Valentine Nenajdenko *Editor*

Fluorine in Heterocyclic Chemistry Volume 2

6-Membered Heterocycles

Springer

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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.

Moscow, Russia Valentine Nenajdenko
2013

Contents of Volume 2

Contents of Volume 1

Synthesis of Fluorinated Pyridines

Anatoliy M. Shestopalov, Lyudmila A. Rodinovskaya, Valeri Yu. Mortikov, and Alexander E. Fedorov

Contents

Abstract Present review contains recent literature data published since 2009 for 2012 as till 2009 four reviews on this field have been published. The methods of synthesis of 2-, 3-, 4-fluoropyridines, di-, tri-, polyfluoropyridines, perfluoroalkylpyridines and also fluoropyridines fused with carbo-, heterocycles are presented. Methods for synthesis of F^{18} substituted pyridines for local radiotherapy of cancer and other biological active compounds are also presented.

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V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 2: 6-Membered Heterocycles*,
DOI 10.1007/978-3-319-04435-4_1, © Springer International Publishing Switzerland 2014

Keywords Fluoropyridines • Perfluoroalkyl pyridines • Umemoto reaction • Balts-Schiemann reaction • Pentafluoropyridine • Substitution reaction • F^{18}-pyridines radiobiology • Cyclization

1 Introduction

The present review contains the literature published since 2009 for 2012. Till 2009 four reviews on this field have been published, completely [1, 2] or in part [3] devoted to methods syntheses C-F pyridines and perfluoroalkyl pyridines [2, 4]. To display full information about synthesis fluorinated pyridines in the present review earlier classical works also are included.

An arising interest towards fluoropyridines is explained by their interesting and unusual physical, chemical and biological properties owing to the presence of the strong electron-withdrawing substituent(s) in the aromatic ring. Fluoropyridines have reduced basicity and are usually less reactive than their chlorinated and brominated analogues. A selective synthesis of fluoropyridines remains a challenging problem. Here a synthetic methods for preparation of 2-, 3-, 4-fluoropyridines and di- and poly-fluoropyridines are reviewed along with some synthetic routes towards ^{18}F-substituted pyridines, which present a special interest as potential imaging agents for various biological applications.

In the search for new agricultural products having improved physical, biological, and environmental properties, one of the most generally useful chemical modifications is the introduction of fluorine atoms into lead structures. Fluorine-containing substituents are most commonly incorporated to carbocyclic aromatic rings, and a large number of compounds possessing fluorine-containing substituents on aryl rings have been commercialized as agricultural active ingredients [5, 6].

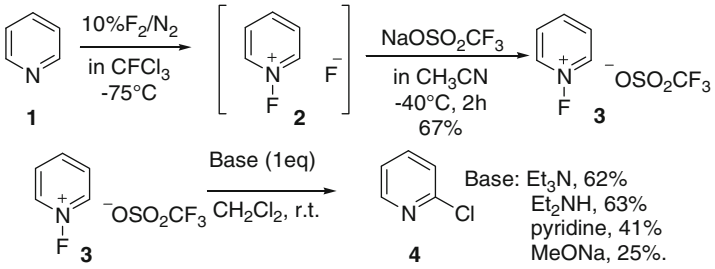
About 10 % of the total sales of pharmaceuticals currently used for the medical treatment are drugs containing fluorine atom. Over 50 years, many fluorinated medicinal and agrochemical candidates have been discovered and the interest toward development of fluorinated chemicals has been steadily increased. High availability of the fluorinated synthetic blocks and the effective fluorinating reagents, the widely reliable fluorination technology, and the accumulation of basic and advanced knowledge of the fluorine chemistry rapidly accelerated developments in this field [7].

2 Synthesis of 2-Fluoropyridines

2.1 N-Fluoropyridinium Salts. The Umemoto Reaction

The chemistry of the pyridine ring has been enriched by the development of many significant transformations. These reactions include addition, addition-elimination, elimination-addition, and ring-opening, as well as proton-abstraction reactions followed by nucleophilic substitution. The course of the reaction depends on the

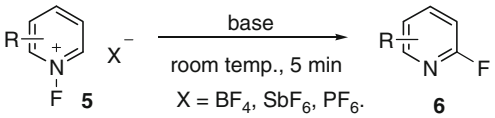
nature of the pyridine rings and bases employed [8]. New reactions involving *N*-fluoropyridinium salts **3** have now been added to the field of pyridine chemistry. In 1986, stable *N*-fluoropyridinium salts **3** were isolated and fully characterized by the T. Umemoto and his coworker [9–12]. These salts were synthesized by the counteranion replacement reaction of unstable pyridine-F_2 compounds [13] which violently decompose above -2 °C. The isolation of the stable salts followed shortly after Gakh's earlier report that the pyridine-F_2 compound, proposed as an JV-fluoropyridinium structure, reacted in situ with a trinitromethane salt to form 2-(trinitromethyl)pyridine in a 14 % yield [14]. The results of these efforts, including the discovery of the stable *N*-fluoropyridinium salts, have opened up a new area in pyridine chemistry [15, 16]. In 1987, the T. Umemoto and coworker reported novel base-induced reactions of the stable *N*-fluoropyridinium salts **3** [17] (Scheme 1).



1 **2** **3** **3** **4**

Scheme 1

N-Fluoropyridinium salts **5** are efficient precursors in the synthesis of substituted 2-fluoropyridines. They can be conveniently prepared in good yields by the reaction of the corresponding pyridine with F_2/N_2 at the presence of strong acid [17]. *N*-Fluoropyridinium tetrafluoroborates, hexafluoroantimonates or hexafluorophosphates (**5**, X=BF_4, SbF_6, PF_6) upon treatment with a base undergo an exothermic reaction to form selectively 2-fluoropyridines in moderate to high yield (Table 1) [18]. The reaction yields depend on the media's basicity and in a stronger degree on the presence of substituents in the pyridine ring. In addition, it was demonstrated that the yields of compounds **6** using ammonium fluoride as a base without a solvent were identical to the yields of **6** using Et_3N. Based on experimental data it was suggested that the fluorine substituent in products **6** arrives from counter anion (BF_4^-, SbF_6^- or PF_6^-) [18] (Scheme 2).



5 **6**

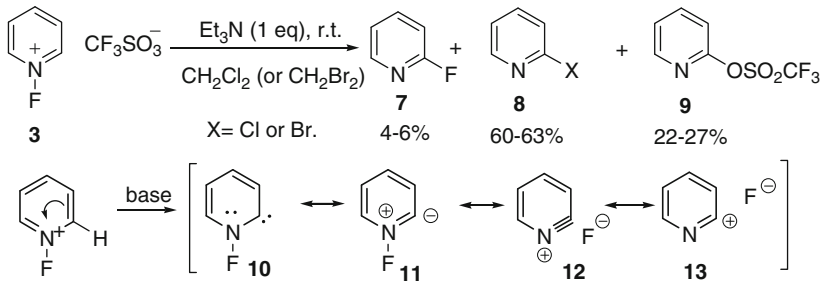
Scheme 2

Compounds **6** can be obtained in one-pot process by reacting the corresponding pyridines with F_2/N_2 mixture, followed by the subsequent treatment with Et_3N [18]. However, the yields of the fluorinated pyridines obtained by this protocol are significantly lower (22–35 %).

Table 1 Preparation of 2-fluoropyridine **6** from *N*-fluoropyridinium salts **5** [18]

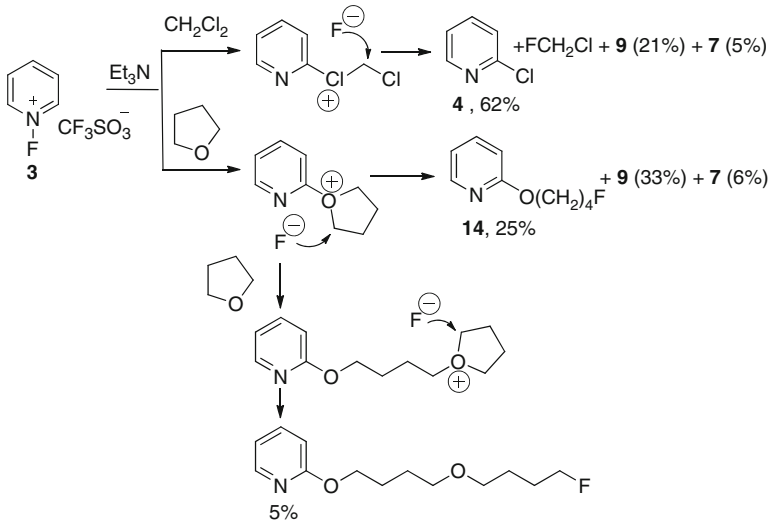
R	X	Base (equiv.)	Yield, %
H	BF_4	Et_3N (1)	66
H	BF_4	Et_3N (3)	73
H	BF_4	Et_3N (10	79
H	BF_4	*n*-$Bu^4N^+F^-$(2.6)	80
H	SbF_6	Et_3N (10)	78
H	BF_4	KF (9) (7 days, 40 °C)	26
H	PF_6	Et_3N (10)	74
4-Me	BF_4	Et_3N (10)	80
3,5-$(Me)_2$	BF_4	Et_3N (10)	87
3,5-$(Me)_2$	BF_4	Py (10)	30
4-*t*-Bu	BF_4	Et_3N (10)	91
2-MeO	BF_4	Et_3N (10)	75
2-MeO	BF_4	Py (10)	10
3,5-*bis*(CF_3)	BF_4	Et_3N (10)	99
3-CN	BF_4	Et_3N (10)	51
3-CN	BF_4	Py (10)	49
4-NO_2	BF_4	Et_3N (10)	21
4-NO_2	BF_4	Py (10)	31

The mechanism of this reaction was discussed in several publications [17, 18]. It was demonstrated that under workup with triethylamine in CH_2Cl_2 or CH_2Br_2 triflate salt **3** gives a mixture of three compounds: 2-fluoropyridine (7), 2-halopyridine **8**, and compound **9** [17] (Scheme 3). Similarly, it was demonstrated that salts **5** give 2-diethylaminopyridines, 2-phenylaminopyridines, or 2-(2-furyl and 3-furyl) pyridines when they are reacted with Et_2NH, benzene, or furan.

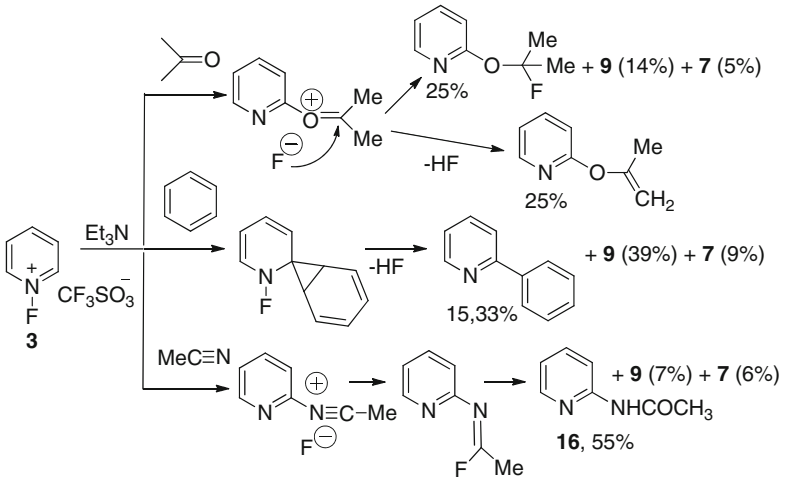


Scheme 3

It was proposed that under basic conditions salt **3** undergoes heterolytic C^2-H bond cleavage to form carbene **10↔11**, which in its turn eliminates F^- to give cation **12↔13**. A subsequent reaction of **12↔13** with nucleophiles or *n*-π-electron containing molecules gives above mentioned products. Some transformations of salt **3** leading to 2-substituted pyridines are shown below [17, 19] (Schemes 4 and 5).



Scheme 4

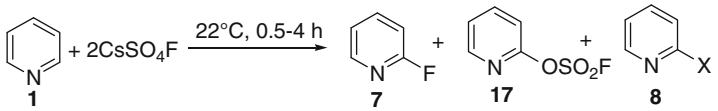


Scheme 5

Direct fluorination of pyridine also can be carried out using $CsSO_4F$ as a source of fluorine. It was shown that pyridine readily reacts with $CsSO_4F$ at room temperature producing a mixture of products (2-fluoro-, 2-fluorosulfonate- and 2-chloro- or 2-alkoxy-pyridines) (Table 2) [20] (Scheme 6).

Table 2 Products distribution in reaction between pyridine and $CsSO_4F$ [20]

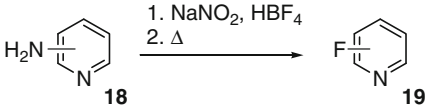
	Yield, %				Yield, %		
Solvent	**7**	**17**	**8**	Solvent	**7**	**17**	**8**
n-C_5H_{12}	56	44	–	$CHCl_3$	47	17	36; X = Cl
$(CH_3CH_2)_2O$	61	39	–	CH_2Cl_2	26	12	62; X = Cl
c-C_6H_{12}	70	30	–	$C(CH_3)_3OH$	64	18	18; X = $OC(CH_3)_3$
CCl_4	70	30	–	$CH(CH_3)_2OH$	22	7	71; X = $OCH(CH_3)_2$



Scheme 6

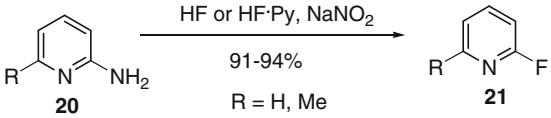
2.2 Synthesis of 2-Fluoropyridines from 2-Aminopyridines

One of the typical examples of the Baltz-Schiemann reaction is synthesis of fluoro-substituted pyridines **19** from aminopyridines **18** [21]. In this variation the Baltz-Schiemann reaction is most often used for the synthesis of 2-fluoropyridines [22]. On the first step a diazonium tetrafluoroborate is generated from 2-aminopyridine, $NaNO_2$ and solution of HF and BF_3 (HBF_4), while subsequent thermal decomposition of the diazonium salt leads to formation of 2-fluoropyridines (Scheme 7). In this part of the chapter examples of synthesis 2-fluoropyridines and illustrations of specific use Baltz-Schiemann reaction for preparation of biologically active derivatives of 2-fluoropyridines are described.



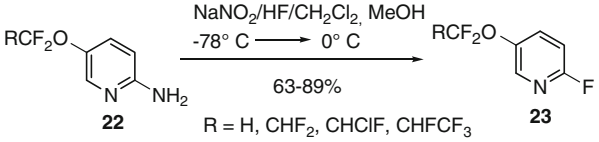
Scheme 7

The reaction has general character. It is applied for the synthesis of various 2-, 3- or 4-fluoropyridines and is full enough described in earlier reviews [1, 3, 4]. Practical use the Baltz-Schiemann reaction for preparation of pesticides or medicines is described in reviews [6, 7]. Several variations of the Baltz-Schiemann reaction allow synthesis of fluorinated pyridines in almost quantitative yields. For example, 2-fluoropyridines **21** were prepared in 91–94 % yields by diazotization of 2-aminopyridines **20** with sodium nitrite in anhydrous HF or HF-pyridine complex [23] (Scheme 8).



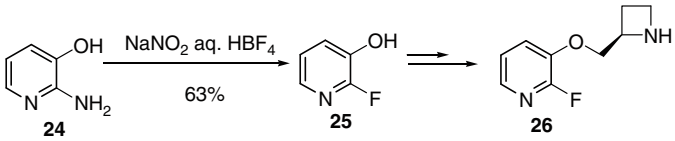
Scheme 8

Substituted 2-fluoro-5-fluoroalkoxypyridines (23) were prepared in good to high yields by diazotization of substituted 2-aminopyridines **22** with $NaNO_2$ in HF. Subsequently they were used as starting materials for the synthesis of some herbicides and insecticides [24] (Scheme 9).



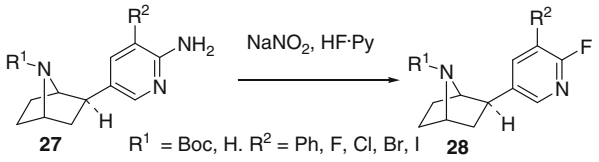
Scheme 9

3-Hydroxy-2-fluoropyridine (25) was prepared from 2-amino-3-hydroxypyridine (24) by diazotization with $NaNO_2$ in HBF_4 solution [25]. Next, compound **25** was used for the preparation of 2-fluoro-3-[2(S)-2-azetidinylmethoxy]pyridine (26), a closely related analog of the high affinity nicotinic ligand A-85380 (Scheme 10).



Scheme 10

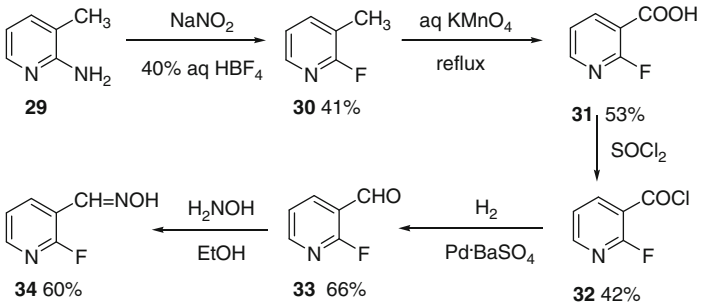
Synthesis of *exo*-2-(2′-fluorosubstituted 5′-pyridinyl)-7-azabicyclo[2.2.1]heptanes (28), novel nicotinic receptor antagonists, was based on diazotization reaction of corresponding 2-aminopyridines **27** using HF-pyridine complex [26–29] (Scheme 11). Classical examples of use of this reaction are resulted in earlier works [23–29]. Now the Baltz-Schiemann reaction continues to use for synthesis fluorinated pyridines.



Scheme 11

2-Amino-3-methylpyridine (29) has been used for synthesis fluorine-containing pyridine aldoximes of potential use for the treatment of organophosphorus nerve-agent poisoning [30]. The Baltz-Schiemann technique was used to convert 2-amino-3-methylpyridine into 2-fluoro-3-methylpyridine (30), subsequent permanganate oxidation of **30** provided acid **31**. Finally conversion of **31** to acyl chloride **32** and Rosenmund reduction resulted in carboxaldehyde **33**. Previously this technique was reported to give poor yields with heterocyclic acyl chlorides. The conversion of **32**

to carboxaldehyde **33** in good yield (66 %) demonstrated that fluoroheterocyclic compounds could undergo facile catalytic reduction by hydrogen in boiling xylene. Carboxaldehyde **33** reacted smoothly with hydroxylamine to provide oxime **34** in 60 % yield (Scheme 12). 2-Fluoropyridine-6-aldoxime was prepared similarly from 2-amino-6-methylpyridine (→ 2-fluoro-6-methylpyridine 39 % → -6-carboxylic acid 50 % → -6-carboxylic acid chloride 72 % → -6-carboxaldehyde 68 % → 6-oxime 71 %) [30].

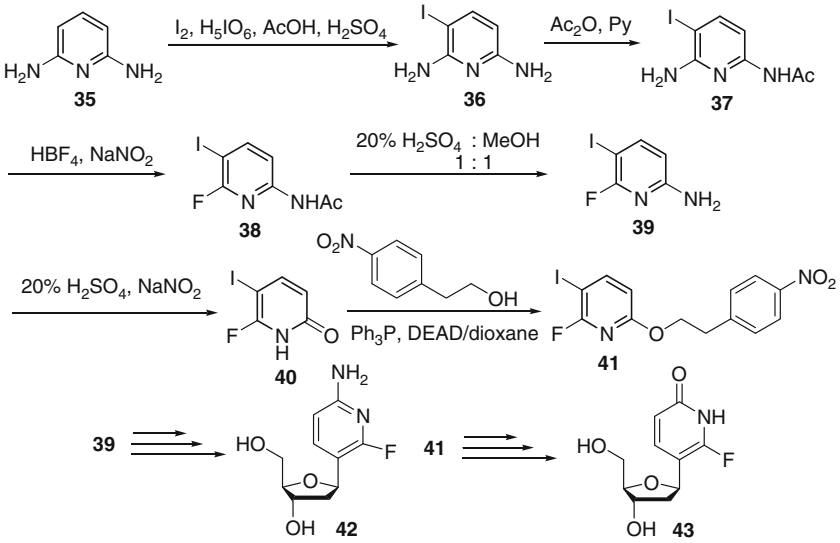


Scheme 12

Recently the Baltz-Schiemann reaction occupies important practical place for synthesis substituted 2-fluoropyridines as an inhibitor and modulators of various kinase [31–33] and other biologically active compounds [1, 2, 34, 35], including F^{18}-pyridines for radiotherapy of a cancer. Nucleoside analogues can be used to investigate a variety of enzyme substrate interactions, including polymerase dNTP recognition or protein-DNA targeting. They can also be incorporated into nucleic acid sequences using conventional synthesis protocols to explore the structural and functional aspects of DNA or RNA. In one class of DNA analogues fluorine replaces the carbonyls and methyl replaces the exocyclic amino groups in the nucleobase heterocycle yielding a hydrophobic isostere of the natural nucleoside with the desired molecular shape [36–38]. Substituted 2-fluoropyridines were recently used in the synthesis of pyridine C-nucleosides as analogues of the natural nucleosides dC and dU [39]. Commercially available 2,6-diaminopyridine (35) was used as the starting material for these synthesis. Compound **35** was fist transformed into the 2,6-diamino-3-iodopyridine (36) which was acylated and then converted into 6-amino-2-fluoro-3-iodopyridine (39), which was transformed into 6-(4-nitrophenyldimethoxy)-2-fluoro-3-iodopyridine (41). Both **39** and **41** were used for the synthesis of nucleosides **42** and **43** [39] (Scheme 13).

2.3 Nucleophilic Substitution in 2-Substituted Pyridines

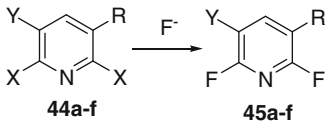
Pyridines containing leaving groups (Hal, R_3N^+, SO_2R, NO_2) in position 2 are often used as starting materials for preparation of 2-fluoropyridines in nucleophilic substitution reactions. Typical nucleophiles are fluorides of alkaline metals, hydrofluoric acid, tetrabutylammonium fluoride, and fluoroboric acid. Although this



Scheme 13

method allows preparation of 2-fluoropyridines in good yields, its main disadvantages include a set of special demands towards fluorine producing reagents, which, if not otherwise met, will significantly reduce the yield of the final products. In majority of all cases these reactions must be conducted in a dry aprotic solvents (DMSO, DMF, THF) with fluoride source introduced as a fine dry powder (normally due to its low solubility of fluorides in these solvents), since the hydration significantly reduces the nucleophilicity of fluoride anion. Dry environment for these reactions is dictated by a very high solvation ratio of the fluoride anion in water, which in its turn significantly increases its steric hindrance and reduces its nucleophilicity. However, in some cases high reactivity of the fluoride anion in water-organic solvent two-phase system can be maintained, for example, using crown ethers [40]. Recently it was shown that bulky *tert*-butanol as a solvent in nucleophilic substitution reactions gives only partially shielded solvates with fluoride anion and actually increases fluoride anion reactivity [40].

It was shown that 2-halopyridines **44** containing chlorine substituent in position 3, can be selectively converted into 2-fluoropyridines **45** by treatment with KF [41] (Scheme 14). The reactions were conducted at elevated temperature (100–200 °C) producing final pyridines **45** in 14–94 % yields (Table 3).

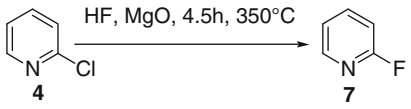


Scheme 14

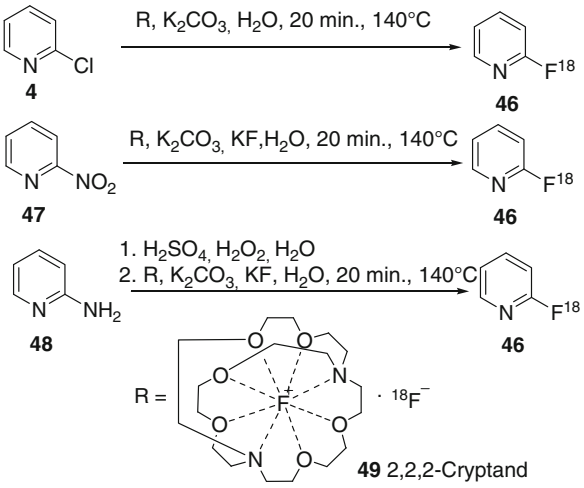
Table 3 Preparation of 2-fluoropyridine **45** [41]

Compound	X	Y	R	Temp. °C	Compound	Y	R	Yield %
44a	Cl	Cl	Cl	200	**45a**	Cl	Cl	76.6
44b	Cl	H	Cl	200	**45b**	H	Cl	72.4
44c	Cl	H	CH_3	200	**45c**	H	CH_3	33
44d	Cl	Cl	CH_3	200	**45d**	Cl	CH_3	69.4
44e	Cl	H	CF_3	200	**45e**	H	CF_3	83–94
44f	Br	H	NO_2	100	**45f**	H	NO_2	14

One-step synthesis 2-fluoropyridine (7) from 2-chloropyridine (4) in HF at temperature 350 °C with use as catalyst MgO is of interest for the industry [42] (Scheme 15). This method is the advanced of three-steps method [43]. For synthesis 2-F^{18}-pyridines (46) reactions of nucleophilic substitution of F-, NO_2- and NH_2-groups by F^{18} are used [44–46] (Scheme 16). The effective reagent – catalyst in synthesis 2-F^{18}-pyridines appeared 2,2,2-Cryptand (49) at the presence of which time of reaction is reduced up to 20 min. It is necessary to note, that 2-F^{18}-pyridines are used in radiobiology of a cancer, and half-life period of F^{18} is equal to 12 h.



Scheme 15

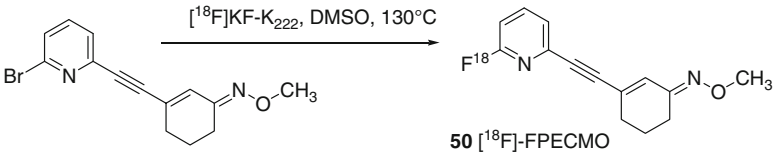


Scheme 16

Fluorination of pyridine by complex AlF_3 and CuF_2 at 450–500 °C forms a mixture of 2-fluoropyridine and 2,6-difluoropyridine in yields 32 and 11 % accordingly [47]. 3-Bromo-2-nitropyridine reacts with $Bu_4N^+F^-$ in DMF at 20 °C to form

2-fluoro-3-bromopyridine. Nucleophilic substitution proceeds highly regioselectively in the second position of pyridine [48]. 5-Amino-2-fluoropyridine used as an epilepsy medicine [49] was it is synthesized from 2-chloro-5-nitropyridine.

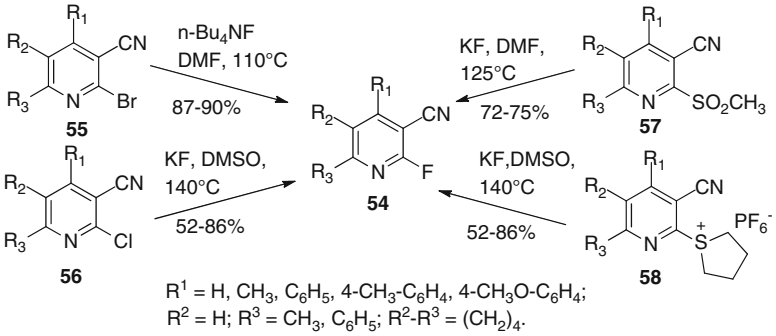
Fluorine-18 labeling and the pharmacological evaluation of a 2-fluoropyridine analog of ABP688, [^{18}F]-(E)-3-((6-fluoropyridin-2-yl)ethynyl)cyclohex-2-enone O-methyl oxime ([^{18}F]-FPECMO) (50), as a potential mGluR 5 imaging agent is described in the work [50]. Compound **50** was synthesized by reaction of nucleophilic substitution with use Kryptofix K_{222} (Scheme 17).



Scheme 17

3-Cyano-2-fluoropyridines are an important class of biologically active compounds that include potent kinase inhibitors, potassium channel inhibitors, and CNS active agents **51–53** (Fig. 1) [51–55]. In addition, fluorinated pyridines can be potentially used as labeling agents for various spectroscopic techniques such as positron emission tomography, X-ray photoelectron spectroscopy, and NMR spectroscopy.

Paper [56] describes the synthesis of 3-cyano-2-fluoropyridines (54) by nucleophilic substitution of 2-nucleofuge-containing substituted 3-cyanopyridines (Scheme 18). This method employs classic sources of nucleophilic fluoride such as KF and Bu_4NF in DMF or DMSO at higher temperatures. The use of chloride and bromide 2-nucleofuges affords 3-cyano-2-fluoropyridines in moderate to good yields. The 2-bromo substituted starting materials (55) present the advantage of being synthesized in one step in good yields, contrary to the 2-chloro-3-cyanopyridines (56) which are prepared in moderate yields. Readily available 3-cyanopyridine-2(1*H*)-thiones have also been C2-fluorinated in good yields via 3-cyano-2-methanesulfonylpyridines (57) and tetrahydrothiophenium (58) salt [56].



Scheme 18

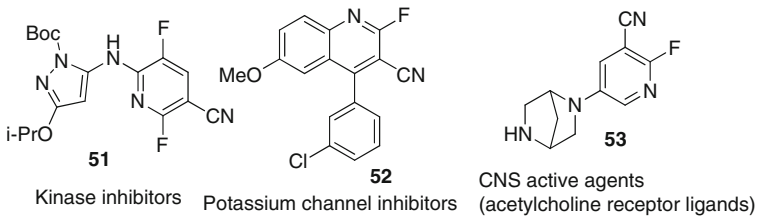
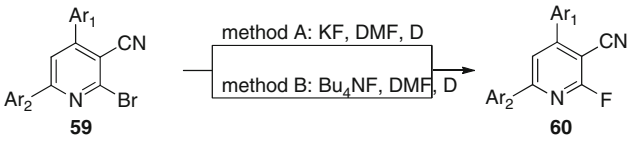


Fig. 1 Examples of biologically active fluorinated pyridines

Substituted 2-bromo-3-cyanopyridines (59) were successfully converted into substituted 3-cyano-2-fluoropyridines (60) (Scheme 19). A nucleophilic replacement of bromine with fluorine was achieved in heated DMF with dry KF (Method A) or with dry TBAF (Method B). The yields of 2-fluoropyridines **60** were 15–20 % higher for Method B [56].



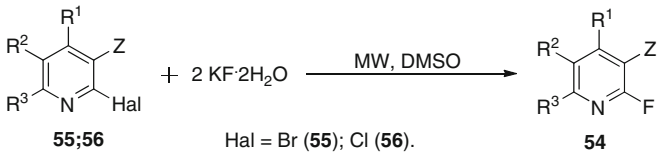
Ar^1	Ar^2	Yield (method A)	Yield (method B)
C_6H_5	C_6H_5	62	90
C_6H_5	4-F-C_6H_4	62	82
4-Cl-C_6H_4	C_6H_5	68	76
4-CH_3-C_6H_4	C_6H_5	76	87
4-CH_3O-C_6H_4	C_6H_5	76	90
2-C_4H_3S	C_6H_5	63	76

Scheme 19

Due to hydration significantly reduces the nucleophilicity of the fluoride anion [1, 56], these reactions are normally conducted in dry aprotic solvents (DMSO, DMF, THF) with the fluoride source introduced as a fine dry powder (due to its low solubility in these solvents). At the same time, reactions of 2- and 4-halopyridines with $KF{\cdot}2H_2O$ or reactions in aqueous solutions were shown to be very slow and incomplete. Although, considerable effort has gone into the development and optimization of anhydrous conditions for the preparation of fluorinated pyridines, to the best of our knowledge, there are no reports on these reactions in untreated reagent grade solvents or in aqueous medium.

Recently it has been shown a practical synthetic approach towards 3-cyano-2-fluoropyrines based on nucleophilic substitution of various leaving groups at the

2-postion of pyridine using "spray-dried" KF or Bu_4NF in dry DMF and DMSO [56]. The developed protocols offered good to high yields of the fluorinated pyridines, however, they suffered from relatively harsh conditions, prolonged reaction times, and the necessity to use anhydrous solvents and reagents. As such, 3-cyano-2-fluoropyridines (54) were obtained from pyridines **55, 56** by heating for 8 h at 140 °C (Scheme 20) (Table 3).



Scheme 20

Being based on fact that microwave irradiation can promote dehydration, nucleophilic substitution reaction using a series of substituted halogen azines under microwave irradiation using readily available $KF{\cdot}2H_2O$ in non-dry reagent-grade dimethylsulfoxide were investigated [57].

2-Bromo(chloro)-3-cyanopyridines (55, 56) were reacted with $KF{\cdot}2H_2O$ in DMSO in a sealed vessel using a focused microwave synthesis system (CEM Discover BenchMate) under continuous stirring [57]. The incubation time was 1.5–4 min with a fixed 300 W microwave irradiation power and a maximum temperature of 120 °C. Under such conditions the highest yields of the target compounds were achieved when the ratio of halogenazine to $KF{\cdot}2H_2O$ was 1:2 (Table 4).

Taking into account that nucleophilic substitution reactions of azines **55, 56** typically do not occur in untreated DMSO and $KF{\cdot}2H_2O$ under traditional heating, it is safe to assume that microwave irradiation promotes dissociation of KF and desolvation of the fluorine anion, which subsequently takes part in the nucleophilic substitution reaction, similarly to "spray-dried" KF in anhydrous DMSO (Fig. 2).

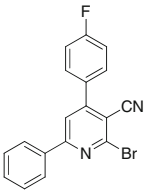
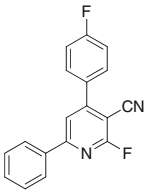
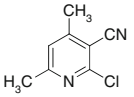
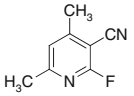
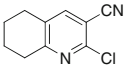
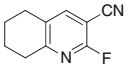
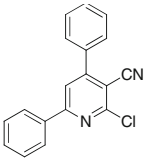
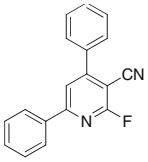
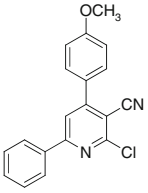
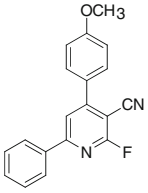
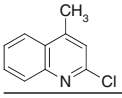
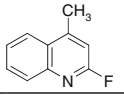
3 Synthesis of 3-Fluoropyridines

3.1 Synthesis of 3-Fluoropyridines from 3-Aminopyridines

The Baltz-Schiemann reaction is frequently used in synthesis substituted 3-fluoropyridine **58**–intermediate for synthesis of biologically active compounds [58–62]. In particular, compound **58** was used for synthesis of compound **59** active against atherosclerosis dyslipidemias [59, 60] (Scheme 21).

2,6-Dibromopyridine-3-diazonium tetrafluoroborate (60) was transformed at heating into 2,6-dibromo-3-fluoropyridines (61), which was used in synthesis inhibitors of Btk (Bruton's Tyrosine Kinaze) (62) [63] (Scheme 22).

Table 4 Structures of starting materials **55, 56** and yields of fluoroazines **54**

Starting material	Reaction product	Yield, %	
		"Spray-dried" KF, anhydrous DMSO, 140 °C, 8 h[56]	KF·2H$_2$O, DMSO, MW 300 W[57]
		–	68
		–	67
		75	78
		52	75
		86	77
		–	75
		–	62[c]

The modified method for the synthesis of 3-fluoropyridine (63) by heating of borofluoropyridines diazonium salts (64) or 3-(diisopropyltriazo)-pyridine (65) in perfluorohexane [64] was recently developed (Scheme 23).

The Baltz-Schiemann reaction was applied for the synthesis of 2-amino-5-fluoropyridine (67) which is a starting material for synthesis pyridothiadiazene 1,1-dioxides (68) acting as AMPA potentiators [65]. 2-Amino-5-fluoropyridine (67) was obtained from 2-amino-5-nitropyridine (66) by row of transformations: acetylation by acetic anhydride to protect a 2-amino group, hydrogenation of nitro group to the amine and then by Baltz-Schiemann reaction enter atom of fluorine and at a final stage removing protection of 2-amino group afforded **67** (Scheme 24).

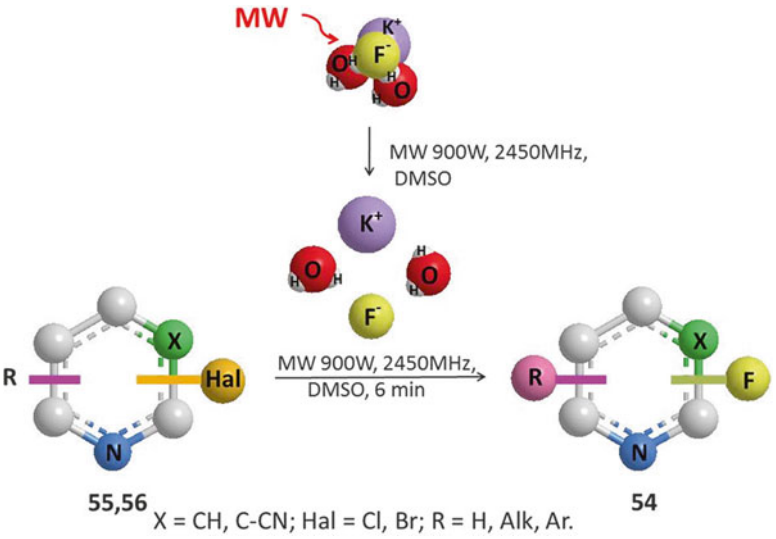
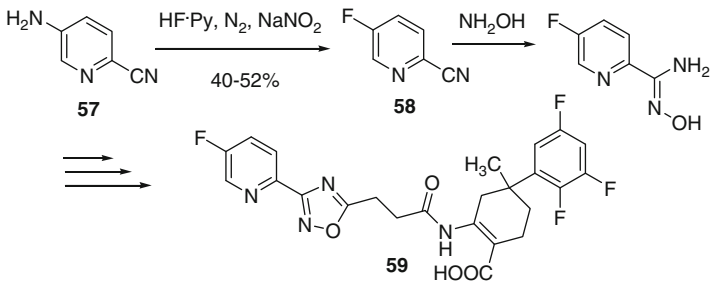
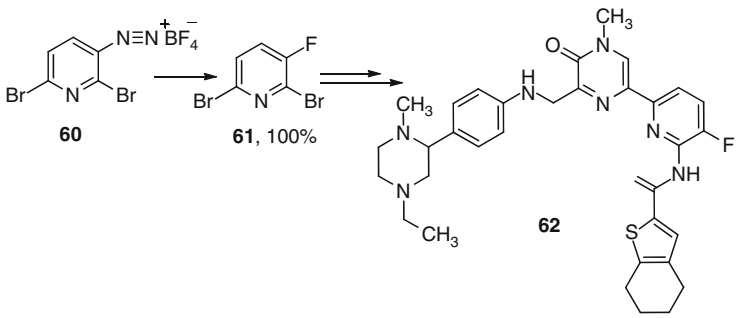


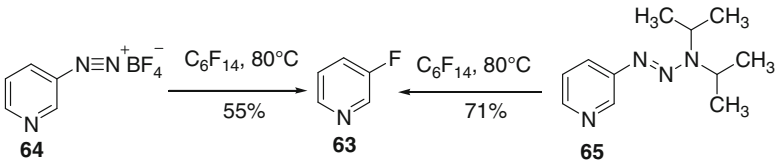
Fig. 2 Desolvation of F^- anion under microwave irradiation



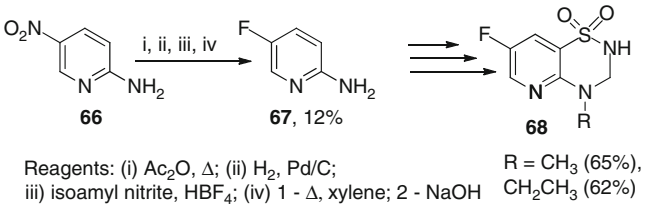
Scheme 21



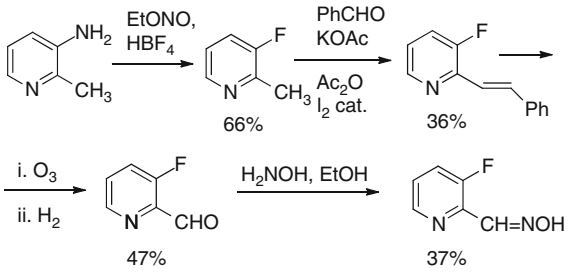
Scheme 22



Scheme 23



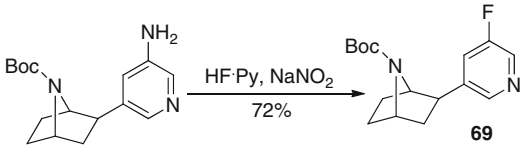
Scheme 24



Scheme 25

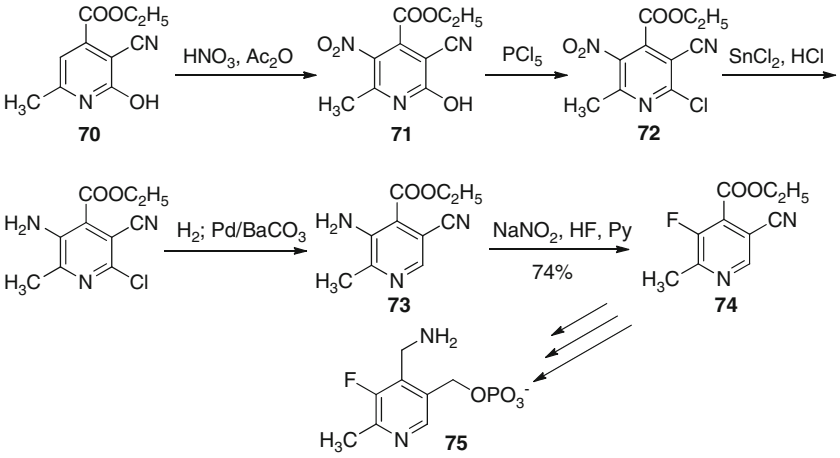
3-Fluropyridine-2-aldoxime was prepared similarly compound **34** from 3-amino-2-methylpyridine [30] (Scheme 25).

The Baltz-Schiemann reaction is the most often used method for the synthesis of 3-fluoropyridines. This method utilizes readily accessible 3-nitropyridies as the precursors; since they can be readily reduced into amines and then used in the Baltz-Schiemann reaction. In this section selected examples applied for the synthesis of practically important compounds are given. For example, the Baltz-Schiemann reaction was used for the synthesis of fluorosubstituted epibatidine analog **69** (epibatidine is a high affinity nonselective ligand for nicotinic cholinergic receptor (nAChRs)) [66] (Scheme 26).



Scheme 26

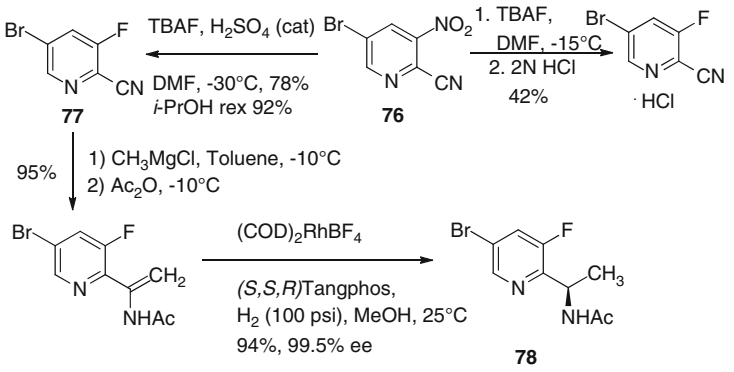
3-Deoxy-3-fluoropyridoxamine 5′-phosphate (75) (a coenzyme B_6 analog) was also synthesized using the Baltz-Schiemann reaction [67]. First substituted pyridine **70** was nitrated to form 3-nitropyridine **71**, which was subsequently treated with PCl_5 to form 2-chloro-5-nitropyridine **72**. It was then reduced in two steps to form 3-aminopyridine **73**, converted into 3-fluoropyridine **74** by the Baltz-Schiemann reaction, and afterwards was transformed into 3-deoxy-3-fluoropyridoxamine 5′-phosphate (F-PMP) (75) (Scheme 27).



Scheme 27

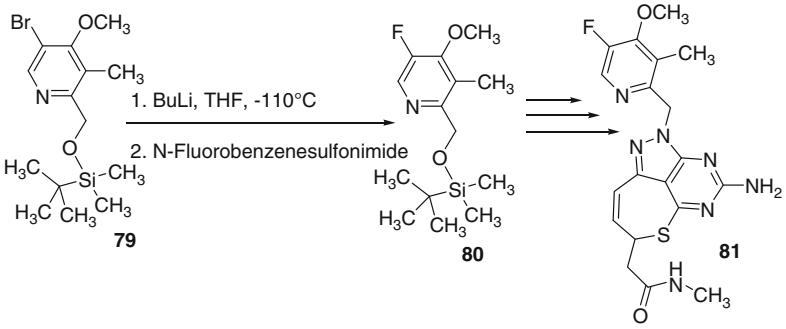
3.2 Substitution Reactions in the Synthesis of 3-Fluoropyridines

The nucleophilic substitution reactions leading to 3-fluoropyridines are rare. Although 2-amino (or buthylthio)-3-aminopyridines do not react with TBAF [68], the introduction of the electron-withdrawing group in position 2 of the pyridine ring in some cases makes possible such transformations. For example, 2-cyano-3-nitropyridine reacts with TBAF forming 2-cyano-3-fluoropyridine in 64 % yield [68]. Similar transformations were reported for 3-substituted-4-carbethoxypyridines, which also undergo nucleophilic substitution at the position 3 of pyridine ring [69]. Potent *Bradykinin B* was synthesized from bromopyridine **77**. This compound was obtained from 5-bromo-2-cyano-3-nitropyridine (76). At the reaction of nucleophilic substitution of NO_2-group the TBAF and H_2SO_4 as the catalyst were used. The further transformations result in compound **78** [70] (Scheme 28). The similar method of synthesis of compound **77** was used in synthesis of biologically active substances [71]. The nucleophilic substitution of NO_2-group by fluorine in compound **76** followed by addition of 2 N HCl results in muriatic 5-bromo-2-cyano-3-fluoropyridine [72].



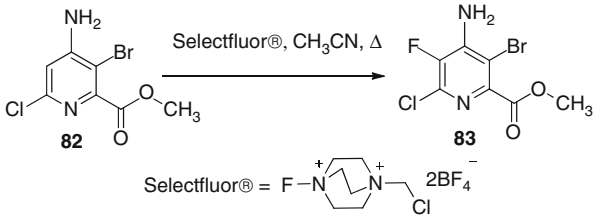
Scheme 28

The replacement of bromine into fluorine in compound **79** was performed in two-steps. Transmetallation with BuLi followed by fluorination of the organolithium compound with N-fluorobenzenesulfonimide resulted in 3-fluoropyridine **80**. It was used as a starting material for synthesis of substituted 6-thia-1,2,3,5-tetraazabenzoazulenes (81) – anticancer medicines [73] (Scheme 29).



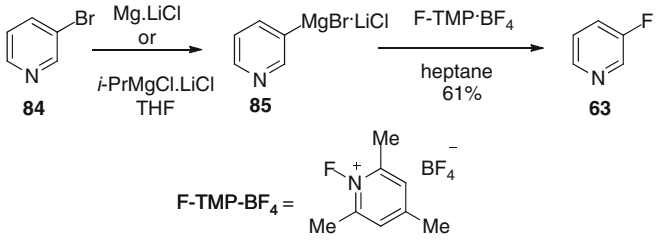
Scheme 29

High yield method for the preparation of substituted 3-fluoropyridines **83** with use Selectfluor® (1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo-[2.2.2] octane bis (tetrafluoroborate)) has been applied in synthesis of compounds possessing by herbicidal activity [74] (Scheme 30). This way allows to incorporate into a molecule atom of fluorine, not touching an amino group and halogens in initial compound **82**.



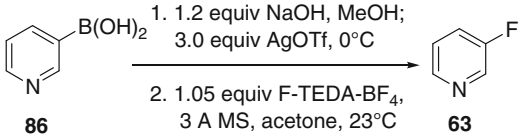
Scheme 30

N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (F-TMP-BF_4) is also effective fluorinating reagent which have been used in synthesis 3-fluoropyridine (63) from Grignard mediated compound (85) [75] (Scheme 31).



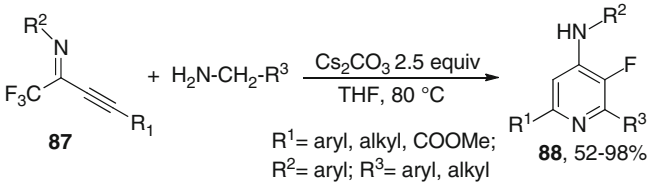
Scheme 31

Wide spectrum of fluorinated aromatic compounds has been synthesized by electrophilic fluorination of arylboronic acids. So 3-fluoropyridine (63) has been obtained from 3-pyridine boronic acids **86** and F-TEDA-BF_4 in 72 % yield [76] (Scheme 32).



Scheme 32

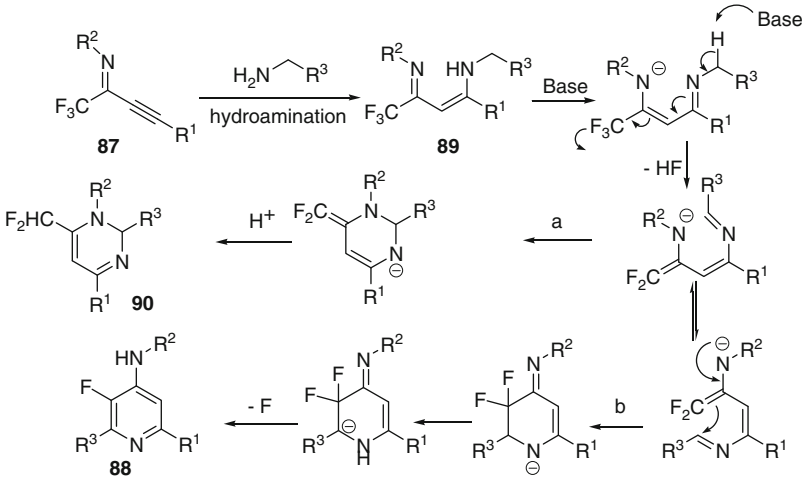
A new strategy for the synthesis of poly-substituted pyridines **88** based on C-F bond breaking of the anionically activated fluoroalkyl group **87** is described (Scheme 33). A series of 2,6-disubstituted 4-amino pyridines were prepared through this domino process in high yields under noble metal-free conditions, making this method a supplement to pyridine synthesis [77].



Scheme 33

A possible mechanism of this transformation includes hydroamination of alkynylimine with amine to form the intermediate vinylogous amidine **89** (Scheme 34), which undergoes deprotonation and dehydrofluorination to generate an anion and

an imine coexisting in one molecule. When the reaction is carried out at a low temperature with a soluble base (path a), the in situ generated amide nucleophile attacks imine immediately without isomerization to form dihydropyrimidine **90** through a kinetically controlled pathway. Raising the reaction temperature (path b), however, makes the carbon nucleophilic addition become an option, rendering a 1,2-dihydropyridine ring under thermodynamic control, which finalizes the pyridine ring after proton migration, β-F elimination, and isomerization, and an insoluble base can effectively inhibit the kinetic pathway.



Scheme 34

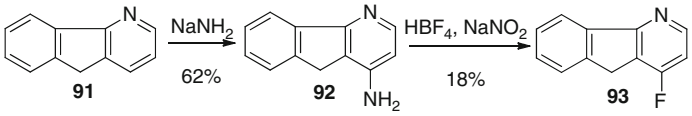
4 Synthesis of 4-Fluoropyridines

In general, the reactivity of the pyridine ring in nucleophilic substitution reaction decreases in the row C2 > C4 > C3. Consequently, more synthetic routes are reported for 4-fluoropyridines compared to 3-fluoropyridines. Pyridines can form cationic complexes with electrophiles resulting in activation of heterocyclic ring towards nucleophilic substitution. On the other hand, pyridines have significantly reduced reactivity towards electrophiles and typically undergo electrophilic substitution reactions in the presence of strong Lewis acids selectively in the position 3 [78].

4.1 Baltz-Schiemann Reaction in the Synthesis of 4-Fluoropyridines

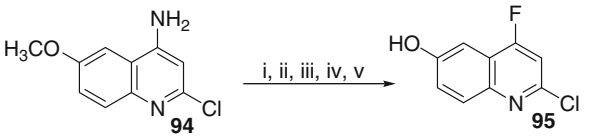
The Baltz-Schiemann reaction can also be used for the synthesis of 4-fluoropyridine derivatives [21, 22, 26–29]. For example, it was successfully applied to the synthesis of 4-fluoroazafluorene [79]. First, 1-amino-4-azafluorene (92) was synthesized

by amination of 4-azafluorene (91) using the Chichibabin reaction and then was converted into 1-fluoro-4-azafluoren (93) in 18 % yield (Scheme 35).



Scheme 35

6-Hydroxy-2-chloro-4-fluoroquinolones (95) have been synthesized by Baltz-Schiemann reaction for creation of novel quinolone compounds applied as S-nitrosoglutathione reductase (GSNOR) inhibitors [80] (Scheme 36). 4-Fluoropyridinone synthesized by Baltz-Schiemann reaction from 2-chloro-4-fluoropyridine, it is used in synthesis 4-fluorocytisine [81].

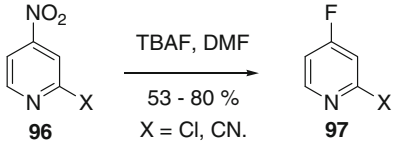


(i) Olah's reagent, rt - 10 °C; (ii) $NaNO_2$, 0 °C; (iii) H_2O coled;
(iv) NaOH, H_2O, pH 17; (v) BBr_3, CH_2Cl_2,12 h, 20°C.

Scheme 36

4.2 Substitution Reaction in the Synthesis of 4-Fluoropyridines

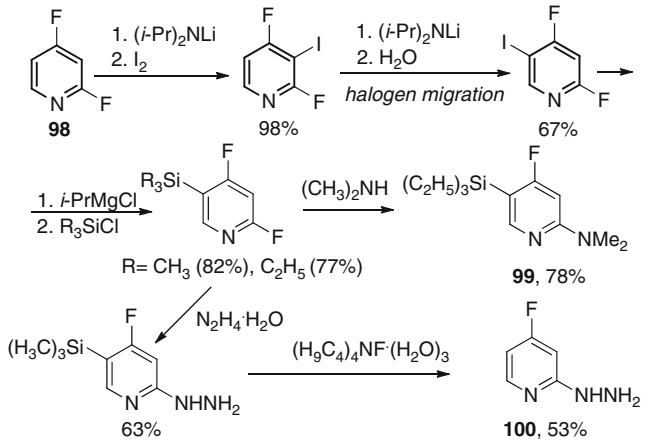
Usually 4-fluoropyridines are synthesized from their nucleofuge-containing precursors by the nucleophilic substitution reaction. For example, 4-nitropyridines **96** react with TBAF in DMF with the formation of substituted 4-fluoropyridines **97** [68] (Scheme 37). This reaction is highly regioselective despite of the presence of relatively good leaving group (Cl or CN) in position 2 of pyridine.



Scheme 37

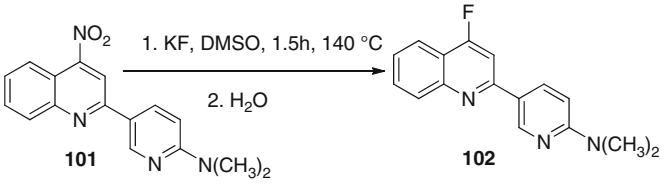
Radiolabeled 4-[^{18}F]fluoropyridine can be synthesized by no-carrier-added nucleophilic aromatic substitution with K[^{18}F]F-K_{222} [82]. In another instances, the nucleophilic substitution reaction was also employed for the synthesis of steroids containing 4-fluoropyridine motif [83, 84], and for the synthesis of 4-fluoropyridines annulated with pyrrole (azoindoles) [85, 86]. Substantial difference in the reactivity

of the pyridinium ring toward nucleophilic substitution in 5-iodo-2,4-difluorpyridine was effectively used for the preparation of 4-fluoropyridines **99, 100** using difluoropyridine **98** as starting material [87] (Scheme 38).



Scheme 38

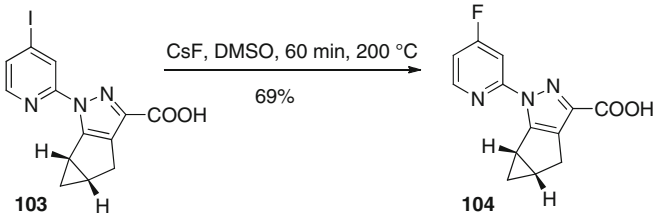
Unsubstituted 4-fluoropyridine has been synthesized by reaction of 4-nitropyridine with Bu_4NF at heating in DMSO [88]. Nucleophilic substitution of NO_2-group in quinolone **101** proceeds with use KF in DMSO at 140 °C (1.5 h) with formation substituted 4-fluoroquinolone **102** in 37 % yield [89] (Scheme 39).



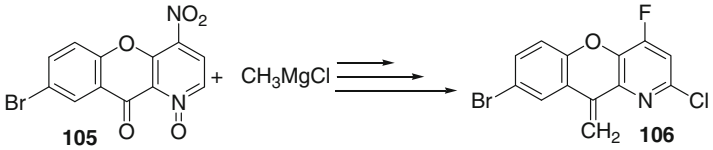
Scheme 39

New anesthetic compound – tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c] pyrazole (104) has been prepared by reaction iodopyridine **103** with CsF in DMSO without change of stereochemistry at rather hard conditions (60 min. at 200 °C) [90] (Scheme 40). Compounds **104** are modulators of receptors of cannabinoids and can be used against a cancer and Alzheimer's and Parkinson's diseases [90].

Compound **106** was obtained by multistep approach including nucleophilic substitution of NO_2 group by F (using Bu_4NF as fluorination agent) in **105** (Scheme 41). Compound **106** is used in synthesis of new drugs against Alzheimer's



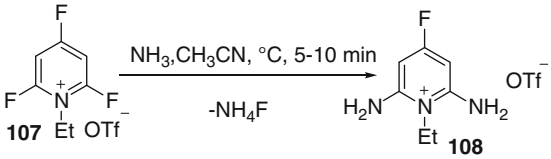
Scheme 40



Scheme 41

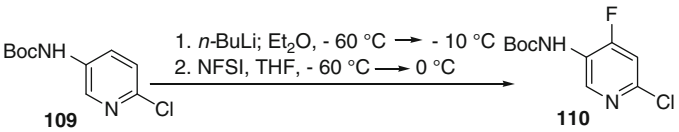
disease, schizophrenia and others [91]. The reaction of nucleophilic substitution used for synthesis of 4-fluoro(pyridines)quinolones as starting materials to obtain new biologically active compounds [89, 92, 93]. It is possible to note, that in various conditions for this reaction have been published, however as a whole this method became classical, that is evidently displayed in reviews [1–4], and also in book of Fainzil'berg and Furin [94].

Monofluoropyridines were obtained also from polyfluoropyridines, using reactions of nucleophilic substitution. N-Ethyl-2,6-diamino-4-fluoropyridinium triflate (108) was synthesized from N-ethyl-2,4,6-trifluoropyridinium triflate (107) by interaction anhydrous ammonia gas in MeCN at 0 °C during 5–10 min. in 72 % yield [95] (Scheme 42). Compound **108** is used for synthesis biologically active 8-fluoro-4-ethyl-4H-bis[1,2,3]dithiazolo[4,5-b:5′,4′-e]pyridine-3-yl [95].



