. Hydrophobicity of the substituent at this position seems to be one of the key factors for antiviral activity. However, in this case the introduction of a CF_3O group at the C-8 position proved to be superior to that of a CHF_2O group to achieve higher anti-HIV-activity (Fig. 17) [87].

The new des-6-fluoro-quinolone garenoxacin, a DNA topoisomerase ATP hydrolyzing inhibitor, is currently in phase III clinical tests. Garenoxacin [88] (Fig. 18) is a quinolone that demonstrates activity against a wide range of Gram-positive and Gram-negative bacterial pathogens such as *E. coli*, *Enterococcus* spp. and *Pseudomonas aeruginosa.*

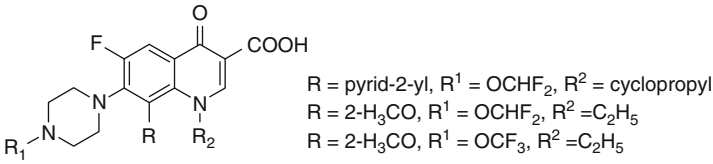
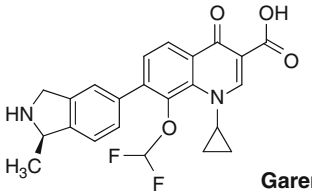


Fig. 17 $OCHF_2$- and OCF_3-containing HIV-drugs

Fig. 18 Garenoxacin



6 Conclusion

The present review portraying α-fluorinated ethers- and thioethers-containing heterocycles has introduced as an additional factor of complexity the anomeric effect and thus pushed the door open to the bonding/nonbonding continuum.

To get immersed in organofluorine chemistry entails the challenge to compile better experimental results, computational data, and intellectual arguments until one has established a sufficiently large and solid basis to rationalize all observations made and to foresee the outcome of new reactions or assays. However, product-oriented chemistry cannot delay its day-to-day business until the moment when the ultimate degree of theoretical sophistication and parametrization has been attained and the crucial technical or biological benchmarks such as surface tension, wettability, polymer elasticity, dielectrical anisotropy, acidity, lipophilicity, metabolic stability, and target binding can be predicted with numerical reliability.

Therefore, fluorine will continue to be exploited on the basis of empirical knowledge. In the life science field, one employs single fluorine atoms, difluoromethylene units, and trifluoromethyl or trifluoromethoxy groups to tailor p*K*a values, to foster cell penetration by improving the passive permeation through the blood/brain barrier and all kinds of biological membranes, to help accumulate substances in tissues, and to enhance the substrate binding to protein-type receptors by making use of the "polar hydrophobic effect". All this contributes to the critical "bioavailability" of therapeutically active compounds.

There are well-tried recipes to confer metabolic stability to biologically active compounds. On the other hand, metabolic lability can be a blessing in itself. Unlike the closely related lead compound prosulfuron, the post-emergent herbicide primisulfuron-methyl exterminates the weed in corn (maize) fields without harming the crop. The two difluoromethoxy groups attached to the pyrimidine ring offer the

possibility to the plant, but not the weed, to detoxify itself in the course of a few hours by oxidative degradation, the $OCHF_2$ substituents thus acting as a specific metabolic breakseal.

A particularly intriguing subject is the role of fluorine as a mimic. The isosteric relationship between fluorine and oxygen is often emphasized. However, unlike the hydroxy group, organic fluorine is a very poor hydrogen bond acceptor and no hydrogen bond donor at all. Thus, the replacement of a hydroxy group by a fluorine atom may totally perturb the interaction pattern. On the other hand, fluorine and hydrogen, both monovalent elements, are sufficiently similar in size to be able to imitate each other.

In general, fluorine should prove practically isosteric with hydrogen as far as substrate-enzyme and agonist-receptor recognition is concerned. Fluorinated pheromones may even serve to confuse insects and disrupt their mating. Anyway, we have no choice. "There is no other element that can pose as hydrogen except fluorine. Therefore let us do our best to exploit cunningly the similarities and dissimilarities of these unlike twins."

In other words, fluorine will remain an important tool to modulate the properties of biologically active substances. α-fluorinated ethers- and thioethers-containing heterocycles will without doubt claim a major role in the future evolution of the field.

References

1. Manteau B, Pazenok S, Vors JP, Leroux FR (2010) New trends in the chemistry of α-fluorinated ethers, thioethers, amines and phosphines. J Fluorine Chem 131:140–158. doi:10.1016/j.jfluchem.2009.09.009
2. Jeschke P, Baston E, Leroux FR (2007) α-Fluorinated ethers as "exotic" entity in medicinal chemistry. Mini-Rev Med Chem 7:1027–1034. doi:10.2174/138955707782110150
3. (a) Leroux FR, Manteau B, Vors JP, Pazenok S (2008) Trifluoromethyl ethers – synthesis and properties of an unusual substituent. Beilstein J Org Chem 4(13):1–15. doi:10.3762/bjoc.4.13; (b) Leroux F, Jeschke P, Schlosser M (2005) α-fluorinated ethers, thioethers, and amines: anomerically biased species. Chem Rev 105(3):827–856. doi:10.1021/cr040075b
4. (a) Boiko VN (2010) Aromatic and heterocyclic perfluoroalkyl sulfides. Methods of preparation. Beilstein J Org Chem 6:880–921. doi:10.3762/bjoc.6.88; (b) Vovk MV, Pinchuk OM, Sukach VA, Tolmachov AO, Gakh AA (2009) Trifluoromethoxy containing azoles and azines: synthesis and biological activity. In: Gakh AA, Kirk KL (eds) ACS Symp Ser, vol 1003. ACS, Washington, DC, pp 307–345
5. Jimonet P, Audiau F, Barreau M, Blanchard JC, Boireau A, Bour Y, Coleno MA, Doble A, Doerflinger G, Do Huu C, Donat M-H, Duchesne JM, Ganil P, Gueremy C, Honore E, Just B, Kerphirique R, Gontier S, Hubert P, Laduron PM, Le Blevec J, Meunier M, Miquet JM, Nemecek C, Pasquet M, Piot O, Pratt J, Rataud J, Reibaud M, Stutzmann JM, Mignani S (1999) Riluzole series. Synthesis and in vivo "antiglutamate" activity of 6-substituted-2-benzothiazolamines and 3-substituted-2-imino-benzothiazolines. J Med Chem 42:2828–2843. doi:10.1021/jm980202u
6. (a) Kromer W (2000) The relationship between pH-selectivity, chirality, and efficacy of gastric proton pump inhibitors. Curr Top Pharmacol 5:45–69; (b) Badwan AA, Nabulsi LN, Al Omari MM, Daraghmeh NH, Ashour MK, Abdoh AM, Jaber AMY (2002) Pantoprazole sodium. Anal Profiles Drug Subst Excipients 29:213–259; (c) Cheer SM, Prakash A, Faulds D, Diana

HM (2003) Pantoprazole: an update of its pharmacological properties and therapeutic use in the management of acid-related disorders. Drugs 63:101–132. doi:10.2165/00003495-200363010-00006; (d) Riel MA, Kyle DE, Bhattacharjee AK, Milhous WK (2002) Mechanisms of action: physiological effects efficacy of proton pump inhibitor drugs against plasmodium falciparum in vitro and their probable. Pharmacophores Antimicrob Agents Chemother 46:2627–2632. doi:10.1128/AAC.46.8.2627-2632.2002; (2002) Chem Abstr 137:259873

7. Page GO (1993) The mild oxidation of some alpha-difluoro sulfides to sulfones with sodium perborate. Synth Commun 23:765–769. doi:10.1080/00397919308009837
8. (a) British Crop Protection Council. The e-pesticide manual (2005–2006) A world compendium, version 3.2, 13 ed., British Crop Protection Council; (b) British Crop Protection Council. The e-pesticide manual (2005–2006) A world compendium, version 5.2, 15 ed., British Crop Protection Council
9. Harder HH, Riley SL, McCann SF, Irving SN (1996) DPX-MP062: a novel broad-spectrum, environmentally soft, insect control compound. Br Crop Prot Conf Pest Dis 2:449–454
10. Sheets JJ (2007) Chitin Synthesis. In: Kramer W, Schirmer U (Eds), Modern crop protection compounds. Wiley-VCH, Weinheim, p 813
11. Benefiel RL, Krumkalns EV (1977) Novel fluoroalkoxyphenyl-substituted nitrogen heterocycles. US Patent 4,002,628, 11 Jan 1977
12. O'Reilly P, Kobayashi S, Yamane S, Phillips W, Raymond P, Castanho B (1992) MON 24000: a novel fungicide with broad-spectrum disease control. Br Crop Prot Conf Pest Dis 1:427–434
13. Santel HJ, Bowden BA, Sorensen VM, Müller KH (1999) Flucarbazone-sodium – a new herbicide for the selective control of wild oat and green foxtail in wheat. Br Crop Prot Conf Pest Dis 1:23–28
14. Mauer W, Gerber HR, Rufener J (1987) Proc – British Crop Prot Conf Weeds 1:41–48; (1988) Chem Abstr 108:145332
15. Miura Y, Ohnishi M, Mabuchi T, Yanai I (1993) ET–751 a new herbicide for use in cereals. Brighton Crop Prot Conf – Weeds 1:35–41; (1994) Chem Abstr 121:101822
16. (a) Colliot F, Kukorowski KA, Hawkins DW, Roberts DA (1992) Fipronil: a new soil and foliar broad spectrum insecticide. Brighton Crop Prot Conf Pest Dis 1:29–34; (b) Hamon N, Shaw R, Yang H (1996) Worldwide development of fipronil insecticide. Proc Beltwide Cotton Conf 2:759–765
17. (a) Yagupol'skii LM (1955) Dokl Akad Nauk SSSR 105:100; (b) Yagupol'skii LM (1964) OVV Zh Obshch Khim 34:1979; (c) Yagupol'skii LM, Troitskaya VI (1961) Zh Obshch Khim 31:915–924
18. Louw R, Franken P (1977) Chem Ind 127
19. Feiring AE (1979) Chemistry in hydrogen fluoride. 7. A novel synthesis of aryl trifluoromethyl ethers. J Org Chem 44:2907–2910. doi:10.1021/jo01330a017
20. Yarovenko NN, Vasil'eva AS (1958) A new method for the introduction of trihalomethyl groups into organic molecules. Zh Obshch Khim 28:2502–2504
21. Sheppard WA (1964) α-Fluorinated ethers. I. Aryl fluoroalkyl ethers. J Org Chem 29:1–11. doi:10.1021/jo01024a001
22. Kuroboshi M, Suzuki K, Hiyama T (1992) Oxidative desulfurization-fluorination of xanthates. A convenient synthesis of trifluoromethyl ethers and difluoro(methylthio)methyl ethers. Tetrahedron Lett 33:4173–4176. doi:10.1016/S0040-4039(00)74681-8
23. (a) Umemoto T, Adachi K, Ishihara S (2007) CF_3 oxonium salts, O-(trifluoromethyl)dibenzofuranium salts: in situ synthesis, properties, and application as a real CF_3^+ species reagent. J Org Chem 72:6905–6917. doi:10.1021/jo070896r; (b) Umemoto T, Ishihara S (1990) Power-variable trifluoromethylating agents, (trifluoromethyl)dibenzothio- and -selenophenium salt system. Tetrahedron Lett 31:3579–3582. doi:10.1016/S0040-4039(00)94447-2; (c) Umemoto T, Ishihara S (1993) Power-variable electrophilic trifluoromethylating agents. S-, Se-, and Te-(trifluoromethyl)dibenzothio-, -seleno-, and -tellurophenium salt system. J Am Chem Soc 115:2156–2164. doi:10.1021/ja00059a009; (d) Umemoto T, Adachi K (1994) New method for trifluoromethylation of enolate anions and applications to regio-, diastereo- and enantioselective trifluoromethylation. J Org Chem 59:5692–5699. doi:10.1021/jo00098a030

24. Yagupol'skii LM, Kondratenko NV, Timofeeva GN (1984) Zh Org Khim 20:115–118; J Org Chem USSR (Engl. Transl.) 1984, 20, 103–106
25. Manteau B, Genix P, Brelot L, Vors JP, Pazenok S, Giornal F, Leuenberger C, Leroux FR (2010) A general approach to (trifluoromethoxy)pyridines: first X-ray structure determinations and quantum chemistry studies. Eur J Org Chem 31:6043–6066. doi:10.1002/ejoc.201000958
26. Chiefari J, Mayadunne RTH, Moad CL, Moad G, Rizzardo E, Postma A, Skidmore MA, Thang SH (2003) Thiocarbonylthio compounds (S = C(Z)S – R) in free radical polymerization with reversible addition-fragmentation chain transfer (RAFT polymerization). effect of the activating group Z. Macromolecules 36:2273–2283. doi:10.1021/ma020883
27. (a) Fuss A, Koch V (1990) Chemistry of 3-hydroxypyridine part 3: synthesis of substituted 3-[fluoro(chloro)alkoxy]pyridines from halo- or amino-3-hydroxypyridines. Synthesis 7:604–608. doi:10.1055/s-1990-26956; (b) Morimoto K, Makino K, Sakata G (1992) Reaction of quinoxalin-2-ones with difluorocarbene. J Fluorine Chem 59:417–422. doi:10.1016/S0022-1139(00)80339-5; (c) Langlois BR (1988) Improvement of the synthesis of aryl difluoromethyl ethers and thioethers by using a solid-liquid phase-transfer technique. J Fluorine Chem 41:247–261. doi:10.1016/S0022-1139(00)81548-1
28. (a) Kamada K, Kawamoto S, Yaegashi M, Shiraishi S (1988) EP0257415 2 Mar 1988; (b) Li X, Pan H, Jiang X (1984) Spontaneous reactions of potassium phenoxide with dibromoperflouroalkanes · first evidence for bromophilic attack on C-Br bonds by the phenoxide. Tetrahedron Lett 25:4937–4940. doi:10.1016/S0040-4039(01)91263-8; (c) Rico I, Wakselman C (1981) Synthese de composes aromatiques comportant les groupements OCF_2Br et SCF_2Br I – Action du dibromodifluoronéthane sur les thiophénate et phénate de potassium. Tetrahedron Lett 22:323–326. doi:10.1016/0040-4039(81)80087-1; (d) Numata S, Kitajima K, Kodaka K, Fukushi Y, Shiraishi S, Nakamura M, Ooka M (1987) Chlordifluormethoxyphenyl-derivate Und Diese Derivate Als Wirkstoff Enthaltendes Milben-Abtoetendes Mittel DE3708222, 17 Sept 1987
29. Salomé J, Mauger C, Brunet S, Schanen V (2004) Synthesis conditions and activity of various Lewis acids for the fluorination of trichloromethoxy-benzene by HF in liquid phase. J Fluorine Chem 125:1947–1950. doi:10.1016/j.jfluchem.2004.08.002
30. Sokolenko TM, Davydova YA, Yagupolskii YL (2012) Efficient synthesis of 5′-fluoroalkoxythiazoles via α-bromo-α-fluoroalkoxyacetophenones Hantzsch type cyclization with thioureas or thioamides. J Fluorine Chem 136:20–25. doi:10.1016/j.jfluchem.2012.01.005
31. Joule JA, Mills K (2000) Heterocyclic chemistry. Blackwell Publishing, Oxford, 2000
32. (a) Huang C, Liang T, Harada S, Lee E, Ritter T (2011) Silver-mediated trifluoromethoxylation of aryl stannanes and arylboronic acids. J Am Chem Soc 133:13308–13310. doi:10.1021/ja204861a; (b) Kolomeitsev AA, Vorobyev M, Gillandt H (2008) Versatile application of trifluoromethyl triflate. Tetrahedron Lett 49:449–454. doi:10.1016/j.tetlet.2007.11.105
33. Peláez WJ, Argüello GA (2010) Co-thermolysis: a one-pot synthetic method for novel 2-substituted-5-(trilfuoromethoxy)thiophenes. Tertrahedron Lett 51:5242–5245. doi:10.1016/j.tetlet.2010.07.111
34. Marrec O, Billiard T, Vors J-P, Pazenok S, Langlois BR (2010) A deeper insight into direct trifluoromethoxylation with trifluoromethyl triflate. J Fluorine Chem 131:200–207. doi:10.1016/j.fluchem.2009.11.006
35. (a) Clark RF, Simons JF (1955) Difluoromethyl phenyl ether. J Am Chem Soc 77:6618. doi:10.1021/ja01629a060; (b) Miller TG, Thanassi JW (1960) The preparation of aryl difluoromethyl ethers. J Org Chem 25:2009–2012. doi:10.1021/jo01081a048
36. Sokolenko TM, Yagupolskii LM (2011) Chem Heterocyclic Compd 46:1335–1343; (2010) transl from Khimiya Geterotsiklicheskikh Soedinenii 46:1649–1658
37. Baiocchi L, Corsi G, Palazzo G (1978) Synthesis, properties, and reactions of 1*H*-indazol-3-ols and 1,2-dihydro-3*H*-indazol-3-ones. Synthesis 9:633–648. doi:10.1055/s-1978-24840
38. (a) Yagupolskii LM, Kondratenko NV, Sambur VP (1975) A new method for the syntheses of aryl and heteroaryl trifluoromethyl sulfides. Synthesis 11:721–723. doi:10.1055/s-1975-23905; (b) Oksengendler IG, Kondratenko NV, Luk'yanets EA, Yagupolskii LM (1978) Zh Org Khim 14:1046–1051; (1978) Chem Abstr 89:112289v

39. (a) Remy DC, Rittle KE, Hunt CA, Freedman MB (1976) Trifluoromethylthiocopper. A reagent for the introduction of the trifluoromethylthio group into aromatic nuclei. J Org Chem 41:1644–1646. doi:10.1021/jo00871a037; (b) Remy DC, Freedman MB (1977) US Patent 4,020,169, 26 Apr 1977; (1977) Chem Abstr 87:52939d
40. (a) Kolomeitsev A, Médebielle M, Kirsch P, Lork E, Röschenthaler G-V (2000) Synthesis, structure and reactivity of a trifluoromethyl sulphide anionic salt stabilized with tetrakis (dimethylamino)ethylenedication (TDAE). J Chem Soc Perkin Trans 1 2183–2185. doi:10.1039/b002252; (b) Kolomeitsev A, Kirsch P, Röschenthaler G-V (2001) Preparation of perfluoroalkylthiolates, useful as intermediates for e.g. plant agents and pharmaceuticals, comprises reaction of (aryl)perfluoro-alkylsilanes with elemental sulfur, in the presence of a fluoride ion donor, DE 10254597 (Merck KGaA), priority 21.12.2001
41. Dmowski W, Haas A (1985) Chimia 39:185; (b) Dmowski W, Haas A (1987) Trifluoromethanethiolate ion. Part 2. Nucleophilic substitution in pentafluoropyridine. Synthesis and characteristics of trifluoromethylthio and trifluoromethylsulphonyl derivatives. J Chem Soc Perkin Trans 1 2119–2124. doi:10.1039/P19870002119; (c) Dmowski W, Haas A (1988) Trifluoromethanethiolate ion. Part 3. Reactions with tetrafluoropyridazine and tetrafluoropyrimidine. J Chem Soc Perkin Trans 1 1179–1181. doi:10.1039/P19880001179
42. Clark JH, Tavener SJ (1997) The preparation of trifluoromethyl aryl sulfides using KF and thiophosgene. J Fluorine Chem 85:169–172. doi:10.1016/S0022-1139(97)00057-2
43. Tyrra W, Naumann D, Hoge B, Yagupolskii YL (2003) A new synthesis of trifluoromethanethiolates – characterization and properties of tetramethylammonium, cesium and di(benzo-15-crown-5)cesium trifluoromethanethiolates. J Fluorine Chem 119:101–107. doi:10.1016/S0022-1139(02)00276-2
44. (a) Teverovskiy G, Surry DS, Buchwald SL (2011) Pd-catalyzed synthesis of Ar-SCF_3 compounds under mild conditions. Angew Chem Int Ed 50:7312–7314. doi:10.1002/anie.201102543; (b) Adams DJ, Clark JH (2000) Preparation of trifluoromethyl aryl sulfides using silver(I) trifluoromethanethiolate and an inorganic iodide. J Org Chem 65:1456–1460. doi:10.1021/jo9915933; (c) Clark JH, Jones CW, Kybett AP, Mcclinton MA, Miller JM, Bishop D, Blade RJ (1990) The introduction of SCF_3 into aromatic substrates using $CuSCF_3$ and alumina-supported $CuSCF_3$. J Fluorine Chem 48:249–253. doi:10.1016/S0022-1139(00)80437-6
45. Haas A, Niemann U (1977) Perhalogenmethylthio-heterocyclen, VIII. (Perchlorfluormethylthio)- und (halogenformylthio)-N-heteroaromaten. Chem Ber 110:67–77. doi:10.1002/cber.19771100108
46. Mirek J, Haas A (1981) The reaction of indolizines and acetylindolizines with trifluoromethylsulfenyl chloride. J Fluorine Chem 19:67–70. doi:10.1016/S0022-1139(00)85240-9
47. (a) Gerstenberger MRC, Haas A, Liebig F (1982) Perhalogenmethylthioheterocyclen. XI: CF3S-substituierte N-methyl-pyrrole; migration der CF_3S-gruppe. J Fluorine Chem 19:461–474. doi:10.1016/S0022-1139(00)83146-2; (b) Gerstenberger MRC, Haas A (1983) (Perhalogenmethylthio)-heterocyclen, XV Säure- und basekatalysierte Umsetzungen von Furan, Selenophen und Pyridin. J Fluorine Chem 23:525–540. doi:10.1016/S0022-1139(00)85137-4
48. Haas A, Hellwig V (1976) Perhalogenmethylthio-heterocyclen, VI: (perchlorfluormethylthio)- und (halogenformylthio)thiophene. Chem Ber 109:2475–2484. doi:10.1002/cber.19761090715
49. Haas A, Niemann U (1978) Perhalogenmethylmercapto-heterocyclen, IX (perchlormethylmercapto)- und (perfluormethylmercapto)pyridine. J Fluorine Chem 11:509–518. doi:10.1016/S0022-1139(00)82464-1
50. Haas A, Hellwig V (1975) Perhalogenmethylmercapto-heterocyclen, (VII) [1] konkurrenzreaktionen elektronenarmer, substituierter aromaten um die halogenmethylmercapto- BZW. Chlorgruppe von Cl3-nFnCSCl in starken saeuren. J Fluorine Chem 6:521–532. doi:10.1016/S0022-1139(00)81691-7
51. Dorn S, Eggenberg P, Gerstenberger MRC, Haas A, Niemann U, Zobrist P (1979) (Perhalogenmethylthio)heterocyclen. X. Säurekatalysierte Substitutionen an (Perchlorfluormethylthio)pyrrolen und deren agrobiologische Wirkung. Helv Chim Acta 62:1442–1450. doi:10.1002/hlca.19790620508
52. Croft TS, McBrady JJ (1975) Fluoroalkylthio five-membered heteroaromatics. J Heterocycl Chem 12:845–849. doi:10.1002/jhet.5570120507; (1976) Chem Abstr 84:43948s

53. Suda M, Hino C (1997) Preparation of bromodifluoromethyl sulfide and its conversion to trifluoromethyl sulfide. Tetrahedron Lett 22:1997–2000. doi:10.1016/S0040-4039(01)92888-6
54. Boiko VN, Shchupak GM, Yagupolskii LM (1977) Anionic sigma-complex of 2,4-bis(trifluoromethylsulfonyl)anisole with sodium methoxide. J Org Chem USSR 13:972
55. Wakselman C, Tordeux M (1985) Chemistry of halogenoperfluoroalkanes. Synthesis of fluorinated ethers and thioethers via radical or anionic intermediates. J Org Chem 50:4047–4051. doi:10.1021/jo00221a017
56. (a) Billard T, Langlois BR (1996) A new simple access to trifluoromethyl thioethers or seleno-ethers from trifluoromethyl trimethylsilane and disulfides or diselenides. Tetrahedron Lett 37:6865–6869. doi:10.1016/0040-4039(96)01530-4; (b) Quiclet-Sire B, Saicic RN, Zard SZ (1996) convenient synthesis of trifluoromethyl aryl sulfides. Tetrahedron Lett 37:9057–9058. doi:10.1016/S0040-4039(96)02127-2; (c) Roques N (2001) Nucleophilic perfluoroalkylation of diaryldisulfides with perfluorocarboxylate salts. J Fluorine Chem 107:311–314. doi:10.1016/S0022-1139(00)00374-2; (d) Blond G, Billard T, Langlois BR (2001) New stable reagents for the nucleophilic trifluoromethylation. Part 4: trifluoromethylation of disulfides and diselenides with hemiaminals of trifluoroacetaldehyde. Tetrahedron Lett 42:2473–2475. doi:10.1016/S0040-4039(01)00225-8
57. (a) Boiko VN, Shchupak GM, Yagupolskii LM (1977) Zh Org Khim 13:1057–1061; (1997) Chem Abstr 87:134226h; (b) Boiko VN, Dashevskaya TA, Shchupak GM, Yagupolskii LM (1979) Zh Org Khim 15:396–400; (1979) Chem Abstr 91:20439g; (c) Boiko VN, Shchupak GM, Popov VI, Orlova RK, Yagupolskii LM (1979) USSR Patent 687,067 (1980) Chem Abstr 92:22503t
58. Barton DHR, Lacher B, Zard SZ (1986) The invention of new radical chain reactions: part XIII. Generation and reactivity of perfluoroalkyl radicals from thiohydroxamic esters. Tetrahedron 42:2325–2328. doi:10.1016/S0040-4020(01)90613-1
59. Tanabe Y, Matsuo N, Ohno N (1988) Direct perfluoroalkylation including trifluoromethylation of aromatics with perfluoro carboxylic acids mediated by xenon difluoride. J Org Chem 53:4582–4585. doi:10.1021/jo00254a033
60. (a) Sipyagin AM, Pomytkin IA, Pal'tsun SV, Aleinikov NN, Kartsev VG (1990) Dokl Akad Nauk SSSR 311:1137–1139; (1990) Chem Abstr 113:152212k; (b) Sipyagin AM, Pomytkin IA, Pal'tsun SV, Aleinikov NN (1994) Reactions of polyhalopyridines. Part 4. Interaction of mercaptopolychloropyridines with fluorine-containing xenon(II) compounds. Khim Geterotsikl Soedin 58–62;(1995) Chem Abstr 122:31274j; (c) Sipyagin AM, Enshov VS, Boiko GN, Lebedev AT, Karakhanova NK (2003) Khim Geterotsikl Soedin (2003) 1698–1706
61. Quiclet-Sire B, Saicic RN, Zard SZ (1996) Convenient synthesis of trifluoromethyl aryl sulfides. Tetrahedron Lett 37:9057–9058. doi:10.1016/S0040-4039(96)02127-2
62. Kieltsch I, Eisenberger P, Togni A (2007) Mild electrophilic trifluoromethylation of carbon- and sulfur-centered nucleophiles by a hypervalent iodine(III)–CF_3 reagent. Angew Chem Int Ed 46:754–757. doi:10.1002/anie.200603497
63. (a) Pooput C, Medebielle M, Dolbier WR (2004) A new and efficient method for the synthesis of trifluoromethylthio- and selenoethers. Org Lett 6:301–303, doi:10.1021/ol036303q; (b) Pooput C, Dolbier WR, Medebielle M (2006) Direct synthesis of esters and amides from unprotected hydroxyaromatic and -aliphatic carboxylic acids. J Org Chem 71:3564–3574. doi:0.1021/jo052293q
64. Harsanyi A, Dorko E, Csapo A, Bako T, Peltz C, Rabai J (2011) Convenient synthesis and isolation of trifluoromethylthio-substituted building blocks. J Fluorine Chem 132:1241–1246. doi:10.1016/j.jfluchem.2011.07.008
65. Zhang C-P, Vicic DA (2012) Nickel-catalyzed synthesis of aryl trifluoromethyl sulfides at room temperature. J Am Chem Soc 134:183–185. doi:10.1021/ja210364r
66. (a) Lal GS, Pez GP, Pesaresi RJ, Prozonic FM, Cheng H (1999) Bis(2-methoxyethyl)aminosulfur trifluoride: a new broad-spectrum deoxofluorinating agent with enhanced thermal stability. J Org Chem 64:7048–7054. doi:10.1021/jo990566; (b) Lal GS, Lobach E, Evans A (2000) Fluorination of thiocarbonyl compounds with bis(2-methoxyethyl)aminosulfur trifluoride

(Deoxo-Fluor reagent): a facile synthesis of gem-difluorides. J Org Chem 65:4830–4832. doi:10.1021/jo000020j
67. Tyrra W, Naumann D (1996) Trifluoromethyl zinc bromide – a useful trifluoromethylation and difluoromethylation reagent. J Prakt Chem Chem-Ztg 338:283–286. doi:10.1002/prac.19963380155
68. Zhang W, Zhu J, Hu J (2008) Electrophilic (phenylsulfonyl)difluoromethylation of thiols with a hypervalent iodine(III)–CF_2SO_2Ph reagent. Tetrahedron Lett 49:5006–5008. doi:10.1016/j.tetlet.2008.06.064
69. Fujiwara Y, Dixon JA, Rodriguez RA, Baxter RD, Dixon DD, Collins MR, Blackmond DG, Baran PS (2012) A new reagent for direct difluoromethylation. J Am Chem Soc 134(3):1494–1497. doi:10.1021/ja211422g
70. Olah GA, Yamato T, Hashimoto T, Shih JG, Trivedi N, Singh BP, Piteau M, Olah J (1987) Aromatic substitution. 53. Electrophilic nitration, halogenation, acylation, and alkylation of (. alpha., alpha., alpha.-trifluoromethoxy)benzene. J Am Chem Soc 109:3708–3713. doi:10.1021/ja00246a030
71. Sheppard WA (1963) The effect of fluorine substitution on the electronic properties of alkoxy, alkylthio and alkylsulfonyl groups. J Am Chem Soc 85:1314–1318. doi:10.1021/ja00892a021
72. Haas A (1984) The element displacement principle: a new guide in P-block element chemistry. Adv Inorg Chem Radiochem 28:167–202. doi:10.1016/S0898-8838(08)60208-1
73. Böhm H-J, Banner D, Bendels S, Kansy M, Kuhn B, Müller K, Obst-Sander U, Stahl M (2004) Fluorine in medicinal chemistry. ChemBioChem 5:637–643. doi:10.1002/cbic.200301023
74. (a) Yagupolskii LM, Yagupolskaya LN (1960) Dokl Akad Nauk SSSR 134:1381–1383; (b) Yagupol'skii LM, Bystrov VF, Stepanyants AU, Fialkov YA (1964) Zh Obshch Khim 34:3682–3690
75. Sheppard WA (1962) The electrical effect of the sulfur pentafluoride group. J Am Chem Soc 84:3072–3076. doi:10.1021/ja00875a007
76. (a) Kortüm G, Vogel W, Andrussow K (1961) Dissociation constants of organic acids in aqueous solution. Pure Appl Chem 1:187–536. doi:10.1351/pac196001020187; (b) Hansch C, Leo A, Taft RW (1991) A survey of Hammett substituent constants and resonance and field parameters. Chem Rev 91:165–195. doi:10.1021/cr00002a004
77. Aldrich PE, Sheppard WA (1964) α-Fluorinated ethers. II. Alkyl fluoroalkyl ethers. J Org Chem 29:11–15. doi:10.1021/jo01024a002
78. Nauen R, Bretschneider T (2002) New modes of action of pesticides. Pestic Outlook 12:241–245.doi:10.1039/b211171n; (2002) Chem Abstr 140:1823
79. Colliot F, Kukorowski KA, Hawkins DW, Roberts DA (1992) Fipronil: a new soil and foliar broad spectrum incecticide. Brighton Crop Prot Conf Pest Dis 1:29–34; (1993) Chem Abstr 118:228183
80. Stetter J, Lieb F (2000) Innovation im Pflanzenschutz: Trends in der Forschung. Angew Chem 112:1792–1812.doi:10.1002/(SICI)1521-3757(20000515)112:10<1792::AID-ANGE1792>3.0.CO;2–5 (2000) Innovation in crop protection: trends in research. Angew Chem 39:1724–1744. doi:10.1002/(SICI)1521-3773(20000515)39:10<1724::AID-ANIE1724>3.0.CO;2–5
81. Theodoridis G (2006) Fluorine-containing agrochemicals: an overview of recent developments. In: Tressaud A (ed) Fluorine and the environment, vol 2. Elsevier, Amsterdam, p 145.
82. Jeschke P (2004) The unique role of fluorine in the design of active ingredients for modern crop protection. ChemBioChem 5:570–589. doi:10.1002/cbic.200300833
83. Hamon N, Shaw R, Yang H (1996) Worldwide development of fipronil insecticide. Proc Beltwide Cotton Conf 2:759–765
84. Cheon HG, Kim HJ, Kim SS, Choi JK, Kong. Y (1998) Pharmacological studies on the new quinoline derivative1-(2-methylphenyl)-4-[(3-hydroxypropyl)amino]-6-trifluoromethoxy-2,3-dihydropyrrolo[3,2-c] quinoline with potent anti –ulcer effect Arzneimittel-Forschung 48:1168–1171; (1999) Chem Abstr 130:191692
85. (a) Ning X, Li Q, Xiang H, Liu F, Cao J (2012) Apoptosis induced by 7-difluoromethyoxyl-5, 4′-di-n-ocytl genistein via inactivation of FoxM1 in ovarian cancer cells. Oncol Rep 27(6):1857–1864. doi:10.3892/or.2012.1739; (b) Xiang H, Liu F, Quan M, Cao J, Lv Y (2012)

7-difluoromethoxyl-5,4′-di-n-octylgenistein inhibits growth of gastric cancer cells through downregulating forkhead box M1.World J Gastroenterol 18:4618–4626. doi:10.3748/wjg.v18.i33.4618

86. Kashiwase H, Momota K, Ohmine T, Komai T, Kimura T, Katsube T, Nishigaki T, Kimura S, Shimada K, Furukawa H (1999) A new fluoroquinolone derivative exhibits inhibitory activity against human immunodeficiency virus type 1 replication. Chemotherapy 45:48–55. doi:10.1159/000007164; (1999) Chem Abstr 130:276301
87. Ohmine T, Katsube T, Tsuzaki Y, Kazui M, Kobayashi N, Komai T, Hagihara M, Nishigaki T, Iwamoto A, Kimura T, Kashiwase H, Yamashita M (2002) Anti-HIV-1 activities and pharmacokinetics of new arylpiperazinyl fluoroquinolones. Bioorg Med Chem Lett 12:739–742. doi:10.1016/S0960-894X(02)00003-3
88. Hayashi K, Takahata M, Kawamura Y, Todo Y (2002) Synthesis, antibacterial activity, and toxicity of 7-(isoindolin-5-yl)-4-oxoquinoline-3-carboxylic acids: discovery of the novel des-F(6)-quinolone antibacterial agent garenoxacin (T-3811 or BMS-284756). Arzneimittel-Forschung 52:903–913

Fluorinated Porphyrins and Corroles: Synthesis, Electrochemistry, and Applications

Stephen G. DiMagno, Justin C. Biffinger, and Haoran Sun

Contents

S.G. DiMagno (✉)
Department of Chemistry, University of Nebraska-Lincoln, Lincoln, NE, USA
e-mail: sdimagno@unlserve.unl.edu

J.C. Biffinger
Chemistry Department, US Naval Research Laboratory, Washington, DC, USA

H. Sun
Department of Chemistry, University of South Dakota, Vermillion, SD, USA

V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_14,

Abstract Fluorination alters the electronic structure of aromatic systems in a predictable manner, and these effects can be exploited in the design of aromatic, macrocyclic ligand systems for a variety of applications. Equally important is that ring fluorination has an exceptionally modest steric effect. Thus, fluorination permits electronic effects to be severed from structural changes that confound interpretations of other substituent effect studies. Here the preparation, physical properties, and applications of fluorinated and perfluoroalkylated porphyrins and corroles are briefly reviewed. Special attention is given to the preparation of the most useful fluorinated heterocyclic building blocks underlie most of the synthetic approaches to these macrocycles. Among the predictable changes fluorination engenders in the properties of these aromatic, tetrapyrrole ligands, the most commonly exploited in applications are: (1) an increase in oxidative stability, and (2) a decrease in ring nitrogen basicity that is reflected in more Lewis-acidic, electron-deficient chelated metal ions.

Keywords Porphyrins • Corroles • Fluorination • Fluoropyrroles • Macrocycle synthesis • Electrochemistry • Catalysis

1 Introduction

Fluorine's position at the end of the second row of the periodic table imparts the element with several unique advantages as a substituent. Fluorine is the smallest non-hydrogen substituent (atomic radius = 1.47 Å) but it is also the most electronegative. This combination of small steric influence and an outsized electronic effect means that fluorine can be used to modulate strongly the electronic properties of macrocyclic ligands, such as porphyrins and corroles, but fluorine can do so without inducing large structural deformations. Fluorination of porphyrins is generally performed with one of four goals in mind: (1) Fluorine is used to alter the electronic properties of the ligand system and the electronic properties of chelated metal ions; (2) to make the ligand less prone to oxidative decomposition reactions; (3) fluorination and perfluoroalkylation can drastically alter the solubility of this important ligand system; and (4) selective fluorination can introduce a useful magnetic label (^{19}F is S = ½) that provides excellent signal to noise ratio for NMR spectroscopy owing to the 100 % natural abundance of the magnetic isotope and the absence of background signals from fluoroorganic compounds in biology. This chapter will provide a current survey of synthetic techniques and precursors for preparing fluorinated porphyrins. The common nomenclature that defines the regiochemistry of porphyrin substitution is shown in Fig. 1. This review's focus is on porphyrins that possess fluorine substituents on the porphyrin ring or directly bonded to the meso- and/or beta-positions, however, perfluoroalkylated porphyrins will also be briefly discussed. Synthetic techniques for preparing these fluorinated macrocycles, the changes in ligand physical properties engendered by fluorination, and applications exploiting new electronic, magnetic, or solubility properties conferred by fluorination are addressed.

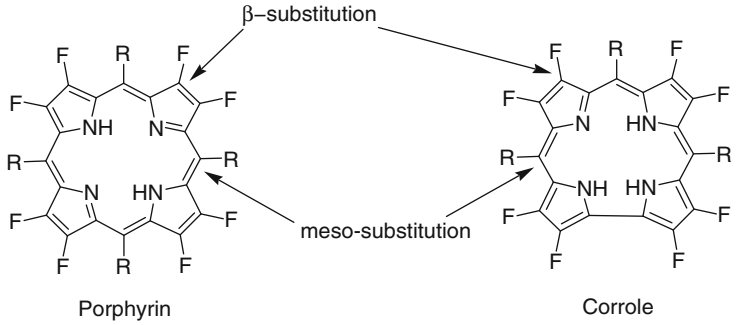


Fig. 1 Substitution patterns for porphyrins and corroles

Corroles (Fig. 1), like porphyrins, are aromatic macrocyclic tetrapyrroles. Their aromaticity distinguishes them from corrins, the prosthetic group that makes up the active sites of Vitamin B_{12} containing enzymes [1], but the direct pyrrole-pyrrole bond in corroles means that they differ fundamentally from porphyrins since full deprotonation results in a trivalent ligand coordination environment in the corroles. In contrast, the coordination sphere provided by the porphyrin is dianionic. The trivalent coordination environment of corroles makes greater stabilization of high-valent metal oxidation states possible, and an increased nucleophilicity and more negative reduction potential for the low-valent metal oxidation states of coordinated transition metal ions is noted for metallocorroles in comparison to metalloporphyrins. Even though corroles were first synthesized in 1964 as part of Vitamin B_{12} research [2], a scalable route to isolate substituted corroles was first reported only in 1999 [3]. After the first direct synthesis appeared, the number of corrole metal complexes synthesized expanded rapidly, enabling significant research into the basic physical and chemical properties of transition metal metallocorroles.

In the porphyrin and corrole macrocyclic aromatic systems, fluorine substituents are generally considered to be amphoteric, that is, they withdraw electron density through the σ-system while they donate electron density back to the π-system. This behavior is manifest in the Hammett σ-values; fluorine exhibits the greatest difference between σ_m and σ_p among the halogens [4]. Despite a partial compensation by back donation of electron density into the macrocycle π-system, fluorine substituents bear substantial negative charges; the net effect of fluorine substitution is to remove electron density from the aromatic system. In highly fluorinated ring systems the aromatic quadrupole moment is reversed, as has been amply demonstrated by studies of the 1:1 stacked complex of benzene and hexafluorobenzene [5]. This reversed quadrupole effect of fluorinated arenes has recently been used to stabilize pristine graphene sheets in solution [6]. The impact of perfluoro-substitution on the porphyrin system is similar, as is shown in electron density maps of porphyrin compared to octafluoroporphyrin [7]. The impact of fluorination upon observable physical properties (optical absorption, redox potential) depends strongly upon the position of the fluorine substituent(s) and the type, number, and location of the remaining substituents.