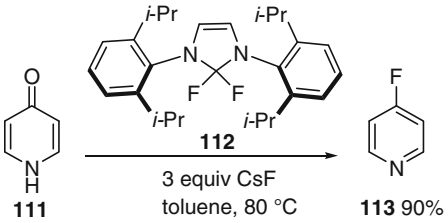
Scheme 42

Substituted 4-fluoropyridine **110** was synthesized from 2-chloro-5-tert-butylcarbonylaminopyridine (109). Treatment of **109** (Scheme 43) with *n*-BuLi followed by quenching with *N*-fluorobenzenesulfonimide (NFSI) gave the desired fluoropyridine **110** in 60 % yield [96]. Compound **110** is used in synthesis a potent, orally active, brain penetrant inhibitor of phosphodiesterase 5 (PDE5).



Scheme 43

New effective deoxyfluorination reagent – N,N-diaryl-2,2-difluoroimidazol (112) was applied for synthesis of fluorinated pyridines from corresponding hydroxypyridines [97]. Fluorination of pyrine-4(1H)-one (111) with compound **112** in toluene at the presence of 3 equivalents of CsF at 80 °C lead to 4-fluoropyridine (113) [98] (Scheme 44). Similarly 3-fluoro- and 2-fluoropyridines were obtained in 84 and 50 % yields accordingly.



Scheme 44

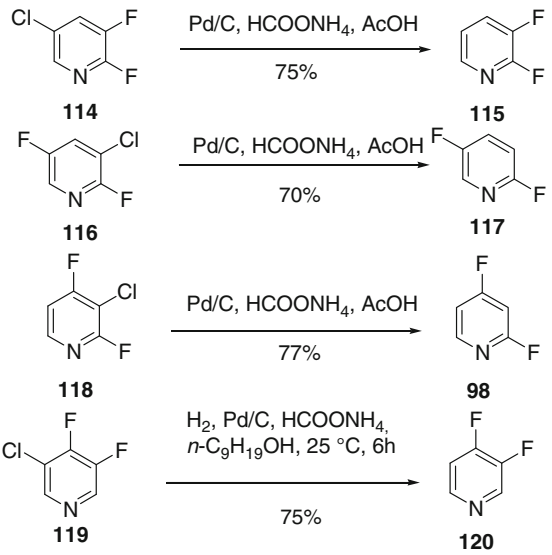
5 Synthesis of Di- and Polyfluoropyridines

In many cases, di- and polyfluoropyridines can be prepared using the same reactions for preparation of monofluorinated analogues. The degree of fluorination in some case can be controlled, however often it leads to mixtures of polyfluorinated compounds. Some polyfluoropyridines can be reduced back to di- or monofluoropyridines, which can be successfully used for a selective synthesis of these compounds.

5.1 Synthesis of Difluoropyridines

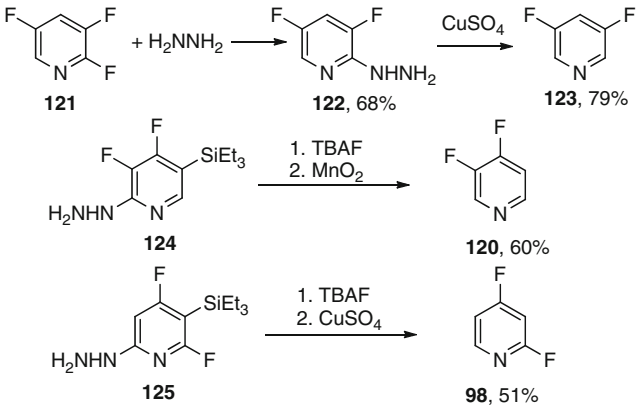
Pentafluoro- and tetrafluoropyridines, which are usually prepared from pentachloropyridine using Halex process, can be used as the starting materials for the synthesis of difluoropyridines [99]. For example, it was demonstrated that pentafluoropyridine can be utilized in the synthesis of substituted 3,5-difluoropyridines, which were investigated as new antithrombotic drugs [100, 101]. However, one of the most commonly used reaction for the synthesis of difluoropyridines is a selective reduction of polyhalogenated pyridines [99]. For example, chlorodifluoropyridines **114, 116, 118** can be reduced to the corresponding difluoropyridines **115, 117** and **98** using palladium on carbon/ammonium formate in 80 % acetic acid. The described reaction is highly

selective and only chlorine atom is getting reduced. Similarly, a catalytic hydrogenation of 3-chloro-4,5-difluoropyridine (119) provided mixture of 3,4-difluoropyridine (120) along with small amount of 3-fluoropyridine (ratio 95:3) [99] (Scheme 45).



Scheme 45

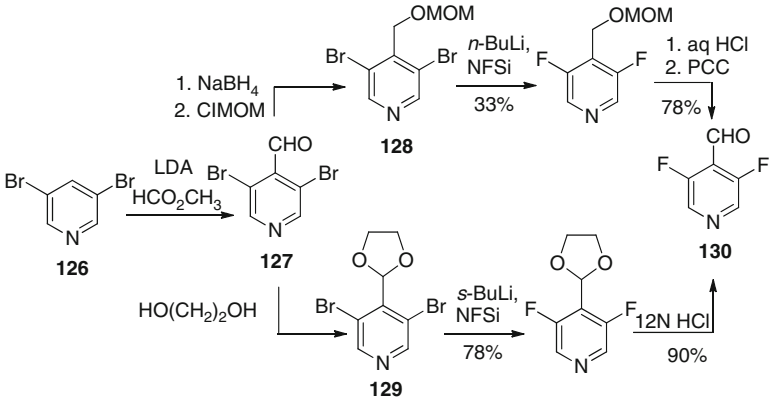
Other possible synthetic route leading to difluoropyridines such as **123, 120** and **98** is based on the reductive deamination of difluoropyridinehydrazines in the presence of $CuSO_4$ or MnO_2 combined with the removal of SiR_3 group [99] (Scheme 46).



Scheme 46

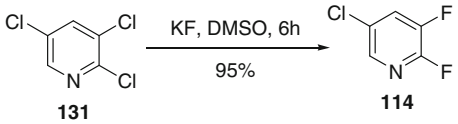
3,4-Difluoropyridine (**120**, 79 %) can be synthesized by the nucleophilic substitution of chlorine in 4-chloro-3-fluoropyridine with KF [99], while, 2,5-difluoropyridine (**117**, 75 %) can be prepared by deamination reaction of 2-hydrazino-3,6-difluropyridine in the presence of NaOH [99].

An interesting example is synthesis of 3,5-difluoropyridine **130** [102]. This compound was prepared from 3,5-dibromo-4-formylpyridine (127) by electrophilic fluorination of its protected forms **128** or **129** by *N*-fluoro-benzenesulfonimide (NFSI) (Scheme 47).



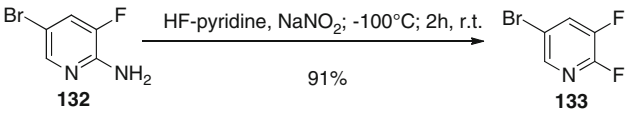
Scheme 47

As it was mentioned, substituted difluoropyridines can be used for the synthesis of monofluorinated pyridines. For example, varied difluoropyridines were converted into monofluoropyridyl-carboxylic acids [103, 104] and hydrazines [79, 105] by the reaction with the corresponding nucleophilic reagents. Reactions of nucleophilic substitution in dichloro-, trichloro- and also trifluoro-or tetrafluoropyridines by waterless KF, Bu_4NF and others nucleophilic reagent most are frequently used for synthesis difluoropyridines. For example, the reaction of 2,3,5-trichloropyridine (131) with KF in DMF proceeds during 6 h at 150 °C to give 5-chloro-2,3-difluoropyridine (114) in 95 % yield [106] (Scheme 48). Similarly compound **114** was obtained using Bu_4NBr in a mixture with KF in 42 % yield [107].



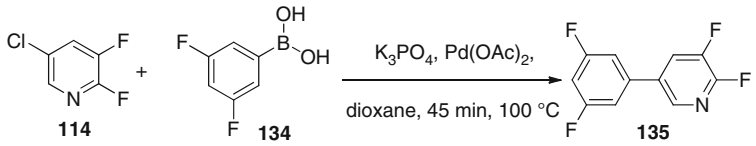
Scheme 48

5-Bromo-2,3-difluoropyridine (133) it is synthesized by Baltz-Schiemann reaction from 2-amino-5-bromo-3-fluoropyridine (132) [108] (Scheme 49).



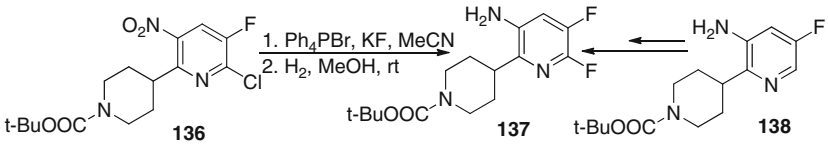
Scheme 49

Reaction of compound **114** with boronic acid **134** resulted in a derivative 2,3-difluoropyridine **135**, used as HGF (Hepatocyde Growth Factor) modulators [109] (Scheme 50).



Scheme 50

Substituted 2,3-difluoropyridine **137** was prepared from 3-fluoropyridine precursor **136** using nucleophilic substitution with KF [110] (Scheme 51). Compound **137** was obtained similarly from substituted 3-fluoropyridine **138** by multistep sequence including chlorination, protection amino group, nucleophilic substitution with KF and removal of protective acyl groups [111] (Scheme 51). Compound **137** is used for synthesis of insecticides [110, 111].



Scheme 51

4- or 5-halosubstituted 2,3-difluoropyridines are widely used for synthesis of biologically active compounds [108, 112–115]. These reactions of nucleophilic substitution are highly regioselective. Various heterocycles containing 2,3-difluoropyridine group **139–143** were synthesized by this method (Fig. 3).

Various polyfluoropyridines have found application in synthesis hardly available difluoropyridines fused with others heterocycles [116]. Reaction of pentafluoropyridine (144) with 2-amino-3-picoline (145) under basic conditions in acetonitrile at reflux or under microwave heating gave only one product – dipyridoimidazole **146** (Scheme 52).

Reaction of 2-amino-3-picoline (145) with 4-phenylsulfonyl-tetrafluoropyridine (147) was less selective than the reactions described above and three major

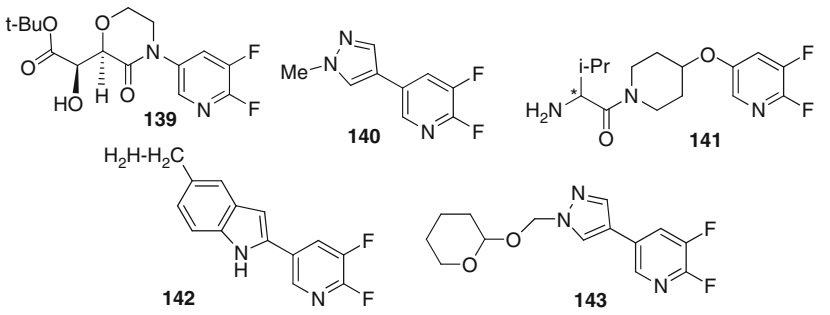
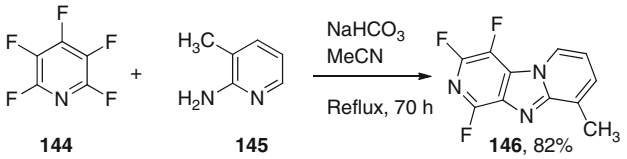
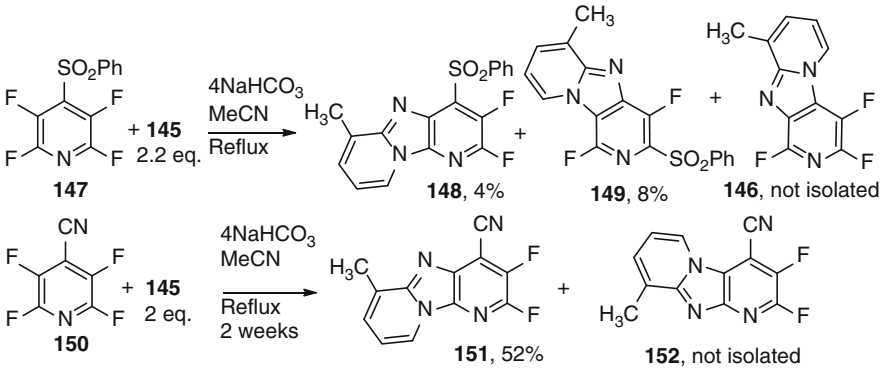


Fig. 3 Derivatives of 2,3-difluoropyridine



Scheme 52

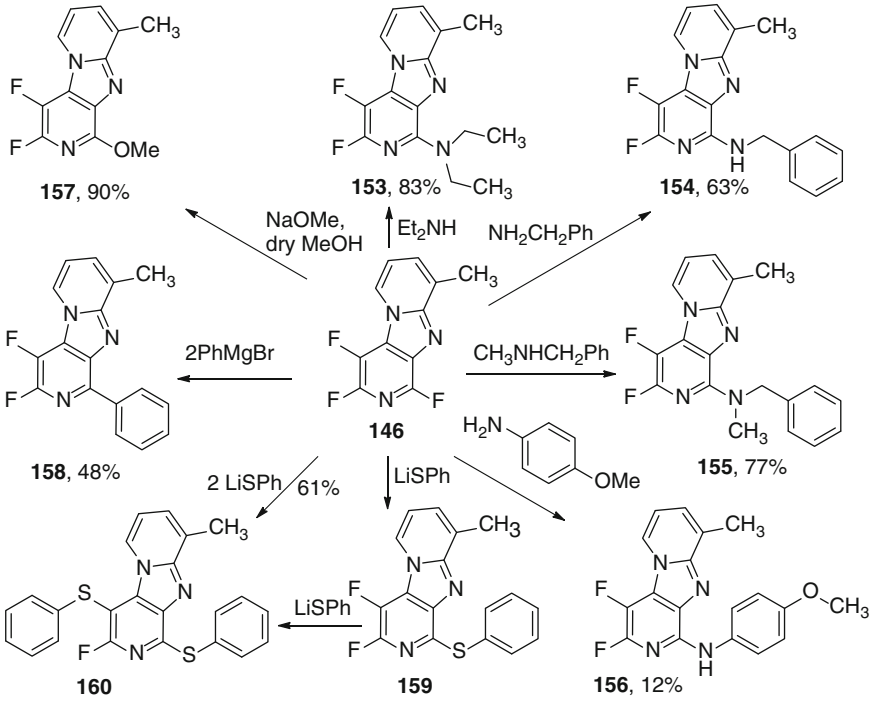
products, **148**, **149** and **146**, were synthesized accordingly ^{19}F NMR. Interaction of 4-cyano-tetrafluoropyridine (150) with 2-amino-3-methylpyridine (145) also resulted in formation a mixture of isomers of dipyridoimidazoles **151, 152** [116] (Scheme 53).



Scheme 53

Various substituted difliorodipyridoimidazoles **153–158** have been synthesized on the basis of obtained dipyridoimidazole **146** [116]. All reactions of **146** with nucleophiles gave products arising from selective displacement of fluorine located at the C-1 position. Reaction with only one equivalent of lithium benzenethiolate

gave the disubstituted derivative **160** as the major product (44 %) arising from displacement of fluorine atoms located at the C-1 and C-4 positions, with only a small amount of the monosubstituted product **159** (2 %). Subsequently, reaction of **146** with two equivalents of lithium benzenethiolate gave high yields of **160** [116] (Scheme 54).

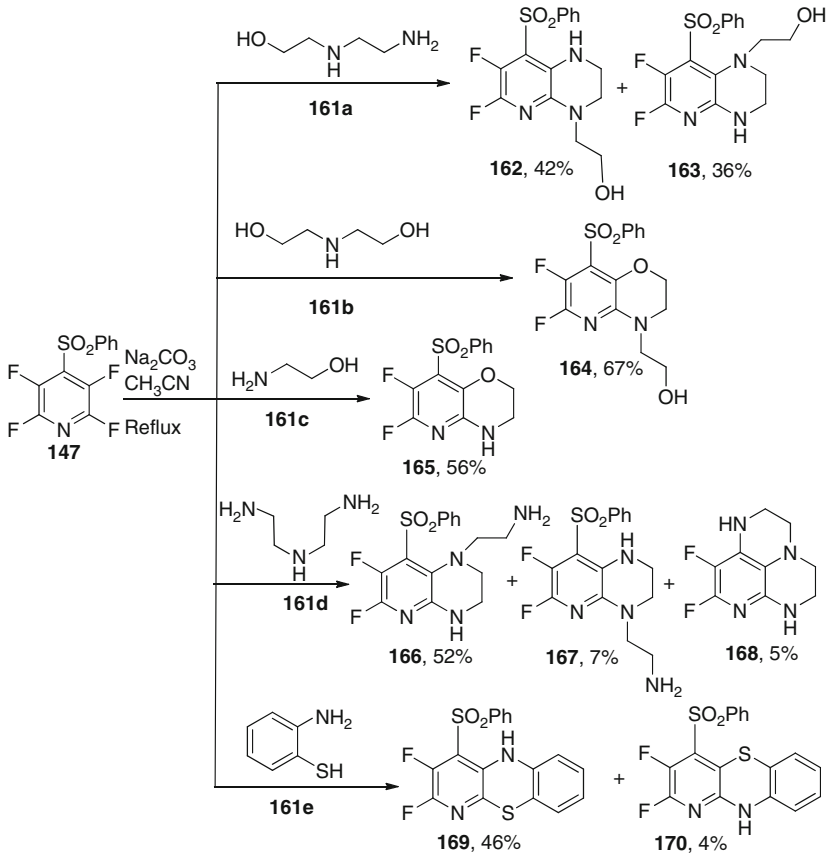


Scheme 54

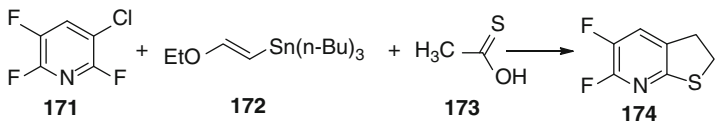
4-Phenylsulfonyl tetrafluoropyridine (147) was used successfully for synthesis difluoropyridines fused with hydrogenated pyridines **162–170** [117]. Synthesis of such compounds is based on reaction double (threefold) nucleophilic substitution of atoms of fluorine (sulfonyl groups) with 1,4-dinucleophiles (161) (Scheme 55).

By reaction of 5-chloro-2,3,6-trifluoropyridine (171) with vinylstannane **172** and monothioacetic acids (173) 5,6-difluoro-2,3-dihydrothieno[2,3-b]pyridine (174) was obtained and used as precursor for synthesis of anticancer drugs [118] (Scheme 56).

Examples of synthesis substituted 2,6-difluoropyridines are not numerous (Scheme 57). 3-Chloro-2,6-difluoropyridine (176) was obtained by interaction 2,3,6- trichloropyridine (175) with KF in sulfolane in 89 % yield [119]. 4-Bromo-2,6-difluoropyridine (178) it is synthesized from symmetric trifluoropyridine (177) [120]. Reaction of 2,6-dichloropyridine (179) with KF at heating in sulfolane at



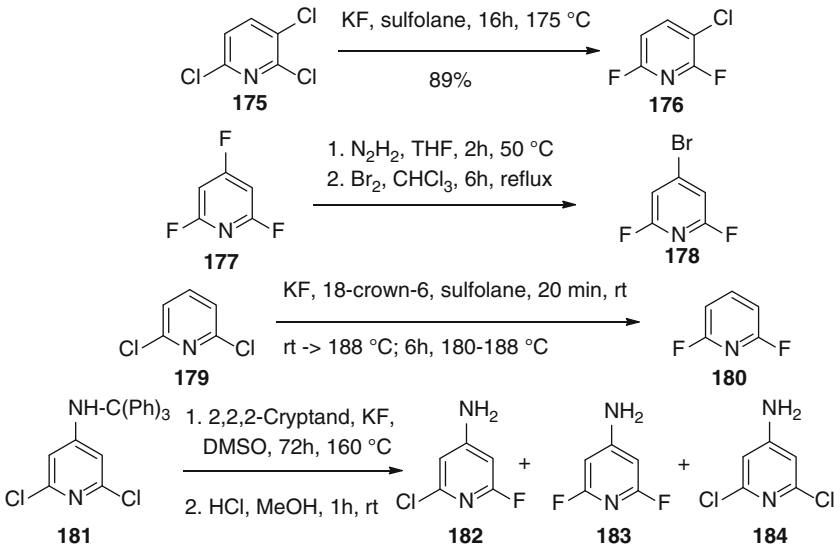
Scheme 55



Scheme 56

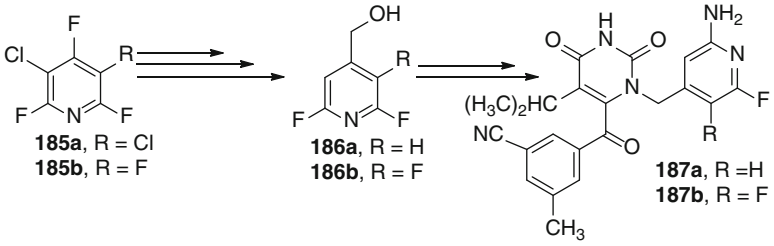
presence of 18-crown-6 give 2,6-difluoropyridine (180) in 78 % yield [121]. Heating of 2,6-dichloro-4-triphenylmethylaminopyridine (181) with 2,2,2-cryptand, KF in DMSO during 72 h give a mixture of compounds **182–184** [122].

Synthesis of substituted 2,6-difluoropyridine – starting materials for generation of potential medicines, is based on use of polyhalogenated pyridines in reactions of nucleophilic substitution. Compound **185a** was transformed successively to



Scheme 57

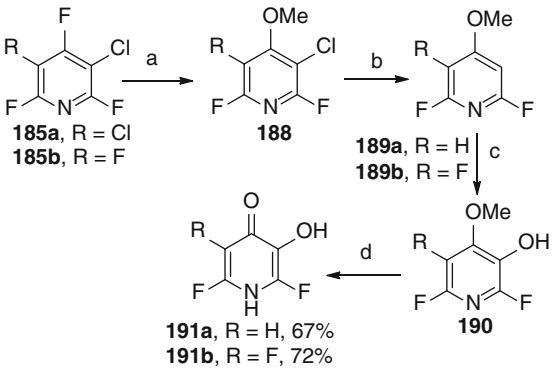
substituted 2,6-difluoro-4-hydroxymethylpyridine (**186a**), which was used in synthesis of HIV-1 non-nucleoside reverse transcriptase inhibitor **187a** [123] (Scheme 58).



Scheme 58

A range of fluorinated 3-hydroxypyridin-4-ones having fluorine or fluorinated substituent attached at 2- or 5- position of the pyridine ring has been synthesized in order to improve biological properties of 3-hydroxypyridin-4-ones. The syntheses of di- and trifluoro-3-hydroxypyridin-4-ones (**191a**) and (**191b**) started from the pentahalo substituted pyridines **185**. Treatment of the commercially available 3,5-dichloro-2,4,6-trifluoropyridine (**185a**) or 3-chloro-2,4,5,6-tetrafluoropyridine (**185b**) with 1 equivalents of sodium methoxide yielded **188** in good yield. Treatment of **188** with 10 % Pd/C at the presence of ammonium formate at 50 °C for 10 h gave

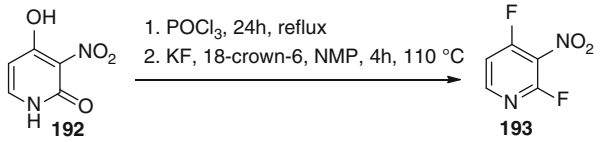
compounds **189** in high yields. Subsequent lithiation, electrophilic substitution, and oxidation as outlined above, introduced a hydroxyl group to afford compound **190**. The 4-methyl protecting group was removed to produce **191a** and **191b**, respectively [124] (Scheme 59).



(a) NaOMe; (b) Pd/C, $HCOONH_4$; (c) (i) LDA in THF at –75 °C for 0.5 h, (ii) $B(OMe)_3$ at –75 °C for 2 h, (iii) CH_3CO_3H at 0 °C for 1 h; (d) BBr_3, overnight

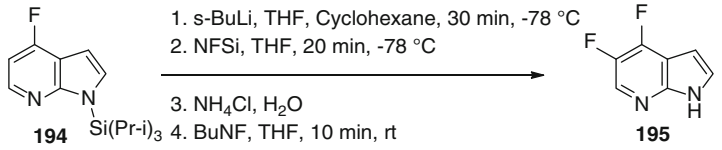
Scheme 59

2,4-Difluoro-3-nitropyridine (**193**) was used for synthesis antibacterial agents. **193** was prepared from 4-hydroxy-3-nitropyridine-2(1H)-on (**192**) by sequential processing with $POCl_3$ and then with KF [125] (Scheme 60).



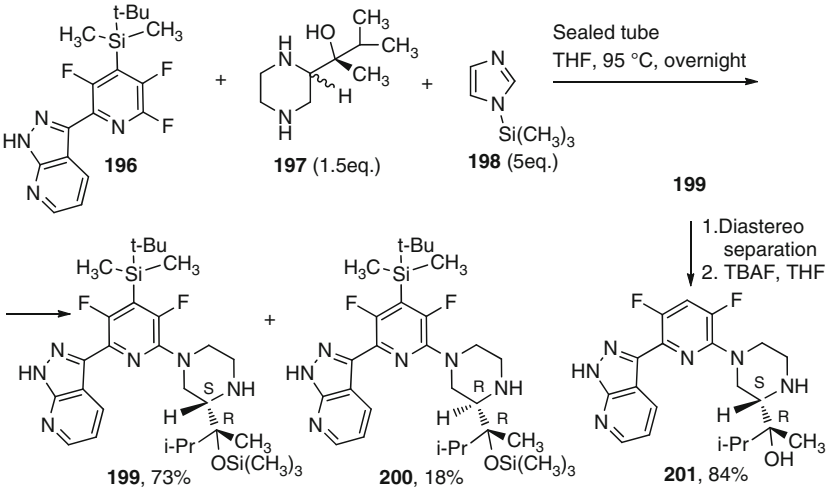
Scheme 60

Sequential reactions of N-substituted 4-fluoroindole **194** with s-BuLi, NFSI and then with Bu_4NF led to 4,5-difluoroindole **195** in 60 % yield. Compound **195** was used as a starting material for synthesis of kinase inhibitors [126] (Scheme 61).



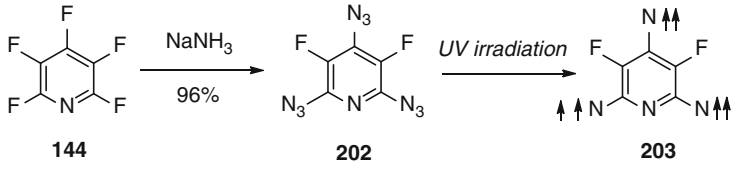
Scheme 61

Pyrazolopyridine kinase inhibitors, containing 3,5-difluoropyridine fragment **201** were prepared by multistep synthesis. Three-component reaction of trifluoropyridylpyridopyrazole (**196**), 3-methyl-2-(piperazin-2-yl)butan-2-ol (**197**) and 1-trimethylsilylimidazole (198) proceeded with formation of a mixture isomers **199** (R, S) and **200** (R, R). The reaction of isomer **199** (R, S) with TBAF in THF gives target compound **201** having (R, S) configuration [127] (Scheme 62).



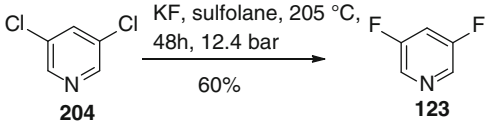
Scheme 62

3,5-Difluoro-2,4,6-triazidopyridine (**202**) has been synthesized by reaction of nucleophylic substitution from pentafluoropyridine (144) and sodium azide [128, 129]. The 3,5-difluoro-2,4,6-trinitren (**203**) has been obtained further from this compound and investigated by IR-spectroscopy [128, 129] (Scheme 63).



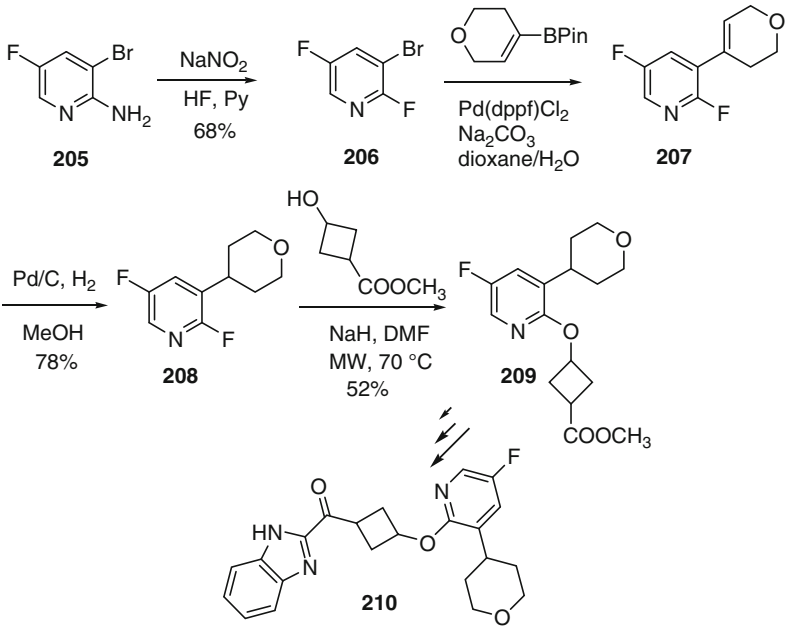
Scheme 63

Nucleophilic substitution of 3,5-dichloropyridine (**204**) with KF led to 3,5-difluoropyridine (123) [130] (Scheme 64).



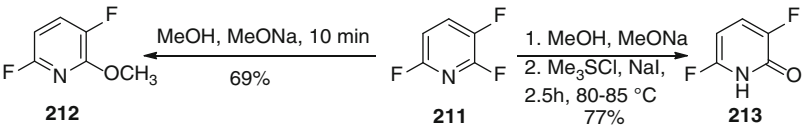
Scheme 64

Substituted 2,5-difluoropyridines **206** are obtained from the corresponding aminopyridines **205** by Baltz-Schiemann reaction, which are used in various areas of organic synthesis, including synthesis of biologically active compounds [108, 131–133]. For example, by few steps reaction 2-amino-3-bromo-5-fluoropyridine (**205**) was converted to biologically active compounds (**210**) by few steps [133] (Scheme 65).



Scheme 65

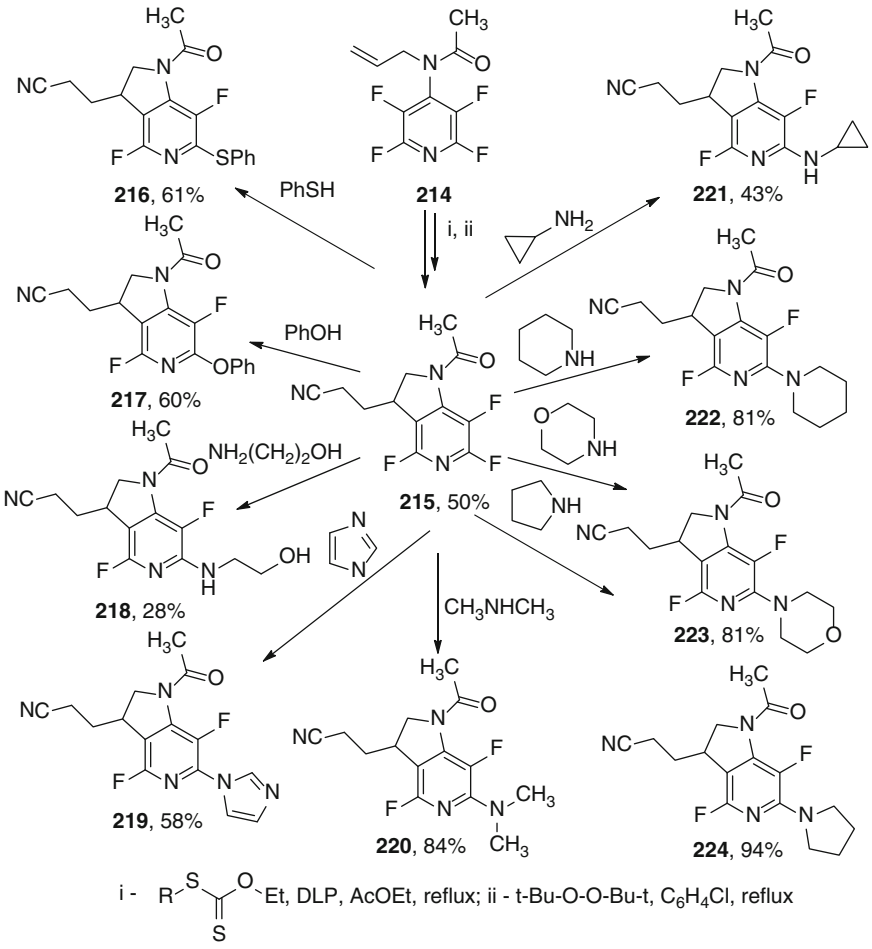
2,3,6-Trifluoropyridines were used for synthesis of substituted 2,5-difluoropyridines. The atom of fluorine which is taking place in the position 2, is most nucleophilic. Therefore, reactions with nucleophilic reagent proceeded highly regioselectively. 3,6-Difluoro-2-methoxypyridine (**212**) has been obtained from 2,3,6-trifluoropyridine (**211**) in methanol at presence MeONa [134–136] (Scheme 66). Pyridine (**212**) was applied in synthesis of antiviral compounds [134].



Scheme 66

3,6-Difluoropyridine-2(1*H*)-one (**213**) has been obtained by reaction of **121** with MeONa in MeOH followed by treatment with Me_3SiCl and NaI in MeCN [136, 137] (Scheme 66).

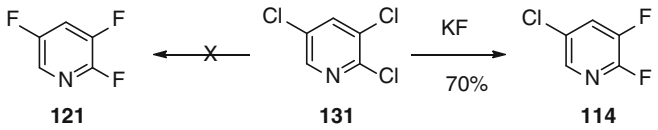
Trifluoroazoindoline **215** has been widely used in reaction of nucleophilic substitution for synthesis substituted difluoroazoindolines **216–224**. The starting compound **215** has been obtained from tetrafluoropyridine **214** by two steps (Scheme 67). It is interesting to note, that pyrrole ring formation at the second step of process proceeds under action of peroxide and explained by the radical mechanism. Nucleophilic substitution with various N-, O- and S-nucleophiles proceeded regioselectively with replacement of atom F in the second position as well as in the previous cases [138].



Scheme 67

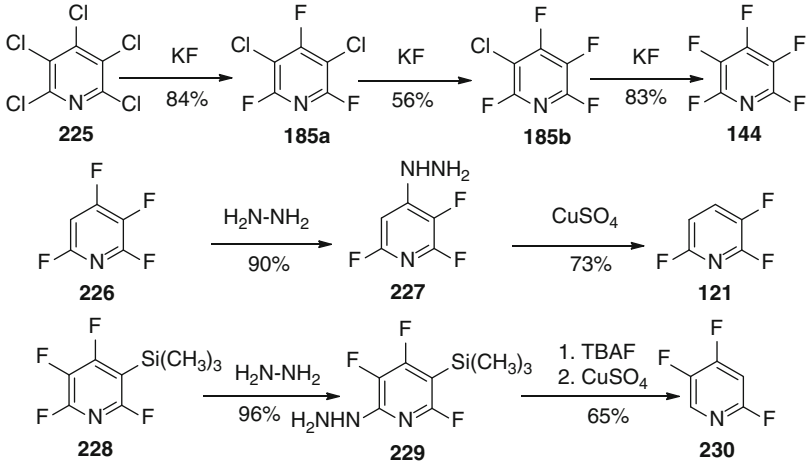
5.2 *Synthesis of Trifluoropyridines and Polyfluoropyridines*

Usually trifluoropyridines are prepared by the reduction or nucleophilic substitution of perhalogenated pyridines [99]. However, the reaction of the corresponding 2,3,5-trichloropyridine (131) with KF (in sulfolane, dimethylpropyleneurea, 220 °C, 16 h) resulted in only partial fluorination and formation of 2,3-difluoro-5-chloropyridine (114) [99]. Attempts to prepare 2,3,5-trifluoropyridine (121) from the corresponding trichloropyridine were unsuccessful (Scheme 68).



Scheme 68

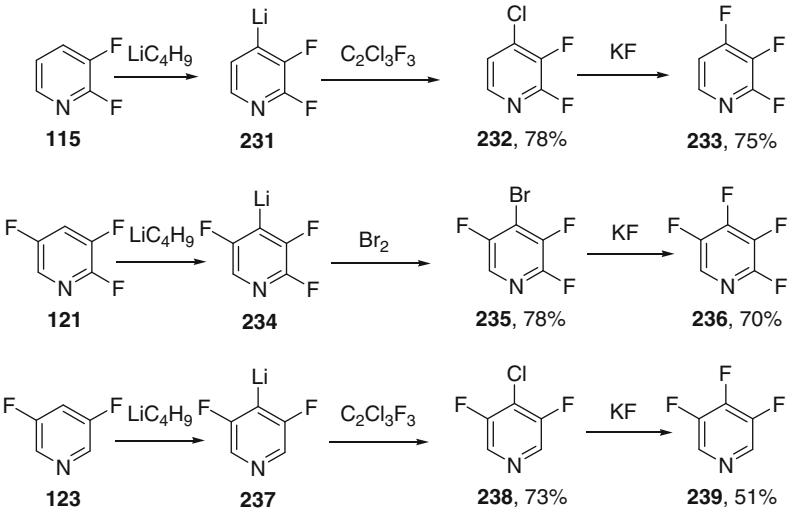
Pentachloropyridine (**225**) was used as the starting material in the reaction with KF, first producing dichlorotrifluoropyridine (**185a**). At higher temperature, this compound was converted into 3-chlorotetrafluoropyridine (**185b**) and then pentafluoropyridine (144) [99]. Tetrafluoropyridines **226, 228** were used in the reduction reactions for the selective synthesis of 2,3,6-trifluoropyridine (121) or 2,4,5-trifluoropridine (**230**) [99] (Scheme 69).



Scheme 69

Various tri- and tetrafluoropyridines **233, 236** and **239** have been synthesized from the corresponding di- and trifluoropyridines **115**, **121, 123.** The starting material was first lithiated by *n*-BuLi and transformed into chlorofluoropyridines **232**,

238 and bromofluoropyridine **238** by the reaction with $C_2Cl_3F_3$ or Br_2. The last step of the synthesis is based on Halex exchange reaction using spray-dried KF in anhydrous DMSO to give corresponding polyfluorinated pyridines **233**, **236**, **239** [99] (Scheme 70).

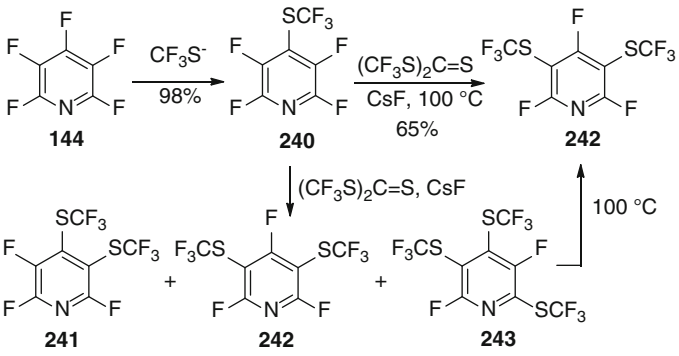


Scheme 70

Mixtures of polyfluorinated pyridines can be obtained from the corresponding pyridines by fluorination with tetrafluorocobaltates (III) [139], this reaction has a low selectivity. For example, the reaction mixture derived from the reaction of pyridine with $KCoF_4$ at 220 °C is reported to contain more than seven fluoropyridines, two fluoro-2-azahexenes, three azahexadienes, and two fluoro-N-methylpyrrolidines. Four fluorinated products were isolated from a fluorination of pyridine by CoF_3 at 150 °C: a 2-azahexene, two *N*-methylpyrrolidines and 4*H*-nona-fluoropiperidine [140].

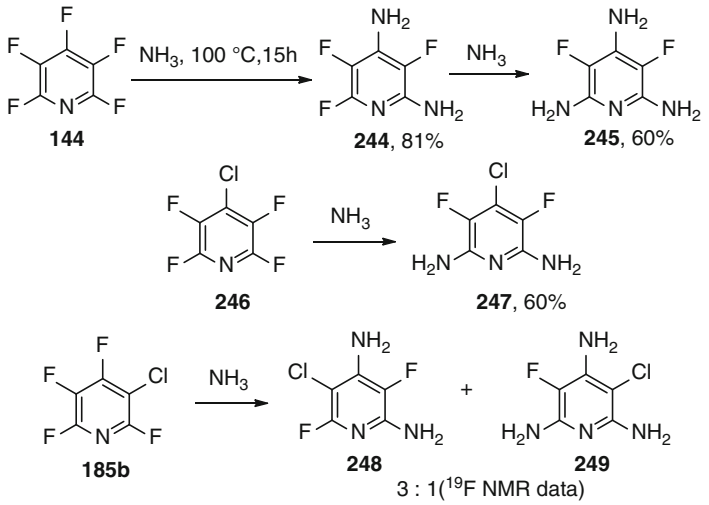
2,3,5,6-Tetrafluoro-4-trifluoromethylthiopyridine (**240**) was prepared in high yield by the reaction of pentafluoropyridine (144) with the CF_3S^- anion, generated from $F_2C{=}S$ or its trimer, and cesium fluoride at –15 °C [139] (Scheme 71). When the trimer was used as a precursor of the CF_3S^- anion compound **240** reacted further at 20 °C to give a mixture of polysubstituted pyridines **241–243** in the ratio of 4.5: 2: 1, respectively. When the reaction mixture was then heated at 100 °C both compounds **241** and **243** were fully converted into compound **242**. Compound **242** was the only product (65 %) of the reaction which was carried out at 100–110 °C [141] (Scheme 71).

Pentafluoropyridine (144) was applied for the synthesis 2,4-diamino-3,5,6-trifluoropyridine (**244**) [142]. Thus double nucleophilic substitution of fluorine atoms in 2 and 4 positions of the pyridine **144** occurred to give **244**. The same



Scheme 71

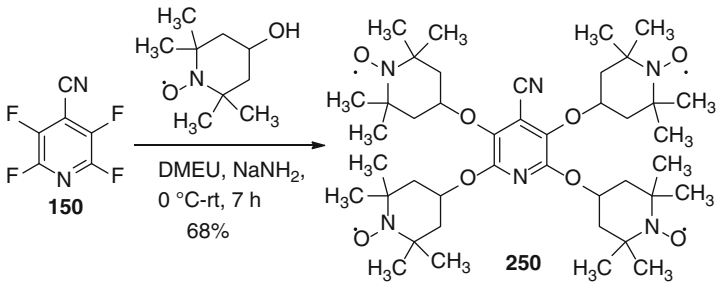
reaction of nucleophilic substitution with 4-chloro-2,3,5,6-tetrafluoropyridine (**246**) or 3-chloro-2,4,5,6-tetrafluoropyridine (**185b**) results to diamino-difluoropyridines **247** or mixture of isomers of diaminodifluoropyridine **248** and triaminofluoropyridine **249** [142] (Scheme 72).



Scheme 72

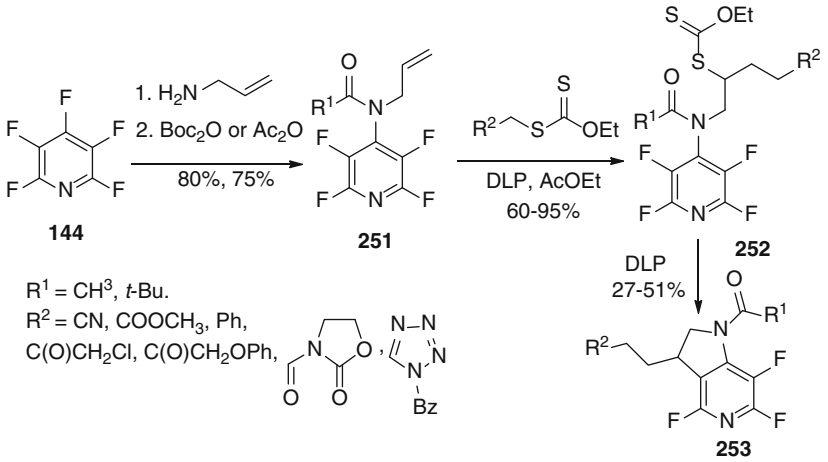
The scope and limitation of the synthesis of polynitroxides (**250**) by nucleophilic substitution of electron-deficient fluorinated pyridines was described [143] (Scheme 73). The method provided a facile route to the formation of polynitroxides exhibiting strong electron exchange between nitroxide groups.

The tendency perfluoropyridines to nucleophilic substitution is widely used in synthesis fluorinated and fused pyridines. In most cases the first nucleophilic



Scheme 73

substitution proceeds at 4 or 2 positions, sometimes at once 2,4-disubstituted trifluoropyridine is formed. Selective double substitution is used for synthesis fluoroazoindoles **253,** through intermediate **251, 252** [144] (Scheme 74).



Scheme 74

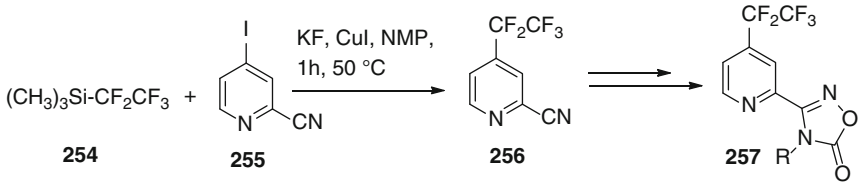
Various compounds benzothieno(furano)pyridines [145], 4-cyclopentadienylpyridines [146], 4-phenoxypyridines [147], 4-acetylenepyridines [148], furano[2,3-b]pyridines [149], 4-aminopyridines [150], bistetrafluoro-4,4′-pyridine [151] and others practically important pyridines [152–155] were obtained by the reaction of nucleophilic substitution.

6 Synthesis of Perfluoroalkylpyridines

Perfluoroalkylpyridines have reliably come in synthetic practice. These compounds are components of molecules applied as medicines, pesticides, dyes and other practically important compounds [1–3, 21].

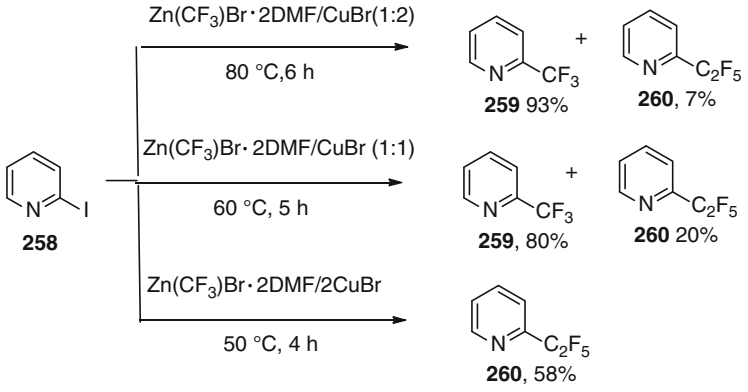
6.1 Substitution Reaction

Various perfluoroalkylhalides, perfluoroalkylsilanes and also fluorinated organometallic compounds were used most frequently for reactions of substitution. Pentafluoroethyltrimethylsilane **(254)** reacts selectively with 2-cyano-4-iodopyrydine (**255**) at presence KF and CuI in NMP to form substituted 4-pentafluoroethylpyridine (**256**) which is used for synthesis of pesticides **257** [156] (Scheme 75).



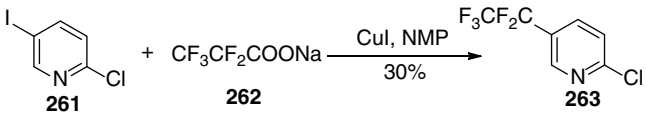
Scheme 75

2-Trifluoromethylpyridine (**259**) and 2-pentafluoroethylpyridine (**260**) were obtained by the reaction of 2-iodopyridine (**258**) and tri- and pentafluoroethylcooper at heating in DMF Trifluoromethylcopper and pentafluoroethylcopper are prepared conveniently via the reaction of the solid complex $Zn(CF_3)Br{\cdot}2DMF$ with copper(I) bromide in N,N-dimethylformamide (Scheme 76). The maintenance of trifluoromethyl- and pentafluoroethyl derivatives was determined by ^{19}F NMR spectroscopy in both the mixtures [157].



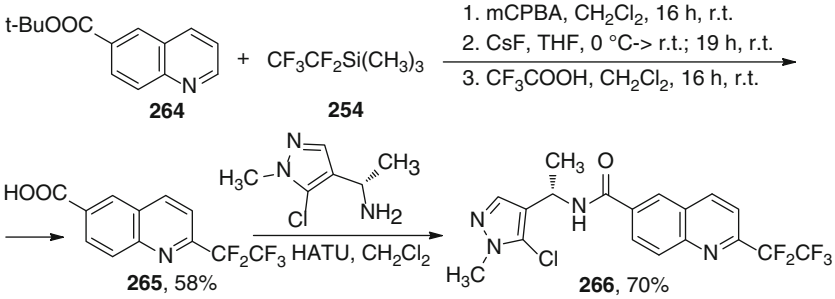
Scheme 76

Reaction of 2-chloro-5-iodopyridine **(261)** and sodium pentafluoropropionate (**262**) at presence CuI in NMP resulted in 2-chloro-5-pentafluoroethylpyridine (**263**) in 30 % yield [158] (Scheme 77).



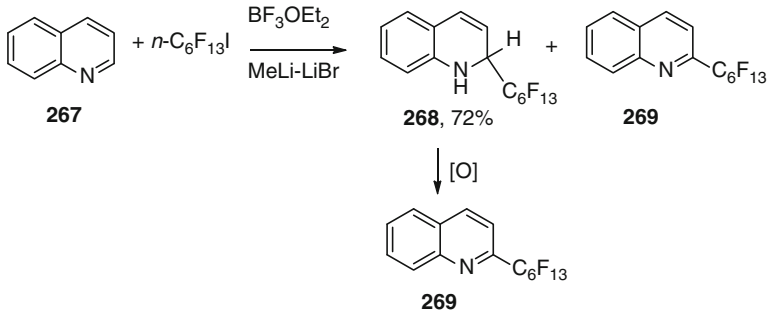
Scheme 77

Pentafluoroethylquinoline **265** was obtained by the reaction of pentafluoroethyltrimethylsilane **(254)** with substituted quinoline **264** [159]. Compound **265** was a precursor for the synthesis of **266** as VR1 receptor for treating pain, inflammation and other diseases (Scheme 78).



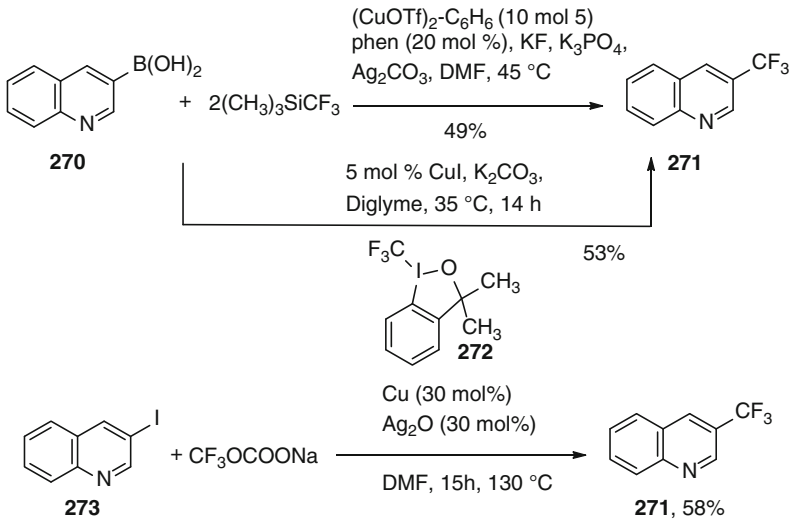
Scheme 78

2-Perfluorohexyl-1,2-dihydroquinoline (**268**) was obtained in 72 % yield together with trace amounts of 2-(periluorohexyl)quinoline (**269**), the latter being formed by the autoxidation of **268**. The perfluoroalkylation was improved up to 90 % yield by using 2 equiv. each of pertluorohexyl iodide, boron trifluoride, and methyllithium-lithium bromide. The autoxidation of dihydroquinoline **268** was complete in chloroform after 2 days and **269** was obtained quantitatively [160] (Scheme 79).



Scheme 79

Some articles have described synthesis of 3-trifluoromethylquinoline (**271**) [161–165]. Catalytic oxidative trifluoromethylation of 3-qunolineboronic acid **(270)** resulted in 3-trifluoromethylquinoline in 49 % yield [161]. Use Togni's reagent **(272)** in reaction with boronic acids **270** resulted in increase yield of **271** up to 53 % [162]. 3-Trifluoromethylquinoline was also obtained by reaction of boronic acids **270** with CF_3I [163] or with trifluoromethyl sulfonium salts [164] in 87 % yield. Interaction of 3-iodoquinoline (**273**) with sodium trifluoromethyl formate at presence Cu and Ag_2O also led to compound **271** [165] (Scheme 80).

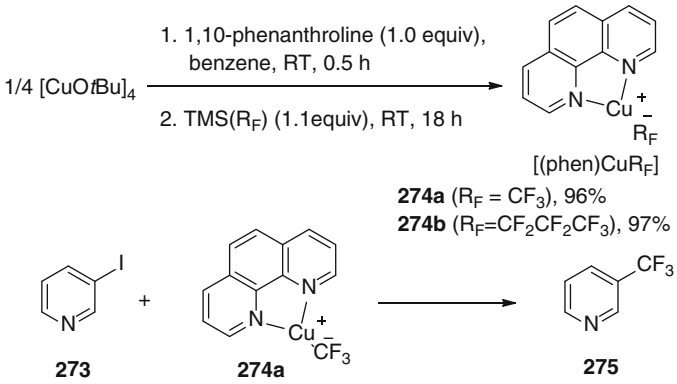


Scheme 80

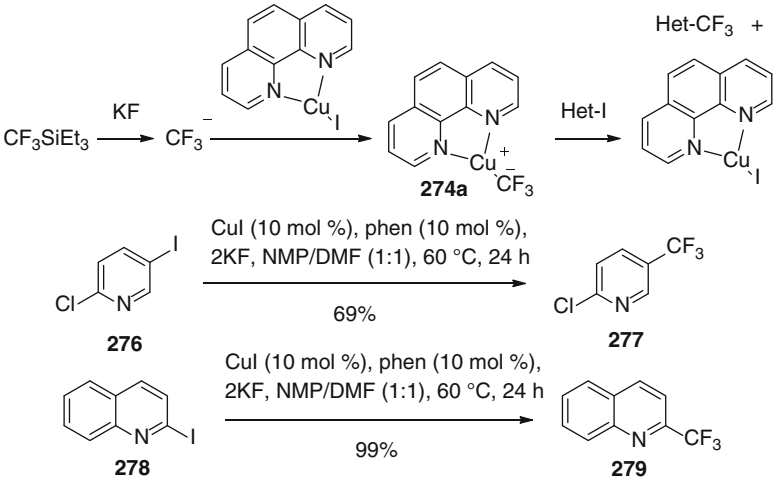
Convenient reagents for incorporation of perfluoroalkyl groups in a molecule of pyridine are 1,10-phenanthroline-ligated (perfluoroalkyl) copper (I) complexes **274** [166], which were obtained by reaction of copper 1,10-phenanthroline complex with Ruppert reagent and its C_2F_5-analog. The 1,10-phenanthroline complex **(274a)** has been used in reaction with 3-iodopyridine **(273)** for synthesis 3-trifluoromethylpyridine **(275)** [167, 168] (Scheme 81).

Cu(I)-diamine complexes were found to catalyze the trifluoromethylation of other heterocycles. In the presence of a small amount of CuX (X = Cl, Br, I) and 1,10-phenanthroline, the cross-coupling reactions of iodoazines with trifluoromethylsilanes proceeded smoothly to afford trifluoromethylated azines in good yields [169]. For example, trifluoromethylazines **277, 279** have been synthesized in good yields [169] by such method from iodoazines **276, 278** (Scheme 82).

The corresponding trichloromethylazines **280** are frequently used for synthesis trifluoromethylazines **281** (pyridine, quinoline, phenantroline and others.). SbF_3, SbF_5, liquid HF or their mixtures can be used for chlorine-fluorine replacement

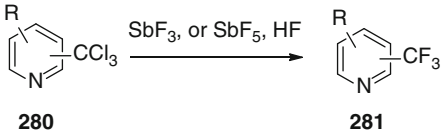


Scheme 81



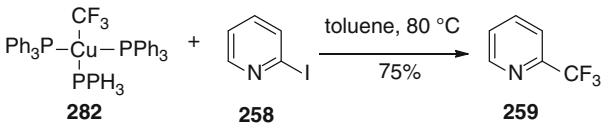
Scheme 82

[170–173] (Scheme 83). Trifluoromethylazines **281** are formed by this method usually in good yield.



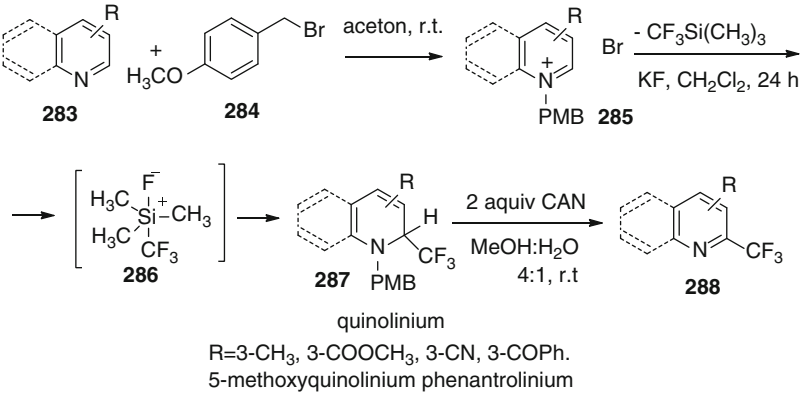
Scheme 83

Interaction of complex **282** obtained from copper difluoride, trifluoromethyltrimethylsilane and three moles of PPh_3 with 2-iodopyridine (**258**) led to 2-trifluoromethylpyridine (**259**) in 75 % yield [174] (Scheme 84).



Scheme 84

Ample opportunities are opened with synthesis of trifluoromethylated azines via oxidative nucleophilic substitution of hydrogen by trifluoromethyl carbanions [175]. This pathway to the synthesis of trifluoromethylazines includes reaction of quaternization of azines **283** by p-methoxybenzylbromide (PMB) (**284**) to obtain salts **285**. Further KF is added to reaction mixture of salt **285** and $CF_3Si(CH_3)_3$ to generate anion **286**. Regioselective trifluoromethylation results in formation of 1,2-dihydropyridines **287** which then have been oxidized by action CAN to get appropriate trifluoromethylazines **288** (Table 4) [175] (Scheme 85). Regioselectivity of the reactions is determined by the nature of substituent at pyridine's cycle. So in case of an ether of nicotinic acid and 3-benzoylpyridine the mixture of 2-and 6-trifluoromethylpyridines are formed (Table 5).