2 Synthesis of Fluorinated Porphyrins and Corroles

2.1 Fluorine Substitutions at the 3- and 4-Positions of Pyrrole

In contrast to the availability of several successful strategies for the direct perhalogenation of all porphyrin β-positions with chlorine and bromine, direct perfluorination has proved to be impossible to date. Tsuchiya and Seno reported a direct route for the fluorination of the porphyrin ring using 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin zinc(II) complex and cobalt fluoride or silver fluoride [8], however, the analytical characterization of the putative fluorinated complex was not in accord with definitive samples synthesized later [9, 10]. The synthesis of authentic β-octafluorinated porphyrins required the use of fluorinated pyrroles in the macrocyclization. The fluorinated pyrrole building block approach (Fig. 2) is less convergent, but it permits the synthesis of both selectively fluorinated and perfluorinated porphyrins and corroles. Given the practical success of the fluorinated building block approach, a review of fluorinated pyrrole synthetic methodology is in order to show examples of the potential variability in fluorine substitution patterns on the beta positions of porphyrins and corroles.

2.1.1 Mono-Fluorinated Pyrroles (1–4)

The first β-fluorinated pyrrole **(1)** used in the synthesis of the first partially fluorinated porphyrin was reported by Ogoshi and coworkers in 1985 [11]. The key step in the pyrrole synthesis was a light induced Balz-Schiemann reaction of the corresponding diazonium tetrafluoroborate to yield the β-fluoropyrrole in 17 % yield (Scheme 1). The 2-methyl group of the β-fluoropyrrole was subsequently oxidized using lead acetate to yield the formyl species which was then reduced to the hydroxymethyl derivative. Even though **(1)** is singly fluorinated, the substitution pattern is set of the resulting porphyrin is set be the substituents at the 2- and 5-positions, thus it would be difficult to create other porphyrin substitution patterns using this particular pyrrole. There have been several methods reported for

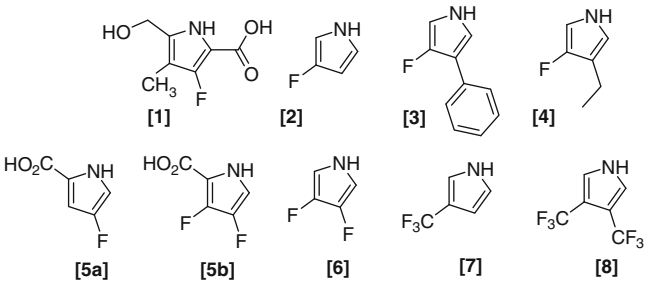
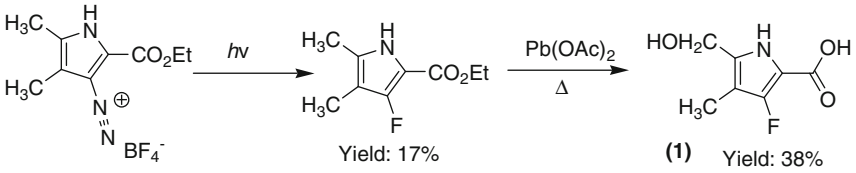
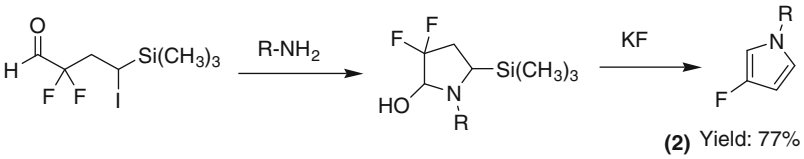


Fig. 2 Substitution patterns for fluorinated pyrroles

the synthesis of 3-fluoropyrrole **(2)**. The original routes introduced fluorine using N-F reagents (N-fluorobenzenesulfonimide, NFSI) by direct reaction with the pyrrole [12], or through the intermediacy of the lithated pyrrole [13]. The synthesis of 3-fluoropyrrole **(2)** was recently revisited. A Reformatsky reaction generated the silylated starting compound shown (Scheme 2) [14], was followed by facile cyclization and elimination reactions to provide the desired fluorinated pyrrole in good yield under mild reaction conditions.

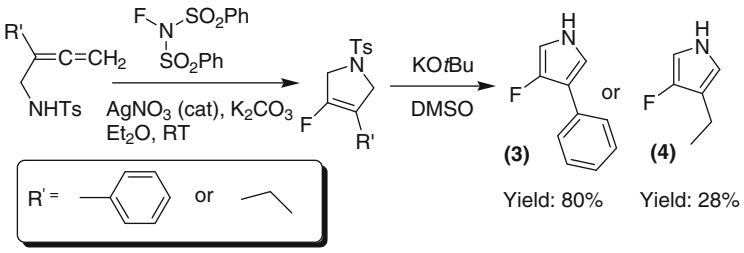


Scheme 1 Key reaction sequence to isolate mono-fluorinated precursor **(1)**



Scheme 2 The synthesis of 3-fluoropyrrole **(2)** after Reformatsky reaction

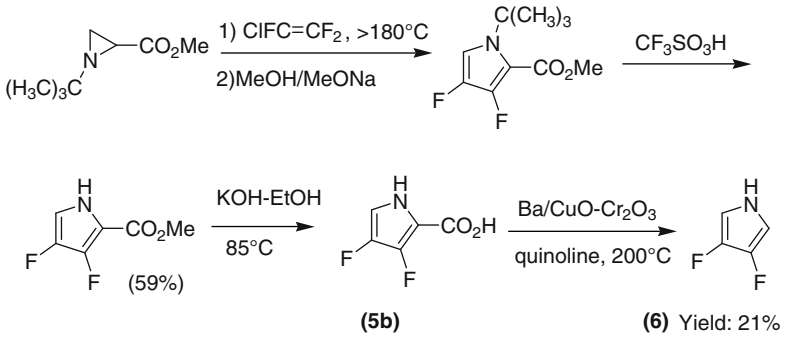
Liu and coworkers have recently published the synthesis of **(3)** and **(4)**, as well as several other fluorinated pyrrole analogues (not shown), by aminofluorination of allenes; the synthetic approach is shown in Scheme 3 [15]. This strategy takes advantage of a selective, silver-catalyzed intramolecular fluorination reaction, but the approach works best with substrates that possess electron-withdrawing R'-groups on the 3-position. Because of this limitation, the yield of **(3)** is significantly higher than **(4)**, 80 % versus 28 %, respectively. 4-Fluoro-pyrrole-2-carboxylic acid **(5a**, Fig. 2), synthesized from a fluorinated proline, was explored as a potential intermediate on the route to **(3)**, but only extensive decomposition products were observed when **(5a)** was subject to flash pyrolysis [16].



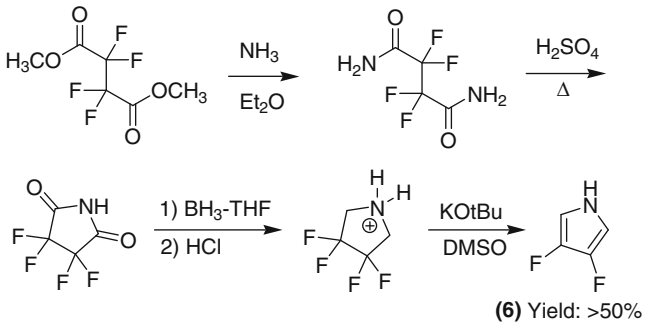
Scheme 3 Strategy of direct aminofluorination of allenes

2.1.2 3,4-Difluoropyrrole (6)

The interest in using ((**5a),** Fig. 2) as a precursor to synthesize **(3)** in high yields led to **5b** (Fig. 2) being considered as a potential precursor to 3,4-difluoropyrrole **(6)**. However, thermal decarboxylation yielded extensive decomposition. Leroy and Wakselman first reported preparation of 3,4-difluoropyrrole **(6)** in 1994 (Scheme 4). [17] Their route used a high temperature decarboxylation step that proved to be difficult to scale. The first scalable route for the isolation of **(6)** was reported by DiMagno and coworkers [18], who employed the multistep sequence outlined in Scheme 5. The key step in this approach was a double dehydrofluorination of tetrafluoropyrrolidinium chloride using potassium tert-butoxide in DMSO. The yields of **(6)** were >50 % for gram-scale preparations. One concern that both Leroy and Wakselman and DiMagno and coworkers reported is the volatility of 3,4-difluoropyrrole; this compounds sublimates rapidly at room temperature and careful handling at low temperature (< −5 °C) during isolation is required for efficient recovery.



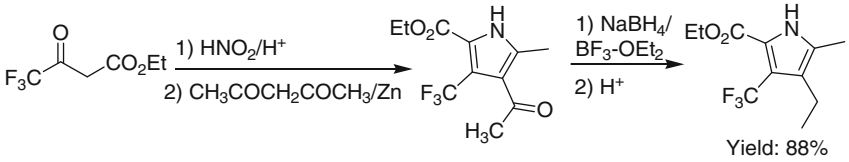
Scheme 4 Leroy synthetic route to 3,4-difluoropyrrole **(6)**



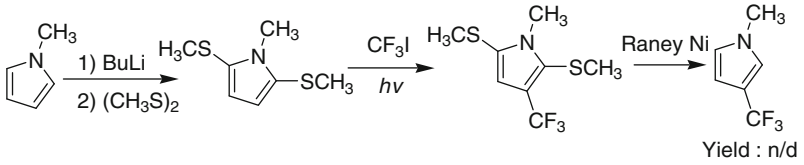
Scheme 5 DiMagno scalable synthesis of 3,4-difluoropyrrole **(6)**

2.1.3 3-Trifluoromethylpyrrole (7) and 3,4-bis(Trifluoromethyl) Pyrrole (8)

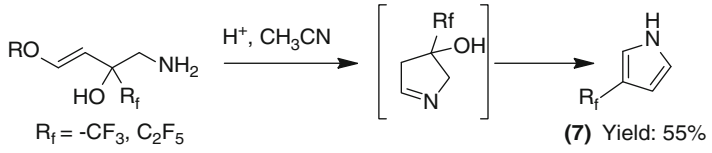
Pyrroles with fluoroalkyl groups in the β-positions are potentially useful precursors to extremely electron-deficient porphyrins. However, the preparation an isolation of simple pyrroles bearing only 3-trifluoromethyl or 3,4-bis(trifluoromethyl) substituents has proved to be exceedingly difficult. The first synthesis of 3-trifluoromethylpyrrole **(7)** employed a modified Knorr condensation starting with ethyl trifluoroacetoacetate (Scheme 6) [19, 20]. Subsequent synthetic routes used radical trifluoromethylation reagents; photolysis of difluorodiiodomethane or trifluoromethyl iodide precursors in the presence of pyrroles yielded some functionalized products (Scheme 7) [21]. Due to the instability of (7) the compound was not isolated and only NMR spectroscopic data were presented. An elegant recent synthetic approach to perfluoroalkylated pyrroles features 1, 2-additions of trimethylsilyl cyanide to perfluoroalkylated enones in the presence of base [22] (Scheme 8). After the reduction of the intermediate cyanohydrin with $LiAlH_4$, the resulting amino alcohol readily cyclized to form the pyrrole via an intramolecular Schiff base condensation. Subsequent dehydration gave the pyrrole **(7)** in good yield.



Scheme 6 Modified Knorr condensation for the synthesis of a 3-trifluoromethylpyrrole

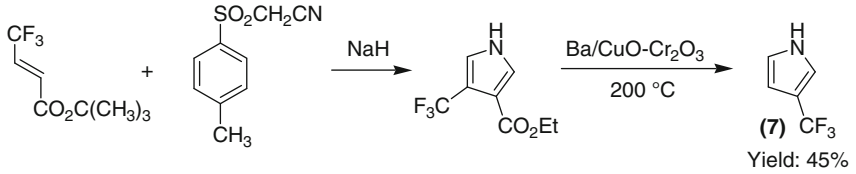


Scheme 7 Photolysis pathway to a 3-trifluoromethyl pyrrole

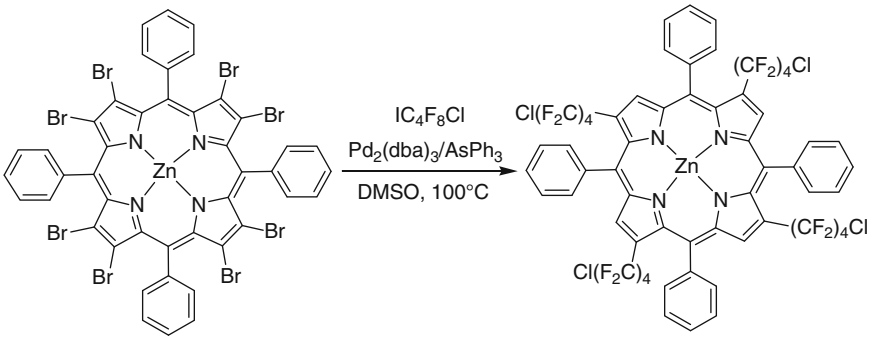


Scheme 8 Cyclization of an aminocarbonyl intermediate for the synthesis of **(7)**

Leroy and coworkers reported the first synthesis of 3,4-bis(trifluoromethyl)-pyrrole **(8)** in 1982 [23] and attempted to extend their synthetic methodology to the synthesis of **(7)** as well (Scheme 9) [24]. Unfortunately, due to the extremely electron-withdrawing nature of perfluoroalkyl groups, and the reliance of most porphyrin syntheses upon the generation of a cationic intermediate that reacts with the pyrrole by electrophilic aromatic substitution, the direct synthesis of porphyrins using **(8)** has not been reported [25]. The refractory behavior of extremely electron-poor pyrroles in traditional macrocyclization reactions, such as the Lindsey condensation [26], has spurred exploration of methods for direct trifluoromethylation by substitution of β-brominated or β-chlorinated porphyrins. Several reports of porphyrin perfluoroalkylation by halogen substitution have appeared [27, 28]. Perfluoroalkylation of β-octabrominated porphyrins by Pd-catalyzed cross-coupling is reported to be surprisingly efficient for the isolation of extremely sterically hindered perfluoroalkylated porphyrin derivatives (Scheme 10) [29].



Scheme 9 Decarboxylative synthesis of 3-trifluoromethylpyrrole **(7)**



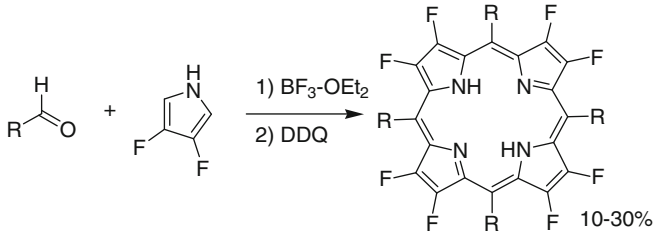
Scheme 10 Pd-catalyzed perfluoroalkylation of β-brominated porphyrins

2.2 Synthesis of β-Fluorinated Porphyrins and Corroles

2.2.1 β-Fluorine Substitution

The Ogoshi and Suzuki groups published the first confirmed report of partially β-fluorinated porphyrins in the mid-1980s. The Ogoshi group performed a tetramerization of the fluorine substituted pyrrole **(1)** with potassium ferricyanide,

resulting in first β-fluorinated porphyrin [11]. Suzuki et al. utilized selectively fluorinated dipyrromethene analogues to access fluorinated porphyrins efficiently [30]. The most common pathway for the synthesis of β-fluorinated porphyrins is based on the methodology reported by Lindsey in 1987 [26]. This one-pot macrocyclization features a Lewis acid-catalyzed (BF_3•OEt_2) condensation of aldehydes with pyrrole derivatives in anhydrous aprotic solvents (Scheme 11), followed by oxidation. This classic and versatile synthetic route also yields sapphyrins, corroles, expanded porphyrins, and N-fused porphyrins. On occasion the presence of other cyclized or linear polypyrroles can complicate the isolation of the desired porphyrin. DiMagno [9] and Leroy et al. [10] independently reported the first syntheses of 2,3,7,8,12,13,17,18-octafluoro-5, 10,15,20-tetraarylporphyrin in 1997 using the Lindsey methodology (Scheme 11). Typical yields of the octafluorinated porphyrins were reported to be between 10 and 30 %. The reliance of the Lindsey method on reactive aldehydes means that this approach does not allow for the synthesis of fluorinated analogues of naturally occurring porphyrins, in which the meso-positions are typically unsubstituted. However, several fluorinated analogues of naturally occurring porphyrin pigments have been prepared using alternative methods [31].



Scheme 11 The synthesis of 2,3,7,8,12,13,17,18-octafluoro-5,10,15,20-tetraarylporphyrin

In contrast to the relatively longstanding interest in β-fluorinated porphyrins, research on the preparation and study of β-fluorinated corroles is quite new. Corroles have been shown to have distinctive coordination chemistry and lower oxidation potentials compared to porphyrins, but the coordination environment offered by corroles can chelate transition metal ions with an avidity similar to that of porphyrins. [1, 32]. Figure 3 shows the structural differences among β-octafluorinated porphyrins, β-octafluorinated corroles, and β-octafluorinated (with meso fluorinated aryl rings) "Hangman" corroles.

The synthetic route into β-octafluorinated corroles is somewhat different from the Lewis acid-catalyzed macrocyclization under dilute conditions used for β-octafluoroporphyrins. The most successful route employs a neat condensation of pyrrole and aryl aldehydes, which was first demonstrated with non-fluorinated corroles [3, 33]. Solutions of these two reactants are combined in the presence of basic alumina, heated to evaporate the solvent, concentrate the reactants, and initiate cyclization. A DDQ oxidative quench results in several macrocyclic compounds, including the corrole (6–8 % yield) (Scheme 12).

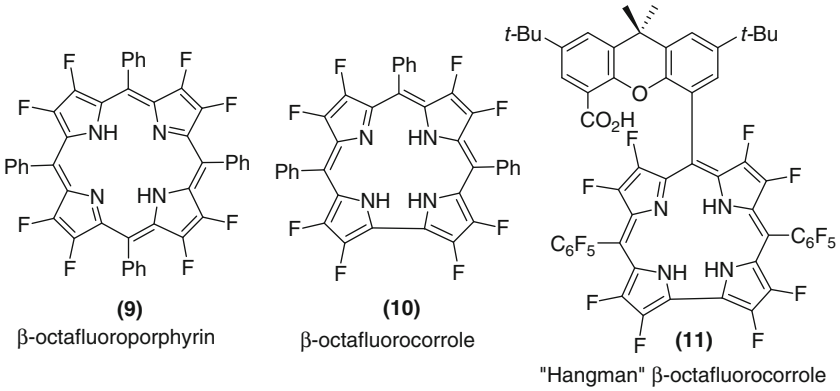
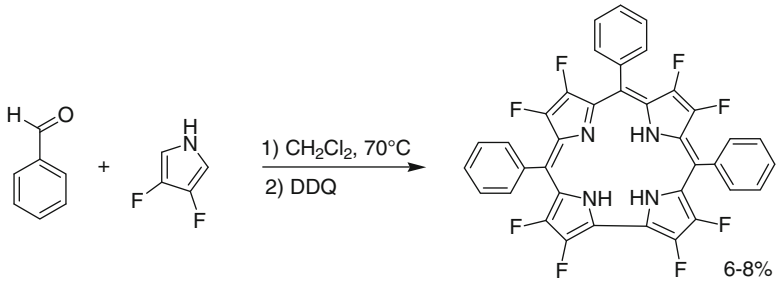


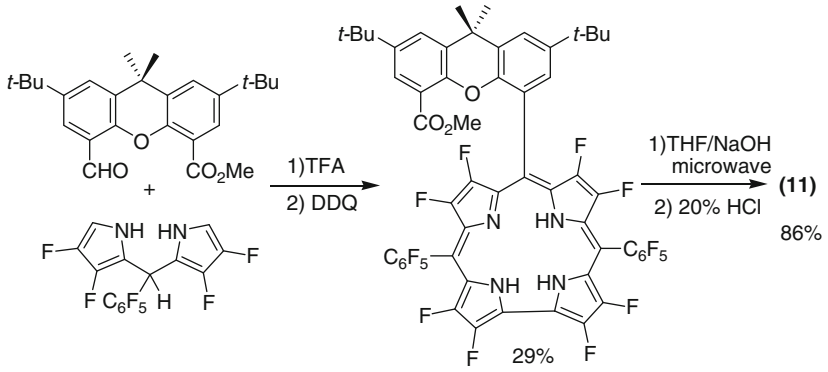
Fig. 3 Three variations on β-fluorinated macrocycles



Scheme 12 General pathway for the synthesis of β-fluorinated corroles

The first synthesis of a fluorinated corrole was of the perfluorinated derivative [34]. The synthesis of selectively fluorinated corroles was published later in the same year [35]. The alumina (in the case of the fluorinated corroles) most likely serves a dual role in the condensation, acting as both a catalyst and as a heterogeneous adsorbent to reduce the volatility of 3,4-difluoropyrrole.

In contrast to the "solvent-free" procedures used in the initial reports of fluorinated corrole syntheses, Chang, Ghosh, and Nocera and coworkers used the standard Lindsey approach to prepare "Hangman" β-octafluorinated corrole (Fig. 3, **(11)**), a prosthetic group that was used to develop electrocatalysts for water splitting reactions [36]. The Nocera synthesis used a modified Lindsey approach to obtain excellent yields of **(11)** (29 %) after chromatographic separation of the protected xanthene protected ester, which was subsequently deprotected in 86 % yield (Scheme 13).



Scheme 13 General synthesis of "Hangman" corroles

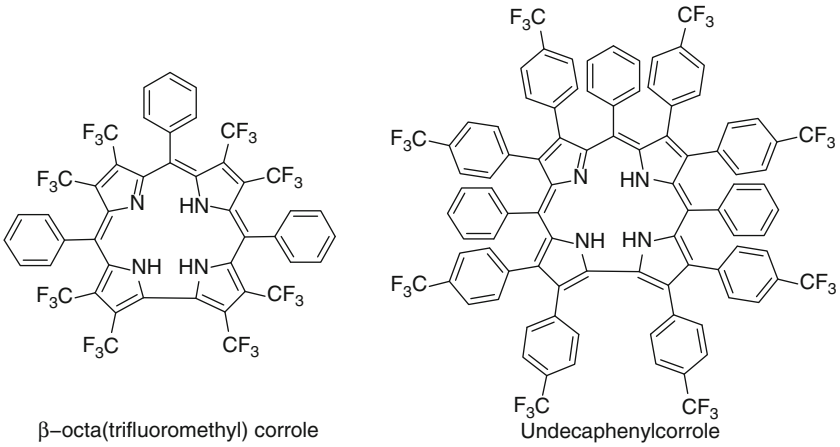
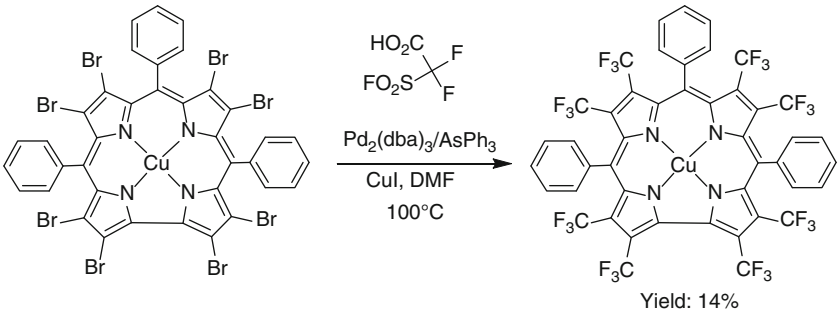


Fig. 4 Structure of trifluoromethyl and 4-(trifluoromethyl)phenyl substituted corroles at the β-position

2.2.2 β-Trifluoromethyl Substitution

The synthetic routes into β-trifluoromethylated corroles are significantly different from those used to prepare the β-fluorinated derivatives (Fig. 4). Direct trifluoromethylation of the β-position by halogen substitution in octabromocorroles was accomplished using Pd cross-coupling chemistry [37] identical to methodology used to isolate trifluoromethylated porphyrins (Scheme 14) [29, 38]. The β-octakis-(trifluoromethyl)corrole was shown to be one the most electron-poor trivalent ligands ever reported for copper, as was gauged by cyclic voltammetry.

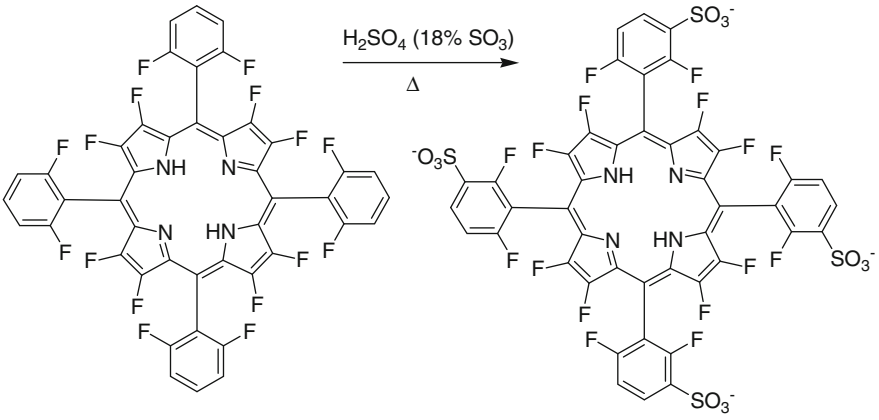


Scheme 14 Pd-coupling method for synthesis of copper β-trifluoromethyl corrole

In a somewhat different exploitation of the electron-withdrawing power of the perfluoroalkyl group, 4-(trifluoromethyl)phenyl substituents have been introduced onto the corrole β-positions to create undecaphenylcorrole (Fig. 4) [39], a member of a class of extremely sterically hindered corroles. The extremely crowded nature of undecaphenylcorrole may be useful for creating unique shape-selective catalysts or generating coordination complexes requiring steric protection from the formation of bimetallic dimers. The synthesis of undecaphenylcorrole was very similar to the trifluoromethylation route except that Suzuki-Miyaura coupling conditions of the aryl boronic acids were used. Here the trifluoromethyl groups serve to reduce the arene quadrupole moments of the β-phenyl substituents, thereby decreasing the $\pi-\pi$ repulsion of the substituents and leading to a more rigid, and less dynamic structure. Increased rigidity is potentially advantageous in applications relying on shape selective molecular recognition.

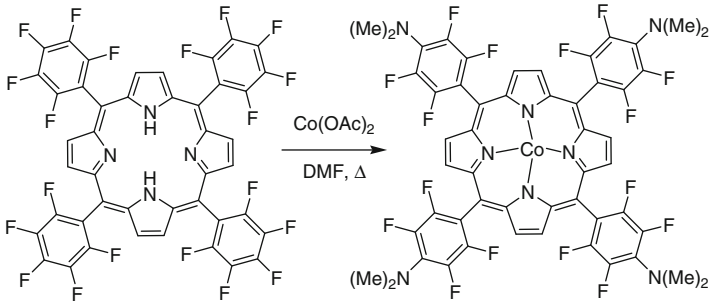
2.3 Synthesis of Porphyrins and Corroles Bearing Fluorine Substituents at the Meso Positions

In traditional acid-catalyzed macrocycle syntheses, the variation of substituents at the porphyrin meso position is limited largely by the availability of the appropriate aldehyde starting materials, and the facility with which the porphyrin products are separated from the reaction mixture. For in β-octafluorinated porphyrins, the most common substitution motif features aryl groups at the meso-positions. Post-cyclization aryl substituent group functionalization is sometimes necessary if the desired aryl substituents are not compatible with the macrocyclization conditions or if the aryl groups greatly complicate isolation of the porphyrins and/or corroles from the mixture of oligomeric polypyrrole side products. Such is the case if charged functional groups are desired on the meso-aryl substituents. For example, the preparation of sulfonated, water soluble β-fluorinated porphyrins was facilitated by post-cyclization sulfonation (20 % SO_3 in sulfuric acid) of 2,3,7,8,12,13,17,18-octafluoro-5,10,15-20-tetrakis(2,6-difluorophenyl) porphyrin to create the first heavily fluorinated water-soluble porphyrins (Scheme 15) [40]. To date, no β-fluorinated water-soluble corroles have been reported, but water-soluble corroles fluorinated at the meso-positions have been described [41, 42].

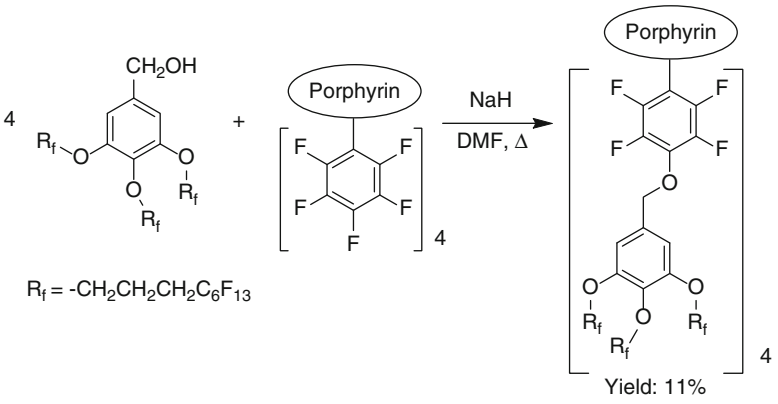


Scheme 15 Synthesis of water-soluble β-octafluorinated porphyrins

A second strategy for post-cyclization functionalization of fluorinated porphyrins is S_NAr modification of meso-pentafluorophenyl substituents. This reaction was first reported by Kadish and coworkers, who observed para-dimethylamine adducts during the metalation 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin in DMF (Scheme 16) [43]. Briza and coworkers utilized the reactivity of fluorinated aryl substituents to synthesize dendritic porphyrin assemblies [44]. They reported that a classical building block approach in which covalently linked aryl aldehyde precursors were subjected to classic Lindsey cyclization conditions provided very poor yields of the desired dendritic products,. In contrast, crosslinking of pre-formed 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin using S_NAr reactions proved to be a successful strategy (Scheme 17). Nucleophilic aromatic substitution at the para-position of tetrakis(pentafluorophenyl)porphyrins has also been used to create "clickable" thioester linkages [45]. To date, no dendritic β-octafluoro-meso-tetraarylporphyrins have been isolated; however, the S_NAr approach appears to be a promising general method for preparing such assemblies from derivatives such as 2,3,7,8,12,13,17,18-octafluoro-5,10,15,20-tetrakis(pentafluorophenyl)porphyrin.

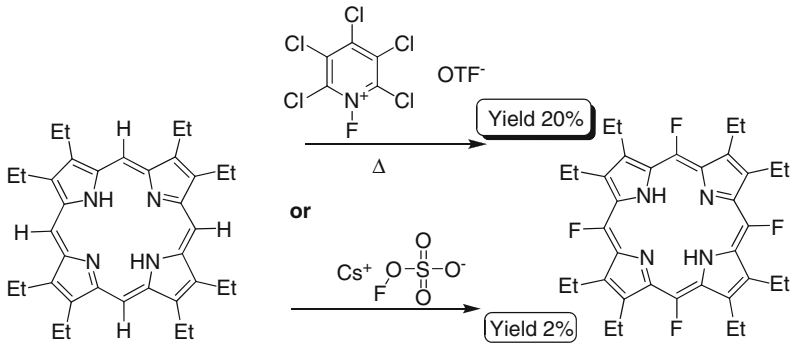


Scheme 16 Indirect method for the isolation of dimethylamine adducts to fluorinated porphyrin meso aryl groups



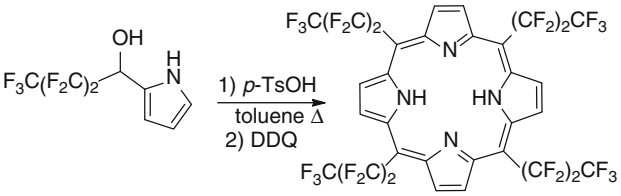
Scheme 17 Nucleophilic substitution on tetrakis(pentafluorophenyl)porphyrins

As an alternative to cyclization of fluorinated pyrrole precursors, several groups have advanced direct fluorination reactions of preformed porphyrins. Mirroring the history of fluorinated pyrrole synthesis, the earliest approaches to meso-fluorinated porphyrins exploited the thermal decomposition of the corresponding diazonium tetrafluoroborate analogue (Balz-Schiemann reaction), however these reactions generally provided poor yields of the desired fluorinated products (Scheme 1) [46]. The advent of "tamed" electrophilic fluorinating agents such as cesium fluoroxysulphate [47] and N-fluoropyridinium triflate [48, 49] allowed meso-fluorinations of 2,3,7,8,12,13,17,18-octaalkylporphyrins to be performed efficiently (Scheme 18). A few examples of meso-fluorinated porphyrins derived from naturally-occurring hemes have also been prepared in this manner, including 5-fluorodeuteroporphyrin IX dimethyl ester [46] and several mesoporphyrin derivatives [50–52]. Meso-fluorinated derivatives of protoporphyrin IX have not been prepared to date. Direct electrophilic aromatic fluorination also serves as a convenient route to monofluoro chlorophyll derivatives [53–55].

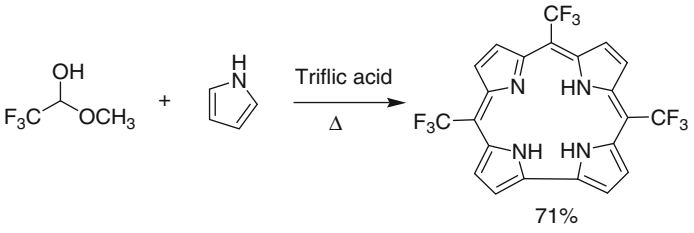


Scheme 18 Two methods for the direct fluorination at the porphyrin meso-position

Therien and DiMagno developed a modified condensation methodology that enabled the facile, high yield synthesis of a new class of electron deficient porphyrins that featured perfluoroalkyl groups fused directly to the porphyrin meso-positions (Scheme 19) [56]. Later work by Therien reported the photoelectron spectroscopy and potentiometric properties of these systems and demonstrated that meso-perfluoroalkylporphyrins are among the most electron-deficient porphyrinic species known. These species also differ from all other previously reported highly electron deficient porphyrins in that they possess long-lived, fluorescent excited states that can be utilized as potent photooxidants [57]. The ground-state electronic properties of these structures highlight their prospects as ligands [58–60]. The meso substituted trifluoromethyl corrole was isolated from a one-pot method using trifluoromethanesulfonic acid as the catalyst for cyclization (Scheme 20) [61]. Demonstrating the sensitivity of this type of condensation to water, the authors reported that a minimal yield of the corrole was obtained (<1 %) if trifluoroacetaldehyde hydrate was the starting material, but an excellent yield (71 %) was observed when trifluoroacetaldehyde methyl hemiacetal was employed.

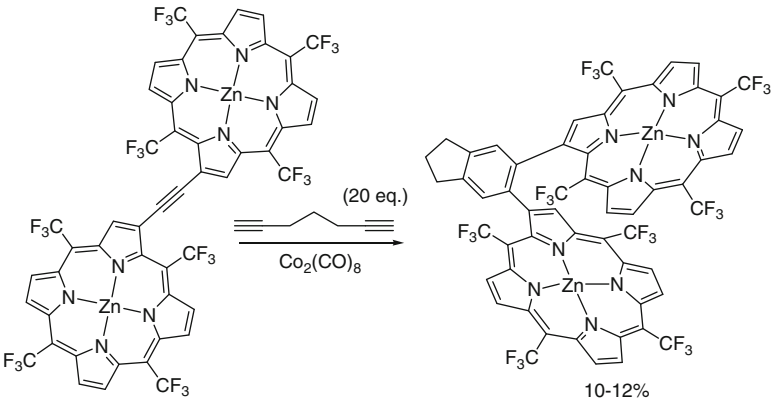


Scheme 19 Synthetic strategy for meso-perfluoroalkyl porphyrins



Scheme 20 Synthetic route to meso-substituted trifluoromethyl corrole

Metal-assisted cycloaddition reactions involving meso-perfluoroalkylated porphyrinic templates define a versatile methodology for the syntheses of both cofacial porphyrin structures and facially-functionalized (porphinato)metal species [62], and corresponding compositions that offer new opportunities for development of small molecule redox catalysts [63, 64]. Scheme 21 shows the versatile metal-mediated [2+2+2] cycloaddition step for the isolation of meso-perfluoroalkyl cofacial porphyrins that results in the purified indane complexes in 10–12 % yields. These cofacial complexes are directly applicable to multi-electron redox reactions such as oxygen or nitrogen reduction and even hydrocarbon oxidation.



Scheme 21 The synthesis of perfluoroalkylated cofacial metalloporphyrin complexes

3 Effect of Fluorination on Porphyrin and Corrole Electrochemistry and Electron-Transfer Mechanisms

By dint of its exceptional electronegativity, fluorine withdraws electron density from aromatic systems, thereby stabilizing these rings against one-electron oxidation and increasing their propensity to undergo one-electron reduction. Fundamental electrochemical studies (cyclic voltammetry, polarography, differential pulse voltammetry, and square wave voltammetry) have verified the relationship of the extent of fluorination to observed porphyrin ring redox potential. However, porphyrin ring fluorination does impart some surprising and peculiar effects on electron transfer rate constants and electrocatalytic behavior, and nonlinear transmission of electronic effects to chelated transition metal ions is observed. Here, we will briefly review the progress of the electrochemistry of fluorinated porphyrins, including how fluorination affects the thermodynamic, kinetic, and electrocatalytic properties of porphyrins and metalloporphyrins. The general abbreviations used in Sect. 3 are summarized in Figs. 5, 6, and 7.

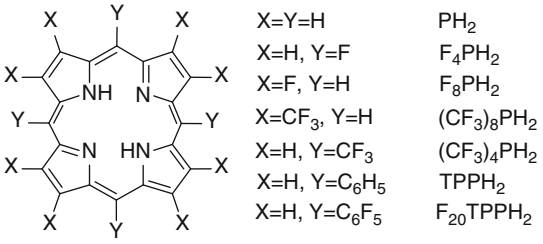
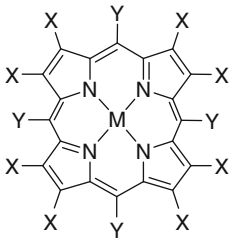


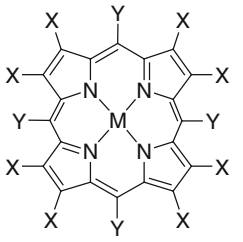
Fig. 5 Selected porphyrin structures



X=phenyl, Y=phenyl $DPPH_2$
X=phenyl, Y=4-fluorophenyl F_4DPPH_2
X=4-fluorophenyl, Y=pentafluorophenyl $F_{28}DPPH_2$
X=3,5-difluorophenyl, Y=pentafluorophenyl $F_{36}DPPH_2$ (a)
X=2,6-difluorophenyl, Y=pentafluorophenyl $F_{36}DPPH_2$ (b)
X=pentafluorophenyl, Y=pentafluorophenyl $F_{60}DPPH_2$
X=2,6-difluorophenyl, Y=phenyl $F_{16}DPPH_2$
M=2H, Fe

Fig. 6 Structures of selected dodecaphenylporphyrins

Fig. 7 Fluorinated tetraphenylporphyrin metal complexes



X=H, Y=C_6H_5 TPP
X=H, Y=C_6F_5 $F_{20}TPP$
X=F, Y=C_6H_5 F_8TPP
X=F, Y=C_6F_5 $F_{28}TPP$
M=2H, Co, Ru, Rh

3.1 Effect of Fluorination on the Redox Potentials of Porphyrins and Metalloporphyrins

Fluorine substituents on the porphyrin ring shift ring redox potentials to the positive. Much experimental and theoretical work has been performed to gain a fundamental understanding of the relationship between fluorination (including the position(s) and total number of fluorine substituents) and porphyrin electronic and thermodynamic properties. On the basis of the results of DFT calculations Ghosh described the impact of porphyrin ring fluorination on ionization potentials (IPs) and their relevance to electrochemical and photoelectron spectroscopy data [65]. The theoretical and experimental data showed that meso-substitution generally has a greater electronic effect on the porphyrin ring than the β-substitution on a per substituent basis. The lowest IP value of 5,10,15,20-tetrafluoroporphyrin (F_4PH_2) is about 0.49 eV higher than that of unsubstituted porphyrin (porphine, PH_2); and β-octafluoroporphyrin (F_8PH_2) possesses 0.84 eV higher IP value than that of porphine (Fig. 5). It is also interesting to note that the effect seen for β-perfluorination is roughly comparable to the effect of arene perfluorination in tetraphenylporphyrin, which shifts the lowest IP value to positive by 0.95 eV in $F_{20}TPPH_2$.

The large impact of meso-substituents is reflected in the lowest IP value of meso-tetrakis(trifluoromethyl)porphyrin (a shift of 1.74 eV compared to $TPPH_2$); this large shift is due to the strong electron withdrawing ability of the -CF_3 substituent (Fig. 5) as well as the comparatively large conjugative effects of the meso-arene groups in the $TPPH_2$ standard of comparison. Interesting enough, the lowest IP value of β-octakis(trifluoromethyl)porphyrin ($(CF_3)_8PH_2$) is identical to meso-tetrakis

(trifluoromethyl)porphyrin ($(CF_3)_4PH_2$); both meso-pertrifluoromethylation and β-pertrifluormethylation shift the ionization potential by approximately 1.3 eV from that of porphine. Using DFT calculation results as a basis for their analysis, Liao et al. discussed the effects of porphyrin fluorination on conversion between low-spin and high-spin states of cobalt porphyrins. The reduced ligand field and reduction in nitrogen basicity provided by the fluorinated ligand leads to greater accessibility of the high-spin state, consistent with previous experimental observations of the cobalt spin state conversion by DiMagno et al. [66, 67]. Kadish and coworkers reported comprehensive electrochemical studies showing fluorination's impact upon porphyrin redox potentials and axial ligation [68]. The electrochemical behavior of a series of free base and metalated dodecaphenylporphyrins (DPPs) with varying degrees of fluorination of the peripheral phenyl rings (FxDPPs) were investigated for studying electronic effects in nonplanar porphyrins (Fig. 6). The reduction potentials of FxDPPs were shown to be dependent upon the number of fluorine substituents on the phenyl rings. The maximum reduction potential shift is in the range of 0.58 V to 0.79 V for $ClFe^{(III)}F_{36}DPP$ compared to $ClFe^{(III)}DPP$. In addition, the extent of reversibility of the redox reactions was sensitive to the extent of phenyl fluorination.