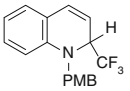
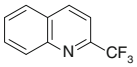
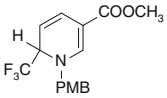
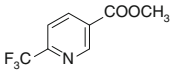
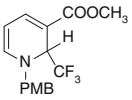
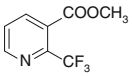
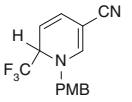
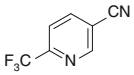
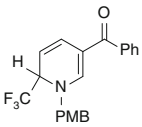
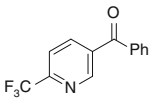
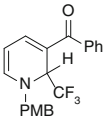
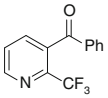
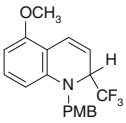
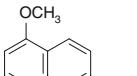


Scheme 85

6.2 Synthesis of Perfluoroalkylpyridines Based on Cyclization Reactions

Reactions of cyclization are widely used for synthesis hardly available multifunctional perfluoroalkylpyridines [2, 3, 176]. As a rule, these reactions proceed regioselectively and in good yields. A perfluorocarbonyls, 1,3-dicarbonyls, α,β-unsaturated carbonyl compounds and enamines are basic raw material for this synthesis [2, 3, 176]. For example, condensation of trifluoromethyl substituted 1,3-dicarbonyl compounds **289** with cyanacetamide (**290**) proceeds highly regioselectively to form substituted 4-trifluoromethylpyridine-2(1H)-ones (**291**) [2, 3, 176–179]. 1,3-Dicarbonyl

Table 5 Aromatization of 2-Trifluoromethyl-1,2-dihydroazines **287**

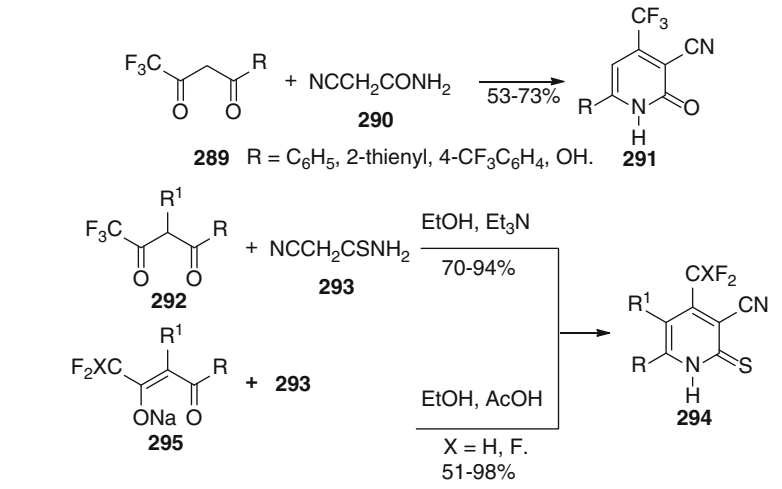
Substrate **287**	Product **288** (yield)		Overall yield for three steps	Total yield of two isomers
		(77 %)	59 %	
		(79 %)	32 %	46 %
		(47 %)	14 %	
		(62 %)[a]	18 %	
		(91 %)	40 %	62 %
		(60 %)	22 %	
		(90 %)	68 %	

[a]DDQ was used it stead of CAN (2.2 equiv. of DDQ, CH_2Cl_2, 0 °C to rt)

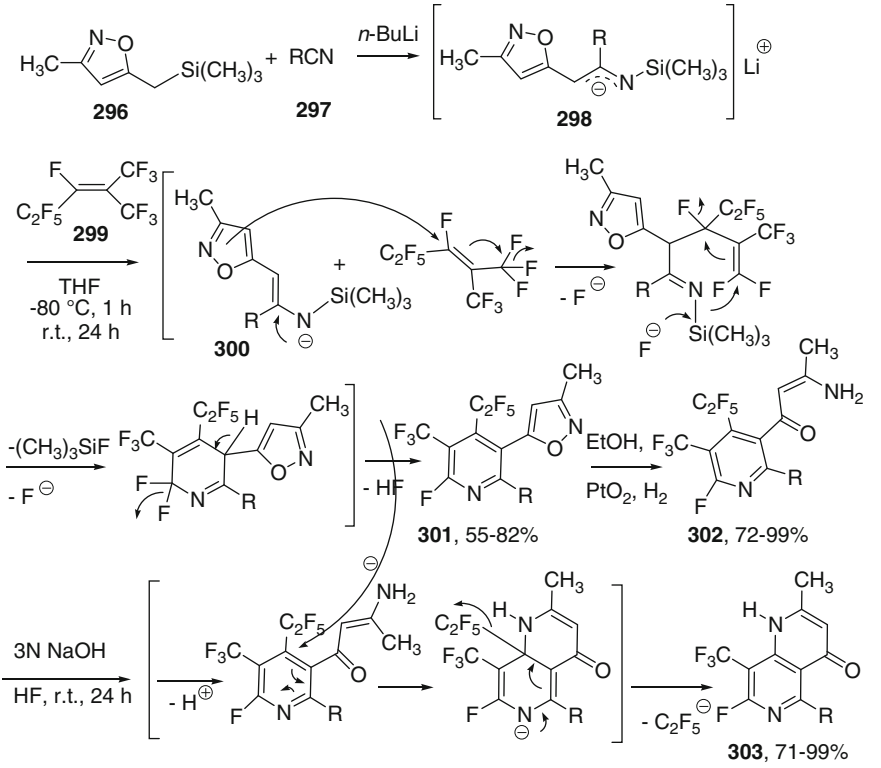
compounds **292** and cyanthioacetamide **(293)** are used for synthesis substituted 4-trifluoromethylpyridine-2(1H)-thiones **294** [180–182]. More simple and convenient way of synthesis of compounds **294** is based on use of sodium salt of 1,3-dicarbonyl compounds **295** and cyanthioacetamide **(293)** [183]. Thus isolation and purification of 1,3-diketones **292** is not required. As a whole, synthesis of 4-three(di)fluoromethylpyridine-2(1H)-thiones **294** from sodium salts **295** and **293** proceeded highly regioselective in good yields (Scheme 86).

New method for synthesis 7-fluoro-8-(trifluoromethyl)-1H-1,6-naphthyridines **(303)** is based on intermolecular cyclization of N-silyl-1-azaallyl anion **(298)** with perfluoroalkylethylenes **299** [184] (Scheme 87).

Reaction of aniline **(304)** and ethyl trifluoroacetoacetate **(305)** resulted in formation of 4-trifluoromethylquinolin-2-one **(306)** from which 2-brom-4-trifluoromethylquinoline **(307)** was synthesized further. Reaction of compound **307** with pyridines **308** at the presence of a palladium complex as the catalyst resulted in quinoline ligands **309** [185] (Scheme 88).

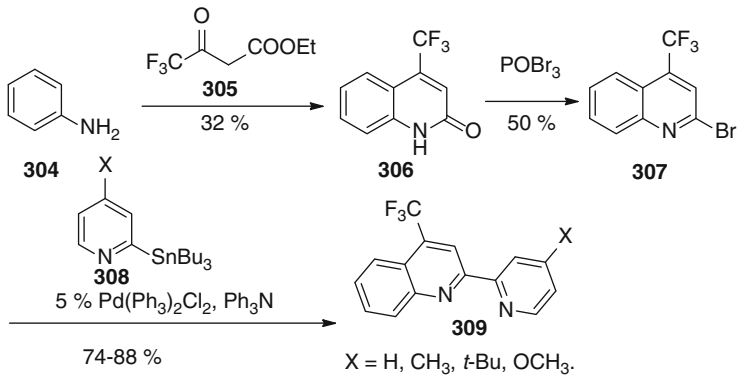


Scheme 86



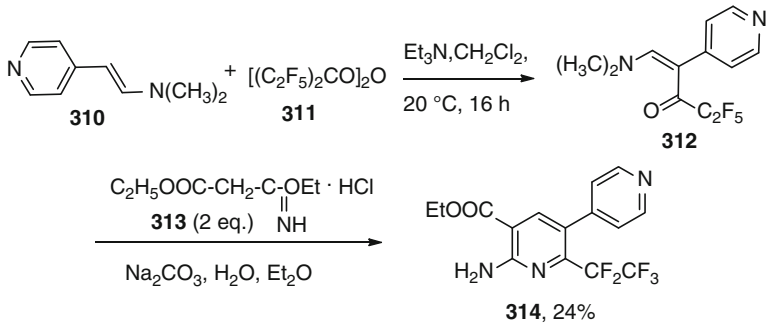
R = 4-CH_3-C_6H_4, 4-CH_3O-C_6H_4, 4-$(CH_3)_2N$-C_6H_4, 4-Cl-C_6H_4, 4-CF_3-C_6H_4, 2-Py, 4-Py, Et, CH_3-O-CH_2-.

Scheme 87



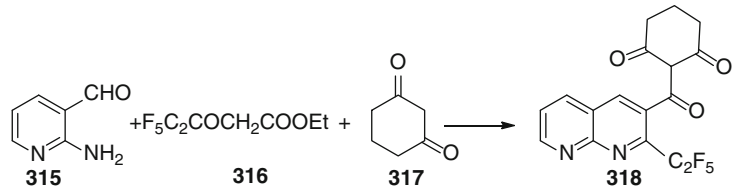
Scheme 88

Reaction of enamine **310** with pentafluoropropionic anhydride **(311)** gives compound **312**. The condensation of **312** with two moles of diethyl iminomalonate hydrochloride **(313)** led to substituted perfluoroalkylpyridine **314**, which further is used in synthesis inhibitors of phosphoesterase [186] (Scheme 89).



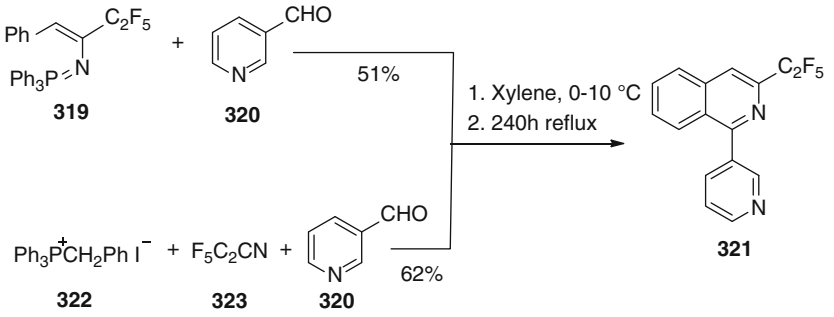
Scheme 89

Perfluoroalkyl [1, 8]-naphtiridine (**318**) with herbicidal effect was synthesized by reaction of 2-amino-3-formylpyridine (**315**), 1,3-dicarbonyl compound **316** and 1,3-cyclohexanedione (**317**) [187] (Scheme 90).



Scheme 90

Substituted 3-perfluoroethylisoquinoline **(321)** was obtained by interaction of compound **319** and pyridine-3-carbaldehyde (**320**). Compound **321** has been obtained also by three-component condensation directly from salt **322**, pentafluoroacetonitrile (**323**) and pyridine-3-carbaldehyde (**320**) [188]. These reactions proceed with formation of two cycles at hard conditions (reflux in xylene for a long time) (Scheme 91).



Scheme 91

The methods of synthesis of fluorine-containing pyridines described in the given review specify growing interest to chemistry of these compounds that is caused by the big practical importance of fluorinated azines.

Acknowledgment The authors gratefully acknowledge the financial support of a grant from the Russian Foundation for Fundamental Research (RFBR), project no. 12-03-00429.

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Fluorinated Quinolines: Synthesis, Properties and Applications

Galina N. Lipunova, Emiliya V. Nosova, and Valery N. Charushin

Contents

Abstract The data on the chemistry of fluorinated quinolines available in the literature of the last 10–15 years are presented. A variety of synthetic methods exploiting cyclization and cycloaddition reactions, displacements of halogen atoms or the diaza group, as well as direct fluorinations have been considered. Novel approaches to functionalization of polyfluorinated quinolines, including nucleophilic displacement of fluorine atoms, cross-coupling reactions, and synthesis on the basis of organometallic compounds are discussed. Selected representative examples of fluoroquinolines

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V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 2: 6-Membered Heterocycles*, 59
DOI 10.1007/978-3-319-04435-4_2,

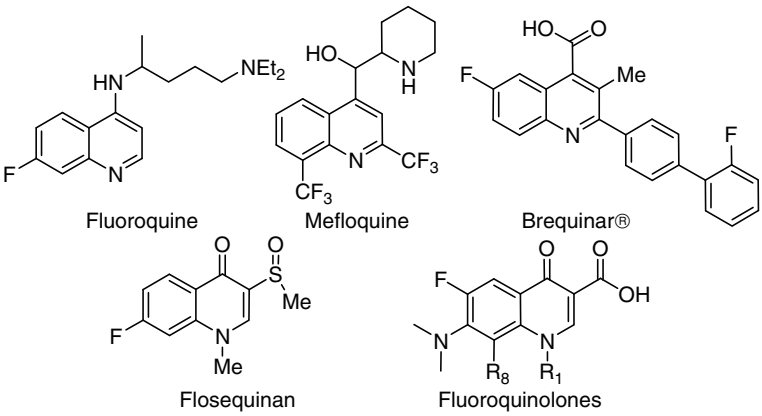
exhibiting a remarkable biological activity or those quinolines which have already found their applications in medicine will also be discussed in the text. The bibliography – 158 references.

Keywords Quinoline • Cyclocondensation • Nucleophilic substitution of fluorine atom • Cross-coupling reactions • Antibacterial activity • Enzyme inhibitor

1 Introduction

The quinoline ring system, the first representative of the family of benzazines bearing one nitrogen atom, is widespread in the nature. Alkaloid quinine has long been used traditionally as antimalarial drug, and it has happened to possess a toning effect. Oxamniquine is used for suppression of shistosoma, which is considered to cause many diseases in tropical regions. Being inhibitors of various enzymes, many synthetic quinolines proved to exhibit antibacterial, antineoplastic, and antiviral activities.

Incorporation of a fluorine atom into azaaromatics is known to enhance biological activity of fluorinated compounds, and provide some other unique properties. The quinoline skeleton has been used for a long time as a basic structure for search of synthetic antimalarial drugs, such as fluoroquine [7-fluoro-4-(diethyl-amino-1-methylbutylamino)quinoline] and mefloquine. The antineoplastic drug Brequinar® and its analogs proved to be useful in transplantation medicine, and also for treatment of rheumatic arthritis and psoriasis. Flosequinan is one of drugs of new generation for treatment of heart diseases. However, the most known drugs belong certainly to the family of fluoroquinolones exhibiting a broad spectrum of antibacterial activity (Scheme 1).



Scheme 1 Structure of fluorinated quinolones with unique properties

A number of fluorinated quinolines have found application in agriculture, and also as components for liquid crystals. Cyanine dyes on the basis of quinolines also make a considerable share in commercial production.

A growing interest in fluorinated derivatives of quinolines stimulates research studies aimed at development of novel methods of synthesis, studying of reactivity of fluorinated quinolines and their plausible practical applications, as indicated by numerous publications, including recent monograph and review articles [1–4].

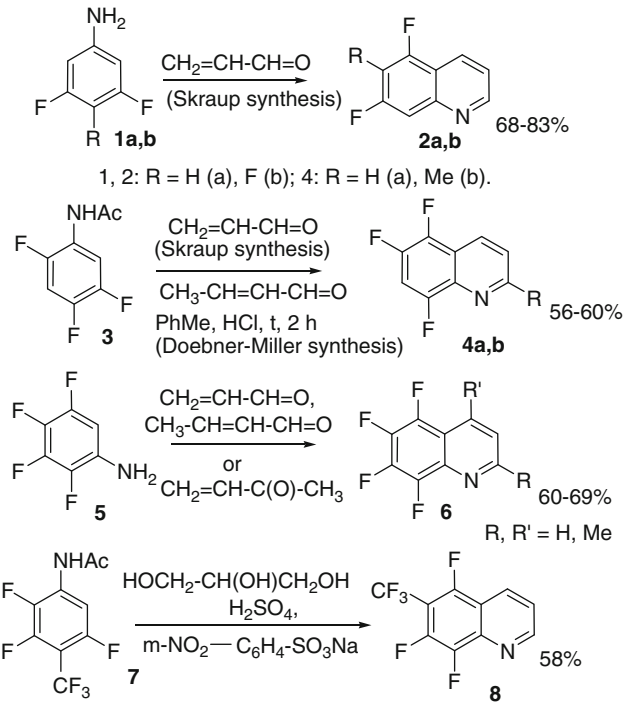
In the frames of this chapter we would like to outline briefly the recent data on fluorine-containing quinolines in which fluorine atoms are attached directly to carbons of the benzene or pyridine rings, and a special attention will be given to mono-fluorinated derivatives.

2 Synthesis and Structure

Cyclization reactions appear to be the most common synthetic method for obtaining of fluorinated derivatives of quinolines and their analogs (Scheme 2). The most important way of synthesis of quinolines, bearing fluorine atoms in benzene or pyridine rings, is ***condensation of anilines having no substituent at least in one of two ortho-positions with carbonyl compounds capable of donating a three-carbon fragment***.

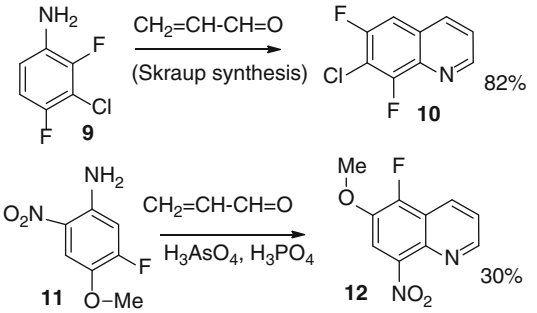
Scheme 2 Formation of pyridine ring of fluorinated quinolines

The Skraup reaction is a good illustration of this common approach, as illustrated by the series of syntheses of 5,7-difluoro- and 5,6,7-trifluoroquinolines **2a,b** proceeding in high yields on the basis of 3,5-difluoro- and 3,4,5-trifluoro-anilines **1a,b** (Scheme 3) [5]. In a similar way 5,6,8-trifluoroquinolines **4a,b** have been obtained from 2,4,5-trifluoro substituted acetanilide **3** and acrolein or crotonic aldehyde [6–8]. 5,7,8-Trifluoroquinoline has also been obtained from 2,3,5-trifluoroacetanilide, while 6-trifluoromethyl-5,7,8-trifluoroquinoline – from 2,3,5-trifluoro-4-trifluoromethyl acetanilide, respectively [6]. The Skraup cyclization is also an effective synthetic took to transform 2,3,4,5-tetrafluoro substituted aniline **5** into 5,6,7,8-tetrafluoroquinoline, 2-methyl-5,6,7,8-tetrafluoroquinoline and 4-methyl-5,6,7,8-tetrafluoroquinoline **6** by reacting aniline **5** with acrolein, crotonic aldehyde and methylvinylketone, correspondingly (Scheme 3). The reaction takes place even in the presence of a strong electron-withdrawing trifluoromethyl group, as shown by the synthesis of 6-trifluoromethyl-5,6,8-trifluoroquinoline **8** from 2,3,5-trifluoro-4-trifluoromethylacetanilide **7** (Scheme 3) [6].



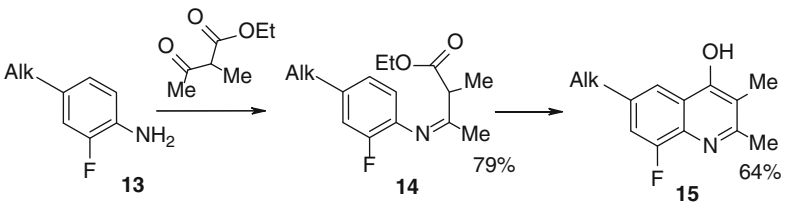
Scheme 3 Synthesis of quinolones **2**, **4**, **6**, **8**

Also the synthesis of 6,8-difluoro-7-chloroquinoline **10** has been performed in a high yield by means of the modified Skraup reaction from 3-chloro-2,4-difluoroaniline **9** [5]. Similarly 5-fluoro-6-methoxy-8-nitroquinoline **12** was obtained from 3-fluoro-4-methoxy-6-nitroaniline (Scheme 4) **11** [9].



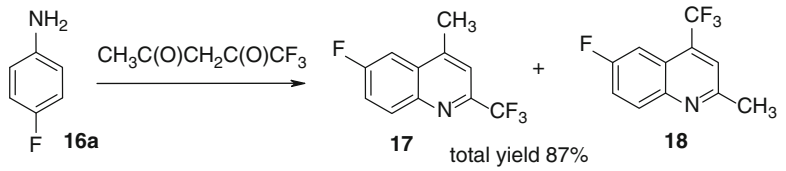
Scheme 4 Synthesis of quinolones **10**, **12**

There are some other synthetic methods to obtain fluorine-containing quinolines which are based on using of fluorinated anilines with a free *ortho*-position and three-carbon reagents. For instance, 8-fluoro-2,3,6-trialkyl substituted 4-hydroxyquinolines **15** were synthesized by the reaction of **13** with ethyl 2-methylacetoacetate and cyclization of the obtained enamines **14** into 8-fluoroquinolines **15** (Scheme 5) [10].



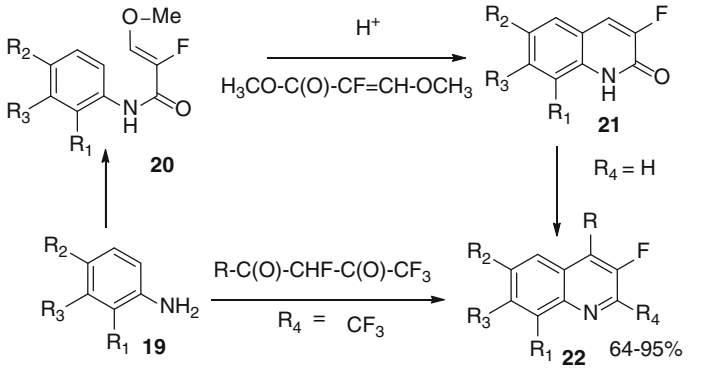
Scheme 5 Synthesis of 4-hydroxy-8-fluoroquinoline **15**

The reaction of 4-fluoroaniline **16** with trifluoromethyl diketone has been established to give a rise to 6-fluoroquinolines **17** and **18** in the ratio 1:1 (Scheme 6) [11].



Scheme 6 Interaction of 4-fluoroaniline **16** with trifluoromethyl diketone

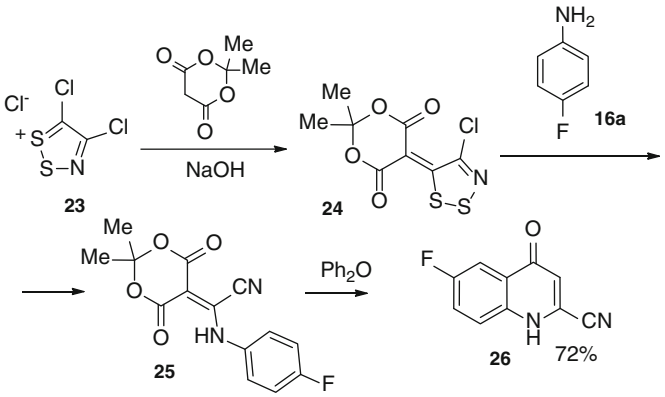
2-Fluoro-3-methoxyprop-2-enyl anilides **20** were obtained by condensation of anilines **19** with methyl 2-fluoro-3-methoxyacrylate. Compounds **20** can be transformed in the presence of strong acids into 3-fluoro-2-quinolines **22** (Scheme 7) [12]. A substituent in the *meta*-position relative to the amino group in starting anilines **19** directs the formation of a mixture of two regioisomers in the ratio 1:1, with 3-methoxy- and 3-fluoroanilines being exceptions [13]. 2-Trifluoromethyl-3-fluoroquinolines **22** were derived from anilines **19** and trifluoromethyl ketones [11].



R = Me, Et, i-Pr, t-Bu; R_1 = OMe, H, Cl, Br; R_2 = H, F, Cl, Br; R_3 = H, Cl.

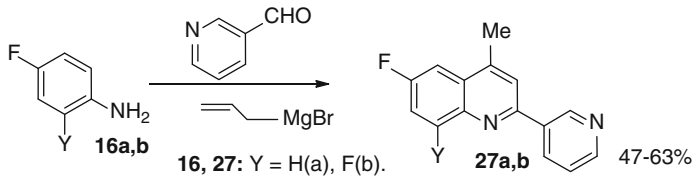
Scheme 7 Synthesis of 3-fluoroquinoline **22**

The synthesis of 6-fluoro-2-cyanoquinolone **26** from 4-fluoroaniline **16** is shown in Scheme 8. 4,5-Dichloro-5H-1,2,3-dithiazolium chloride **23** reacts with the Meldrum acid to form 5-(4-chloro-5H-1,2,3-dithiazol-5-ylidene)-2,2-dimethyl-1,3-dioxan-4,6-dione **24**, which on treatment with 4-fluoroaniline **16** is transformed into 5-[(arylamino)(cyano)methylene]-2,2-dimethyl-1,3-dioxan-4,6-dione **25** in high yield. Heating of compound **25** in biphenyl ether results in the formation of 2-cyanoquinolone **26** [14, 15].



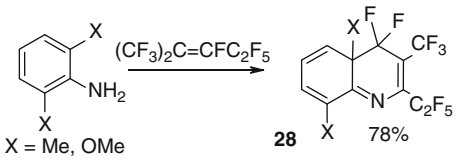
Scheme 8 Synthesis of 2-cyano-6-fluoroquinolone **26**

6-Fluoro- and 6,8-difluoro-4-methyl-2-(3-pyridinyl)-1,2,3,4-tetrahydroquinolines and the corresponding aromatic quinolines **27a,b** have been obtained from 4-fluoro- or 2,4-difluoroanilines **16a,b**, and pyridine-3-carbaldehyde and allylmagnesium bromide (Scheme 9) [16].



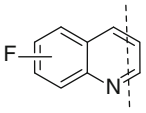
Scheme 9 Synthesis of quinolones **27**

The reaction of perfluoro-2-methylpent-2-ene with 2,6-dimethylaniline or 2,6-dimethoxyaniline has been shown to afford dihydroquinolines **28** (Scheme 10) [17].



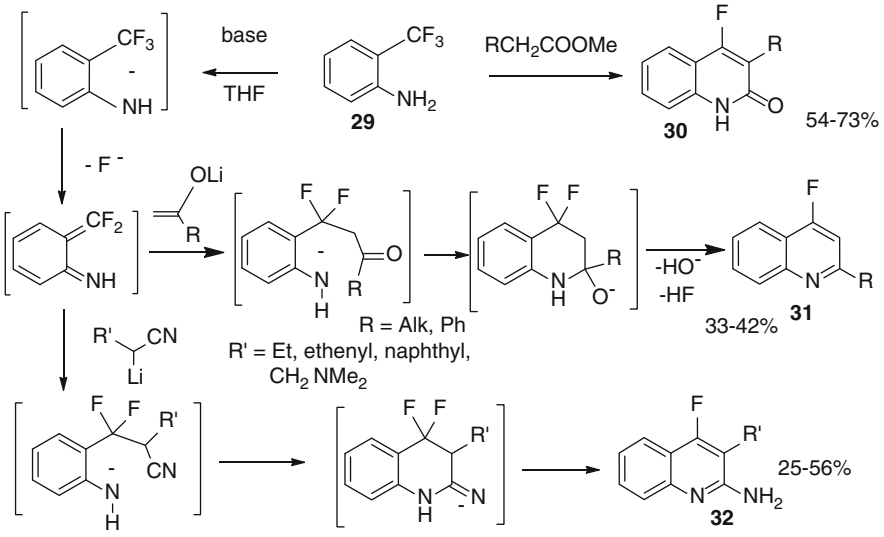
Scheme 10 Synthesis of compound **28**

Another synthetic approach to fluoroquinolines is based on ***cyclocondensations of fluorinated anilines bearing in the ortho-position a carbon-containing functional group*** (trifluoromethyl, nitrile, formyl, carbonyl groups, etc.), ***with reagents containing a two-carbon fragment*** (Scheme 11).



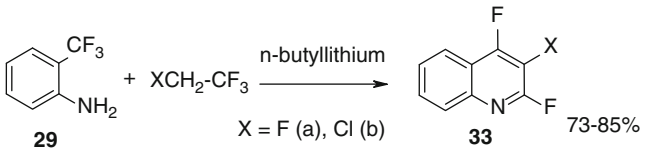
Scheme 11 Formation of fluorinated quinolones from two-carbon reagents

In accordance with this protocol 4-fluoroquinolones (**30**, R = Ar, N-methylindol-3-yl) were obtained by cyclocondensation of 2-trifluoromethylaniline **29** with methyl acetates in the presence of a base (Scheme 9) [18]. The lithium reagents, generated from methylketones, phenylacetylene and substituted acetonitriles, were allowed to react with 2-trifluoromethylaniline **29** to give the corresponding 4-fluoroquinolines **31, 32** (Scheme 12) [8, 19–21].



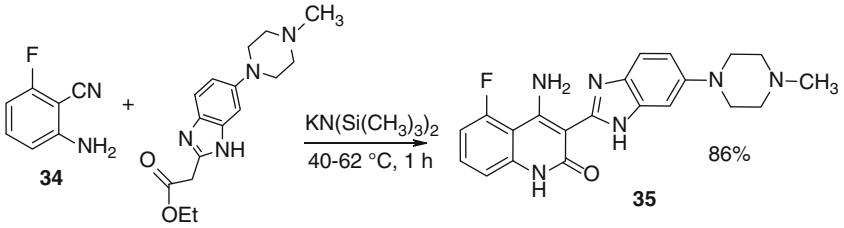
Scheme 12 Synthesis of 2-aminoquinoline **32**

Trifluorovinyl lithium (prepared from 1,1,1,2-tetrafluoroethane) was allowed to react with 2-trifluoromethylaniline **29** at −78 °C to give 1,2,3-trifluoroquinoline **33a** in moderate to good yield. In a similar cyclization with aniline **29** 1-chloro-2,2-difluorovinyl lithium (prepared from 1-chloro-2,2,2-trifluoroethane) afforded 2-chloro-1,3-difluoroquinoline **32b** (Scheme 13) [22].



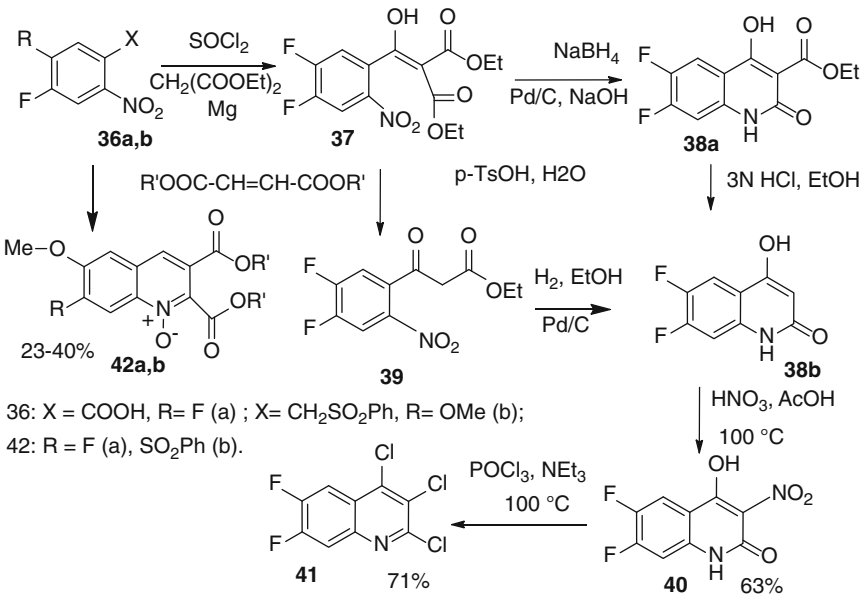
Scheme 13 Synthesis of 2,4-difluoroquinoline **33**

The reaction of 2-amino-6-fluorobenzonitrile **34** with ethyl 6-(4-methylpiperazinyl)-1H-benzimidazolyl acetate takes place in the presence of *bis*-(trimethylsilyl) amide, thus resulting in the formation of quinolin-2-one **35** (Scheme 14) [23].



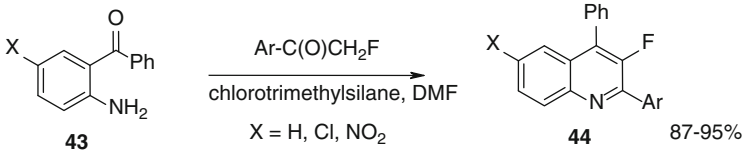
Scheme 14 Synthesis of quinolin-2-one **35**

The synthesis of 6,7-difluoro-3-nitro-4-hydroxy-2-quinolone **40** and 2,3,4-trichloro-6,7-difluoroquinolone **41** from 4,5-difluoro-2-nitrobenzoic acid **36a** is shown in Scheme 15. Diester **37** has been transformed smoothly into 4-hydroxyquinolone **38a** due to reductive cyclization proceeding in basic media in the presence of sodium borohydride. Diethyl 4,5-difluoro-2-nitrobenzoyl malonate **37** on treatment with *p*-toluolsulfonic acid affords ethyl 3,4-difluoro-2-nitrobenzoyl acetate **39**. Reductive cyclization of **39** was shown to take place in case of catalytic hydrogenation of the nitro group on Pd/C in ethanol, thus enabling one to obtain 6,7-difluoro-4-hydroxyquinolin-2(*1H*)-one **38b** in high yield. Decarboxylation of **38a** also affords 4-hydroxyquinolin-2(*1H*)-one **38b**. Compound **38b** can be nitrated into derivative **40**, followed by treatment of the latter with $POCl_3$ to form quinoline **41** [24]. In addition to condensation process, the reaction of **36b** with α,β-unsaturated esters (dimethyl fumarate and diethyl maleate) is accompanied by participation of the nitro group and desulfonisation leading to **42a**; finally displacement of fluorine atom and reduction of the N-oxide moiety afford a mixture of **42b** and **42b** in the ratio 1:2 [25].



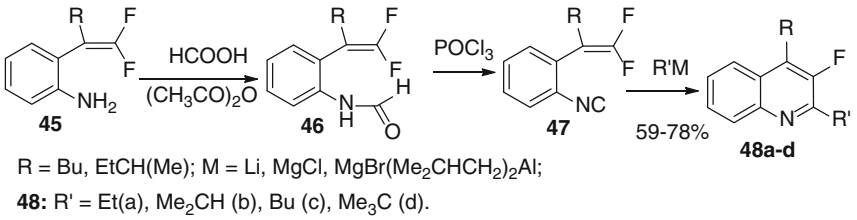
Scheme 15 Synthesis of 2,3,4-trichloroquinoline **41**

A convenient synthetic route to 3-fluoroquinolines **44** which exploits the organosilane-promoted Friedlander reaction of aromatic α-fluoroketones **43** has been suggested (Scheme 16) [26].



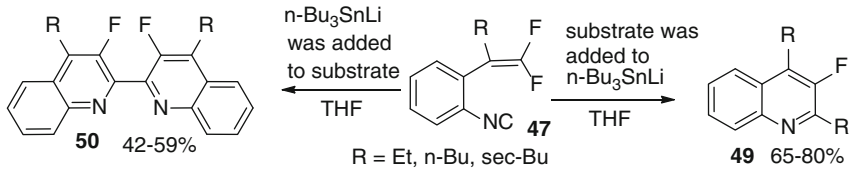
Scheme 16 Synthesis of 2,4-diarylquinoline **44**

To obtain quinolines bearing fluorine atoms in the pyridine ring, ***cyclizations of fluorinated ortho-vinylphenylnitriles and isonitriles*** proved to be an effective approach. Indeed, 3-fluoroquinolines **48a–d** have been obtained by cyclocondensation of organometallic reagents with 2-(2,2-difluorovinyl)phenyl substituted isonitriles **47** (Scheme 17). 2-(2,2-Difluorovinyl)anilines **45**, derived from the reaction of 2,2,2-trifluoroethyl tosylate, butyl magnesium salt of 2-iodoaniline, butyl lithium and trialkylborane, have been transformed into isonitriles **47** [27, 28].



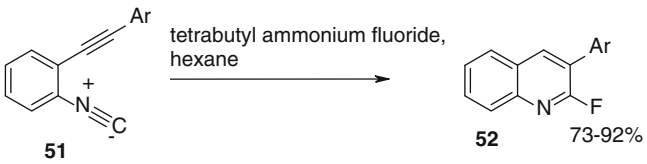
Scheme 17 Synthesis of 3-fluoroquinolines **48**

2,4-Disubstituted 3-fluoroquinolines **49** and 4,4′-disubstituted 3,3′-difluoro-2,2′-bisquinolines **50** have been obtained from *ortho*-isocyano substituted *β,*β-difluorostyrenes **47** through their reduction with tributylstannyl lithium, and intra-molecular arrack at the carbon of the isocyano group (Scheme 18) [29]. It is interesting to note that when compound **47** is added to a solution of n-Bu_3SnLi only quinoline **49** is formed, while the opposite order of mixing of reactants leads to bisquinoline **50** as the main product.



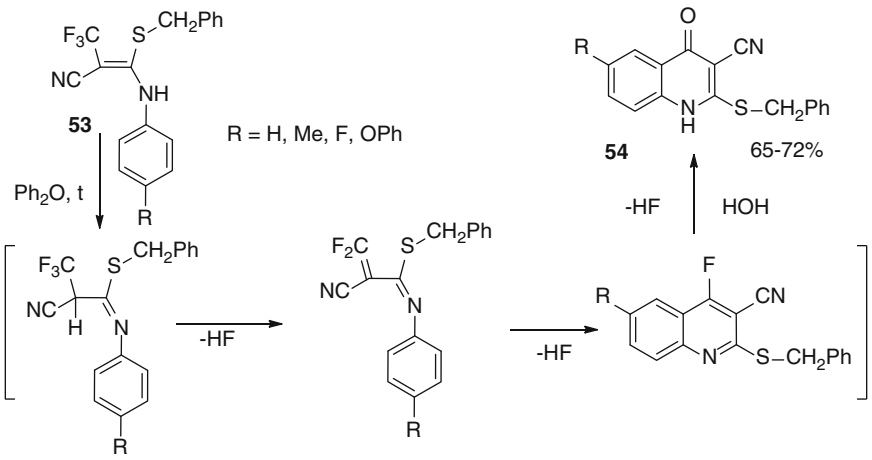
Scheme 18 Synthesis of 3-fluoroquinolines **49**

The intramolecular cyclization takes place on treatment of *ortho*-alkynyl substituted aryl isocyanides **51** with tetrabutyl ammonium fluoride affording the corresponding 2-fluorinated quinolines **52** in good to excellent yields (Scheme 19) [30].



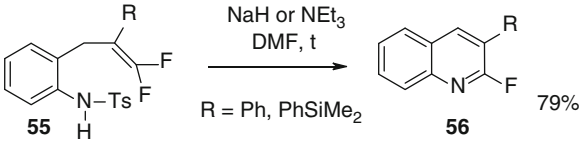
Scheme 19 Synthesis of 2-fluoroquinolines **52**

2-Benzylthio-3-cyanoquinolines bearing fluorine atom in position 4 have been obtained on heating of functionalized N-vinyl anilines **53**; the latter are prepared by condensation of the corresponding α-fluorine-containing vinyl sulfides with anilines (Scheme 20) [31]. Alkaline hydrolysis of the reaction products afforded the corresponding 3-cyanoquinolin-4-ones **54**.



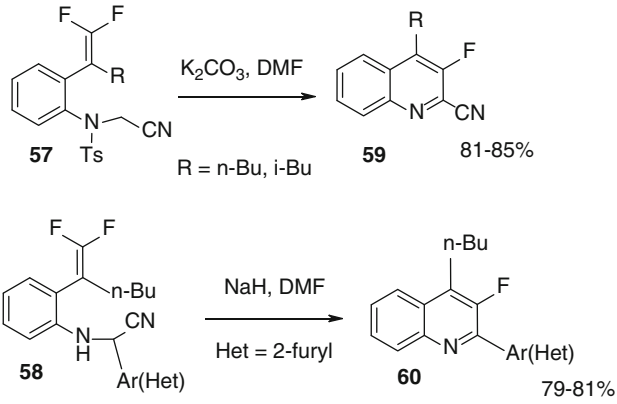
Scheme 20 Condensation of α-fluorine-containing vinyl sulfides with anilines

The intramolecular cyclization takes place smoothly in the 6-*endo-trig* fashion on treatment with a base (sodium hydride or triethylamine) of *N*-[*ortho*-(3,3-difluoroallyl)phenyl] substituted *p*-toluenesulfonamides **55**. As a result 2-fluoroquinolines **56** are formed in high yields (Scheme 21) [32].



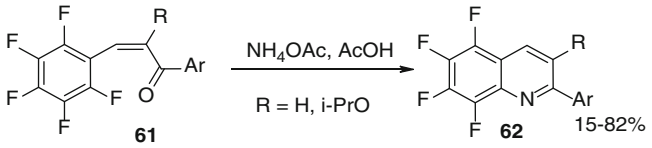
Scheme 21 Synthesis of 2-fluoroquinoline **56**

Intramolecular cyclization of *ortho*-cyanomethylamino-*β,β*-difluorostyrenes **57** and **58** have been observed to occur in the presence of K_2CO_3 or NaH to afford 2-substituted 3-fluoroquinolines **59, 60** (Scheme 22) [33, 34].



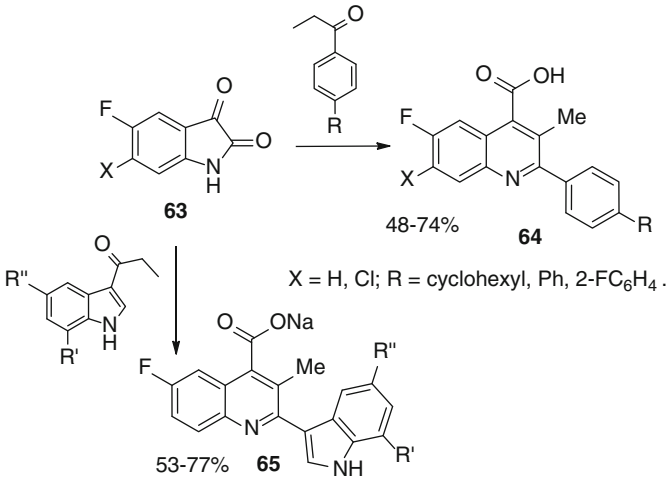
Scheme 22 Synthesis of 3-fluoroquinolines **59**, **60**

Also 2,3,4,5,6-pentafluorophenyl substituted chalcones **61** undergo the intramolecular cyclization into 5,6,7,8-tetrafluoroquinolines **62** on treatment with ammonium acetate in acetic acid (Scheme 23) [35].



Scheme 23 Synthesis of 5,6,7,8-tetrafluoroquinolines **62**

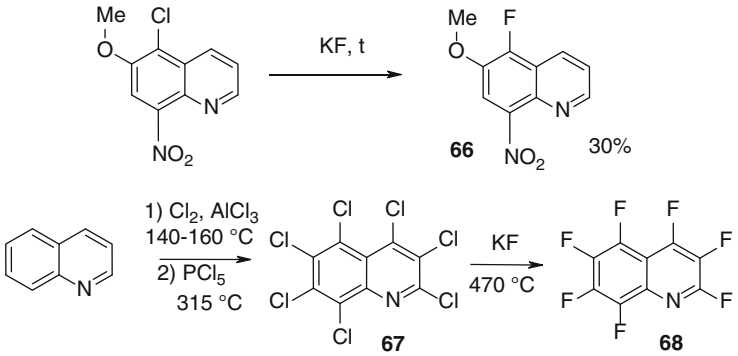
Fluorinated isatines appear to be important intermediates in the synthesis of fluoroquinolines. Indeed, 2-aryl- and 2-heteryl substituted derivatives **64, 65** were obtained from 5-fluoroisatines **63** (Scheme 24) [36].



Scheme 24 Reactions of 5-fluoroisatines **63**

Nucleophilic displacement of chlorine atoms with the fluoride ion is undoubtedly one of the most common methods to obtain fluorinated quinolines from their chloro analogues. For instance, treatment of perchloroquinoline with cesium fluoride in DMSO at 100° has resulted in a mixture of 2-fluoro-3,4,5,6,7,8-hexachloroquinoline, 4-fluoro-2,3,5,6,7,8-hexachloroquinoline, 4,5-difluoro-2,3,6,7,8-pentachloroquinoline and 2,4-difluoro-3,5,6,7,8-penta-chloroquinoline. In similar way 3,5,6,7,8-pentachloroquinoline was transformed into a mixture of 5-fluoro-3,6,7,8-tetrachloroquinoline,7-fluoro-3,5,6,8-tetrachloroquinoline,6,7-difluoro-3,5,8-trichloroquinoline and 5,7-difluoro-3,6,8-trichloroquinoline. Nucleophilic fluoro-dechlorination of 5,6,7,8-tetrachloroquinoline gave a mixture of

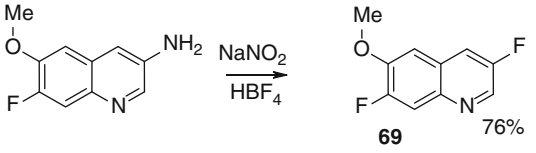
7-fluoro-5,6,8-trichloroquinoline, 5-fluoro-6,7,8-trichloroquinoline and 6,7-difluoro-5,8-dichloroquinoline, while 7-fluoro-4-chloroquinoline was obtained as the only product from 4,7-dichloroquinoline [37]. Also 5-fluoro-6-methoxy-8-nitroquinoline **66** was obtained by replacement of chlorine atom in 5-chloro-6-methoxy-8-nitroquinoline (Scheme 25) [9], and potassium fluoride proved to be an appropriate reagent to cause full transformation of heptachloroquinoline **67** into heptafluoroquinoline **68** (Scheme 25) [38].



Scheme 25 Nucleophilic displacement of chlorine atoms with the fluoride ion

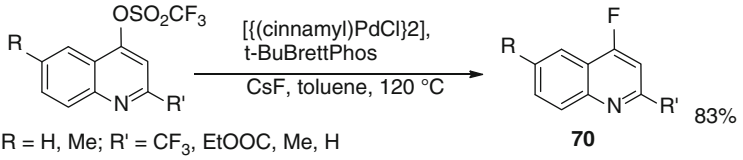
Heating of 4-chloroquinolines with potassium fluoride (tetrabutylphosphonium fluoride) in DMSO affords only low yields of the corresponding 4-fluoro compounds [39, 40], however use of microwave irradiation (300 W) results in the formation of 2-fluoroquinolines from 2-chloroquinolines in 60–62 % yields [41].

Replacement of the diaza group with the fluoride ion, the method which is widely used in heterocyclic chemistry, has also found its application to obtain fluoroquinolines, as illustrated, for instance, by the syntheses of 3-fluoroquinoline from 3-aminoquinoline [42] and 3,5-difluoroquinoline from 3-fluoro-5-aminoquinoline, respectively [43]. 3,7-Difluoro-6-methoxyquinoline **69**, one of the key intermediates for the synthesis of antibacterial agents, has been obtained by the reaction of 3-amino-7-fluoro-6-methoxyquinoline with sodium nitrite in the presence of hydrogen borotetrafluoride (Scheme 26) [44].



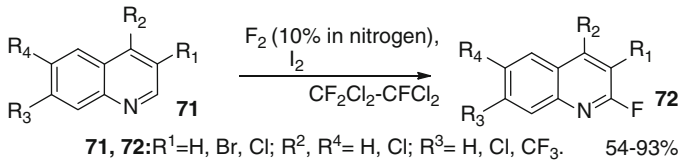
Scheme 26 Synthesis of 3,7-difluoroquinoline **69**

Replacement of other groups with the fluoride ion can be illustrated by the palladium-catalyzed C-F bond formation affording a number of 4-fluoro-quinolines **70** from the corresponding 4-susbstituted quinolines bearing OTf group (Scheme 27) [45].



Scheme 27 Synthesis of 4-fluoroquinoline **70**

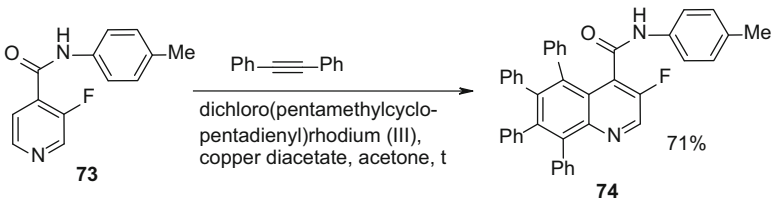
The direct fluorination of quinolines has a limited use since a low selectivity of the reaction, and also due to technological and ecological difficulties. However, there are several examples of selective syntheses of monofluorinated quinolines. For instance, 2-fluoroquinolines **72** were obtained by interacting quinoline **71** with elementary fluorine in the presence of I_2 [46], yields proved to be in the range of 54–93 %, ratio I_2-quinoline **71** was 1:1, and ratio F_2-quinoline **71** was 2:1 (Scheme 28). To obtain 2-fluoro-4-chloroquinoline and 2-fluoro-4,7-dichloroquinoline the reaction was carried out in the presence of triethylamine.



Scheme 28 The direct fluorination of quinolines

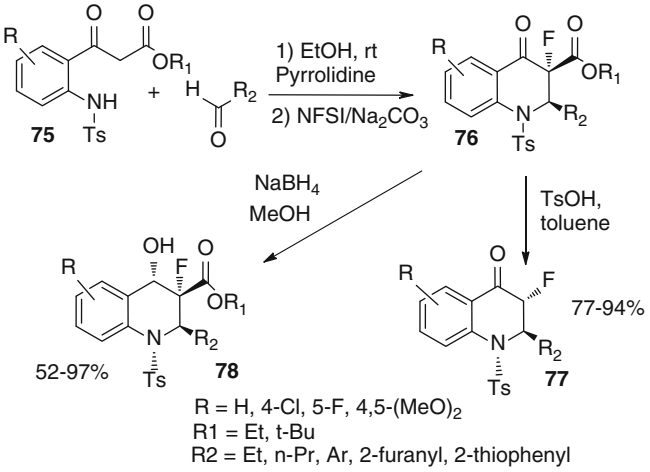
Also direct fluorination of quinoline **71a** under acidic conditions has been reported [47, 48]. Electrophilic substitution in the series of quinolines proceeds not selectively, therefore a mixture of 5-fluoroquinoline**,** 6-fluoroquinoline, 8-fluoroquinoline and 5,8-difluoroquinoline is formed. 6-Methoxyquinoline was shown to undergo direct fluorination at the position 5, and 5,5-difluoroquinolin-6-one was isolated in addition to the main 5-fluoro-6-methoxy compound [48]. 5-Fluoro-6-methoxy-8-nitroquinoline was obtained by the reaction of 6-methoxy-8-nitroquinoline with N-fluorobenzolsulphonamide [9]**.**

***Other methods*.** An unusual example of the synthesis of 3-fluoroquinoline system **74** through annelation of the benzene ring has been reported to occur in the Rh(III)-catalyzed oxidative condensation of 3-fluoropyridine **73** with two molecules of diphenyl acetylene [49] (Scheme 29).



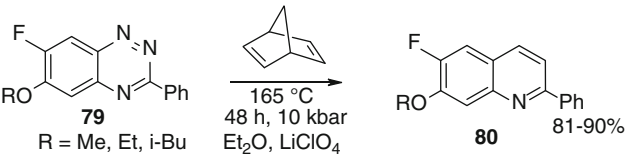
Scheme 29 Synthesis of 3-fluoroquinoline **74**

Stereoselective multi-steps synthesis of fluorinated 2,3-dihydroquinolin-4(1H)-ones proceeding as a one-pot transformation has been described [50]. The Ts-protected *β*-(2-anilino)-*β*-ketoesters **75** are capable of reacting with a variety of aldehydes under mild conditions to form fluorinated quinolines **76** in good yields (up to 98 %) and high diastereo selectivities (*dr* up to 99:1) (Scheme 30). The compounds **76** are considered as versatile synthetic intermediates, and, indeed, they can be transformed into functionalized heterocyclic derivatives. For example, decarboxylation of compounds **76** results in the formation of 3-fluoroquinolines **77**, while reduction with $NaBH_4$ affords *α*-fluoro-*β*-hydroxy esters **78**.



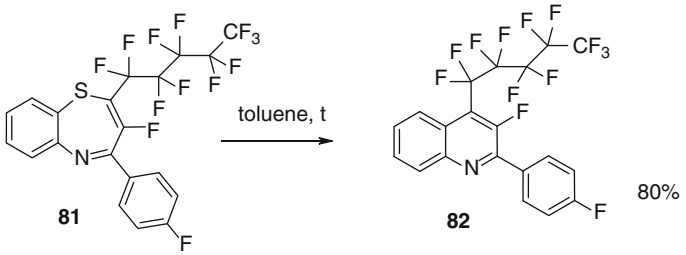
Scheme 30 Formation of compounds **77**, **78**

2-Phenyl-6-fluoroquinoline **80** has been obtained through the cycloaddition reaction of bicyclo[2.2.1]heptadiene on 1,2,4-benzotriazine **79**, taking place under high pressure conditions (Scheme 31) [51].



Scheme 31 Transformation of benzotriazine **79** into quinolone **80**

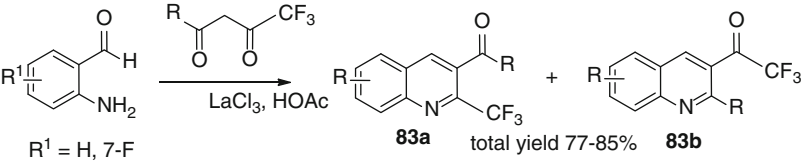
Ring transformation of the thiazepine ring in compound **81** bearing fluorine atom and perfluoroalkyl substituent into the pyridine one enabled to obtain the corresponding 3-fluoroquinoline derivative **82** (Scheme 32) [52].



Scheme 32 Synthesis of 3-fluoroquinoline **82**

Synthetic methods leading to **quinolines bearing the trifluoromethyl group** in the benzene ring are similar in many respects to those which are applied in the chemistry of fluoroquinolines, containing fluorine atoms in the benzene ring. As for quinolines containing the trifluoromethyl group in the pyridine ring, this series of fluorinated quinolines has been discussed in detail in the book [53]. Some recent examples are given below.

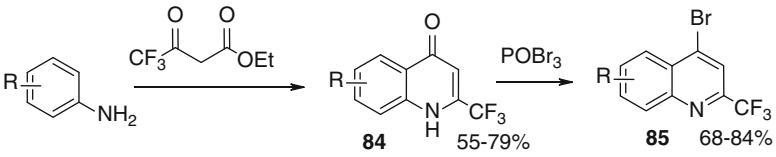
Various synthetic approaches to ***2-(trifluoromethyl)quinolines*** are based on use of the trifluoromethyl-containing reagents. In particular, 2-aminoaryl aldehydes (ketones) or *ortho*-vinyl substituted anilines are appropriate starting materials to be condensed with readily available trifluoromethyl 1,3-diketones or aldehyde hydrates respectively. For instance, the regioselective Friedlaender reaction of unsymmetrical trifluoromethyl 1,3-diketones with 2-aminoaryl aldehydes appears to be an efficient way to 2-trifluoromethylquinolines **83a** and **83b** (Scheme 33) [54].



83a/83b R = Ph 100:0, R = 2-thienyl 100:0 R = Me 89:11, R = naphthyl 100:0, R = t-Bu 100:0

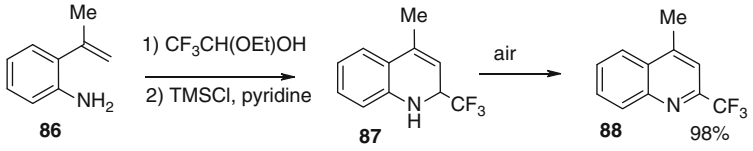
Scheme 33 Reaction of trifluoromethyl 1,3-diketones with 2-aminoaryl aldehydes

The acid-catalyzed condensation of anilines with ethyl 4,4,4-trifluoro acetoacetate affords 1,4-dihydro-2-trifluoromethyl-4H-4-quinolinones, which can easily be converted into 4-bromo-2-(trifluoromethyl)quinolines (Scheme 34) [55].



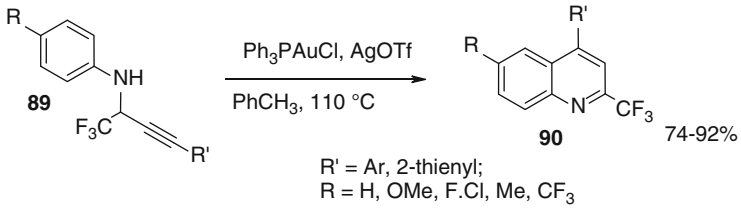
Scheme 34 Synthesis of 2-(trifluoromethyl)quinolones **85**

Also 2-(trifluoro-methyl)-4-methylquinoline **88** has been obtained through intermediacy of the corresponding imine derived from the reaction of *ortho*-vinylaniline **86** with perfluorinated carbonyl compounds taken in the forms of semiacetals or aldehyde hydrates (Scheme 35) [56].



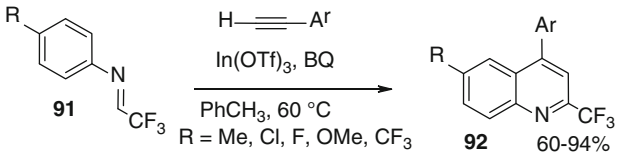
Scheme 35 Synthesis of 2-(trifluoromethyl)quinolone **88**

Cyclizations of alkynyl derivatives proved to be a synthetically convenient way to 2-(trifluoromethyl)quinolines. Indeed, the intramolecular cyclization of N-(α-trifluoromethyl)propargyl anilines **89** takes place with the gold(I) catalyst under extremely mild conditions to afford 2-trifluoromethylquinolines **90** (Scheme 36). The reaction mechanism has been suggested to involve cyclization and oxidation steps [57].



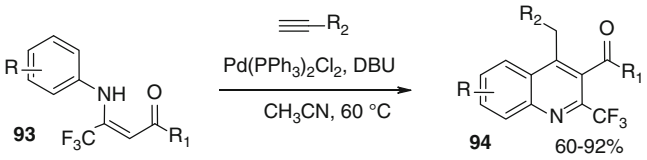
Scheme 36 Synthesis of 2-(trifluoromethyl)quinolones **90**

Also the indium(III)-catalyzed Diels-Alder reaction of N-aryl trifluoroethylimine **91** with a variety of readily available alkynes affords the corresponding 2-trifluoromethyl-4-arylquinolines **92** (Scheme 37) [58].



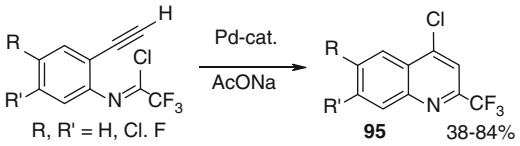
Scheme 37 Synthesis of 2-(trifluoromethyl)quinolones **92**

Rapid method to prepare 3,4-disubstituted 2-trifluoromethylquinolines **94** by a palladium catalyzed tandem Sonogashira-alkyne carbocyclization of β-trifluoromethyl β-enaminoketones **93** with arynes has been suggested (Scheme 38) [59].



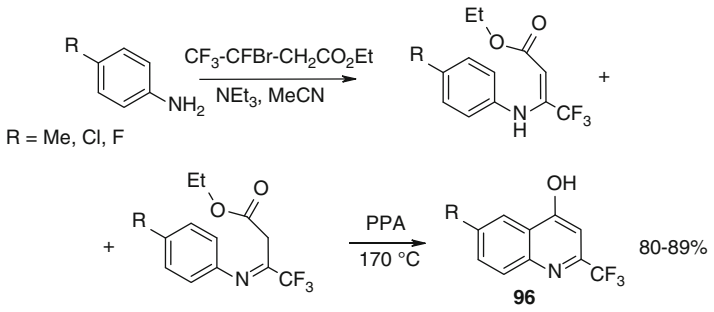
Scheme 38 Synthesis of 2-(trifluoromethyl)quinolones **94**

4-Chloro-2-trifluoromethyl quinolines **95** can be obtained from the corresponding N-aryl trifluoroacetimidoyl chlorides through the Rh(I)-catalyzed intramolecular cyclizations with the alkyne moieties (Scheme 39) [60, 61].



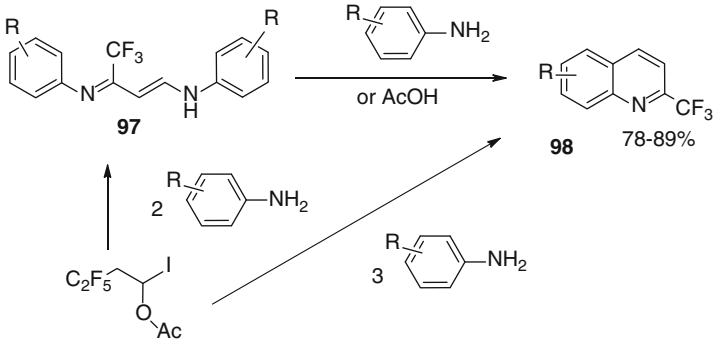
Scheme 39 Synthesis of 2-(trifluoromethyl)quinolones **95**

Treatment of ethyl 2,2-dihydrotrifluoropropionate with aromatic amines in acetonitrile at 70 °C in the presence of triethylamine affords a mixture of the corresponding enamines and imines, which undergoes cyclization on heating in polyphosphoric acid (PPA) at 170 °C to give 2-trifluoromethyl-4-hydroxyquinoline in a good yield (Scheme 40) [62].