Che and coworkers reported fluorination's effects on the $Ru^{VI/V}$ redox potential of ruthenium 5,10,15,20-tetraphenylporphyrins (Fig. 6) and the effects of fluorination on rate constants of metalloporphyrin catalyzed C-H activation reactions [69]. The experimental results show that the rate constants of C-H activation reactions correlate well with the C-H bond dissociation energies. This correlation indicates a hydrogen-atom abstraction mechanism for Ru porphyrins in C-H activation reactions. DiMagno et al. reported the systematic effects of β-fluorination on 5,10,15,20-tetraarylporphyrin redox potentials and solution phase electrochemical behavior [7, 9, 40, 70, 71]. For free base porphyrins and zinc porphyrins, β-perfluorination results in 0.3–0.46 V positive shifts in the redox potentials of the porphyrin ring. The corresponding perfluorination of meso-phenyl groups contributes a similar value of positive shift on the redox potentials [9], and these two effects are additive. For cobalt porphyrins, the porphyrin ring first oxidation of perfluorinated tetraphenylporphyrin $Co(F_{28}TPP)$ shifts 800 mV compared to CoTPP; indicating that the effects of β-perfluorination and aryl ring perfluorination are almost perfectly additive. However, β-perfluorination (F_8TPP) and perfluorination ($F_{28}TPP$) of cobalt porphyrins only changes the $Co^{3+/2+}$ redox potential by 170 mV and 403 mV, respectively, compared to CoTPP [70], indicating that there is a significant attenuation of the fluorine substituents' effects on the chelated transition metal by the macrocycle sigma bonded framework (Fig. 7).

Leroy et al. reported the synthesis and characterization of partially β-fluorinated porphyrins (e.g. $\beta\text{-}F_4TPP$) [16]. They found that the redox potential of $\beta\text{-}F_4TPP$ is the average of TPP and $\beta\text{-}F_8TPP$. Therien and coworkers discussed the formation of an $Fe^{(II)}$ porphyrin with the very electron-deficient 5,10,15,20-tetrakis(perfluoropropyl)porphyrin ligand [59]. The redox potential of $Fe^{(III)/(II)}$ redox couple shifts around 400–500 mV more positive compared to typical $Fe^{(II)}$porphyrins. In contrast, the zinc complex of the same porphyrin ligand showed a 670 mV positive redox

potential shift on both first reduction and first oxidation [56] compared to ZnTPP. The structural factors resulting in the highly efficient transfer of porphyrin substituent electronic effects to the metal center are summarized by Therien et al.

3.2 *Effect of Fluorination on Electron Transfer Kinetics of Porphyrins*

Despite the many reports on the effects of fluorination on redox potentials of the porphyrins, work on the effects of fluorination on the electron transfer (ET) kinetics of porphyrins are rarely presented in the literature. DiMagno and coworkers reported that β-fluorination of metalloporphyrins not only shifted the ring and metal redox potentials significantly to positive, but also changed the kinetics of homogeneous and heterogeneous ET reactions [70]. For example, the homogeneous electron transfer (ET) self-exchange rate constant for the Co^{3+}/Co^{2+} redox couple of $CoF_{28}TPP$, is 10^{-7} times lower than that of CoTPP in solution. The heterogeneous ET rate constant for $CoF_{28}TPP$ is 10^{-4} times lower than that of CoTPP at a glassy carbon electrode (Fig. 7). These studies pointed to a potential strategy for modulating electron transfer rate constants in metalloporphyrins over a large range: substituents that lower C-C, C-N, and N-M vibrational frequencies or minimize porphyrin orbital overlap with the metal-centered orbital will increase k_{ET}. Thus, one could interpret that the heme ruffling noticeable in cytochrome c, an electron transfer protein, as nature's exploitation of this design strategy. This design strategy could potentially benefit the design of new electrocatalysts, for example, in the preparation of metalloporphyrin-based molecular catalysts for fuel cells.

3.3 *Electrochemistry of Fluorinated Corroles*

Few articles describing the electrochemical studies of fluorinated corroles appear in the literature. Ghosh et al. reported the first synthesis of β-octafluorocorrole and triaryl derivatives thereof (Fig. 8) [35]. The fundamental physicochemical properties of these octafluorocorroles were characterized extensively, and compared to those of benchmark (unsubstituted) corroles and β-octabromocorroles [72]. The first ring oxidation potential of β-octafluorocorrole shifts by approximately +400 mV compared to that of the unsubstituted ligand. This effect is even more pronounced with the trifluoromethylated corrole copper complex [37]. Despite the fact that fluorine is more electronegative than bromine, the oxidation potential of β-fluorinated corrole is the same as the oxidation potential of β-bromocorrole. Kadish recently reported the electrochemical and spectroelectrochemical properties of corroles and protonated corroles sporting electron-donating and electron–withdrawing substituents [73, 74]. Extensive structural and electrochemical analyses of Cu(II) and Au(III) fluorinated corrole complexes [75] affirm that corroles stabilize the high

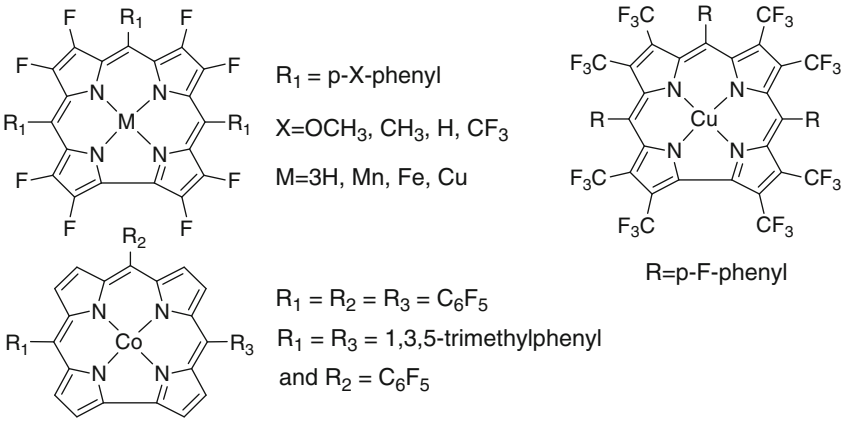


Fig. 8 Representative corroles and their transition metal complexes

valent oxidation states of these metal ions (compared to the corresponding metalloporphyrins) because of the trivalent nature of the corrole ligand. This feature has been promoted in attempts to design high-valent metal oxo complexes of corroles for water oxidation catalysts. For such compounds to be functional, fluorination and trifluoromethylation serve as potential methods to stabilize the corrole ligand system against the oxidative degradation.

4 Effect of Fluorination on Electrocatalytic Reactions and Other Applications

4.1 Catalytic Redox Reactions

Metalloporphyrins have been studied as electrocatalysts for the reduction of oxygen [76–78], CO_2 [79, 80], and protons [81] for more than three decades. Recently, researchers have attempted to exploit the positive shifts in chelated metal ion redox potentials engendered by fluorination to decrease the overpotential for these three classes of reduction reactions. Girault and coworkers reported electrocatalytic reduction of oxygen by free base fluorinated porphyrins at liquid/liquid interface [82]. In the presence of a weak electron donor (ferrocene), the deprotonated form of 5-(4-aminophenyl)-10, 15, 20-tris(pentafluorophenyl)porphyrin catalyzes the reduction of oxygen to hydrogen peroxide at a water/1, 2-dichloroethane interface. However this catalytic reaction only occurs in the presence of the tetrakis (pentafluorophenyl)borate (TB^-) counterion in the organic phase. Neta and coworkers reported CO_2 reduction at significantly less negative potentials with fluorinated cobalt porphyrins compared to the corresponding CoTPP derivatives [83]. Rhodium octaethylporphyrin has been shown to be an active electrocatalyst for CO oxidation

for fuel cell applications [84]. DiMagno and coworkers reported that β-fluorinated, water-soluble rhodium porphyrins catalyze the preferential oxidation of carbon monoxide in presence of hydrogen at low temperature [71]. The PROX reaction is important for hydrogen fuel cell application in which ppm levels of CO could poison the Pt catalyst. The selectivity of the CO oxidation and increased CO oxidation rate with fluorinated porphyrin rhodium complexes is likely due to the shift of the redox potential and increased acidity of the corresponding Rh(III) hydride complex.

The oxidation of water to dioxygen and protons is a key reaction for artificial photosynthetic catalysis [85, 86]. Both cobalt hangman porphyrins [87] and cobalt hangman corroles [88] are viable catalysts for water oxidation. Recently, cobalt (II) hangman β-octafluorinated corrole catalysts with engineered carboxylic acid groups (to facilitate proton transfer) showed improved reactivity compared to the corresponding non-halogenated derivatives (Fig. 3) [36]. Quantum chemical modeling of the fluorinated hangman corrole suggests that fluorination leads to stabilization of the reactive radical cation [89].

The selective oxidation and functionalization of saturated and unsaturated hydrocarbons is one of the most active application areas for halogenated porphyrins; the improved performance of fluorinated metalloporphyrins in alkane hydroxylation and alkene epoxidation has been documented in several studies [90, 91]. The two principle reasons for the use of fluorinated porphyrins in this particular application are that fluorination increases catalyst longevity under the highly oxidizing conditions required for C-H oxidation, and that the transmission of electronic effects to the metal center yields more reactive, high-valent transition metal oxo intermediates. Originally, the goal of these studies was to create biomimetic cytochrome P450 analogues. Fluorination permits electrochemical tuning of the reactive M(IV)-oxo radical cation oxidation state [69, 92, 93, 94], where M = Fe, Mn, Ru. However, most hydrocarbon oxidation reaction exploiting electron-deficient metalloporphyrins have been proven to proceed through autoxidation pathways, where peroxide intermediates propagate the radical chains. The goal of using electron-deficient metalloporphyrins to perform concerted, selective C-H oxidation has remained elusive [95].

In an alternative di-metalloradical approach to C-H functionalization with metalloporphyrins, Wayland and coworkers have shown that rhodium porphyrins are able to perform selective and reversible C-H activation of alkanes [96–99]. The di-metalloradical approach relies on the formation of strong Rh-H and Rh-C bonds to drive the activation. Fluorination of the porphyrin periphery weakens these bonds to rhodium slightly, but has a much larger impact upon the Rh(III)/Rh(I) redox couple; the enhanced stabilization of the Rh(I) state in the fluorinated porphyrin ligand allows alkyl group transfer by nucleophilic attack on the alkyl-rhodium(III) complex to be favorable [100].

Metalloporphyrins and metallocorroles have been shown to acts as alkene aziridination catalysts, and the extent of macrocycle halogenation has been shown to correlate with catalyst performance. Mn(III) complexes of 5,10,15-Tris(pentafluorophenyl) corrole are active in aziridination catalysis [101, 102]; electron-withdrawing substituents on the corrole are required to facilitate amide transfer to the alkene. Fluorination of corroles also leads to stable metal imide intermediates during aziridination reactions.

4.2 Biomedical Applications

Photodynamic therapy (PDT) is a cancer treatment modality in which diseased tissue is ablated by singlet oxygen, a cytotoxic species, which is generated by visible or near-IR irradiation of a dye that is localized within the vicinity of a tumor. In order to produce singlet oxygen, the dye, or photosensitizer, must possess a readily accessible excited state triplet [103]. Excited state of the photosensitizer reacts with (ground state triplet) dioxygen by triplet-triplet annihilation to generate the reactive, short-lived excited state singlet oxygen. The relatively short lifetime and short diffusion length of singlet oxygen makes PDT a potentially less disruptive therapy than unselective chemotherapeutic agents, since the reactive species is only formed and consumed in the immediate vicinity of the point of illumination. Significant research has been focused on porphyrins for PDT, since they absorb relatively long-wavelength visible light strongly (red to near IR absorption is optimal for tissue penetration), and because these pigments localize in cancerous tissues [104].

Fluorinated porphyrins and corroles show great potential as agents in photodynamic therapies because they are more photostable (longer lasting) than their non-fluorinated counterparts. Fluorinated porphyrins and corroles can also be used as contrast agents for imaging, in addition to exhibiting cytotoxic effects. For example, fluorinated gallium corrole complexes not only localize in tumor cells, but their emission can be used to locate the tumor cells to which these compounds are cytotoxic. In one example, fluorinated ruthenium porphyrins were shown to be more toxic to melanoma cells than to fibroblast cells [105]. Shao and coworkers recently published a comparison of three series of meso-substituted fluorophenyl corroles coordinated to gallium(III) as potential photodynamic therapy agents (Fig. 9) [106]. Swavey and co-workers recently reported that visible-light-induced photocleavage of DNA by 5-(pentafluorophenyl)-10,15,20-tris(4-pyridyl)porphyrin was significantly more efficient that exhibited by the corresponding non-fluorinated derivatives [107].

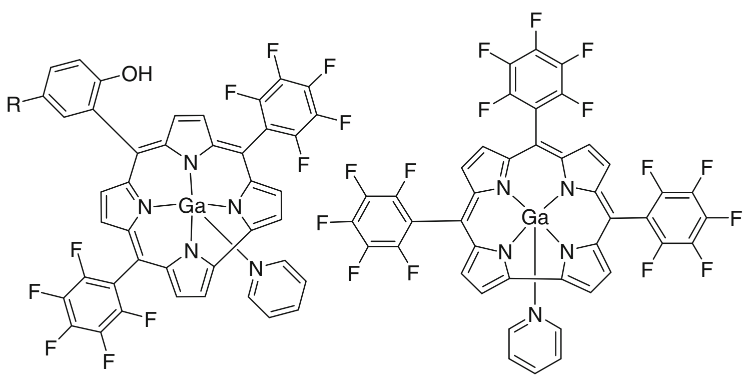


Fig. 9 Selected Gallium(III) fluorinated corroles used as PDT agents

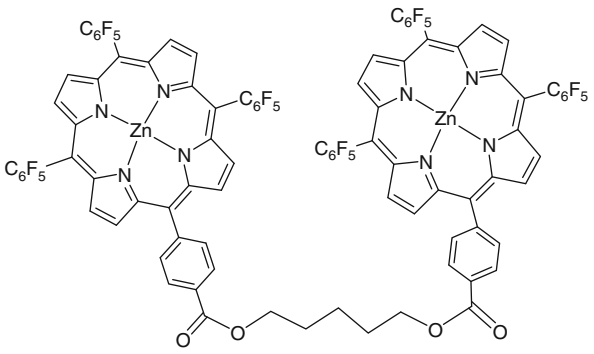


Fig. 10 Structure of a fluorinated zinc(II) chiroptical "tweezer"

A recent excellent review summarizes comprehensively biomedical applications using fluorinated porphyrins and corroles [108].

4.3 Stereochemical Resolution

The development of techniques for the determination of the absolute stereochemistry of chiral diols, amino alcohols, and diamines present in natural products is a dynamic area of research. Non-fluorinated porphyrin "tweezer" compounds (similar to the structure in Fig. 10) have been used to determine the absolute stereochemistry of chiral alcohols, amines, and carboxylic acids [109–111]. However, weak binding of chiral Lewis bases is sometimes observed to the metal center of electron-rich porphyrins. Thus, fluorinated, electron-deficient metalloporphyrins were investigated for use in chiroptical sensor applications. The increased Lewis acidity in the fluorinated metalloporphyrins is expected to increase the binding equilibrium constant for the exogenous chiral ligands. A dimeric porphyrin "tweezer" zinc complex bearing pentafluorophenyl groups (Fig. 10) was shown to bind chiral Lewis bases efficiently, permitting their absolute stereochemistry to be determined using Exciton Circular Dichroism (ECCD). The binding to the chiral compound induces a defined helical orientation of the two metalloporphyrin chromophores, which then produces a predicable ECCD spectrum. [112].

4.4 Dyes for Optics

Pt(II) porphyrins are interesting dyes for optical sensor applications because they have long excited state lifetimes, large Stokes shifts, and room temperature phosphorescence [81, 113]. Fluorinated derivatives of Pt(II) porphyrins show improved hydrophobicity and enhanced oxidative stability; thus, they have been utilized as luminescent dyes. In addition, as was described previously, the use of pentafluorophenyl groups on the porphyrin meso-position has permitted the direct

functionalization of the porphyrin through S_NAr reactions. The ability to modify the porphyrin after the macrocycle is formed permits the preparation of diverse porphyrins bearing different substituents, (and different photophysical properties) to be prepared with a minimum of synthetic effort. Zhao and coworkers have demonstrated a functional optical oxygen sensor for seawater applications that exploits the unique properties of a xerogel containing Pt(II) 5,10,15,20-tetrakis(pen tafluorophenyl)porphyrin [114]. However, porphyrin aerogel sensor systems suffer from pigment leaching and migration if soluble porphyrin complexes are merely trapped in the matrix. Leaching of the sensor pigments was addressed by Koren and coworkers, who bound Pt(II) tetrakis(pentafluorophenyl)porphyrins to an aerogel matrix using a thiol-based click-coupling strategy [45]. Covalent ligation of the porphyrins was shown to improve the long-term stability of the sensor platform without compromising the desirable photophysical properties or oxygen sensing ability of the fluorinated porphyrin complexes.

4.5 Dyes for Solar Cells

The enormous optical cross section of metallocorroles and metalloporphyrins has spurred attempts to fabricate dye-sensitized solar cells, electroluminescent devices, and photo-driven water splitting catalysts incorporating these dyes. There are two factors that limit conversion efficiencies these devices. The first is the limited diffusion length of excited electrons over a micron length scale, and the second is the destructive overlap between the dye absorption spectrum and wavelength of light absorbed. As has been discussed extensively above, the potential energy of the delocalized π-system of the porphyrin can be modulated extensively by substitution with electron-donating and electron-withdrawing groups.

The modulation of photophysical properties and dye lifetime that result from ring fluorination can lead beneficial effects for dye-sensitized solar cell performance. A straightforward comparison of photoelectric activity of these cells in which meso-substituted porphyrins featuring variable fluorine and chlorine substitution was published recently [115]. However, the results from this study indicated that chlorine substitution provided an enhanced photocurrent output in comparison to the corresponding fluorinated derivatives.

Materials that contain “push-pull” porphyrins been used in dye-sensitized solar cells. By introducing electron-withdrawing and electron-donating groups to the porphyrin periphery, one can modulate the light harvesting properties of these dyes and typically produce higher power conversion efficiencies (approximately 11 %) [116]. Mathew and coworkers reported a “push-pull” porphyrin zinc(II) system with 4-carboxy-2, 3, 5, 6-tetrafluorophenylethynyl anchoring group at the meso-position (Fig. 11) [117]. Unfortunately, their power conversion efficiency was only 4.6 % which suggests that the fluorine substitution in this case led to a deleterious interaction with the TiO_2 surface. Nevertheless, the results suggested that the design of future solar cells using these materials could be successful.

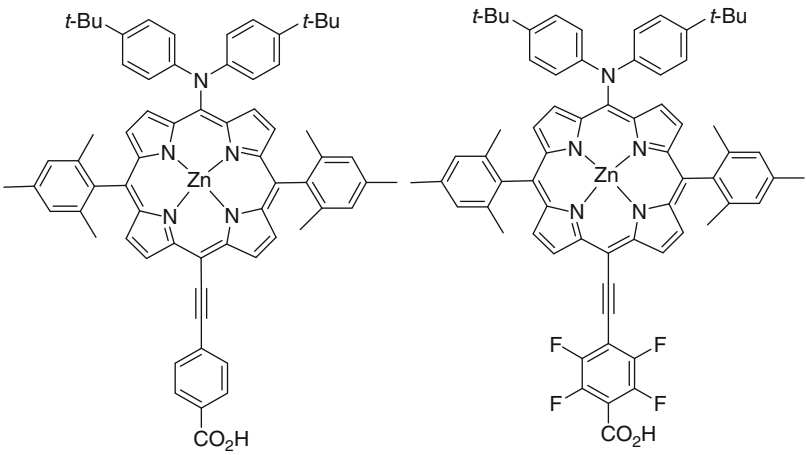


Fig. 11 Zinc porphyrin complexes used for "Push-Pull" dye sensitizer

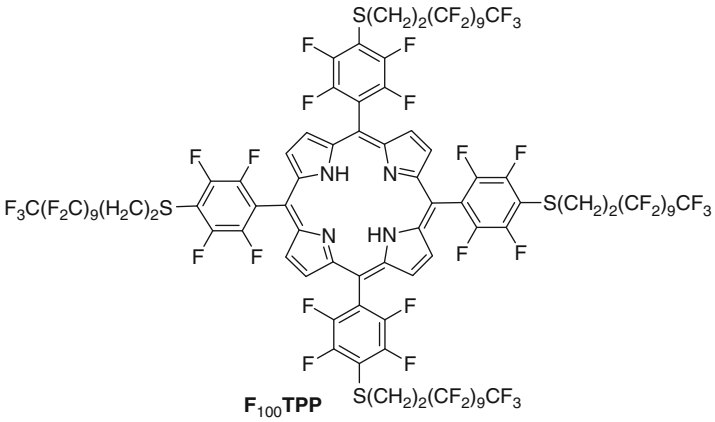


Fig. 12 Structure of $F_{100}TPP$

A recent approach to creating thin photoactive films for solar cell applications exploits supramolecular interactions of fluorinated porphyrins and fullerenes. Co-crystallization of fullerenes (C_{60}) with fluorinated porphyrin free-bases leads to high quality composite films, while non-fluorinated porphyrins and C_{60} typically phase separate during the coating process. The supramolecular C-F → C(fullerene) interaction between the perfluoroalkylated derivative of tetrakis(pentafluorophenyl) porphyrin, $F_{100}TPP$, (Fig. 12) and C_{60} permits thin, stable, presumably layered photo-responsive films of these materials to be constructed [118]. Even though the actual crystal structure of $F_{100}TPP$ and C_{60} was not determined, quenching of the fluorescence after the addition of the fullerene suggested that the two macromolecules were in close proximity, and that the composite functional material could be well ordered.

5 Conclusions

The unique advantages of fluorine substitution in aromatic systems can be applied to porphyrin and corrole ligand systems to generate improved performance in several applications. A fundamental understanding of the impact of fluorination is essential to the successful in implementation of fluorination strategies. In porphyrins, direct ring fluorination is associated with (1) a minimal steric perturbation, (2) an increase in the in-plane bonding frequencies of the porphyrin C-C and C-N bonds, (3) a decrease in electron density in the porphyrin ring, that may result in inversion of the porphyrin ring quadrupole moment, (4) stabilization of the porphyrin against oxidation, (5) anodic shifts in the ring redox potentials, (6) susceptibility of the ring toward nucleophilic attack, (7) enhanced Lewis acidity and electrophilicity of chelated metal ions, (8) predictable changes in electron transfer rate constants, and (9) small changes in the photophysical properties that are largely the result of increased ring rigidity. Substitution of porphyrins and corroles with perfluoroalkyl groups generally has a larger electronic impact than direct fluorination, but this effect is complicated by large steric effects, which can lead to widely varying properties of perfluoroalkylated metalloporphyrins compared to the directly fluorinated compounds. Taken as a set, these two substituent groups allow the porphyrin chemist to prepare dyes, catalysts, and molecular materials that span a wide range of properties despite the fact that the core "active element", the porphyrin or corrole macrocycle, remains the same.

Acknowledgements SGD acknowledges the National Science Foundation for support of this work, HS acknowledges the Army Research Office for financial support (grant number W911NF-09-1-0472), and JCB acknowledges ONR/NRL BLK 6.2 block program for supporting this work.

References

1. Aviv-Harel I, Gross Z (2011) Coordination chemistry of corroles with focus on main group elements. Coord Chem Rev 255(7–8):717–736
2. Johnson AW, Kay IT (1964) The pentadehydrocorrin (corrole) ring system. In: Proceedings of the Chemical Society, London, March, pp 89–90
3. Gross Z, Galili N, Saltsman I (1999) The first direct synthesis of corroles from pyrrole. Angew Chem Int Ed 38(10):1427–1429
4. Hansch C, Leo A, Taft RW (1991) A survey of Hammett substituent constants and resonance and field parameters. Chem Rev 91(2):165–195
5. Battaglia MR, Buckingham AD, Williams JH (1981) The electric quadrupole moments of benzene and hexafluorobenzene. Chem Phys Lett 78(3):421–423
6. Oyer AJ, Carrillo J-MY, Hire CC, Schniepp HC, Asandei AD, Dobrynin AV, Adamson DH (2012) Stabilization of graphene sheets by a structured benzene/hexafluorobenzene mixed solvent. J Am Chem Soc 134(11):5018–5021
7. Sun H, Biffinger JC, DiMagno SG (2005) Ion pairing in tetraphenylporphyrin oxidation: a semiquantitative study. Dalton Trans 19:3148–3154
8. Tsuchiya S, Seno M (1989) Novel synthetic method of phenol from benzene catalyzed by perfluorinated hemin. Chem Lett 2:263–266

9. Woller EK, DiMagno SG (1997) 2,3,7,8,12,13,17,18-Octafluoro-5,10,15,20-tetraarylporphyrins and their zinc complexes: first spectroscopic, electrochemical, and structural characterization of a perfluorinated tetraarylmetalloporphyrin. J Org Chem 62(6):1588–1593
10. Leroy J, Bondon A, Toupet L, Rolando C (1997) 2,3,7,8,12,13,17,18-Octafluoro-5,10,15,20-tetraphenylporphyrin: first synthesis and x-ray crystal structure of the Zn II complex. Chem Eur J 3(11):1890–1893
11. Onda H, Toi H, Aoyama Y, Ogoshi H (1985) Fluoropyrroles and tetrafluoroporphyrins. Tetrahedron Lett 26(35):4221–4224
12. Barnes KD, Hu Y, Hunt DA (1994) Electrophilic fluorination of a highly functionalized pyrrole. Synth Commun 24(12):1749–1755
13. Dvornikova E, Bechcicka M, Kamienska-Trela K, Krowczynski A (2003) Synthesis and NMR studies of 2- and 3-fluorosubstitued five-membered heterocycles. J Fluor Chem 124(2):159–168
14. Kim BM, San Q-Z, Bhatt LR, Kim SK, Chai K-Y (2010) Efficient preparation of 3-fluoropyrrole derivatives. Bull Korean Chem Soc 31(1):31–34
15. Xu T, Mu X, Peng H, Liu G (2011) Silver-catalyzed intramolecular aminofluorination of activated allenes. Angew Chem Int Ed 50(35):8176–8179
16. Leroy J, Porhiel E, Bondon A (2002) Synthesis and characterization of partially β-fluorinated 5, 10, 15, 20-tetraphenylporphyrins and some derivatives. Tetrahedron 58(33):6713–6722
17. Leroy J, Wakselman C (1994) First access to 3, 4-difluoro-1H-pyrrole. Tetrahedron Lett 35(46):8605–8608
18. Woller EK, Smirnov VV, DiMagno SG (1998) A straightforward synthesis of 3,4-difluoropyrrole. J Org Chem 63(16):5706–5707
19. Ogoshi H, Homma M, Yokota K, Toi H, Aoyama Y (1983) Synthesis of β-trifluoromethylpyrroles. Tetrahedron Lett 24(9):929–930
20. Homma M, Aoyagi K, Aoyama Y, Ogoshi H (1983) Electron-deficient porphyrins. 1. Tetrakis(trifluoromethyl)porphyrin and its metal complexes. Tetrahedron Lett 24(40):4343–4346
21. Nishida M, Kimoto H, Fujii S, Hayakawa Y, Cohen LA (1991) Photochemical trifluoromethylation of 1-methylimidazoles and 1-methylpyrroles containing methylthio groups. Bull Chem Soc Jpn 64(7):2255–2259
22. Shaitanova EN, Gerus II, Kukhar VP (2008) A new synthetic route to 3-polyfluoroalkyl-containing pyrroles. Tetrahedron Lett 49(7):1184–1187
23. Leroy J, Cantacuzene D, Wakselman C (1982) Synthesis of 3,4-bis[trifluoromethyl]-1H-pyrrole. Synthesis 4:313–315
24. Leroy J (1991) Improved synthesis of 3-(trifluoromethyl)pyrrole. J Fluor Chem 53(1):61–70
25. Leroy J, Bondon A (2008) β-fluorinated porphyrins and related compounds: an overview. Eur J Org Chem 3:417–433
26. Lindsey JS, Schreiman IC, Hsu HC, Kearney PC, Marguerettaz AM (1987) Rothemund and Adler-Longo reactions revisited: synthesis of tetraphenylporphyrins under equilibrium conditions. J Org Chem 52(5):827–836
27. Jin L-M, Yin J-J, Chen L, Guo C-C, Chen Q-Y (2005) Metal-dependent halogenation and/or coupling reactions of porphyrins with PhIX2 (X = Cl, F). Synlett 19:2893–2898
28. Jin L-M, Zeng Z, Guo C-C, Chen Q-Y (2003) Fluoroalkylation of porphyrins: synthesis and reactions of β-fluoroalkyltetraarylporphyrins. J Org Chem 68(10):3912–3917
29. Liu C, Chen Q-Y (2005) General and efficient synthesis of meso- and β-perfluoroalkylated porphyrins via Pd-catalyzed cross-coupling reaction. Synlett 8:1306–1310
30. Suzuki A, Toi H, Aoyama Y, Ogoshi H (1992) Synthesis of 1-fluoro-1-demethylmesoporphyrin-IX. Heterocycles 33(1):87–90
31. Kumadaki I, Ando A, Omote M (2001) Synthesis of fluorinated analogs of natural porphyrins potentially useful for the diagnosis and therapy of cancer. J Fluor Chem 109(1):67–81
32. Aviv-Harel I, Gross Z (2009) Aura of corroles. Chem Eur J 15(34):8382–8394
33. Gross Z, Galili N, Simkhovich L, Saltsman I, Botoshansky M, Blaeser D, Boese R, Goldberg I (1999) Solvent-free condensation of pyrrole and pentafluorobenzaldehyde: a novel synthetic pathway to corrole and oligopyrromethenes. Org Lett 1(4):599–602

34. Liu H-Y, Lai T-S, Yeung L-L, Chang CK (2003) First synthesis of perfluorinated corrole and its Mn: O complex. Org Lett 5(5):617–620
35. Steene E, Dey A, Ghosh A (2003) β-octafluorocorroles. J Am Chem Soc 125(52):16300–16309
36. Dogutan DK, McGuire R, Nocera DG (2011) Electrocatalytic water oxidation by cobalt(III) hangman β-octafluoro corroles. J Am Chem Soc 133(24):9178–9180
37. Thomas KE, Wasbotten IH, Ghosh A (2008) Copper β-octakis(trifluoromethyl)corroles: new paradigms for ligand substituent effects in transition metal complexes. Inorg Chem 47(22):10469–10478
38. Terazono Y, Dolphin D (2003) Synthesis and characterization of β-trifluoromethyl-meso-tetraphenylporphyrins. J Org Chem 68(5):1892–1900
39. Berg S, Thomas KE, Beavers CM, Ghosh A (2012) Undecaphenylcorroles. Inorg Chem 51(18):9911–9916
40. Biffinger JC, Sun H, Nelson AP, DiMagno SG (2003) Differential substituent effects of β-halogens in water-soluble porphyrins. Org Biomol Chem 1(4):733–736
41. Gershman Z, Goldberg I, Gross Z (2007) DNA binding and catalytic properties of positively charged corroles. Angew Chem Int Ed 46(23):4320–4324
42. Okun Z, Gross Z (2012) Fine tuning the reactivity of corrole-based catalytic antioxidants. Inorg Chem 51(15):8083–8090
43. Kadish KM, Han BC, Franzen MM, Araullo-McAdams C (1990) Syntheses and spectroscopic characterization of (T(p-Me2N)F4PP)H2 and (T(p-Me2N)F4PP)M where T(p-Me2N)F4PP = the dianion of meso-tetrakis(o, o, m, m-tetrafluoro-p-(dimethylamino)phenyl) porphyrin and M = cobalt(II), copper(II), or nickel(II). Structures of (T(p-Me2N)F4PP)Co and meso-tetrakis(pentafluorophenyl)porphinatocobalt(II), (TF5PP)Co. J Am Chem Soc 112(23):8364–8368
44. Briza T, Kaplanek R, Havlik M, Dolensky B, Kejik Z, Martasek P, Kral V (2008) Synthesis of highly functionalized fluorinated porphyrins. Supramol Chem 20(3):237–242
45. Koren K, Borisov SM, Klimant I (2012) Stable optical oxygen sensing materials based on click-coupling of fluorinated platinum(II) and palladium(II) porphyrins-A convenient way to eliminate dye migration and leaching. Sens Actuators B 169:173–181
46. Billig MJ, Baker EW (1969) Mesomonofluorodeuteroporphyrin IX dimethyl ester. Chem Ind (London, United Kingdom) (20):654–655
47. Andrews LE, Bonnett R, Kozyrev AN, Appelman EH (1988) Meso-reactivity of porphyrins and related compounds. Part 10. Direct fluorination of octaethylporphyrin with cesium fluoroxysulfate. J Chem Soc Perkin Trans 1 Org Bio-Org Chem (1972–1999) (7):1735–1738
48. Naruta Y, Tani F, Maruyama K (1992) Meso-perfluorination of porphyrins with N-fluoropyridinium triflate. Tetrahedron Lett 33(8):1069–1072
49. Maruyama K, Narita Y, Tani F (1993) Method for fluorination of porphyrins. Jp Patent 05059059
50. Yamada T, Kikushima S, Hikita T, Nara A, Nishio E, Ohtsuka T, Nango M (2000) Molecular assembly of manganese fluorinated mesoporphyrin monolayer on a gold electrode. Chem Lett 6:644–645
51. Yamada T, Kikushima S, Hikita T, Yabuki S, Nagata M, Umemura R, Kondo M, Ohtsuka T, Nango M (2005) Molecular assembly of manganese mesoporphyrin derivatives on a gold electrode and their electron transfer activity. Thin Solid Films 474(1–2):310–321
52. Li G, Chen Y, Missert JR, Rungta A, Dougherty TJ, Grossman ZD, Pandey RK (1999) Application of Ruppert's reagent in preparing novel perfluorinated porphyrins, chlorins and bacteriochlorins. J Chem Soc Perkin Trans 1 Org Bio-Org Chem 13:1785–1787
53. Michalski TJ, Appelman EH, Bowman MK, Hunt JE, Norris JR, Cotton TM, Raser L (1990) 20-fluoromethylpyropheophorbide: the first synthesis of a fluorine-substituted derivative of chlorophyll. Tetrahedron Lett 31(47):6847–6850
54. Tamiaki H, Takeuchi S, Tsudzuki S, Miyatake T, Tanikaga R (1998) Self-aggregation of synthetic zinc chlorins with a chiral 1-hydroxyethyl group as a model for in vivo epimeric bacteriochlorophyll-c and d aggregates. Tetrahedron 54(24):6699–6718

55. Kureishi Y, Tamiaki H (1998) Synthesis and self-aggregation of zinc 20-halochlorins as a model for bacteriochlorophylls c/d. J Porphyrins Phthalocyanines 2(2):159–169
56. DiMagno SG, Williams RA, Therien MJ (1994) Facile synthesis of meso-tetrakis(perfluoroalkyl) porphyrins: spectroscopic properties and x-ray crystal structure of highly electron-deficient 5,10,15,20-tetrakis(heptafluoropropyl)porphyrin. J Org Chem 59(23):6943–6948
57. Goll JG, Moore KT, Ghosh A, Therien MJ (1996) Synthesis, structure, electronic spectroscopy, photophysics, electrochemistry, and X-ray photoelectron spectroscopy of highly-electron-deficient [5,10,15,20-tetrakis(perfluoroalkyl)porphinato]zinc(II) complexes and their free base derivatives. J Am Chem Soc 118(35):8344–8354
58. Moore KT, Horvath IT, Therien MJ (2000) Mechanistic studies of (porphinato)iron-catalyzed isobutane oxidation. Comparative studies of three classes of electron-deficient porphyrin catalysts. Inorg Chem 39(15):3125–3139
59. Moore KT, Fletcher JT, Therien MJ (1999) Syntheses, NMR and EPR spectroscopy, electrochemical properties, and structural studies of [5,10,15,20-tetrakis(perfluoroalkyl)porphinato] iron(II) and -iron(III) complexes. J Am Chem Soc 121(22):5196–5209
60. Moore KT, Horvath IT, Therien MJ (1997) High-pressure NMR studies of (porphinato)iron-catalyzed isobutane oxidation utilizing dioxygen as the stoichiometric oxidant. J Am Chem Soc 119(7):1791–1792
61. Thomas KE, Conradie J, Hansen LK, Ghosh A (2011) Corroles cannot ruffle. Inorg Chem 50(8):3247–3251
62. Fletcher JT, Therien MJ (2000) Transition-metal-mediated [2 + 2 + 2] cycloaddition reactions with ethyne-containing porphyrin templates: new routes to cofacial porphyrin structures and facially-functionalized (porphinato)metal species. J Am Chem Soc 122(49):12393–12394
63. Fletcher JT, Therien MJ (2002) Strongly coupled porphyrin arrays featuring both π-cofacial and linear-π-conjugative interactions. Inorg Chem 41(2):331–341
64. Fletcher JT, Therien MJ (2002) Extreme electronic modulation of the cofacial porphyrin structural motif. J Am Chem Soc 124(16):4298–4311
65. Ghosh A (1995) Substituent effects on valence ionization potentials of free base porphyrins: a local density functional study. J Am Chem Soc 117(16):4691–4699
66. Smirnov VV, Woller EK, DiMagno SG (1998) 19F NMR and structural evidence for spin-state modulation of six-coordinate cobalt(II) in a weak field porphyrin ligand. Inorg Chem 37(19):4971–4978
67. Liao M-S, Watts JD, Huang M-J (2005) Effects of peripheral substituents and axial ligands on the electronic structure and properties of cobalt porphyrins. J Phys Chem A 109(51):11996–12005
68. Kadish KM, Van Caemelbecke E, D'Souza F, Lin M, Nurco DJ, Medforth CJ, Forsyth TP, Krattinger B, Smith KM, Fukuzumi S, Nakanishi I, Shelnutt JA (1999) Synthesis and electrochemical studies of a series of fluorinated dodecaphenylporphyrins. Inorg Chem 38(9):2188–2198
69. Che C-M, Zhang J-L, Zhang R, Huang J-S, Lai T-S, Tsui W-M, Zhou X-G, Zhou Z-Y, Zhu N, Chang CK (2005) Hydrocarbon oxidation by β-halogenated dioxoruthenium(VI) porphyrin complexes: effect of reduction potential (RuVI/V) and C-H bond-dissociation energy on rate constants. Chem Eur J 11(23):7040–7053
70. Sun H, Smirnov VV, DiMagno SG (2003) Slow electron transfer rates for fluorinated cobalt porphyrins: electronic and conformational factors modulating metalloporphyrin ET. Inorg Chem 42(19):6032–6040
71. Biffinger JC, Uppaluri S, Sun H, DiMagno SG (2011) Ligand fluorination to optimize preferential oxidation of carbon monoxide by water-soluble rhodium porphyrins. ACS Catal 1(7):764–771
72. Collman JP, Decreau RA (2003) Microwave-assisted synthesis of corroles. Tetrahedron Lett 44(6):1207–1210
73. Ou Z, Shen J, Shao JEW, Galezowski M, Gryko DT, Kadish KM (2007) Protonated free-base corroles: acidity, electrochemistry, and spectroelectrochemistry of $[(Cor)H_4]+$, $[(Cor)H_5]_2+$, and $[(Cor)H_6]_3+$. Inorg Chem 46(7):2775–2786

74. Shen J, Shao J, Ou ZEW, Koszarna B, Gryko DT, Kadish KM (2006) Electrochemistry and spectroelectrochemistry of meso-substituted free-base corroles in nonaqueous media: reactions of $(Cor)H_3$, $[(Cor)H_4]+$, and $[(Cor)H_2]$. Inorg Chem 45(5):2251–2265
75. Thomas KE, Alemayehu AB, Conradie J, Beavers CM, Ghosh A (2012) The structural chemistry of metallocorroles: combined X-ray crystallography and quantum chemistry studies afford unique insights. Acc Chem Res 45(8):1203–1214
76. Shigehara K, Anson FC (1982) Electrocatalytic activity of three iron porphyrins in the reduction of dioxygen and hydrogen peroxide at graphite cathodes. J Phys Chem 86(14):2776–2783
77. Collman JP, Denisevich P, Konai Y, Marrocco M, Koval C, Anson FC (1980) Electrode catalysis of the four-electron reduction of oxygen to water by dicobalt face-to-face porphyrins. J Am Chem Soc 102(19):6027–6036
78. Bettelheim A, Kuwana T (1979) Rotating-ring-disk analysis of iron tetra(N-methylpyridyl) porphyrin in electrocatalysis of oxygen. Anal Chem 51(13):2257–2260
79. Bhugun I, Lexa D, Saveant J-M (1994) Ultraefficient selective homogeneous catalysis of the electrochemical reduction of carbon dioxide by an iron(0) porphyrin associated with a weak Broensted acid cocatalyst. J Am Chem Soc 116(11):5015–5016
80. Hammouche M, Lexa D, Momenteau M, Saveant JM (1991) Chemical catalysis of electrochemical reactions. Homogeneous catalysis of the electrochemical reduction of carbon dioxide by iron("0") porphyrins. Role of the addition of magnesium cations. J Am Chem Soc 113(22):8455–8466
81. Esswein AJ, Nocera DG (2007) Hydrogen production by molecular photocatalysis. Chem Rev (Washington, DC, USA) 107(10):4022–4047
82. Hatay I, Su B, Mendez MA, Corminboeuf C, Khoury T, Gros CP, Bourdillon M, Meyer M, Barbe J-M, Ersoz M, Zalis S, Samec Z, Girault HH (2010) Oxygen reduction catalyzed by a fluorinated tetraphenylporphyrin free base at liquid/liquid interfaces. J Am Chem Soc 132(39):13733–13741
83. Behar D, Dhanasekaran T, Neta P, Hosten CM, Ejeh D, Hambright P, Fujita E (1998) Cobalt porphyrin catalyzed reduction of CO_2. Radiation chemical, photochemical, and electrochemical studies. J Phys Chem A 102(17):2870–2877
84. Yamazaki S-i, Ioroi T, Yamada Y, Yasuda K, Kobayashi T (2006) A direct CO polymer electrolyte membrane fuel cell. Angew Chem Int Ed 45(19):3120–3122
85. Ruettinger W, Dismukes GC (1997) Synthetic water-oxidation catalysts for artificial photosynthetic water oxidation. Chem Rev (Washington, DC) 97(1):1–24
86. Sala X, Romero I, Rodriguez M, Escriche L, Llobet A (2009) Molecular catalysts that oxidize water to dioxygen. Angew Chem Int Ed 48(16):2842–2852
87. McGuire R Jr, Dogutan DK, Teets TS, Suntivich J, Shao-Horn Y, Nocera DG (2010) Oxygen reduction reactivity of cobalt(II) hangman porphyrins. Chem Sci 1(3):411–414
88. Dogutan DK, Stoian SA, McGuire R, Schwalbe M, Teets TS, Nocera DG (2011) Hangman corroles: efficient synthesis and oxygen reaction chemistry. J Am Chem Soc 133(1):131–140
89. Ertem MZ, Cramer CJ (2012) Quantum chemical characterization of the mechanism of a supported cobalt-based water oxidation catalyst. Dalton Trans 41(39):12213–12219
90. Stephenson NA, Bell AT (2007) Mechanistic study of iron(III) [tetrakis(pentafluorophenyl) porphyrin triflate (F20TPP)Fe(OTf) catalyzed cyclooctene epoxidation by hydrogen peroxide. Inorg Chem 46(6):2278–2285
91. Shul'pin GB (2004) Oxidations of C-H compounds catalyzed by metal complexes. In: Transition metals for organic synthesis, 2nd edn, vol 2. Wiley-VCH, pp 215–241
92. Grinstaff MW, Hill MG, Labinger JA, Gray HB (1994) Mechanism of catalytic oxygenation of alkanes by halogenated iron porphyrins. Science (Washington, DC, USA) 264(5163):1311–1313
93. Labinger JA (1994) A simplified model for catalyzed isobutane autoxidation: implications for the mechanism of catalysis by halogenated porphyrin complexes. Catal Lett 26(1–2):95–99
94. Bagchi V, Bandyopadhyay D (2010) The mechanistic aspects in hydroxylation reactions catalyzed by fluorinated porphyrins of manganese and iron: role of aqueous phosphate. Inorg Chim Acta 363(12):2786–2790

95. Sheldon RA (ed) (1994) Metalloporphyrins in catalytic oxidations. Marcel Dekker, New York
96. Fu X, Wayland BB (2004) Equilibrium thermodynamic studies in water: reactions of dihydrogen with rhodium(III) porphyrins relevant to Rh-Rh, Rh-H, and Rh-OH bond energetics. J Am Chem Soc 126(8):2623–2631
97. Cui W, Wayland BB (2004) Activation of C-H/H-H bonds by rhodium(II) porphyrin bimetalloradicals. J Am Chem Soc 126(26):8266–8274
98. Zhang X-X, Wayland BB (1994) Rhodium(II) porphyrin bimetalloradical complexes: preparation and enhanced reactivity with CH_4 and H_2. J Am Chem Soc 116(17):7897–7898
99. Wayland BB, Ba S, Sherry AE (1991) Activation of methane and toluene by rhodium(II) porphyrin complexes. J Am Chem Soc 113(14):5305–5311
100. Nelson AP, DiMagno SG (2000) Umpolung of a metal-carbon bond: a potential route to porphyrin-based methane functionalization catalysts. J Am Chem Soc 122(35):8569–8570
101. Zdilla MJ, Abu-Omar MM (2006) Mechanism of catalytic aziridination with manganese corrole: the often postulated high-valent Mn(V) imido is not the group transfer reagent. J Am Chem Soc 128(51):16971–16979
102. Mueller P, Fruit C (2003) Enantioselective catalytic aziridinations and asymmetric nitrene insertions into CH bonds. Chem Rev (Washington, DC, USA) 103(8):2905–2919
103. Wilson BC, Patterson MS (1986) The physics of photodynamic therapy. Phys Med Biol 31(4):327–360
104. Ethirajan M, Chen Y, Joshi P, Pandey RK (2011) The role of porphyrin chemistry in tumor imaging and photodynamic therapy. Chem Soc Rev 40(1):340–362
105. Rani-Beeram S, Meyer K, McCrate A, Hong Y, Nielsen M, Swavey S (2008) A fluorinated ruthenium porphyrin as a potential photodynamic therapy agent: synthesis, characterization, DNA binding, and melanoma cell studies. Inorg Chem 47(23):11278–11283
106. Shao W, Wang H, He S, Shi L, Peng K, Lin Y, Zhang L, Ji L, Liu H-Y (2012) Photophysical properties and singlet oxygen generation of three sets of halogenated corroles. J Phys Chem B 116:14228–14234
107. Cunningham M, McCrate A, Nielsen M, Swavey S (2009) Highly efficient visible-light-induced photocleavage of DNA by a ruthenium-substituted fluorinated porphyrin. Eur J Inorg Chem 11:1521–1525
108. Goslinski T, Piskorz J (2011) Fluorinated porphyrinoids and their biomedical applications. J Photochem Photobiol C Photochem Rev 12(4):304–321
109. Huang X, Fujioka N, Pescitelli G, Koehn FE, Williamson RT, Nakanishi K, Berova N (2002) Absolute configurational assignments of secondary amines by CD-sensitive dimeric zinc porphyrin host. J Am Chem Soc 124(35):10320–10335
110. Kurtan T, Nesnas N, Koehn FE, Li Y-Q, Nakanishi K, Berova N (2001) Chiral recognition by CD-sensitive dimeric zinc porphyrin host. 2. Structural studies of host-guest complexes with chiral alcohol and monoamine conjugates. J Am Chem Soc 123(25):5974–5982
111. Huang X, Rickman BH, Borhan B, Berova N, Nakanishi K (1998) Zinc porphyrin tweezer in host-guest complexation: determination of absolute configurations of diamines, amino acids, and amino alcohols by circular dichroism. J Am Chem Soc 120(24):6185–6186
112. Li X, Tanasova M, Vasileiou C, Borhan B (2008) Fluorinated porphyrin tweezer: a powerful reporter of absolute configuration for erythro and threo diols, amino alcohols, and diamines. J Am Chem Soc 130(6):1885–1893
113. Sergeeva NN, Senge MO (2012) Photochemical transformations involving porphyrins and phthalocyanines. In: CRC handbook of organic photochemistry and photobiology, 3rd edn, vol 1. CRC Press, pp 831–879
114. Zhao Y, Ye T, Chen H, Huang D, Zhou T, He C, Chen X (2011) A dissolved oxygen sensor based on composite fluorinated xerogel doped with platinum porphyrin dye. Luminescence 26(1):29–34
115. Wrobel D, Siejak A, Siejak P (2010) Photovoltaic and spectroscopic studies of selected halogenated porphyrins for their application in organic solar cells. Sol Energy Mater Sol Cells 94(3):492–500

116. Bessho T, Zakeeruddin SM, Yeh C-Y, Diau EW-G, Graetzel M (2010) Highly efficient mesoscopic dye-sensitized solar cells based on donor-acceptor-substituted porphyrins. Angew Chem Int Ed 49(37):6646–6649
117. Mathew S, Iijima H, Toude Y, Umeyama T, Matano Y, Ito S, Tkachenko NV, Lemmetyinen H, Imahori H (2011) Optical, electrochemical, and photovoltaic effects of an electron-withdrawing tetrafluorophenylene bridge in a push-pull porphyrin sensitizer used for dye-sensitized solar cells. J Phys Chem C 115(29):14415–14424
118. Varotto A, Smeureanu G, Aggarwal A, Drain CM (2011) Highly fluorinated porphyrins: from ultra-thin films to nanoparticles in catalysis. In: ACS symposium series 1064 (Fluorine-related nanoscience with energy applications), pp 55–68

Fluorinated Phthalocyanines and Their Analogues

Pavel A. Stuzhin

Contents

P.A. Stuzhin (✉)
Research Institute of Macroheterocycles, Ivanovo State University of Chemical Technology, Friedrich Engels Pr-t, 7, 153000 Ivanovo, Russian Federation
e-mail: stuzhin@isuct.ru

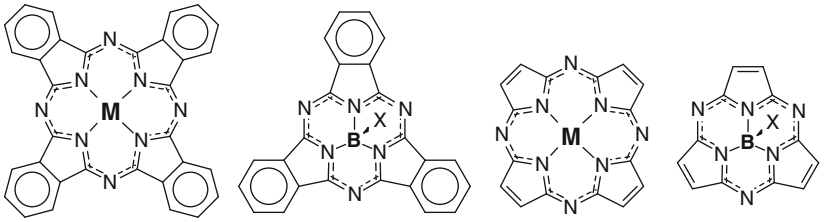
V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_15,

Abstract This chapter describes the synthesis of phthalocyanines, subphthalocyanines and porphyrazines bearing fluorine atoms and/or perfluorinated alkyl or aryl groups. Influence of fluorination of macrocycle on its physico-chemical properties and perspectives of application is also briefly considered.

Keywords Phthalocyanine • Porphyrazine • Subphthalocyanine • Fluorine • Perfluoroalkyl and aryl groups

1 Introduction

Phthalocyanines (Pcs) are widely used as dyes and pigments, materials for different optical, electronic and photoelectronic devices [1]. They have wide application perspectives in other fields [2] including medicine (fluorescence imaging and photodynamic therapy of cancer [3], etc.) The useful properties of Pcs are strongly influenced by substituents present in benzene rings, and introduction of electronegative fluorine atoms or perfluorinated alkyl or aryl groups is an important tool for tuning properties of phthalocyanines and related macrocycles. Fluorinated phthalocyanines are investigated for the use in molecular electronics as components of diodes (rectifying junctions) [4] hybrid materials for photovoltaic applications [5], organic thin film transistors [6–8], etc.; in catalytic oxidation of hydrocarbons [9] and reduction of oxygen [10] and in medicine as well [11].

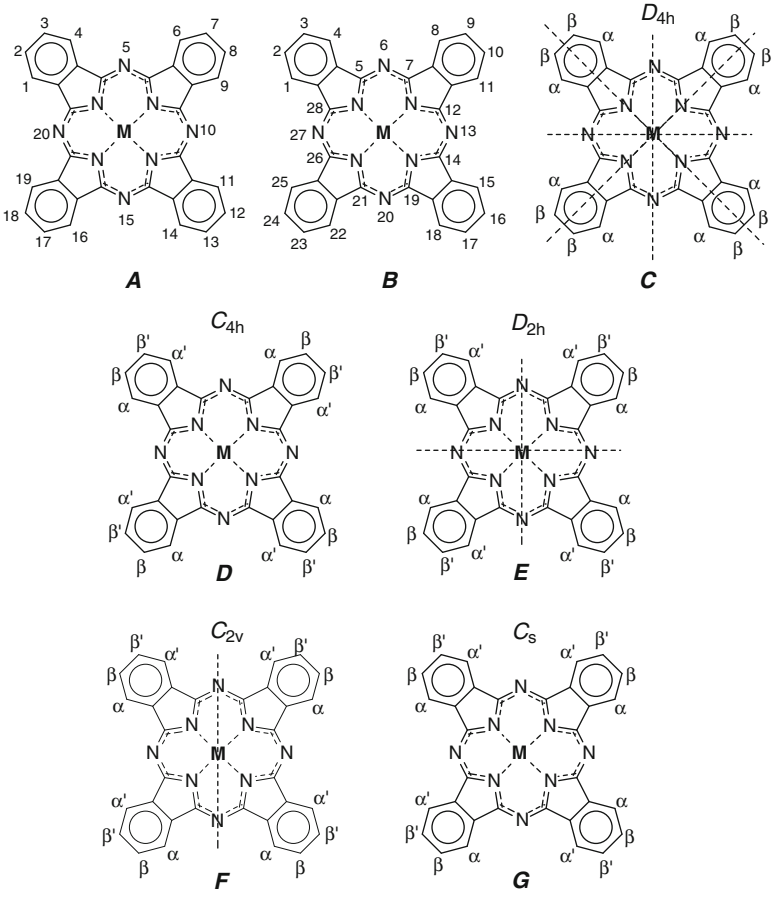


This chapter describes synthesis of fluorinated phthalocyanines containing from one to four fluorine atoms in each benzene ring, their substituted derivatives bearing perfluoroalkyl or perfluorophenyl groups directly attached to benzene ring of the macrocyclic core. The fluorinated phthalocyanine analogues with contracted macrocycle containing three instead of four isoindole subunits (subphthalocyanines, SubPcs), and homologues without fused benzene rings (porphyrazines, PAs, and subporphyrazines, SubPAs) are considered as well.

2 Fluorinated Phthalocyanines

2.1 Nomenclature

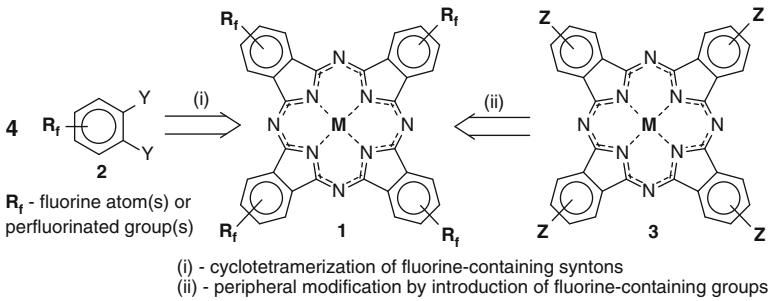
Phthalocyanines belongs to tetrapyrrolic macroheterocycles and can be considered as tetrabenzoannulated derivatives of *meso*-tetraazasubstituted porphyrin (porphyrazine), i.e. 5,10,15,20-tetraazatetrabenzo[*b,g,l,q*]porphyrin, or tetrabenzo[*b,g,l,q*] porphyrazine. Each of four benzene rings can contain up to four fluorine atoms or fluorinated substituents. The substituents location can be most conveniently numbered using the IUPAC recommendation for fused aromatic systems (*A*), however the numbering system which is used commonly for substituted phthalocyanines (*B*) is different and somewhat confusing. It includes the carbon atoms of internal 16-membered macrocycle, which are not involved in substitution. Throughout this chapter the numbering system *A* will be used.



Among 16 carbon atoms of phthalocyanine macrocycle that can be bear substituents it is useful to distinguish eight non-peripheral α-carbon atoms (1,4,6,9,11,14,16,19) and eight peripheral β-carbon atoms (2,3,7,8,12,13,17,18) (*C*). Phthalocyanines that have a similar substitution pattern in each of four benzene rings are often named symmetrical. If pairs of substituents at α, α′ and β, β′ positions are equivalent, the phthalocyanine molecule has D_{4h} symmetry and exists as a single isomer (*C*). However, if the substituents in α,β and α′,β′ positions of each benzene ring are different for such quasi-symmetrical phthalocyanine four positional isomers (randomers) with C_{4h}, C_{2v}, D_{2h} and C_s symmetry are possible (*D*, *E*, *F*, *G*, respectively). These randomers have very similar optical properties and their mixture, which is formed in template cyclotetramerization of synthons with nonequivalent ααα′ββ′ substitution pattern is usually studied and used as is without troublesome chromatographic separation.

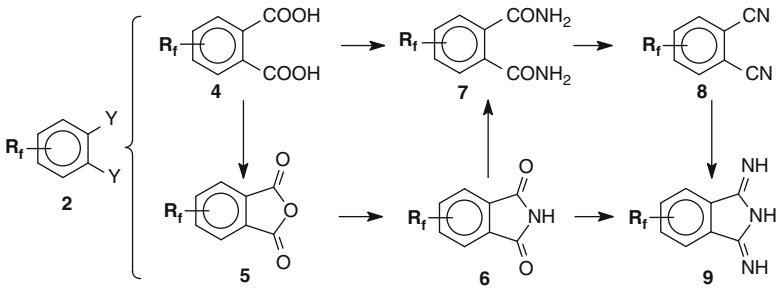
2.2 General Synthetic Approaches

There are two general synthetic approaches to fluorinated phthalocyanines **1** (Scheme 1): (i) assembly of phthalocyanine macrocycle from fluorine-containing precursors **2** or (ii) introduction of fluorine atoms or fluorine-containing substituents in benzene rings of appropriately substituted phthalocyanines **3**, i.e. peripheral modification of phthalocyanine macrocycle.



Scheme 1 General synthetic approaches to fluorinated phthalocyanines

The first approach (i) is well applicable in most cases, since the phthalocyanine macrocycle is usually easily prepared by template cyclotetramerization of a suitable synthon **2** derived from phthalic acid **4**: its anhydride **5**, imide **6**, diamide **7**, or more reactive dinitrile **8** or diiminoimide **9** (Scheme 2).



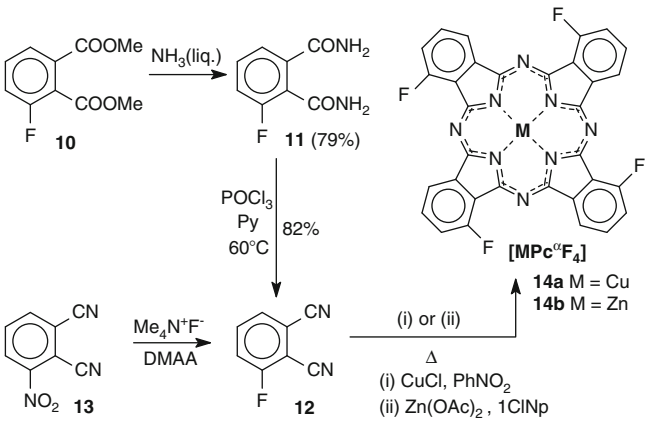
Scheme 2 Synthons suitable for synthesis of fluorinated phthalocyanines by cyclotetrametrization approach

Therefore the synthetic access to fluorinated phthalocyanines is mainly determined by availability of such synthons appropriately substituted with fluorine atoms or/and fluorinated groups. A limitation that should be taken into account is connected with a possibility of aromatic nucleophilic substitution of fluorine. This side-reaction can be usually avoided by choosing appropriate non-nucleophilic conditions for template cyclotetramerization.

The approach (ii) is usually applied for modification of perfluorinated phthalocyanines by nucleophilic substitution of fluorine atoms or in the case of easy accessibility of non-fluorinated phthalocyanines containing active groups, which can be exchanged by fluorine or fluorinated substituents.

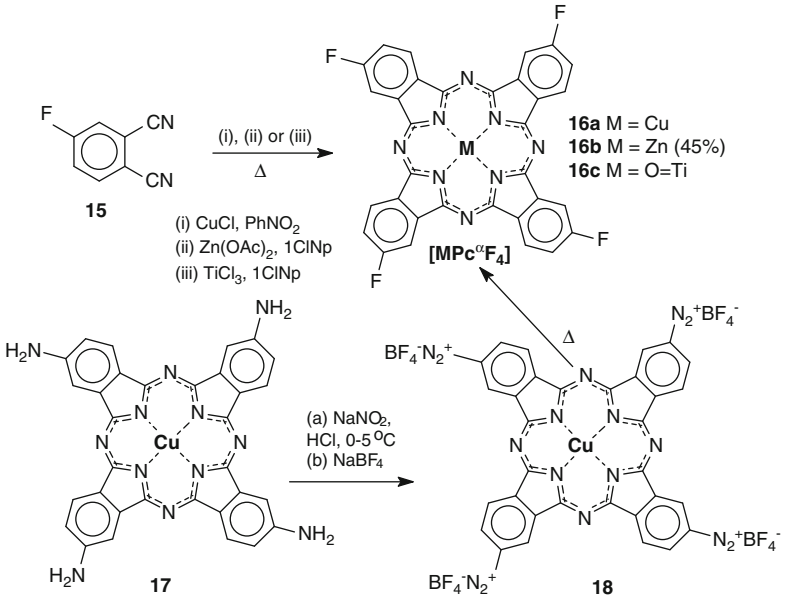
2.3 Tetrafluorinated Phthalocyanines

Although 3-fluorophthalonitrile **12** – precursor for α-substituted tetrafluorophthalocyanines [$MPc^{\alpha}F_4$] – is commercially available and can be also easily prepared either from dimethyl 3-fluorophthalate **10** using an amidation-dehydration procedure [12], or by nucleophilic substitution from 3-nitrophthalonitrile **13** upon its treatment with dry tetramethylammonium fluoride in N,N-dimethylacetamide (DMAA) [5], so far only Cu^{II} [12] and Zn^{II} [5] complexes (**14a** and **14b**) were briefly reported (Scheme 3).



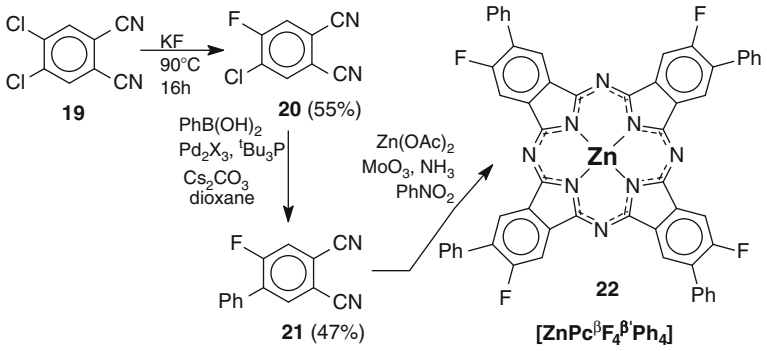
Scheme 3 Synthesis of α-substituted tetrafluorophthalocyanines

The Cu^{II} [12] and Zn^{II} [8] complexes of β-tetrafluorophthalocyanine [$MPc^{\beta}F_4$] (M = Cu, Zn, **16a** and **16b**) were also prepared by template approach from 4-fluorophthalodinitrile **15** by reflux with CuCl in nitrobenzene or using dry Zn^{II} acetate in 1-chloronaphthalene (1ClNp) (Scheme 4). The Ti^{IV} complex [O=Ti$Pc^{\beta}F_4$] (**16c**) was prepared from the dinitrile and $TiCl_3$ in 1ClNp (210 °C, 2.5 h) and used for fabrication of photoconductive elements [13]. The Cu^{II} complex [$CuPc^{\beta}F_4$] **16a** was also obtained in 90 % yield by diazotization of tetraamino substituted phthalocyanine [$CuPc(NH_2)_4$] **17** in 1 *N* HCl at 0–5 °C followed by thermolysis of tetrafluoroborate salt **18** [14]. Interestingly, the electric conductivity of [$CuPc^{\beta}F_4$] is ca 30000 times higher than that of unsubstituted [CuPc] [14].



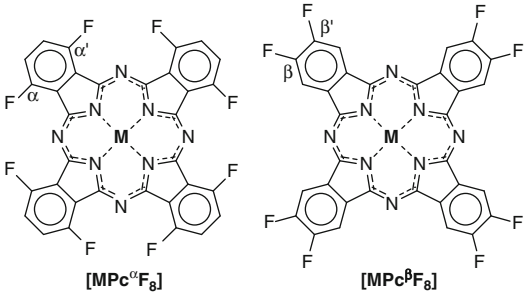
Scheme 4 Synthesis of β-substituted tetrafluorophthalocyanines

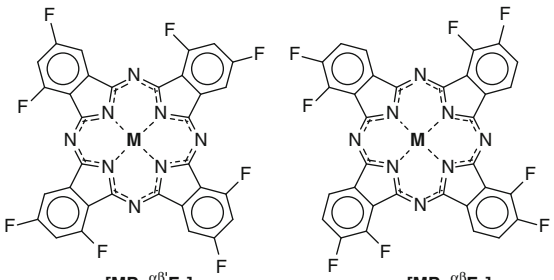
The Zn^{II} complex of phthalocyanine combining β-tetrafluro and β′-tetraphenyl substitution [$ZnPc^{\beta}F_4{}^{\beta'}Ph_4$] (**22**) was recently prepared for application on organic solar cells [15] starting from 4,5-dichlorophthalodinitrile **19** (Scheme 5). On the first stage one of chlorine atoms in **19** were substituted by fluorine by treatment with KF in N,N′-dimethylimidazolidinotetramethylguandinium chloride to give 4-chloro-5-fluorophthalonitrile **20**, and then phenyl group was incorporated instead of the second chlorine using a Pd-catalyzed reaction with phenylboronic acid (tris(dibenzylideneacetone)dipalladium(0) (90 °C, 10 h, 47 %). The resulting dinitrile **21** was then cyclotetramerized with Zn^{II} acetate in the presence of MoO_3 and NH_3 in nitrobenzene to give **22** as a regioisomeric mixture.



Scheme 5 Synthesis of β-tetrafluoro-β′-tetraphenyl substituted phthalocyanines

2.4 Octafluorinated Phthalocyanines

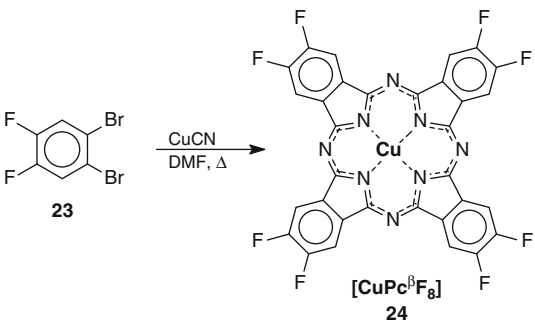




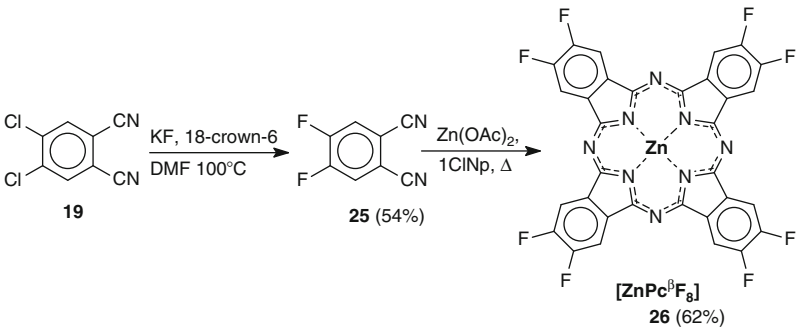
Two isomers with D_{4h} symmetry are possible for octafluorophthalocyanines: non-peripherally α,α′-substituted 1,4,6,9,11,14,16,19-isomer [MPc$^{\alpha}$F$_8$], peripherally β,β′-substituted 2,3,7,8,12,13,17,18-isomer [MPc$^{\beta}$F$_8$], and two quasi-symmetrical α,β- and α,β′-substituted isomers [MPc$^{\alpha\beta}$F$_8$] and [MPc$^{\alpha\beta'}$F$_8$] each present as four randomers with C_{4h}, C_{2v}, D_{2h} and C_s symmetry. So far only syntheses and properties of α,α′ [16], β,β′ [4, 8, 17, 18] and α,β′ [19] substituted octafluorophthalocyanines have been reported.

The Cu^{II} complex of β-octafluorophthalocyanine [CuPc$^{\beta}$F$_8$] (**24**) was prepared [17] in one-pot procedure (Scheme 6) by direct reaction of 1,2-dibromo-4,5-difluorobenzene **23** with copper(I) cyanide in DMF without isolation of intermediate 4,5-difluorophthalonitrile **25**.

Scheme 6 One-pot synthesis of Cu^{II} complex of β-octafluorophthalocyanine

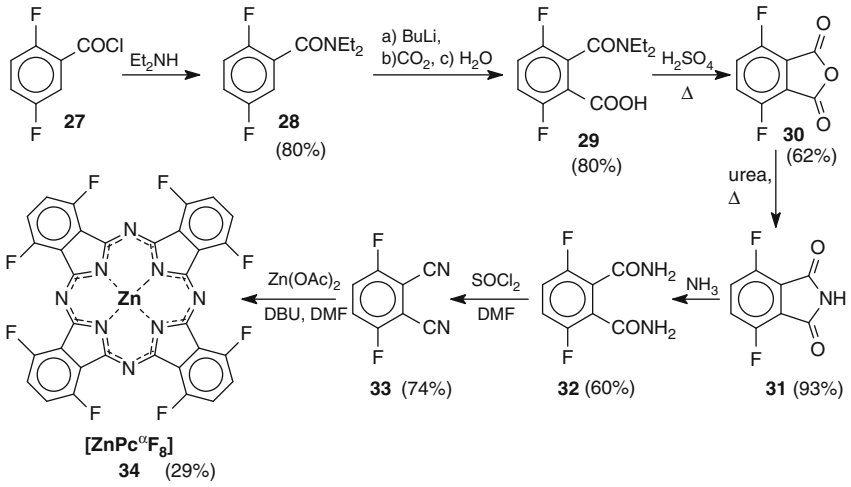


This dinitrile **25** was obtained by heating of commercially available 4,5-dichlorophthalodinitrile **19** with dry potassium fluoride in DMF in the presence of 18-crown-6 (54 %) and used in the template synthesis of the Zn^{II} complex [ZnPc$^{\beta}$F$_8$] (**26**) in the presence of Zn^{II} acetate in 1-chloronaphthalene (1ClNp) (Scheme 7).



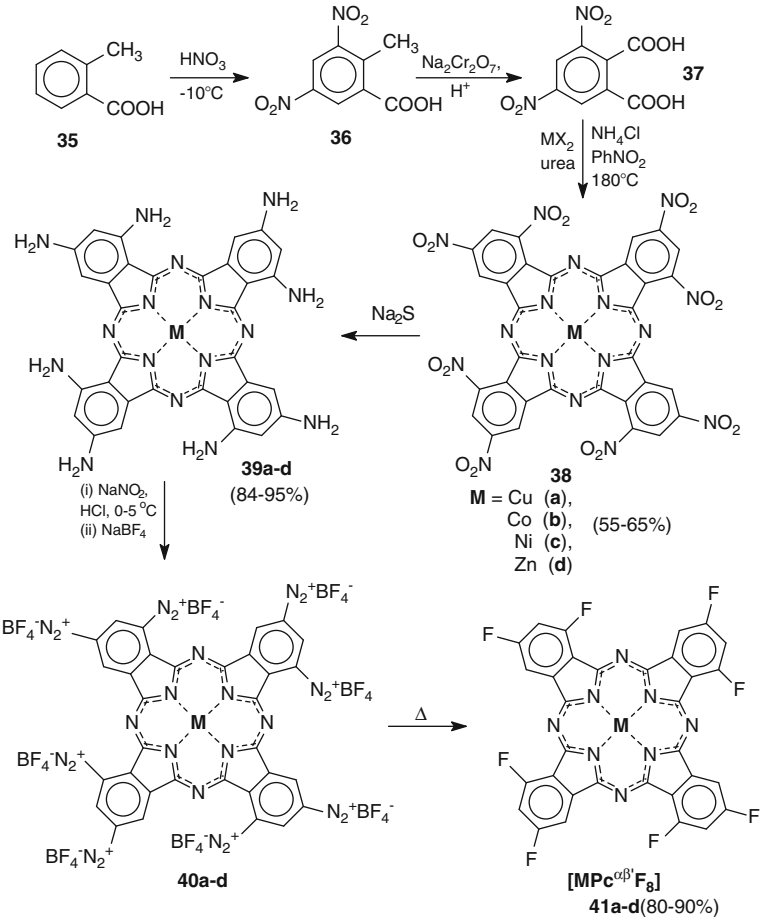
Scheme 7 Synthesis of β-octafluorophthalocyanines from 4,5-dichlorophthalodinitrile

The precursor for α-octafluorophthalocyanines [$MPc^{\alpha}F_8$], 3,6-difluorophthalonitrile **33** can be prepared starting from the commercially available 2,5-difluorobenzoylchloride **27**, which was first transformed to diethylamide **28** (80 %), then carboxylated to amidoacid **29** (80 %) and converted to 3,6-difluorophthalic anhydride **30** (62 %) [20] (Scheme 8). The latter was melted with urea at 125–130 °C to afford imide **31** (93 %), converted upon treatment with 25 % aqueous NH_3 to diamide **32** (60 %), which was dehydrated with $SOCl_2$ in DMF to dinitrile **33** (74 %) [16]. The Zn^{II} complex [$ZnPc^{\alpha}F_8$] (**34**) was then prepared by heating of the dinitrile **33** with Zn^{II} acetate in DMF in the presence of DBU (29 %) [16].



Scheme 8 Synthesis of α-octafluorophthalocyanines

Complexes of α,β′-octafluorophthalocyanine [$MPc^{\alpha\beta'}F_8$] (M = Co^{II}, Ni^{II}, Cu^{II} and Zn^{II}, **41a–d**) were prepared [19] with 80–90 % yields from the corresponding octaamino substituted phthalocyanines **39a–d** using Schiemann reaction through the intermediate octadiazonium salts **40a–d.** Octaaminophthalocyanines **39a–d** were obtained by reduction of octanitro derivatives **38a–d** with sodium sulfide [21]. Template cyclotetramerization of 3,5-dinitrophthalic acid **37** in the presence of metal salt, urea, NH_4Cl, and catalytic amount of $(NH_4)_6Mo_7O_{24}$ [22] was used to synthesize **38**. The diacid **37** was prepared starting from 2-methylbenzoic acid **35** by nitration followed by oxidation of the dinitro derivative **36** (Scheme 9).



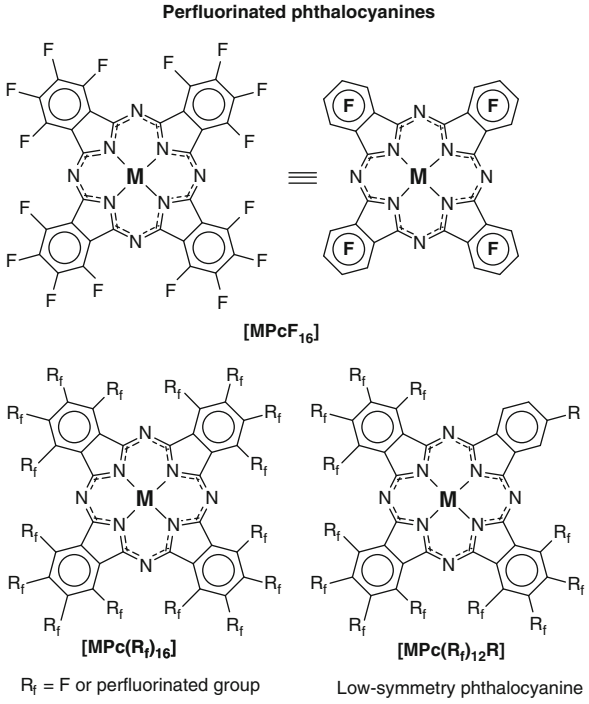
Scheme 9 Synthesis of α,β-octafluorophthalocyanines

The complexes are sparingly soluble in donor organic solvents such as pyridine, DMSO and DMF. UV-VIS spectra were reported [19] only for aqueous (1:1) sulfuric acid solutions (326, 473, 647 and 735 nm for Cu^{II}; 260, 479, 620 nm for Ni^{II}; 243, 444 and 515 nm for Co^{II}; and 254, 553 and 616 nm for Zn^{II} complexes) in which

they exist most likely as protonated and/or aggregated species. The magnetic measurements fulfilled over range of magnetic field strength indicate the presence of intermolecular cooperative effect [19].

2.5 *Hexadecasubstituted Fluorinated Phthalocyanines*

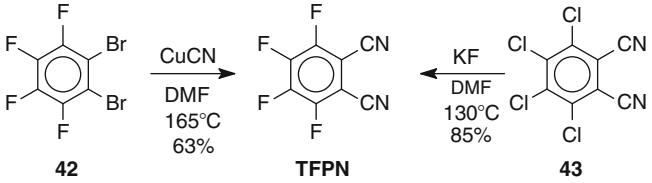
This section surveys synthesis of hexadecasubstituted phthalocyanines having at least one fluorine atom directly attached to each of four tetrasubstituted benzene rings. Among them one can distinguish (i) partly fluorinated hexadecasubstituted phthalocyanines [$MPcF_x(R)_{16-x}$] and two types of perfluorinated phthalocyanines – (ii) hexadecafluorophthalocyanines [$MPcF_{16}$] and (iii) hexadecasubstituted phthalocyanines combining fluorine atoms and perfluorinated substituents [$MPc(R_f)_{16}$]. The low symmetry phthalocyanines with only three perfluorinated isoindole units [$MPc(R_f)_{12}R$] are also considered here.



2.5.1 3,4,5,6-Tetrafluorophthalonitrile (TFPN)

Tetrafluorophthalonitrile (TFPN, Scheme 10) is commercially available precursor for the preparation of hexadecafluorophthalocyanines [$MPcF_{16}$] by template cyclotetramerization method. Its preparation by Rosemund – von Braun cyanation of 1,2-dibromotetrafluorobenzene **42** [23] is accompanied by formation of considerable

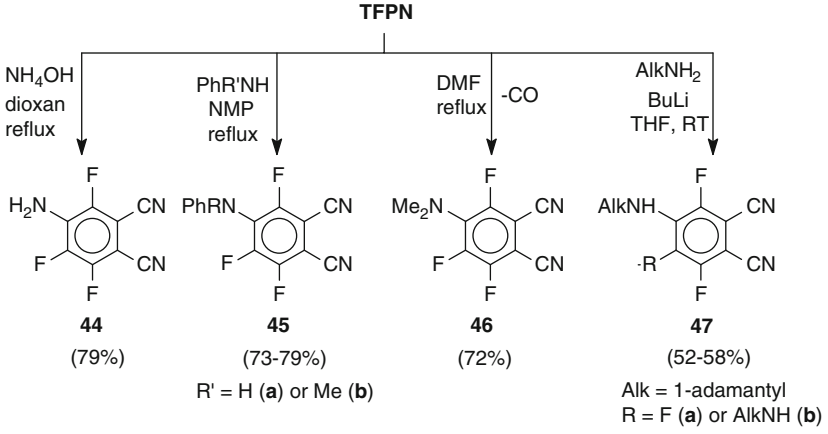
amounts of Cu^{II} perfluorophthalocyanine as a by-product. More conveniently TFPN can be obtained by melting of tetrachlorophthalonitrile **43** with excess of anhydrous KF (200–250 °C, 20 h, yield 65–70 %) [24] or in a milder conditions by heating in an aprotic solvent, such as DMFA (150 °C, 1.5 h, 85 %) [25].



Scheme 10 Synthesis of tetrafluorophthalonitrile (TFPN)

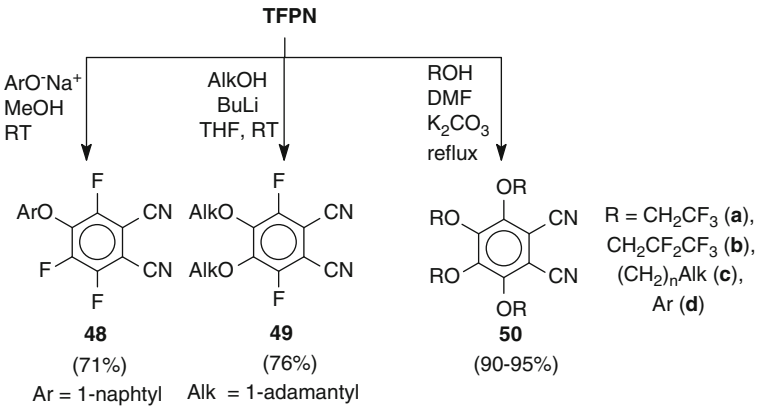
Various N-, O-, S-, P- and C-nucleophiles can substitute fluorine atom(s) in TFPN and it can be therefore also used in the synthesis of the dinitrile precursors for hexadecasubstituted phthalocyanines bearing fluorine atoms along with other substituents. The nucleophilic substitution of fluorine atoms in TFPN occurs most easily in positions 4 and 5 and leads to 3,5,6-trifluoro- or 3,6-difluorophthalodinitriles, which can be used for synthesis of the corresponding α,α′,β-dodeca- and α,α′-octafluorinated phthalocyanines.