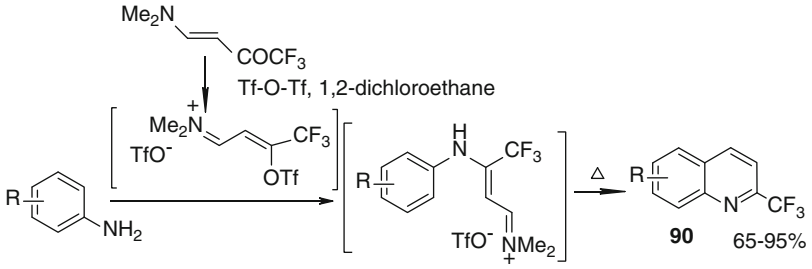


Scheme 40 Synthesis of 2-(trifluoromethyl)quinolones **96**

2-Trifluoromethylquinolines **98** were obtained by condensation of arylamines with fluoroalkyl gem-iodoacetoxy derivative, and the intermediate 1,5-diaryl-2-trifluoromethyl-1,5-diazapentadiene **97** was isolated (Scheme 41) [63]. Use of 3-trifloxy-3-trifluoromethyl propeniminium triflate for the synthesis of 2-trifluoromethylquinolines **90** has been discussed (Scheme 42) [64].

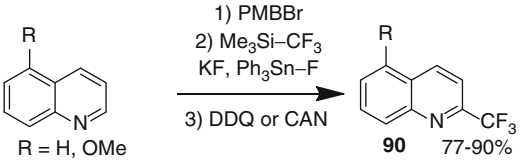


Scheme 41 Synthesis of 2-(trifluoromethyl)quinolones **98**



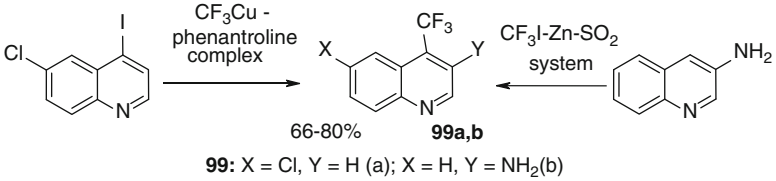
Scheme 42 Synthesis of 2-(trifluoromethyl)quinolones **90**

A three-step procedure for direct trifluoromethylation of quinolines by using the oxidative version of nucleophilic substitution of hydrogen in the pyridine ring by CF_3^- carbanion has recently been advanced (Scheme 43) [65]. The initial step in this process is addition of the CF_3^- carbanion (generated from Me_3SiCF_3 on treatment with KF in the presence of Ph_3SnF as a catalyst), to N-alkylquinolinium salts, resulting in relatively stable 2-trifluoromethyl-1,2-dihydroquinolines. Deprotection of the N-*para*-methoxybenzyl substituent and aromatization of the dihydropyridine ring on treatment with CAN [cerium(IV)ammonium nitrate] provides quinolines bearing CF_3 group in position 2.



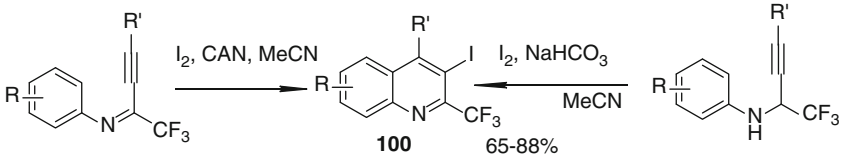
Scheme 43 Another approach to 2-(trifluoromethyl)quinolones **90**

The trifluoromethylation of 4-iodo-7-chloroquinoline by action of trifluoromethylcopper(I)phenanthroline complex represents a modern way to 4-trifluoromethyl-7-chloroquinoline **99a** (Scheme 44) [66]. 4-Trifluoromethyl substituted 3-aminoquinolines **99b** have also been obtained by the reaction of 3-aminoquinoline with trifluoroiodomethane-zinc-sulfur dioxide system (Scheme 44) [67].



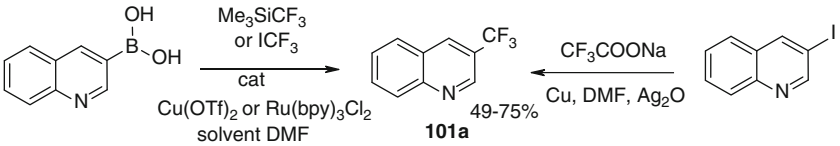
Scheme 44 Synthesis of 4-(trifluoromethyl)quinolones **99**

A series of highly substituted 2-trifluoromethyl-3-iodoquinolines **100** have been prepared in good to excellent yields under rather mild reaction conditions according to the method which involves iodocyclization of trifluoromethyl propargyl imines with I_2-CAN or I_2 and ICl. The starting trifluoromethyl propargyl amines can be obtained by means of the Sonogashira cross-coupling reaction of the corresponding readily accessible imidoyl iodides with alkynes followed by reduction with $NaBH_3CN$ (Scheme 45) [68].



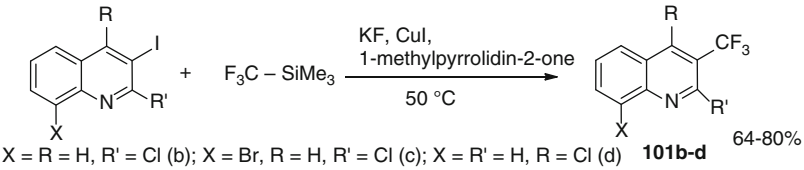
Scheme 45 Synthesis of 2-(trifluoromethyl)quinolones **100**

During the last decade the metal-catalyzed cross-coupling reactions proved to be one of the main methods for obtaining of ***3-(trifluoromethyl)quinolines***. For instance, the copper-catalyzed oxidative trifluoromethylation [Me_3SiCF_3, cat. $Cu(OTf)_2$] of quinolin-3-boronic acid results in the formation of quinoline **101** in 49 % yield (Scheme 46) [69]. Trifluoromethylation of quinolin-3-boronic acid with CF_3I leads to the same compound **101** in 67 % yield, as it has recently been described [70]. The ligand-free trifluoromethylation of quinolin3-boronic acid in the presence of the catalytic system $[Ph_2SCF_3]^+[OTf]^-/Cu(0)$ provides 75 % yield of compound **101** [71], while the copper-catalyzed trifluoromethylation of **100** with the Togni's reagent results in 3-trifluoromethylquinoline **101** in 53 % yield [72]. Also the ligand-free copper-catalyzed decarboxylative trifluoromethylation of 3-iodoquinoline with sodium trifluoroacetate using Ag_2O as a promoter has been reported (Scheme 46) [73].



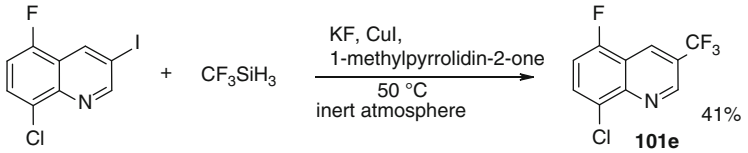
Scheme 46 Synthesis of 3-(trifluoromethyl)quinolone **101a**

2-Chloro- and 4-chloro-3-(trifluoromethyl)-quinolines were obtained from the corresponding iodoquinolines by action of Me_3SiCF_3 (Scheme 47) [74].



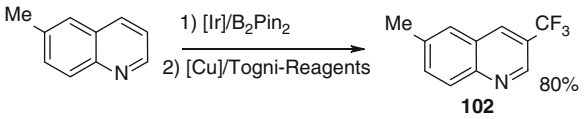
Scheme 47 Synthesis of 3-(trifluoromethyl)quinolone **101b-d**

The reaction of 3-iodo-5-fluoro-8-chloroquinoline with CF_3SiH_3, KF, and CuI proceeds rather smoothly in 1-methyl-pyrrolidin-2-one, leading to the formation of 3-trifluoromethyl-5-fluoro-8-chloroquinoline **101e** in 41 % yield (Scheme 48) [43].



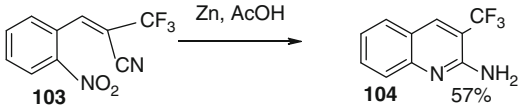
Scheme 48 Synthesis of 3-(trifluoromethyl)quinolone **101e**

2-Propyl-3-iodoquinoline has been transformed into 2-propyl-3-(trifluoromethyl) quinoline by action of $ClCF_2CO_2Me$, CuI, and KF on reflux in DMF [75]. An interesting example of highly selective trifluoromethylation of 6-methylquinoline by means of the iridium-catalyzed reaction is presented in Scheme 49 [76].



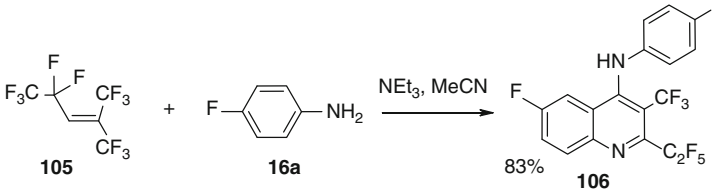
Scheme 49 Synthesis of 3-(trifluoromethyl)quinolone **102**

Another approach to 3-(trifluoromethyl)quinolines is based on cyclizations of trifluoromethyl-containing intermediates, as illustrated, for instance, by the synthesis of 2-amino-3-(trifluoromethyl)quinoline **103** by means of the Leimgruber-Batcho reaction (Scheme 50) [77].



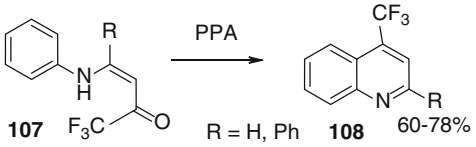
Scheme 50 Synthesis of 2-amino-3-(trifluoromethyl)quinoline **103**

The reaction of perfluoro-2-methylpent-2-ene **105** with 4-fluoroaniline in the presence of Et_3N illustrates one more approach to 3-trifluoromethylquinoline derivatives, in particular to the compound **106** (Scheme 51) [78].



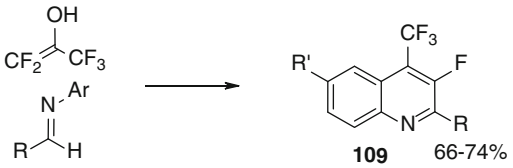
Scheme 51 Synthesis of 3-(trifluoromethyl)quinoline **106**

The synthesis of ***4-(trifluoromethyl)quinolines*** **108** can be realized through the cyclocondensation of oxotrifluoroalkenyl anilines **107** (Scheme 52) [79, 80].



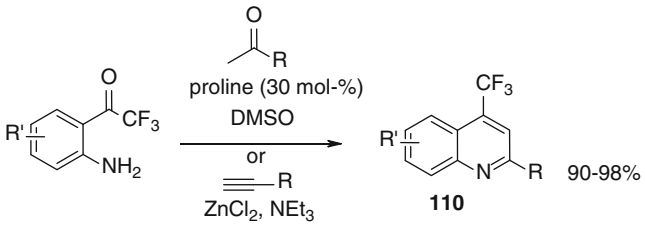
Scheme 52 Synthesis of 4-(trifluoromethyl)quinoline **108**

One-pot conversion of pentafluoropropen-2-ol into quinolines **109** involves the sequence of the Mannich addition to aromatic aldimines followed by the Friedel-Crafts cyclization and aromatization (Scheme 53) [81].



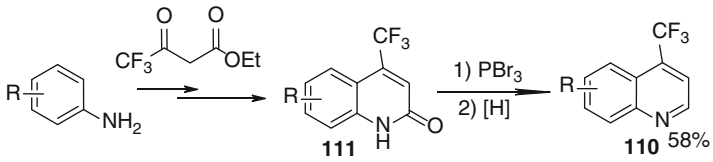
Scheme 53 Synthesis of 4-(trifluoromethyl)quinoline **109**

The proline-catalyzed Friedlander reaction has been used for the synthesis of 2-substituted 4-trifluoromethyl quinolines **110** (Scheme 54) [82]. Compounds **110** have also been obtained through the Zn(II)-mediated alkynylation-cyclization of *o*-trifluoroacetyl anilines (Scheme 54) [83].



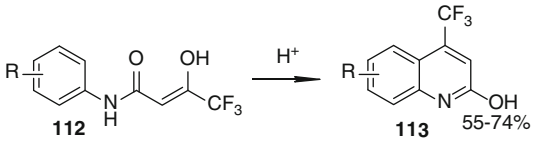
Scheme 54 Synthesis of 4-(trifluoromethyl)quinolines **110**

Condensation of anilines with ethyl 4,4,4-trifluoroacetoacetate have been established to give the corresponding 4,4,4-trifluoro-3-oxobutane substituted anilides, precursors in the synthesis of 4-(trifluoro-methyl)-2-quinolinones **111** [84]. Heating of these compounds with phosphoryl tribromide affords 2-bromo-4-(trifluoro-methyl)quinolines which can be converted into 4-(trifluoromethyl) quinolines **110** by reductive debromination (Scheme 55) [85].



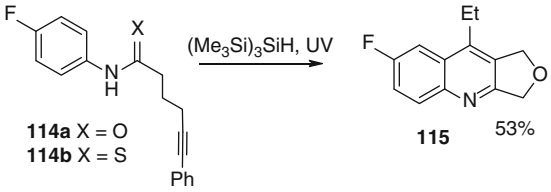
Scheme 55 Another approach to 4-(trifluoromethyl)quinolines **110**

4-Fluoroalkyl-2-quinolinols **113** were obtained regioselectively in moderate to good yields by acid-assisted intramolecular ring-closure reaction of the corresponding N-aryl-3-oxa-polyfluoroalkanamides **112** prepared from 2,2-dihydropolyfluoroalkanoic acids (Scheme 56) [86].



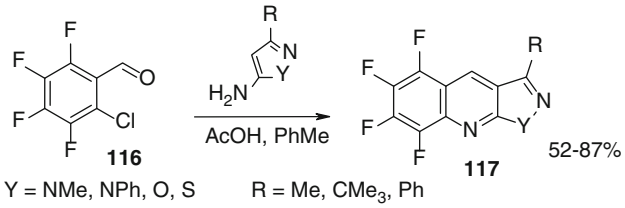
Scheme 56 Synthesis of 4-(trifluoromethyl)quinolines **113**

New approaches to **annelated quinolines** have also been developed, as illustrated by the synthesis of fluorinated tetrahydroquinoline **115** through the radical cyclization of thioamide **114b** by action of 4 equivalents $(Me_3Si)_3SiH$ in benzene on irradiation with UV light. Tioamide **114b** is easily accessible through thionation of amide **114a** with Louwesson's reagent (Scheme 57) [87].



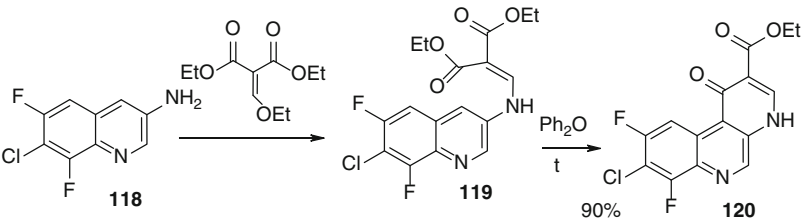
Scheme 57 Synthesis of compound **115**

A number of fluorinated azolo[*b*]quinolines **117** have been obtained by cyclocondensation of *ortho*-chlorobenzaldehyde **116** with 5-amino-1,2-azoles (Scheme 58) [88].



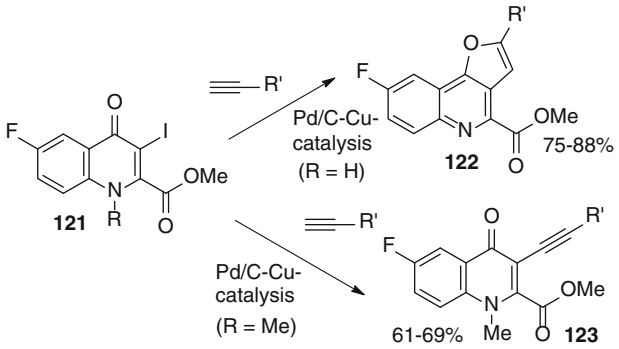
Scheme 58 Condensation of **116** with 5-amino-1,2-azoles

Tricyclic system of benzo[*f*][1,7]naphthyridone **120** was obtained through the Gould-Jacobs cyclization of enamine **119**, derived from 3-amino-6,8-difluoro-7-chloroquinoline **118** and diethyl ethoxymethylene malonate. The cyclization was carried out in diphenyl ether at 240 °C, providing a good yield of compound **120** (Scheme 59) [89].



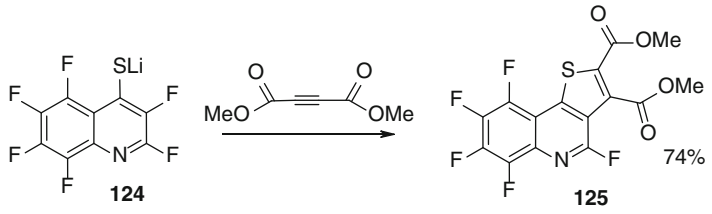
Scheme 59 Synthesis of compound **120**

The Pd/C-Cu catalyzed coupling of 3-iodo-1H-6-fluoroquinolin-4-ones **121** with the series of terminal alkynes proceeds regioselectively and results in the formation of furo[3,2-*c*]quinolines **122** in high yields (Scheme 60). 3-Alkynyl-quinolines **123** were isolated in those cases where the NH hydrogen in the starting 3-iodo-1H-quinolin-4-one **121** was replaced with the methyl group [90].



Scheme 60 Synthesis of compounds **122**, **123**

The action of dimethylacetylenedicarboxylate (DMAD) on lithium salt of 2,3,4,5,7,8-hexafluoro-4-quinolinthiole **124** leads to 74 % of 4,6,7,8,9-pentafluoro-thieno[3,2-*c*]quinoline **125** and 13 % dimethyl 1-(2,3,5,6,7,8-hexafluoro-4-quinolyl-thio)ethen-1,2-dicarboxylate (Scheme 61) [91].



Scheme 61 Synthesis of compound **125**

The structure of fluorine-containing quinolines has been elucidated in crystals and solutions. The data on X-ray crystallography analysis of a number of mono- and difluoroquinolines are available in the literature [47, 92]. In order to elucidate the phenomenon of π-stacking for polyfluoroaromatic rings the X-ray studies of some polifluoroquinolines have been carried out [93]. Main types of internal motives in organisation of these systems appear to be associated with π…π polyfluoroarene…poly-fluoroarene, polyfluoroarene…heteroarene, heteroarene…heteroarene interactions.

Fluorinated quinolines have been studied in detail by calculation methods. In particular, the quantum-chemical calculations of the series of difluoroquinolines have recently been performed [94]. The negative charge of the nitrogen atom extends also on fluorine atoms, because the nitrogen atom exhibits both σ- and π-electron withdrawing nature, while a fluorine atom is a strong σ-acceptor, but at the same it has a π-donative character. Charges on carbon atoms of the pyridine ring are in accordance with π-electron withdrawing effect of the nitrogen atom. Non-substituted carbon atoms of the benzene ring are charged negatively due to π-electron donating effect of fluorine atoms. 5,7-Difluoroquinoline has the lowest energy due to the fact that π-electron donating fluorine atoms are conjugated to the nitrogen atom. 6,8-Difluoroquinoline has a little higher energy, since the arrangement of fluorine atoms in this compound is similar to 5,7-difluoroquinoline, however both fluorine atoms aren't conjugated to the pyridine nitrogen atom. Besides that, a negative charge on nitrogen atom in 5,7-difluoriquinoline exceeds that in 6,8-difluoroquinoline. 6,7-Difluoroquinoline and 5,8-difluoroquinoline have a higher energy, than 5,7-difluoroquinoline and 6,8-difluoroquinoline, since effects of two *meta*-orientated fluorine atoms are in accord with each other.

^{1}H, ^{13}C and ^{19}F NMR spectra for the series of fluoroquinolines have been analysed. Incorporation of a fluorine into the pyridine ring of quinolines proved to cause the same changes in chemical shifts of signals, as in case of pyridine. Indeed, proton H^3 in 2-fluoroquinoline resonates in a higher field relative to the parent quinoline, while proton H^4 – in a lower field. Incorporation of fluorine into the benzene ring of quinolines results in upfield shifts for the resonance signals of H^6, H^7, H^8 of 5-fluoroquinoline and for H^5, H^7 signals in case of 8-fluoroquinoline (Fig. 1) [95]. It should be noted that coupling constant values $^{4}J(H^4,F)$ proved to exceed $^{3}J(H^3,F)$. Also ^{1}H NMR characteristics for quinolines bearing one or two fluorine atoms in the benzene ring have been established [47, 94].

The main features of the ^{13}C NMR spectra of 2-fluoroquinolines associated with the presence of a fluorine atom are similar to those of 2-fluoropyridines. Incorporation of a fluorine atom into positions 5 or 8 of the benzene ring results in upfield shifts of C^6-C^8 (or C^5-C^7) carbon resonances; the biggest shift value is observed for the C^6 signal in case of 5-fluoroquinoline and for C^7 resonance signal of 8-fluoroquinoline (Fig. 1) [94]. The data of ^{13}C NMR spectroscopy for fluoroquinolines with fluorine atoms in the benzene ring are well presented [47].

The resonance signal in the ^{19}F NMR spectrum of 2-fluoroquinoline (−63 ppm) is shifted down field relative to that for 2-fluoropyridine (−68 ppm). Downfield shifts in the ^{19}F NMR spectra of 2-fluoroquinolines, containing in the pyridine or benzene rings chloro, bromo, or trifluoromethyl substituents are even bigger [46].

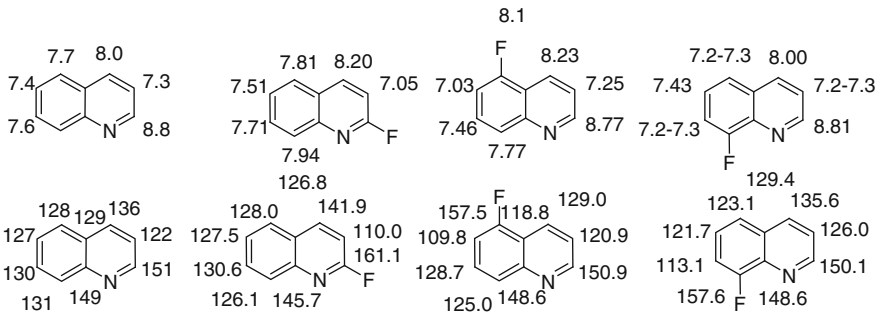


Fig. 1 NMR data of selected fluoroquinolines

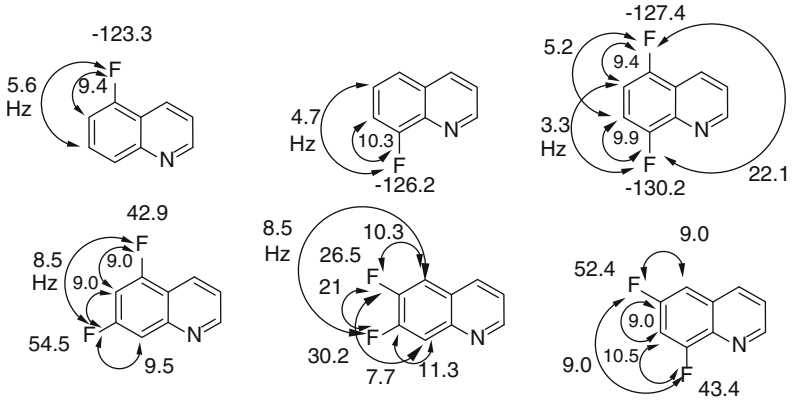


Fig. 2 Chemical shifts and $J_{F,H}$ и $J_{F,F}$ in the ^{19}F NMR spectra

The selected spectral ^{19}F NMR data for quinolines bearing one and two fluorine atoms in the benzene ring are given in Fig. 2 [47, 94]. These data illustrate mutual effects of fluorine atoms.

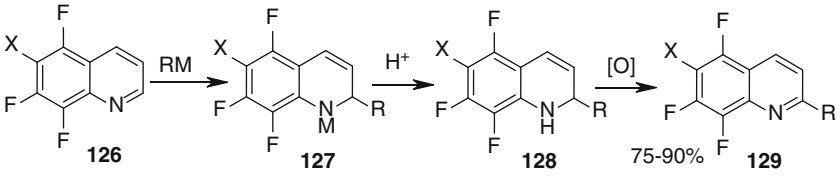
In the ^{19}F NMR spectrum of perfluoroquinoline the F^2 signal is observed in the weakest field; while coupling constants for fluorine atoms in the *peri*-position to each other have the biggest values. Also, the data of ^{19}F NMR spectroscopy are available for fluoroquinolines, bearing phosphorus groups in the benzene ring, and for 2-substituted quinolines with fluorine atoms in the benzene ring [92].

3 Chemical Properties

The quinoline system is of interest as an important building-block for the whole number of biologically active compounds; therefore development of new synthetic routes to fluorinated quinolines, capable of various transformations is a key task of heterocyclic chemistry. One of the most common approaches to functionalization of fluoroquinolines is based on their reactions with nucleophiles. In particular,

nucleophilic replacement of fluorine atoms with a variety of nucleophiles is of significant importance for synthetic use.

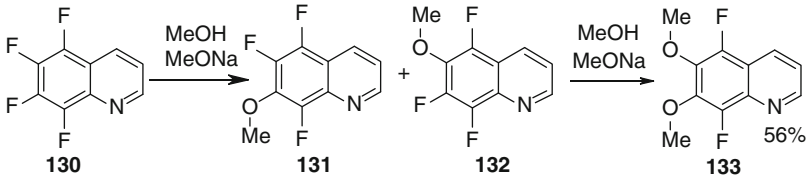
Systematic study on the problem of regioselectivity in the reactions of 6-X-5,7,8-trifluoroquinolines with nucleophiles has been carried out [92–96]. Depending on the nature of nucleophilic reagents either displacement of fluorine atoms takes place or competitive nucleophilic attack at position 2 and C-F bonds of the benzene ring has been shown to occur. Indeed, the reaction of 6-H-trifluoromethyl-5,7,8-trifluoroquinolines **126** (X=F, CF_3) **with rigid nucleophiles – organometal compounds RM** (MeLi, n-BuLi, PhLi and PhMgBr), followed by treatment with hydrochloric acid results in the formation of products of nucleophilic addition **128**. Compounds **128** are oxidized into 2-substituted 6-H-trifluoroquinolines **129** in high yields (75–90 %) using air oxygen or MnO_2 (Scheme 62) [92].



Scheme 62 Reaction of quinolines **126** with organometal compounds RM

In addition to nucleophilic substitution of hydrogen in **126**, as the main route of the reaction (leading to the S_N^H products **129**) [97–100], the second reaction pathway associated with substitution of fluorine atoms can be realized, especially with PhLi as nucleophilic reagent. Authors [92] reported that according to chromatomass spectrometry data product, in which one fluorine atom is replaced by phenyl group, was detected in reaction mixture.

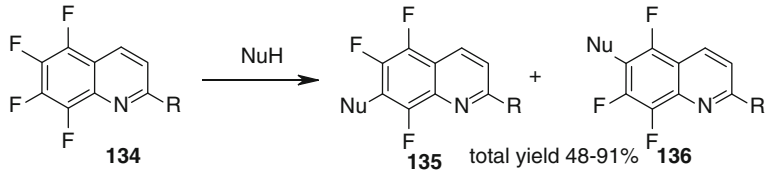
Interaction of polyfluoroquinolines with **O-nucleophiles** is illustrated by the reaction of 5,6,7,8-tetrafluoroquinoline **130** with sodium methoxide (Scheme 63) [92]. When the reaction was carried out in methanol, a mixture of 7-methoxy- and 6-methoxy derivatives **131** and **132** in the ratio 6:1 was obtained, while an excess of sodium methoxide provides a full conversion of both compounds, **131** and **132,** into 6,7-dimethoxy-5,8-difluoroquinoline **133**. The reaction of 5,6,7,8-tetrafluoroquinoline with sodium methoxide in the ratio 1:1.25, 1:1, or 1:0.5 has been established to afford 7-methoxy derivative **131** as the only product.



Scheme 63 Interaction of polyfluoroquinolines with O-nucleophiles

Treatment of 5,7-difluoroquinoline with sodium methoxide in liquid ammonia at 218–240 K results in a mixture of 5-methoxy-7-fluoroquinoline and 5-fluoro-7-methoxyquinoline. In a similar reaction of 6,7-difluoroquinoline 6-fluoro-7-methoxyquinoline and 6-methoxy-7-fluoroquinoline have been isolated. It is interesting to note that the reaction of 6,8-difluoroquinoline with sodium methoxide in liquid ammonia provides only 6-fluoro-8-methoxy derivative, while 5,8-difluoroquinoline doesn't react at all under the same reaction conditions. In case the reaction of 5,8-difluoroquinoline with sodium methoxide was carried out in DMSO at 298–378 K a mixture of 5-methoxy-8-fluoroquinoline and 5-fluoro-8-methoxyquinoline was isolated [95].

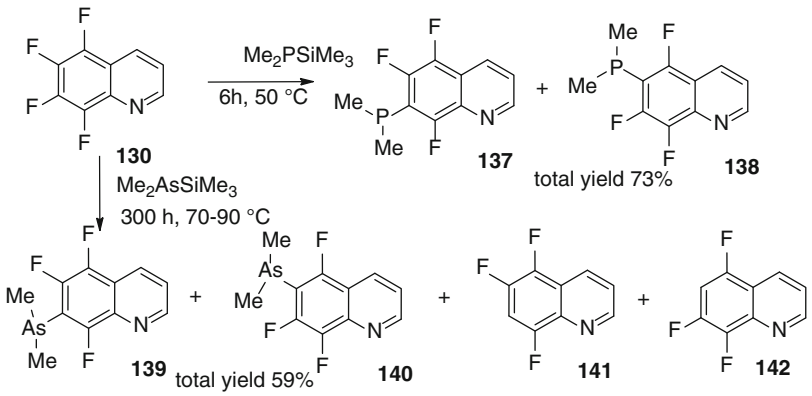
N-Nucleophiles (aqueous ammonia, piperidine, N_2H_4–H_2O in dioxane or sodium amide in liquid ammonia) react with 2-substituted 5,6,7,8-tetrafluoroqui-nolines **134** to form amino-defluorination products with substitution of F^6 and F^7 atoms **135** and **136** in the ratio from 5:1 to 3:1 (Scheme 64) [96, 101]. Interaction of N-nucleophiles with 2- or 4-methylsubstituted 5,6,7,8-tetrafluoroquinolines proceeds in a similar way.



Scheme 64 Amino-defluorination reactions of 5,6,7,8-tetrafluoroquinolines

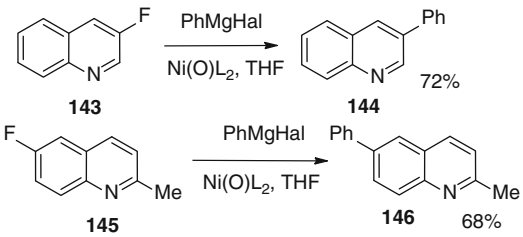
Amination of 5,7-difluoro- and 5,7,8-trifluoroquinoline, 5,7-difluoro-8-chloroquinoline and 6-trifluoromethyl-5,7,8-trifluoroquinoline leads to the formation of rather complicated mixtures of monoaminoquinolines [101]. The reaction of heptafluoroquinoline with **S-nucleophiles** (HS^-, PhS^-, MeS^-, PrS^- и $BuS)^-$ is very indicative, since it demonstrates a high regioselectivity, resulting in displacement of halogen at the position 4 [102].

When 5,6,7,8-tetrafluoroquinoline **130** reacts with P(As)-nucleophiles a mixture of two products is formed due to displacement of fluorine atoms at positions 6 and 7 [92]. Indeed, treatment of **130** with Me_2PSiMe_3 in benzene at 50 °C for 6 h gave 7-dimethylphosphano-5,6,8- and 6-dimethyl-phosphano-5,7,8-trifluoroquino-lines **137** and **138** in the ratio 4:1 (Scheme 65). The feature of the reaction of **130** with $Me_2AsSiMe_3$ is that, in addition to the expected arsines **139** and **140**, defluorination products **141** and **142** have been isolated. Preferable replacement of fluorine atoms in 6 and 7 positions indicates that, besides the ring nitrogen atom, the cooperative effect of four fluorine atoms plays an important role in stabilization of the intermediate σ-complex. Treatment of 6-trifluoromethyl-5,7,8-trifluoroquinoline or 5,7,8-trifluoroquinoline with Me_2PSiMe_3 resulted in the mixture of 7-, 5-, and 8-dimethylphosphano derivatives, while 7-dimethyl-phosphano-5,8-difluoroquinolines were transformed into 7,8-bis(dimethylphosphano)-5-fluoroquinoline [92].



Scheme 65 Reactions of quinoline **130** with P(As)-nucleophiles

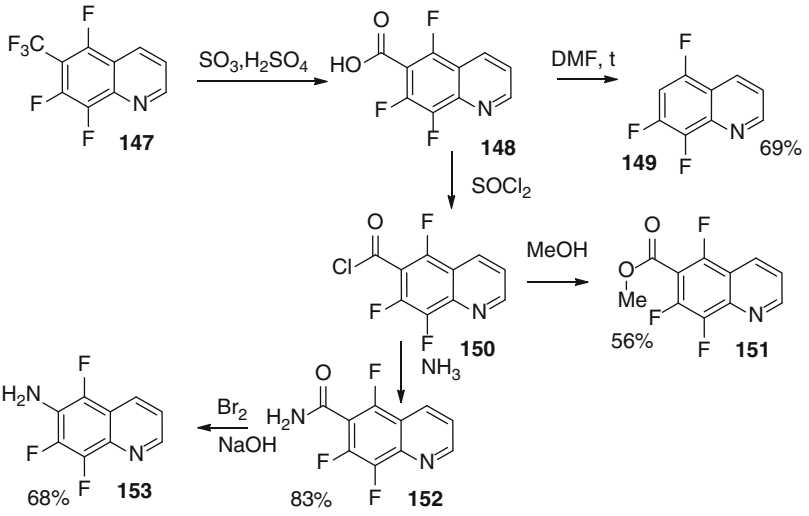
Cross-coupling reactions of fluoroquinolines is also an important synthetic tool to modify the structure of quinolines. Indeed, 3-fluoroquinolines proved to be useful intermediates in the synthesis of 3-substituted quinolines through nickel-catalyzed cross-coupling reactions [103]. For instance, 3-fluoroquinoline **143** can be transformed into 3-phenylquinoline **144** on treatment with phenyl-magnesium bromide in the presence of (1,2-*bis*-diphenylphosphoethane)nickel (II) dichloride or nickel (II) acetyl acetonate (Scheme 66) [103]. In a similar way the cross-coupling reaction of 6-fluoro-2-methylquinoline **145** leads to the formation of 6-phenyl derivative **146**.



Scheme 66 Nickel-catalyzed cross-coupling reactions

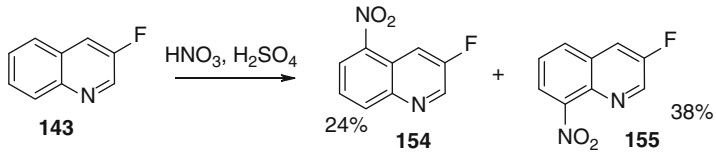
Reactions, ***not being accompanied by the displacement of fluorine atoms*** are also important for functionalization of fluorinated quinolines. For instance, 6-substituted 5,7,8-trifluoroquinolines **148–153** were obtained from 6-trifluoro-methyl-5,7,8-trifluoroquinoline **147** (Scheme 67) through hydrolysis of the CF_3 group in quinoline **147** followed by decarboxylation of 5,7,8-trifluoroquinoline-6-carboxylic acid **148** on heating in DMF [6]. From the acid **148** obtained is the acyl chloride **150**, which gives with methanol the methyl ester **151** and with ammonia – the amide of

5,7,8-trifluoroquinoline-6-carboxylic acid **152**. Involving the latter into the Hoffmann rearrangement leads to 6-amino-5,7,8-trifluoroquinoline **153**.



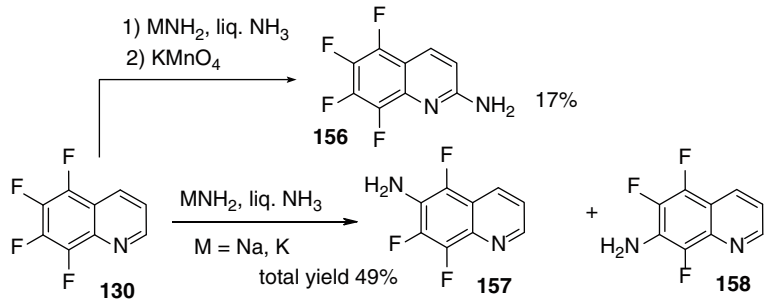
Scheme 67 Functionalization of fluorinated quinolines

The direct nitration of 3-fluoroquinoline **143** has been found to occur by action of a mixture of nitric and sulfuric acids, thus affording 24 % of 5-nitro-3-fluoro-quinoline **154** and 38 % of 8-nitro-3-fluoroquinoline **155** (Scheme 68) [101].



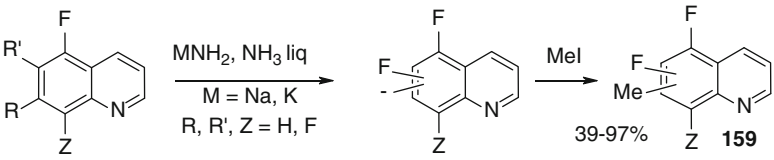
Scheme 68 The direct nitration of 3-fluoroquinoline **143**

Reactivity of 5,6,7,8-tetrafluoroquinoline **130** with the fully fluorinated benzene ring towards the amide anion has been studied [104]. The Chichibabin amination at C-2 has been shown to occur by action of sodium (potassium) amide in liquid ammonia in the presence of potassium permanganate, however only a low yield of the corresponding 2-aminoquinoline has been reached due to concurrent amino-defluorination reactions, taking place at positions 6 and 7 (Scheme 69).



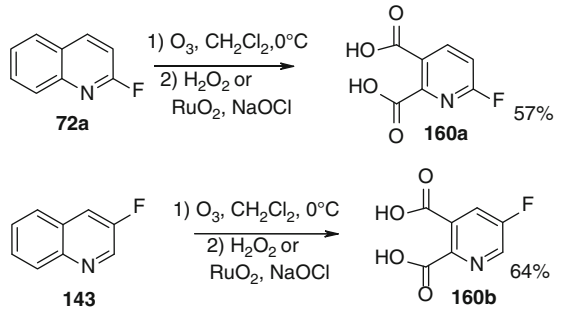
Scheme 69 Amination of quinolone **130**

It is worth mentioning that treatment of difluoro- or trifluoroquinolines with sodium (potassium) amide in liquid ammonia followed by the reaction with methyl iodide has been used to incorporate the methyl group into the benzene ring of these fluoroquinolones (Scheme 70) [101].



Scheme 70 Formation of quinolones **159**

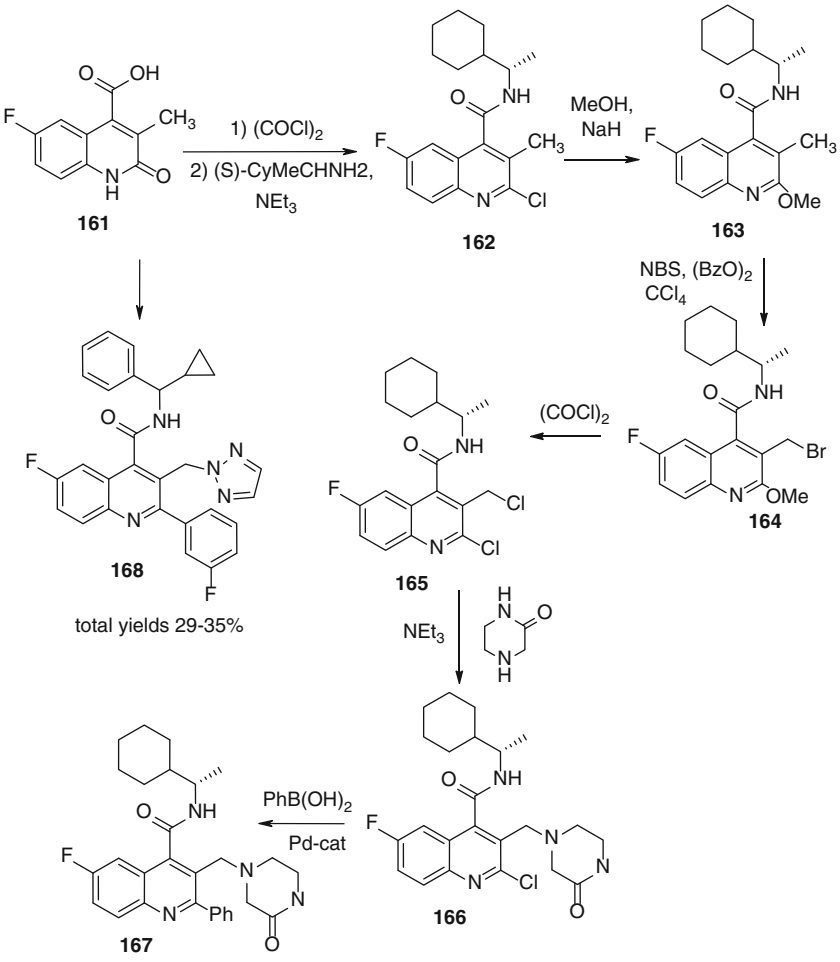
Oxidation of 2-fluoroquinoline **72a** with ozone and hydrogen peroxide or catalytic oxidation in the presence of ruthenium dioxide provides 2-fluoropyridin-5,6-dicarboxylic acid **160a** [105]. Under similar conditions 3-fluoroquinoline **143** is transformed into 3-fluoropyridine-5,6-dicarboxylic acid **160b** (Scheme 71) [104].



Scheme 71 Oxidation of fluoroquinolines **72a** and **143**

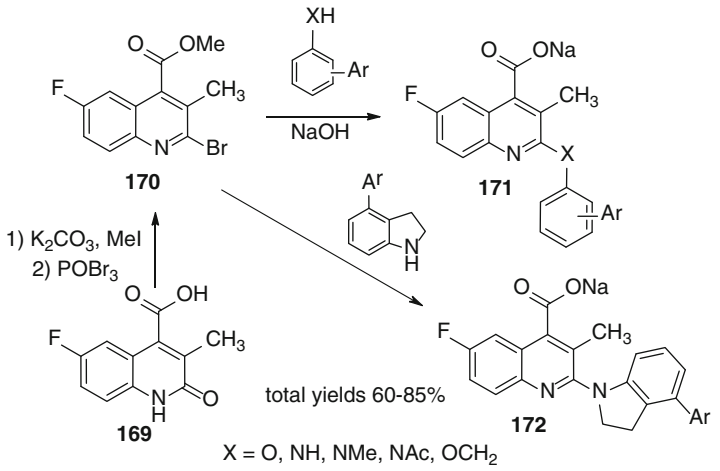
An interesting synthetic approach to 6-fluoro-3-(3-oxopiperazin-1-ylmethyl)-2-phenylquinolin-4-carboxylic acid [(*S*)-1-cyclohexylethyl]amide **167** – dual antagonist for NK2 and NK3 receptors – is presented in Scheme 72 [105]. The reaction

of compound **161** with oxalylchloride initiates conversion of the starting quinolinone into 2-chloroquinoline, while the carboxylic group is transformed first into the corresponding chloroanhydride, and then into amide **162** on treatment with (*S*)-1-cyclohexylethylamine. The next steps involve the formation of 2-methoxyquinoline **163** and 3-bromomethylquinoline **164**, the subsequent reaction of **164** with oxalylchloride and selective substitution of halogen with piperazin-2-one. Amide **166** undergoes the Suzuki cross-coupling reaction to give the corresponding 2-phenylquinoline **167.** Also a multi-steps synthesis of quinoline **168** has been performed [105] (Scheme 72).



Scheme 72 Synthesis of compound **167**

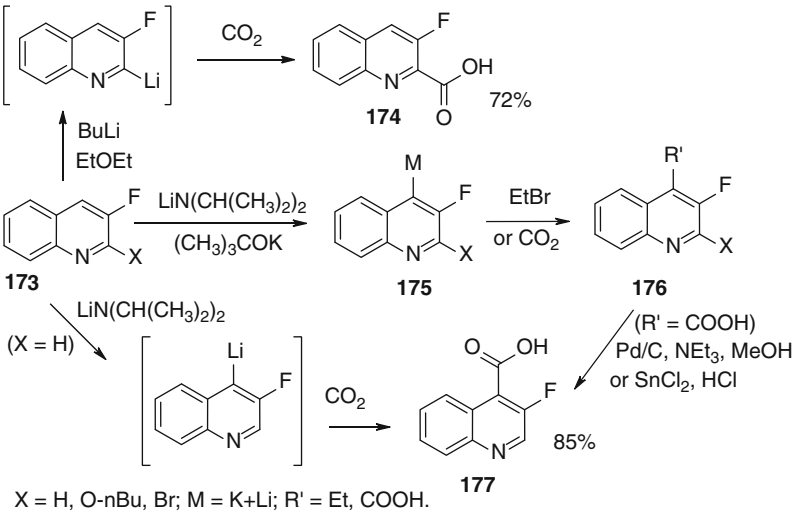
Quinolone **169** after esterification was transformed into bromoquinoline **170**; the latter reacts with aniline, phenol, alcohols or indoline to give 2-substituted 6-fluoroquinolines **171, 172** (Scheme 73) [36].



Scheme 73 Formation of compounds **171**, **172**

Syntheses on the basis of organometallic derivatives have found wide application in the chemistry of fluoroquinolines and their analogs.

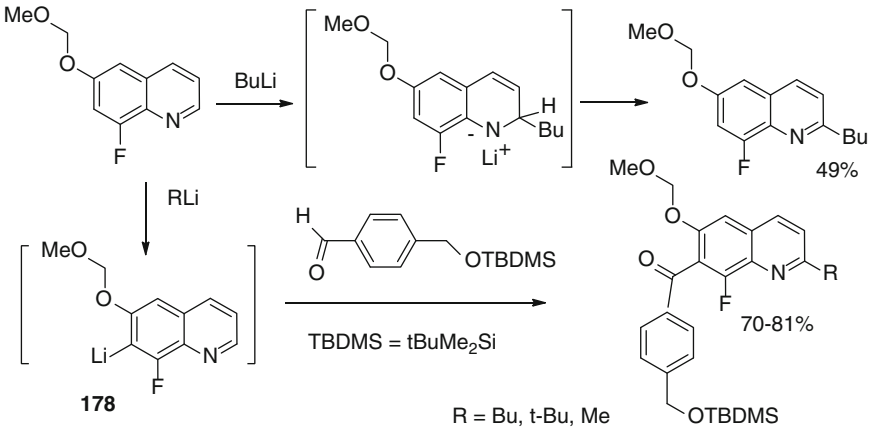
Being treated with a mixture of lithium diisopropylamide and potassium *t-butoxide*, 3-fluoroquinoline (**173**, X=H, $OCH_2CH_2CH_2CH_3$) undergoes the selective metallation of the C-H bond at position 4 of the heterocyclic ring. This reaction allows one to alkylate the position 4 of 3-fluoroquinoline (Scheme 74) [12]. 2-Bromo-3-fluoroquinoline (**173**, X=Br), derived from the reaction of 3-fluoro-quinolin-2(1H)-one with PBr_3, is easily lithiated and transformed into 3-fluoro-quinolin-2-carboxylic acid **174** on treatment of 2-lithium compound with dry carbon dioxide [106].



Scheme 74 Synthesis of quinolincarboxylic acids **174**, **177**

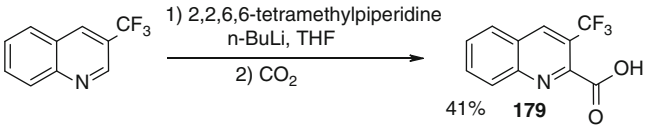
3-Fluoroquinoline (**173**, X=H) was obtained by reduction of 2-bromo-3-fluoroquinoline **173** (X=Br) with Pd/C and NEt_3 in methanol. Bromo derivative **176** (R'=COOH) has been shown to form the corresponding organomagnesium compound, which was transformed on treatment with DMF into aldehyde **176** [R'=COOH, X=C(O)H] and its thiosemicarbazone derivative **176** [R'=COOH, X=CH:NNHC(S)NH_2] [106]. In a similar way 2-bromo-3-fluoroquinolin-4-carbaldehyde and its 1,3-dioxalan were obtained from 4-lithium-3-fluoro-2-bromoquinoline and DMF.

8-Fluoro-6-(methoxymethoxy)quinoline in the reaction with MeLi undergoes a selective *ortho*-metallation at C-7, while BuLi also lithiates the *ortho*-position relative to fluorine atom, however the metallation process is accompanied by nucleophilic addition at C-2 (Scheme 75) [107].



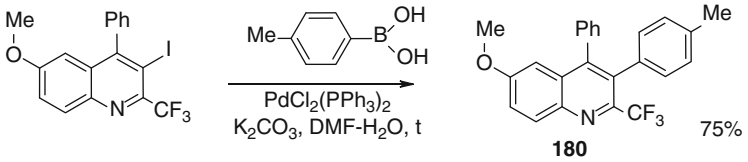
Scheme 75 Reaction of 8-fluoroquinoline with MeLi and BuLi

Use of the direct metallation reactions followed by further functionalization of the obtained organometallic intermediates has been reported for the synthesis of 3-trifluoromethylquinolin-2-carboxylic acid (Scheme 76) [108].



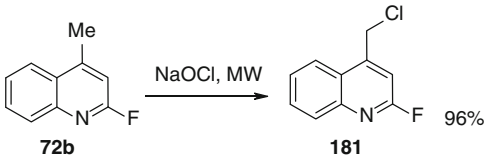
Scheme 76 Synthesis of 3-trifluoromethylquinolin-2-carboxylic acid **179**

The Suzuki -coupling, as well as dehalogenation and carboxylation reactions of 2-trifluoromethyl-3-iodoquinolines have been studied (Scheme 77) [68].



Scheme 77 Synthesis of compound **180**

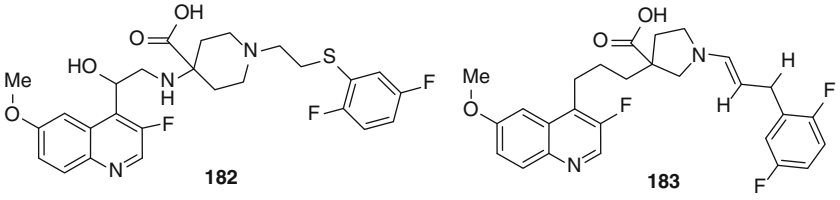
Rapid chlorination of side-chain Me group of 2-fluoro-4-methylquinoline **72b** is reported using sodium hypochlorite under microwave irradiation (Scheme 78) [109].



Scheme 78 Chlorination of Me group of 2-fluoro-4-methylquinoline **72b**

4 Selected Representatives of the Family of Fluoroquinolines

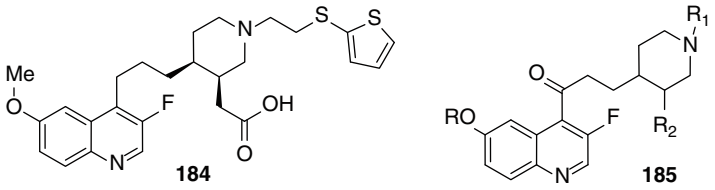
A great deal of fluoroquinolines have demonstrated various types of biological activity, and some of them have already found their applications in medicine. For instance, 3-fluoroquinolines **182** exhibit antibacterial activity against gram-positive and gram-negative bacteria. Compound **182** was obtained by the reaction of 1-(*t*-butyloxycarbonyl)-4-aminopiperidin-4-carboxylic acid with 3-fluoro-6-methoxy-4-(oxyran-2-yl)quinoline, followed be elimination of the protective BOC-group and alkylation of the piperidinyl fragment with 2-[(2-bromo-ethyl) sulphanyl]-1,4-difluorobenzene [110]. Another 3-fluoroquinoline **183** proved to be active against *Staphylococcus aureus IP8203* (Scheme 79) [111].



Scheme 79 Structure of quinolines **182**, **183**

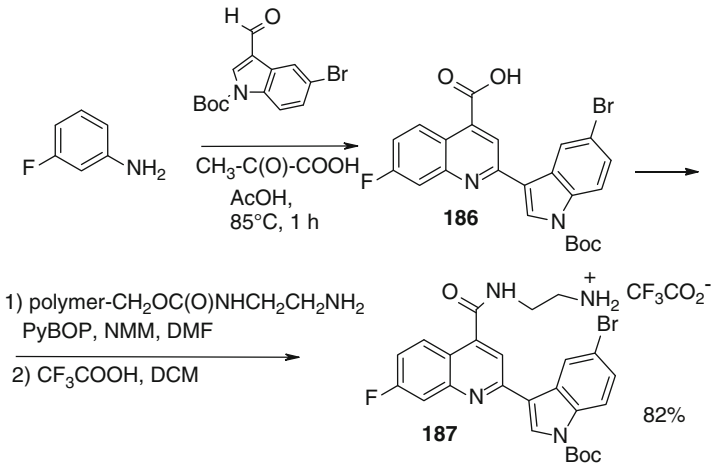
3-Fluoroquinoline **184**, also exhibiting antibacterial activity, has been obtained from 4-iodo-3-fluoro-6-methoxyquinoline through the Pd-catalyzed cross-coupling

reaction followed by N-alkylation with 2-(2-bromoethylthio)thiophene [112]. 3-Fluoroquinoline derivatives **185** have been shown to possess antimicrobial activity (Scheme 80) [113].



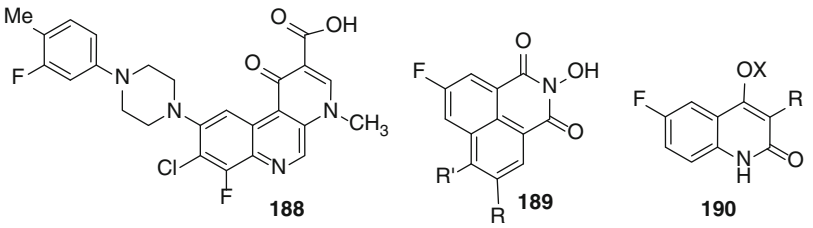
Scheme 80 Structure of quinolines **184**, **185**

The synthesis of 2-(1H-Indol-3-yl)-7-fluoroquinoline **187** from 3-fluoroaniline has been performed (Scheme 81); compound **187** is active against methicillin-resistant *Staphylococcus aureus* strains [114].



Scheme 81 Synthesis of 2-(1H-Indol-3-yl)-7-fluoroquinoline **187**

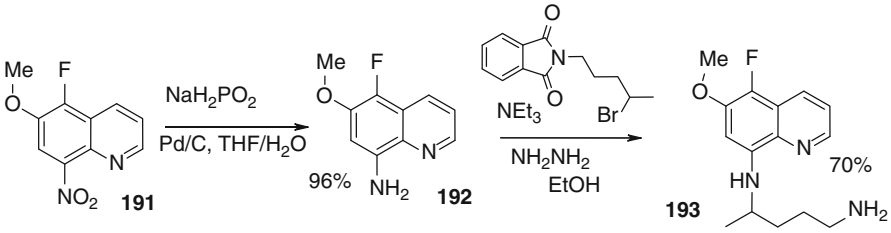
Tricyclic derivative **188** has been established to be active against multi-resistant gram-positive bacteria [90]. Also benzo annelated derivatives of fluorinated 3-hydroxyisoquinolindiones **189** exhibit antibacterial activity [115]. It is worth noting, that derivatives of 6-fluoro-2(1H)quinolinone **190** are of interest as non-nucleoside inhibitors of reverse HIV transcriptase (Scheme 82) [116].



190: R = i-Pr, n-Pr, OEt, Et, iBu, Me; X= (cyclopropyl)-C≡C, cyclopentyl, CH_2-(cyclobutyl), Et(Me)CH-C≡C,CF_3CH_2.

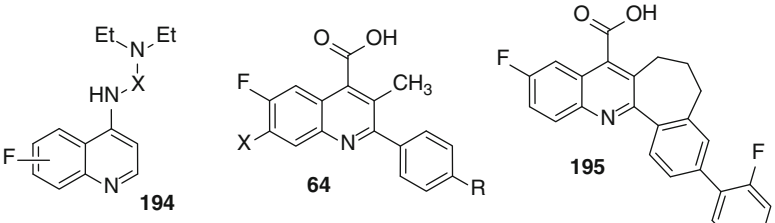
Scheme 82 Structure of quinolines **188–190**

The synthesis of 5-fluoroprimaquin **193**, an analog of the known antimalarial drug, has been reported from compound **191** (Scheme 83) [9].



Scheme 83 Synthesis of 5-fluoroprimaquin **193**

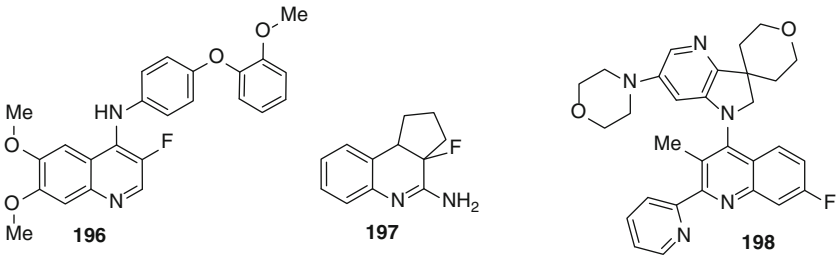
6-Fluoro-, 8-fluoro- and 6,8-difluoro derivatives of 4-aminoquinoline (**194**, X=$(CH_2)_3$, $CHMe(CH_2)_2$) are active against malaria, and can be used for treatment of the diseases caused by chloroquin-resistant strains of *P. falciparum W2* [117]. Also antiplazmodium activity of 7-fluoro derivatives [**194**, $(CH_2)_n$, n = 2, 3, 10, 12 and $CHMe(CH_2)_2$] has recently been reported [118]. 6-Fluoroquinoline-4-carboxylic acids **64** inhibit the melanoma B16 at mice; the sodium salt of **64** (X=H, R=2-FC_6H_4) has been launched by Dupont as Brequinar® drug [119]. The structure-activity relationship for analogs of Brequinar® has been thoroughly investigated [119–123]. Several analogues of this drug are used in transplantation medicine, as well for treatment of rheumatic arthritis and psoriasis. Quinoline **195** proved to be a highly effective immunosuppressant (Scheme 84) [124, 125].



64: X = H, Cl; R = cyclohexyl, phenyl, 2-fluorophenyl.

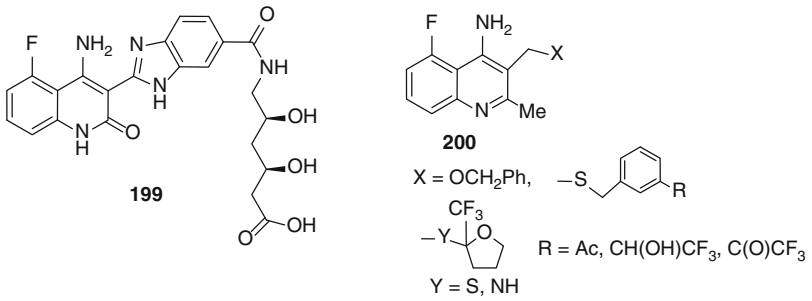
Scheme 84 Structure of quinolines **64**, **194**, **195**

During the recent decade a growing interest in 3-fluorosubstituted quinolines has been observed, since it has been shown that 3-fluoroquinolines, unlike their 5-fluoro analogues, are neither mutagenic not cancerogenic compounds, and can be used in medicine and agriculture [126]. Derivative of 3-fluoroquinoline **196** was shown to act as mitogen-activated protein kinase kinase (MEK) inhibitor [127], while compound **197** – as NOS (nitrogen oxide synthetase) inhibitor [128]. Compound **198** represents a novel type potent phosphoinositide 3-kinase (PI3K) inhibitors, it's valuable for treatment of rheumatoid arthritis (Scheme 85) [129].