Thus, TFPN gives 4-amino derivative **44** upon treatment with three-fold excess of ammonium hydroxide in dioxane under reflux, while 4-arylamino substituted species **45a,b** are formed in reaction with arylamines in boiling N-methylpyrrolidone (NMP) [26] (Scheme 11). Interestingly, 4-dimethylamino derivative **46** can be obtained upon heating of TFPN in DMF (72 %) accompanied by evolution of carbon monoxide [26]. Amination of TFPN with aliphatic amines proceeds in milder conditions (THF, room temperature) if they are first converted to amides by treatment with BuLi. In such way 4-monoadamantyl-3,5,6-trifluoro- and 4,5-diadamantyl-3,6-difluorophthalodinitliles **47a** (58 %) and **47b** (52 %) were obtained [27].



Scheme 11 Reactions of TFPN with N-nucleophiles

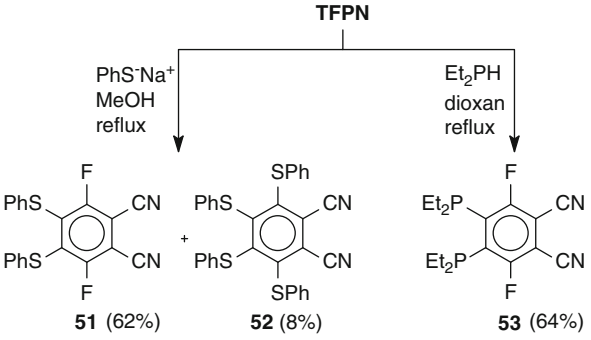
Substitution of fluorine by alkoxy and aryloxy groups occurs especially easily (Scheme 12). Thus, 4-(1-naphthoxy)trifluorophthalonitrile was obtained upon treatment of TFPN with equimolar amount of sodium 1-naphtolate in methanol at room temperature (71 %) [26]. Reaction of TFPN with 1-adamantanol (1:2 ratio) in the presence of BuLi in THF affords 4,5-diadamantyloxy substituted dinitrile (RT, 76 %) [27]. All fluorine atoms are substituted when TFPN is heated with alcohols or phenols in DMF in the presence of K_2CO_3 as a base [27–29]. In such way, among others tetrakis(2,2,2-trifluoroethoxy)- and tetrakis(2,2,3,3,3-pentafluoropropoxy) phthalodinitriles **50a** and **50b** (yields >90 %) – the precursors for the "fluorine-coated" phthalocyanines were obtained [28, 29].



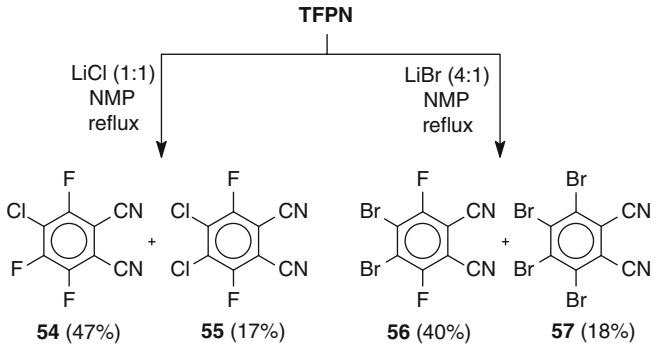
Scheme 12 Reactions of TFPN with O-nucleophiles

S- and P-nucleophiles substitute two fluorine atoms in TFPN and give the corresponding 4,5-substituted 3,6-difluorophthalodinitriles [26] (Scheme 13). Thus, treatment of TFPN with benzenethiolate in 1:1 molar ratio in methanol under short reflux leads predominantly to 4,5-bisphenylsulfanyl derivative **51** (62 %) and admixture of tetrasubstituted phthalodinitrile **52** (8 %), indicating activating action of PhS group [26]. Reaction of TFPN with diethylphosphine (1:2 ratio) in dioxane under reflux (1 h) affords 4,5-bisdiethylphosphanyl-3,6-difluorophthalonitrile **53** (64 %).

Scheme 13 Reactions of TFPN with S- and P-nucleophiles

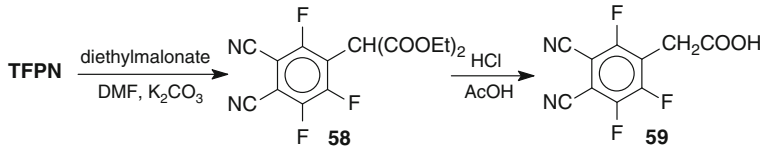


The fluorine atoms in TFPN can be also substituted by chlorine and bromine [26] (Scheme 14). Heating of TFNP with LiCl (1:1 ratio) in NMP lead to a mixture of 4-chloro and 4,5-dichloro derivatives **54** (47 %) and **55** (17 %), while in excess of LiCl all fluorine atoms are substituted. In the case of LiBr taken in 4:1 molar ratio to TFPN a mixture of 4,5-dibromo-3,6-difluorophthalosinitrile **56** (40 %) and tetrabromophthalonitrile **57** (18 %) was formed.

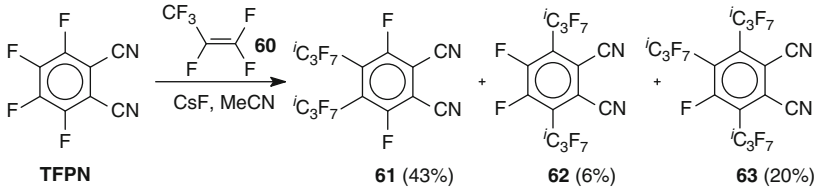


Scheme 14 Substitution of fluorine in TFPN by other halogen

Substitution of fluorine in TFPN can also occur in the presence of C-nucleophiles (Schemes 15 and 16). Thus, reaction of TFPN with diethylmalonate in DMF in the presence of K_2CO_3 affords 4-dicarbethoxymethyl derivative **58**, which can be further hydrolyzed to form 4-carboxymethyl-3,5,6-trifluorophthalodinitrile **59** [30].



Scheme 15 Introduction of carboxymethyl group



Scheme 16 Introduction of perfluoroisopropyl groups

In a nucleophilic reaction of TFPN with perfluoroisopropyl carbanion *i*-$C_3F_7^-$ (generated in situ from perfluoropropene **60** in the presence of CsF) up to three of four fluorine atoms in TFPN can be substituted by perfluoroisopropyl groups [31] (Scheme 16). Three perfluorinated phthalodinitriles bearing perfluoroisopropyl groups in 4,5-, 3,6- and 3,4,6-positions (**61**, **62** and **63**) were isolated and characterized by X-Ray diffraction study. The major product 4,5-perfluoroisopropyl-3,6-difluorophthalodinitrile **61** was used for synthesis of perfluorinated β-isopropyl substituted phthalocyanines (see Sect. 2.5.4).

2.5.2 Hexadecafluorinated Phthalocyanines

Perfluorinated phthalocyanines (hexadecafluorophthalocyanines, [$MPcF_{16}$]) have been first reported in the second half of 1960s [32–35]. However, active studies of perfluorinated phthalocyanines have been started only 25 year later in connection with their possible applications mainly in molecular electronics and catalysis. Since then the free base perfluorophthalocyanine [H_2PcF_{16}] [36], and its complexes with Zn^{II} [35, 37, 38], Cu^{II} [32, 35], Co^{II} [10, 39], Fe^{II} [33, 40], Ru^{II} [9, 41], In^{III} [42], Zr^{IV} [42], Sn^{IV} [35], O=Ti^{IV} [13], O=V^{IV} [43–45], Th^{III} [34] have been prepared, characterized and studied for various applications.

The Co^{II} complex [$CoPcF_{16}$] have advantageous properties as electrocatalyst for the reduction of oxygen as compared to [CoPc] [39]. The Ru^{II} complex [$RuPcF_{16}$] appeared to be an effective catalyst for the room temperature oxidation of cycloalkanes [9]. Encapsulated in zeolite these species were used for catalytic oxidation of alkanes and alcohols [46]. In photoelectrochemical and (photo)conductivity studies it was shown that [$ZnPcF_{16}$] behaves as *n*-type semiconductor in vacuo and photoconductor in the presence of oxygen [37, 47]. Due to its enhanced solubility in different solvents as compared to non-substituted [ZnPc] it has advantages for clinical application in photodynamic tumor therapy [11]. Perfluorinated In^{III}, V^{IV}, Ti^{IV} and Zr^{IV} phthalocyanines exhibit higher performance as optical limiters than non-fluorinated species [42].

Perfluorophthalocyanines are usually easily prepared by template cyclotetramerization of tetrafluorophthalonitrile (TFPN) in the presence of the corresponding metal salt or even metal in a melt or in a highly boiling solvent (see Table 1). Some caution is required to avoid the side-reactions of fluorine substitution, which can easily occur in the presence of nucleophiles both with the dinitrile precursor TFPN or the target complex [$MPcF_{16}$]. The use of iodides, bromides and acetates is generally preferable. Complexes of Zn^{II} [8, 37], Cu^{II} [39], Co^{II} [39], Fe^{II} [40] were prepared from the corresponding metal(II) acetates and TFPN. The microwave heating procedure can strongly shorten the reaction time [38]. The use of Zn^{II}, Fe^{II} and Al^{III} chlorides as templating agents leads to mixture of corresponding polychloropolyfluorophthalocyaninates, the extent of fluorine substitution is increased at higher temperature and higher metal chloride:TFPN ratio [35]. In^{III}, Sn^{II}, Ti^{III} chlorides were used in template cyclotetramerization of TFPN for preparation of corresponding metal complexes [$MPcF_{16}$] (M=ClIn^{III} [42], Cl_2Sn^{IV} [35], O=Ti^{IV} [13]). The vanadyl complex [O=$V^{IV}$$PcF_{16}$] was prepared both from V_2O_5 [44] and $VOCl_3$ [43].

Table 1 Synthesis of perfluorophalocyanines [$MPcF_{16}$]

Phthalocyanine	Reaction conditions	Yield	Ref.
[H_2PcF_{16}]	TFPN + 6 mol%$CeCl_3$ + DBU, pentanol, 160 °C, 24 h	73 %	[36]
[$ZnPcF_{16}$]	TFPN + ZnI_2 (4:1), 250 °C (1.5 h)	77 %[a]	[35]
	TFPN + $ZnBr_2$ (4:1), 250 °C (1.5 h)	85 %[a]	[35]
	TFPN + $ZnCl_2$ (1:1), 160 °C[b] (7 h)	75 %[a]	[35]
	TFPN + Zn (dust) (1:2) in 1ClNp, reflux (48 h)	87 %[a]	[35]
	TFPN + $Zn(OAc)_2 \cdot 2H_2O$ (1:1) at 160 °C for 3 h	50–60 %	[11]
	TFPN + $Zn(OAc)_2 \cdot 2H_2O$ (4:1) in sealed tube at 180 °C (1 h)	85 %	[8, 37]
	TFPN + $Zn(OAc)_2 \cdot 2H_2O$ (~4:1) + DMF, microwave heating 200 °C (10 min)	59 %	[38]
[$CoPcF_{16}$]	TFPN + $Co(OAc)_2$ (4:1.2) 280 °C	nr	[39]
	TFPN + $Co(OAc)_2 \cdot 4H_2O$ (5:1), 1ClNp, reflux (24 h)	54 %	[39]
[$CuPcF_{16}$]	TFPN + CuCl (2:1) in NMP, reflux (2 h)	90 %	[32]
	TFPN + CuCl (1:1), 220 °C (2 h)	87 %[a]	[35]
	TFPN + $CuCl_2$ (1:1), 250 °C (7 h)	62 %[a]	[35]
	TFPN + Cu (turnings) (1:8) in 1ClNp, reflux (48 h)	78 %[a]	[35]
	TFPN + $Cu(OAc)_2$ (5:1), 1ClNp, reflux (24 h)	65 %	[39]
[$FePcF_{16}$]	TFPN + $Fe(CO)_5$ (5:1), 1MeNp, reflux, 2 h	~70 %	[33]
	TFPN + $Fe(OAc)_2$ (4:1) 1ClNp, 280 °C (24 h)	19 %	[40]
[$RuPcF_{16}$]	TFPN + $Ru_3(CO)_{12}$, 1ClNp, 280 °C	nr	[9]
	TFPN + $[Ru(NH_3)_5I]I_2$ (~5:1). 230 °C (1 h)	18 %	[41]
[(I)$ThPcF_{16}$]	TFPN + ThI_4, 240 °C	nr	[33]
[(Cl)$InPcF_{16}$]	TFPN + $InCl_3$ (2.7:1), 120 °C (3 h)		[42]
[(Cl_2)$SnPcF_{16}$]	TFPN + $SnCl_2$ (4:1), 250 °C (1.5 h)	79 %[a]	[35]
[O=$TiSnPcF_{16}$]	TFPN + $TiCl_3$ (2:1), 1ClNp, 210 °C (2.5 h)		[13]
[$(HO)_2ZrPcF_{16}$]	TFPN + $Zr(OEt)_4$ (2.5:1), pentanol, reflux (4 h)	20 %	[42]
[O=$VPcF_{16}$]	TFPN + V_2O_5 (~9:1), pentanol, reflux (20 h)	16 %	[44]
	TFPN + V_2O_5 (4:1), 220 °C (7 h)	15 %	[45]
	TFPN + $VOCl_3$ (4:1), 150 °C	nr	[43]

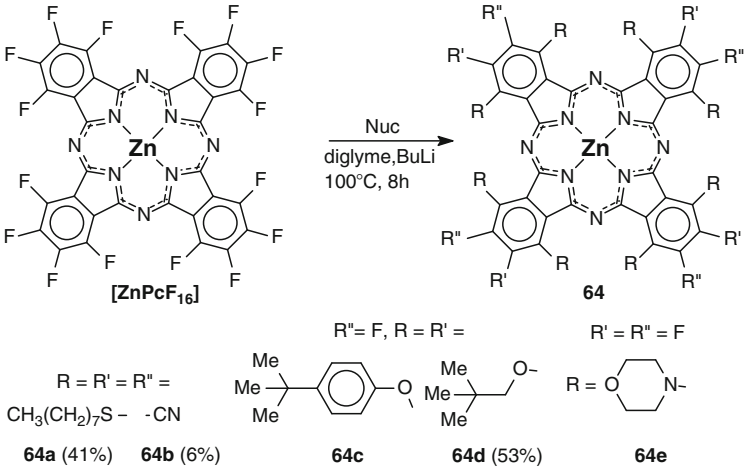
[a]Calculated on TFPN consumed
[b]At 250 °C the substitution product [$ZnPcCl_7F_9$] is obtained
nr not reported

Reaction of TFPN with thorium(IV) tetraiodide at 240 °C leads to perfluorophthalocyaninate of Th^{III} [(I)$ThPcF_{16}$] [33], whereas in the case of non-fluorinated species a sandwich complex [$Th(Pc)_2$] containing Th^{IV} is formed in the same conditions. Metal carbonyls were used for preparation of Fe^{II} [33] and Ru^{II} [9] complexes. Preparation of the Ru^{II} complex from TFPN and $[Ru(NH_3)_5I]I_2$ leads to [$RuPcF_{16}$] contaminated with small admixtures of substitution by-products containing instead of one or two fluorine iodine or hydrogen atom or NH_2 group [41]. The Zr^{IV} complex [$(HO)_2ZrPcF_{16}$] was formed from TFPN and $Zr(OEt)_4$ [42]. However Linstead cyclotetramerization of TFPN in the presence of alcoholates cannot be applied for the synthesis of Li^{I}, or Mg^{II} complexes as the precursors of the free base [H_2PcF_{16}] due to formation of alkoxy substituted phthalocyanines. [H_2PcF_{16}] can be however obtained by cyclotetramerization of TFDN in refluxing *n*-pentanol with addition of DBU (4 eq.) and 6 mol% of Ce^{III} chloride [36].

Hexadecafluorinated phthalocyanines have much higher solubility in organic solvents than unsubstituted species and often column chromatography can be applied for their purification. For example, in the case of [$ZnPcF_{16}$] the impurities in a crude product were first extracted by water and light petroleum and the residue was purified by chromatography in acetone on silica [11]. Due to high thermal stability of [$MPcF_{16}$] their purification by sublimation can be also used [37].

2.5.3 Hexadecasubstituted Partly Fluorinated Phthalocyanines

Fluorine atoms in hexadecafluorophthalocyanines can be substituted by various O-, S-, N-, or C-nucleophiles as has been demonstrated for the Zn^{II} complex [$ZnPcF_{16}$] [48–50] (Scheme 17). In the presence of 20-fold excess of nucleophile per fluorine atom in [$ZnPcF_{16}$] the nucleophilic substitution reactions occur upon heating in diglyme at ca 100 °C for 8 h [48]. The number of substituted fluorine atoms in the obtained Zn^{II} phthalocyanines **64a–e** depends on the type of nucleophile used.



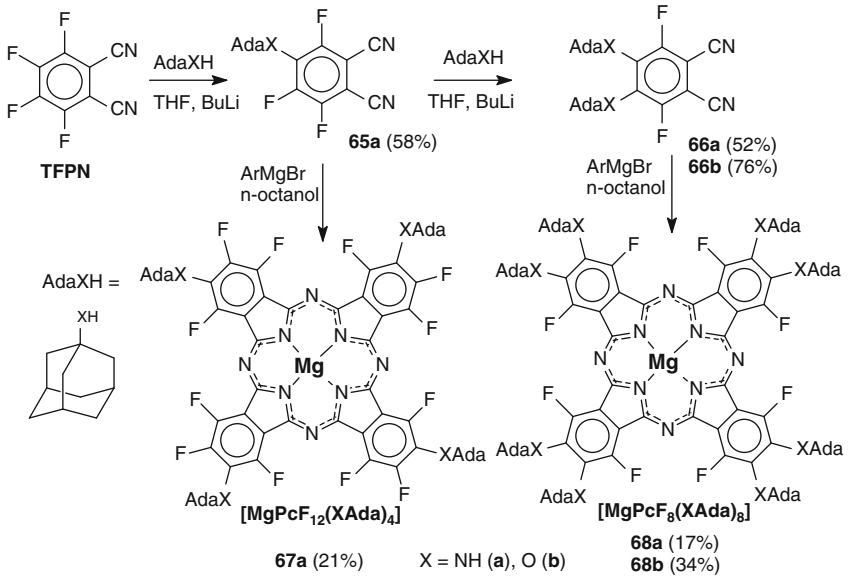
Scheme 17 Nucleophilic substitution of fluorine in hexadecafluorinated Zn^{II} phthalocyanine

All 16 fluorine atoms can be substituted only in the case of such nucleophiles as *n*-alkylthiolate and cyanide (**64a** and **64b**) [48]. In the case of bulky nucleophiles the incomplete substitution takes place – 12 fluorine atoms have been substituted under treatment with aryloxy- and neopentyloxy-anions (**64c** and **64d**) and eight in the presence of morpholine (**64e**) [48]. The regioselectivity of the partial fluorine substitution was not established in this work. However in the case of neopentyloxy derivative **64d** the ^1H NMR data evidenced about preferential substitution of both non-peripheral fluorine atoms in α,α′-positions, while only one β-fluorine atom in each of four isoindole rings is exchanged. In a later study it was demonstrated that changing the reaction conditions one can vary the extent of fluorine substitution in [$ZnPcF_{16}$] by AlkS groups [49]. The reaction with dodecanethiol in THF in the presence of diisopropylethylamine

at 50 °C for 24 h leads to β-tetrasubstituted derivative [$ZnPcF_{12}^{\beta}(SC_{12}H_{25})_4$] (Q-band at 707 nm), heating under reflux in the presence of K_2CO_3 leads to substitution of eight β-F atoms with formation of [$ZnPc^{\alpha}F_8^{\beta}(SC_{12}H_{25})_8$] (Q-band at 735 nm), and only heating in diglyme with solid thiolate at 100 °C for 16 h results in complete substitution of all F atoms affording [$ZnPc(SC_{12}H_{25})_{16}$] (Q-band at 787 nm) [49]. Blends with varying substitution degree obtained from [$ZnPcF_{16}$] and dodecanthiolate cover the broad spectral range in the absorption spectra, which allows the fabrication of bulk heterojunction solar cells with improved performance [49].

Treatment of [$ZnPcF_{16}$] with 2,3,4,6-tetra-O–acetyl-glucosylthioacetate in THF in the presence of K_2CO_3 leads to substitution of the eight F atoms in peripheral β-positions and after following deacylation gives water-soluble octathioglycosylated derivative [$ZnPc^{\alpha}F_8^{\beta}(Glc)_8$] [50]. This compound with non-hydrolysable thioglycosylated cancer cell targeting units exhibits the photonic properties that may enable its potential applications in photodynamic therapy.

Hexadecasubstituted phthalocyanines perfluorinated in α- (and β-) positions can be also prepared from dinitriles obtained by partial substitution of fluorine atoms in TFPN. Thus, α,α′-octafluoro- and α,α′,β-dodecafluoro substituted Pcs with adamantylamino or adamantyloxygroups [$MgPc^{\alpha}F_8(XAda)_8$] **68a,b** and [$ZnPcF_{12}^{\beta}(XAda)_4$] **67a** (Scheme 18) were prepared by cyclotetramerization of corresponding dinitriles **65a** and **66a,b** in the presence of 4-methoxyphenylmagnesiumbromide in *n*-octanol (24 h, 120 °C) [27]. The free base [$H_2Pc^{\alpha}F_8(OAda)_8$] was obtained by demetallation of the Mg^{II} complex **68b** with glacial acetic acid (reflux 4 days, yield 11 %), while the Ni^{II} complex [$H_2Pc^{\alpha}F_8(OAda)_8$] was prepared by heating of dinitrile **66b** and $NiCl_2$ in *N,N*-dimethylaminoethanol (24 h, 145 °C, 24 %).



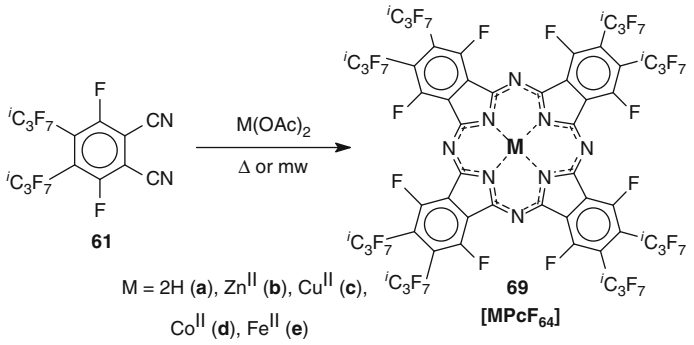
Scheme 18 Synthesis of fluorinated Mg^{II} phthalocyanines with adamantylamino(oxy) groups

Table 2 Synthesis of α-octafluoro-β-octa(perfloroisopropyl)phthalocyanines

Synthetic conditions	Product	Yield, %	Ref.
Dinitrile **61** + zinc(II) acetate (4:1, 180 °C, 1 h)	[$ZnPcF_{64}$] **69b**	21	[51]
Solvent-Free microwave reaction (200 °C, 10 min)		64	[38]
Dinitrile **61** and cobalt(II) acetate (4:1) (230 °C, 100 min)	[$CoPcF_{64}$] **69d**	34.5	[52]
Dinitrile **61** + $Cu(OAc)_2 \cdot H_2O$ (2:1)	[$CuPcF_{64}$] **69c**	21	[52]
In $PhNO_2$ (200 °C, 4 h)		48 %	
Solvent-free microwave reaction (190 °C, 12 min)			
Dinitrile **61** + $Fe(OAc)_2$ (2.25:1, 210 °C, 6 h)	[$FePcF_{64}$] **69e**	50.2	[54]
	[H_2PcF_{64}] **69a**	22.4	

2.5.4 α-Octafluoro-β-Octa(Perfluoroisopropyl)Phthalocyanines

Perfluorinated β-octaisopropylphthalocyanines having 64 fluorine atoms per Pc unit ([$MPcF_{64}$], **69**) derived from perfluoro-4,5-di(isopropyl)-3,6-diphthalonitrile **61** (see Scheme 16) were prepared and studied in a series of works [51–54]. Template cyclotetramerization of the dinitrile **61** proceeds smoothly in a melt with M^{II} acetates at 180–200 °C and especially rapidly and effectively under microwave heating (Scheme 19, Table 2). Interestingly, the reaction with ferrous acetate leads to mixture of the Fe^{II} complex [$FePcF_{64}$] (50.2 %) and the free base [H_2PcF_{64}] (22.4 %) [54].



Scheme 19 Synthesis of perfluorinated β-octaisopropylphthalocyanines

Due to the presence of bulky peripheral perfluoroisopropyl groups [$MPcF_{64}$] have high solubility in organic solvents and exhibit no tendency to aggregation in solutions (at least up to 10 μM). They are easily purified by column chromatography and upon crystallization readily produce single crystals suitable for X-ray diffraction study (see Figs. 1, 2, and 3).

Interestingly, the Cu^{II}, Zn^{II} and Co^{II} complexes have been structurally characterized as stable six-coordinated complexes with two carbonyl-containing ligands as O-donors: such as ethyl acetate in [$(MeCOOEt)_2CuPcF_{64}$] (Fig. 1) [52], acetone in [$(Me_2CO)_2ZnPcF_{64}$] [51] and [$(Me_2CO)_2CoPcF_{64}$] (Fig. 3a) [53].

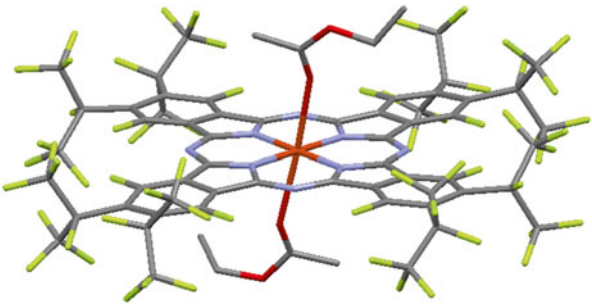


Fig. 1 Molecular structure of $[(MeCOOEt)_2CuPcF_{64}]$ (CCDC81124) [52]

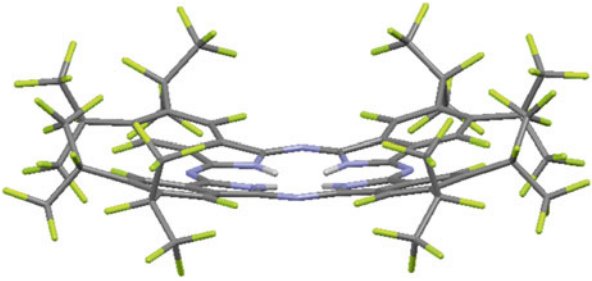


Fig. 2 Molecular structure of $[H_2PcF_{64}]$ (CCDC 201428) [54]

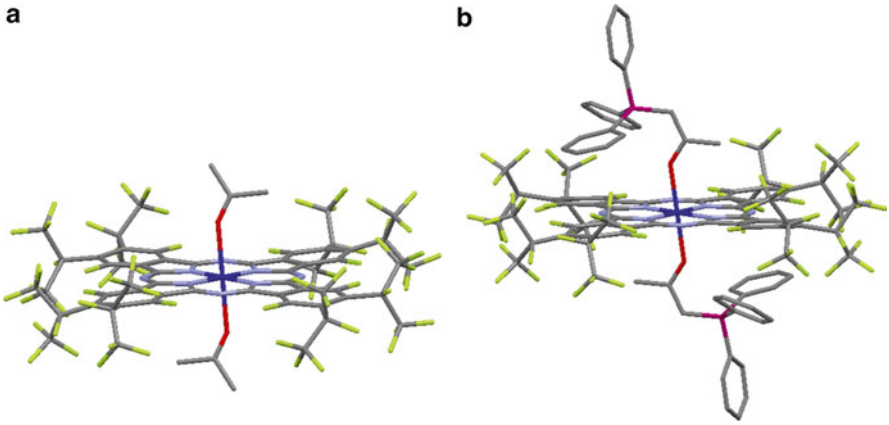


Fig. 3 Molecular structures of (**a**) – $[(Me_2CO)_2CoPcF_{64}]$ (CCDC 174676) and (**b**) -its oxidation product $[(Ph_3P{=}CH_2COMe)_2CoPcF_{64}]$ (CCDC 174676) [53]

Such tendency to form stable coordination bonds with an oxygen atom in carbonyl groups might be related to the strong electron-withdrawing effect of perfluoroalkyl groups, increasing the Lewis acidity of the metal center. While the phthalocyanine macrocycle remains essentially planar in metal complexes $[(RR'CO)_2MPcF_{64}]$ (Fig. 1), for the free-base in $[H_2PcF_{64}]$ the intermolecular interactions in the crystalline state induce the unusual dome-like conformation with the dihedral angle between the opposite isoindole units ~20° (see Fig. 2) [54].

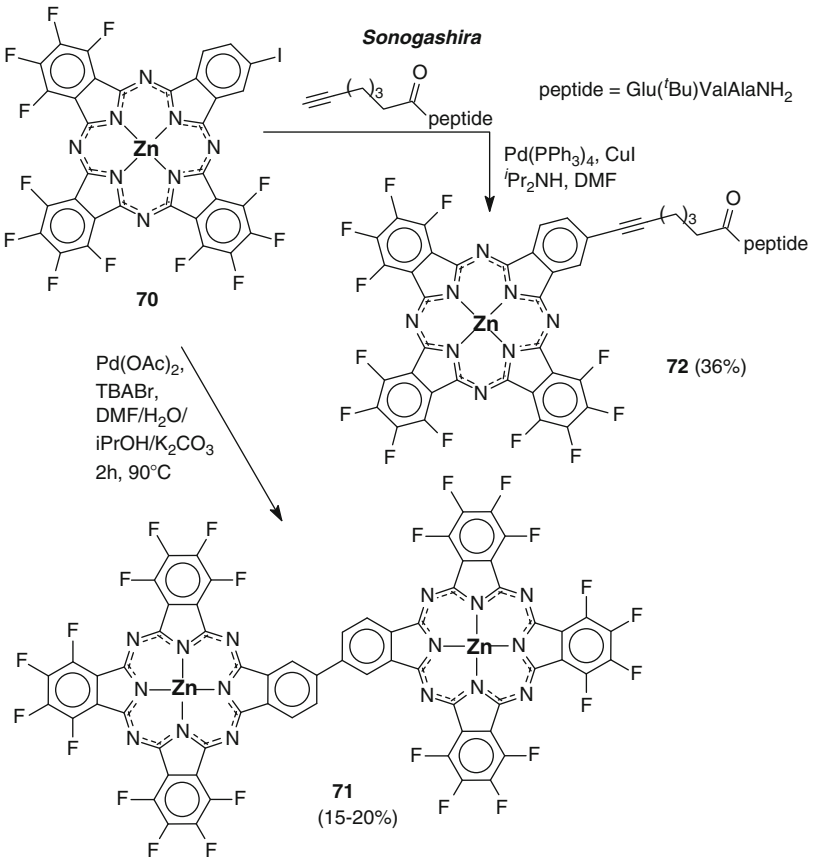
Perfluoroisopropyl groups have a strong electron-withdrawing inductive effect of the phthalocyanine macrocycles and their introduction in β-positions instead of aromatic F-atoms (−I, but +M effects) increases Brønsted acidity of the free base, and Lewis acidity of metal centers in complexes, stabilizes macrocycle to oxidation and facilitates its reduction. Thus, pyrrolic NH groups are unusually acidic ($pK_a = 6$ [55]) The first reduction potential for $[ZnPcF_{64}]$ is −0.43 V in DMF vs Ag/AgCl [56] is less negative than for $[ZnPcF_{16}]$ and [ZnPc](−0.6 and −0.93 V, respectively [57]. Perfluorinated macrocycle in $[MPcF_{64}]$ is highly robust to oxidation and stabilizes the low oxidation states of the central metal. Thus, Co^{II} cannot be oxidized electrochemically in DMF to Co^{III}, but reduction to Co^{I} occurs at −0.22 V vs. SCE [58], easier than for [CoPc] (−0.37 V [59]). Therefore $[MPcF_{64}]$ complexes are perspective oxidation catalysts. Thus, the Co^{II} complex $[CoPcF_{64}]$ effectively oxidized thiols in Merox process through the Co^{II}/Co^{I} pathway [58]. Very unusually it was observed that acetone molecules coordinated to $[CoPcF_{64}]$ upon addition of PPh_3 instead of expected replacement are oxidized catalytically with formation of the carbon-phosphorus bonds [53]. The structure of the resulting ylide complex $[(Ph_3P{=}CH_2COMe)_2CoPcF_{64}]$ was elucidated by X-Ray diffraction study.

$$Ph_3P + CH_3COMe + ½O_2 \rightarrow Ph_3P{=}CH_2COMe + H_2O$$

The Zn^{II} complex $[ZnPcF_{64}]$ is an effective and stable photosensitizer of singlet oxygen production, and might be used as very reactive yet stable photocatalyst for variety of oxygenation reactions [38] and in photodynamic tumor therapy [51]. In this regard the strong binding of the dianion (existing already in neutral medium) is of great importance [55].

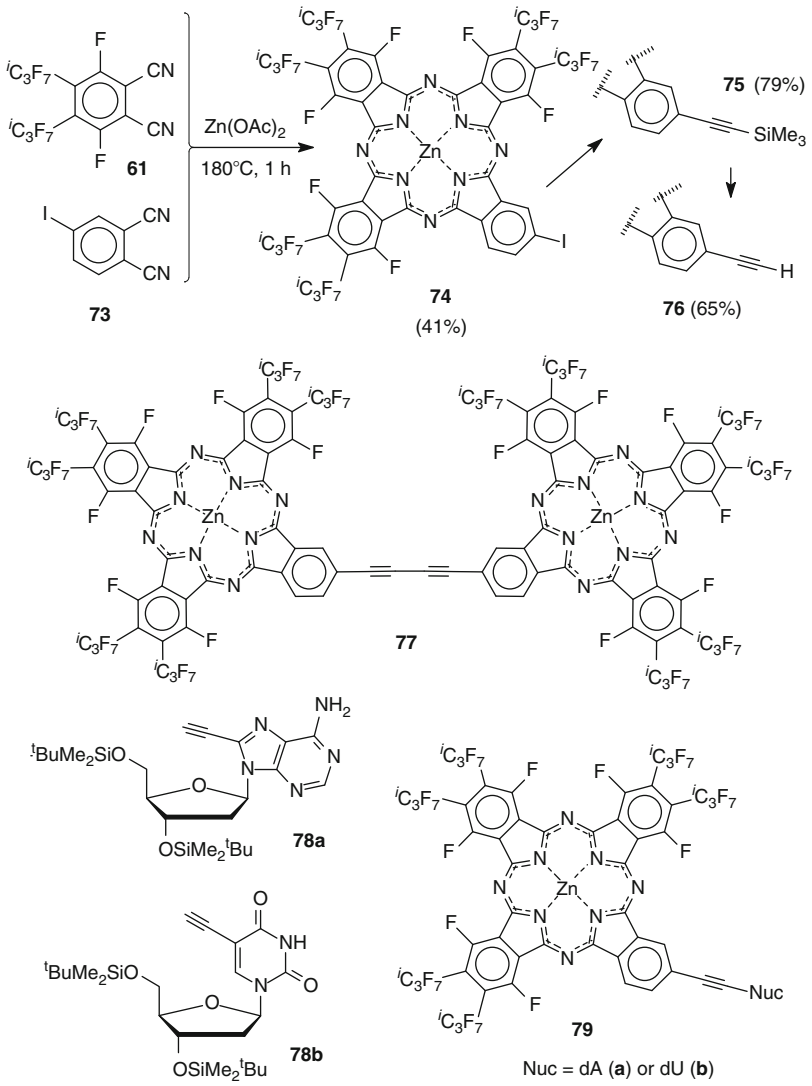
2.5.5 Low-Symmetry Phthalocyanines with Three Perfluorinated Isoindole Units

Low symmetry 1,2,3,4,6,7,8,9,11,12,13,14-dodecafluoro-17-iodophthalocyanine $[ZnPcF_{12}I]$ (**70**) was briefly reported without synthetic details [60, 61]. The conjugated *meta-meta* linked dimer **71** was obtained [61] (Scheme 20) when $[ZnPcF_{12}I]$ (**70**) was heated with Pd^{II} acetate and TBABr in $DMF/H_2O/K_2CO_3/i$-PrOH (2 h, 90 °C). It was also converted to the dodecafluoroPc-peptide conjugate **72** via Pd-catalysed Sonogashira cross-coupling reaction [60].



Scheme 20 Synthesis of fluorinated dimeric phthalocyanine and Pc-peptide conjugate

Another low-symmetry AB_3 type Zn^{II} phthalocyanine **74** having one β-monoiodo substituted isoindole unit (A) and three α-difluoro-β-di(perfluoroisopropyl) substituted units (B) was prepared by cross-cyclotetramerization of 4-iodophthalonitrile **73** and fluorinated dinitrile **61** in the presence of Zn^{II} acetate (180 °C, 1 h, yield 41 %) [62, 63] (Scheme 21).



Scheme 21 Synthesis of low-symmetry phthalocyanines with three α-difluoro-β-di(perfluoroisopropyl) fragments

The monoiodo derivative **74** was then converted to the ethynyl substituted phthalocyanine **76** by reaction with trimethylsilylacetylene ($[Pd(PPh_3)_2Cl_2]$, CuI, Et_3N, THF, RT, 24 h) followed by desylilation of **75** (TBAF, THF, 0 °C-rt, 2 h, 65 %). Then 1,3-butadiyn bridged dimer **77** was obtained by copper catalysed Glaser homo-coupling reaction (CuCl, pyridine, rt, 3 days, 75 %) [62].

This monoiodo substituted phthalocyanine **74** was also used in the synthesis of conjugates with deoxyribonucleosides **79a,b** using Pd-catalyzed Sonogashira cross-coupling reaction with ethynyl-substituted 2-deoxyadenosin (dA) and 2-deoxyuridin (dU) derivatives **78a,b** [63]. The *tert*-butyldimetylsilyl-protected conjugates were obtained from **74** and **78a,b** in high yields (84–87 %) using common Sonogashira conditions ($[Pd(PPh_3)_2Cl_2]$, CuI, Et_3N, THF, Ar, rt, 24 h) and then deprotected with TBAF in THF to give conjugates **79a,b** (2 h, 60–70 % yield). These conjugates of fluorinated Zn^{II} phthalocyanines with deoxyribonucleosides exhibit high fluorescence quantum yields and photocytotoxicity which allow to consider them as promising candidates for the photodynamic therapy of cancer [63].

2.6 Influence of Fluorination on the Electronic Structure and Spectral Properties of Phthalocyanines

Incorporation of electronegative fluorine atoms in benzene rings of phthalocyanine macrocycle has a considerable impact on its electronic structure and spectral properties. The electronic absorption spectra of fluorinated phthalocyanines are typical for symmetrical metal phthalocyanines (Table 3). They contain an intense Q-band in the visible region (650–715 nm) corresponding to the lowest degenerated π-π* transition of the macrocyclic π-chromophore, and a less intense and broader Soret band in the UV-region (300–380 nm).

The spectral data for phthalocyanines with various degree of fluorination are available for Zn^{II} and Cu^{II} complexes (Table 3). The fluorination of the peripheral β-positions leads to a hypsochromic shift of the Q-band, while an opposite bathochromic effect is observed in the case of non-peripheral α-fluorination. This indicates that the fluorine atoms in α-positions exhibit predominantly electron-donating +M effect and increase the energy level of highest occupied π-molecular orbital (HOMO), while in β-positions they are acting as electron acceptors (−I effect) and lower HOMO. These opposite spectral effects of α- and β-fluorination are almost compensated in perfluorinated M^{II} phthalocyanines. Indeed, the available spectral data (Table 3) indicate that for M^{II} complexes (Zn^{II}, Cu^{II} and Co^{II}) perfluorination of the phthalocyanine macrocycle, i.e. substitution or 16 hydrogen atoms by fluorine, has almost no influence on the position of the lowest ππ*-transition (Q-band). Therefore the energy gap between frontier π-molecular orbitals of phthalocyanine π-chromophore is not changed upon perfluorination for M^{II} complexes. For complexes with metals in the higher oxidation state a bathochromic shift of the Q-band is observed upon perfluorination ($ClIn^{III}$ ~15 nm, $O{=}V^{IV}$~20 nm, $O{=}Ti^{IV}$~25 nm). Since the HOMO in phthalocyanines have nodes on coordinating nitrogen atoms, one can conclude that for M^{III} and M^{IV} complexes the observed bathochromic shift of the Q-band might be related to a stronger stabilization of lowest unoccupied π-molecular orbital (LUMO).

Table 3 Electronic absorption spectra of fluorinated phthalocyanines

	λ_{max}, nm[a]			
Complex	Q-band	Soret band	Solvent	Ref.
[ZnPc]	666		THF	[8]
	678, 648sh, 612sh		ClNp	[37]
	672, 646, 606	348	Py	
[$ZnPc^{\beta}F_4$]	660		THF	[8]
[$ZnPc^{\alpha}F_8$]	690, 660, 622	368	$CHCl_3$	[16]
[$ZnPc^{\beta}F_8$]	652		THF	[8]
[$ZnPcF_{16}$]	668		THF	[8]
	678(5.3), 650(4.67), 630(4.56), 612(4.51)	376 (4.56)	Py	[11]
	686, 654sh, 617sh		ClNp	[37]
[CuPc]	678, 648, 611	350	ClNp	
[$CuPc^{\alpha}F_4$]	680(*2.66*), 646(*0.7*), 611(*0.76*)	344(*1*)		[12]
[$CuPc^{\beta}F_4$]	666(*1.18*), 632(*0.36*), 597(*0.36*)	334(*1*)		[12]
[$CuPcF_{16}$]	677, 645, 615		py	[39]
[CoPc]	658, 597	330	py	
[$CoPcF_{16}$]	661, 600		py	[39]
[FePc]	658, 630sh, 600, 415	286	DMF	[40]
[$FePcF_{16}$]	667, 640sh, 608,435	367	DMF	[40]
[$RuPcF_{16}$]	615(4.75), 562(4.11), 352(4.26)	323(4.59)	Me_2CO	[9]
[ClInPc]	700, 668, 629	365	$PnNO_2$	
[$ClInPcF_{16}$]	715, 685, 642, 593	367	1ClNp	[42]
[O=VPc]	695, 665, 619	346	PhCl	
[$O=VPcF_{16}$]	643		Py	[43]
	709		PhH	[43]
	716, 685, 645	368	1ClNp	[42]
[O=TiPc]	690, 662, 623	346	PhCl	
[$O=TiPcF_{16}$]	716, 680, 646	364	1ClNp	[42]
[$(HO)_2ZrPcF_{16}$]	704, 660, 637	370	1ClNp	[42]

[a]Values in parenthesis indicate values of logε (normal font) or relative intensity (A/A_{max}) (*italics*)

The influence of successive fluorination of the phthalocyanine macrocycle on the frontier energy levels of Zn^{II} complexes has been studied by quantum chemistry on the semiempirical level [5, 8, 64]. The calculations predict (see Fig. 4) that fluorination should lead to comparable stabilisation of the both frontier orbitals maintaining the value of the HOMO-LUMO gap (ca. 1.8 eV). In agreement with the experimental spectral data the gap is slightly increased for octa-β-fluorinated species.

The absolute levels of the frontier π-MOs in fluorinated Zn^{II} and Cu^{II} phthalocyanines were experimentally determined using ultraviolet photoelectron spectroscopy (UPES) of the thin films deposited on different surfaces [8, 18, 37, 64]. As can bee seen from Fig. 4 the experimental HOMO and LUMO levels and their trends upon fluorination are in a good agreement with theoretical results. The LUMO level for perfluorinated phthalocyanine complexes is comparable with the energy level of Au (−5.1 V) and lower than for indium-titan oxide (ITO) (−4.8 eV)

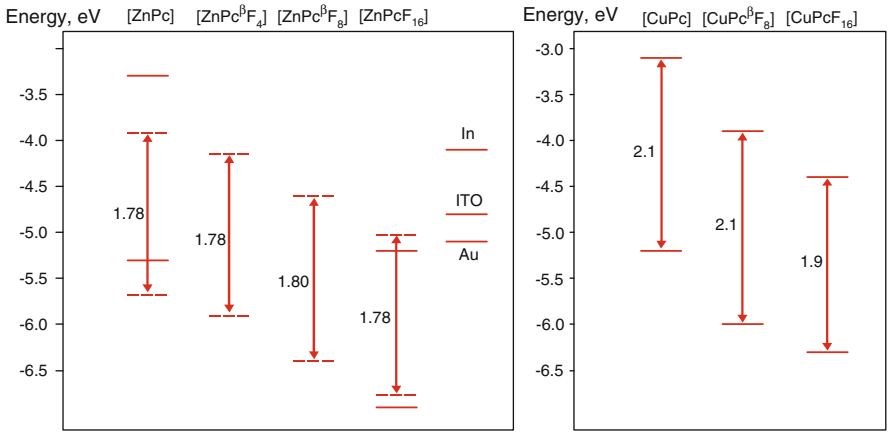


Fig. 4 The frontier MO levels of fluorinated Zn^{II} and Cu^{II} phthalocyanines calculated on the semiempirical level [8] (*dashed lines*) and obtained from UPES and inverse UPES methods (*solid lines*) for thin films deposited on surface of Au (Zn^{II} [37] and Cu^{II} [18])

Table 4 Influence of perfluorination on redox potentials ($E_{½}$, V vs. SCE) of phthalocyanines

Complex	Red1	Red2	Red3	Ox1	Solvent	Ref.
[ZnPcF$_{16}$]	−0.43	−0.64	−0.84	+1.04	DMF	[65]
	−0.6	−0.9			DMF	[57]
[ZnPc]	−0.93	−1.42		+0.64	DMF	[57]
[CoPcF$_{16}$]	−0.13	−1.07			DMSO	[39]
[CoPc]	−0.50	−1.43			DMSO	[39]
[CuPcF$_{16}$]		−0.88	−1.45		DMSO	[39]
[CuPc]	−0.73	−1.43			DMSO	[39]
[FePcF$_{16}$]	−0.78	−1.10	−1.53		DMSO	[40]
[FePc]	−0.77	−1.16	−1.89		DMSO	[40]
[O=VPcF$_{16}$]	−0.29	−0.62	−1.41	+1.34	CH_2Cl_2	[43]

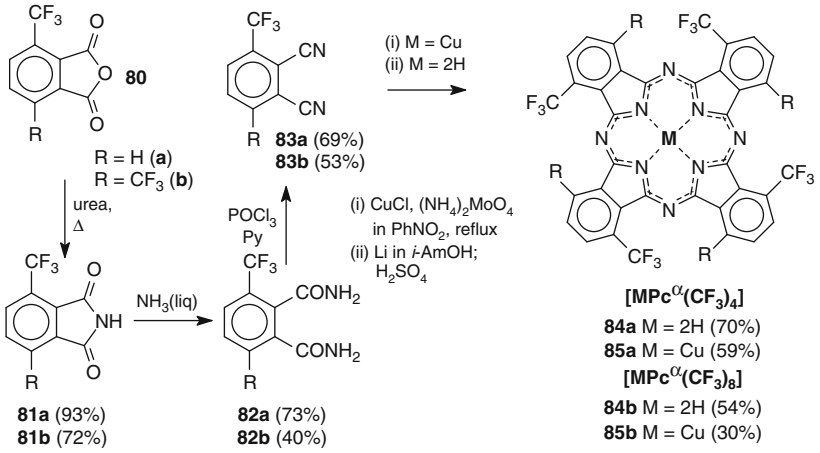
and In (−4.1). Unlike unsubstituted phthalocyanines which are *p*-conductors, this leads to the *n*-type conductivity of films from perfluorinated phthalocyanines [37]. It opens perspectives of their application in different electronic devices, e.g. in photovoltaics [37].

Electrochemical studies (see Table 4) have shown that perfluorinated phthalocyanine macrocycle is extremely stable to oxidation. At the same time fluorination facilitates the reduction of the macrocycle and the redox-active central metal (such as Co^{II}). This, perfluorination of phthalocyanine leads to positive shift of the first reduction potential of the macrocycle by ca 0.3 V for Zn^{II} complexes, and by 0.37 V the Co^{II}/Co^{I} couple. Such positive shift of the redox potentials for perfluorinated phthalocyanines is very important prerequisite for their application in oxidation catalysis.

2.7 *Phthalocyanines with Fluorinated Substituents*

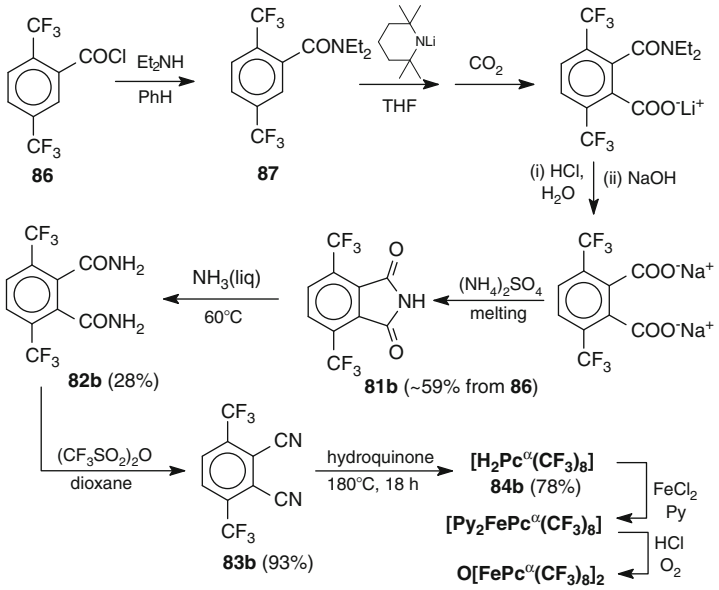
2.7.1 Perfluoroalkyl Substituted Phthalocyanines

α-Tetra- and α,α-octatrifluoromethylphthalocyanines (free bases **84a** and **85a** and Cu^{II} complexes **84b** and **85b**) were first obtained by cyclotetramerization of the corresponding dinitriles **83a,b** prepared from the anhydride precursors **80a,b** [66] (Scheme 22). While 3-mono- and 3,6-bistrifluoromethyl substituted phthalimides **81a,b** are easily formed in a usual manner by melting of anhydrides **80a,b** with urea, their conversion to diamides **82a,b** unlike unsubstituted derivatives can be achieved only with liquid NH_3 treatment under pressure (30–40 °C, 6 h). Dehydration of diamides **82a,b** with $POCl_3$ in pyridine affords the respective dinitriles **83a,b** (yields 69 and 53 %). Condensation of dinitriles **83a,b** with lithium *i*-amylate in *i*-amyl alcohol followed by reprecipitation from sulfuric acid gives the free bases $[H_2Pc^{\alpha}(CF_3)_4]$ **84a** (70 %) and $[H_2Pc^{\alpha}(CF_3)_8]$ **84b** (54 %). Template cyclotetramerization of dinitriles **83a,b** with CuCl in the presence of catalytic amount of ammonium molybdate in nitrobenzene afford the Cu^{II} complexes $[CuPc^{\alpha}(CF_3)_4]$ **85a** (59 %) and $[CuPc^{\alpha}(CF_3)_8]$ **85b** (30 %).



Scheme 22 Synthesis of α-trifluoromethyl substituted phthalocyanines

Later a modified procedure for the preparation of 3,6-bis(trifluoromethyl) phthalodinitrile **83b** was elaborated [67] (Scheme 23), which starts from 2,5-bis(trifluoromethyl)benzoyl chloride **86** and includes its conversion to N,N-diethylamide **87**, carboxylation of the latter in the presence of 2,2,6,6-tetramethylpiperidine, followed by direct formation of the imide **81b** (~59 % overall yield). The diamide **82b** obtained with liquid NH_3 treatment (28 % yield), was then converted to dinitrile **83b** with triflic anhydride in dioxane (yield



Scheme 23 Synthesis of α-octa(trifluoromethyl)phthalocyanines

93 %). Cyclotetramerisation of the dinitrile **83b** in a melt with hydroquinone (180 °C, 18 h) leads to the free-base $[H_2Pc^{\alpha}(CF_3)_8]$ (78 %).

The structure of the free-base **84b** determined by single X-ray diffraction study [68] has revealed the strong saddle-type distortion of the macrocycle due to steric repulsion of the CF_3 groups in the adjacent isoindole units (see Fig. 5).

Complexation of $[H_2Pc^{\alpha}(CF_3)_8]$ with $FeCl_2$ affords the Fe^{II} complex containing two coordinated pyridine molecules $[Py_2FePc^{\alpha}(CF_3)_8]$ [67]. It is oxidized in an acidic medium to Fe^{III} complex isolated as μ-oxo dimeric species μ-$O[FePc^{\alpha}(CF_3)_8]_2$ Its X-Ray crystal structure (see Fig. 6) evidence that severe saddle-type distortion of the macrocycles due to interaction of α-CF_3 groups leads to almost linear μ-(FeOFe) bridge [68]. The μ-oxo species exhibit catalytic activity in epoxidation of olefins with iodosyl benzene to stabilize the Fe^{IV}=O (ferryl) intermediate by electron-accepting CF_3 groups [67].

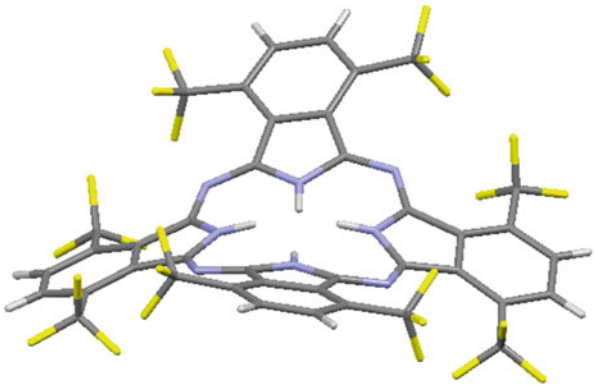


Fig. 5 Molecular structure of $[H_2Pc^{\alpha}(CF_3)_8]$ **84b** (CCDC 613431) [68]

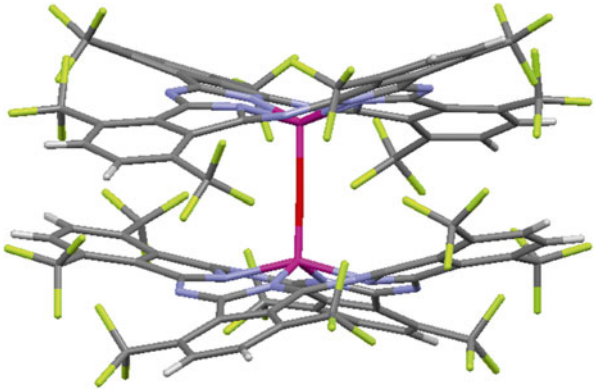
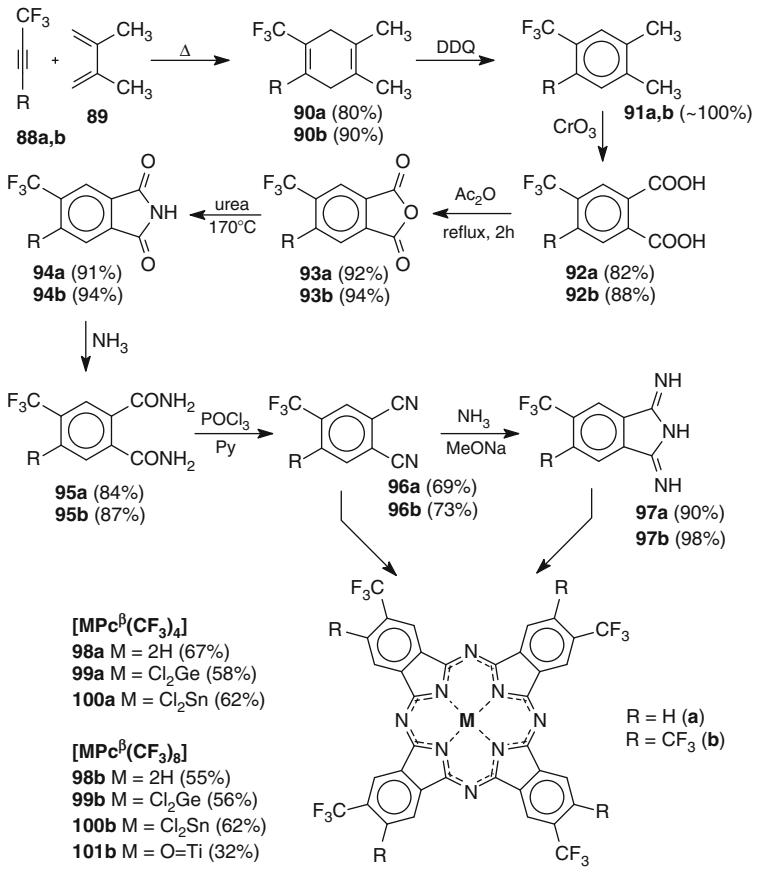


Fig. 6 Molecular structure of μ-$O[FePc^{\alpha}(CF_3)_8]_2$ (CCDC 707384) [68]

The dinitrile precursors for β-tetra- and β-octatrifluoromethylphthalocyanines $[MPc^{\beta}(CF_3)_4]$ and $[MPc^{\beta}(CF_3)_8]$ (Scheme 24) were obtained [69] starting from the mono(bis)trifluoromethyl substituted acetylenes **88a,b** and 2,3-dimetylbutadiene **89** which easily give the Diels-Alder products **90a,b**. These adducts were converted quantitatively upon dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to *o*-xylene derivatives **91a,b**. Their oxidation CrO_3 in a mixture of acetic and sulfuric acids affords the phthalic acids **91a,b** (yield ca. 80 %) which were converted to dinitriles **96a,b** and diiminoimides **97a,b** in a common way through intermediate anhydrides **93a,b**, imides **94a,b**, diamides **95a,b**.

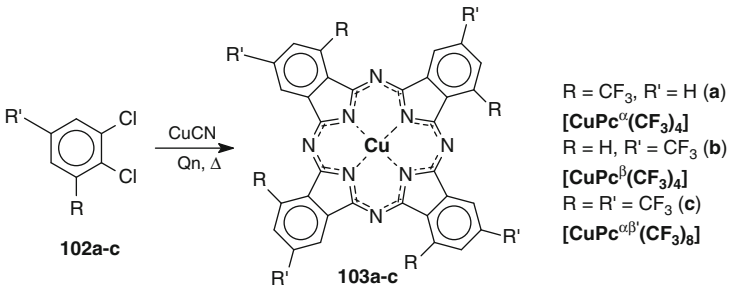


Scheme 24 Synthesis of β-trifluoromethyl substituted phthalocyanines

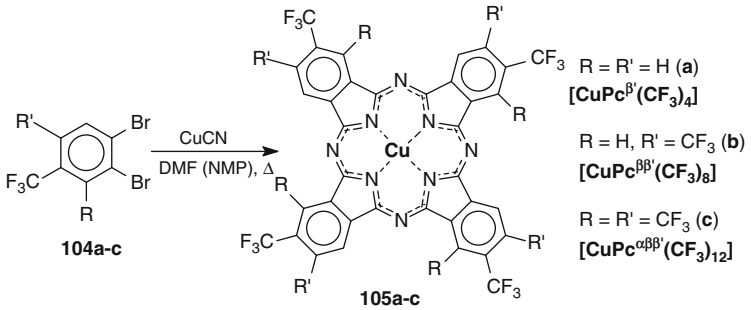
The Sn^{IV} complexes **100a,b** were obtained from the dinitriles **96a,b** and $SnCl_2$ in 1-chloronaphthalene (reflux 4 h), while diiminoimides **97a,b** were used for preparation of the Ge^{IV} complexes **99a,b** (refluxing with $GeCl_4$ in quinoline, 4 h) and the free bases **98a,b** (refluxing in dimethylaminoethanol, 7 h). The Ti^{IV} complex [O=TiPc$^{\beta}$(CF$_3$)$_8$] (**101b**)was obtained [70] by heating of the dinitrile with Ti(OBu)$_4$ and urea in *n*-octanol (190 °C, 6 h, 32 %).

The Cu^{II} complexes can be prepared directly from trifluoromethyl substituted 1,2-dihalobenzenes in the course of Rosemund-Braun reaction with copper(I) cyanide (Scheme 25). Thus, reaction of 3-, 4-trifluoromethyl and 3,5-difluoromethyl substituted 1,2-dichlorobenzenes **102a–c** with CuCN in quinoline (Qn) leads to Cu^{II} complexes of α- or β-tetrafluoromethyl- or α,β′-octatrifluoromethylphthalocyanines **103a–c** [71].

In a similar way 4-, 4,5-bis- and 3,4,5-tristrifluoromethyl substituted 1,2-dibromobenzenes **104a–c** produces directly Cu^{II} complexes of β-tetrafluoromethyl-, β,β′-octatrifluoromethyl- and α,β,β′-dodecatrifluoromethylphthalocyanines **105a–c** [66] in reaction with CuCN in DMF or N-methylpyrrolidone (NMP) (Scheme 26).

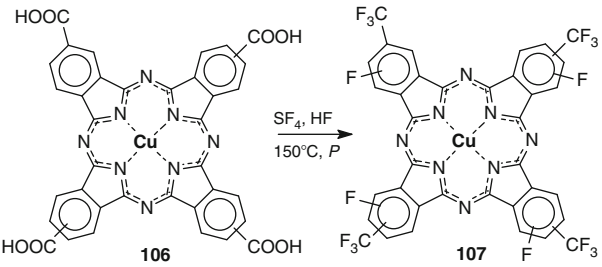


Scheme 25 Direct synthesis of trifluoromethyl substituted Cu^{II} phthalocyanines from 1,2-dichlorobenzenes



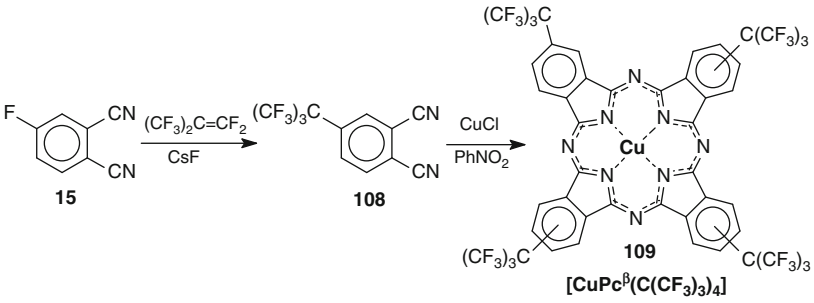
Scheme 26 Direct synthesis of trifluoromethyl substituted Cu^{II} phthalocyanines from 1,2-dibromobenzenes

Trifluoromethyl groups are usually introduced in 1,2-dihalogenobenzenes by heating of the corresponding carboxylic derivatives with SF_4 and HF under pressure. Similarly, treatment of Cu^{II} complex of tetra(4-carboxy)phthalocyanine **106** with SF_4 in the presence of HF in a steel bomb at 150–155 °C (Scheme 27) also leads to conversion of COOH groups to CF_3 groups and concomitant substitution of one hydrogen atom in each benzene ring by fluorine is observed, i.e. isomeric mixture of Cu^{II} complex of β-tetra(trifluoromethyl)tetrafluorophthalocyanine **107** is formed [72].



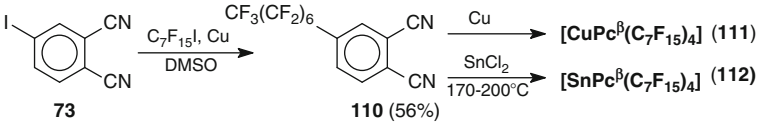
Scheme 27 Synthesis of trifluoromethyl substituted phthalocyanines by fluorination of carboxy groups

Reaction of 4-fluorophthalodinitrile **15** with perfluoroisobutylene in sulfolane in the presence of CsF affords 4-perfluoro-*tert*-butyl substituted phthalonitrile **108** which upon heating with CuCl gives the phthalocyanine complex **109** [12] (Scheme 28). The cyclotetramerization of 3-substituted dinitrile produced similarly failed, evidently due to steric hindrances of bulky perfluoro-*tert*-butyl groups.



Scheme 28 Synthesis of perfluoro-*tert*-butyl substituted phthalocyanines

Another approach to perfluoroalkyl substituted phthalonitrile includes reaction of 4-iodophthalonitrile **73** with perfluoroalkyliodides in the presence of activated Cu in DMSO [73]. In such way 4-perfluoroheptylphthalodinitrile **110** was obtained (115–120 °C, 2 h) (Scheme 29). Some amount of the Cu^{II} complex **111** is formed in a side reaction of cyclotetramerization. Melting of the dinitrile with $SnCl_2$ at 170–200 °C leads to the formation of the Sn complex **112**.



Scheme 29 Synthesis of perfluoroheptyl substituted phthalocyanines

Spectral data on perfluoroalkyl substituted phthalocyanines and their Cu^{II} complexes are presented in Table 5. It can be noticed that introduction of electron-withdrawing perfluoroalkyl group in α- or β-position of each benzene ring results in a hypsochromic shift of the Q-band maximum, which indicates stabilization of HOMO in respect to LUMO. Eight CF_3 groups in β-positions have a similar effect, but in the case of octa-α-substituted species an opposite bathochromic shift of the Q-band is observed. This is evidently connected with the distortion of the planarity of the macrocycle due to steric interaction of CF_3 groups in α-positions of the adjacent isoindole units (Fig. 5) which destabilize HOMO.

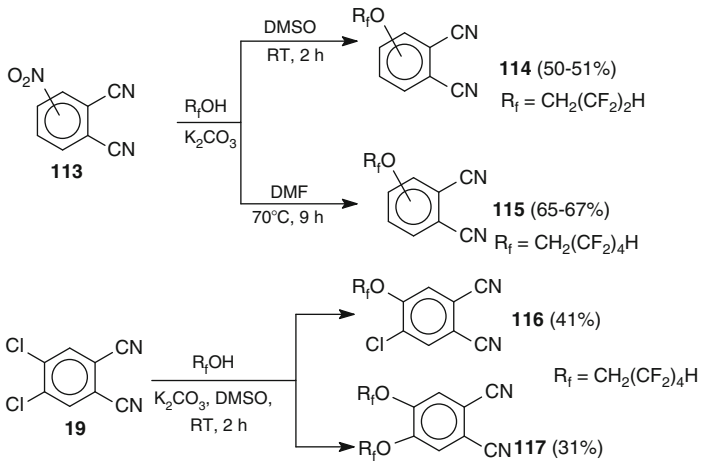
Table 5 UV-vis spectra of perfluoroalkyl substituted phthalocyanines

	λ_{max}, nm[a]			
Complex	Q-band	Soret band	Solv.	Ref.
[H_2Pc]	692(5.21), 665(5.18), 638(4.52), 601(4.43)	350(4.70)	ClNp	
[$H_2Pc^{\alpha}(CF_3)_4$]	681(5.11), 646(5.08), 620(4.55), 584(4.26)	336(4.79)	PhCl	[66]
[$H_2Pc^{\alpha\alpha'}(CF_3)_8$]	702, 674	344	PhCl	[66]
[$H_2Pc^{\beta}(CF_3)_4$]	691, 655, 637, 627, 597, 571sh	363sh, 333	PhH	[69]
[$H_2Pc^{\beta}(C(CF_3)_3)_4$]	692(*2.42*), 655(*1.98*), 638sh, 626sh, 593(*0.48*)	342(*1*)	PhCl	[12]
[CuPc]	678(5.34),648(4.51), 611(4.56)	350(4.76)	ClNp	
[$CuPc^{\alpha}(CF_3)_4$]	660(5.25), 631(4.43), 595(4.42)	339(4.79)	PhCl	[66]
[$CuPc^{\alpha\alpha'}(CF_3)_8$]	680(5.02), 616(4.35)	342(4.85)	PhCl	[66]
[$CuPc^{\beta\beta'}(CF_3)_8$]	669(5.36), 639(4.52),601(4.50)	337(4.80)	PhCl	[66]
[$CuPc^{\alpha\beta\beta'}(CF_3)_{12}$]	669(*2.45*), 639(*0.50*), 601(*0.45*)	344(*1*)	PhCl	[66]
[$CuPc^{\beta}(C(CF_3)_3)_4$]	672(*3.55*), 640sh, 602(*0.6*)	334(*1*)	PhCl	[12]

[a]Values in parenthesis indicate values of logε (normal font) or relative intensity (A/A_{max}) (*italics*)

2.7.2 Perfluoroalkoxy Substituted Phthalocyanines

Phthalocyanines containing (per)fluorinated alkoxygroups are usually obtained by cyclotetramerization of corresponding (per)fluoroalkoxy substituted phthalonitriles. The latter can be easily prepared by nucleophilic substitution reaction of halo or nitrosubstituted phthalonitriles in the presence of the corresponding fluorinated alcohol (Scheme 30).



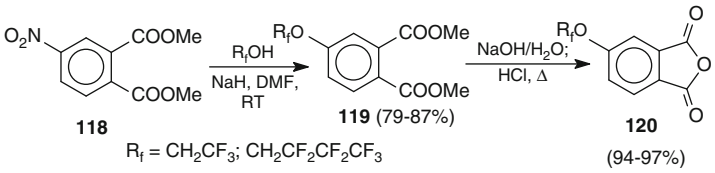
Scheme 30 Synthesis of phthalonitriles with fluorinated alkoxy groups

Thus, phthalonitriles **114**, **116**, **117** bearing 2,2,3,3-tetrafluoropropoxy groups in 3-, 4- or 4,5-positions were obtained from 3(4)-nitro- or 4,5-dichloro phthalonitriles (**113** or **19**) in DMSO in the presence of K_2CO_3 at room temperature (yields 30–50 %) and converted to the corresponding α-, β, and β,β′- 2,2,3,3-tetrafluoropropoxy

substituted Zn^{II} phthalocyanines upon reflux with $Zn(OAc)_2$ in n-pentanol in the presence of DBU (yields 25–56 %) [74]. It was observed [74] that fluorination of alkyl groups in Zn^{II} phthalocyanines increases their photostability and enhances the fluorescence and singlet oxygen quantum yields which important for their application as potential photosensitizes.

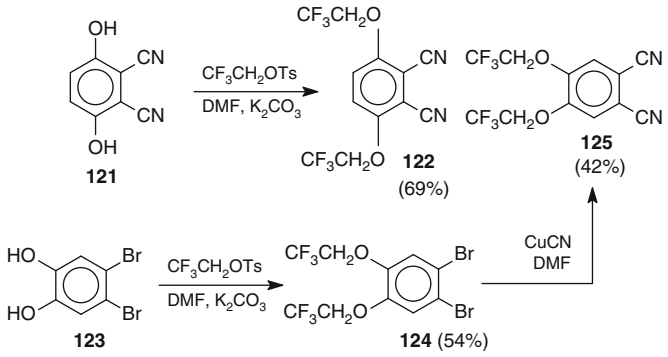
Substitution of the NO_2 group in **113** by fluorinated alkoxy group can be also accomplished in DMF/K_2CO_3 at elevated temperature (70 °C) and more prolonged heating (9 h) [75]. In such way 3- and 4-(2,2,3,3,4,4,5,5-octafluoropentoxy) substituted phthalodinitriles **115** were obtained and converted to the corresponding free base phthalocyanines [$H_2Pc^{\alpha}(OR_f)_4$] and [$H_2Pc^{\beta}(OR_f)_4$] (R_f=$CH_2(CF_2)_4H$) upon reflux with lithium in 1-pentanol (4 h, yield ~30 %), or to their respective Zn^{II}, Ni^{II} and Fe^{III} complexes (1-pentanol, metal chloride, reflux, 4 h, 20–30 %). The Co^{II} complex was also reported [76].

In another approach [77] (Scheme 31) 4-nitro substituted dimethylphthalate **118** was reacted with fluorinated alcohol in DMF in the presence of NaH at room temperature to give 4-fluoroalkoxy substituted diester **119**. It was then converted to 4-fluoroalkoxy substituted phthalic anhydride **120**, which was directly used in template cyclotetramerization with metal acetates (Mg^{II}, Co^{II}, Zn^{II}) or chlorides (Cu^{I}, Fe^{III}, Al^{III}) by urea melt method (urea, ammonium molybdate, NH_4Cl) to give directly the corresponding β-tetrasubstituted metal phthalocyanine complexes (yields 7–26 %).



Scheme 31 Synthesis of phthalic anhydride with fluorinated alkoxy group

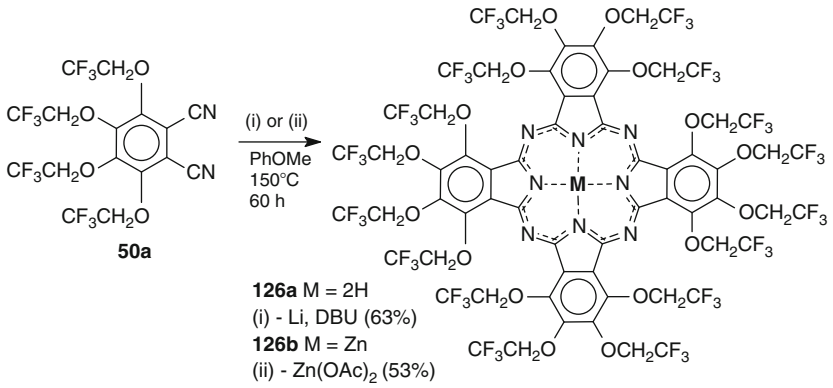
Alkylation of hydroquinone and catechol derivatives can be also applied for the introduction of CF_3CH_2O groups (Scheme 32).



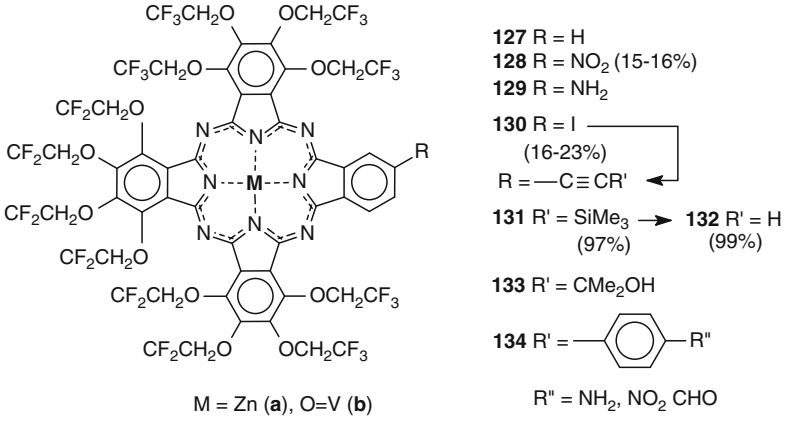
Scheme 32 Synthesis of phthalonitriles with two fluorinated alkoxy groups

3,6-Di(trifluoroethoxy)phthalodinitrile **122** can be prepared from 2,3-dicyanohydroquinone **121** by alkylation with trifluoroethyltosylate in DMF [70]. The 4,5-substituted dinitrile **125** is available from the 4,5-dibromocatechol **123** by consecutive alkylation with tosylate (DMF, K_2CO_3) and cyanation (CuCN, DMF) [70]. O=Ti^{IV} complexes of α- and β-octakis(trifluoroethoxy)phthalocyanines were prepared using these dinitriles **122** and **125** [70]. The Zn^{II} complex of β-octasubstituted phthalocyanine was also reported [78].

Tetra(2,2,2-trifluoroethoxy)phthalonitrile **50a** which was obtained from tetrafluorophthalonitrile and trifluoroethanol in DMF (see Sect. 2.5, Scheme 12) was used for preparation of symmetrical and low-symmetry "trifluoroethoxy-coated" phthalocyanines (Schemes 33 and 34). Prolonged heating of the dinitrile **50a** in anisole in the presence of Li and DBU leads to symmetrical free base phthalocyanine **126a**, while the Zn^{II} complex **126b** was formed in the presence of $Zn(OAc)_2$ [79].



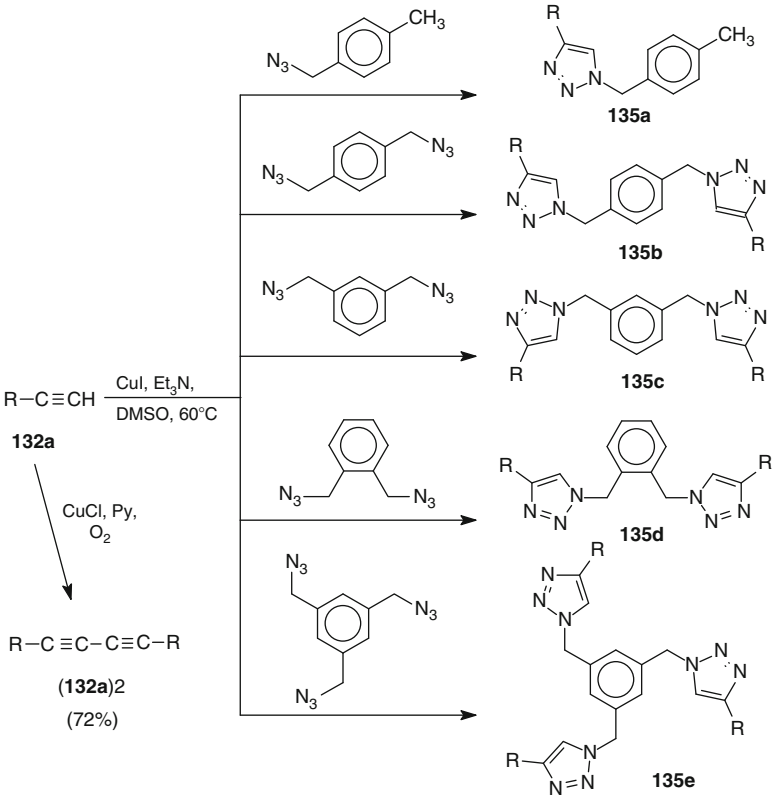
Scheme 33 Synthesis of symmetrical "trifluoroethoxy-coated" phthalocyanines



Scheme 34 Synthesis of low-symmetry "trifluoroethoxy-coated" phthalocyanines

Low-symmetry "trifluoroethoxy-coated" Zn^{II} and $O=V^{IV}$ phthalocyanines **127**–**130** (Scheme 34) were prepared by cross-tetramerization of the trifluoroethoxy substituted dinitrile **50a** and 4-nitro-, 4-amino- or 4-iodophthalodinitriles by urea-melt method in the presence of Zn^{II} or V^{III} chlorides [28, 80, 81]. The iodo substituted derivative **130** was functionalized with various terminal acetylenes using Pd catalyzed cross-coupling reaction ($[Pd(PPh_3)_2Cl_2]$, CuI, Et_3N, THF, yields 85–95 %) affording fluoroethoxy-coated Pc-acetylenes **131**–**134** for application in second-order non-linear optics [80, 81]. The iodo derivative **130a** upon heating in toluene with TBABr, $Pd(OAc)_2$, EtN^iPr_2 gives the directly linked dimer $(\mathbf{130a})_2$ (50 %) and the reduced species **127a** (30 %) [61].

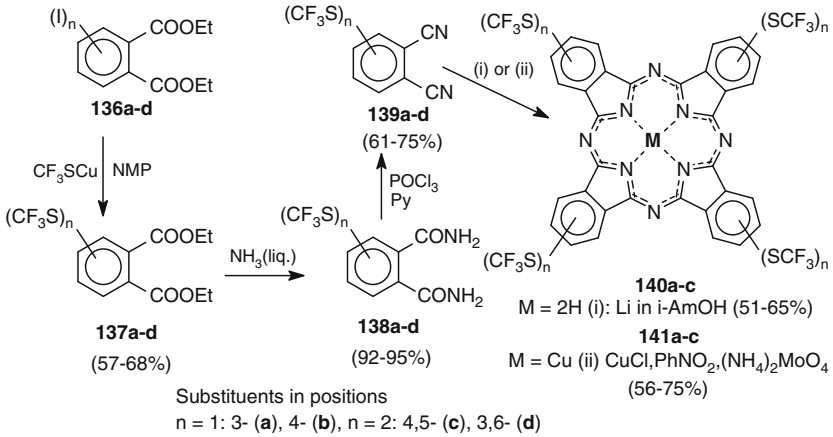
The ethynyl derivative **132a** obtained by desilylation of **131a** was used for the synthesis butadiyn-bridged dimer $(\mathbf{132a})_2$ [82] (Scheme 35). It was also used in a "click" reactions with mono-, bis- and tris-azidomethyl substituted benzenes (CuI, Et_3N, DMSO, 60 °C, 6 h) to give triazole-bridged conjugates **135a-e** with tolyl [83], dimers with *o*-, *m*- and *p*-xyliden and trimer with mesityliden [84]. The peptide conjugates have been also prepared [60].



Scheme 35 Synthesis of triazole-bridged monomeric, dimeric and trimeric "trifluoroethoxy-coated" phthalocyanine conjugates

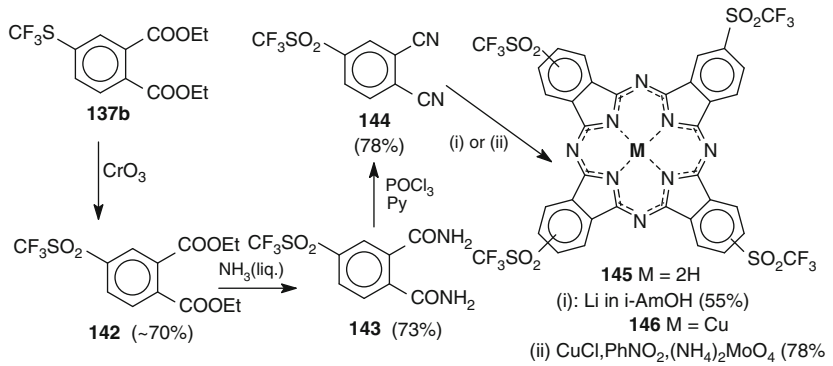
2.7.3 Perfluoroalkylsulfanyl- and –Sulfonyl Substituted Phthalocyanines

Phthalocyanines with trifluoromethylsulfanyl (CF_3S-) groups were first reported as free bases and Cu^{II} complexes of α- and β-tetrasubstituted and β,β′-octasubstituted derivatives **140a–c** [85]. The trifluoromethysulfanyl substituted phthalonitriles (3-, 4-, and 4,5-) **139a–c** which were used as precursors were prepared from corresponding iodo substituted diethylphthalates **136a–c** by reaction with CF_3SCu (in NMP at 150 °C) and following usual amidation-dehydration procedure (Scheme 36). 3,6-Di(trifluoromethylsulfanyl)phthalonitrile **139d**, which was prepared similarly, failed to give phthalocyanine macrocycle due to steric hindrances.