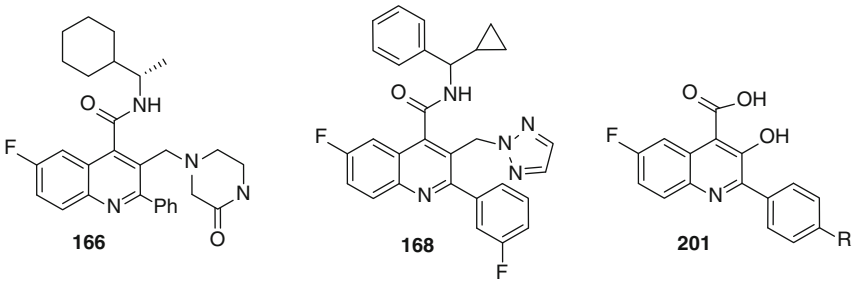
Scheme 85 Structure of quinolines **196–198**

5-Fluoro-2-quinolone **199** proved to be a highly effective protein-kinase inhibitor [130]. Also 5-fluoroquinoline derivatives **200** are inhibitors of acetylcholine esterase, and they are important for treatment of Alzheimer's disease (Scheme 86) [131].



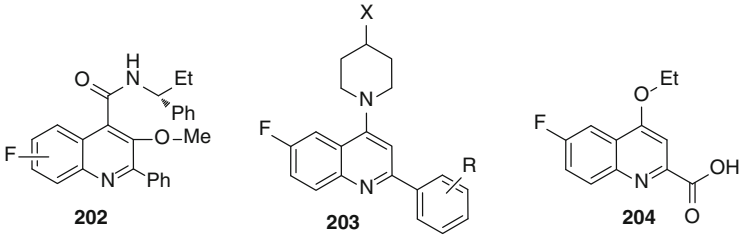
Scheme 86 Structure of quinolines **199**, **200**

Derivatives **166** and **168** are antagonists of neurokinine 3 (NK3) and can be applied to treatment of diseases of the central nervous system [107, 132]. Quinolines **201** are antagonists of P-selectine (Scheme 87) [133].



Scheme 87 Structure of quinolines **166, 168**, **201**

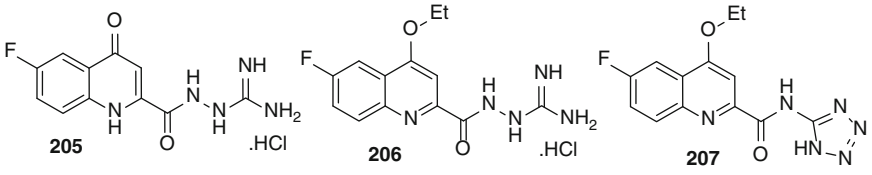
4-Quinolincarboxamides **202**, bearing a fluorine atom in 6, 7 or 8, proved to act as ligands for the NK-3 receptors [134]. Among 2-aryl-4-pyperidinyl-6-fluoro-quinolines **203** ligands of the benzodiazepine receptors have been revealed, and the 1,2,4-oxadiazole fragment appears to act in this case as heterocyclic analogue of COOH and COOR functional groups [135, 136]. 6-Fluoro-4-ethoxyquinolin-2-carboxylic acid **204** can be used for treatment of hyperglycemia, obesity and diabetes (Scheme 88) [137].



203: R = 2-Cl, 2-OMe, 4-F, 4-Cl, 2-OH;
X = $C(O)NH_2$, 3-methyl-1,2,4-oxadiazol-5-yl, COOEt, CN

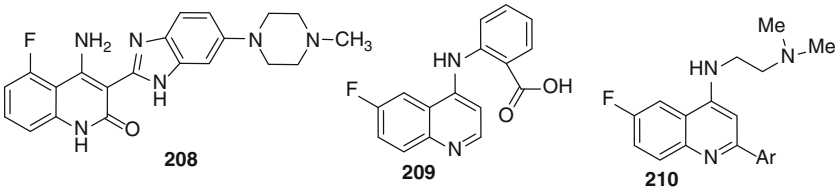
Scheme 88 Structure of quinolines **202–204**

In order to develop new antidiabetic agents, guanidine and tetrazole substituted amides of 6-fluoroquinolin-2-carboxamides **205, 206** and **207** have been obtained [138]. Compound **207** acts as fibroblast growth factor receptor 3 ($FGFR^3$) inhibitor and can be used for treatment of multiple myeloma (Scheme 89) [139, 140].



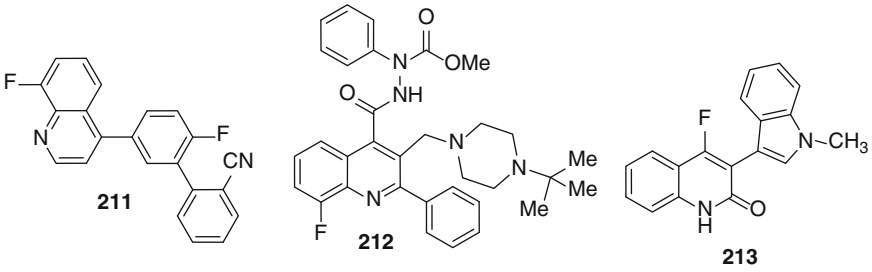
Scheme 89 Structure of quinolines **205–207**

Salt of **208** with lactic acid has been shown to be an effective inhibitor of various kinases, such as receptors for vascular endothelial growth factor 2 (VEGFR2), fibroblast growth factor receptor 1 (FGFR1), platelet-derived growth factor receptor-beta (PDGFRβ) [141, 142]. 6-Fluoroquinolinyl substituted anthranilic acid **209** is used for treatment of metabolic diseases of bones [143]. 6-Fluoro-2-arylquinolin-4-amines **210** are antagonists of immunostimulator CpG-oligonucleotides (Scheme 90) [144].



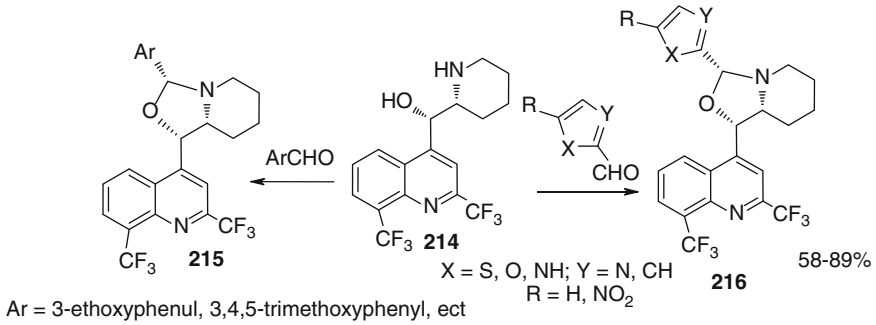
Scheme 90 Structure of quinolines **208–210**

8-Fluoroquinoline derivative **211** is capable of binding with γ-aminobutyric acid receptors, and can be used for treatment of convulsions, mental disturbances, and disorders of memory [145]. Compound **212** is antagonist of NK3 receptor [146], substituted 2-quinolone **213** – inhibitor of tyrosine-kinase vascular endothelial growth factor (VEGF) receptor (Scheme 91) [147]. 2-(Piperazin-1-yl)-5-fluoro-6-nitroquinoline labelled with fluorine-18 was shown to be useful for potential positron-emission-tomography (PET) tracer for imaging the serotonin transporter [148].



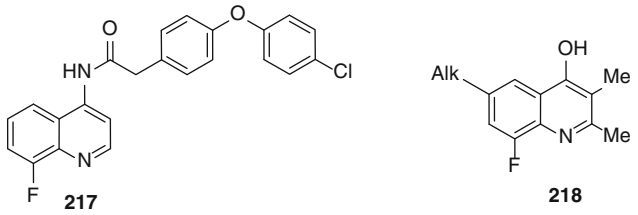
Scheme 91 Structure of quinolines **211–213**

An improved synthesis of mefloquine has been advanced [149]. Also the asymmetric total synthesis of the (+)-enantiomer of mefloquine hydrochloride has been described [150]. Modifications of mefloquine aimed at development of novel biologically active compounds, including antituberculosis drugs, have extensively been performed (Scheme 92) [151]. Compounds **215, 216** were more active than mefloquine against *M. tuberculosis* (MIC 11.9–33 μM), some of derivatives have a better tuberculostatic activity than the first line tuberculostatic agent ethambutol (MIC = 15.9) [151].



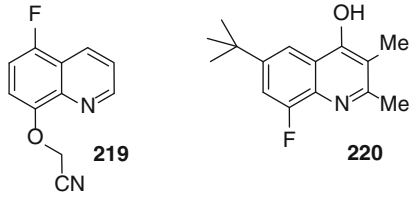
Scheme 92 Modifications of mefloquine

Compound **217** active against nematodes, insects, mites, and plant pathogens [152]. Derivative of 8-fluoroquinoline **218** useful as an agricultural chemical (Scheme 93) [10].



Scheme 93 Structure of quinolines **217**, **218**

5-Fluoro-8-cyanomethoxyquinoline **219** possesses herbicidal activity [153]. 2,3-Dimethyl-4-hydroxy-6-t-butyl-8-fluoroquinoline **220** is useful as rise blast control agent (Scheme 94) [154].



Scheme 94 Structure of quinolines **219**, **220**

2-Amino substituted 6,7-dimethoxy-4-(trifluoromethyl)quinolines have been shown to possess fluorescent properties [155]. 8-Hydroxyquinoline, its numerous derivatives and especially metal chelates on their basis attracted attention of many researchers since publication of the first data on electro-luminescence of the aluminum complex with 8-hydroxyquinoline which possesses thermal stability, high

efficiency of green luminescence, and rather good electronic mobility [156]. Influence of fluorine atoms in various positions of the quinoline system on luminescent characteristics of metal complexes of 8-hydroxyquinoline has been elucidated [157]. Due to specific properties of fluorine atom complexes of 8-hydroxyquinoline with metals proved to have an enhanced electronic mobility, a low temperature of sublimation, a good stability on air, and a wide energetic gap. 2-Methyl-6,7-difluoro-8-oxyquinoline, its stiryl derivatives and Zn (II) complexes have recently been obtained to study luminescence of these compounds [158].

In conclusion it is worth to mention that quinolines and their fluorinated derivatives continue to be one of the most important class of heterocyclic compounds. The medicinal chemistry remains one of the main fields for their applications, and special attention during the last decades is paid to the family of 6-fluoro-1,4-dihydroquinolin-4-oxo-3-carboxylic acids which will be discussed in a separate chapter. Derivatives of 8-hydroxyquinoline have found wide application in analytical, coordination chemistry, while their metal chelates are of interest as the basis to develop new materials.

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Fluoroquinolones: Synthesis and Application

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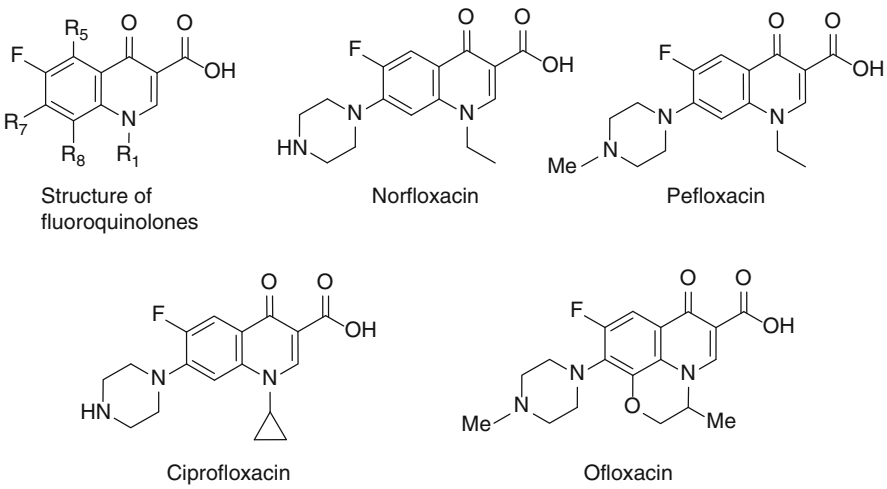
V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 2: 6-Membered Heterocycles*,
DOI 10.1007/978-3-319-04435-4_3,

Abstract The data on 6-fluoro-1,4-dihydroquinolin-4-oxo-3-carboxylic acids and their structural analogues accumulated in the literature for the last 10–15 years are reviewed. Synthetic approaches to the quinolone system, as well as all kind of structural modifications by incorporating substituents into 1–8 positions or by means of annelation have been discussed. The "structure-activity" relationships for antibacterial fluoroquinolones, as well as the data on other types of biological activity for the family of bi- and polycyclic fluoroquinolones are presented. The formation of complexes of fluoroquinolones with metals and their applications have been considered. The bibliography – 377 references.

Keywords Fluoroquinolones • Polycyclic fluoroquinolones • Synthesis • Modifications • Annelation • Activity • Metal complexes

1 Introduction

Nearly three decades passed since the time when the first representatives of the fluoroquinolone family of antibacterials, such as norfloxacin, pefloxacin, ciprofloxacin and ofloxacin had appeared in the world pharmaceutical market (Scheme 1).



Scheme 1 Structure of some fluoroquinolone antibacterials

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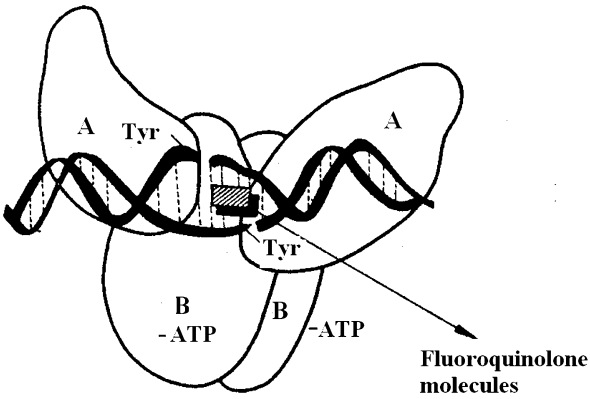


Fig. 1 Inhibiting bacterial DNA-gyrase by fluoroquinolones (Reproduced with permission of publishing Folium [6])

It is worth mentioning that the first drug in the series of quinolones, nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridin-3-carboxylic acid), bearing no fluorine atoms, was launched into medicinal practice in 1963.

Structural modification of the quinolone skeleton by incorporating of fluorine atoms at C-6 and other positions of the benzene ring resulted in a remarkable improvement of antimicrobial properties and opened new prospects in clinical treatment of infections. Indeed, compounds of the fluoroquinolone family proved to exhibit a high level of antibacterial activity and a wide spectrum which surpass many antibiotics, including the third generation of cephalosporin's and other chemotherapeutic antibacterials [1–13]. Due to enhanced penetration ability through cell membranes and their effects on bacteria reproduction by inhibiting bacterial DNA-gyrase, fluoroquinolones possess a high antibacterial activity (Fig. 1) [6].

It is extremely important that fluoroquinolones have a specific mechanism of action, different from antibiotics and other groups of antibacterials (cephalosporins, aminoglycosides, etc.), which allows one to apply fluoroquinolones for treatment of infectious diseases caused by strains resistant to many other classes of antibacterials drugs.

Depending on their behavior relative to bacteria enzymes of three types of fluoroquinolones can be distinguished:

- the first type of fluoroquinolones inhibiting mainly the topoisomerase IV: norfloxacin, enoxacin, fleroxacin, ciprofloxacin, lomefloxacin, trovafloxacin, grepafloxacin, ofloxacin and levofloxacin;
- the second type of fluoroquinolones which inhibit mainly the DNA-gyrase (nadifloxacin and sparfloxacin);
- the third type of fluoroquinolones which have a double effect: they inhibit both topoisomerase IV and DNA-gyrase: gatifloxacin, pazufloxacin, moxyfloxacin, and clinafloxacin.

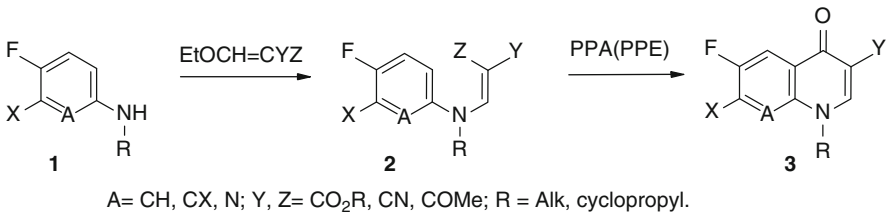
An important feature of fluoroquinolones is their selective biological action: suppressing bacterial DNA-gyrase, they don't influence the mammalian DNA cell processes. In fact, quinolones don't kill bacteria by inhibiting critical cellular processes, but rather break action of two essential enzymes, DNA-gyrase and topoisomerase IV, and use them by causing a rupture of two-spiral DNA.

During the last two decades the whole series of antibacterial fluoroquinolones have found their application in clinical practice, thus demonstrating a beginning of a new era in chemotherapy of bacterial infections. The vast majority of fluoroquinolones, launched into medical practice, are based on the bicyclic structure of 6-fluoro-4-oxo-1,4-dihydroquinolin-3-carboxylic acid. Annelation of the benzene ring, and carbo- or heterocyclic fragments to the quinolone skeleton usually allow one to enhance antibacterial activity of fused fluoroquinolones and their therapeutical properties; in some cases derivatives of this class become capable of exhibiting other types of activity, including antiviral and antineoplastic ones. The most known representatives of tricyclic fluoroquinolones appear to be ofloxacin and levofloxacin. For many years fluoroquinolones have been intensively studied worldwide as evidenced by numerous review articles and monographs [1–13].

2 Synthesis and Antibacterial Activity of Fluoroquinolones

2.1 Bicyclic Fluoroquinolones

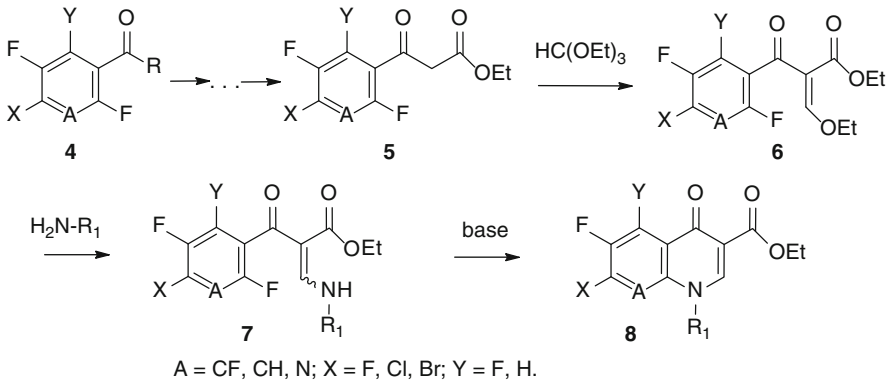
There are two basic approaches which are commonly used for the synthesis of quinolin-4-one-3-carboxylic acids [4, 14]. The first one is based on use of fluorinated anilines (**1**, A = CH, CF) or 2-aminopyridines (**1**, A = N) as starting materials and involves their condensation with ethoxymethylene derivative of malonate, cyanoacetate or acetoacetate to form enamines **2**. The intramolecular cyclization of compounds **2** with polyphosphoric acid (PPA) (the Gould-Jacobs reaction) affords the corresponding fluoroquinolones (**3**, A = CH, CF) or naphthyridones (**3**, A = N) (Scheme 2).



Scheme 2 Synthesis of fluoroquinolones from fluorinated anilines

One of the key problems of the Gould-Jacobs reaction is a choice of high-boiling solvent. Diphenyl ether which has been applied for a long time is not appropriate due to environmental reasons. A good alternative of Ph_2O seems to be a summer diesel fuel, which is cheaper than individual C_{12}-C_{18} hydrocarbons, and allows one to carry out the process at 230–245 °C providing a good purity of the key intermediates in the synthesis of fluoroquinolones.

The second approach suggests use of fluorine-containing benzoyl derivatives (**4**, A = CF, CH) or their nicotinoyl analogs (**4**, A = N) as building-blocks (Scheme 3). The key intermediates in this case are benzoyl- or pyridinoyl acrylates **6** [6]. Cyclization of enaminones **7** can be carried out by heating in DMF in the presence



Scheme 3 Synthesis of fluoroquinolones from fluorinated benzoyl derivatives

of potassium carbonate, or in ethyl acetate with NaH. Other basic conditions can also be applied, including organic amines or amidines, 1,4-diazabicyclo[2.2.2]-octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [4, 15].

The method can be improved by use of the dimethylamino analogue of intermediate **7**, which can be derived from the reaction of ethyl 3-dimethyl aminoacrylate with the corresponding fluorine-containing benzoyl chlorides followed by the displacement of the dimethylamino group with a suitable amine.

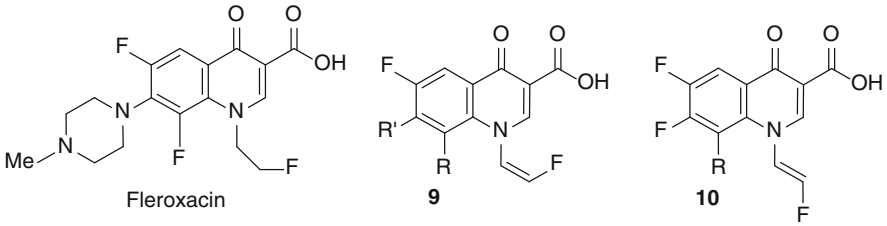
A great deal of research studies aimed at improvement of synthetic procedures leading to fluoroquinolones, enhancing their yields and quality of products, and reducing a number of steps and cost of the synthesis have been performed [16–31]. Improved synthetic procedures have been applied to obtain 1-ethyl-6-fluoro-7-(4-methylpiperazinyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid and 1-ethyl-6-fluoro-7-(piperazinyl-1)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid as well as their intermediates [18–21]. Further research studies on the synthesis of more active bicyclic fluoro-quinolones to expand a range of their biological activity, and to develop antibacterial drugs against resistant strains are in progress now.

2.1.1 Modification of the Position N(1)

The nitrogen atom N-1 and N-substituents are important features of the molecule of fluoroquinolones because of their considerable contribution into antibacterial activity. Replacement of the nitrogen atom with a carbon or oxygen in analogues of the oxolinic acid results in complete deactivation of these molecules. Modification of NH fluoroquinolones is usually based on N-alkylation reaction with the corresponding alkyl halide in the presence of a base. The first representatives of commercial fluoroquinolones bearing the ethyl group at N(1) are presented by norfloxacin, pefloxacin, and enoxacin; fleroxacin has N-fluoroethyl substituent, while amifloxacin contains the N-methylamino group. Research study on activity of the series of analogues of enoxacin, bearing C_1-C_5 aliphatic groups at N(1) have shown the preference of the N-ethyl group [32].

Modification of the N-ethyl group by means of incorporation of a fluorine atom (CH_2CH_2F, fleroxacin) appeared to be a reasonable approach [33]. Also

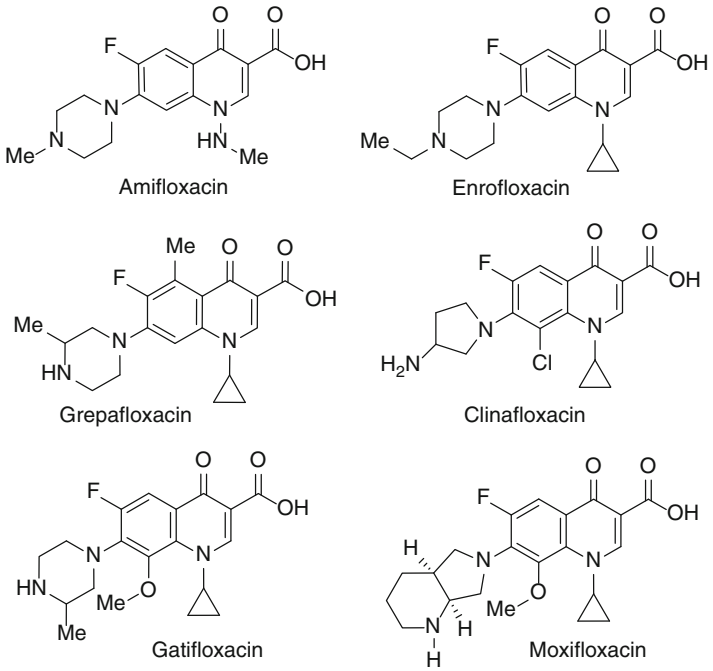
conformationally restricted analogs of fleroxacin **9** and **10** have been synthesized (Scheme 4). The *Z*-isomers proved to be 2–32-fold more potent *in vitro* against gram-positive strains of bacteria then the corresponding *E*-isomers [34].



Scheme 4 Structure of fleroxacin and analogs

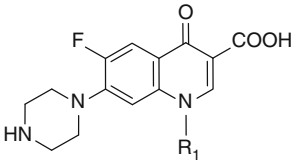
Replacement of N-ethyl group with $NHCH_3$ leads to a highly effective drug amifloxacin. Although it has not exhibited *in vitro* tests a considerable advantage in comparison with norfloxacin and pefloxacin, it shows a better pharmacokinetic profile, being equally active in both oral and parenteral administration.

It has been revealed that a high antibacterial activity of fluoroquinolones is associated with the presence of a small lipophilic group, such as, for instance, N-cyclopropyl substituent in position 1. Indeed, a number of commercially important fluoroquinolones bear the cyclopropyl fragment at N(1): ciprofloxacin, enrofloxacin, grepafloxacin, clinafloxacin, gatifloxacin, moxifloxacin (Scheme 5) [7].



Scheme 5 Structure of amifloxacin and 1-cyclopropyl-fluoroquinolones

Table 1 Activity of N(1)-substituted fluoroquinolones (MIC, μg/ml)

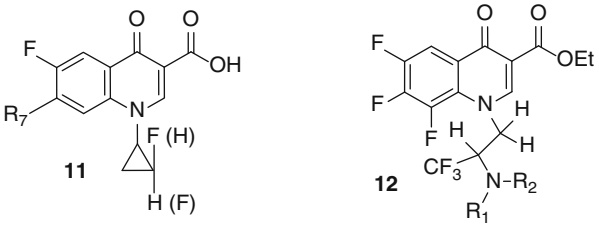


R_1	*St. aur.* A9537	*E. coli* A15119	*Ps. aer.* A 9843
Cyclopropyl (*ciprofloxacin*)	0.13	0.03	0.13
2-methylcyclopropyl (*trans*)	1	0.06	2
2-methylcyclopropyl (*cis*)	0.13	0.13	1
2,2-methylcyclopropyl	1	1	32
1-methylcyclopropyl	0.25	0.06	0.5
1-phenylcyclopropyl	0.13	0.13	4
Cyclobutyl	0.5	0.13	1

Incorporation of methyl or phenyl substituents in the cyclopropane ring, as well as the replacement of the cyclopropyl moiety with cyclobutyl or cyclopentyl ones diminishes the activity of these derivatives (Table 1) [7].

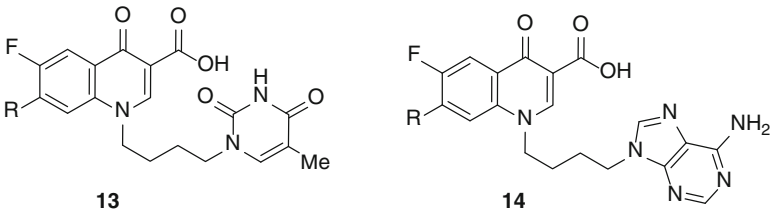
Further modification of the cyclopropyl fragment (for example, 2-fluorocyclopropyl derivatives **11**) gives rise to optically active isomers, which differ considerably in their activities, as illustrated by the fact that *cis*-analogs are more active against gram-positive strains of bacteria, than the corresponding *trans-isomers*, for example, *cis*-isomer of fluoroquinolone **11** (R_7 = 4-methyl-piperazin-1-yl) shows MIC 0,1 μg/ml against *St. aur.,* while *trans*-isomer has only 1,56 μg/ml. New synthetic approaches enabling one to introduce at N-1 of fluoroquinolones a fluorine-containing cyclopropyl fragment with a certain stereo-configuration have been developed [35, 36].

Incorporation of benzyl or *t*-butyl groups at N-1 enhances antibacterial activity of fluoroquinolones [37, 38]. Monofluoro-*t*-butyl derivatives proved to possess a higher antibacterial activity than their non-fluorinated analogs. An opportunity to use 1-trifluoromethyl-1,2-ethylenediamines for modification of position 1 of fluoroquinolones (compounds **12**) (Scheme 6) [39] has been shown.



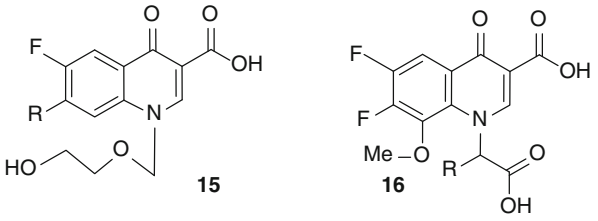
Scheme 6 Structure of fluoroquinolones **11** and **12**

Derivatives of bicyclic pefloxacin **13** and **14** represent an interesting type of hybrid molecules, in which N-butylfluoroquinolone fragments are linked with the pyrimidine and purine heterocyclic bases (Scheme 7) [40].



Scheme 7 Structure of fluoroquinolones **13** and **14**

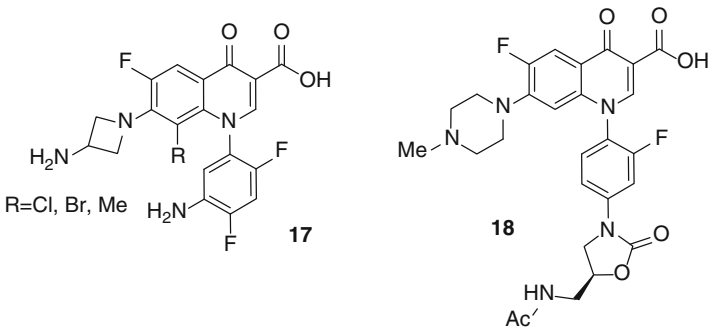
Fluoroquinolones **15** bearing the (hydroxyethoxy)methyl fragment, which is present in acyclovir, the known antiviral agent, can be regarded as acyclic analogs of nucleosides (Scheme 8) [41]. Also 5′-thioalkyl acyclic nucleosides of fluoroquinolones have been obtained by the reaction of mesylate **15** with methanethiolate- or thiophenolate anions [42].



Scheme 8 Structure of fluoroquinolones **15** and **16**

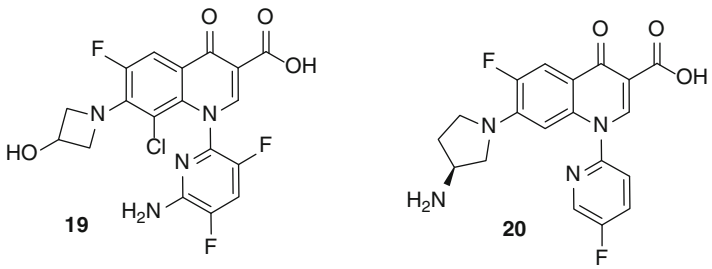
A series of new quinolones **16** bearing the fragments of natural amino acids have been synthesized. According to the data of preliminary biological studies these fluoroquinolones exhibit antibacterial activity against *Bacillus subtilis* and *Staphylococus aureus* [43].

Synthetic routes to new fluoroquinolones, containing in position 1 aryl substituent have also been described [44–46]. As a rule, a fluorophenyl substituent with one or two fluorine atoms has a favorable effect, increasing an activity of fluoroquinolones towards anaerobic bacteria. It has been found that 1-(5-amino-2,4-difluorophenyl)-8-R-substituted quinolones **17** possess a rather high antibacterial activity relative to Gram-positive and Gram-negative microorganisms (Scheme 9) [47]. 7-(Methylpiperazinyl)-6-fluoro-1-(4-fluorophenyl)-1,4-dihydro-4-oxo-3-quinolincarboxylic acids (difloxacin) has been established to be one of the most active fluoroquinolones in experiments *in vitro* against *Chlamydia trachomatis* and other intracellular parasites; also it demonstrates excellent pharmacokinetic properties. Also, the antibacterial drug linezolid **18** bearing at N-1 2-fluoro-(4-oxazolidon-1-yl)phenyl fragment has been developed [48] (Scheme 9). N-(5-Amino-2,4-difluorophenyl)-7-aminoazetidinyl-8-chloro-substituted fluoroquinolone has been found to possess a high antibacterial activity relative to Gram-positive and Gram-negative microorganisms; its activity against *Strentococcus pneumoniae* proved to be 30-fold higher than that of trovafloxacin.



Scheme 9 Structure of fluoroquinolones **17** and **18**

A number of researches were dedicated to incorporating of heterocyclic fragments in position 1 of fluoroquinolones in expectation of enhanced activity [49]. Indeed, 1-(6-amino-3,5-difluoropyridin-2-yl) substituted quinolone **19** (Scheme 10) proved to be rather promising for treatment of serious respiratory diseases and infections of the urinary tract. This fluoroquinolone has a wide range of antibacterial activity, including quinolone-sensitive and resistant staphylococcus and streptococcus, vancomicin-sensitive and resistant enterococcus, anaerobic bacteria and other infections [50], **20** was shown to be more active than ciprofloxacin [51] (Scheme 10).



Scheme 10 Structure of fluoroquinolones **19** and **20**

1-Trifluoromethylated fluoroquinolone shows antibacterial activity at the level of norfloxacin [52]. 1-Hydroxy-2-phenyl- and 1-hydroxy-2-methyl substituted quinolones have been obtained, however they have not shown a remarkable level of antibacterial activity [53, 54].

Analysis of the data of biological trials for N-substituted fluoroquinolones available in literature enables to conclude that compounds bearing in position 1 cyclopropyl, fluorophenyl or *t*-butyl fragments exhibit a higher level of antibacterial activity than their N-unsubstituted analogues.

2.1.2 Modification of the Position C(2)

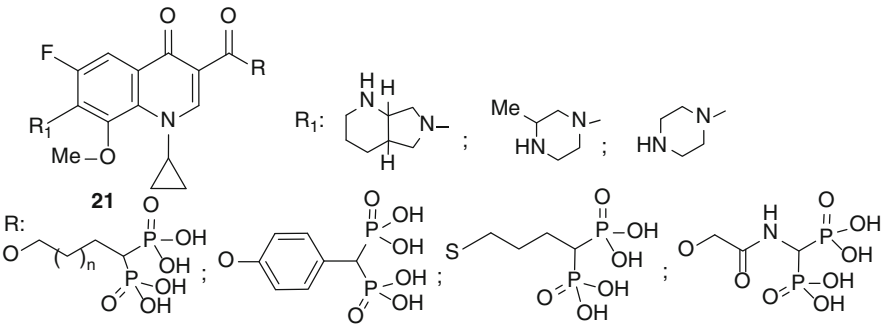
Modifications of the C(2)-position are limited due to synthetic difficulties associated with direct introduction substituents at C-2. However, the synthesis of 2-phenylsubstituted fluoroquinolones has been developed [55], and 6-fluoro-quinolon-2-carboxylic acids have been obtained by cyclization of the corresponding 2-amino-substituted 3-pentafluorobenzoyl acrylic acids [56]. 2-Thio substituted quinolones are widely used for the synthesis [*a*]- or [*b*]-annelated fluoroquinolones, such as thiazolo- and azethydinoquinolones [57–59]. Synthesis of 1-cyclopropyl-2-alkylthio-8-methoxyfluoroquinolones was described; however elucidation of their antibacterial activity revealed no regularities associated with incorporation of 2-alkylthio substituents [60]. All known 2-aza analogues of quinolones and naphthyridines, derivatives of cinnoline, have not exhibited any remarkable antibacterial activity.

2.1.3 Modification of the 3-Carboxyl Group

Modifications of the 3-carboxyl group appear to be worth only in those cases where these derivatives are considered as precursors of the corresponding carboxylic acids [61], however precursors not always exhibit activity *in vivo*. Replacement of the 3-carboxyl group with acyl, ethoxycarbonyl, methoxycarbonyl and other acidic fragments (hydroxamic, acetic, phosphonic, sulphinic or sulpho) results in complete loss or diminishes dramatically antibacterial activity of these compounds.

Functional properties of the carboxyl group have been used to modify it with osteofilic bisphosphonate fragments, as exemplified by structural modifications of moxi-, gati- and ciprofloxacin are developed [62]. Derivatives of these fluoroquinolones **21**, containing bisphosphonate ester, thioester or amide groups have been obtained (Scheme 11). Their abilities to contact bones and to recycle thus active medicinal component have been studied. It has been shown that bisphosphonate derivatives of fluoroquinolones are osteotropic predecessors for prevention of osteomielit.

Amides, hydrazides, and thiourea derivatives are important derivatives of fluoroquinolones [63–65]. It is worth noting that 7-chloroquinolones bearing



Scheme 11 Structure of fluoroquinolones **21**

the amide moiety at C-3 are rather active against *B. subtilis* and *S. aureus*. Also phenylthiourea derivatives proved to be more active against *B. subtilis* than the parent ciprofloxacin [64]. Synthesis of glycosylhydrazides and aminoacids on the basis of the corresponding hydrazido- and azido derivatives of 6-fluoroquinolin-4-one-3-carboxylic acids has been described [66].

Esters and hydrazides of 6-fluoroquinoline-4-oxo-3-carboxylic acids have been used for modification of the position 3 through the formation of heterocyclic fragments, such as oxadiazole, triazole, thiadiazole, benzofuropyrazoline, thiazolidine and others [67, 68]. Synthesis of fluoroquinolones containing in position 3 quinoxalinone, benzoxazinone and benzothiazinone fragments has recently been described [69, 70]. This synthesis was realized through interaction of fluoroquinolones bearing EtOC(O)C(O) residue with aromatic 1,2-binucleophiles. 3-Formyl- and acetyl derivatives of fluoroquinolones and also alcohols and amines have been obtained through transformation of amides [71].

It has been established that after oral administration of 3-formyl analogue of norfloxacin in mice the formyl group is metabolized rather fast into the carboxyl one, thus converting 3-formyl derivatives into norfloxacin. Due to a good solubility, a much higher level (at least two times) of the formyl derivative in blood serum can be reached, than on administration of norfloxacin, which at physiological pH values exists in the form of poor soluble zwitter-ionic form.

During the last two decades a lot of attention has been paid to development of "double mechanism" antibiotics. One of plausible approaches to such compounds is esterification of fluoroquinolone carboxylic acids with derivatives of cephalosporin and penicillin. Such combination allows one to expand a spectrum of antibacterial activity of beta-lactams conjugated with quinolones due to complementary mechanisms of their actions [7, 72].

Displacement of the carboxyl group in position 3 with hydrogen atom and the decarboxylation of fluoroquinolones have been discussed in the literature [73–76]. Since no decarboxylated fluoroquinolones have exhibited antibacterial activity, many authors have come to conclusion on the extremely importance of the 3-carboxy group.

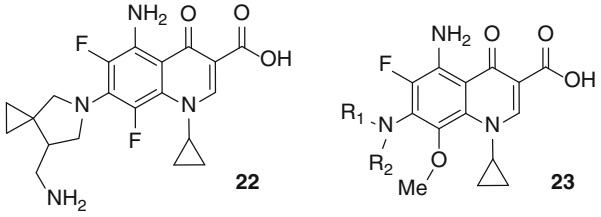
2.1.4 Modification of the 4-Oxo Group

The oxo group can be modified through the formation of oximes, hydrazones, and semicarbazones, as exemplified by transformations of norfloxacin and other fluoroquinolones [73]. Specific methods are needed to convert fluoroquinolones into their 4-alkoxy analogues, due to a preferable N-alkylation of fluoroquinolones at position 1. Another modification is the synthesis of 4*H*-1,4-benzothiazin-1-oxides and 1,1-dioxides [77] with various substituents in the benzene ring. However, these compounds proved to exhibit neither antibacterial activity, nor they inhibit DNA-gyrase. These results show that SO and SO_2 groups in quinolones cannot be regarded as bioisosters of the carbonyl group.

It has to be concluded that the oxo group at C(4) is necessary for linkage of quinolones with DNA-gyrase, and elimination or replacement of the oxo fragment with other moieties lead to inactive compounds.

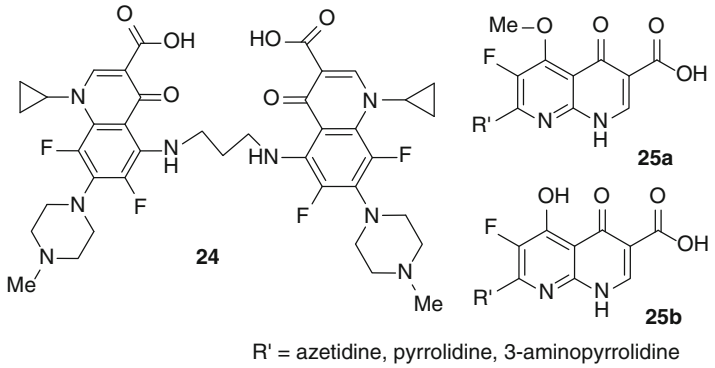
2.1.5 Modification of the Position C(5)

The most promising results have been received in those cases when the amino group was introduced at position 5 of fluoroquinolones. The detailed analysis of the "structure–activity" relationship for 5-substituted 1-cyclopropyl-6-fluoro-quinolones has shown that the positive effects of NH_2 and CH_3 groups are approximately identical, and these fluoroquinolones possess a wide range and high level of antibacterial activity [7]. Indeed, 7-(7-aminomethyl-5-azaspiro[2.4]heptan-5-yl)quinolone **22** proved to be 12 times more active against *S. aureus HPC527* than ciprofloxacin [78, 79]. The methoxy derivative **23**, and also its 8-methyl analogues show a high antibacterial activity towards a great deal of microorganisms [80] (Scheme 12). 5-Also acylaminoquinolones have been synthesized [81].



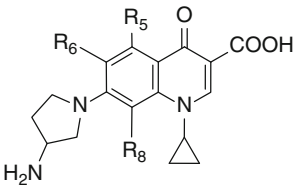
Scheme 12 Structure of 5-aminofluoroquinolones **22**, **23**

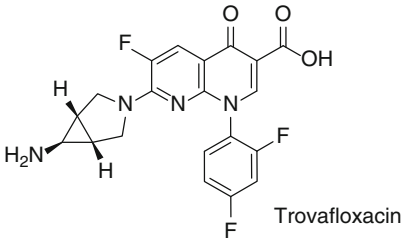
In order to obtain multi-binding therapeutic agents that modulate enzymatic processes, two fluoroquinolone ligands were linked at positions 5 through 1,3-diaminopropane bridge (compound **24**) [82]. Fluoroquinolones bearing the hydrazino group in position 5 appear to be effective antimicrobials towards a number of pathogenic microorganisms; also they possess a good solubility in water relative to other fluoroquinolones [83]. 5-Methoxy- and 5-hydroxy-6-fluoro-1,8-naphthyridin-4-oxo-3-carboxylic acids (**25a,b**) are more active against *S. pneumoniae 7257* than levofloxacin [84] (Scheme 13).



Scheme 13 Structure of fluoroquinolones **24**, **25**

Table 2 Antibacterial activity of mono- and difluoroquinolones (MIC, μg/ml)





Trovafloxacin

R^5	R^6	R^8	*St. aur.*	*E. coli*	*Ps. aer*
H	H	H	0.25	0.008	0.5
H	H	F	0.03	0.008	0.25
F	H	H	1	0.13	4
F	H	F	0.13	0.06	2
H	F	H	0.03	0.004	0.25
H	F	F	0.008	0.008	0.13

Incorporation of such substituents as Cl, Br, SH, SCH_3, CHO into position 5 of 1-cyclopropyl-6,8-difluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydro-3-quinolincarboxylic acids didn't result in substantial increase of their activity. Some substituents at C(5) have a negative effect on antibacterial activity of fluoroquinolones which can possibly be explained by steric hindrance to interaction of the 4-oxo-3-carboxy-fragment of fluoroquinolone molecules with metal ions of the bacterial DNA-gyrase. However, a fluorine atom at C-5 with nearly the same space volume as a hydrogen one also diminishes the activity of fluoroquinolones, and it can't be connected with its steric effect.

2.1.6 Modification of the Position C(6)

Replacement of a fluorine atom in position 6 with other substituents didn't enhance their activity, at the same time it was shown that in order to obtain highly active antibacterial compounds the presence of fluorine atom at C(6) is not obligatory, it is more important to have in the quinolone skeleton the N(1)-cyclopropyl and C(7)-3-aminopyrrolidinyl pharmacophoric groups (Table 2) [85–88].

Studies of antibacterial activity of 6-fluoro-1-[(*1R,2S*)-2-fluorocyclopropan-1-yl]-8-methoxyquinolones and their C(6)-defluoro analogs showed that all of them are in 4–520 times more active against gram-positive bacteria, than trova-, moxi-, gati- or ciprofloxacin [89]. These quinolones have shown the indices of activity against Gram-negative bacteria *E. coli* and *K. pneumoniae* which are comparable with those of trova- and ciprofloxacin.

Incorporation of the nitrogen atom (derivatives of 1,6-naphthiridines) proved to diminish considerably the activity of quinolones.

2.1.7 Modification of the Position C(7)

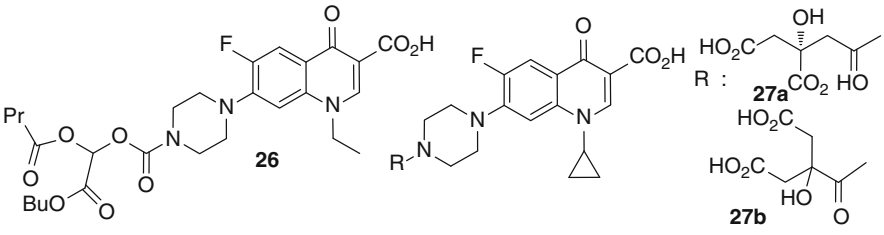
A great deal on the chemistry of 6-fluoroquinolones concerns modification of the position 7. It is due to the fact that a halogen atom at C(7) undergoes easily nucleophilic displacement with N-, S-, O- and C-nucleophiles, thus allowing one to vary the structure of quinolones. Nearly all commercially important fluoroquinolones contain at C-7 the fragments of cycloalkylimines [90–94].

Quinolones bearing in position 7 small or linear substituents, such as H, OH, OEt, COOH, Cl, Me, NH_2, NHR, NH-c-C_3H_5, $NHNH_2$, $SCH_2CH_2NH_2$ etc., have a relatively low activity against gram-positive microorganisms and are practically inactive towards the negative bacteria. Also 7-aza analogues of 6-fluoroquinolon-3-carboxylic acids, derivatives of 1,7-naphthyridines, didn't show any remarkable antibacterial activity.

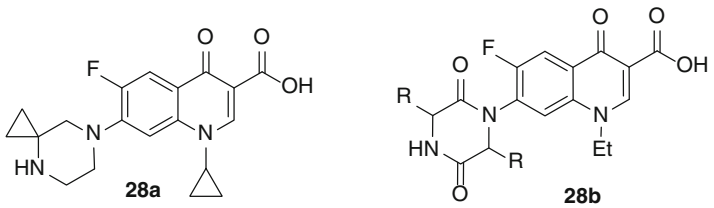
A lot of studies have been directed to the synthesis of fluoroquinolones, bearing a variety of piperazinyl substituents, since this part of quinolone molecule is of significant importance. Indeed, some representatives of 6-fluoroquinolones bearing at C(7) piperazine (norfloxacin, ciprofloxacin), 4-methylpiperazine (pefloxacin), 3-methylpiperazin (lomefloxacin, temafloxacin) proved to possess a much broader range of antibacterial activity, than those without the piperazine moiety, such as nalidixic and oxolinic acids.

In order to introduce the piperazine residue into position 7 of fluoroquinolones the reaction of 7-chloroquinolone with N-alkoxycarbonylpiperazine in high-boiling dipolar aprotic solvent followed by hydrolysis of alkoxycarbonyl group has been exploited. In some cases the borondiacetate complexes of fluoroquinolones have also been used for introduction of the piperazine fragment.

The difference in activity for *R*- and *S*-enantiomers of 7-(3-methylpiperazin-1-yl)quinolones, obtained from the corresponding (*R*)- and (*S*)-*t*-butyl-2-methylpiperazin-1-carboxylates, proved to be in the range from 2 to 64 folds in 52 % of cases [95]. In order to improve transport through biological membranes the piperazine moiety in norfloxacin was modified considerably and compound **26** was obtained [96]. To clarify the mechanism of antibacterial action of fluoroquinolones at the cellular level, two regioisomeric citrate-functionalized derivatives of ciprofloxacin **27a,b** [97] (Scheme 14) have been obtained and studied.



Scheme 14 Structure of fluoroquinolones **26**, **27**

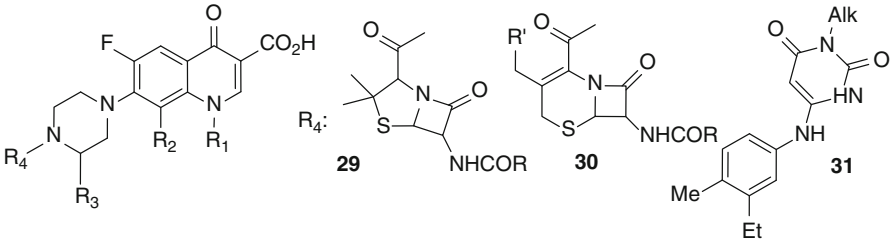


Scheme 15 Structure of fluoroquinolones **28**

Introduction of spiropiperazine or piperazinedione groups in position 7 of 1-cyclopropyl substituted fluoroquinolones has been shown to enhance their antimicrobial activity (compounds **28a,b**) (Scheme 15) [98, 99].

Also the piperazine fragment of fluoroquinolones was modified by introduction of a number of heterocyclic fragments, such as 2,6-diaminopyrimidinyl, 4,6-diamino-1,3,5-triazinyl, 2-aminothiazinyl, 1,3,4-thiadiazolyl, 2-furyl and other groups, thus allowing one to obtain more active antibacterial drugs [100–103].

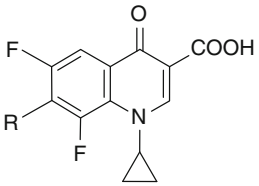
Hybrid derivatives of fluoroquinolones bearing fragments of penicillin and cephalosporin antibiotics or uracils, for example compounds **29–31**, proved to possess a wide spectrum and high level of antibacterial activity, including their potency against resistant to β-lactams strains [74, 104–107] (Scheme 16). High antibacterial activity has also been shown by 7-(N-aryl-2,2,2-trifluoroacetimidoyl)piperazinyl derivatives of fluoroquinolones [108].



Scheme 16 Structure of fluoroquinolones **29–31**

Influence of the second heteroatom in the piperazine ring is not so unequivocal. For instance, the replacement N(4) in the piperazine moiety of amifloxacin with O, S or CH_2 fragments has been shown to diminish activity of these compounds *in vitro* and *in vivo*, however when the piperazine residue in norfloxacin was replaced with thiomorpholine a much more potent compound against Gram-positive bacteria has been obtained. 7-(3-Aminomorpholin-1-yl) and 7-[3-(or 4)-aminomethylpiperidin-1-yl]-derivatives proved also to possess a high activity against St. aur. (Table 3). 7-Azetidinyl substituted fluoroquinolones, in particular *trans*-3-amino-2-methyl-1-azetidinyl derivatives proved to be highly active antibacterial compounds [84, 109, 110].

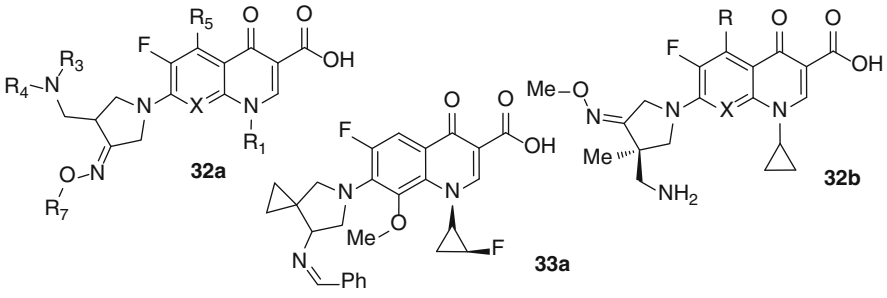
Table 3 Antibacterial activity of 7-substituted fluoroquinolones (MIC, μg/ml)



R	*St.aur.*	*E. coli*	*Ps.aer.*
Piperazin-1-yl	0.10	0.006	0.10
Piperidin-1-yl	0.78	3.13	50
Morpholin-1-yl	0.025	0.10	0.78
3-Aminomorpholin-1-yl	0.025	0.10	0.78
3-Methylaminomorpholin-1-yl	0.025	0.10	3.13
3-Acetylaminomorpholin-1-yl	0.20	1.56	12.5

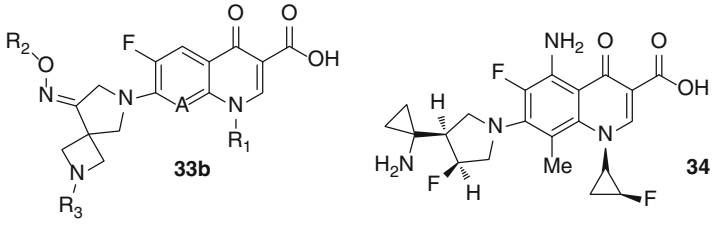
A large group of highly active fluoroquinolones contains the pyrrolidine fragment in position 7, and, therefore, a considerable attention has been paid to the synthesis of 6-fluoro-7-pyrrololidinoquinolones with 3-amino-, 3-aminomethyl- or 3-(2-cyanomethylamino) substituents in the pyrrolidine ring [111–114]. As a rule, the compounds of this series possess a much higher activity towards Gram-positive microorganisms than the corresponding piperazine derivatives.

Fluoroquinolones **32a**, containing alkyloximino substituent at C-4 and the aminomethyl fragment at position 3 of the pyrrolidine ring, exhibit a high antibacterial activity towards Gram-positive and Gram-negative microorganisms, including a methicillin-resistant strain of *S. aureus* (MRSA) [115–118]. Compounds **32b** having an optically active center in the pyrrolidine ring and the methyloximino group proved to possess not only high antibacterial activity, but also a good pharmacokinetic profile [119, 120]. Also, the series of fluoroquinolones, containing spiropyrrolidine substituents at C-7, for example, compound **33a**, have been obtained (Scheme 17) [121, 122].



Scheme 17 Structure of fluoroquinolones **32, 33a**

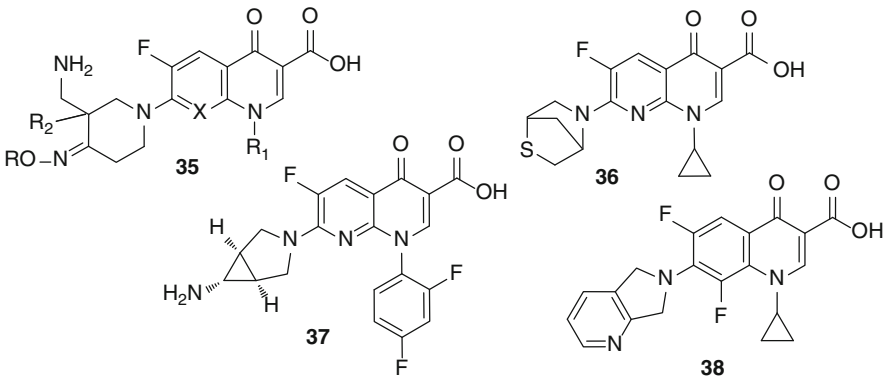
Effects of the chiral fragments, such as 1-(*cis*-2-fluorocyclopropyl) and 7-(7-amino-5-azaspiro[2.4]heptyl) substituents (compounds **32b, 33a**) on antibacterial properties of the series of fluoroquinolones have been studied (Scheme 18) [123]. It has been shown that derivatives of 1-[(*1R,2S*)-2-fluorocyclopropyl]- and 7-[(*7S*)-amino-5-azaspiro[2.4]heptyl]-fluoroquinolones are more active towards a number of Gram-positive and Gram-negative bacteria, than other stereoisomers. The presence of spiropyrrolidine residue at C(7) of fluoroquinolones enhances their lipophilic properties, thus promoting a better assimilation on oral administration [98].



Scheme 18 Structure of fluoroquinolones **33b, 34**

Compounds **33b, 34** with the amino group attached to the spiropyrrolidine or cyclopropyl-substituted pyrrolidine fragment proved to exhibit broad spectrum of antibacterial activity (Scheme 18) [124–129]. Aminomethyl substituted pyrrolidines and their heterocyclic derivatives were incorporated into position 7 of fluoroquinolone [130–132]. Optically active derivatives of 7-(3-hydroxypyrrolidin-1-yl)-6-fluoroquinolones have been shown to be promising antibacterials [133–135].

One more residue which is frequently present in position 7 of active fluoroquinolones is piperidine [136–139]. Indeed, 1-cyclopropyl-6-fluoro-quinolones, containing (*3S*)-amino-(*4R*)-piperidinyl fragment in position 7, show a high activity towards resistant strains of *Staphylococus aureus* and *Streptococus pneumoniae* [140]. A number of substituents, such as 4-amino, 4-hydroxy, 3-aminomethyl, 4-aminomethyl and 3-methylamino were incorporated in the piperidinyl fragment [141, 142]. Novel 6-fluoroquinolones and naphthyridines with 4 (3)-alkoxyimino-3-aminomethyl-3-H(methyl)piperidinyl substituents, for instance **35**, have been obtained (Scheme 19) [143–145]. They shown a high activity against all gram-positive organisms, including those resistant to fluoroquinolones. One of compounds of this series proved to be in 16–128, 2–32 and 4–8 times more active against fluoroquinolone-resistant MSSA, MRSA and MRSE than gemi-, cipro- and levofloxacin, respectively. Introduction of 4-(1*H*-1,2,3-triazol-1-yl)piperidinyl residue in the structure of fluoroquinolone resulted in a good activity against *S. aureus* and *S. epidermidis* [146].

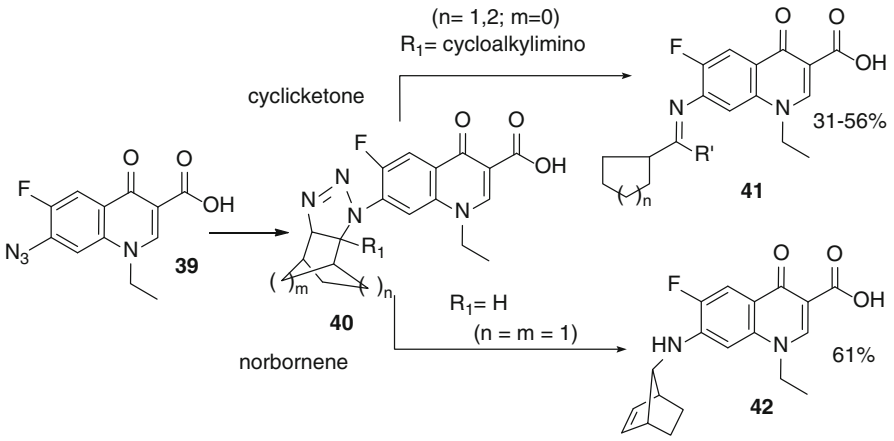


Scheme 19 Structure of fluoroquinolones **35**–**38**

A very promising modification of fluoroquinolones is introduction of bridged cyclic amines in position 7 [147–153]. A series new fluoroquinolones **36** was synthesized (Scheme 19), and one of compounds showed high activity against quinolone-sensitive and multi-resistant bacteria, especially towards *Streptococcus pneumonia* [154].