Scheme 36 Synthesis of trifluoromethylsulfanyl substituted phthalocyanines

Oxidation of 4-CF_3S substituted diethyl phthalate **137b** by CrO_3 in AcOH (Scheme 37) leads to sulfone **142** and then through diamide **143** to dinitrile **144** used for preparation of β-tetra(trifluoromethylsulfonyl)pthalocyanine **145** and its Cu^{II} complex **146** [85].



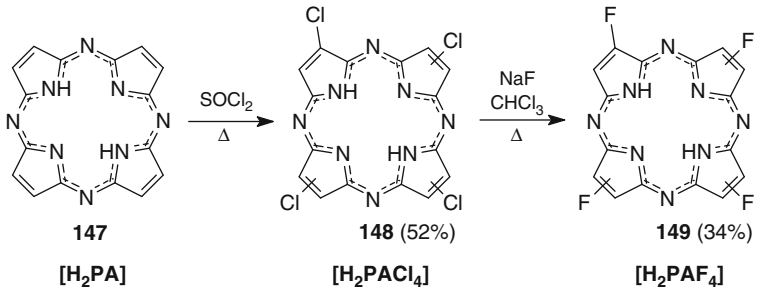
Scheme 37 Synthesis of trifluoromethylsulfonyl substituted phthalocyanines

3 Fluorinated Porphyrazines

Phthalocyanine analogues without fused benzene rings are usually named porphyrazines (PAs). Two types of fluorinated porphyrazines are known – the species with fluorine atoms attached directly in β-pyrrolic positions and compounds with fluorinated β-substituents.

3.1 β–Fluorinated Porphyrazines

Tetrafluoroporphyrazine H_2PAF_4 (**149**) bearing one fluorine atom in each of four pyrrole rings (Scheme 38) can be prepared as a regioisomeric mixture from unsubstituted porphyrazine H_2PA (**147**) in a two-stage procedure.

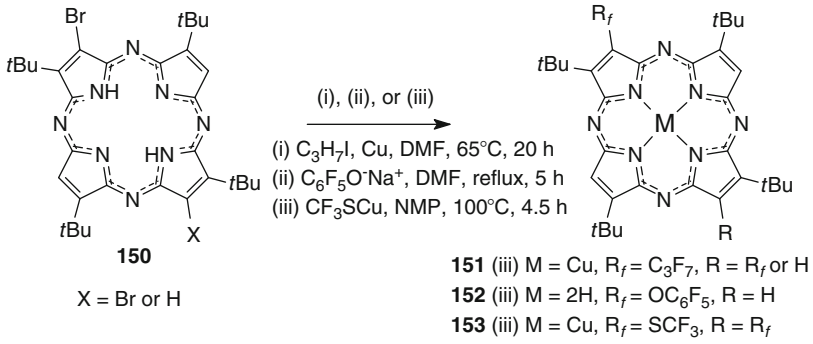


Scheme 38 Synthesis of tetrafluoroporphyrazine

The intermediate tetrachloro derivative H_2PACl_4 (**148**) can be obtained by chlorination of H_2PA by $SOCl_2$ (45–55 °C, 6–8 h, 52 %), or SO_2Cl_2 (20–25 °C, 3 days, 43 %) [86], or by PCl_5 in acetic acid in the presence of H_2SO_4 [87]. The following heating of H_2PACl_4 in $CHCl_3$ in the presence of NaF at 55 °C for 3 days gives H_2PAF_4 with 34 % yield [88].

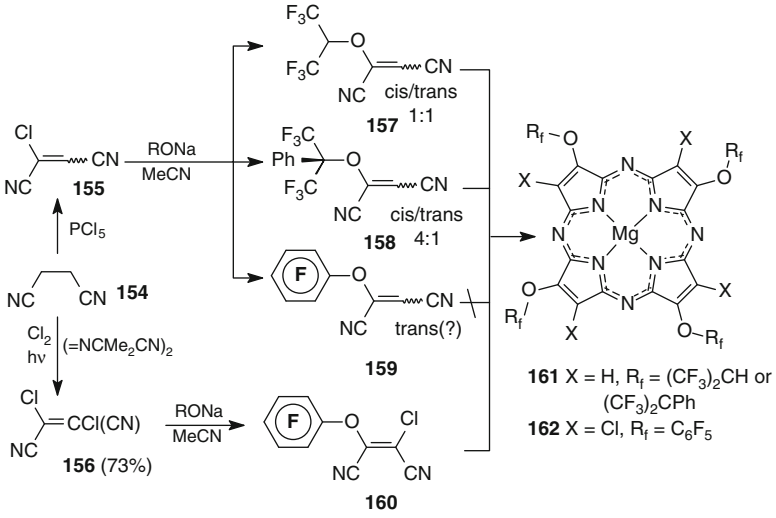
3.2 Porphyrazines with Fluorine-Containing Substituents

β-Halogen atoms in porphyrazines can be also directly substituted by perfluorinated alkyl, aryloxy and alkylthio groups. Thus, it was shown [89] that bromine atoms in mono- and dibromosubstituted porphyrazines **150** obtained by bromination of tetra-tert-butylporphyrazine ($H_2PA^tBu_4$) with N-bromosuccinimide in $CHCl_3$ [90] can be substituted by (i) perfluoropropyl groups upon treatment with C_3F_7Cu in DMF (**151**), (ii) perfluorophenoxy group upon reflux with $C_6F_5O^-Na^+$ in DMF (**152**), and (iii) by trifluoromethylsulfanyl group upon heating with CF_3SCu in N-methylpyrrolidone (**153**). The reactions (i) and (iii) are accompanied by coordination of Cu and reactions (i) and (ii) by reduction of one of the C-Br bonds (Scheme 39).



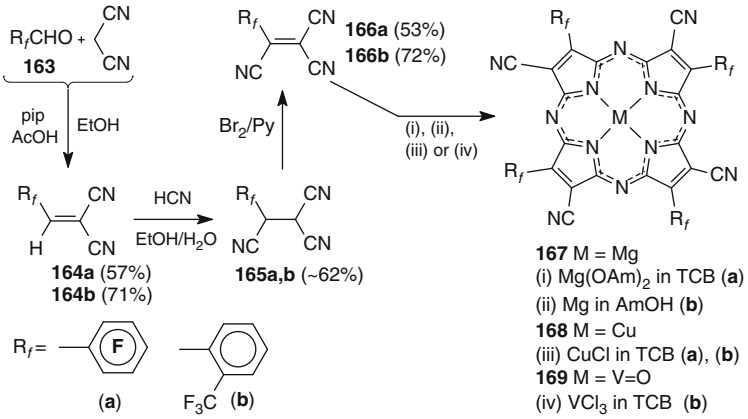
Scheme 39 Introduction of perfluorinated groups to bromo substituted porphyrazines

Porphyrazines with four fluorinated alkoxy and aryloxy groups **161** and **162** were obtained starting from succinonitrile **154** [89] (Scheme 40). Its chlorination with PCl_5 afford monochloromaleo(fumaro)dinitriles **155**, while reaction with Cl_2 under UV irradiation initiated by azobisisobutyronitrile leads to dichloro derivative **156** (73 %). Nucleophilic substitution of one chlorine atom in the dinitriles **155** and **156** with hexafluoro-isopropoxy or perfluorophenyl groups proceeds in mild conditions in MeCN leading to a mixture of maleo(fumaro)dinitriles **157**–**160** with fluorinated alkoxy/aryloxy groups. Only maleodinitriles, i.e. *cis*-isomers of **157** and **158**, afford in the course of template cyclotetramerization with $Mg(OPr)_2$ in *n*-propanol Mg^{II} porphyrazines **161** (as a mixture of regioisomers). Among perfluorophenoxy substituted dinitriles **159** and **160** only chloro containing species **160** give porphyrazine macrocycle **162**, while cyclotetramerization of a non-chlorinated species **159** failed, presumably due to exclusive *trans*-configuration of the nitrile groups. The Mg^{II} complexes **161** and **162** can be demetallated to the free bases in a usual manner upon treatment with CF_3COOH, and then converted to other metal complexes (Cu^{II}, Zn^{II}).



Scheme 40 Synthesis of porphyrazines with perfluorinated alkoxy and aryloxy groups

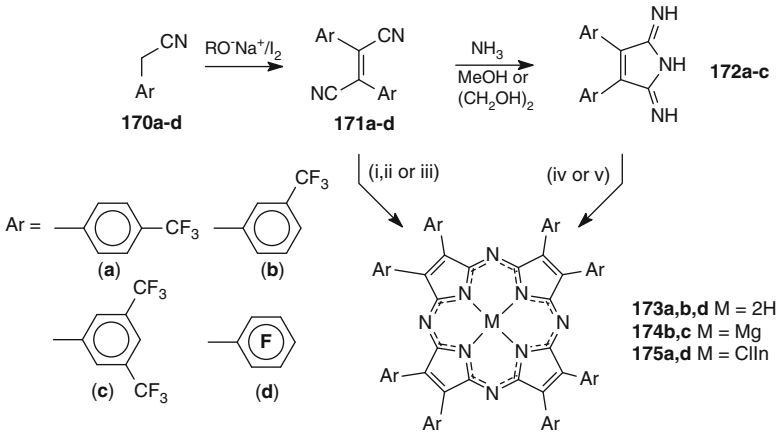
Porphyrazines combining fluorinated aryl groups with cyano group in each pyrrole ring can be conveniently prepared [91] starting from malonodinitrile and fluorinated benzaldehydes **163a,b** (Scheme 41).



Scheme 41 Synthesis of fluorinated tetraaryltetracyanoporphyrazines

Their condensation proceeds smoothly in anhydrous ethanol in the presence of piperidine and acetic acid (20–25 °C, 20 min) affording 1,1-dicyanoethylens **164**. Subsequent addition of HCN leads to 1,1,2-tricyanoethanes **165a,b**, which are oxidized in pyridine solution by Br_2 to give 1,1,2-tricyanoethylenes **166a,b**. The latter can be directly used in template cyclotetramerization in the presence of metal salts and complexes of tetracyanoporphyrazines with Mg^{II} (**167a,b**), Cu^{II} (**168a,b**) and $O{=}V^{IV}$ (**169b**) were obtained [91].

Porphyrazines bearing eight fluorine-containing aryl groups **173** can be synthesized from the corresponding bisaryl substituted maleo(fumaro)dinitriles **171a–d** which are easily available by oxidative dimerization of correspondingly substituted arylacetonitrites **170a–d** when treated with alkoxide in the presence of iodine (Scheme 42).



Scheme 42 Synthesis of fluorinated octaarylporphyrazines

Table 6 Synthesis of fluorine-containing β-octaarylporphyrazines by template cyclotetramerization of dinitriles **171** or diiminoimides **172** (Scheme 42)

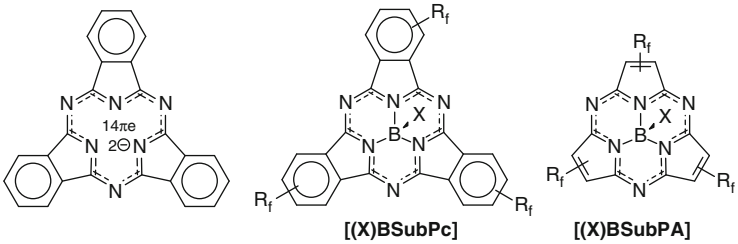
Ar =	M =		Conditions of cyclotetramerization	Yield	Ref.
p-CF_3Ph	2H	**173a**	(iv) diiminoimide **172a** + NaOMe, *n*-AmOH, 140 °C, 16 h	53 %	[92]
p-CF_3Ph	InCl	**175a**	(i) dinitrile **171a** + $InCl_3$ + DBU in quinoline, 230 °C, 8 h	30 %	[92]
m-CF_3Ph	2H	**174a**	(iv) diiminoimide **172b** + NaOMe, *n*-AmOH, 140 °C, 16 h	54 %	[92]
m-CF_3Ph	Mg	**174b**	(ii) dinitrile **171b** + Mg in *n*-AmOH/octanol-1 (1:5), reflux 12 h	13 %	[93]
3,5-$(CF_3)_2$Ph	Mg	**174c**	(v) diiminoimide **172c** + Mg in *n*-BuOH, reflux 12 h	78 %	[94]
C_6F_5	InOAc	**175d**	(iii) dinitrile **171d** + In^{III} acetate, melting	25 %	[97]

In such way trifluoromethyl substituted octaarylporphyrazines **173a–c** have been prepared (Table **6**) [92–94]. When the mixture of maleo(fumaro)dinitriles **171a–c** is used directly for preparation of porphyrazine complexes the yields do not exceed 30 %, evidently due to low reactivity of *trans*-isomer present in excess [92, 93]. The template cyclotetramerization proceeds more smoothly when the mixture of *cis*- and *trans*-dinitriles **171a–c** is preliminary converted to more reactive diiminoimide **172a–c** upon treatment with NH_3 in the presence of catalytic amounts of sodium alcoholate [92, 94]. Low-symmetry porphyrazines bearing from two to six *m*-trifluoromethyl groups and fused benzene rings have been also studied [95, 96].

Recently we have succeeded in preparation of octakis(perfluorophenyl)substituted porphyrazine [97]. Bis(perfluorophenyl) substituted maleo(fumaro)dinitrile **171d** was cyclotetramerized to form the In^{III} complex **175d** in non-nucleophilic conditions (melting with In^{III} acetate) in order to avoid substitution of fluorine in phenyl rings. Then the free-base porphyrazine **173d** was obtained by catalytic demetallation with CF_3COOH in the presence of TBACl.

4 Fluorinated Subphthalocyanines and Subporphyrazines

Homologues of phthalocyanines containing three isoindole units instead of four are commonly named subphthalocyanines (SubPc). The unique 14π-electron macrocyclic system of subphthalocyanine dianion is known to exist only in the form of boron complexes [(X)BSubPc]. Their analogues without fused benzene rings are named as boron subporphyrazines [(X)BSubPA].



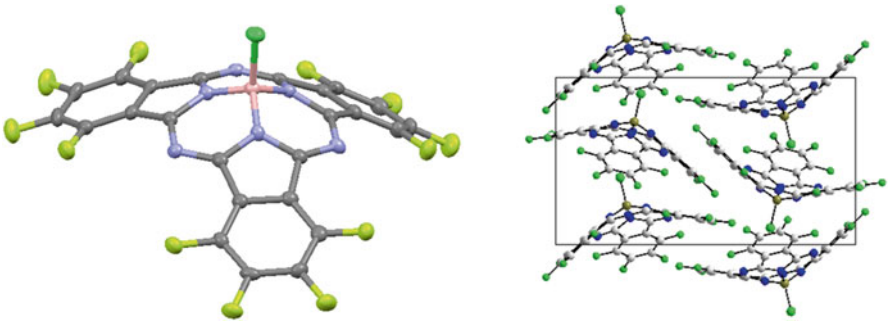


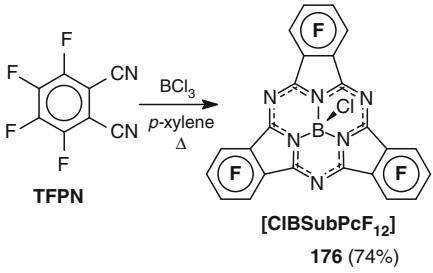
Fig. 7 Molecular structure of [ClBSubPcF$_{12}$] **176** (CCDC 181314) [100]

Among fluorinated derivatives perfluorinated boron subphthalocyanines, fused fluorinated subphthalocyanines with extended π-system and perfluorophenyl substituted boron subporphyrazines are known.

4.1 Perfluorinated Subphthalocyanines

The perfluorinated subphthalocyanine [ClBSubPcF$_{12}$] (**176**) first reported in 1998 was obtained by reaction of TFPN with BCl_3 in benzene [98]. Later the procedure was optimized by changing solvent to a higher boiling *p*-xylene (Scheme 43) which allows to obtain [ClBSubPcF$_{12}$] using equimolar amounts of TFPN and BCl_3 in 74 % yield after only 20 min reflux [99]. Other high-boiling solvents can be also used, thus [ClBSubPcF$_{12}$] was obtained in 51 % yield in boiling 1,2,4-trichlorobenzene (214 °C, 30 min) [100].

Scheme 43 Synthesis of perfluorinated subphthalocyanine

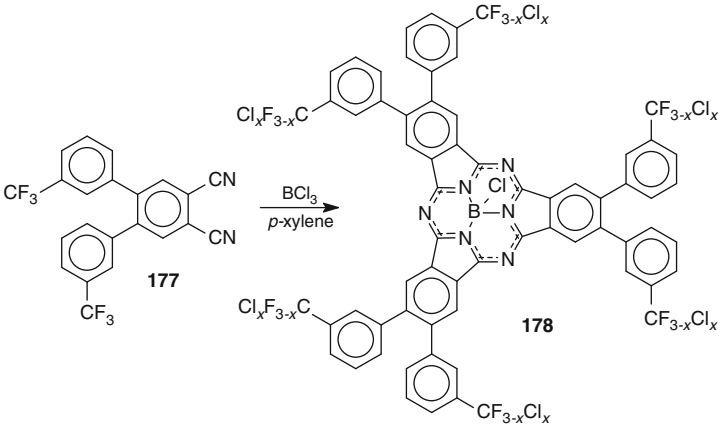


The structure of [ClBSubPcF$_{12}$] was determined by X-ray diffraction study [100] (Fig. 7). [ClBSubPcF$_{12}$] is well soluble in organic solvents, the solutions are stable in the dark, but tend to decompose in the presence of light due to weak B-Cl bond and long-lived triplet states [98, 99]. So far BCl_3 is the only boron derivative successfully used in the preparation of fluorinated subphthalocyanines. Reactions

of chlorine substitution in [ClBSubPcF$_{12}$] (**176**) and axial functionalization of fluorinated subphthalocyanines are considered in Sect. 4.3.

Perfluorination of subphthalocyanine macrocycle leads to a relatively small bathochromic shifts of the π-π* absorption maxima in the UV and visible regions (from 300 to 560 nm for [ClBSubPc] to 310 and 570 nm for [ClBSubPcF$_{12}$] in acetonitrile [98]), indicating that HOMO is slightly less stabilized than LUMO. Indeed, perfluorination shifts the 1st reduction potentials by ca 700 mV to the positive region ($E_{½}^{Red}$ = −0.43 V vs. SCE in MeCN [98]). The irreversible oxidation for [(X)BSubPc] is observed only at ca. +1.5 V, at potentials by 500 mV more positive as compared to non-fluorinated species [98, 104]. [ClBSubPcF$_{12}$] exhibit the strong fluorescence in solution (emission maxima at 586 nm) and have high fluorescence quantum yield (ϕ = 0.6) [98], which is comparable with the data for non-fluorinated species.

While aromatic fluorine in TFPN appears to be stable against chlorination by BCl_3, fluorine atom in trifluoromethyl group can be exchanged by chlorine in the course of cyclotrimerization reaction. Thus, it was observed in reaction of BCl_3 with 4,5-bis(3-trifluoromethylphenyl)phthalodinitrile **177** that from one to two fluorine atoms in trifluoromethylgroup can be exchanged by chlorine leading to a mixture of hexaphenylsubphthalocyanines with $CF_{3-x}Cl_x$ groups (x = 0–2) **178** [101] (Scheme 44). It was demonstrated that these mixed species have high photostability and display non-linear optical effects and saturable absorbers and reverse saturable absorbers of 532 nm laser pulses.



Scheme 44 Partial chlorination occurring during subphthalocyanine synthesis from 4,5-bis(3-trifluoromethylphenyl)phthalodinitrile

4.2 π-Extended Fluorinated Subphthalocyanines

Reaction of TFPN with BCl_3 in the presence of other *ortho*-dintriles leads to a mixture of [ClBSubPcF$_{12}$] with another symmetrically substituted species and two low-symmetry octafluoro and tetrafluoro derivatives having symmetry lower than C_{3v}.

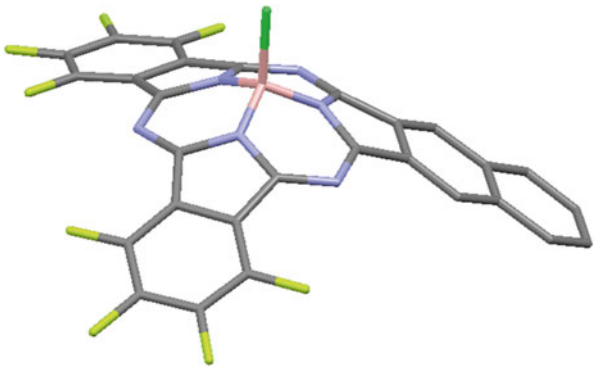
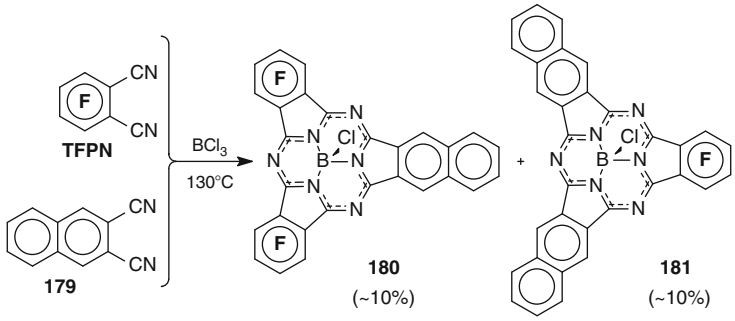


Fig. 8 Molecular structures of naphtho-fused subphthalocyanine **180** (CCDC XAQGEB) [102]

Co-cyclotrimetrization of TFPN with 2,3-naphthalenedicarbonitrile **179** in the presence of BCl_3 (1:2:1.5 ratio) in 1,2,4-trichlorobenzene:1-methylnaphthalene (4:1) at 130 °C gives mixture of two low symmetry subphthalocyanines **180** and **181** (~1:1, overall yield 20 % based on TFPN) with some admixture of two symmetrical species [102] (Scheme 45).

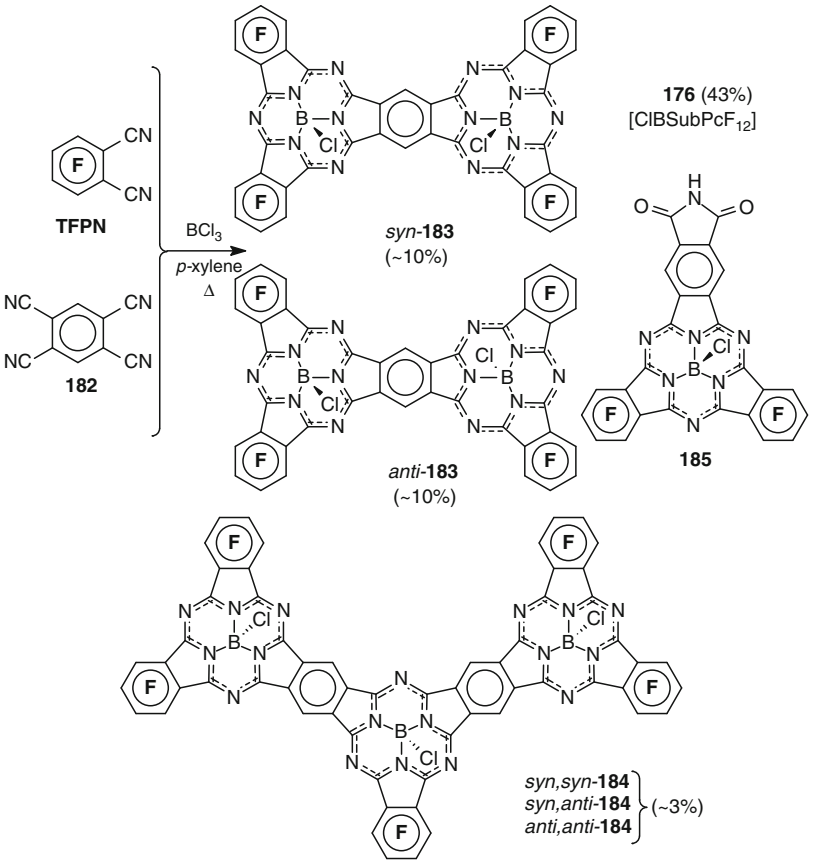


Scheme 45 Synthesis of fluorinated subphthalocyanines with naphthalene fragment(s)

The structure of mononaphthalene-fused derivative was established by X-ray crystallography (Fig. 8). The extension of the π-system by replacing of tetrafluorobenzene fragments by naphthalene rings leads to increased red shift of the lowest π-π* transition (*Q*-band) from 573 nm in **176** to 617 and 640 nm in mononaphtho- and dinaphtho-fused species **180** and **181**, respectively.

In the case of tetracarbonitriles very interesting fused dimeric and trimeric subphthalocyanines can be obtained [100, 103] (Scheme 46). Thus, co-condensation of TFPN, pyromellitic tetranitrile (1,2,4,5-tetracyanobenzene) **182** and BCl_3 (10:1:36 ratio) in *p*-xylene under reflux (3 h) gives along with the monomeric [ClBSubPcF_{12}] **176** (43 %), dimeric **183** (20 %) and trimeric **184** (3 %) forms [103, 104]. It was shown [104] that 10:1 ratio of dinitriles TFPN:**182** affords the highest yield of dimers **183** (16 % at 20:1 and 5 % at 5:1 ratio) in these reaction conditions.

The lower 1:2 ratio gives <1 % of the dimers and along with [ClBSubPcF$_{12}$] (26 %), octafluorophthalimide derivative **185** (16 %) and tetrafluorophthalimide (12 %) were isolated [104].



Scheme 46 Synthesis of dimeric and trimeric fluorinated subphthalocyanines

Co-cyclotetramerization in 1,2,4-trichlorobenzene at higher temperature (TFPN:**182** ratio 20:1, 216 °C, 30 min) [100] affords mainly [ClBSubPcF$_{12}$] **176** (51 %) while < 1 % of dimers **183** were isolated. As was concluded from analysis of ^{1}H NMR spectra [103] the dimer **183** exists in two topoisomeric forms – *syn*- and *anti*-isomers(or *cis*- and *trans*-isomers) which have the axial bonded ligand on one or opposite sides of the macrocyclic surface. These topoisomers were separated by column chromatography [100, 103] and their structure was established by single crystal X-ray diffraction study [100] (Fig. 9). The trimer **184** was isolated as a mixture of three possible topoisomers (*syn,syn*-, *syn,anti*- and *anti,anti*-) [103, 104].

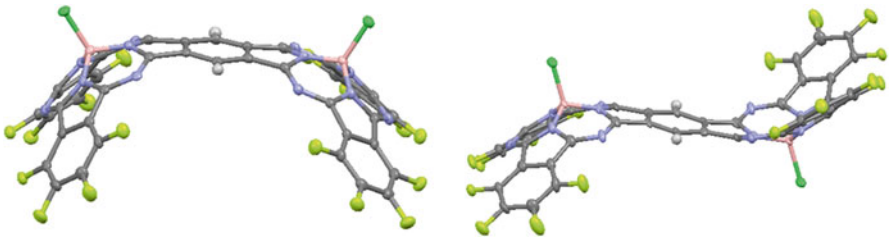
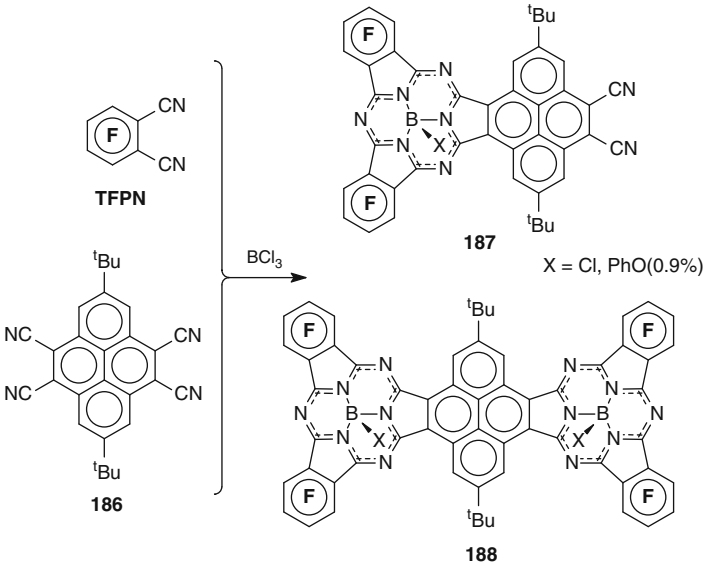


Fig. 9 Molecular structure of *syn*- and *anti*-topoisomers of the fluorinated dimer **183** (CCDC 181315, 181316) [100]

The position of the lowest π-π*-transition (*Q*-band in the UV-VIS spectra) is shifted bathochromically upon going from the monomer [ClBSubPcF$_{12}$] **176** (573 nm) to dimers **183** (690–693 nm) and further to trimeric species **184** (755 nm) due to extension of the π-chromophoric system.

Co-condensation of TFPN with *tert*-butyl substituted 4,5,9,10-pyrenetetracarbo nitrile **186** and BCl_3 in 1-chloronaphthalene (230 °C) (Scheme 47) leads to a mixture of [ClBSubPcF$_{12}$] **176** and pyrene fused monomeric and dimeric boron subphthalocyanines **187** and **188** [105]. While the formation of the dimer **188** was only evidenced by MALDI-TOF measurements, the pyrene fused monomer **187** was isolated as an axial phenoxy derivative and characterized by single crystal X-Ray diffraction study (Fig. 10), as well as its co-crystallizate with fullerene C_{60}. Interestingly, fusion of the pyrene moiety instead of one of tetrafluorobenzene fragments results in a lesser bathochromic shift of the Q-band [105], than was observed in the case of naphtho-ring fusion [102] (593 and 617 nm for **187** and **180**, respectively).



Scheme 47 Synthesis of pyrene-fused fluorinated subphthalocyanines

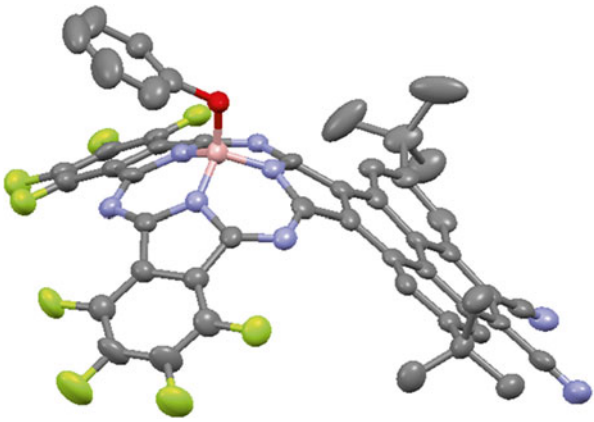


Fig. 10 Molecular structure of fluorinated pyrene-fused phenoxyboron subphthalocyaninate **187** (CCDC 780572) [105]

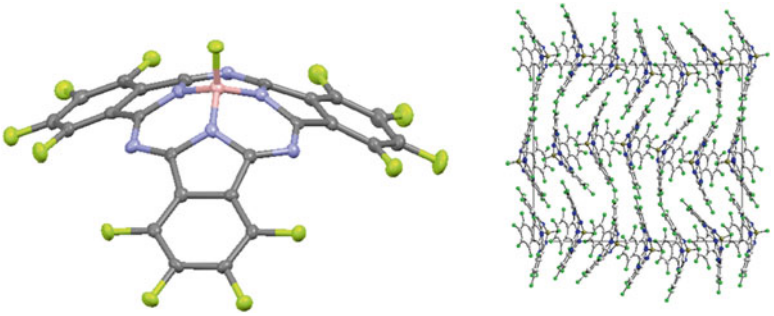
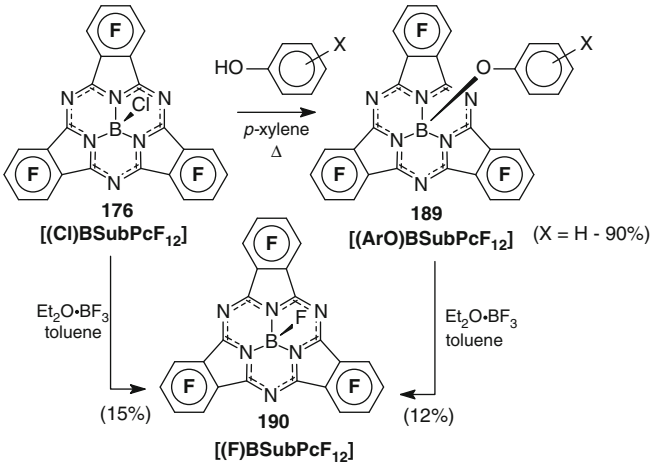


Fig. 11 Molecular structure and crystal packing of axially fluorinated perfluorosubphthalocyanin atoboron(III) **190** (CCDC 680083) [106]

4.3 Axially Functionalized Fluorinated Subphthalocyanines

Axial functionalization of [(Cl)BSubPcF$_{12}$], i.e. substitution of the axial chloride by various nucleophiles is very important for design of new materials based on perfluorinated subphthalocyanines. The B-Cl bond have relatively low stability and to avoid the side-reactions, such as hydrolysis (e.g. in the course of chromatography) it is convenient to handle more stable derivatives. The B-F bond is more stable and the axially fluorinated derivative [(F)BSubPcF$_{12}$] can be obtained by treatment of chloro (or phenoxy) derivatives with excess of $Et_2O{\cdot}BF_3$ in toluene under reflux (yields 15 and 12 %, respectively). It is noteworthy that molecules of [(F)BSubPcF$_{12}$] exhibit stacking alignment (see Fig. 11) in the chiral space group $P2_12_12_1$ – might be an important prerequisite for the second order non-linear properties in the crystal state [106].

The axial chloride in [ClBSubPcF$_{12}$] can be easily substituted with aryloxy groups by refluxing with the corresponding phenol in toluene or *p*-xylene [99] (Scheme 48) forming stable aryloxy derivatives [(ArO)BSubPcF$_{12}$]. The structure phenoxy [103] derivative was determined by X-ray diffraction study (Fig. 12).



Scheme 48 Synthesis of dodecafluorosubphthalocyanines bearing axial aryloxy group or fluorine atom

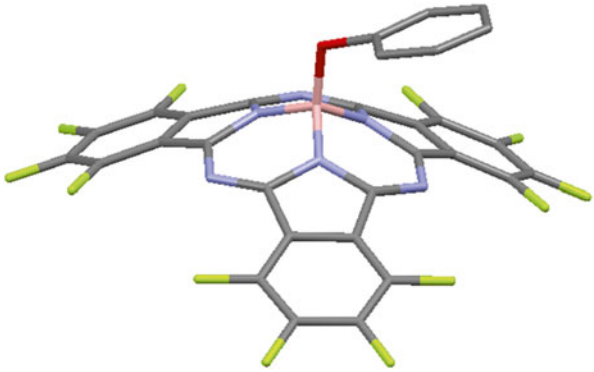
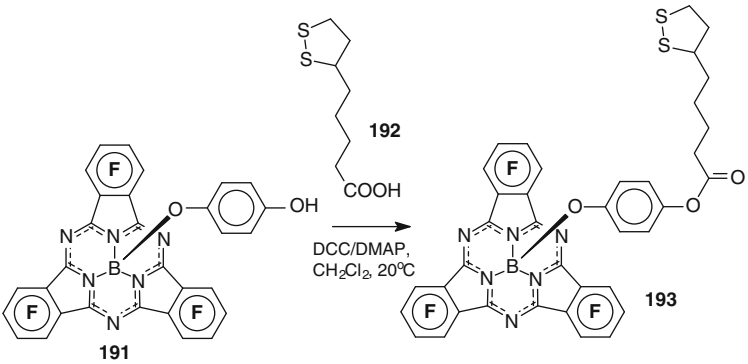


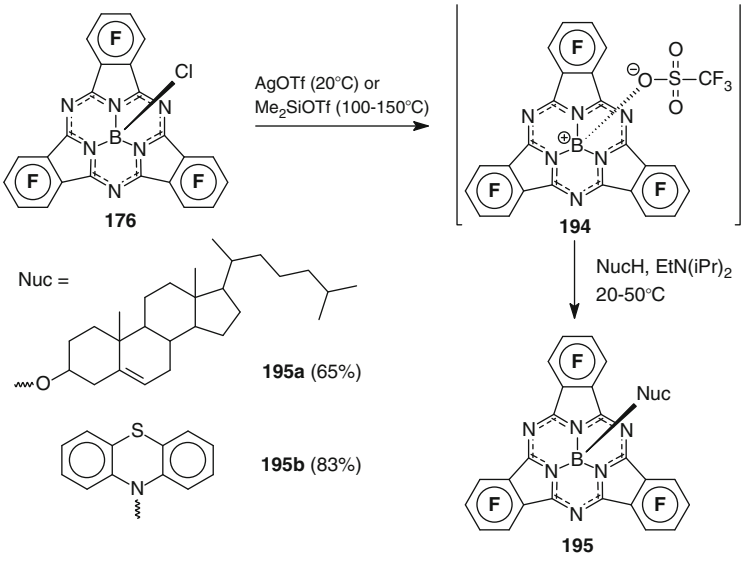
Fig. 12 Molecular structure of [(PhO)BSubPcF$_{12}$] **189** (CCDC 179556) [103]

The hydroquinone derivative **191** was esterified by thioctic acid **192** in the presence of 4-dicyclohexylcarbodiimide (DCC) and (N,N-dimethylamino)pyridine (DMAP) to give thiolane substituted perfluorinated BSubPc **193** (Scheme 49) which exhibited an enhance ability for self-assembling of monolayers on gold-substrates [107].



Scheme 49 Synthesis of thiolane substituted perfluorinated subphthalocyanine

The efficient one-pot two step procedure through intermediate triflate derivative **194** was elaborated for substitution of chloride in **176** with less reactive O- and N-nucleophiles [108] (Scheme 50). On the first stage [(Cl)BSubPcF$_{12}$] is treated with $Me_3SiOSO_2CF_3$ at 100–150 °C or with $AgOSO_2CF_3$ at 20 °C to form reactive species **194** – [$^{+}$BSubPcF$_{12}$] cation with weakly coordinated triflate anion.



Scheme 50 One-pot two-step procedure for preparation of axially substituted perfluorinated subphthalocyanines through the triflate derivative **194**

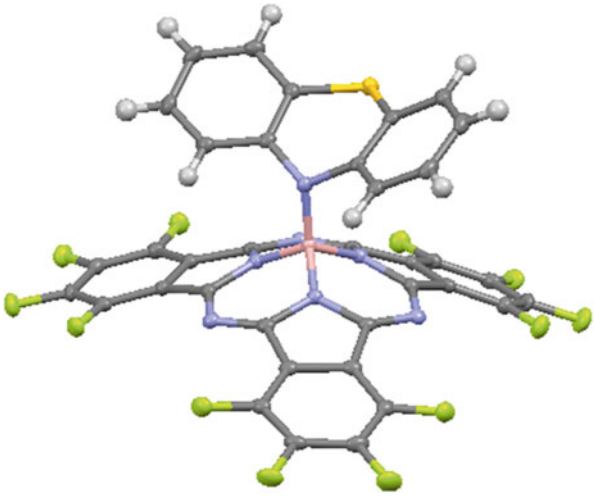
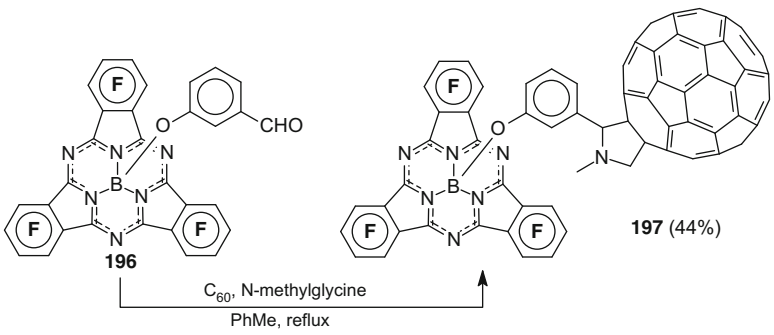


Fig. 13 Molecular structure of phenothiazine derivative of perfluorosubphthalocyaninato boron(III) **195b** (CCDC 798231) [108]

On the next step it reacts with a nucleophile in the presence of EtN(*i*Pr)$_2$ at 20–50 °C. Interestingly, cholesterol and 10*H*-phenothiazine derivatives **195a** and **195b**, which cannot be obtained directly from the chloride, are accessible through the intermediate triflate with high yields of (65 and 83 %, respectively). The structure of phenothiazine derivative **195b** was established by X-ray diffraction study (Fig. 13).

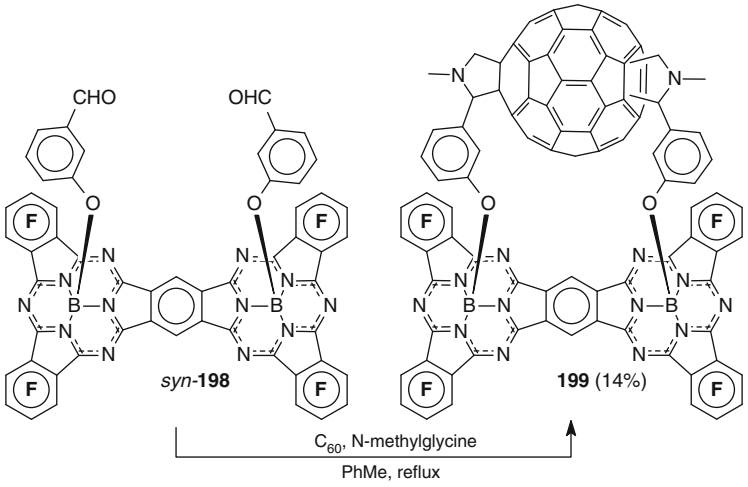
4-*tert*-Butylphenoxy derivative of perfluorinated subphthalocyaninatoboron(III) **189** (X = *t*-Bu) along with other peripherally substituted SubPcs was studied as narrow band red-light emitting material for potential OLED application [109].