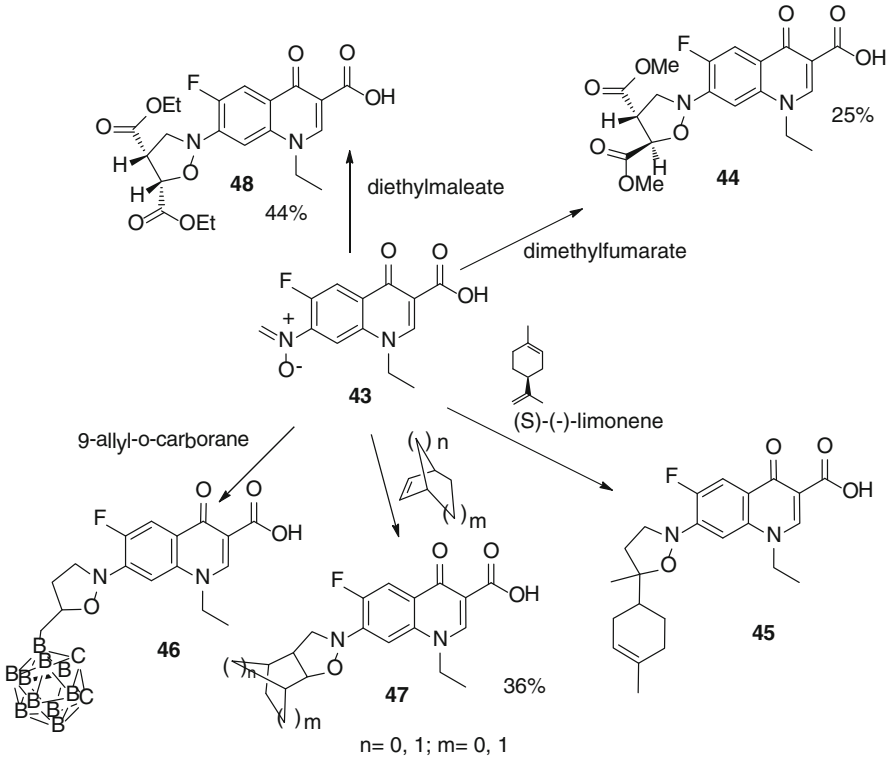
Trovafloxacin **37**, the very active compound with a wide spectrum of action, contains 7-(1α, 5α, 6α)-3-azabicyclo[3.1.0]hexyl substituent (Scheme 19) [155, 156]. 6-Fluoro-1-[(*1R, 2S*)-2-fluorocyclopropan-1-yl]-4-oxoquinolin-3-carboxylic acids, containing in position 7 2-amino-8-azabicyclo[4.3.0]nonan-8-yl fragment have been shown to inhibit bacterial DNA topoisomerase IV very effectively [157]. A great deal of research are dedicated to the synthesis and biological tests of 7-di- and triazabicyclononyl substituted 6,8-difluoroquinolones, for instance **38** (Scheme 19) [158–163].

An effective way for introduction of a variety of heterocyclic fragments in the position 7 of the fluoroquinolone skeleton is the methodology of 1,3-dipolar cycloaddition reactions [164–167]. Indeed, the reaction of 7-azido derivative of 6-fluoroquinolone **39** with enamines of cyclic ketones and norbornene proceeds rather smoothly with the formation of the corresponding *exo*-1,2,3-triazolines **40** which undergo the cationic rearrangements into amidines **41** or aminonorbornane **42** [164, 165]. 7-Azido derivatives **39** are capable of reacting with heterocyclic amines to form new 7- fluoroquinolones (Scheme 20) [168].



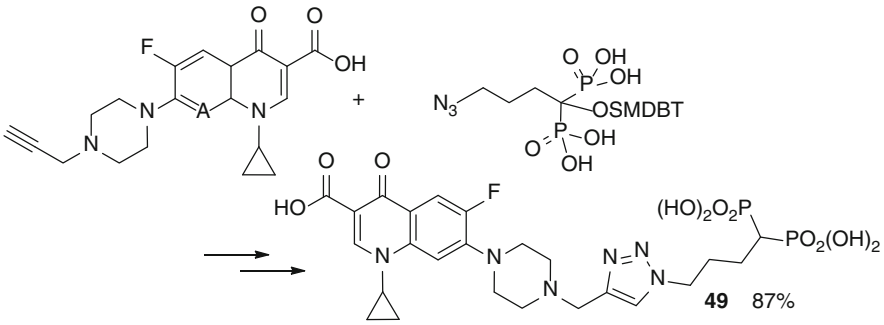
Scheme 20 1,3-Dipolar cycloaddition reactions of 7-azido derivative **39**

The cycloaddition reaction of azomethine **43** with alkenes proceeds in regio- and stereoselective manner and represents a convenient way to obtain a variety of stereoisomeric 7-isoxazolidinyl quinolones **44–48** [166, 167] (Scheme 21).



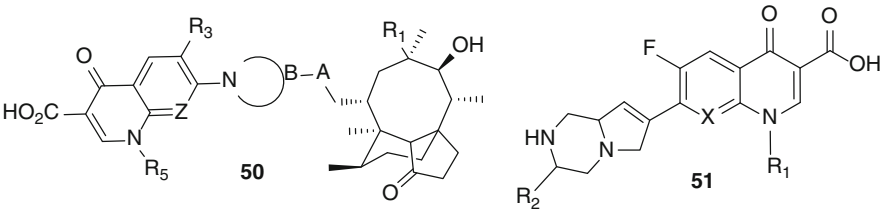
Scheme 21 The cycloaddition reactions of azomethine **43**

Synthesis of new hydroxybisphosphonate derivatives of ciprofloxacin **49** has been performed by using Cu-catalyzed 1,3-dipolar cycloaddition reaction between the corresponding azide and N-alkynyl substituted quinolone [169] (Scheme 22). Derivatives of gati- and moxifloxacin have been obtained similarly. All of these modified compounds maintained antibacterial activity of the starting quinolones and, in addition to that, exhibit osteotropic properties.



Scheme 22 Synthesis of fluoroquinolone **49**

A number of 6-fluoroquinoline- and 6-fluoronaphthyridine-3-carboxylic acids, containing at C(7) rather complicated fragment of multiline (compounds **50**) have been synthesized (Scheme 23) [170]. Quinolones **50** exhibit a high activity against resistant bacteria, in particular, methicillin- and quinolone-resistant *Staphylococcus, Streptococcus pneumoniae*, etc.



Scheme 23 Structure of fluoroquinolones **50**, **51**

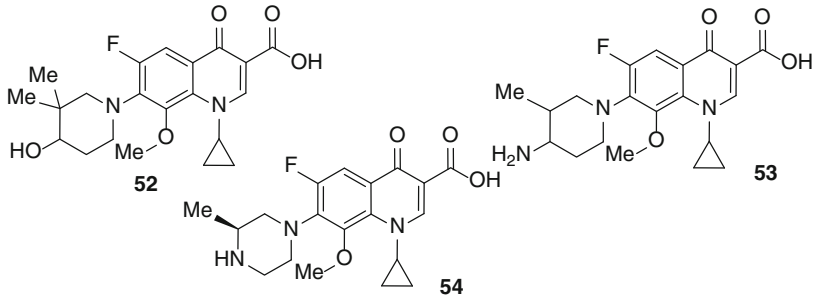
Synthesis on the basis of organoelement compounds play an important role for modification of position 7 in fluoroquinolones [171]. As mentioned above, fluoroquinolones, containing hetaryl residues in position 7 are promising for medicinal chemistry [172]. In particular, a number of highly active fluoroquinolones have been obtained on the basis of 7-nitromethyl derivatives [173, 174].

The 7-(1,2,3,4-tetrahydropirrolo[1,2-*a*]pyrazin-7-yl) fragment has been incorporated in the structure of quinoline and naphthiridine carboxylic acids **51** through the carbon-carbon bond formation by reacting 7-halogeno or tosyl-substituted quinolones with the corresponding borates (Scheme 23) [175]. It should be noted that several compounds of this series have exhibited a high activity against ciprofloxacin-resistant bacteria of *Streptococcus pneumoniae*.

Thus, varying substituents in position 7 provides a good platform for development of novel antibacterial drugs. New opportunities for modification of position 7 are associated with design of hybrid molecules, as illustrated, for instance, by the development of the double action drugs containing both a fluoroquinolone and β-lactam antibiotic fragments.

2.1.8 Modification of Position C(8)

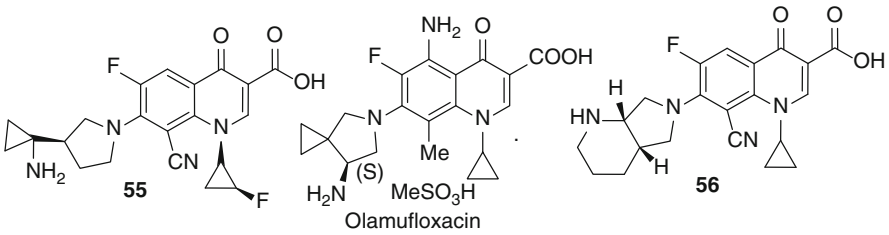
The nature of substituents in position 8 of fluoroquinolones also makes a certain impact on antibacterial activity. The key role of the 8-methoxy substituent is demonstrated by the fact that this fragment is a part of such effective drugs, as moxifloxacin and gatifloxacin [176–180]. Indeed, fluoroquinolone **52** shows a high activity against *H. influenza* and *M. catarrhalis* [181], while compound **53** is 4 times more active against *S. pneumoniae* than levofloxacin [182, 183]. 8-Methoxy-6-fluoroquinolone **54** has smaller side effects on the cardio-vascular system, than gatifloxacin (Scheme 24) [184].



Scheme 24 Structure of fluoroquinolones **52**–**54**

Fluoroquinolones, containing 8-methyl substituent usually demonstrate a high antibacterial activity, e.g. olamufloxacin is of great importance for treatment of urological diseases [185–188]. Also the cyano group in position 8 proved to be an appropriate substituent, as illustrated by the synthesis of 8-cyanoquinolones **55** and **56** [189] (Scheme 25). Indeed, compound **55** has been shown to possess a high antibacterial activity towards Gram-positive and Gram-negative bacteria [193], while 8-cyanoquinolone **56**, containing the diazobicyclononane residue in position 7 is more active antibacterial compound than enrofloxacin (Scheme 25) [190].

Substituents NO_2, NH_2, SCH_3, CF_3 in position 8 have usually a negative impact on both *in vitro* and *in vivo* activities, especially towards Gram-negative microorganisms.

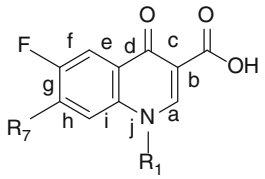


Scheme 25 Structure of olamufloxacin and fluoroquinolones **55**, **56**

In order to obtain "structure-biological activity" relationships mathematic methods have been used [191–193]. Quantitative correlations between molecular structure and pharmacokinetic and pharmacodynamic characteristics of fluoroquinolones in combination with informative hemometric approach have been used to forecast anti-pneumococcus activity [194]. Elucidation of the structure – activity relationships in the series of fluoroquinolones is the subject of numerous publications [195–197]. Dependence of antibacterial activity on the nature of substituents has been established for several series of bicyclic fluoroquinolones [11, 198–200].

2.2 Polycyclic Fluoroquinolones

Modification of fluoroquinolones by annelation of carbo- or heterocyclic rings leads to fused polycyclic systems (Scheme 26).

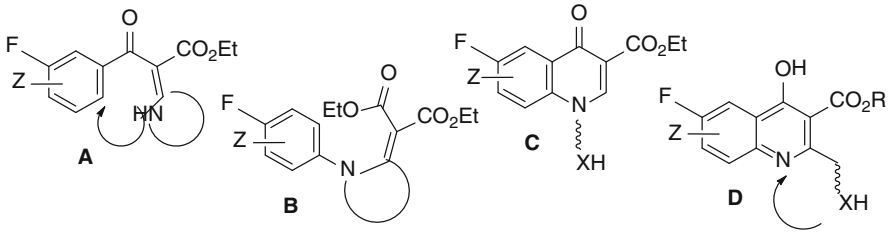


Scheme 26 Possible locations of additional rings in polycyclic fluoroquinolones

2.2.1 [*a*]-Annelated Fluoroquinolones

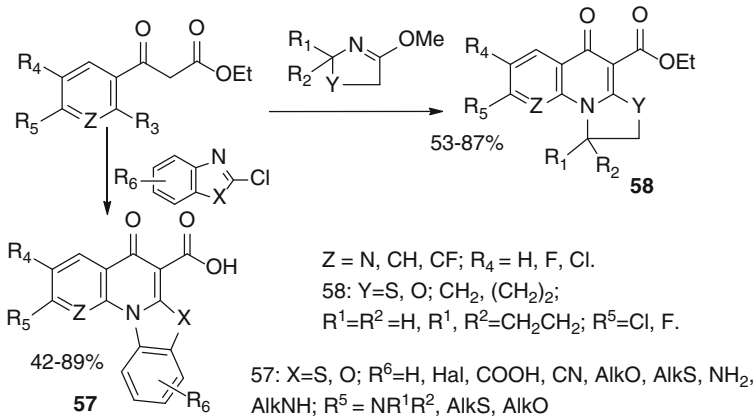
There are two principal approaches to the synthesis of [*a*]-annelated fluoroquinolones. The first one suggests that an [*a*]-annelated ring is already involved in the structure of intermediates, such as aminoacrylates A or malonates B, followed

by their cyclization into the corresponding fluoroquinolones. The second approach is based on use of 1- or 2-substituted quinolones C or D, which undergo intramolecular [*a*]-fusion (Scheme 27) [10].



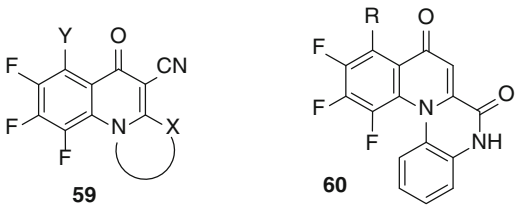
Scheme 27 Approaches to the synthesis of [*a*]-annelated fluoroquinolones

The first approach has been used to obtain [*a*]-annelated fluoroquinolones **57** and **58** from the correspondingly substituted ethyl acetates and 2-chlorobenzazoles or iminoesters (Scheme 28). 7-(1-Piperazinyl)- and 7-(4-methyl-1-piperazinyl)-benzothiazolo-[3,2-*a*]quinolones **57** have been established to exhibit rather good activity against a number of bacteria [201].



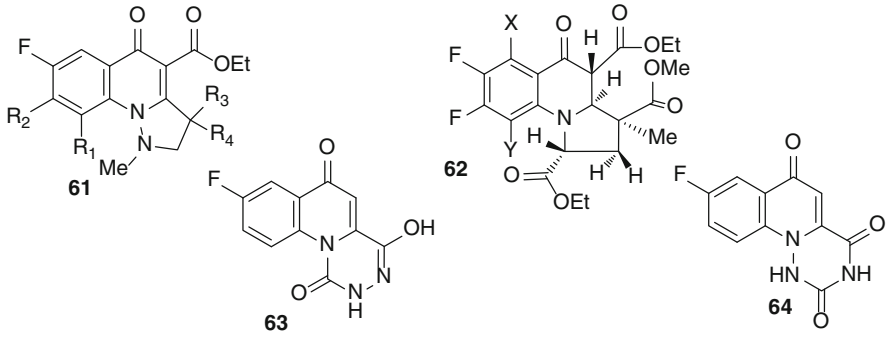
Scheme 28 Synthesis of azolo[*a*]quinolones

Synthetic routes to [*a*]-fused quinolones of general formula **59** from the corresponding polyfluorobenzoyl chlorides and α-azahetaryl acetonitriles have been developed [202]. Heterocyclization of quinoxalones, containing polyfluoroaroyl fragment in position 3 in DMSO in the presence of triethylamine affords **60** (Scheme 29) [203].



Scheme 29 Structure of fluoroquinolones **59**, **60**

The [*a*]-annelation in which the starting material is N-methylaminoquinolone has been described [204, 205]. Use of the 1,4-addition to the activated multiple bonds followed by the Michael intramolecular reaction leads to tetrahydropyrazolo[1,5-*a*] quinolones **61**, which are oxidized into the corresponding pyrazolo[1,5-*a*]quinolones. Hexahydropyrrolo[1,2-*a*]quinolones **62** can be regarded as [3+2] adducts derived from the reactions of N-(ethoxycarbonyl)methyl substituted ethyl esters of di-, three- and tetrafluoro-4-oxo-1,4-dihydroquinolin-3-carboxylic acids with methylmetacrylate (Scheme 30) [206].

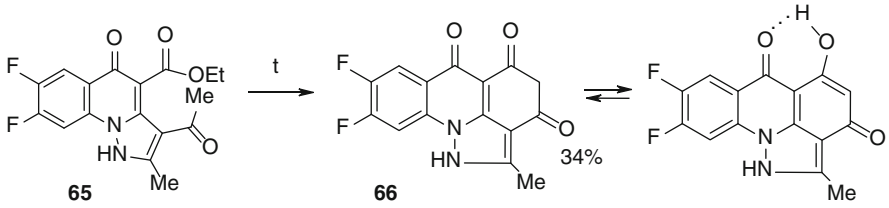


Scheme 30 Structure of fluoroquinolones **61**–**64**

Derivative of [1, 2, 4]triazino[1,6-*a*]quinoline **63** has been obtained from methyl 6-fluoro-4-oxo-1,4-dihydro-2-quinolincarboxylate through the N-amination followed by condensation of the corresponding aroyl isocyanate and cyclization of the obtained α-semicarbazidocarboxylate [207]. 8-Fluoro-4-hydroxy-*1H*-[1,2,4]-triazino[4,5-*a*]-quinolin-1,6(*2H*)-dione **64** has been obtained by condensation of 6-fluoro-4-oxo-1,4-dihydro-2-quinolinecarbohydrazide by action of phosgene [208]. 8-Fluoro-1,2-dihydro[1,4]oxazino[4,3-*a*]quinolin-4,6-dione was derived from intramolecular cyclization of 2-chloroethyl 6-fluoro-4-oxo-1,4-dihydro-2-quinolincarboxylate [209]. New tetracyclic system containing fluoroquinolone fragment **66** was obtained by intramolecular condensation of ethyl 3-acetyl-5-oxopyrazolo[1,5-*a*]quinolin-4-carboxylate **65** on heating [210] (Scheme 31).

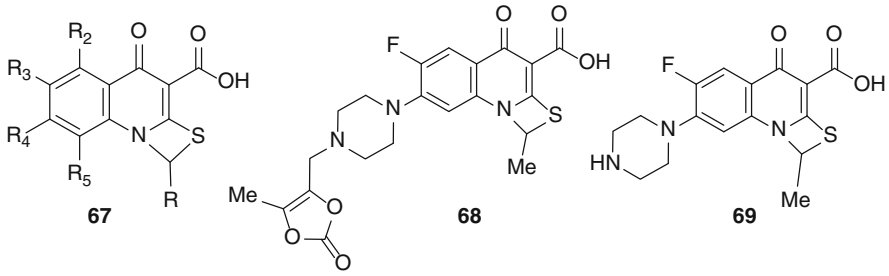
Table 4 Activity of **67** (R = Me, $R^2 = R^5 = H$, $R^3 = F$), MIC, μg/ml

R^4	*St. aur.*	*E. coli*	*Ps. aer.*
Piperazinyl	0.05	0.0125	0.2
4-Methylpiperazinyl	0.1	0.025	0.39
Morpholinyl	0.1	0.1	0.39
Thiomorpholinyl	0.025	0.2	0.39



Scheme 31 Synthesis of tetracyclic fluoroquinolone **66**

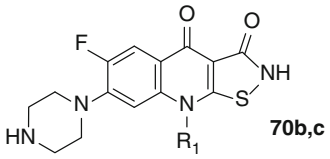
2-Mercapto-6-fluoroquinolin-3-carboxylic acids are considered as important intermediates in schemes leading to [*a*]-annelated fluoroquinolones, as shown by the synthesis of a number of thiazeto[*a*]quinolones **67** possessing a high level of antibacterial activity (Table 4) [211–213]. For instance, modification of position 7 of thiazeto[3,2-*a*]quinolones results in the formation of highly effective tricyclic antibacterials, such as prulifloxacin **68**, which is metabolized in organisms into ulifloxacin **69** (Scheme 32) [214–217]. It is worth noting that decarboxylation of ulifloxacin drops down the antibacterial activity in 60–12,000 times. A similar phenomenon has been observed in case of cipro- and moxifloxacin [60], thus showing an extremely important role of the carboxyl group. The synthesis of thiazolo[3,2-a]-, [1,3]benzothiazino[3,2-*a*]- and [1,3]benzothiazino[1,2-*a*]quinolin-6-carboxylic acids has also been reported [218, 219].



Scheme 32 Structure of thiazeto[*a*]quinolones **67–69**

It should be noted that [*a*]-annelation of additional rings through the reactions of1- or 2-substituted fluoroquinolones has certain restrictions, while cyclocondensation of fluorinated benzoyl chlorides with C,N-bifunctional nucleophiles appears

Table 5 Antibacterial activity of [*b*]-annelated fluoroquinolones (MIC, μg/ml)



70b,c

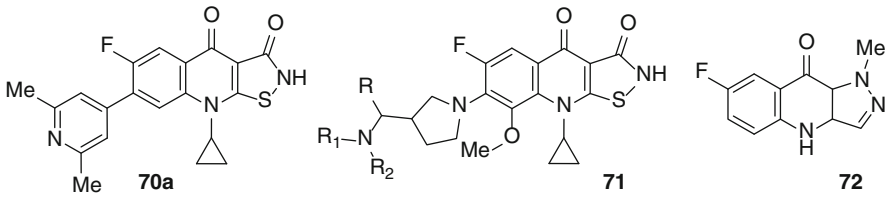
Compound	*St. aur.*	*E. coli*	*Ps. aer.*
70b (R^1 = ethyl)	0.02	0.005	0.05
Norfloxacin	0.20	0.01	0.1
70c (R^1 = cyclopropyl)	0.1	0.1	0.20
Ciprofloxacin	0.78	0.1	0.39

to be a more common method for the synthesis of a broad range of [*a*]-annelated fluoroquinolones. Incorporation of original bicyclic amines at position 7, as well as the synthesis of new derivatives through reactions of the carboxyl group are the main directions for modification of [*a*]-annelated fluoroquinolones.

2.2.2 [*b*]-Annelated Fluoroquinolones

The thesis concerning necessity of the carboxyl group in position 3 of fluoroquinolones to provide their antibacterial properties is not in agreement with the data on activity of [*b*]-annelated isothiazolo-, pyrido-, pyrimido- and pyrazinoquinolones which stimulated research studies of this group of compounds [7]. Indeed, a whole number of oxoisothiazolo[5,4-*b*]quinolones possessing a high antibacterial activity (Table 5), for instance compound **70a** and its analogues, have been obtained [220–224]. Also 9-cyclopropyl-6-fluoro-8-methoxy-7-(2-methylpyridin-4-yl)-9*H*-isothiazolo[5,4-*b*]-quinolin-3,4-dione has shown a high activity *in vitro* against methicillin-sensitive strains of *Staphylococcus aureus* (MRSA), high level of inhibiting of DNA-gyrase and topoisomerase IV of *S. aureus*, in combination with a neglect able effect on human topoisomerase II and low cytotoxicity [225, 226]. A series of 7-(3′-substituted) pyrrolidinyl-8-methoxyisothiazolo[*b*] quinolones **71** has been obtained and their antibacterial activity towards methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli*, including stereochemical aspects and influence of substituents, has been elucidated [226].

The synthesis of 1-methyl-1,4-dihydro-9H-pyrazolo[4,3-*b*]quinoline-9-one **72,** inhibitor of protein kinase C, has been performed by means of cyclization of 4-[(4-fluorophenyl)amino]-1-methyl-1H-pyrazole-5-carboxylic acid (Scheme 33) [227]. The main trends in development of research studies in the field of [*b*]-annelated fluoroquinolones are dealt with use of these compounds for the synthesis of novel [*i,j*]-annelated systems, a varying of substituents at C-7, and also with obtaining of new 2-substituted fluoroquinolones.



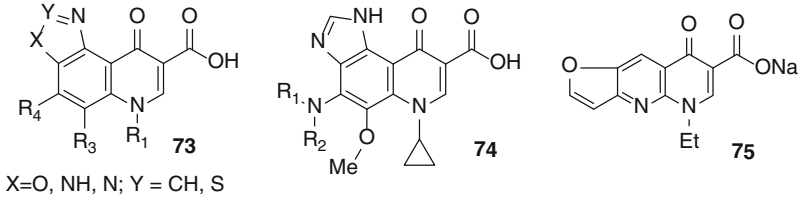
Scheme 33 Structure of [*b*]-annelated quinolones **70a-72**

2.2.3 [*c*]- and [*d,e*]-Annelated Fluoroquinolones

The targeted synthesis of these types of fused fluoroquinolones has never been carried out, since the oxo-group in position 4 which is responsible for linkage of fluoroquinolones with DNA gyrase has to be eliminated [7].

2.2.4 [*f*]- and [*g*]-Annelated Fluoroquinolones

Both [*f*], and [*g*]-annelation results in loss of fluorine atom in position 6 the presence of which has long been associated with a high level of antibacterial activity of fluoroquinolones. However, a number of highly active compounds have been revealed in the series of oxazolo-, thiazolo- and imidazo[4,5-*f*] fused fluoroquinolones. For instance, derivative **73** ($R^3 = R^4 = F$) has shown a good activity against both Gram-positive, and Gram-negative bacteria [228]. According to *in vitro* biological tests 5-methoxyimidazo[4,5-*f*]quinolones **74** exceeds in activity the corresponding analogs of ofloxacin [229]. Furonaphthyridine **75** has found application as the basis to obtain antibacterials (Scheme 34) [230].



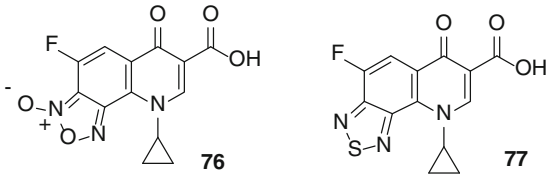
Scheme 34 Structure of [*f*]-and [*g*]-annelated fluoroquinolones **73–75**

2.2.5 [*h*]-Annelated Fluoroquinolones

6-Oxo-6,9-dihydro[1,2,5]oxadiazolo[3,2-*h*]quinolin-7-carboxylic acid **76** was synthesized from 7-azido-8-nitroquinolone [231]. A convenient method for the synthesis of 6-oxothiazolo[3,4-*h*]quinolin-7-carboxylic acids 77 has been suggested (Scheme 35) [232]. The structure of compounds **76** and **77** has been confirmed by X-ray crystallography. Biological tests of fluoroquinolone **77** have revealed that this compound possesses a high activity against Gram-positive *bacilli* and *staphylococci*, including methicillin-resistant strains, as well as Gram-negative bacteria (Table 6).

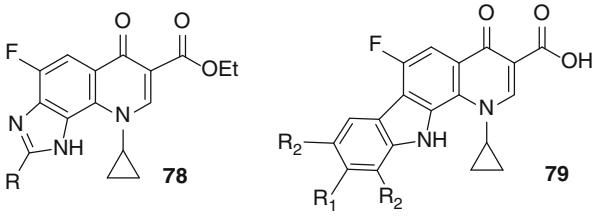
Table 6 Activity of **77** (MIC, μg/ml)

Compound	*Bacillus cereus*	*Bacillus subtilus ATCC 6633*	*Methicillin-resistant S. aureus*	*E. coli* ATCC8739
Ciprofloxacin	0.15	0.03	0.7	0.015
77	0.15	0.07	1.5	0.7



Scheme 35 Structure of [*h*]-annelated fluoroquinolones **76**, **77**

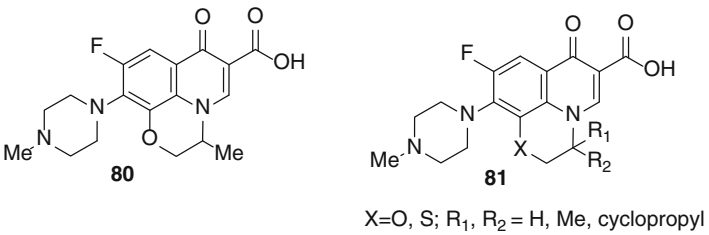
A series of ethyl 2-R(Ar)-9-cyclopropyl-4-fluoro-6-oxo-1H-imidazo[4,5-*h*] quinoline-7-carboxylates **78** have been obtained through cyclocondensations of the corresponding 7,8-diamino quinolones [233]. Also a number of tetracyclic [*h*]-annelated fluoroquinolones, such as 1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-pyrido[2,3-*a*]carbazole-3-carboxylic acids **79** and their thiene isosters have been obtained (Scheme 36) [198]. All derivatives proved to possess a high activity against *Bacillus subtilus* and *Staphylococci*.



Scheme 36 Structure of [*h*]-annelated fluoroquinolones **78**, **79**

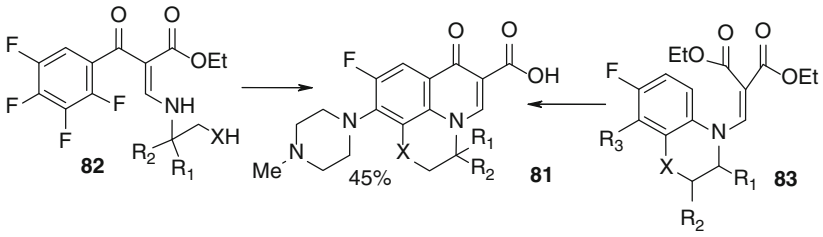
2.2.6 [*i,j*]-Annelated Fluoroquinolones

The most known representatives of tricyclic [*i,j*]-annelated fluoroquinolones are **ofloxacin 80** and its analogues **81** (Scheme 37) [234]. Ofloxacin is well-known to clinical physicians, since more than 15 years it has been applied in medical practice. Ofloxacin has produced in two ready forms, peroral and injective ones, and both of them are characterized by a high clinical efficiency, wide range of indications for treatment, relative stability of the ofloxacin molecule in the process of bio-transformations in organism, and a low interference with drugs of other pharmacological groups. The oxygen atom in the oxazine ring is supposed to be an important element of the structure, thus providing an optimal antibacterial effect of this compound. Ofloxacin represents a racemic mixture of the right- and left-rotating optical isomers. The left-rotating enantiomer, levofloxacin, which proved to be much more active than its stereo analogue against nearly all bacteria, had been launched into medicinal practice in 1997. Inhibition of *E. coli* DNA gyrase by levofloxacin (I_{50} 2,50 μg/ml) was shown to surpass inhibition of the same enzyme by ofloxacin (I_{50} 6,20 μg/ml) [235].



Scheme 37 Structure tricyclic [*i,j*]-annelated fluoroquinolones

The starting materials **82** for the synthesis of ofloxacin and its analogues have been obtained by interacting ethyl 2-(tetrafluorobenzoyl)-3-ethoxy acrylates with 2-aminopropanol [236]. It is clear that use of optically active *S*-(-)-2-aminopropanol enables one to obtain levofloxacin [237–241]. Another approach to fluoroquinolones **81** is cyclization of compounds **83**, derived from condensation of the corresponding benzoxa(thia)zines with diethylethoxy methylenemalonate (Scheme 38). In this way the synthesis of levofloxacin has been realized from the (*S*)-isomer of 7,8-difluoro-2,3-dihydro-3-methyl-4H[1, 4]benzoxazine [242].

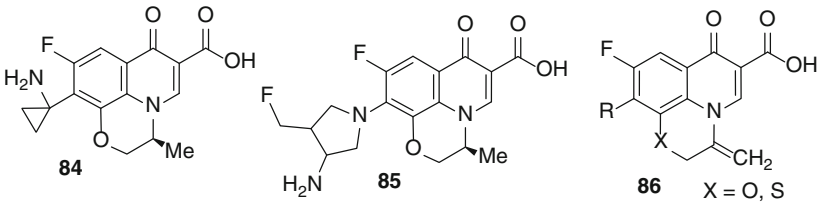


Scheme 38 Synthesis of fluoroquinolones **81**

During the last two decades the synthesis of levofloxacin and its *S*-(-)-precursors has been improved considerably, and new approaches have been advanced [243–255]. In particular, kinetic resolution of 7,8-difluoro-2,3-dihydro-3-methyl-4H-[1,4]-benzoxazine racemate using naproxen, N-[sulphonylsubstituted]-(*R*)-proline and (*2S*)-(6-methoxynapht-2-yl)propionyl chloride, has been advanced [256–261]. The optically active (*S*)-isomer obtained by this method has been used for the synthesis of levofloxacin (*S*)-(-)-**80** [256]. Also a new synthetic approach to (*S*)-isomer through catalytic reduction of 7,8-difluoro-3-methyl-2*H*-1,4-benzoxazine with use of chiral Bronsted acids as catalyst and substituted dihydropyridine as a source of hydrogen has been described [262].

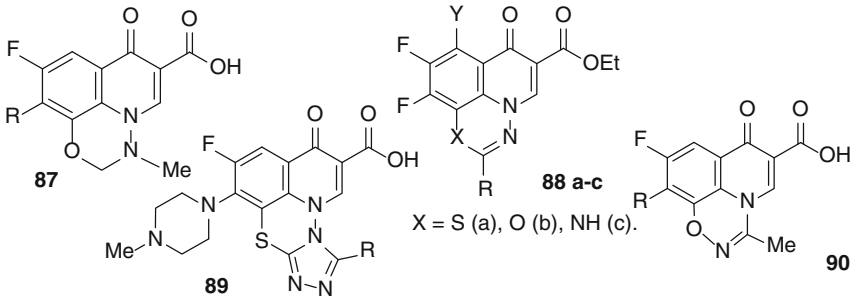
A number of ofloxacin analogues modified in position 10, including the well-known antibacterial drug pazufloxacin **84**, have been synthesized [263–265]. Some compounds of this series show a high activity towards a number of microorganisms, such as *Shigella flexneri*, *Proteus vulgaris* [263]. It is worth noting that (3S)-10-[*Cis*-(*3S,4S*)-3-amino-4-(fluoromethyl)pyrrolidin-1-yl]-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-*d,e*]

[1,4]benzoxazin-6-carboxylic acid **85** is more active than levofloxacin against *Staphylococcus aureus 870307* [266]. An analogue of ofloxacin, containing a macrocyclic fragment in position 6 has been described [267]. All kinds of modifications of the structure of ofloxacin have been performed by varying substituents not only in positions 6 and 10, but also in the oxazine ring. In particular, compounds **86** show a comparable with ofloxacin activity against Gram-positive and negative microorganisms, and a high activity towards methicillin-resistant strain of *S. aureus MR5867* [MIC 0,016–0,25 μg/ml for compound **86** (X = O, R = 3-cyclopropylaminomethyl-1-pyrrolidine)] (Scheme 39) [268].



Scheme 39 Structure of fluoroquinolones **84–86**

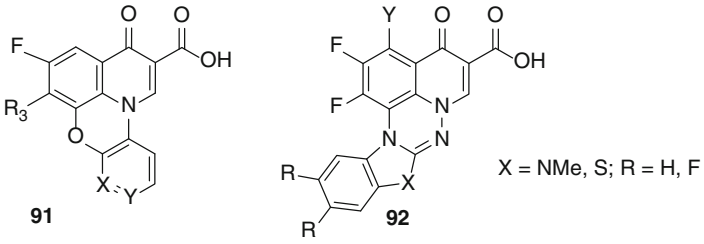
Marbofloxacin 87 is a representative of another promising group of tricyclic fluoroquinolones, pyridino[3,2,1-*i,j*]-1,3,4-benzoxadiazines, is widely used in veterinary practice (Scheme 40) [269].



Scheme 40 Structure of fluoroquinolones **87–90**

Synthetic methods to obtain other members of the family of [*i,j*]-annelated fluoroquinolones have been developed. For instance, derivatives of 1,3,4-thiadiazino[6,5,4-i,*j*]-, 1,3,4-oxadiazino[6,5,4-*i,j*]- and 1,2,4-triazino[5,6,1-*i,j*]-annelated quinolones **88a-c** have been obtained by means of cyclization of 2-polyfluorobenzoyl acrylates bearing hydrazide, thiosemicarbazide or amidrazone moieties in position 3 [270–275]. Thiadiazino-fused quinolones **88a** and compounds derived from displacement of fluorine atoms in positions 8 and 10 with cycloalkylimines are of great interest as promising compounds exhibiting not only

antibacterial but also other types of biological activity [276, 277]. Synthesis of tetracyclic quinolones **89**, in which the thiadiazine fragment is fused with both the pyridine and triazole rings has been described [278]. Activity of compounds **89** with R = H, Me against Gram-positive and Gram-negative bacteria is comparable with that of ofloxacin. Another core structure close to ofloxacin is 1,2,4-oxadiazino[*i,j*]-annelated fluoroquinolone **90** which was obtained by cyclization of 3-[1-(hydroxyiminoethyl)amino] acrylate [279]. The synthesis of tetracyclic fluoroquinolones **91** has been reported [280, 281]. The structure of novel pentacyclic fluoroquinolones **92** (Scheme 41), obtained by cyclization of ethyl 3-(benzazol-2-yl)hydrazino-2-polyfluorobenzoyl acrylates, was elucidated by X-ray crystallography [282–284].

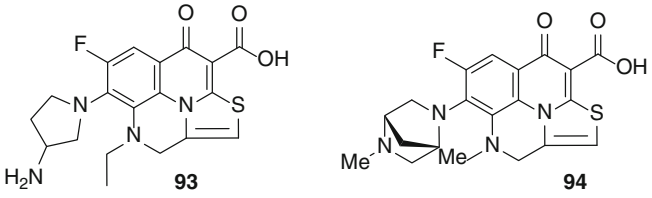


Scheme 41 Structure of fluoroquinolones **91, 92**

As a rule, cyclizations of 1-substituted 8-fluoroquinolones have an advantage in comparison with annelation of the pyridine ring to a benzazine moiety, thus allowing one to vary annelated fragments to a greater extent. However, the synthesis of levofloxacin is an exception, since the scheme suggesting to obtain first the optically active benzoxazine, as the key intermediate, followed by annelation of the pyridone fragment proved to be a more successful one.

2.2.7 Tetracyclic [*a,i,j*]-Annelated Fluoroquinolones

Several examples of tetracyclic [*a,i,j*]-annelated fluoroquinolones are available in the literature. In particular, compounds **93** and **94**, bearing 3-aminopyrrolidine and (*1S,4S*)-5-methyl-2,5-diazabicyclo[2.2.1]heptane fragments, respectively are considered to be rather promising because they both exceed ofloxacin in antibacterial activity (Scheme 42) [285, 286].



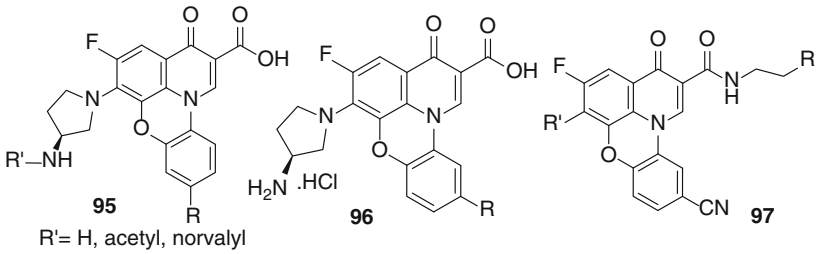
Scheme 42 Structure of tetracyclic fluoroquinolones **93**, **94**

3 Other Types of Biological Activity of Fluoroquinolones

During the last decades compounds of the fluoroquinolone family proved to be not only effective inhibitors of bacterial enzymes; their antineoplastic [287], antiviral [41] (including concerning HIV [288]), anti-diabetic [289] and other types [290, 291] of biological activity have been intensively elucidated.

3.1 Anticancer Activity

Some representatives of the fluoroquinolone family, especially polycyclic compounds, are capable of inhibiting topoisomerase II, the key enzyme for replication DNA, and this is why they are promising for development of antineoplastic drugs [172, 292, 293]. In particular, a profound antineoplastic activity is demonstrated by quinobenzoxazines **95–97** (Scheme 43) [293–298]. Fluoroquinolone **95** (R'=H) is more active towards some tumor cells than such antineoplastic drugs, as adriamicin, camptotecin and etoposide [299]. Relationships between the nature of substituents in the amino fragment and the benzene ring of compounds **95–96** and their abilities to suppress the growth of tumor cells have been studied. Compounds with R'=H and R=Cl, NO_2 were shown to inhibit not only topoisomerase II, but also topoisomerase I [280, 299–301]. Amides **97** proved to suppress effectively the growth of HCT-116 cells, IC_{50} values 0,03–0,4 μM [295].

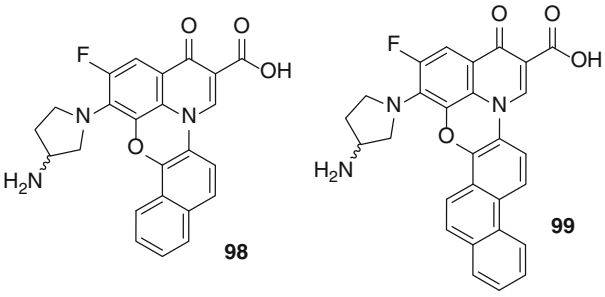


Scheme 43 Structure of fluoroquinolones **95–97**

Further steps to modify the structure quinobenzoxazines **95** involve annelation of the benzene rings to the benzoxazine fragment, as illustrated by the synthesis of benzo- and dibenzoderivatives **98** and **99** (Scheme 44) [299, 302]. Research studies on activity of pentacyclic derivatives **98** towards a number of tumor cells have shown that *R*-isomers are much more active, than *S*-isomers (Table 7). Also it has been revealed that a molecular target for fused fluoroquinolones **99** is the site of DNA capable of forming the quadruplex [303]. It has been shown that R-isomer **99** is characterized by a strong linkage with G-quadruplex and a low influence on topoisomerase II, while the *S*-isomer **99** has a strong linkage with topoizomerase II and a low interaction with G-quadruplex [296].

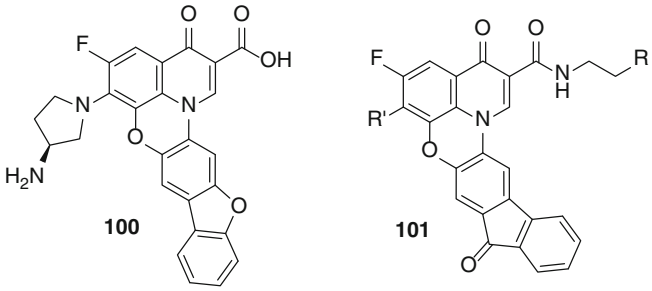
Table 7 Inhibition of cancer cells by pentacyclic fluoroquinolones **98**

Cell lines	Value IC_{50} *in vitro*, μM	
	(*S*)-isomer	(*R*)-isomer
B16 (melanoma)	0.2	0.02
MDA-231 (breast cancer)	0.08	0.005
H226 (lung cancer)	0.03	0.01
HT-29 (colon cancer)	0.05	0.03
DU 145 (prostate cancer)	0.06	0.03



Scheme 44 Structure of fluoroquinolones **98**, **99**

The data of biological tests on activity of compound **100** (drug QQ58), as an intercalator of DNA [304] confirmed that this compound inhibits human telomerase (IC_{50} 28 μM); in organisms it is transformed into qarfloxacin which is linked with DNA G-quadruplexes [300, 304–306]. Polynuclear fluoroquinolones, containing the amide fragment, for example **101** (Scheme 45), have been shown to inhibit effectively the HeLa (mammalian cancer) growth (IC_{50} 0,1–0,2 μM) [303, 307, 308].



Scheme 45 Structure of fluoroquinolones **100**, **101**

Other fused fluoroquinolones, derivatives of benzazolotriazino[*i,j*]-annelated quinolon-6-carboxylic acids **92** have shown anticancer activity [309]. Biological tests on 9 types of tumors revealed that annelation of 1-methylbenzimidazo fragment to the triazine ring is more effective for suppression of cell growth, than that of the benzothiazole ring. An increase in numbers of fluorine atoms in the benzene rings of quinoline or benzazole fragments enhance antineoplastic action of pentacyclic

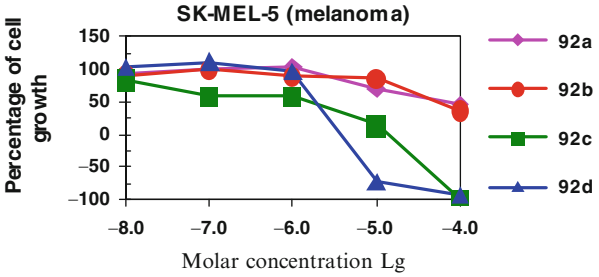
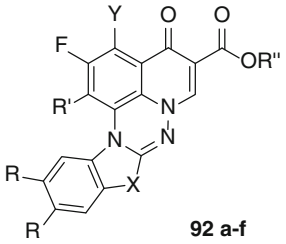


Fig. 2 Cells growth suppression for derivatives **92a-d**



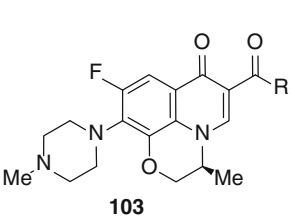
92 a-f

92: X=S, Y=R=R'=R''=H (a),
X=NMe, Y=R=R'=H, R''=Et (b),
X=NMe, Y=R=R'=R''=H (c),
X=NMe, Y=R=R'=F, R''=H (d),
X=NMe, Y=R=F, R''=H,
R'=pyrrolidin-1-yl (f).

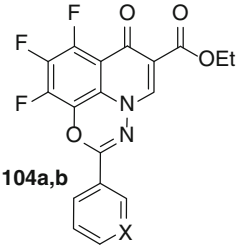
Scheme 46 Structure of fused fluoroquinolones **92**

derivatives; acids suppress growth of cells more strongly, than the corresponding ethyl esters. The biggest effect on melanoma has been observed *in vivo* experiments for fluoroquinolone **92d** (Scheme 46, Fig. 2) [310].

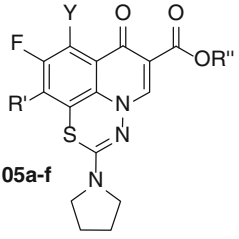
Derivatives of levofloxacin **103** (Scheme 47), bearing in position 3 a lipophilic fragment, or the benzothiazole fragment instead of the carboxyl group, proved to exhibit antineoplastic activity (Table 8) [311]. The highest level of activity against glioblastoma has been observed for the ester **103a**.



103



104a,b



105a-f

103: R = $OCH_2OC(O)C_{11}H_{23}$(a), $OCH_2OC(O)C_{17}H_{35}$(b), NHC_8H_{17}(c);

104: X = C-NO_2(a), N (b); 105: R''=Et, Y=R'=F (a), Y=R'=$Me_2N(CH_2)_3NH$ (b),
Y = H, R'=F (c); R''=H, Y=H, R'=F (d), Y = R' = F (f).

Scheme 47 Structure of fluoroquinolones **103–105**

Table 8 Activity of levofloxacin derivatives **103** against some cancer cells

Compound	IC_{50} *in vitro,* mkM				
	U373-MG (glioblastoma)	A549 (lung cancer)	PC-3 (prostate cancer)	LoVo (colon cancer)	MCF-7 (breast cancer)
Levofloxacin	188	70	238	67	622
103a	0.2	65	86	0.3	0.3
103b	0.9	593	100	4	12
103c	2.3	2.2	1.5	0.8	2.1

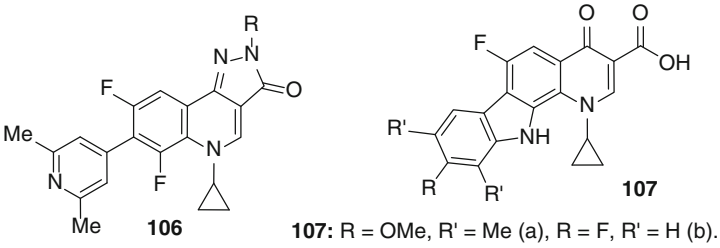
Table 9 Inhibitory and cytotoxicity properties of pyrazoloquinolones **106**

R	HeLa cell topo II inhibitory properties (EC_{50}, μM)	Cytotoxicity properties for P388 *in vitro* (IC_{50}, μM)
$(CH_2)_2NMe_2$	2.6	0.26
$(CH_2)_3NMe_2$	1.7	0.16
Cyclohexyl	0.9	0.68
$CH(CH_2CH_2)_2O$	1.7	0.29
$CH(CH_2CH_2)_2NMe$	3.2	0.094
$CH(CH_2CH_2)_2CHNH_2$(*cis*)	0.5	0.44
$CH(CH_2CH_2)_2CHNMe_2$(*cis*)	1.7	0.067
$CH(CH_2CH_2)_2CHNMe_2$(*trans*)	4.4	0.26
1-Cyclopropyl-6,8-difluoro-7-(2,6-di-methyl-4-pyridinyl)-4*H*-4-oxoquinoline-3-carboxylic acid	7.6	29
1-Cyclopropyl-6,8-difluoro-7-(2,6-di-methyl-4-pyridinyl)-4*H*-quinoline-4-one	17	15

Antineoplastic activity of fluorine-containing derivatives of 1,3,4-oxa(thia)-diazine[6,5,4-*i,j*]quinolon-6-carboxylic acids **104, 105** has been studied on cultures of 60 lines of cancer cells for nine groups, such as leukemia, lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, mammalian cancer [309, 310]. In the series of thiadiazinoquinolines the highest effect on antineoplastic activity gas been observed for compounds **105a** and **105b** bearing such pharmacophoric fragment, as N,N-dimethyl-1,3-diaminopropane. In case of compound **105b** the full death of nearly all tumor cells MCF7 and SF-268 (more than 90 %) has been reached. Biological tests of compounds **105a,c,d,f** have shown that the presence of a fluorine atom in position 8 facilitates suppression of cell growth. Also a high activity of compound **105a** towards leukemia has been established [309, 310].

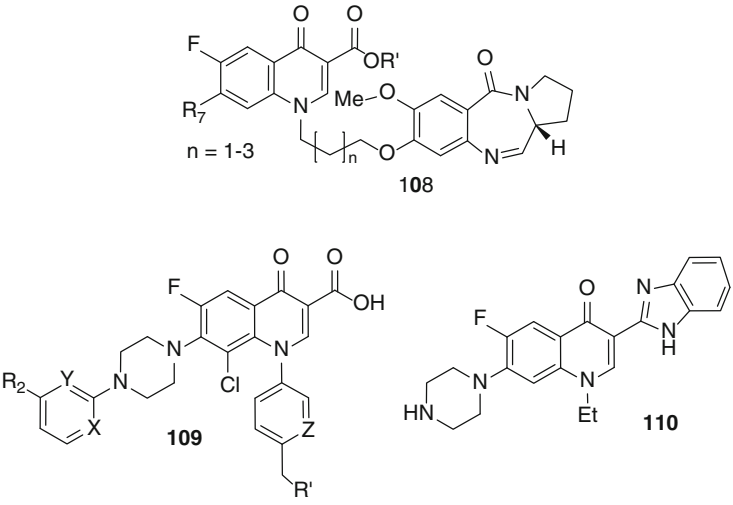
Not only [*i,j*]-annelated fluoroquinolones, but also polycyclic fluoroquinolones, in which an additional ring is annelated to [*c*]- or [*h*]-sides proved to possess antineoplastic action. Research studies on antineoplastic activity of 5-cyclopropyl-6,8-difluoro-7-(2,6-dimethyl-4-pyridinyl)-5H-pyrazolo[4,3-*c*] quinolin-3(2H)-ones **106** have shown that derivatives containing the cyclohexyl group in position 2 are the most effective inhibitors of topoisomerase II of HeLa cells (mammalian cancer), while the dimethylaminocyclohexyl compound has shown the best data on cytotoxicity towards P388 (leukemia) cells (Table 9) [312].

6-Fluoro-4-oxopyridino[2,3-*a*]-carbazol-3-carboxylic acids **107** inhibit MCF-7 (breast cancer) and A549 (lung cancer), activity of **107b** towards MCF-7 is twice higher, than that of ellipticine (Scheme 48) [198].



Scheme 48 Structure of fluoroquinolones **106**, **107**

Also a number of bicyclic fluoroquinolones are capable of suppressing the growth of tumor cells. Incorporation of pyrrolo[2,1-*c*][1,4]benzodiazepine fragment in position 1 of fluoroquinolones resulted in compounds **108**, which inhibit the growth of HT-29 (colon cancer) cells and A549 (lung cancer) up to 80 % [313]. Derivatives of 1-phenylsubstituted fluoroquinolones **109** suppress the growth of Solo205 (carcinoma) cells (IC_{50} values 2–20 nM) [314]. 3-Benzimidazolyl fluoroquinolone **110** and its analogues (Scheme 49), including [*i*,*j*]-oxazino



Scheme 49 Structure of fluoroquinolones **108–110**

Table 10 Tuberculostatic activity of some fluoroquinolones

Quinolone	MIC, μg/ml	Quinolone	MIC, μg/ml
Sparfloxacin	0.25	Trovafloxacin	16
Sitafloxacin	0.25	Grepafloxacin	1
Clinafloxacin	0.5	Pefloxacin	8
Gatifloxacin	0.12	Tosufloxacin	16
Ciprofloxacin	0.5	Temafloxacin	4
Moxifloxacin	0.5	Fleroxacin	6.25
Levofloxacin	0.5	Enoxacin	8
Ofloxacin	1	Oxolinic acid	32
Gemifloxacin	4	Flumequin	64
Garenofloxacin	2	Pipemidic acid	128
Norfloxacin	4	Nalidixic acid	128

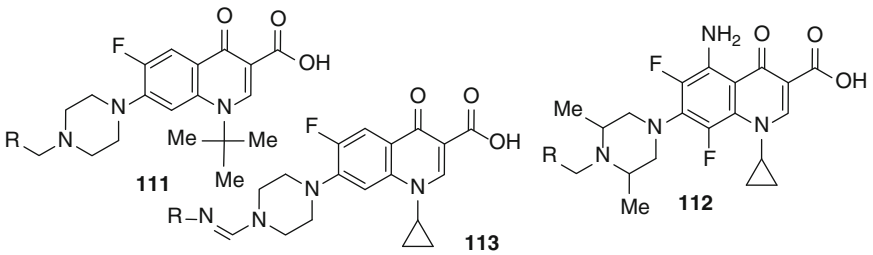
annelated compounds, proved to suppress the growth of tumor KV, A2780 and Bel7404 cells [315].

Rather high antineoplastic activity of ciprofloxacin derivatives, containing a substituent in position 4 of the piperazine fragment has been shown [302]. Elucidation of the "structure-activity" relationships for 1-(2-thiazolyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridin-3-carboxylic acids has shown that several compounds of this series exhibit activity, comparable with the well-known drug *etoposide* [316–318]. Also the data on activity of amides of 7-substituted 1-(2-thiazolyl)- and 1-(2-benzothiazolyl)-1,8-naphthyridin-4-on-3-carboxylic acids have been reported [319]. Ethyl 1-(4-cyano-2,3,5,6-tetrafluorophenyl)-6,7,8-trifluoro-4-oxo-1,4-dihydroquinolin-3-carboxylate proved to inhibit the phosphorylation process of transcription STAT3 activator that plays an important role for cancer therapy [320].

3.2 Tuberculostatic Activity

Being effective inhibitors of DNA-gyrase of mycobacteria some derivatives of fluoroquinolones are important for therapy of rifampicin-resistant tuberculosis [321]. In particular, values of minimum inhibitory concentrations against *M. tuberculosis* for a number of elucidated fluoroquinolones proved to be in the range from 0,12 to 128 μg/ml (Table 10) [322, 323].

An important synthetic approach for development of fluoroquinolones which are active against *Mycobacterium tuberculosis* appears to be introduction of isoniazide and pyrazinamide residues into the piperazine fragment in position 7. Indeed, 1-*tert*-butyl substituted fluoroquinolones **111** and 1-cyclopropyl-5-amino-fluoroquinolones **112** proved to exhibit a high activity towards *Mycobacterium tuberculosis in vivo* [38]. The minimum inhibitory concentration against *M. tuberculosis* $H_{37}R_v$ for compound **113b** is 0,78 μg/ml (Scheme 50) [324]. Also quinolones, bearing residues of hydrazides of substituted benzoic acids, which can be regarded as

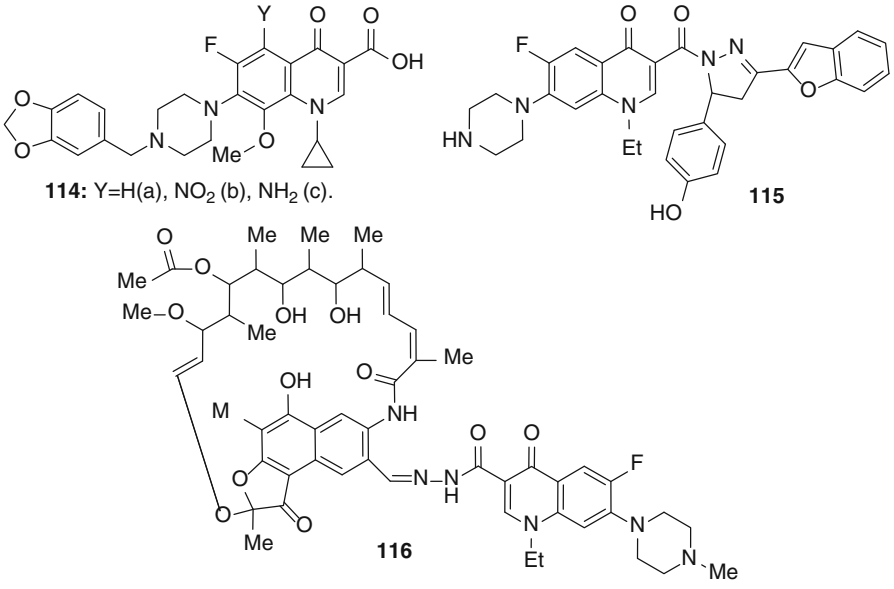


111, 112: R=(pyridin-4-yl)-C(O)NHN=C(Me)(a), (pyrazin-2-yl)-C(O)NHCH$_2$(b).
113: R=(pyridin-4-yl)-C(O)NH(a), (pyrazin-2-yl)-C(O)(b).

Scheme 50 Structure of fluoroquinolones **111**–**113**

isosters of isoniazide, proved to be active compounds (MIC 0,5 μg/ml for multiresistant *M. tuberculosis A8 241*) [325].

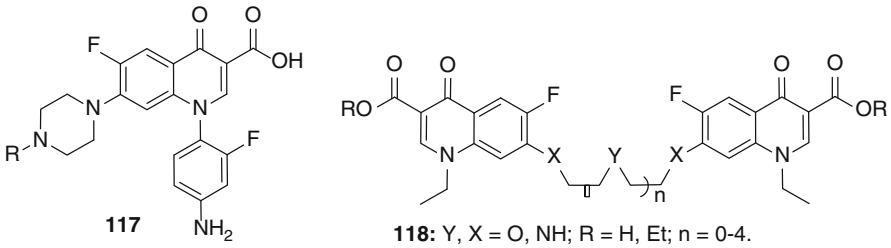
1-Cyclopropyl-8-methoxyquinolones **114** are active against *Mycobacterium tuberculosis,* its multi-resistant strains, as well as *Mycobacterium smegmatis* [326]. Derivative **115** possesses tuberculostatic activity against *Meningitis tuberculosis* $H_{37}R_v$ (MIC 0,16–0,35 μg/ml) [327]. 1-[(6′-Fluoro-1′,4′-dihydro-7-(4”-methyl-1”-piperazinyl)-1′-ethyl-4′-oxo-3′-quinolylamido)-3-iminomethyl]-rifampicin **116** proved to exhibit a considerable tuberculostatic activity (Scheme 51) [328].



114: Y=H(a), NO_2 (b), NH_2 (c).

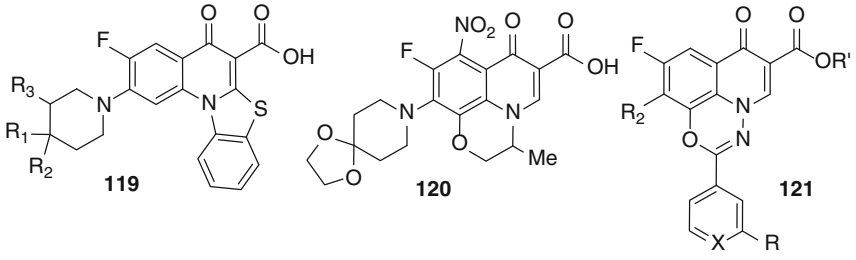
Scheme 51 Structure of fluoroquinolones **114**–**116**

1-(4′-Amino-2′-fluoro)phenyl substituted fluoroquinolones **117** (R = H, Me) inhibit the growth of *M. tuberculosis* [329]. Incorporation of aminoester or polyethyleneamino fragments has been suggested to increase their ability to penetrate through cellular membranes. Indeed, fluoroquinolones **118** have been established to possess a high specific activity against mycobacteria and a low toxicity [330]. Tuberculostatic activity of derivatives **118** (R = H; X, Y = 0; n = 4) proved to be five times higher than that of pefloxacin (Scheme 52).



Scheme 52 Structure of compounds **117**, **118**

Several compounds [331] of the benzothiazolo[3,2-*a*]quinolone-6-carboxylic acids **119** family (Scheme 53) exhibit high tuberculostatic activity relative to multiresistant strain of *M. tuberculosis* (Table 11).



Scheme 53 Structure of fluoroquinolones **119–121**

Ofloxacin and its analogs are promising drugs for tuberculosis treatment. Ofloxacin (daily dose 300–800 mg) and levofloxacin (250–500 mg a day) in

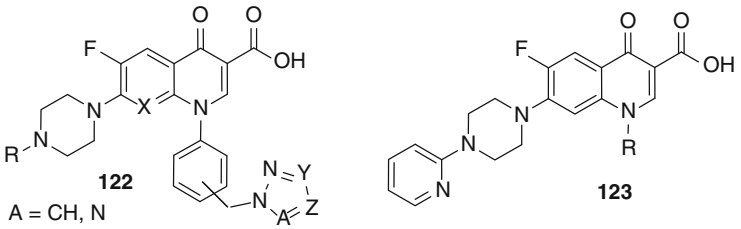
Table 11 Tuberculostatic activity of fluoroquinolones **119**

	MIC, μg/ml		
R^1, R^2, R^3	*Mycobacterium tuberculosis*	Multiresistant strain of *M. tuberculosis*	*M. smegmatis* ATCC 14468
R^1 = pyperidin-1-yl, $R^2 = R^3 = H$	0.39	0.19	6.53
R^1 = 4-ClC_6H_4, R^2 = OH, R^3 = H	0.36	0.36	2.98
$R^1 = R^2$ = H, $R^3 = Et_2NC(O)$	0.18	0.08	3.15
R^3 = H, R^1, $R^2 = OCH_2CH_2O$	0.86	0.86	6.89

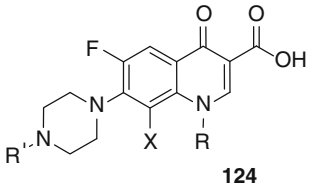
combination with *p*-aminosalicylic acid, cycloserine, or ethionamid are effective for the treatment of multi-resistant strains of tuberculosis. On using of these fluoroquinolones, a relatively high concentration in cells is reached, that increasing their antibacterial activity [38]. Derivatives of ofloxacin, containing the nitro group in position 8, e.g. **120** proved to possess a high tuberculostatic activity [332]. Also compounds showing tuberculostatic activity have been found among oxadiazinoquinolines **121** and thiadiazinoquinolines **105** (MIC 0,2–0,4 μg/ml) [276, 277].

3.3 Antiviral Activity

Fluoroquinolones **122**, bearing the (triazolylmethyl)phenyl fragment in position 1 and an aryl substituent in position 4 of piperazine, are capable of protecting the HIV-infected cells from a virus-induced destruction (IC_{50} 0,25–0,7 μM). They appear to be a new structural type of effective drugs for treatment and prevention of viral diseases caused by HIV retroviruses [333]. Fluoroquinolones **123** with 4-(2′-pyridinyl)-1-piperazine fragment in position 7, inhibit reverse transcriptase of HIV-1 [334]. 8-Difluoromethoxy- and 8-trifluoromethylcarboxylic acids **124** inhibit replication of HIV-1, while CF_3- derivatives are more active against HIV-1 than the corresponding difluoromethoxy compounds (Scheme 54, Table 12) [335–338].



123, 124: R=t-Bu (a), cyclopropyl (b), Me (c). X=$OCHF_2$, CF_3.



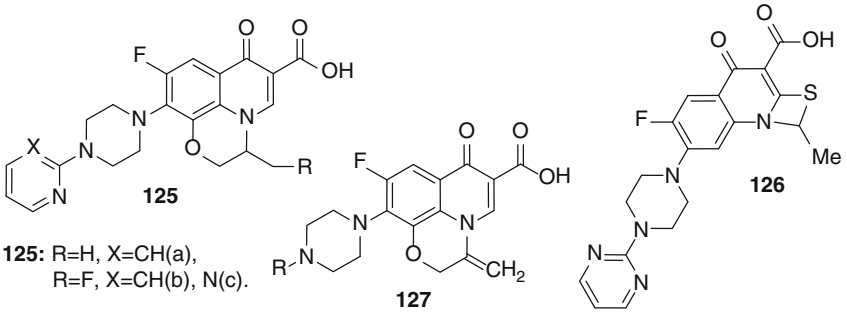
Scheme 54 Structure of fluoroquinolones **122–124**

[*i,j*]-Annelation of the oxazine ring is favorable for exhibiting of antiviral activity, but does not lead to such promising compounds, as 8-methoxy- and

Table 12 Inhibition of HIV-1 by **124**

R	R'	IC_{50}, μM	
		8-CF_3	8-$OCHF_2$
Me	2-$OMeC_6H_4$	0.054	0.35
Et	2-$OMeC_6H_4$	0.11	0.22
Cyclopropyl	2-$OMeC_6H_4$	0.069	0.56
Me	2-pyrimidinyl	0.049	0.31
Et	2- pyrimidinyl	0.095	0.47
Cyclopropyl	2- pyrimidinyl	0.19	3.7
Me	2-pyridyl	0.014	0.24
Et	2- pyridyl	0.026	0.89
Cyclopropyl	2- pyridyl	0.065	0.49

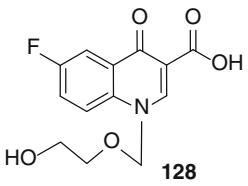
difluoro-methoxy derivatives [339]. Fluoroquinolone **125c** is more active against the virus HIV-1, than thiazeto derivative **126** [336]. Values IC_{50} 3,7 μM for **125a** and 1,7 μM for **125b** have been found, while values EC_{50} 0,074 μg/ml for **125c** and 0,4 μg/ml for **126** have been obtained. Also a number of tricyclic fluoroquinolones **127** proved to possess a high activity (EC_{50} 0,008–2.3 μg/ml) (Scheme 55) [340]. Also effective compounds against HIV-1 have been discovered in the series of the Mannich bases of norfloxacin [341].



Scheme 55 Structure of fluoroquinolones **125**–**127**

Fluoroquinolone **128** bearing the (2-hydroxyethoxy)methyl fragment at N-1 is active against **herpes virus** HSV-1 (EC_{50} 2,30 μM), however the level of its activity is lower than that of *acyclovir* (EC_{50} 1,09 μM) [41]. 8-Trifluoromethylquinolones **124** have been reported to suppress **human cytomegalovirus** [342]. Fluoroquinolones **129**, containing the sulphamidomethyl group in a piperazine fragment, are active against **influenza** H1N1, H3N2 and H5N1 **viruses** [343]. Tricyclic fluoroquinolones **130, 131** were found to possess a high activity against hepatitus B virus (IC_{50} 0,1 μM) (Scheme 56) [344, 345].

Ciprofloxacin and levofloxacin are recommended for treatment of patients after transplantation surgery operations in order to prevent the disease caused by poliomavirus BK [346].



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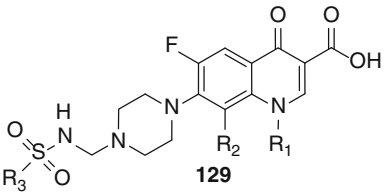
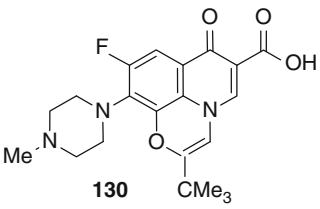


129

129 :R_1=Et, cyclopropyl; R_2=H,OMe;
R_3=2-pyrimidinyl, 4,6-dimethyl-2-pyrimidinyl.



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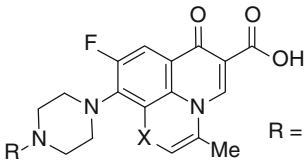


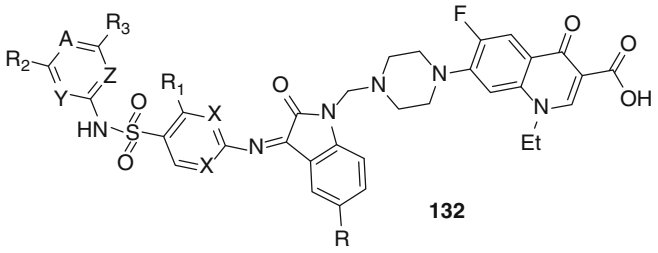
R = H, cyclopropyl

131

Scheme 56 Structure of fluoroquinolones **128**–**131**

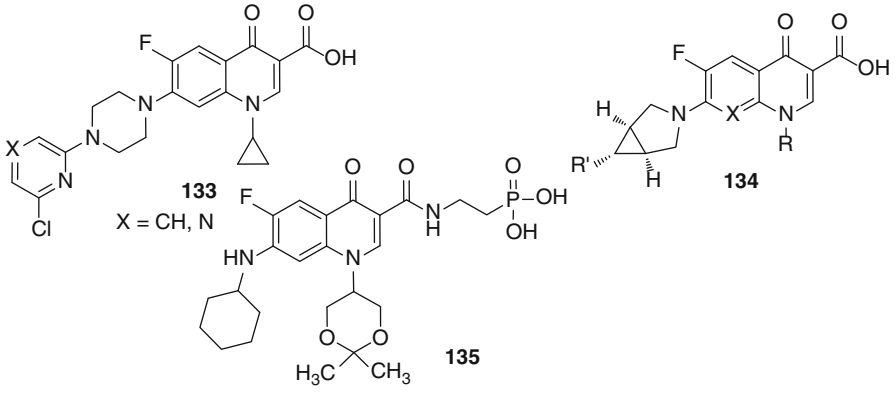
3.4 Other Types of Biological Activity

Some fluoroquinolones appear to be active against **fungi and parasites**. For instance, the Mannich derivatives of *norfloxacin* **132** demonstrate a considerable antifungal activity against *Histoplasma capsulatum.* One of compounds of this family is more active than *clotrimazole* towards *Microsporum audouinii*, while other derivatives surpass *clotrimazole* in relation to *Cryptococcus neoformans* or *Microsporum gypsum*. From all derivatives **132** which have been studied (Scheme 57), compound with R=Br, X=N, $R^1=NH_2$, Y-Z=CH, A=COMe, R^2-R3=OMe proved to exhibit the highest antifungal activity (MIC for *Cryptococcus neoformans* and *Microsporum audouinii* 0,6 μg/ml) [341].



Scheme 57 Structure of fluoroquinolones **132**

Moxifloxacin, gatifloxacin, trovafloxacin, and grepafloxacin belong to a new generation of fluoroquinlones, showing anti-parasitic activity against *Toxoplasma gondii* and *Plasmodium falciparum* which cause such severe diseases as toxoplasmosis and malaria, respectively. These fluoroquinolones are targeting at the DNA-gyrase, located in a top layer of parasites [347]. For example, the IC_{50} value for trovafloxacin against *Toxoplasma gondii* is 0,96 μM. The data on activity of fluoroquinolones **133** against parasites (*Coccidia*) [348], and activity of 7-(3′-azabicyclo[3.1.0]hexyl)quinolones **134** in relation to plasmodium have recently been reported (Scheme 58) [149].

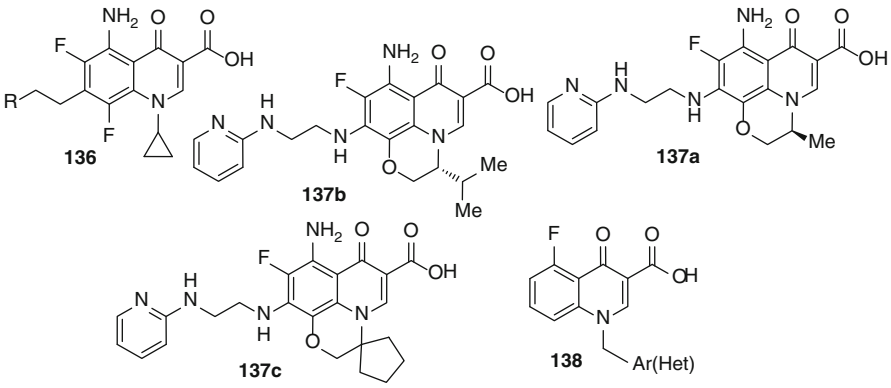


Scheme 58 Structure of fluoroquinolones **133–135**

Table 13 Inhibition of GSK by fluoroquinolones **136, 137**

Compound	R	IC_{50}, nM
136a	4-$NH_2C_6H_4$	900
136b	C_6H_5	440
136c	imidazol-1-yl	3,400
136d	$CH_2C_6H_5$	45
136e	(imidazol-1-yl)methyl	45
136f	$CH_2CH_2C_6H_5$	290
136g	(pyridin-2-yl)amino	22
137a		44
137b		31
137c		12

Some fluoroquinolones have been shown to exhibit **cardiovascular, hypertensive**, and **antitrombocyte** activities. For instance, compound **135** inhibits aggregation of trombocytes [349]. According to the recently published data, 5-amonofluoroquinolones **136** and **137** are active as **glicogensyntase-kinase-3β inhibitors** (GSK, serine-treonine-proteinkinase) [265]. Bi- and tricyclic fluoroquinolones, bearing the fragment of N-(2-pyridinyl)ethylenediamine appear to be promising GSK inhibitors (Table 13) [265]. **138**, their 8-fluoro- and 5,8-difluoroderivatives proved to be selective allosteric **modulators of M1 receptor**, activation of which is important for therapy of the Alzheimer's disease (Scheme 59) [350–353].



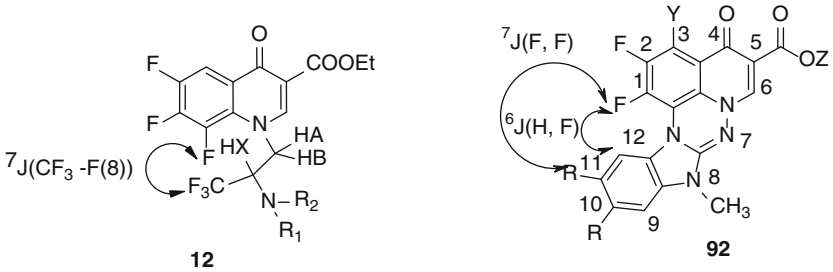
138: Het = 1-methyl-2,3-dihydroindol-5-yl, 1-methylindazol-5-yl, indazol-5-yl, 5-arylpyridin-2-yl.

Scheme 59 Structure of fluoroquinolones **136–138**

4 Structure and Spectral Characteristics

The structure of fluoroquinolones has been elucidated in crystals and solutions. The data on X-ray crystallography analysis of fluoroquinolines are available in the literature for both quinolones [89, 123, 354, 355], and their polycyclic [204, 231, 232, 270, 271, 282, 283, 356] condensed systems.

The ^{1}H, ^{13}C and ^{19}F NMR spectra for the series of fluoroquinolines have been registered and analyzed. ^{1}H, ^{13}C NMR spectra of fluoroquinolones bearing rather complicated optically active fragments, including heteronuclear correlation experiments, have been discussed in the literature [164–168]. Elucidation of NMR ^{19}F spectra of compounds **12** has revealed long-range coupling constants $^{7}J_{F\text{-}F}$ between the trifluoromethyl group and fluorine atom in position 8, which are realized through space due to vicinity of interacting spins [39]. The ^{19}F NMR spectra of benzimidazo [2′,3′:3,4]-1,2,4-triazino[5,6,1-*i,j*]quinoline ring system **92** demonstrate unusual through space ^{1}H-^{19}F and ^{19}F-^{19}F spin-spin interactions with coupling constants $^{7}J(F^{1}, F^{11}) = 3.5–4.0$ Hz and $^{6}J(F^{1}, H^{12}) = 2.0–3.0$ Hz (Scheme 60) [284].



Scheme 60 Long-range coupling constants in compounds **12**, **92**

5 Complexes of Fluoroquinolones with Metals

Due to the presence of the carboxyl and β – oxo groups, as well as azaheterocyclic fragments, fluoroquinolones have a profound ability to form metal-chelates, and other ionic structures. It is known that complexes with metals may enhance activity of fluoroquinolones due to a better solubility and endocellular accumulation [357, 358]. The crystal structures of a number of metal complexes, results of their thermal analysis, IR and NMR spectra of complexes and their bioactivity have been considered [359]. In the recently published review article [360] the data concerning the structure and properties of metal complexes of fluoroquinolones, and their interaction

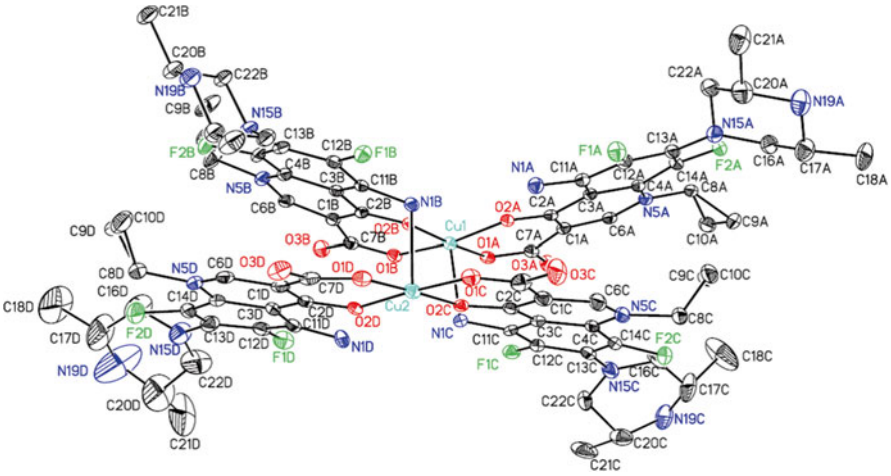
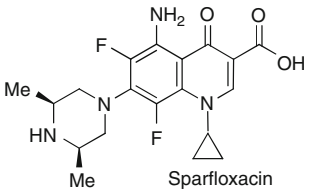


Fig. 3 Structure of complex $Cu_2(sflx)_2$ (Reproduced with permission of Elsevier [365])

with DNA have been analyzed. Also physical and chemical characteristics, as well as pharmacokinetic data and antibacterial properties of fluoroquinolones complexes with a variety of metals have been reviewed [361].

The Cu(II)-complex of ciprofloxacin was shown to possess a high activity against *Mycobacterium tuberculosis* than the parent compound [362]. An enhanced solubility of metal complexes in lipids facilitates their transport into bacteria cells, while an easily proceeding reduction of metal leads to the formation of Cu(I) and activation of oxygen which kills mycobacteria. Authors came to a conclusion that redox-active metal complexes are very promising compounds for development of highly active antitubercular drugs. Indeed, the minimum inhibitory concentration for enrofloxacin complex $Cu(erx)_2(H_2O)$ against *E. coli* и *P. aeruginosa* is 0.125 μg/ml, while the same index for the parent enrofloxacin is 1.0 μg/ml [363]. Antibacterial activity of N-propyl norfloxacin (pr-norf) complex with $CuCl_2$ and phenanthroline (phen) [Cu(pr-norf)(phen)Cl] has been was reported [364]. For instance, the formation of sparfloxacin (sflx) (Scheme 61) dimeric complex with Cu(II) [$Cu_2(sflx)_2$] and mononuclear complex with phenanthroline [Cu(phen)(sflx)H_2O] has been shown (Figs. 3 and 4) [365].



Scheme 61 Structure of sparfloxacin (sflx)

Antiproliferative effect of sparfloxacin and its metal complexes against hormone independent BT20 breast cancer cell line has been studied (Fig. 5) [365].

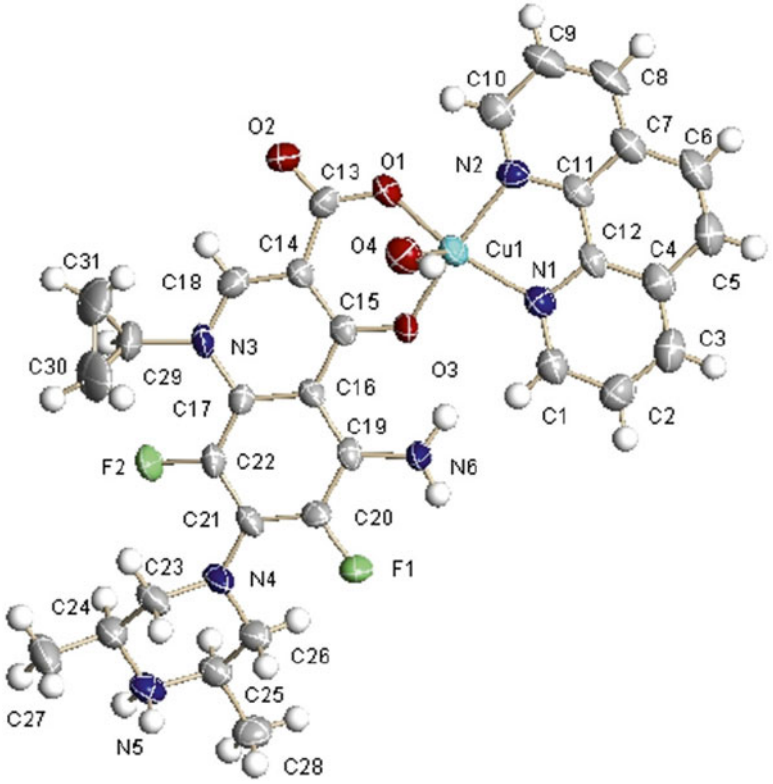


Fig. 4 Structure of complex Cu(phen)(sflx)H_2O (Reproduced with permission of Elsevier [365])

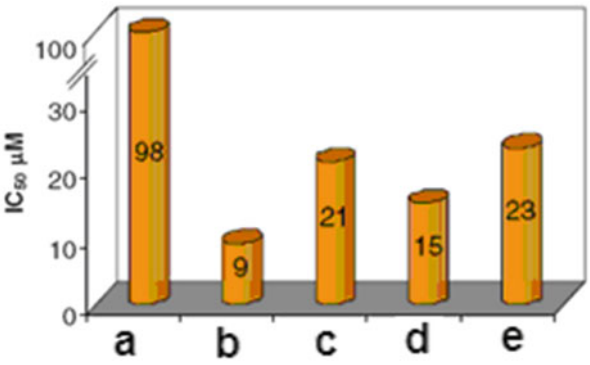


Fig. 5 Suppression of cells growth by sparfloxacin and its metal complexes, a- spfx, b-$Cu_2(sflx)_2$, c-[Cu(bpy)(sflx)H_2O], d-[Cu(phen)(sflx)H_2O], e-[Cu(df)(sflx)H_2O]; bpy = bipyridine, phen = phenanthroline, df = 4,5-diazafluoren-9-one (Reproduced with permission of Elsevier [365])

Coordination of sparfloxacin with copper in the form of dimeric complex $Cu_2(sflx)_2$ has been established to diminish the value of inhibitor concentration IC_{50} (μM) in approximately ten times. These data are in agreement with a hypothesis that biological activity of fluoroquinolones is in many respects caused by their ability for

metal chelate formation. Antitumor activity of moxifloxacin-copper complexes against breast cancer cell lines has also been described [366].

Complex of norfloxacin $[Fe(nf)_2(H_2O)_2]Cl_3 \cdot 6H_2O$ was shown to exhibit a higher antibacterial activity than the parent norfloxacin against *E. coli* and *Bacillus dysenteriae bacteria* [367]. Also it is worth noting that antimicrobial activity of cobalt complexes of ciprofloxacin is less, than that of copper complexes [368].

The reaction of ciprofloxacin (cfH) with metal salts in the presence of aromatic polycarboxylate ligands (or under basic conditions) has been found to give original metal–cfH complexes, for example, $[Ba_2(cf)_2(1,4\text{-bdc})(H_2O)_2]\cdot H_2O$ and [Mn(cfH)(1,3-bdc)] (bdc = benzenedicarboxylate). The structure of $[Ba_2(cf)_2(1,4\text{-bdc})(H_2O)_2]\cdot H_2O$ consists of unique two-dimensional arm-shaped layers (Fig. 6), while the second complex contains double-chain-like ribbons constructed from $[Mn_2(cfH)_2(CO_2)_2]$ dimers and 1,3-bdc (Fig. 7) [369].

Supramolecular structure of cadmium complexes of ciprofloxacin $[Cd_2(cf)_2(bptc)(H_2O)_2]\cdot 8H_2O$ is shown in Fig. 8 [369]. Two units are connected together by μ_3-O atoms of carboxylic groups from cf ligands in an edge-sharing mode to form $[M_2(cfH)_2(H_2O)_2]$ dimers.

Complexes of norfloxacin with zinc(II), such as $[Zn(nf)_2]\cdot 4H_2O$ and $[Zn(H_2O)_2(nf)_2](NO_3)_2$, were found to exhibit a strong blue fluorescent emission [370]. The complex of Zn(II) with enrofloxacin and pyridine, as the second N-donative ligand, $[Zn(erx)_2(py)_2]\cdot 6H_2O\cdot MeOH$ has been obtained (Fig. 9). Such complexes were found to interact with CT-DNA, thus demonstrating their ability to bind with DNA. According to the data obtained by using the UV spectroscopic titration technique, the binding strength for $Zn(orx)_2(py)_2$ corresponds to the highest K_b value [371].

The formation of ofloxacin complexes with magnesium has been studied by using NMR ^{1}H and 2D ^{1}H-^{13}C HSQC methods [372]. Behavior of coordinative compounds of ciprofloxacin, levofloxacin and lomefloxacin with Al(III) in water solutions has been elucidated by NMR ^{1}H and ^{13}C spectroscopy [373]. Tetrakis[4-(3-carboxy-1-ethyl-6-fluoro-4-hydroxonio-1,4-dihydro-7-quinolyl)-1-methyl-piperazin-1-ium] di-μ_2-chlorido-bis[tetrachloridobismuthate(III)] tetrachloride octahydrate, $(C_{17}H_{22}FN_3O_3)_4[Bi_2Cl_{10}]Cl_4\cdot 8H_2O$, is composed of edge-shared centrosymmetric dinuclear $[Bi_2Cl_{10}]^{4-}$anions, Cl^-anions, dihydrogen pefloxacinium cations and water molecules. The Bi^{III} coordination polyhedron is a distorted octahedron [374].

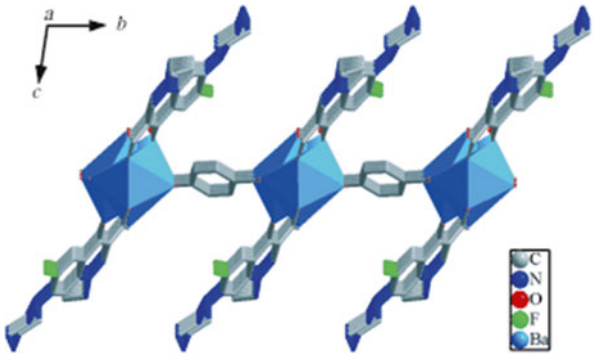


Fig. 6 Structure of complex $[Ba_2(cf)_2(1,4\text{-bdc})(H_2O)_2]\cdot H_2O$ (Reproduced with permission of Wiley [369])

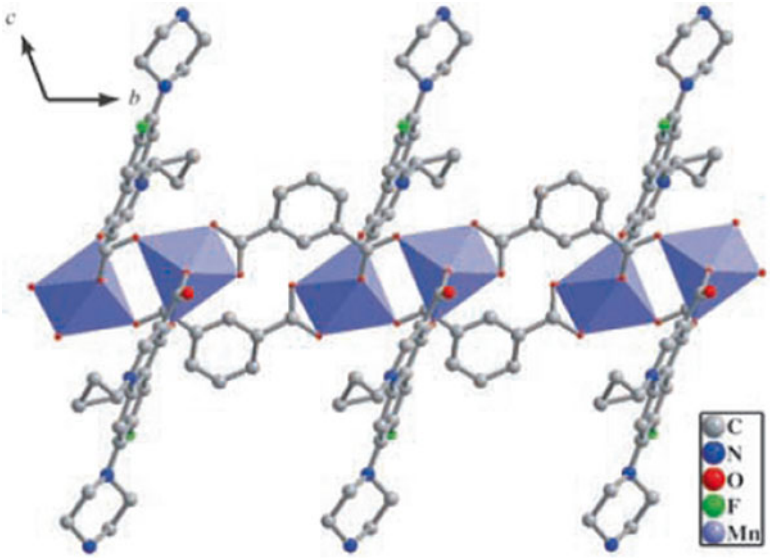


Fig. 7 Structure of complex, [Mn(cf)(1,3-bdc)] (Reproduced with permission of Wiley [369])

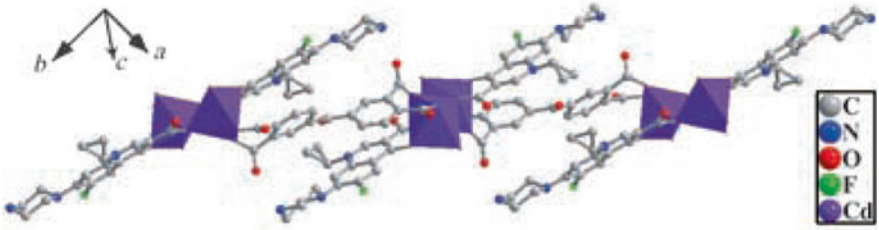


Fig. 8 Supramolecular structure of ciprofloxacin complex, $[Cd_2(cf)_2(bptc)(H_2O)_2]\cdot 8H_2O$ (bptc = 3,3′,4,4′-benzophenontetracarboxylate) (Reproduced with permission of Wiley [369])

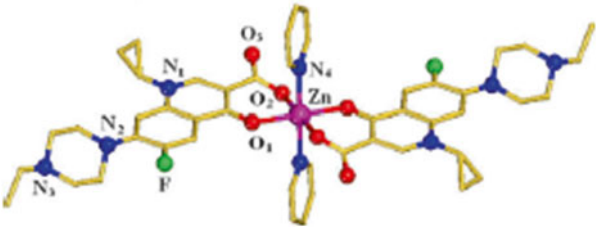
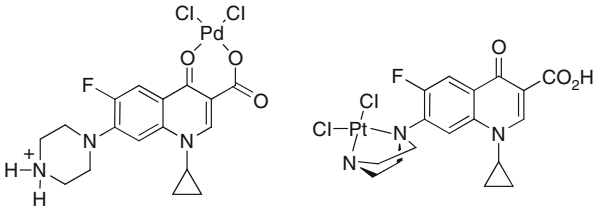


Fig. 9 Structure of complex $[Zn(erx)_2(py)_2]\cdot 6H_2O\cdot MeOH$ (Reproduced with permission of Elsevier [371])

One of the modern trend in the chemistry of fluoroquinolones is the formation of Pd(II) and Pt(II) complexes with a number of fluoroquinolones, such as ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin and gatifloxacin [375, 376]. Two examples are given below Scheme 62.



Scheme 62 Pd(II) and Pt(II) complexes of fluoroquinolones

A great deal of complexes derived from enoxacin, norfloxacin, lomefloxacin, fleroxacin, ofloxacin, rufloxacin, gatifloxacin and sparfloxacin and their luminescence properties of Tb^{3+}– and Eu^{3+}–complexes have been investigated (Fig. 10) [377]. Complexes of Tb^{3+}–enoxacin, Tb^{3+}–norfloxacin, Tb^{3+}– lomefloxacin and Tb^{3+}–fleroxacin were shown to display a relatively strong emission intensity compared with Tb^{3+}–ofloxacin, Tb^{3+}–rufloxacin, Tb^{3+}–gatifloxacin and Tb^{3+}– sparfloxacin. Quite weak peaks with unique characters of Eu^{3+} at 590 and 617 nm have been observed in the luminescence spectra of Eu^{3+}–enoxacin, however no luminescence of Eu^{3+} could be detected when Eu^{3+} was added to other fluoroquinolones. The distinct changes in emission intensities for Tb^{3+}–fluoroquinolone and Eu^{3+}–fluoroquinolone complexes might originate from different energy gaps between the triplet levels of fluoroquinolones and the excited levels of Ln^{3+}. Thus, research studies in the field of complexes of fluoroquinolones with metals are aimed at obtaining of biologically active coordination compounds, and also to use of complex formation for quantitative analysis of fluoroquinolones.

In conclusion it is worth noting that despite the successes reached in area of synthesis, studying of biological activity and application of fluoroquinolones, tasks of design of new structures, development of synthetic approaches, modifications of existing drugs by means of incorporation of substituents into positions 1–8 as well as annelation of additional rings to quinolone fragment continue to remain actual. Not less important studying of structure–activity relations among fluoroquinolones as in process of accumulation of such material all new dependences of antibacterial activity on positions and the nature of the substituents in a fluoroquinolone fragment become clear. The increasing attention is given to the synthesis of optically active isomers among fluoroquinolones and to their use as medicines. Fluoroquinolones are known to be not only antibacterial drugs, but also as compounds exhibiting other types of biological activity. Development of novel anticancer and antiviral agents in the series of fluoroquinolones is in progress. Researches in the field of metalocomplexes of fluoroquinolonecarboxylic acids directed to elucidation of “structure – bioactivity”

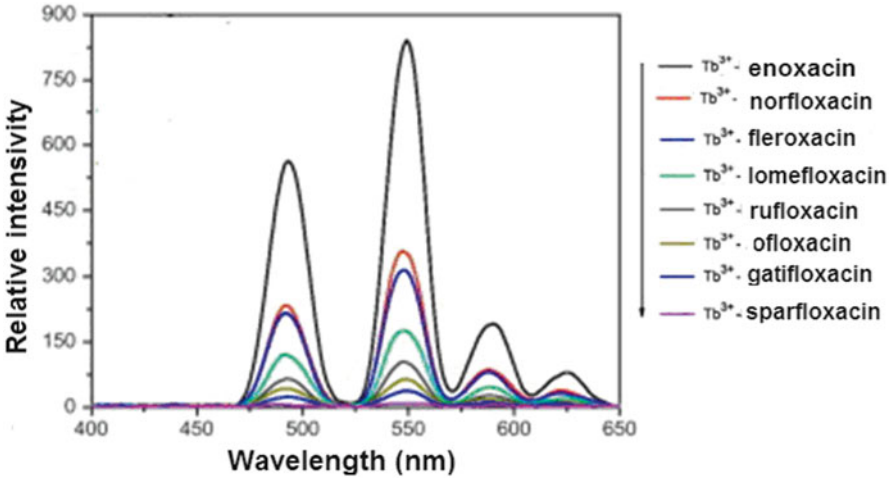


Fig. 10 Emission spectra of Tb^{3+}–complexes of some fluoroquinolones (Reproduced with permission of Elsevier [377])

relations and cation roles in interaction of fluoroquinolones with DNA are developed. Studying of complex formation of fluoroquinolones plays a crucial role for obtaining the fullest data on pharmacokinetic interaction of fluoroquinolones with other drugs.

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Syntheses, Properties, and Applications of Fluorinated Isoquinolines

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Contents

Abstract Fluorinated isoquinolines attract widespread attention as important components of pharmaceuticals and materials, because of their unique characteristics such as biological activities and light-emitting properties. Thus, a number of fluorinated isoquinolines have been synthesized. This chapter covers the syntheses, properties, and applications of ring-fluorinated isoquinolines starting from earlier studies, as well as the syntheses of pyridine-ring-trifluoromethylated isoquinolines. Modern synthetic methodologies for fluorinated isoquinolines have been greatly developed during last decade. These approaches are presented according to the classification based on the standpoint of organic synthesis: (i) the direct introduction of fluorine (or CF_3 group) onto the isoquinoline ring, (ii) the construction of a fused pyridine ring via cyclization of a precursor bearing a pre-fluorinated benzene ring, and (iii) the simultaneous installation of an isoquinoline framework and a fluorine substituent. This chapter also presents a discussion of the application of fluorinated isoquinoline derivatives.

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V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 2: 6-Membered Heterocycles*,
DOI 10.1007/978-3-319-04435-4_4,

Keywords Fluorine • Isoquinoline • Trifluoromethyl group • Baltz–Shiemann reaction • Halex reaction • Bischler–Napieralski reaction • Catalysis • Addition–elimination • Bioactivity • Supramolecular chemistry • Organic light-emitting diode

1 Synergy of Isoquinoline and Fluorine

Isoquinoline, which is a structural isomer of quinoline, possesses a nitrogen-containing heteroaromatics and benzene-ring-fused system. Isoquinolines are widely found in naturally occurring alkaloids [1–3]. Isoquinolines are essential in pharmaceutical, agricultural, and materials sciences because they exhibit various bioactivities and useful physical properties. Among isoquinolines, some tetrahydroisoquinoline derivatives exhibit severe neurotoxicity, which leads to Parkinson's disease [4]. In contrast, a number of isoquinoline-related medicines are flourishing in worldwide pharmaceutical markets. For example, papaverine hydrochloride, morphine, and berberine tannate are prescribed as an antispasmodic drug, a painkiller, and an antidiarrheal, respectively [5].

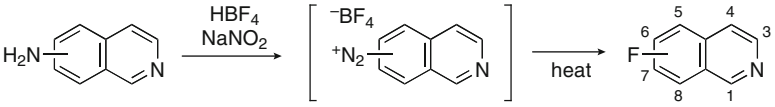
In general, supply of fluorine-containing heterocycles has been mainly expanded for pharmaceutical uses, because electrostatic and steric effects that result from the introduction of fluorine atoms often cause unique bioactivities [6–8]. Fluorinated isoquinolines, i.e., hybrid compounds with an isoquinoline framework and a fluorine substituent, have thus attracted a great deal of attention over the past several decades. A number of fluorinated isoquinolines have been synthesized because of the remarkable progress in synthetic methodologies for fluorinated heterocycles. Substantial enhancements of bioactivities have been observed with respect to some fluorinated isoquinoline derivatives in comparison with the activities of the corresponding fluorine-free compounds. Furthermore, because other isoquinoline-related compounds have exhibited unique light-emitting properties, such compounds are expected to serve as electronic materials.

Some results of previous studies on perfluoroalkylated isoquinolines were recently summarized by Petrov [7]. This chapter focuses on the syntheses, properties, and applications of ring-fluorinated isoquinolines (limited to compounds that retain the aromatic isoquinoline scaffold), starting from the historical background of earlier studies. Additionally, an overview of the syntheses of pyridine-ring-trifluoromethylated derivatives is also given.

2 Earlier Studies on Fluorinated Isoquinolines

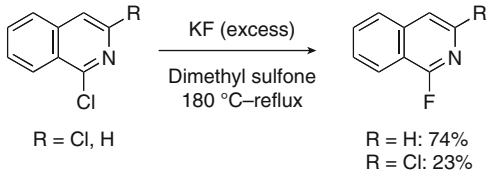
Several typical synthetic methodologies for the preparation of fluorinated isoquinoline derivatives emerged in the 1950s and 1960s. Fundamental reactivities and properties of such compounds were also concomitantly reported. In 1951, Roe and Teague reported the first synthesis of monofluorinated isoquinolines (Scheme 1) [9]. They successfully prepared 1-, 3-, 4-, and 5-fluoroisoquinolines via heating diazonium intermediates

derived from the corresponding aminoisoquinolines on treatment with sodium nitrite and fluoroboric acid, which is the Baltz–Schiemann reaction [10]. In the 1960s, Belsten and Dyke synthesized 8-fluoroisoquinoline, [11] and Bellas and Suschitzky reported the first synthesis of 6- and 7-fluoroisoquinolines (Scheme 1) [12]. Both syntheses involved Baltz–Schiemann reactions similar to those used by Roe and Teague.



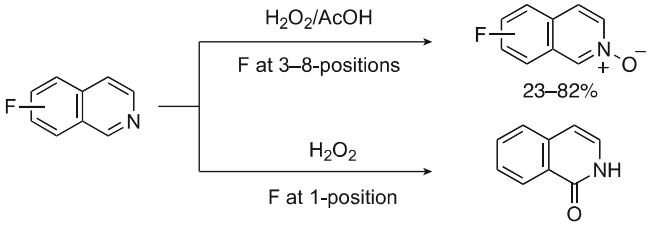
Scheme 1 The Baltz–Shiemann reaction toward ring-fluorinated isoquinolines

An alternative approach to the synthesis of 1-fluoroisoquinolines was accomplished by the nucleophilic aromatic substitution (S_NAr) [12]. The chlorine–fluorine exchange reaction (Halex reaction) [13, 14] was effected in 1-chloroisoquinolines with potassium fluoride to provide 1-fluoroisoquinolines in high yield (Scheme 2). In the case of 1,3-dichloroisoquinoline used as a substrate, 3-chloro-1-fluoroisoquinoline was selectively obtained despite the use of an excess of potassium fluoride. The chemoselectivity was attributed to the lability of the carbon–halogen bond at the 1-position of the isoquinoline ring.



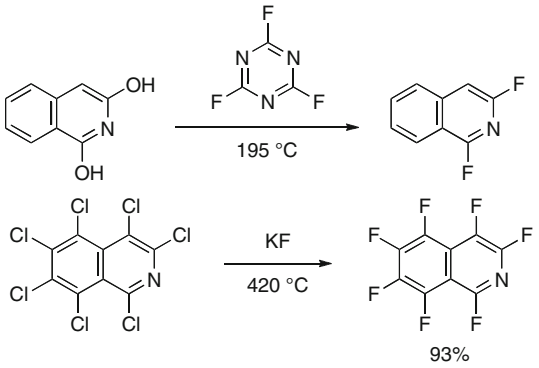
Scheme 2 The Halex reaction toward 1-fluoroisoquinolines

The carbon–fluorine bond at the 1-position of isoquinoline is also reactive. Although isoquinolines bearing a fluorine atom at one of the 3–8-positions were easily converted to the corresponding *N*-oxides by addition of hydroperoxide, 1-fluoroquinoline gave 1-isoquinolone (isocarbostyryl) via nucleophilic replacement of the fluorine substituent under the same reaction conditions (Scheme 3) [12].



Scheme 3 Difference in reactivities of fluorinated isoquinolines

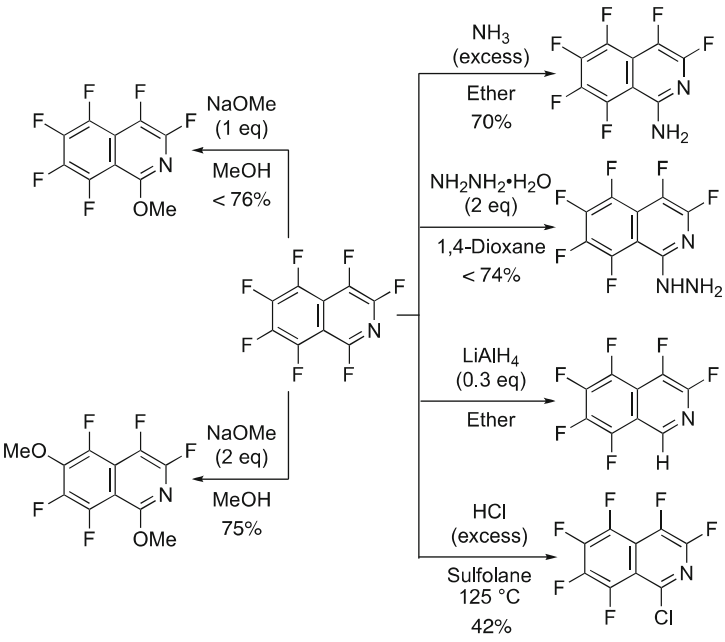
More than one fluorine atoms were introduced onto the isoquinoline framework (Scheme 4). In 1960, Bayer patented the synthesis of 1,3-difluoroisoquinoline, which was derived from 1,3-dihydroxyisoquinoline and cyanuric fluoride [15]. Six years later, Chambers and Musgrave successfully prepared heptafluoroisoquinoline, [16] in which all hydrogen atoms of the parent isoquinoline were replaced by fluorine atoms via a chlorine–fluorine exchange reaction. In this case, heating the mixture of heptachloroisoquinoline and potassium fluoride to 420 °C facilitated global fluorination to provide an excellent yield of heptafluoroisoquinoline.



Scheme 4 Syntheses of di- and perfluorinated isoquinolines

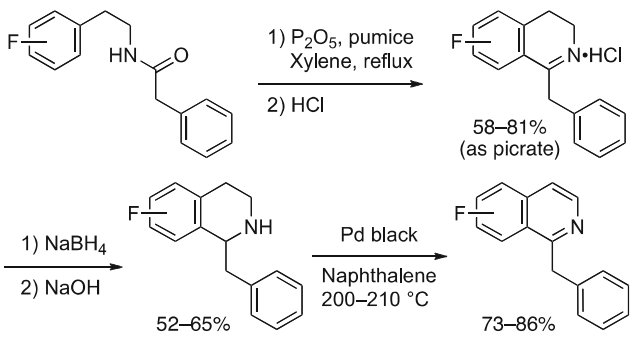
Heptafluoroisoquinoline thus formed easily underwent further S_NAr reactions with various nucleophiles (Scheme 5). Treatment of heptafluoroisoquinoline with an equimolar amount of sodium methoxide selectively afforded hexafluoro-1-methoxyisoquinoline because of the remarkable reactivity of the 1-fluoro substituent (vide supra) [17, 18]. Monosubstitution at the 1-position also selectively occurred in reactions with ammonia, hydrazine, and lithium aluminum hydride to provide 1-aminohexafluoroisoquinoline, 1-hidrazinoisoquinoline, and 1*H*-hexafluoroisoquinoline, respectively. Even anhydrous hydrogen chloride gradually reacted with heptafluoroisoquinoline at a high temperature to give the corresponding 1-chlorinated product [19]. Meanwhile, addition of two equivalents of sodium methoxide selectively gave pentafluoro-1,6-dimethoxyisoquinoline.

For the synthesis of functionalized fluoroisoquinolines, cyclization of *N*-[2-(fluorophenyl)ethyl]amides followed by aromatization was effective, which is called the Bischler–Napieralski reaction and is a typical method for 1-substituted 3,4-dihydroisoquinolines directed toward isoquinoline synthesis [20]. The reaction smoothly proceeded, irrespective of the positions of fluorine, when *N*-[2-(fluorophenyl)ethyl]-2-phenylacetamides were used (Scheme 6) [11]. Notably, 8-fluoro-3,4-dihydroisoquinoline was not obtained by this method because *N*-[2-(3-fluorophenyl)ethyl]-2-phenylacetamides gave 6-fluoro-3,4-dihydroisoquinolines exclusively. The reduction of 3,4-dihydroisoquinolines to



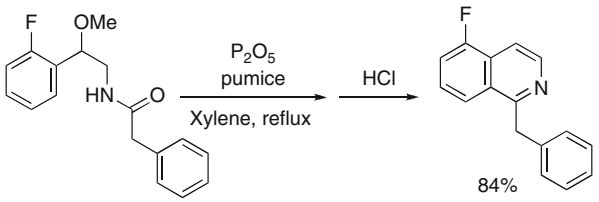
Scheme 5 Nucleophilic aromatic substitutions of heptafluoroisoquinoline

tetrahydroisoquinolines followed by oxidative aromatization provided the corresponding 1-benzyl-fluoroisoquinolines, whereas the direct oxidation of fluorinated 3,4-dihydroisoquinolines failed and led to the loss of fluorine with palladium species [21].



Scheme 6 Synthesis of fluoroisoquinolines via the Bischler–Napieralski reaction

The Pictet–Gams reaction, [22] which is known as a variation of the Bischler–Napieralski reaction, enabled a sequential reaction consisting of cyclization and aromatization to give 1-benzyl-5-fluoroisoquinoline from *N*-[2-(2-fluorophenyl)-2-methoxyethyl]-2-phenylacetamide (Scheme 7) [21].



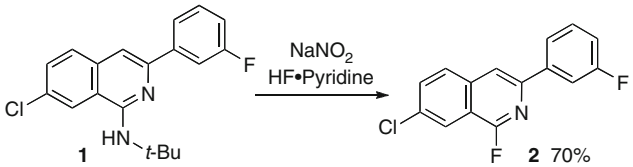
Scheme 7 Synthesis of 5-fluoroisoquinoline via the Pictet–Gams reaction

As it was described previously, fluoroisoquinoline chemistry has begun about half a century ago. Since the predawn of fluoroisoquinoline chemistry, various syntheses of ring-fluorinated isoquinoline derivatives have been accomplished, accompanied by remarkable progress in the aromatic ring fluorination and in the construction of fluorine-containing heterocycles. From the standpoint of organic synthesis, methodologies for fluorinated isoquinolines can be classified into three major groups: (i) the direct fluorination onto the isoquinoline ring, (ii) the construction of a fused pyridine ring via cyclization of a precursor bearing a pre-fluorinated benzene ring, and (iii) the simultaneous installation of an isoquinoline framework and a fluorine substituent. In the following section, modern synthetic methodologies for fluorinated isoquinolines are presented according to this classification. The last section of this chapter presents a discussion of the application of fluorinated isoquinoline derivatives in various scientific fields.

3 Syntheses of Ring-Fluorinated Isoquinolines

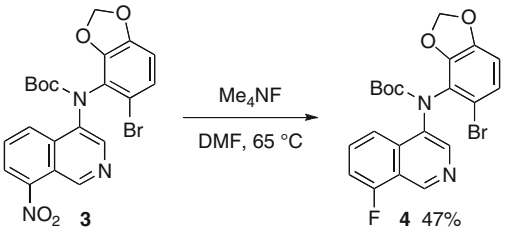
3.1 Direct Ring Fluorination

The Baltz–Schiemann reaction is still one of the most common methods for direct ring fluorination because of the accessibility to aminated isoquinoline derivatives. The original conditions, which involve the use of tetrafluoroboric acid (fluoroboric acid), are still often employed, [23–27] even though several modified procedures have been reported. For example, Myers synthesized 1-fluoroisoquinoline **2** by the dealkylative diazotization of 1-*tert*-butyl-aminoisoquinoline **1** with pyridine hydrofluoride instead of HBF_4 (Scheme 8) [28].



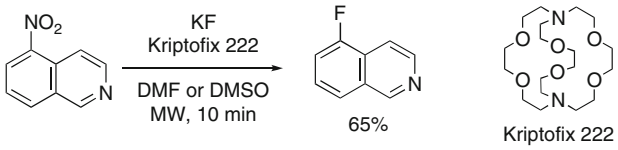
Scheme 8 Synthesis of 1-fluoroisoquinoline via dealkylative diazotization

Among neutral nitrogen substituents, a nitro group on an aromatic ring can be directly converted to a fluorine substituent via the S_NAr mechanism [29–32]. In this fluorodenitration method, tetraalkylammonium fluorides and inorganic fluoride salts have been used as fluorine sources. For example, upon treatment with tetramethylammonium fluoride, 8-nitroisoquinoline **3** afforded 8-fluorinated isoquinoline **4** (Scheme 9) [25].



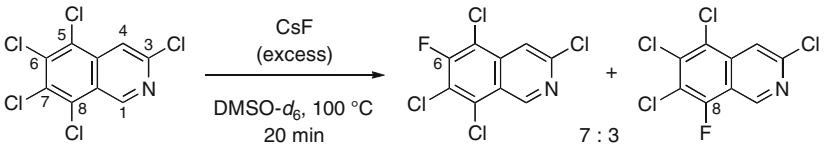
Scheme 9 Synthesis of 8-fluoroisoquinoline via fluorodenitration with Me_4NF

Even potassium fluoride induced fluorodenitration of 5-nitroquinoline with the aid of 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8,8,8]-hexacosane (Kryptofix 222) [33, 34] as a phase transfer agent under microwave irradiation, which led to 5-fluoroquinoline (Scheme 10) [35].

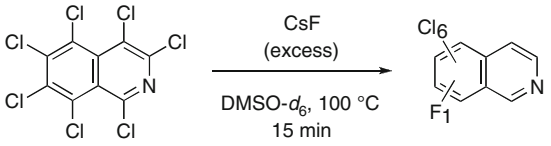


Scheme 10 Synthesis of 5-fluoroisoquinoline via fluorodenitration with KF

The Halex reaction for the synthesis of multi-fluorinated isoquinoline was investigated in detail by Matthews et al., and they attempted chlorine–fluorine exchange reactions of several multi-chlorinated isoquinolines [36]. When 3,5,6,7,8-pentachloroisoquinoline was treated with an excess of cesium fluoride in deuterated dimethyl sulfoxide (DMSO-d_6) at 100 °C, 3,5,7,8-tetrachloro-6-fluoroisoquinoline and 3,5,6,7-tetrachloro-8-fluoroisoquinoline were formed in a 7:3 ratio after 20 min (Scheme 11). The observation of the predominant substitution at the 6-position was consistent with the fact that the 6-position of heptafluoroisoquinoline was the second most reactive to nucleophiles after the 1-position (vide supra, Scheme 5) [17]. Similar reaction conditions were also employed in the reaction of heptachloroisoquinoline, where the 1-position was found to be more reactive than other positions (Scheme 12).



Scheme 11 The Halex reaction of 3,5,6,7,8-pentachloroisoquinoline

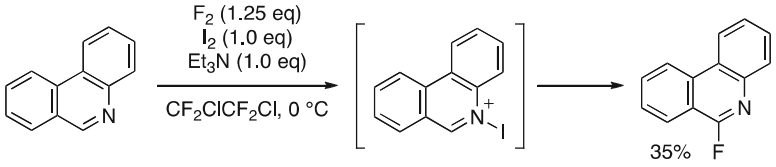


Position	1	3	4	5	6	7	8
Ratio	65	4	0	4	8	6	7

Scheme 12 The Halex reaction of heptachloroisoquinoline

With respect to other positions, Matthews concluded that the reactivity for substitution in heptachloroquinoline was 1>>6=7=8>3=5>4. Notably, the 3-position of haloisoquinolines was less reactive toward nucleophilic substitution even though it was adjacent to the nitrogen atom, whereas the 1-position of haloisoquinolines and the 2-position of haloquinolines were substantially reactive [37].

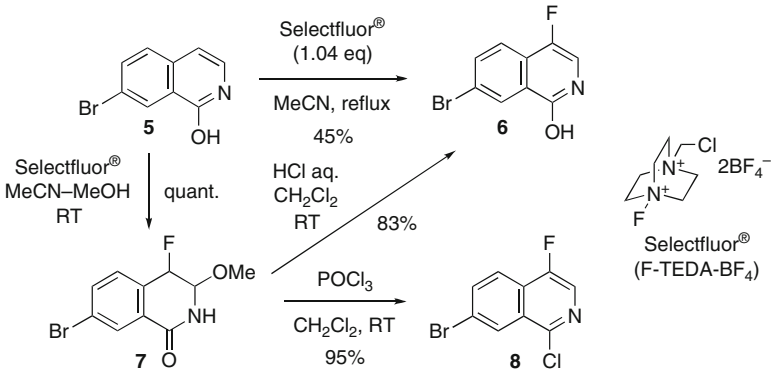
The direct fluorination of a C–H bond of nitrogen-containing heterocycles was achieved with gaseous fluorine and iodine by Chambers and Sandford et al [38]. The mixture of fluorine and iodine served as sources of both I^+ and F^- (Scheme 13). The heterocycles activated by *N*-iodination underwent fluoride attack at the carbon adjacent to the nitrogen atom. Elimination of hydrogen iodide gave the corresponding ring-fluorinated heterocycles. In this report, phenanthridine, a benzo analogue of isoquinoline, was fluorinated to afford 6-fluorophenanthridine.



Scheme 13 Synthesis of 6-fluorophenanthridine via fluorination with F_2 and I_2

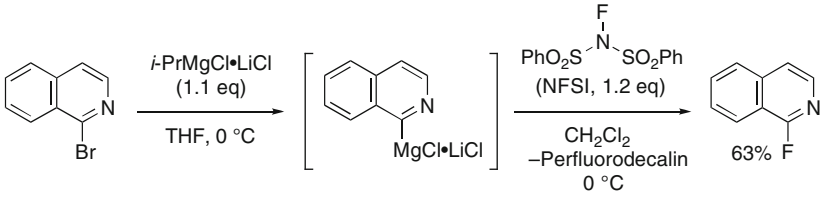
In contrast to nucleophilic fluorination, fluoroisoquinoline syntheses via direct electrophilic fluorination were reported relatively recently. In 2007, Price developed direct electrophilic C–H bond fluorination of an isoquinoline derivative with Selectfluor® (1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), F-TEDA), [39] which is known as an efficient electrophilic fluorine source [40–42].

Refluxing the mixture of 6-bromo-1-hydroxyisoquinoline (**5**) and Selectfluor® in acetonitrile afforded 7-bromo-4-fluoro-1-hydroxy-isoquinoline (**6**) as a single isomer in a one-pot reaction (Scheme 14). In contrast, fluorinated methanol adduct **7** was quantitatively produced, when the reaction was conducted at ambient temperature in an acetonitrile–methanol mixed solvent. Subsequent aromatization of **7** with hydrochloric acid gave **6** in high overall yield, whereas the reaction with phosphoryl chloride provided 1-chlorinated 4-fluoroisoquinoline **8** as another variation of 4-fluorinated isoquinoline derivatives.



Scheme 14 Electrophilic fluorination with Selectfluor®

In 2010 Knochel et al. reported the electrophilic fluorination of heteroarylmagnesium reagents by applying their magnesiation methodology, [43, 44] in which heteroaryl bromides underwent a Br–Mg exchange through the addition of an isopropylmagnesium chloride–lithium chloride complex [45–47]. *N*-fluorobenzenesulfonimide (NFSI) was used as an electrophilic fluorinating agent to trap the generated heteroarylmagnesium species in good to excellent yield (Scheme 15). Although electrophilic fluorination of standard aryl Grignard reagents had already been reported, [48] Knochel's method significantly improved the product yields. Thus, 1-fluoroisoquinoline was readily prepared from 1-bromoisoquinoline.

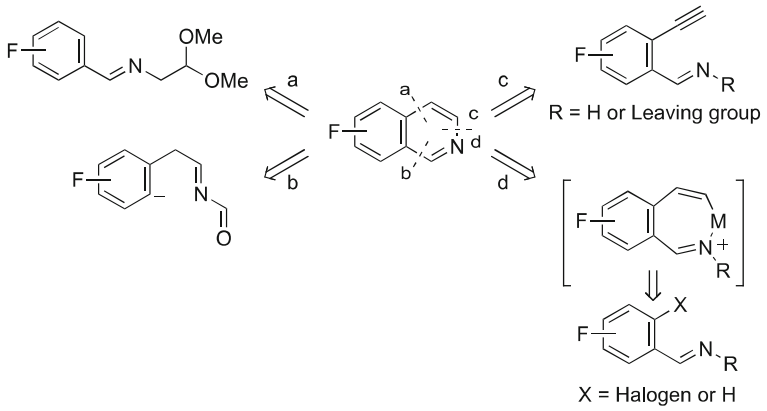


Scheme 15 Electrophilic fluorination of 1-isoquinolylmagnesium reagent

3.2 *Ring Construction of Pre-fluorinated Substrates*

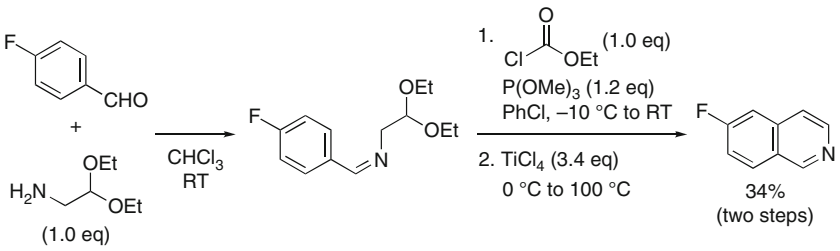
The construction of heterocycles from fluoroarene substrates is an efficient approach to synthesize ring-fluorinated heterocycles with a fused benzene ring because fluoroarenes are relatively easy to access and aromatic C–F bonds are sufficiently robust to survive most of the reaction conditions. Nowadays a wide variety of methodologies for heterocyclic ring construction have been established, this strategy has been predominant in the syntheses of benzene-ring-fluorinated isoquinolines. To employ this strategy, the nitrogen atom must be located at appropriate positions, and cyclization accompanied or followed by aromatization must smoothly proceed.