Perfluorinated BSubPc bearing axial *m*-formylphenoxy group **196** [99] was used for preparation conjugates with fullerene (Scheme 51) as tunable molecular scaffolds for intramolecular electron and energy transfer processes [110]. The azomethine ylide formed by treatment of the formyl derivative **196** with *N*-methylglycine gives the conjugate with fullerene **197** (44 %) in a dipolar 1,3-cycloaddition (Prato reaction).



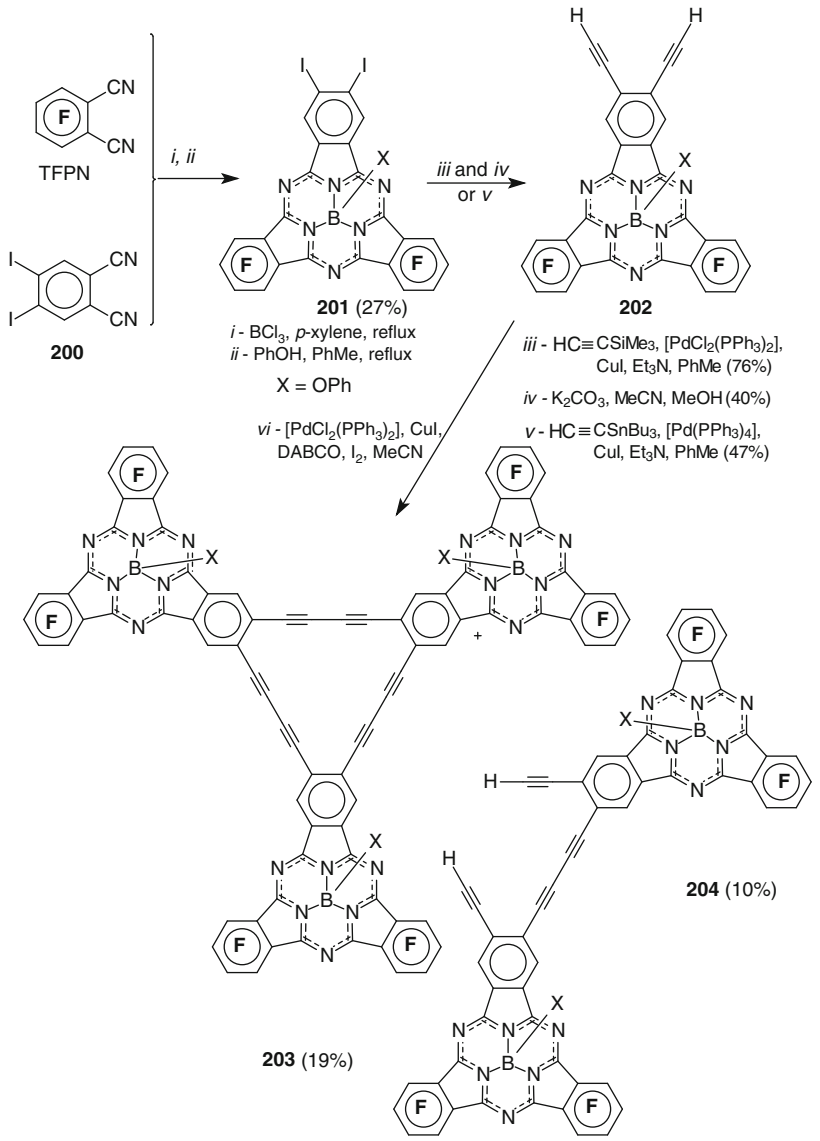
Scheme 51 Synthesis of fullerene conjugate with perfluorinated subphthalocyanine

Similar methodology was used for the synthesis of fullerene conjugates with hexadecafluorinated binuclear fused BsubPc derivative **198** [111, 112] (Scheme 52). Interestingly that only *syn*-dichloro derivative *syn*-**183** can be converted to bis-*m*-formylphenoxy derivative *syn*-**198** (yield 47 %), while the *anti*-topoisomer *anti*-**183** gives only decomposition products. The following conversion of **198** to bis-ylide and 1,3-cycloaddition to fullerene leads to a double-bridged conjugate as a mixture of isomers **199** (yield 14 %).



Scheme 52 Synthesis of fullerene conjugate with dimeric perfluorinated subphthalocyanine

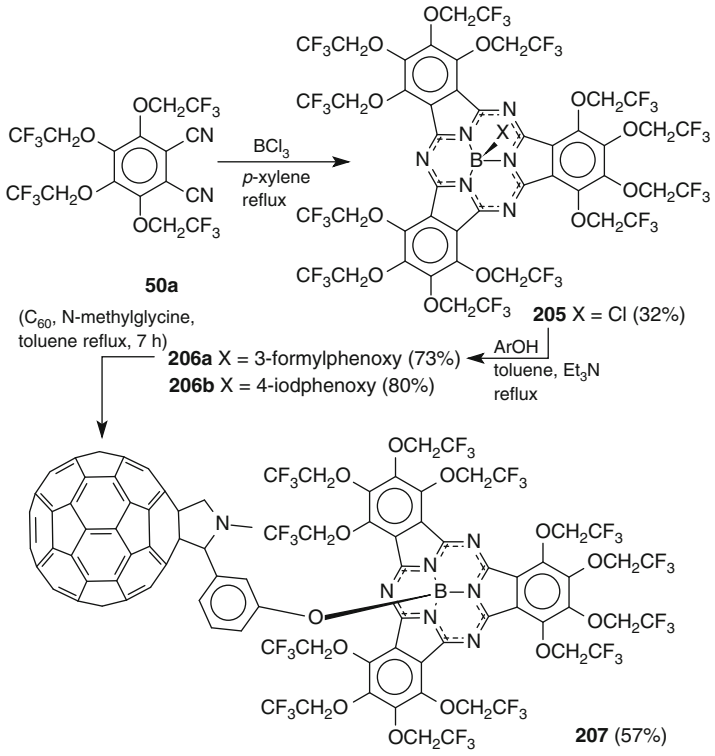
Low-symmetry octafluorodiiodo subphthalocyanine **201** prepared from TFPN and 4,5-diiodophthalonitrile **200** in 27 % yield was used for design of interesting trimeric fluorinated subphthalocyanine arranged around dehydro[18]annulene macrocycle **203** [113] (Scheme 53). The diethynyl-functionalized SubPc **202** was synthesized by palladium-catalyzed Sonogashira cross-coupling with trimethylsilyl-protected acetylene (76 %) followed by removal of TMS protecting group in basic or nucleophilic conditions (yield 40 %). An alternative single-step cross-coupling with ethynyltributylstannane produces diethynyl derivative **202** with 47 % yield, but additional amount can be obtained from Sonogashira cross-coupling byproducts by acid treatment quantitatively removing the Bu_3Sn appendages. Formation of the trimeric dehydro[18]annulene **203** was achieved using mild Pd-catalyzed procedure in an oxidative environment ($[PdCl_2(PPh_3)_2]$, CuI, DABCO, I_2, MeCN). Along with trimer (19 %), monoethynylbridged dimer **204** (10 %) was formed, but no dimeric dehydro[12]annulene was detected.



Scheme 53 Synthesis of butadiyn-linked dimeric and trimeric fluorinated subphthalocyanines

4.4 *Trifluoroethoxy Substituted Subphthalocyanines*

Among subphthalocyanines with fluoroalkyl groups dodecatrifluoroethoxy substituted derivatives are known [114]. The chloro derivative [(Cl)BSubPc(OCH_2CF_3)$_{12}$] **205** was obtained by a standard cyclotrimerization of 3,4,5,6-tetrakis(2,2,2-trifluoroethoxy) phthalonitrile **50a** in the presence of BCl_3 in *p*-xylene (3 h, reflux, 32 %) (Scheme 54) and its X-ray crystal structure was established (Fig. 14).



Scheme 54 Synthesis of "trifluoroethoxy-coated" subphthalocyanine and its fullerene conjugate

The trifluoroethoxy-coating is advantageous for high solubility in organic solvents and lacking tendency to aggregation. The axial chlorine atom can be easily substituted by various O-nucleophiles in by refluxing with excess of corresponding alcohol or substituted phenol in toluene in the presence of Et_3N [114]. The yields of nucleophilic substitutions in case of trifluoroethoxy-coated BSubPc are higher than

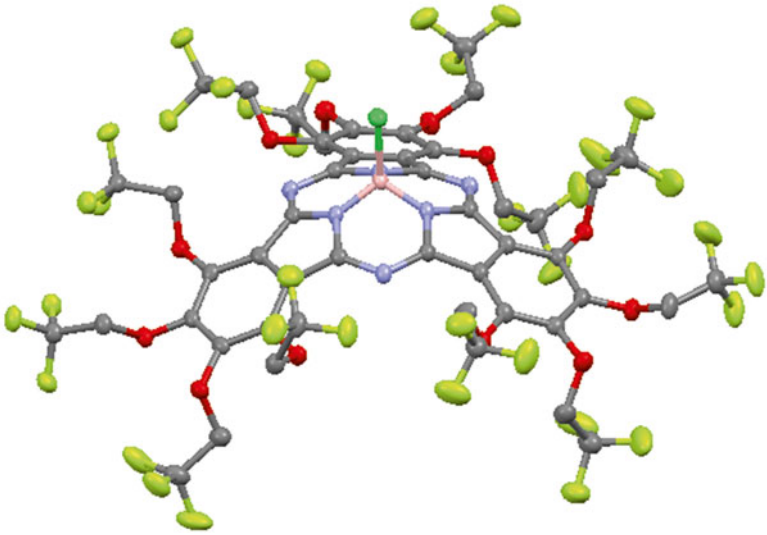
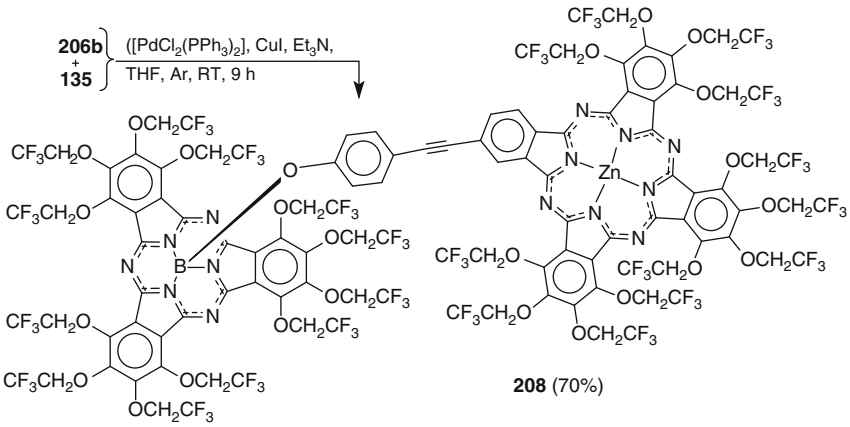


Fig. 14 Molecular structure of **205** (CCDC 758071) [114]

were observed for perfluorinated species. The 3-formylphenoxy derivative **206a** was used for the synthesis of conjugate with fullerene **207** (*N*-methylglycine, toluene reflux, 7 h, 57 %) [114].

The *p*-iodophenoxy derivative **206b** were used in palladium-catalysed Sonogashira cross-coupling reaction with Zn-phthalocyanines containing one terminal triple bond **135** (see Scheme 34) ([$PdCl_2(PPh_3)_2$], CuI, Et_3N, THF, Ar, RT, 9 h) to afford the ethynyl-bridged ZnPc-BSubPc conjugates **208** (70 %) [114] (Scheme 55).

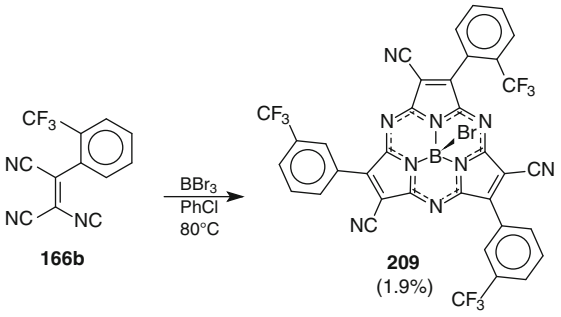


Scheme 55 Synthesis of "trifluoroethoxy-coated" subphthalocyanine – phthalocyanine conjugate

4.5 Fluorine Containing Subazaporphyrins

Subazaporphyrin containing trifluoromethyl group **209** was prepared in a low yield (1.9 %) by cyclotrimerization of 1,1,2-tricyano-2-(2-trifluoromethylphenyl)ethylene **166b** (see Scheme 41) in the presence of boron(III) bromide in chlorobenzene at 80 °C [115] (Scheme 56).

Scheme 56 Synthesis of *m*-trifluoromethylphenyl substituted subazaporphyrin **209**



5 Conclusion

Fluorinated phthalocyanines and their analogues (porphyrazines and subphthalocyanines) exhibit perspective properties for application as new materials in organic electronics (charge generating and transfer materials, light-harvesting supramolecular assemblies, etc.), catalysis and medicine (photodynamic therapy and fluorescence imaging of cancer). The main synthetic approach to fluorinated phthalocyanines, subphthalocyanines and porphyrazines is template cyclocondensation of corresponding fluorinated dinitrile precursors (phthalodinitriles or maleo(fumaro) dinitriles). Another less elaborated approach is peripheral modification of the macrocycle using substitution reactions. While perfluorinated phthalocyanines and subphthalocyanines are easily obtained from perfluorophthalodinitrile, methods should be elaborated for preparation of perfluorinated porphyrazines and heterocyclic phthalocyanines analogues, such as pyrido and pyrazino annulated porphyrazines. Another important target for synthetic chemists is porphyrazine-type macrocycles lacking CH bonds and bearing perfluorinated aryl or alkyl substituents. Such compounds should combine enhanced solubility in organic solvents with high resistance to oxidation and ability to stabilize low oxidation states of central metals, which should be advantageous for application in oxidation catalysis.

Acknowledgement The author is thankful for support to Russian Foundation of Basic Research (Grant No 13-03-00902a)

References

1. Wöhrle D, Schnurpfeil G, Makarov SG, Kazarin A, Suvorova ON (2012) Practical applications of phthalocyanines – from dyes and pigments to materials for optical, electronic and photo-electronic devices. Macroheterocycles 5:191–202. doi:10.6060/mhc2012.120990w
2. (a) Phthalocyanines: properties and applications. Leznof CC, Lever APB (eds) VCH Publishers, Weinheim, 1989–1996, vols 1–4; (b) The porphyrin handbook. Kadish KM, Smith KM, Guilard R (eds) Academic Press, Amsterdam, 2003, vols 15–20
3. Lukyanets EA (1999) Phthalocyanines as photosensitizers in the photodynamic therapy of cancer. J Porphyrins Phthalocyanines 3:424–432
4. Pietro WJ (1994) Rectifying junctions based on metallophthalocyanine thin films. Adv Mater 6:239–242
5. Mayer T, Weiler U, Kelting C, Schlettwein D, Makarov S, Woehrle D, Abdallah O, Kunst M, Jaegermann W (2007) Silicon–organic pigment material hybrids for photovoltaic application. Sol Energy Mater Sol Cells 91:1873–1886
6. Bao Z, Lovinger AJ, Brown J (1998) New air-stable *n*-channel organic thin film transistors. J Am Chem Soc 120:207–208
7. Ling M-M, Bao Z (2006) Copper hexafluorophthalocyanine field-effect transistors with enhanced mobility by soft contact lamination. Org Electron 7:568–575
8. Brinkmann H, Kelting C, Makarov S, Tsaryova O, Schnurpfeil G, Wöhrle D, Schlettwein D (2008) Fluorinated phthalocyanines as molecular semiconductor thin films. Physica Status Solidi A Appl Res 205:409–420
9. Balkus KJ Jr, Eissa M, Levado R (1995) Oxidation of alkanes catalyzed by aeolite-encapsulated perfluorinated ruthenium phthalocyanines. J Am Chem Soc 117:10753–10754
10. Ouyang J, Shigehara K, Yamada A, Anson FC (1991) Hexadecafluoro- and octacyano phthalocyanines as electrocatalysts for the reduction of dioxygen. J Electroanal Chem 297:489–498
11. Boyle RW, Rousseau J, Kudrevich SV, Obochi MOK, Van Lier JE (1996) Hexadecafluorinated zinc phthalocyanine: photodynamic properties against the EMT-6 tumour in mice and pharmacokinetics using 65Zn as a radiotracer. Br J Cancer 73:49–53
12. Oksengendler IG, Kondratenko NV, Luk'yanets EA, Yagupol'ski LM (1977) Fluor- and perfluor-tert-butyl substituted phthalocyanines. Zh Org Khim 13:2234
13. Hung Y, Klose TR, Regan TM, Rossi LJ (1987) Photoconductive phthalocyanine pigments, electrophotographic elements containing them and a method of use. US Patent 4701396
14. Achar BN, Jayasree PK (2000) "Molecularmetals" based on copper(II) 2,9,16, 23-tetrahalosubstituted phthalocyanine derivatives. Synth React Inorg Metal-Org Chem 30:719–734
15. Sundarraj S, Bruder I, Hwang JH, Schoeneboom J, Koenemann M, Bahulayan S, Ojala A, Leow A, Wui Y, Erk P, Sens R, Gessner T (2012) Use of phthalocyanine compounds with aryl or hetaryl substituents in organic solar cells. US Patent 20120068123
16. Crucius G, Lyubimtsev A, Kramer M, Hanack M, Ziegler T (2012) 1,4,8,11,15,18,22,25-Octafluorophthalocyaninato zinc (F_8PcZn). Synlett 23:2501–2503
17. Anderson TL, Komplin GC, Pietro WJ (1993) Rectifying junctions in peripherally-substituted metallophthalocyanine bilayer films. J Phys Chem 97:6577–6588
18. Murdey R, Sato N, Bouvet M (2006) Frontier electronic structures in fluorinated copper phthalocyanine thin films studied using ultraviolet and inverse photoemission spectroscopies. Mol Cryst Liq Cryst 455:211–218
19. Venugopala Reddy KR, Harish MNK, Fassiulla, Moinuddin Khan MH, Keshavayya J (2007) Synthesis, spectral, magnetic and thermal studies on symmetrically substituted metal(II)-1,3,8,10,15,17,22,24-octafluorophthalocyanines. J Fluor Chem 128:1019–1025
20. Krapcho AP, Getahun Z, Avery KJ Jr (1990) The synthesis of 1,4-difluoro-5,8-dihydroxyanthracene-9,10-dione and ipso substitutions of the fluorides by diamines leading to 1,4-bis-[(aminoalkyl) amino]-5,8-dihydroxyanthracene-9,10-diones. Synth Commun 20:2139–2146

21. Venugopala Reddy KR, Keshavayya J (2002) Synthesis, magnetic, spectral, and thermal studies on metal(II) 1,3,8,10,15,17,22,24-octaaminophthalocyanines. Synth React Inorg Metal-Org Chem 32:1235–1244
22. Venugopala Reddy KR, Keshavayya J (2002) Synthesis and magnetic, spectral and thermal studies on metal 1,3,8,10,15,17,22,24-octanitrophthalocyanines. Turk J Chem 26:573–580
23. Belf LJ, Buxton MW, Fuller G (1965) Reactions of polyfluoroaryl bromides with cuprous salts in dimethylformamide. J Chem Soc 1965:3372–3379
24. Haszeldine RN (1966) Aromatic Fluorine Compounds. British Patent 1026290 [Chem Abstr 64:19507]
25. Nalewajek D, Lockyer GD, Eibeck RE, Pyszczek MF (1987) Method of synthesizing tetrafluorophthalonitrile. US Patent 1987007267
26. Birchall JM, Haszeldine RN, Morley JO (1970) Polyfluoroarens. Part XI. Reactions of tetrafluorophthalonitrile with nucleophilic reagents. J Chem Soc C 1970:456–462
27. Causey PW, Dubovyk I, Leznoff CC (2006) Syntheses and characterization of phthalonitriles substituted with adamantane moieties. Can J Chem 84:1380–1387
28. Tian M, Wada T, Sasabe H (1997) Synthesis of unsymmetrically substituted dodecakis (trifluoroethoxy)phthalocyaninato vanadyl complexes. J Heterocycl Chem 34:171–176
29. Eberhardt W, Hanack M (1997) Synthesis of hexadecaalkoxy-substituted nickel and iron phthalocyanines. Synthesis 1997:95–100
30. Ikeno I (2001) Phthalonitrile derivative and its production. Japanese Patent 2000327652 [Chem Abstr 134:4768]
31. Gorun SM, Bench BA, Carpenter G, Beggs MW, Mague JT, Ensley HE (1998) Synthesis and structural characterization of non-planar perfluoro phthalonitriles. J Fluor Chem 91:37–43
32. Wotton DEM (1966) Fluorinated copper phthalocyanine. British Patent 1037657
33. Jones JG, Twigg MV (1969) A fluorinated iron phthalocyanine. Inorg Chem 8:2018–2019
34. Lux F, Brown D, Dempf D, Fischer RD, Hagenberg W (1969) Pthalocyanin- und Perfluorophthalocyanin Komplexe von Thorium, Protactinium, Uran und Neptunium. Angew Chem 81:913 [Angew Chem Int Ed 8: 894]
35. Birchall JM, Haszeldine RN, Morley JO (1970) Polyfluoroarens. Part XIV. Synthesis of halogenophthalocyanines. J Chem Soc C 1970:2667–2672
36. Lee C-H, Ng DKP (2002) Cerium promoted formation of metal-free phthalocyanines. Tetrahedron Lett 43:4211–4214
37. Hiller S, Schlettwein D, Armstrong NR, Woehrle D (1998) Influence of surface reactions and ionization gradients on junction properties of F_{16}PcZn. J Mater Chem 8:945–954
38. Gerdes R, Lapok L, Tsaryova O, Gorun SM, Woehrle D (2009) Rational design of a reactive yet stable organic-based photocatalyst. Dalton Trans:1098–1100
39. Balkus KJ Jr, Gabrielov AG, Bell SL, Bedioui F, Roue L, Devynck J (1994) Zeolite encapsulated cobalt(II) and copper(II) perfluorophthalocyanines. Synthesis and characterization. Inorg Chem 33:67–72
40. Gabrielov AG, Balkus KJ Jr, Bell SL, Bedioui F, Devynck J (1994) Faujasite-type zeolites modified with iron perfluorophthalocyanines: synthesis and characterization. Microporous Mater 2:119–126
41. Christendat D, David MA, Morin S, Lever ABP, Kadish KM, Shao J (2005) Synthesis and characterization of highly soluble hexadecachloro- and hexadecafluorophthalocyanine ruthenium(II) complexes. J Porphyrins Phthalocyanines 09:626–636
42. Dini D, Yang GY, Hanack M (2003) Perfluorinated phthalocyanines for optical limiting: evidence for the direct correlation between substituent electron withdrawing character and the nonlinear optical effect. J Chem Phys 119:4857–4864
43. Handa M, Suzuki A, Shoji S, Kasuga K, Sogabe K (1995) Spectral and electrochemical properties of vanadyl hexadecafluorophthalocyanine. Inorg Chim Acta 230:41–44
44. Schlettwein D, Tada H, Mashiko S (2000) Substrate-induced order and multilayer epitaxial growth of substituted phthalocyanine thin films. Langmuir 16:2872–2881
45. Basova T, Plyashkevich V, Hassan A (2008) Spectral characterization of thin films of vanadyl hexadecafluorophthalocyanine $VOPcF_{16}$. Surf Sci 602:2368–2372

46. Balkus KJ, Khanmamedova A, Eissa M (1995) Alkane oxidation catalyzed by zeolite encapsulated ruthenium perfluorophthalocyanines. Stud Surf Sci Catal 97:189–195
47. Karmann E, Meyer JP, Schlettwein D, Jaeger NI, Anderson M, Schmidt A, Armstrong NR (1996) Photoelectrochemical effects and (photo)conductivity of "n-type" phthalocyanines. Mol Cryst Liq Cryst 283:283–291
48. Leznoff CC, Sosa-Sanchez JL (2004) Polysubstituted phthalocyanines by nucleophilic substitution reactions on hexadecafluorophthalocyanines. Chem Commun 2004:338–339
49. Varotto A, Radivojevioc I, Drain CM, Nam CY, Black CT, Tome JPC, Cavaleiro JAS (2010) Phthalocyanine blends improve bulk heterojunction solar cells. J Am Chem Soc 132:2552–2554
50. Aggarwal A, Singh S, Anthes M, Drain CM, Zhang Y, Gao R, Samaroo D (2011) Synthesis and photophysics of an octathioglycosylated zinc(II) phthalocyanine. Tetrahedron Lett 52:5456–5459
51. Bench BA, Brennessel WW, Lee HJ, Gorun SM (2002) Introduction of bulky perfluoroalkyl groups at the periphery of zinc perfluorophthalocyanine: chemical, structural, electronic, and preliminary photophysical and biological effects. Angew Chem 114:774–776 [Angew Chem Int Ed 41:748–750]
52. Moons H, Lapok L, Loas A, Van Doorslaer S, Gorun SM (2010) Synthesis, X-ray structure, magnetic resonance, and DFT analysis of a soluble copper(II) phthalocyanine lacking C-H bonds. Inorg Chem 49:8779–8789
53. Bench BA, Beveridge A, Sharman WM, Diebold GJ, van Lier JE, Gorun SM (2002) Synthesis and structure of a biconcave cobalt perfluorophthalocyanine and its catalysis of novel oxidative carbon – phosphorus bonds formation by using air. Angew Chem 114:776–780, [Angew Chem Int Ed 41:750–754]
54. Lee HJ, Brennessel WW, Lessing JA, Brucker WW, Young VG, Gorun SM (2003) Dome-distortion and fluorine-lined channels: synthesis, and molecular and crystal structure of a metal- and C–H bonds-free fluorophthalocyanine. Chem Commun 2003:1576–1577
55. Minnes R, Weitman H, Lee HJ, Gorun SM, Ehrenberg B (2006) Enhanced acidity, photophysical properties and liposome binding of perfluoroalkylated phthalocyanines lacking C-H bonds. Photochem Photobiol 82:593–599
56. Keizer SP, Mack J, Bench BA, Gorun SM, Stillman MJ (2003) Spectroscopy and electronic structure of electron deficient zinc phthalocyanines. J Am Chem Soc 125:7067–7085
57. Hesse K, Schlettwein D (1999) Spectroelectrochemical investigations on the reduction of thin films of hexadecafluorophthalocyaninatozinc (F_{16}PcZn). J Electroanal Chem 476:148–158
58. Loas A, Gerdes R, Zhang Y, Gorun SM (2011) Broadening the reactivity spectrum of a phthalocyanine catalyst while suppressing its nucleophilic, electrophilic and radical degradation pathways. Dalton Trans 2011:5162–5165
59. Clack DW, Hush NS, Woosley IS (1976) Reduction potentials of some metal phthalocyanines. Inorg Chim Acta 19:129–132
60. Ali H, Ait-Mohand S, Gosselin S, van Lier JE, Guerin B (2011) Phthalocyanine-peptide conjugates via palladium-catalyzed cross-coupling reactions. J Org Chem 76:1887–1890
61. Ali H, Baillargeon P, van Lier JE (2008) Synthesis and properties of C-C conjugated phthalocyanine dimers. Tetrahedron Lett 49:7253–7255
62. Shibata N, Das B, Hayashi M, Nakamura S, Toru T (2009) Synthesis, photophysical and electrochemical properties of perfluoroisopropyl substituted binuclear phthalocyanine conjugated with a butadiyne linker. J Fluor Chem 130:1164–1170
63. Das B, Tokunaga E, Tanaka M, Sasaki T, Shibata N (2010) Perfluoroisopropyl zinc phthalocyanines conjugated with deoxyribonucleosides: synthesis, photophysical properties and in vitro photodynamic activities. Eur J Org Chem 2010:2878–2884
64. Weiler U, Mayer T, Jaegermann W, Kelting C, Schlettwein D, Makarov S, Woehrle D (2004) Electronic energy levels of organic dyes on silicon: a photoelectron spectroscopy study of ZnPc, F_{16}ZnPc, and ZnTPP on p-Si(111):H. J Phys Chem B 108:19398–19403
65. Schöllhorn B, Germain JP, Pauly A, Maleysson C, Blanc JP (1998) Influence of peripheral electron-withdrawing substituents on the conductivity of zinc phthalocyanine in the presence of gases. Part 1: Reducing gases. Thin Solid Films 326:245–250

66. Oksengendler IG, Kondratenko NV, Luk'yanets EA, Yagupol'skii LM (1977) Trifluoromethylsubstituted phthalocyanines. Zh Org Khim 13:1554–1561 (in Russian) [J Org Chem USSR 13:1530–1434 (Engl transl)]
67. Chen MJ, Fremgen DE, Rathke JW (1998) Oxygen atom transfer from μ-oxo-bis[1,4,8,11,15,18,22,25-octakis(trifluoromethyl)phthalocyaninato]diiron(III): evidence for an Fe^{IV}=O intermediate. J Porphyrins Phthalocyanines 2:473–482
68. Gorun SM, Rathke JW, Chen MJ (2009) Long-range solid-state ordering and high geometric distortions induced in phthalocyanines by small fluoroalkyl groups. Dalton Trans 2009:1095–1097
69. Pawlowski G, Hanack M (1981) A convenient synthesis of trifluoromethyl substituted phthalocyanines. Synth Commun 11:351–363
70. Winter G, Heckmann H, Haisch P, Eberhardt W, Hanack M, Lüer L, Egelhaaf HJ, Oelkrug D (1998) Study of substituent effects on the photoconductivity of soluble 2, (3)- and 1, (4)-substituted phthalocyaninato- and naphthalocyaninatotitanium(IV) oxides. J Am Chem Soc 120:11663–11673
71. Braun E, Koeberle K (1940) Dyestuffs of the phthalocyanine series. US Patent 2225441 [Chem Abstr (1941) 35:2337]
72. Weinmayr V (1961) Trifluoromethyl substituted phthalocyanines. US Patent 3006921 [Chem Abstr (1962) 56:10171]
73. Keller TM, Griffith JR (1979) The synthesis of fluorinated phthalocyanine. J Fluor Chem 13:73–77
74. Guerol I, Durmus M, Ahsen V (2010) Photophysical and photochemical properties of fluorinated and nonfluorinated *n*-propanol-substituted zinc phthalocyanines. Eur J Inorg Chem 2010:1220–1230
75. Sugimori T, Horike SI, Handa M, Kasuga K (1998) Preparation and some properties of perfluoroalkoxy-substituted phthalocyanine complexes of iron(III), nickel(II) and zinc(II). Inorg Chim Acta 278:253–255
76. Kondratenko NV, Nemykin VN, Lukyanets EA, Kostromina NA, Volkov SV, Yagupolskii LM (1997) The synthesis and properties of some polyfluoroalkoxy substituted phthalocyanines. J Porphyrins Phthalocyanines 1:341–347
77. Gao L, Qian X (2002) Synthesis and photosensitizing properties of fluoroalcoxyl phthalocyanine metal complexes. J Fluor Chem 113:161–165
78. Sukeguchi D, Yoshiyama H, Shibata N, Nakamura S, Toru T (2009) Synthesis and spectroscopic investigations of trifluoroethoxy semi-coated zinc(II) phthalocyanine. Heterocycl Commun 15:195–202
79. Weitman H, Schatz S, Gottieb HE, Kobayashi N, Ehrenberg B (2001) Spectroscopic probing of the acid–base properties and photosensitization of a fluorinated phthalocyanine in organic solutions and liposomes. Photochem Photobiol 73:473–481
80. Tian M, Wada T, Sasabe H (2000) Syntheses of new unsymmetrically dodecakis(trifluoroethoxy)-substituted metallophthalocyanines by a palladium-catalyzed cross-coupling reaction. J Heterocycl Chem 37:1193–1202
81. Tian M, Wada T, Kimura-Suda H, Sasabe H (1997) Novel non-aggregated unsymmetrical metallophthalocyanines for second-order nonlinear optics. J Mater Chem 7:861–863
82. Yoshiyama H, Shibata N, Sato T, Nakamura S, Toru T (2008) Synthesis and properties of trifluoroethoxy-coated binuclear phthalocyanine. Chem Commun 2008:1977–1979
83. Yoshiyama H, Shibata N, Sato T, Nakamura S, Toru T (2009) Synthesis of trifluoroethoxy-coated binuclear phthalocyanines with click spacers and investigation of their clamshell behaviour. Org Biomol Chem 2009:2265–2269
84. Das B, Umeda M, Tokunaga E, Toru T, Shibata N (2010) Synthesis of benzene-centered trinuclear phthalocyanines by triple-click chemistry. Chem Lett 39:337–339
85. Oksengendler IG, Kondratenko NV, Luk'yanets EA, Yagupol'skii LM (1978) Trifluoromethylthio- and trifluoromethylsulfonyl substituted phthalocyanines. Zh Org Khim 14(5):1046–1051, (in Russian) [J Org Chem USSR 976–979 (Engl transl)]
86. Khelevina OG, Timofeeva SV, Berezin BD (1994) Synthesis and spectra of tetrachlorotetraazaporphine. Zh Org Khim 30:295–296 (in Russian)

87. (a) Chizhova NV, Khelevina OG, Berezin BD (1999) Abstracts of 2nd international science conference. 'Actual Problems of Chemistry and Chemical Technology' (Chemistry-99), Ivanovo, May 1999; 121; (b) Khelevina OG, Chizhova NV, Stuzhin PA (2000) Modification of β-positions in porphyrazines by substitution reactions. J Porphyrins Phthalocyanines 4:555–563
88. Khelevina OG, Timofeeva SV, Berezin BD (1994) Nucleophilic substitution in tetraazaporphines. Zh Org Khim 30:1780–1781 (in Russian)
89. Kondratenko NV, Movchun VN, Kopranenkov VN, Luk'yanets EA, Yagupol'skii LM (1992) (Perfluoroalkyl)-, (polyfluoroalkoxy)-, and [(perfluoroalkyl)thio]-substituted porphyrazines and their metal complexes. Zh Org Khim 28:2149–2155, (in Russian) [Russ J Org Chem 28:1723–1728 (Engl transl)]
90. (a) Kolomeitsev AA, Kondratenko NV, Popov VI, Yagupol'skii LM (1984) USSR patent 1129206; (b) Makarova EA, Kopranenkov VN, Shevtsov VK, Luk'yanets EA (1994) Synthesis of mono and disubstituted tetra-*tert*-butylporphyrazines. Khim Geterotsikl Soedin 1206–1212 (in Russian) [Chem Heterocycl Comp 30:1043–1048 (Engl transl)]
91. Troitskaya VI, Trushanina LA, Kopranenkov VN, Luk'yanets EA, Yagupol'skii LM (1989) Metal complexes of fluorine-substituted tetracyanotetraarylporphyrins. Zh Org Khim 25:571–576 (in Russian) [J Org Chem USSR 25:513–517 (Engl transl)]
92. Vagin S, Barthel M, Dini D, Hanack M (2003) Synthesis and characterization of (octaaryltetraazaporphyrinato)indium(III) complexes for optical limiting. Inorg Chem 42:2683–2694
93. Vagin SI, Hanack M (2002) Synthesis and spectroscopic properties of non-symmetrical benzoannulated porphyrazines and their metal complexes. Eur J Org Chem 2002:2859–2865
94. Altunkaya M, Gonca E (2011) Synthesis and characterization of new soluble fluorinated seco-porphyrazines. Polyhedron 30:1035–1039
95. Vagin S, Hanack M, Kammerer B, Frickenschmidt A (2004) Some reactions of magnesium arylporphyrazines: evidence of dehydroporphyrazine formation. Eur J Org Chem 2004:4245–4250
96. Khelevina OG, Bubnova AS, Makarova ON, Lukina SA, Vagin SI, Stuzhin PA (2006) Koord Khim 32:468–475 (in Russian) [Russ J Coord Chem 32:451–457 (Engl transl)]
97. Stuzhin PA, Goryachev MYu, Ivanova SS, Nazarova A, Pimkov I, Koifman OI (2013) Perfluorinated porphyrazines 1: Synthesis and UV-vis spectral study of perfluorinated octaphenylporphyrazine and its indium(III) complex, $[MPA(F_5Ph)_8](M = 2H, In^{III}(OH))$ J Porphyrins Phthalocyanines 17:905–912
98. Kipp RA, Simon JA, Beggs M, Ensley HE, Schmehl RH (1998) Photophysical and photochemical investigation of a dodecafluorosubphthalocyanine derivative. J Phys Chem A 102:5659–5664
99. Claessens CG, Gonzalez-Rodrıguez D, del Rey B, Torres T, Mark G, Schuchmann HP, von Sonntag C, MacDonald JG, Nohr RS (2003) Highly efficient synthesis of chloro- and phenoxy-substituted subphthalocyanines. Eur J Org Chem 2003:2547–2551
100. Fukuda T, Stork JR, Potucek RJ, Olmstead MM, Noll BC, Kobayashi N, Durfee WS (2002) *cis* and *trans* forms of a binuclear subphthalocyanine. Angew Chem 114:2677–2680 [Angew Chem Int Ed 41:2565–2568]
101. Dini D, Vagin S, Hanack M, Amendola V, Meneghetti M (2005) Nonlinear optical effects related to saturable and reverse saturable absorption by subphthalocyanines at 532 nm. Chem Commun 2005:3796–3798
102. Stork JR, Potucek RJ, Durfee WS, Noll BC (1999) The synthesis and structure of mixed subphthalocyanine/subnaphthalocyanine complexes. Tetrahedron Lett 40:8055–8058
103. Claessens CG, Torres T (2002) Synthesis, separation, and characterization of the topoisomers of fused bicyclic subphthalocyanine dimers. Angew Chem 114:2673–2677 [Angew Chem Int Ed 41:2561–2565]
104. Iglesias RS, Claessens CG, Torres T, Herranz MA, Ferro VR, Garcıa de la Vega JM (2007) Subphthalocyanine-fused dimers and trimers: synthetic, electrochemical, and theoretical studies. J Org Chem 72:2967–2977
105. Shimizu S, Nakano S, Hosoya T, Kobayashi N (2011) Pyrene-fused subphthalocyanine. Chem Commun 47:316–318

106. Rodriguez-Morgade MS, Claessens CG, Medina A, Gonzalez–Rodriguez D, Gutirrez-Puebla E, Monge A, Alkorta I, Elguero J, Torres T (2008) Synthesis, characterization, molecular structure and theoretical studies of axially fluoro-substituted subazaporphyrins. Chem Eur J 14:1342–1350
107. Gonzalez-Rodriguez D, Martinez-Diaz MV, Torres T, Abel J, Echegoyen L, Perl A, Huskens J (2010) Self-assembled monolayers of subphthalocyanines on gold substrates. Org Lett 12:2970–2973
108. Guilleme J, Gonzalez-Rodriguez D, Torres T (2011) Triflate-subphthalocyanines: versatile, reactive intermediates for axial functionalization at the boron atom. Angew Chem 123:3568–3571 [Angew Chem Int Ed 50:3506–3509]
109. Díaz DD, Bolink HJ, Cappelli L, Claessens CG, Coronado E, Torres T (2007) Subphthalocyanines as narrow band red-light emitting materials. Tetrahedron Lett 48:4657–4660
110. Gonzalez-Rodrıguez D, Torres T, Guldi DM, Rivera J, Herranz MA, Echegoyen L (2004) Subphthalocyanines: tunable molecular scaffolds for intramolecular electron and energy transfer processes. J Am Chem Soc 126:6301–6313
111. Iglesias RS, Claessens CG, Torres T, Aminur Rahman GM, Guldi DM (2005) Synthesis and photophysical characterization of a subphthalocyanine fused dimer–C_{60} dyad. Chem Commun 2005:2113–2115
112. Iglesias RS, Claessens CG, Aminur Rahman GM, Herranz MA, Guldi DM, Torres T (2007) Subphthalocyanine fused dimers–C_{60} dyads: synthesis, characterization, and theoretical study. Tetrahedron 63:12396–12404
113. Iglesias RS, Claessens CG, Herranz MA, Torres T (2007) Subphthalocyanine-dehydro[18] annulenes. Org Lett 9:5381–5384
114. Shibata N, Das B, Tokunaga E, Shiro M, Kobayashi N (2010) Trifluoroethoxy-coating improves the axial ligand substitution of subphthalocyanine. Chem Eur J 16:7554–7562
115. Kobayashi N, Ishizaki T, Ishii K, Konami H (1999) Synthesis, spectroscopy, and molecular orbital calculations of subazaporphyrins, subphthalocyanines, subnaphthalocyanines, and compounds derived therefrom by ring expansion. J Am Chem Soc 121:9096–9110

ERRATUM

Fluorine in Heterocyclic Chemistry Volume 1

5-Membered Heterocycles and Macrocycles

Valentine Nenajdenko

V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3,

DOI 10.1007/978-3-319-04346-3_16

Acknowledgment

This work was supported by the Russian Science Foundation (Grants 14-13-00083 and 14-13-00388).

The online version of the original book can be found at http://dx.doi.org/10.1007/978-3-319-04346-3