Aryl or benzyl imines have been commonly used as precursors of isoquinolines. In cases starting with *N*-substituted imines, the substituents on the nitrogen atom should be efficiently incorporated or eventually removed (Scheme 16, routes a–c). The method via simultaneous reductive elimination and removal of *N*-substituents from nitrogen-containing metallacycles is also effective (Scheme 16, route d). The intermediary metallacycles can be mainly obtained from (*ortho*-haloaryl)methanimines.



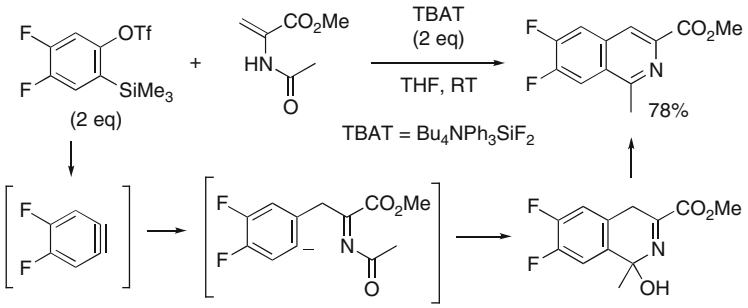
Scheme 16 Approaches to fluoroisoquinolines starting from imines bearing a fluoroaryl group

Benzylideneaminoacetoaldehyde acetals prepared from benzaldehydes have been key intermediates of a well-established method for isoquinoline synthesis known as the Pomeranz–Fritsch reaction (Scheme 16, route a) [49, 50]. Intramolecular cyclization of this type of imines under acidic conditions provided isoquinolines, where the two-carbon substituent on the nitrogen atom was transformed into a part of the isoquinoline ring. For the synthesis of 8-fluoroisoquinoline, the application of the standard procedure gave a low yield of the desired product (3 % in two steps from 2-fluorobenzaldehyde) [51]. However, in the modified procedure using ethyl chloroformate, trimethyl phosphite, and titanium tetrachloride for the cyclization step [52] provided 6-fluoroisoquinoline from 4-fluorobenzaldehyde in 34 % overall yield (Scheme 17) [25].



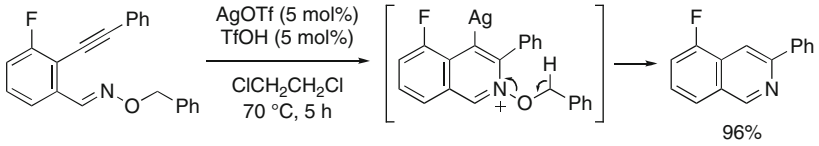
Scheme 17 Synthesis of 6-fluoroisoquinoline via the Pomeranz–Fritsch reaction

Stoltz et al. [53] and Ramtohul et al. [54] independently and almost simultaneously reported an isoquinoline synthesis via the reaction of *N*-acetylenamines with benzynes (Scheme 16, route b; Scheme 18). In this reaction, intermediary *N*-acetylimines underwent nucleophilic attack of the aryl anions to give the corresponding isoquinolines after aromatization. The carbonyl carbon on the nitrogen atom was incorporated into the 1-position of the resulting isoquinolines.



Scheme 18 Synthesis of 6,7-difluoroisoquinoline via the reaction of *N*-acetylenamine with benzyne

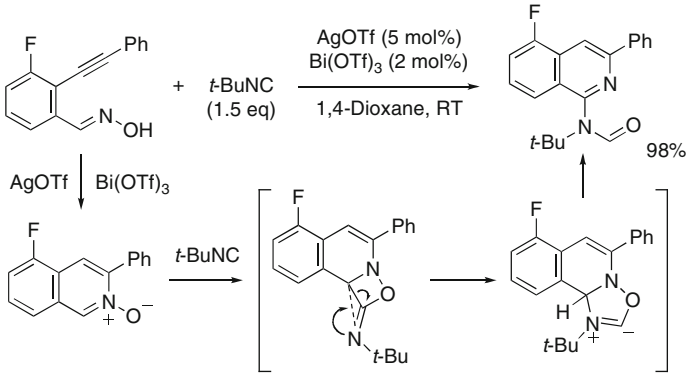
2-Alkynylbenzaldehyde *O*-alkyl oximes were also used as precursors of isoquinolines (Scheme 16, route c). After intramolecular electrophilic cyclization, *N*-alkoxy groups were eliminated to form aldehydes (for example benzaldehyde). Shin et al. synthesized 5-fluoro-3-phenylisoquinoline using a AgOTf/TfOH catalytic system (Scheme 19), [55] while Wu achieved Cu-catalyzed synthesis of several 7-fluoroisoquinoline derivatives [56].



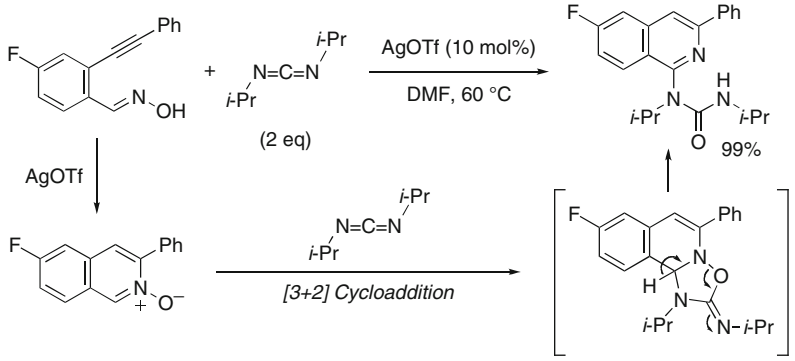
Scheme 19 Ag-catalyzed electrophilic cyclization of 2-alkynylbenzaldehyde *O*-alkyl oxime for 5-fluoroisoquinoline synthesis

The intramolecular electrophilic cyclization of *N*-(2-alkynylbenzylidene)hydrazides or 2-alkynylbenzoaldoximes afforded isoquinolinium-2-ylamides or isoquinoline *N*-oxides, respectively (Scheme 16, route c). The carbon atoms at the 1-position of these compounds were substantially electrophilic because of the polarization of the N–O or N–N bond. Therefore, these isoquinoliniums readily underwent [3+2] cycloaddition and nucleophilic attack to the 1-position, as discussed in the subsequent paragraph.

Wu et al. synthesized a 5-fluoroisoquinoline derivative via the reaction of a 2-alkynylbenzoaldoxime and an isocyanide with a AgOTf/$Bi(OTf)_3$ catalyst (Scheme 20) [57]. Sequential rearrangements were triggered by the addition of the isocyanide to the 1-position of the intermediary isoquinoline *N*-oxide. The [3+2] cycloaddition of the *N*-oxide with a carbodiimide followed by ring-opening also afforded 6- and 7-fluoroisoquinoline derivatives (Scheme 21) [58]. Recently, similar approaches to functionalized fluoroisoquinolines have been frequently adopted [59–65]. In addition to the above-mentioned imine derivatives, *N*-*tert*-butyl imines were used, where the *tert*-butyl group was removed from the nitrogen atom [66]. Furthermore, primary imines have been shown to serve as precursors of fluorinated isoquinolines, albeit under harsh conditions [67, 68].

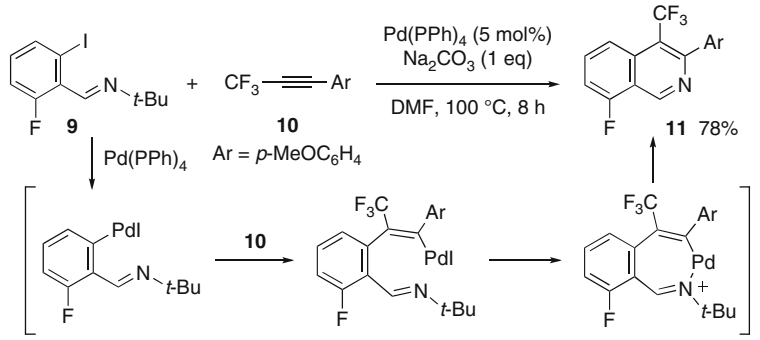


Scheme 20 Ag/Bi-cocatalyzed electrophilic cyclization of 2-alkynylbenzoaldoxime for 5-fluoroisoquinoline synthesis

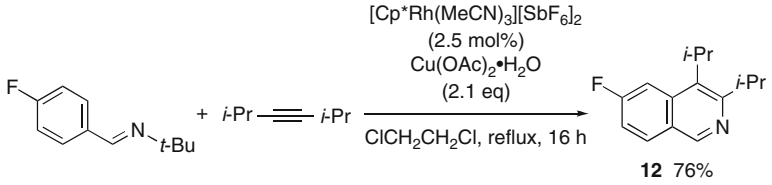


Scheme 21 Ag-catalyzed electrophilic cyclization of 2-alkynylbenzoaldoxime for 6-fluoroisoquinoline synthesis

The reductive elimination from seven-membered nitrogen-containing metallacycles also leads to the construction of the isoquinoline framework (Scheme 16, route d). Such metallacycles result from the insertion of alkynes into metal–aryl bonds mainly formed by oxidative addition of aryl–halogen bonds. Konno et al. achieved the synthesis of 8-fluoroisoquinoline **11** via the reaction of 2-iodobenzylidenamine **9** with trifluoromethylalkyne **10** with the aid of a palladium catalyst (Scheme 22) [69]. Related synthetic methodologies have been established with a nickel catalyst [70] as well as palladium catalysts [71–73]. Fagnou et al. succeeded in a similar isoquinoline synthesis via C–H bond activation with a rhodium catalyst, which provided 6-fluoroisoquinoline **12** (Scheme 23) [74].



Scheme 22 Pd-catalyzed domino insertion/cyclization sequence for 8-fluoroisoquinoline synthesis

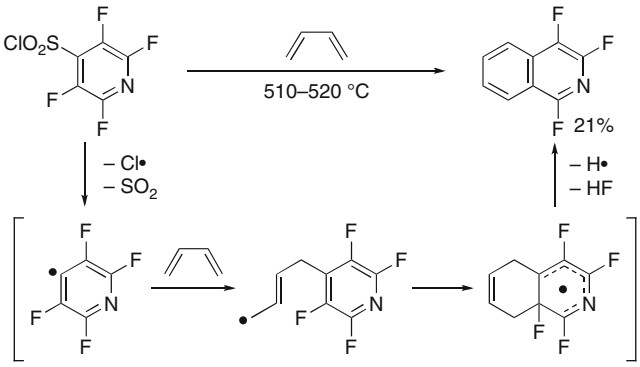


Scheme 23 Route to 6-fluoroisoquinoline via Rh-catalyzed C–H bond activation

Nitrogen-containing functional groups other than imines can also participate in this type of isoquinoline synthesis. For example, nitriles were convenient because they possess no extra groups on the nitrogen atom to be removed. Fluorinated isoquinolines were prepared via the intramolecular and intermolecular reactions of nitriles. The nitrogen atom of nitriles exhibited sufficient nucleophilicity to form C–N bonds that contributed to the construction of isoquinoline scaffolds [75, 76]. Imine-metal species derived from nitriles and organometallic reagents were effective for this purpose [28, 77–79]. Amines, [80–82] amides, [83–86] azides, [87] triazoles, [88] and enamine-type intermediates [89, 90] also served as key precursors for fluorinated isoquinolines.

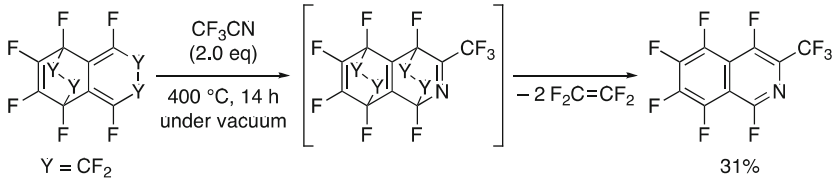
Construction of benzene rings has rarely been conducted in the last stage of fluoroisoquinoline synthesis. The use of fluorinated pyridines as starting materials allows the introduction of fluorine on the heterocyclic ring carbons. Queguiner et al. reported

the multi-step synthesis of an indole-fused 1-fluoroisoquinoline. [91] Platonov et al. synthesized 1,3,4-trifluoroisoquinoline via the copyrolysis of 2,3,5,6-tetrafluoropyridine-4-sulfonyl chloride with butadiene (Scheme 24) [92].



Scheme 24 Synthesis of 1,3,4-trifluoroisoquinoline via copyrolysis of pyridine-4-sulfonyl chloride with butadiene

Exceptionally, there is an example for simultaneous construction of both benzene and pyridine rings toward a perfluorinated isoquinoline. Feast et al. reported the synthesis of perfluoro-3-methylisoquinoline via the hetero Diels–Alder reaction of perfluoro-1,4,6,7-tetrahydro-1,4-ethanonaphthalene with trifluoroacetonitrile followed by pyrolysis, which involved elimination of tetrafluoroethylene (Scheme 25) [93].



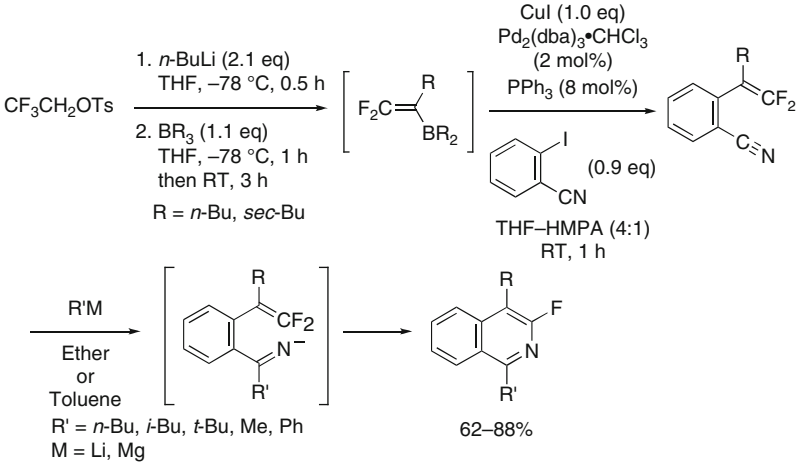
Scheme 25 Synthesis of perfluoro-3-methylisoquinoline via the hetero Diels–Alder reaction

3.3 Simultaneous Installation of an Isoquinoline Framework and a Fluorine Substituent

Intramolecular cyclizations of *ortho*-functionalized *β*,*β*-difluorostyrenes provide a general access to ring-fluorinated heterocycles. In this methodology, both the construction of a heterocyclic nucleus and the introduction of a fluorine substituent are simultaneously effected.

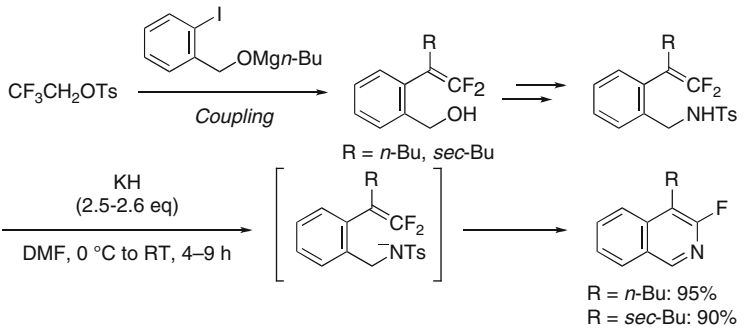
The difluoromethylene carbon of 1,1-difluoro-1-alkenes exhibits strong electrophilicity because of the electron-deficient and highly polarized carbon–carbon

double bond, and thus difluoroalkenes readily react with nucleophiles instead of electrophiles. Furthermore, the nucleophilic attack to difluoroalkenes followed by fluoride elimination (vinylic nucleophilic substitution; S_NV) provides products bearing a fluorovinylic moiety. Ichikawa et al. constructed 5-membered and 6-membered heterocycles via intramolecular S_NV reactions of 1,1-difluoro-1-alkenes [94–96]. This strategy can introduce a fluorine substituent at a prescribed position, whereas the direct fluorination methods generally require regioselective pre-functionalization. This methodology has been successfully applied to the synthesis of 3-fluoroisoquinolines, which has been difficult to prepare with previous methods, including heterocyclic ring construction. *β*,*β*-difluorostyrenes as cyclization precursors have been mainly prepared via palladium-catalyzed coupling of *ortho*-functionalized aryl iodides and difluorovinylborans, which were generated from 2,2,2-trifluoroethyl 4-methylbenzenesulfonate [97, 98]. *o*-Cyano-*β*,*β*-difluorostyrenes thus formed reacted with organometallics to give the corresponding iminyl metal intermediates, which in turn underwent 6-*endo* cyclization to give 3-fluoroisoquinolines (Scheme 26) [99].

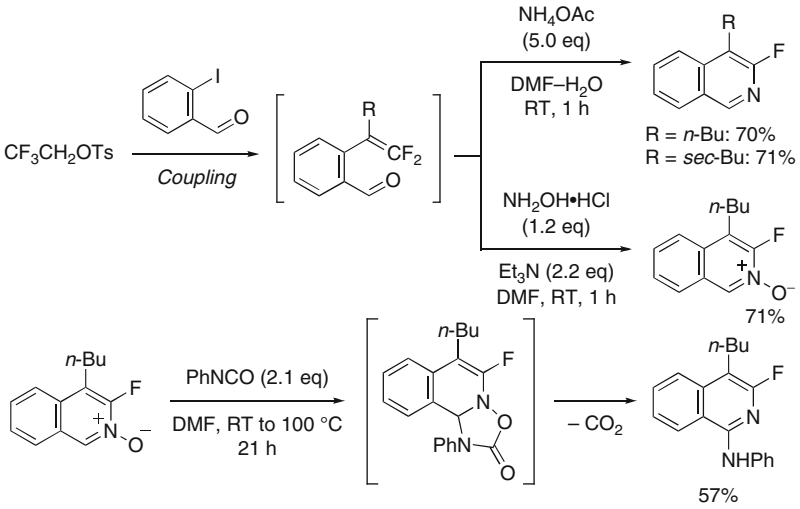


Scheme 26 Synthesis of 3-fluoroisoquinolines via the intramolecular S_NV reaction of iminyl metal intermediates

Sulfonamides are sufficiently reactive to serve as nucleophiles in the reaction with difluorostyrenes under basic conditions (Scheme 27) [100]. Imines and oximes have also been utilized as nucleophiles to provide 3-fluoroisoquinolines and their *N*-oxides, respectively (Scheme 28) [101]. When the isoquinoline *N*-oxide was treated with an isocyanate, the oxygen atom on the nitrogen was consequently eliminated after the 1,3-dipolar addition to afford a 1-amino-3-fluoroisoquinoline (Scheme 28).



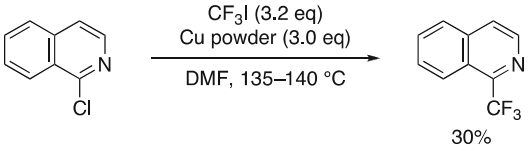
Scheme 27 Synthesis of 3-fluoroisoquinolines via the intramolecular S_NV reaction of difluorostyrenes bearing a sulfonamide moiety



Scheme 28 Synthesis of 3-fluoroisoquinolines via the intramolecular S_NV reaction of difluorostyrenes bearing a formyl group

4 Syntheses of Pyridine-Ring-Trifluoromethylated Isoquinolines

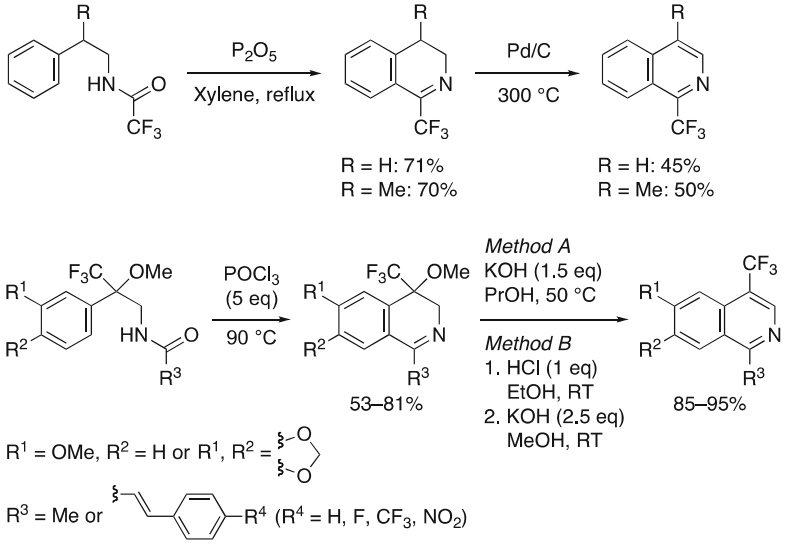
As well as a fluorine substituent, a trifluoromethyl group have recently attracted much attention as the shortest perfluoroalkyl group. A variety of methodologies for the introduction of a trifluoromethyl group into heteroaromatics have been also developed [102]. In 1970, Kobayashi et al. reported the copper-mediated direct trifluoromethylation of aryl and heteroaryl halides using trifluoromethyl iodide as a source of a trifluoromethyl group [103]. Thus, 1-(trifluoromethyl)isoquinoline was synthesized, albeit in low yield (Scheme 29).



Scheme 29 Copper-mediated trifluoromethylation for 1-(trifluoromethyl)isoquinoline synthesis

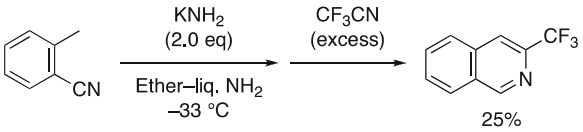
Pyridine-ring-trifluoromethylated isoquinolines are easier to access compared to ring-fluorinated counterparts. Syntheses of pyridine-ring-fluorinated isoquinolines via pyridine-ring construction are mostly difficult except for the 3-fluoroisoquinoline synthesis, which was effected via the intramolecular S_NV reaction of *β*,*β*-difluorostyrenes (see also Sect. 3.3). This is because pyridine-ring closure using fluorine-presubstituted components could be retarded by considerable reactivity changes caused by fluorine substituents. On the other hand, the trifluoromethyl group is rather chemically inert. Thus, pyridine-ring-trifluoromethylated isoquinolines have been successfully synthesized via ring closure of trifluoromethylated precursors. The following is an overview of the syntheses of pyridine-ring-trifluoromethylated isoquinolines.

The Bischler–Napieralski reaction [20] and the Pictet–Gams reaction [22] are both known as typical methods for the construction of the isoquinoline framework as described in Sect. 2. Cambon et al. synthesized 1-(trifluoromethyl)isoquinolines via the Bischler–Napieralski reaction of *N*-(phenethyl)trifluoroacetamides, [104] whereas Simig et al. utilized the Pictet–Gams reaction of *N*-(2-aryl-3,3,3-trifluoro-2-methoxypropyl)amides of acetic or cinnamic acids for the synthesis of 4-(trifluoromethyl)isoquinolines (Scheme 30) [105].

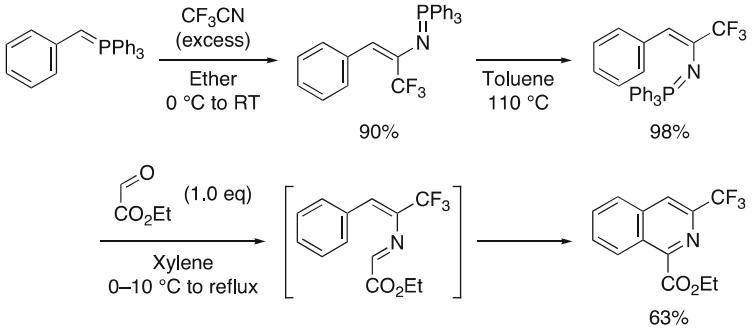


Scheme 30 Syntheses of 1- or 4-(trifluoromethyl)isoquinolines via the Bischler–Napieralski reaction or the Pictet–Gams reaction

Upon pyridine ring construction, small molecules bearing a trifluoromethyl group can be applied to intermolecular reactions as ring components. Trifluoroacetonitrile has been used not only as a component of the pyridine ring but also as a source of a trifluoromethyl group. Nauta et al. reported the synthesis of 3-(trifluoromethyl)isoquinoline via the reaction of 2-methylbenzonitrile with trifluoroacetonitrile under basic conditions (Scheme 31) [106]. Palacios et al. synthesized a 3-trifluoromethylated isoquinoline via electrocyclization of the aza-Wittig reaction product of an *N*-vinylic phosphazene, which was prepared via [2 + 2] cycloaddition of a phosphorus ylide and trifluoroacetonitrile (Scheme 32) [107]. As previously described, Feast et al. also used trifluoroacetonitrile for the synthesis of a 3-(trifluoromethyl)isoquinoline via the hetero Diels–Alder reaction (Scheme 25) [93]. Stoltz et al. used an *N*-trifluoroacetyl dehydroalanine ester for the synthesis of a 1-trifluoromethylated isoquinoline (Scheme 18) [53], whereas Konno et al. used trifluoromethylalkynes for the synthesis of 4-(trifluoromethyl)isoquinolines (Scheme 22) [69].

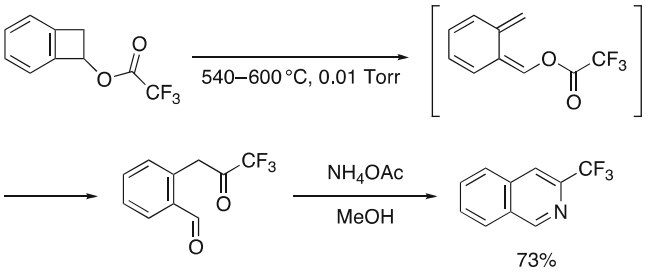


Scheme 31 Synthesis of 3-(trifluoromethyl)isoquinoline using trifluoroacetonitrile



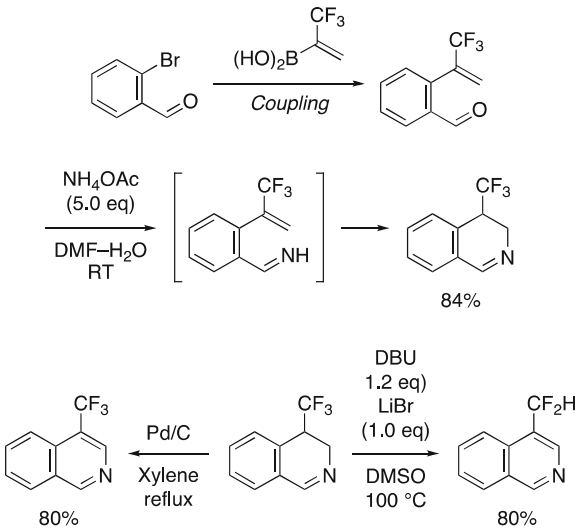
Scheme 32 Synthesis of 3-(trifluoromethyl)isoquinoline using trifluoroacetonitrile via the aza-Wittig reaction

The trifluoromethyl group is inert enough to survive under harsh reaction conditions. Schiess et al. synthesized 3-(trifluoromethyl)isoquinoline via flash vacuum pyrolysis of trifluoroacetyloxybenzocyclobutene (Scheme 33) [108]. Although the skeletal rearrangement required an ultra-high temperature, this reaction proceeded without the loss of the trifluoromethyl group.



Scheme 33 Route to 3-(trifluoromethyl)isoquinoline via flash vacuum pyrolysis

Since the trifluoromethyl group stabilizes the carbanion at its proximal carbon atom due to the strong electron-withdrawing nature, 2-trifluoromethyl-1-alkenes are subject to nucleophilic attack at their 1-positions. Ichikawa et al. have applied such a chemical property of the trifluoromethyl group to intramolecular cyclizations with carbon and heteroatom nucleophiles, which led to various fluorine-containing carbo- and heterocycles [95, 109, 110]. Among the studies, 4-trifluoromethyl-3,4-dihydroisoquinoline was synthesized via 6-*endo-trig* cyclization of the aldimine intermediate derived from an α-trifluoromethylstyrene bearing an *o*-formyl group (Scheme 34) [111]. 4-Trifluoromethyl-3,4-dihydroisoquinoline provided 4-(trifluoromethyl)isoquinoline and 4-(difluoromethyl)isoquinoline under oxidative and basic conditions, respectively. The difluoromethyl group is one of recently-highlighted fluoroalkyl groups, as well as the trifluoromethyl group [112].



Scheme 34 Intramolecular cyclization of *o*-formyl-α-(trifluoromethyl)styrene for 3-(trifluoromethyl)- or 3-(difluoromethyl)isoquinoline synthesis

5 Properties and Applications of Ring-Fluorinated Isoquinoline Derivatives

Ring-fluorinated isoquinoline derivatives thus synthesized exhibit a wide range of bioactivities that rival or surpass those of the original fluorine-free compounds. In addition to such remarkable potentials in the field of pharmaceutical sciences, the formation of supramolecular structures and the use of ligands of light-emitting metal complexes have also attracted considerable attention as possible functions of fluoroisoquinolines. This section describes concrete examples of the properties and applications of fluoroisoquinoline derivatives.

In the 1960s, isoquinoline derivatives were tested in an antitumor assay [113]. French et al. found that 1-formylisoquinoline thiosemicarbazone **13a** was effective for a variety of mouse tumors (Fig. 1a). They subsequently carried out a comprehensive study of antitumor assays using various thiosemicarbazones of 1-formylisoquinolines [24]. Among the compounds tested, 5-fluoro derivative **13b**, along with non-fluorinated compound **13a**, exhibited the strongest activity against L-1210 leukemia and the Lewis lung carcinoma. 7-Fluorinated derivative **13c** was found to be specifically active against the B-16 melanoma. Recently, Zhu et al. developed isoquinoline–pyridine-based protein kinase B/Akt antagonists [114]. 3-Fluorinated isoquinoline derivative **14** served as an effective Akt1 inhibitor (IC_{50}=3.5 nM), and the related compounds worked even in MiaPaCa-2 human pancreatic cancer cells (Fig. 1b).

Isoquinoline derivatives have been expected to serve as drugs for type II diabetes. Protein tyrosine phosphatase 1B (PTB1B) is considered to be one of the targets because it works as a negative regulator of the insulin-signaling pathway. A series of 1-(isoquinolin-1-yl)guanidines was tested as a PTB1B inhibitor by Liu and Wu et al. (Fig. 2a) [65]. They found that 6-fluorinated isoquinoline **15** was highly effective (IC_{50}=6.38 μg/mL). 11β-Hydroxydehydrogenase 1 (11β-HSD1), which catalyzes the transformation of cortisone to cortisol, is another target compound for diabetes therapy. Investigation of various 1-(benzylthio)isoquinolines and 1-(benzylthio)-5,6,7,8-tetrahydroisoquinolines revealed that ring-fluorinated isoquinoline derivatives **16b**, **16c**, and **16e** possess significant activity against 11β-HSD1 as non-fluroinated compound **16a** (Fig. 2b) [115]. Among compounds bearing isoquinoline scaffolds, 7-fluorinated compound **16d** showed the highest activity in the inhibition of both mouse (IC_{50}=7 nM) and human (IC_{50}=2 nM) 11β-HSD1 enzymes.

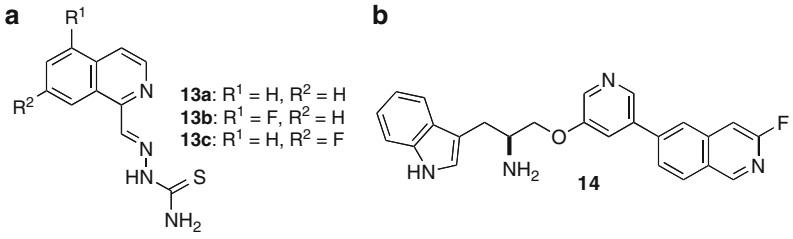
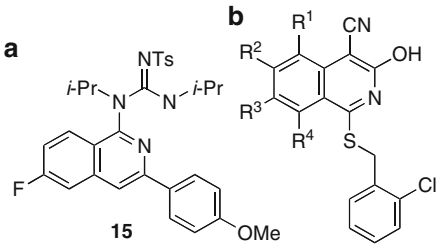


Fig. 1 Antitumor active fluoroisoquinolines



Sample	11β-HSD1 IC_{50} (nM)	
	Human	Mouse
16a: $R^1 = R^2 = R^3 = R^4 = H$	4	19
16b: $R^1 = F$, $R^2 = R^3 = R^4 = H$	8	7
16c: $R^2 = F$, $R^1 = R^3 = R^4 = H$	8	14
16d: $R^3 = F$, $R^1 = R^2 = R^4 = H$	2	7
16e: $R^4 = F$, $R^1 = R^2 = R^3 = H$	6	10

Fig. 2 Drug candidate fluoroisoquinolines for type II diabetes

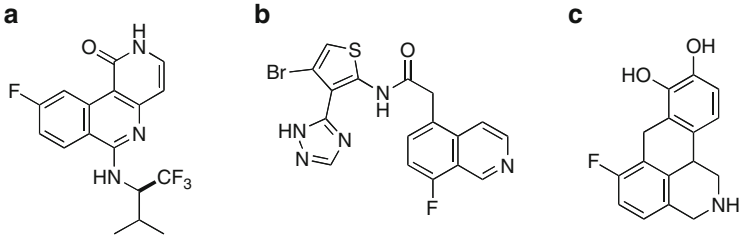


Fig. 3 Fluoroisoquinolines as competitive inhibitors of enzymes and receptors

Napthyridinones inhibit the activity of Janus kinase 2 (JAK2), which plays important roles in hematopoiesis and immune response (Fig. 3a). Among napthyridinones, compounds bearing a 6-fluoroisoquinoline substructure exhibited extraordinary potency as JAK2 inhibitors [85]. Besides above-mentioned fluorinated isoquinolines, aminothiophene-containing fluorinated isoquinolines contributed to the inhibition of the c-Jun N-terminal kinases (JNKs), which are members of the mitogen-activated protein kinase (MAPK) family (Fig. 3b) [27]. Dinapsoline derivatives prepared from fluorinated isoquinolines also showed substantial bioactivities as dopamine receptor agonists (Fig. 3c) [25].

In addition to exhibiting bioactivities, polyfluoroaromatic compounds often display unique properties for accessing supramolecular architectures in crystalline states. Arene and polyfluoroarene molecules are well known to alternately stack through π–π interactions in their 1:1 co-crystals to give columnar structures [116].

Homocrystals of 1,2,3,4-tetrafluoronaphthalene, a partially fluorinated naphthalene, showed an obvious π–π stacking structure with a head-to-tail orientation like co-crystals of arenes and polyfluoroarenes (Fig. 4a) [117]. In contrast, the CF/π interaction [118, 119] was predominant in homocrystals of 1,3,4-trifluoroisoquinoline, in which the C2–F fragment of 1,2,3,4-tetrafluoronaphthalene was replaced by a nitrogen atom (Fig. 4b) [117]. This difference forced 1,3,4-trifluoroisoquinoline to adopt a head-to-head orientation without π–π stacking.

Iridium complexes bearing isoquinoline-based bidentate ligands are phosphorescent (Scheme 35). 1-Phenylisoquinolinyliridium complexes emit red phosphorescence as the result of spin-forbidden triplet metal-to-ligand charge transfer (^{3}MLCT) excitation [26]. Such complexes, including some based on 5-fluoroisoquinoline,

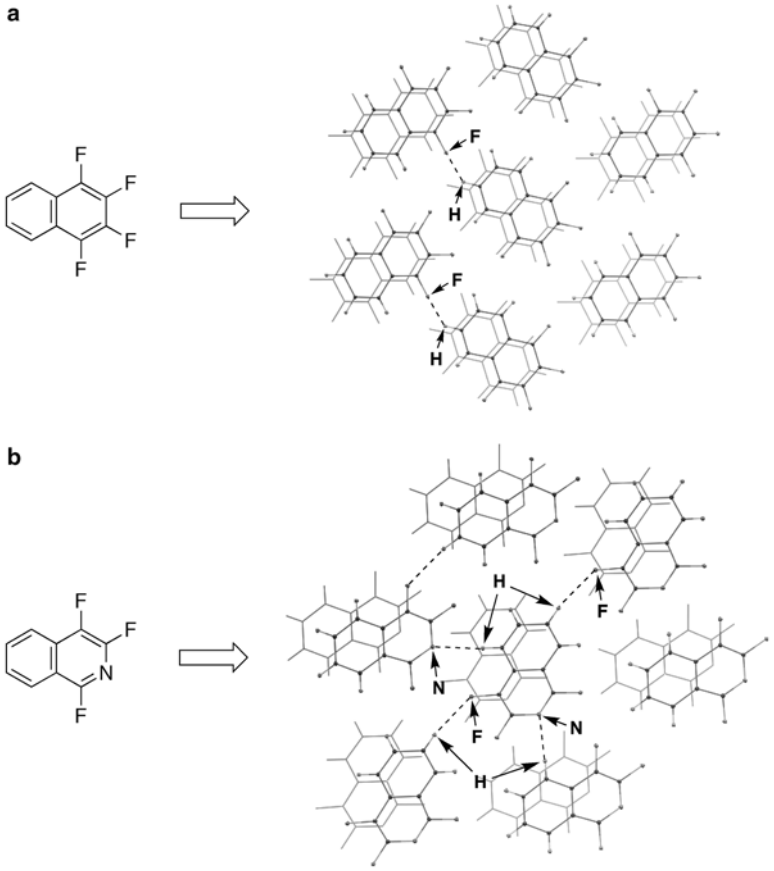
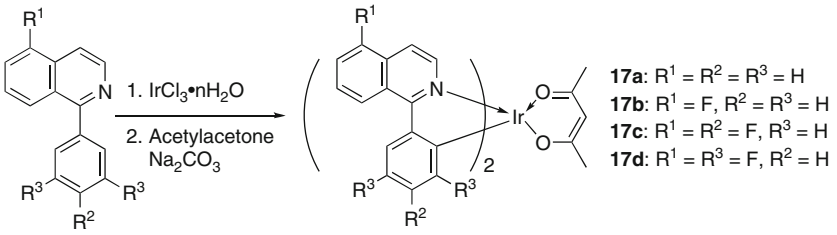


Fig. 4 Supramolecular networks in crystal structures of (**a**) 1,2,3,4-tetrafluoronaphthalene and (**b**) 1,3,4-trifluoroisoquinoline

were utilized for organic light-emitting devices (OLEDs), which were fabricated as follows: 4,4′-*N*,*N*′-dicarbazolebiphenyl (CBP) was used as a host material for iridium complexes, bathocuproine (BCP) was used as a hole blocker, 4,4′-bis(*N*-naphthylphenylamino)biphenyl (NPB) was used as a hole transport layer, and tris(8-hydroxyquinolinyl)aluminum(III) (Alq_3) was used as an electron transport layer. The OLEDs thus fabricated from iridium complexes **17** showed good emission quantum yields and high brightness. For example, [Ir(5-f-1piq)$_2$(acac)] (**17b**; 5-f-1piq = 5-fluoro-1-phenylisoquinoline) showed a turn-on voltage of 35 V, low-working voltages (1,883 cd m^{-2} at 7.1 V and 8,329 cd m^{-2} at 9.0 V), and a maximum brightness of 38,218 cd m^{-2} (14.0 V), which suggests that this complex has strong potential for use in full color displays (Table 1). The emission color coordinates of **17b** on the Commission Internationale de I'Éclairage (CIE) chart were ($x = 0.68$, $y = 0.31$), which is close to the standard red color.



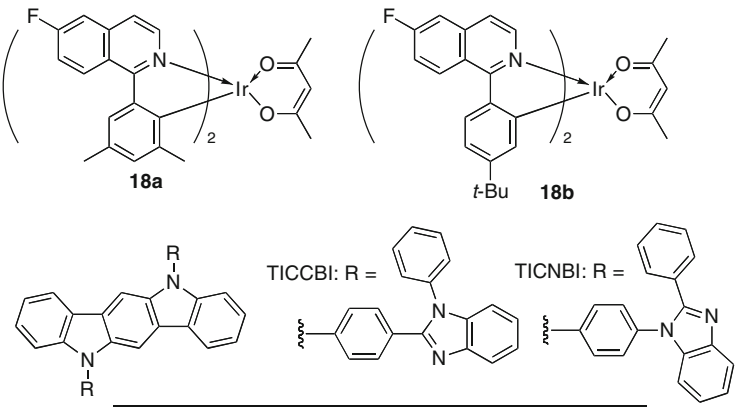
Scheme 35 Preparation of 1-phenylisoquinolinyliridium complexes

Table 1 Electrophosphorescent data of iridium complexes bearing isoquinoline-based bidentate ligands

Complex	Brightness (cd/m^2)	External quantum efficiency (%)	Voltage (V)	CIE coordinates
17a	1,514[a]	8.46	8.53	x = 0.68
	8,224[b]	9.21	11.01	y = 0.32
	24,978[c]	7.00	13.92	
	31,776[d]			
17b	1,883[a]	10.15	7.12	x = 0.68
	8,329[b]	9.00	8.98	y = 0.31
	24, 038[c]	6.50	11.04	
	38,218[d]			
17c	2,603[a]	7.41	7.29	x = 0.60
	9,644[b]	5.28	8.79	y = 0.36
	12,151[c]	4.80	9.16	
	23,606[d]			
17d	1,511[a]	5.48	9.02	x = 0.66
	7,008[b]	5.10	11.35	y = 0.33
	19,661[c]	3.86	14.10	
	31,490[d]			

[a] $J = 20$ mA/cm^2
[b] $J = 20$ mA/cm^2
[c] $J = 20$ mA/cm^2
[d] Maximum brightness at 14 V

Later, iridium complexes with 6-fluoroquinoline-based ligands, (35dmPh-6Fiq)$_2$Ir(acac) (**18a**; 35dmPh-6Fiq = 6-fluoro-1-(3,5-dimethylphenyl)isoquinoline) and (4*t*BuPh-6Fiq)$_2$Ir(acac) (**18b**; 4*t*BuPh-6Fiq = 6-fluoro-1-(4-*tert*-butylphenyl) isoquinoline) were developed as red color emitting phosphorescent materials (Fig. 5) [120]. When these iridium complexes as red emitters were combined with benzimidazole–indolo[3,2-*b*]carbazole-linked molecules (TICCBI and TICNBI) as donor–acceptor bipolar hosts, the OLEDs exhibited high external quantum efficiencies (14.4–15.6 %).



Host: 10% Dopant	η_{ext} (maximum) / %	CIE (x,y)
TICCBI: **18a**	14.4	(0.70, 0.30)
TICCBI: **18b**	15.3	(0.68, 0.32)
TICNBI: **18a**	15.6	(0.69, 0.30)
TICNBI: **18b**	15.5	(0.67, 0.32)

Fig. 5 OLEDs fabricated with iridium complexes bearing 6-fluoroquinoline-based ligands as emitters and TICCBI and TICNBI as donor–acceptor bipolar hosts

6 Conclusions and Perspectives

In this decade, synthetic methodologies for ring-fluorinated isoquinolines have been greatly developed as described above. The Baltz–Shiemann reaction provides a versatile method for the syntheses of isoquinolines bearing a fluorine atom at any position, albeit with difficulties in regioselective prefunctionalization. In the syntheses of benzene-ring-fluorinated isoquinolines, a wide variety of methods can be employed to construct pyridine rings starting from fluorobenzene derivatives. In terms of heterocyclic-ring-fluorinated isoquinolines, 1-fluoroisoquinolines are effectively prepared via either nucleophilic or electrophilic substitution from 1-haloisoquinolines. 3-Fluoroisoquinolines can be selectively synthesized via various intramolecular S_NV reactions of *ortho*-functionalized β,β-difluorostyrenes. 4-Fluoroisoquinolines can be obtained via electrophilic fluorination of 1-hydroxyisoquinolines. As for the syntheses of pyridine-ring-trifluoromethylated isoquinolines, pyridine-ring construction methods are also quite effective.

In addition to the increasing diversity of ring-fluorinated isoquinolines obtained, they have already been utilized not only as drug candidates but also as functional materials. The chemistry of the ring-fluorinated isoquinolines will continue to progress; thus, in the near future, fluoroisoquinolines with predominant properties will emerge in which the characteristics of the fluorine substituent are fully utilized.

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Fluorinated Pyrones, Chromones and Coumarins

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Contents

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V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 2: 6-Membered Heterocycles*, 211
DOI 10.1007/978-3-319-04435-4_5, © Springer International Publishing Switzerland 2014

Abstract The synthesis, reactivity and applications of fluorinated α- and γ-pyrones, chromones and coumarins are reviewed. The literature data clearly indicate that these heterocycles are very attractive building blocks for the synthesis of various heterocyclic compounds containing the R^F group. This chapter reviews the significant advances in this area, highlighting new and interesting trifluoromethylated derivatives and their novel transformations. The bibliography includes 204 references.

Keywords Fluorinated heterocycles • 4-Pyrones • 2-Pyrones • Chromones • Coumarins

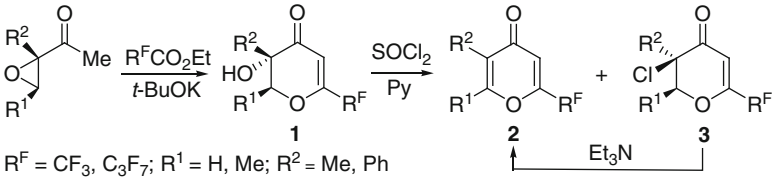
1 Fluorinated 4-Pyrones

4*H*-Pyran-4-ones (4-pyranones, 4-pyrones, γ-pyrones) containing polyfluoroalkyl substituents, especially the CF_3 group, serve as key precursors to a variety of fluorinated pyridine derivatives having a wide range of biological activities. For example, 2,6-bis(trifluoromethyl)-4-pyridols have been found useful as herbicides and fungicides as disclosed in patent literature [1a, b]. Certain 2-aryl-6-tri(di)fluoromethyl-4-pyrones selectively inhibit COX-2 in preference to COX-1 and are useful in the treatment of COX-2 mediated diseases, such as inflammation, pain, fever, and asthma with fewer side effects [1c]. Due to the powerful electron-withdrawing ability of R^F groups the insertion of polyfluoroalkyl substituents into the 2-position of 4-pyrone activates these molecules and dramatic differences in the reactivity of 2-alkyl(aryl)- and 2-(polyfluoroalkyl)-4-pyrones with respect to nucleophilic reagents are observed.

1.1 Synthesis of 2-(Polyfluoroalkyl)-4-Pyrones

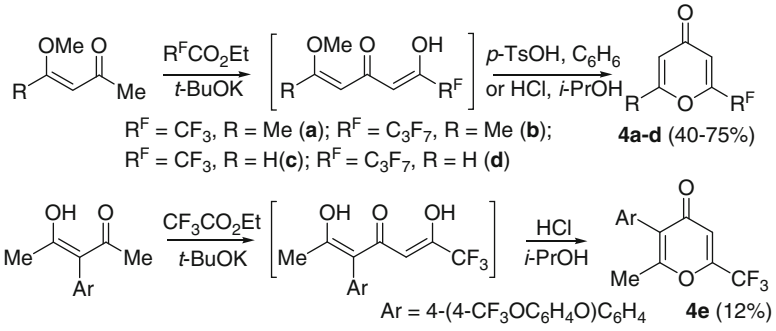
In addition to the considerable variety of methods for the synthesis of non-fluorinated γ-pyrones [2], Tyvorskii and co-workers have described three new procedures, which produced 2-(perfluoroalkyl)-4-pyrones. One of them is a convenient two-step synthesis of 5-substituted 2-(perfluoroalkyl)-4*H*-pyran-4-ones **2** by dehydration of 2,3-dihydro-3-hydroxy-6-(perfluoroalkyl)-4*H*-pyran-4-ones **1** prepared

by condensation of 2-acetyloxiranes with ethyl perfluoroalkanoates [3]. The reaction of dihydropyranones **1** with thionyl chloride in pyridine provides the desired pyrones **2** in 61–79 % yields with 10–15 % of chlorine-containing dihydropyrones **3**. Pure compounds **2** were prepared in good yields by the treatment of **1** with $SOCl_2$ followed by reflux of the crude products in Et_3N [4] (Scheme 1).



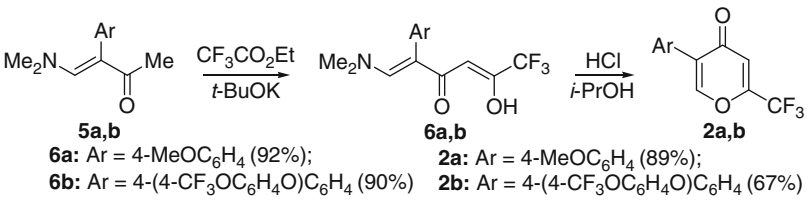
Scheme 1 Synthesis of pyrones **2**

Additionally, unsubstituted and 6-substituted 2-(perfluoroalkyl)-4*H*-pyran-4-ones **4** have been prepared using alkyl enolates derived from β-dicarbonyl compounds. The reaction of acetylacetone enol ether with ethyl perfluoroalkanoates in the presence of *t*-BuOK, followed by *p*-TsOH catalyzed cyclization in benzene afforded pyrones **4a,b** in 57–75 % yields. Similarly, the parent compounds **4c,d** were obtained from the formylacetone derivative in 40–64 % yields [4]. Analogue **4e** was accessible in low yield from the corresponding triketone [5] (Scheme 2).



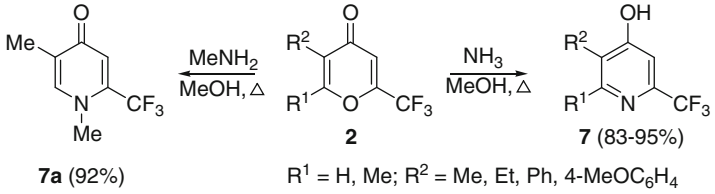
Scheme 2 Synthesis of pyrones **4**

The alternative way to 5-aryl substituted γ-pyrone **2a,b** is based on the readily available aminoenones **5a,b**. Reaction of **5a,b** with ethyl trifluoroacetate in the presence of *t*-BuOK afforded enamino diketones **6a,b** cyclized to pyrones **2a,b** [6]. Compounds **6b** and **2b** are starting materials for the preparation of 4-pyridones exhibited potent antimalarial activity [5] (Scheme 3).



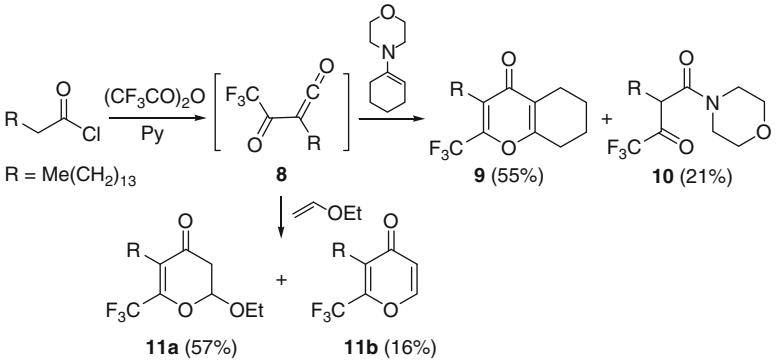
Scheme 3 Synthesis of pyrones **2a,b**

The ready availability of pyrones **2** and the enhanced reactivity at their α-position have made them the starting materials of choice for the synthesis of 2-(trifluoromethyl)-4-pyridinols **7** by reaction with ammonia or methylamine [6–8] (Scheme 4).



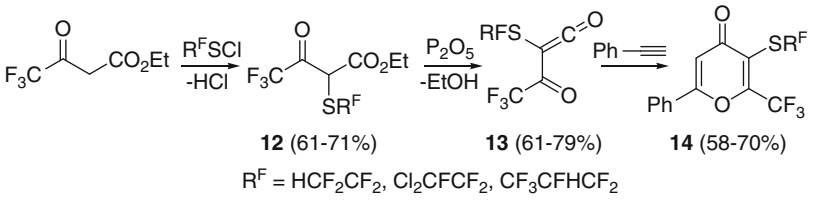
Scheme 4 Reactions of pyrones **2** with amines

Trifluoromethylated pyrones can also be prepared from acyl chlorides by reaction with pyridine and trifluoroacetic anhydride followed by capture of the intermediate trifluoroacyl ketene **8** with suitable reagents. Thus, addition of *N*-cyclohexenylmorpholine to the intermediate from palmitoyl chloride gave pyrone **9** as the major product, accompanied by amide **10**. Ethyl vinyl ether yielded pyrones **11a** and **11b** (through β-elimination of ethanol) [9] (Scheme 5).



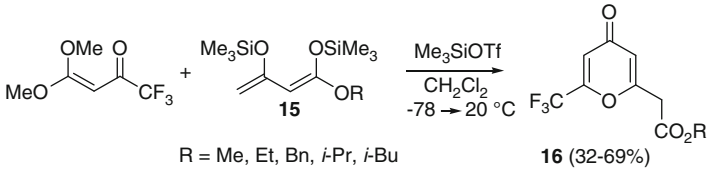
Scheme 5 Synthesis of pyrones **9** and **11**

Acylketene methodology [10] was also developed for the synthesis of 4-pyrones bearing a polyfluoroalkylthio substituent. The reaction of ethyl trifluoroacetoacetate with fluoroalkanesulfenyl chlorides afforded compounds **12** (Scheme 6).



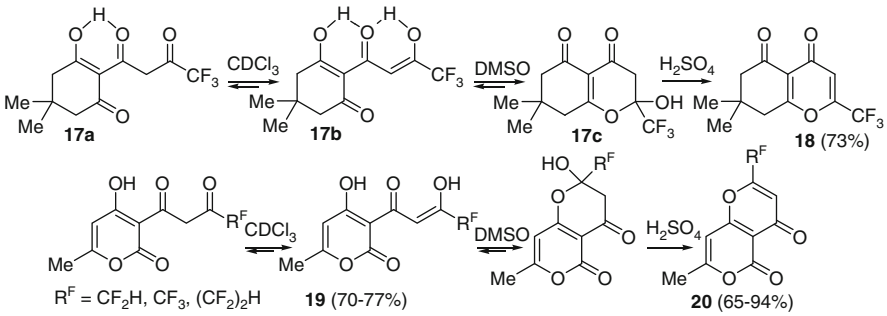
Scheme 6 Synthesis of pyrones **14**

The latter reacting with P_2O_5 gave rise to fluoroalkylthio(trifluoroacetyl)ketenes **13**, which were demonstrated to act as heterodienes in the Diels–Alder reaction with phenylacetylene to form 4-pyrones **14** [11]. Langer et al. reported that the Me_3SiOTf-mediated cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes **15** with 4,4-dimethoxy-1,1,1-trifluorobut-3-en-2-one resulted in the formation of trifluoromethylated pyran-4-ones **16** [12] (Scheme 7).



Scheme 7 Synthesis of pyrones **16**

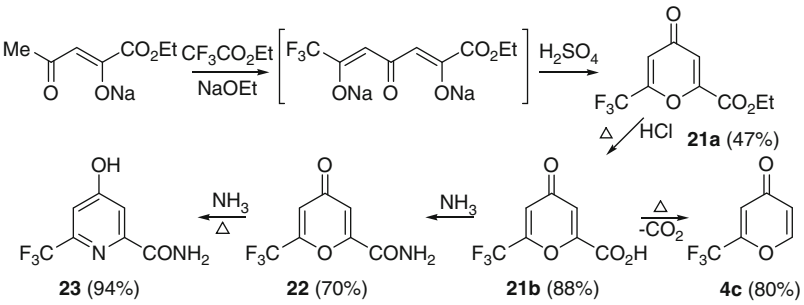
Condensation of 2-acetyldimedone with ethyl trifluoroacetate in the presence of LiH afforded tetraketone **17** in 65 % yield existing in $CDCl_3$ as an equilibrium mixture of **17a** and **17b**. In a mixture of DMSO-d_6 and CCl_4, **17** occurs as cyclic hemiketal **17c** (95 %) and open forms **17a** and **17b** (5 %). Treatment of **17** with concentrated H_2SO_4 at ~20 °C for 5 h afforded the carbofused 4-pyrone **18** [13] (Scheme 8).



Scheme 8 Synthesis of pyrones **18** and **20**

If dehydroacetic acid is used as the methylene component in the condensation with R^FCO_2Et under the same conditions, the reaction gives fluorine-containing pyrones **19**, which underwent cyclization to 2-(polyfluoroalkyl)-7-methylpyrano[4,3-b]pyran-4,5-diones (**20**) on treatment with H_2SO_4 [14].

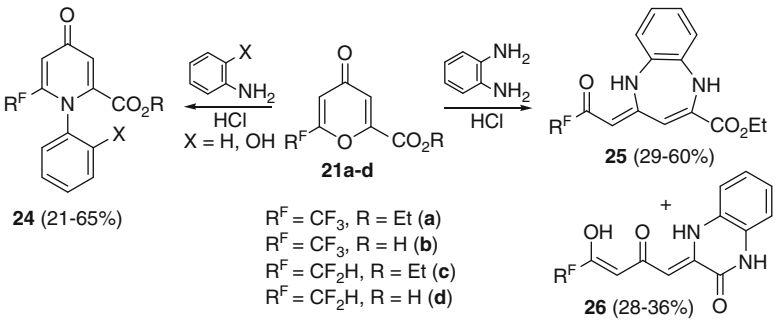
The reaction of ethyl 2,4-dioxopentanoate with ethyl trifluoroacetate in the presence of NaOEt leads to ester **21a**. This ester is smoothly hydrolyzed to acid **21b** by reflux in 20 % HCl, whereas its treatment with 20 % ammonia depending on conditions applied affords amides **22** and **23** in high yields [15]. Decarboxylation of 6-(trifluoromethyl) comanic acid (**21b**) gave 2-(trifluoromethyl)-4*H*-pyran-4-one (**4c**) [4, 16] (Scheme 9).



Scheme 9 Synthesis of pyrones **21** and **22**

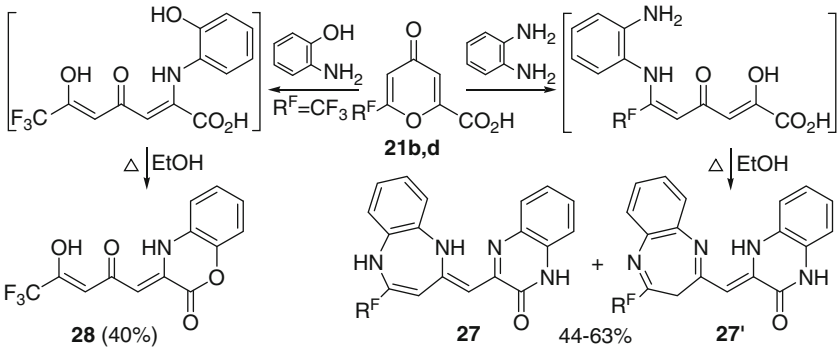
1.2 Reactions of 2-(Polyfluoroalkyl)-4-Pyrones

Obydennov and Usachev have reported [17] that 2-R^F-4-pyrones **21a–d** react with aniline and *o*-aminophenol under acidic conditions to give the corresponding 2-R^F-1-aryl-4-pyridones **24**. Their reaction with *o*-phenylenediamine in the presence of HCl gave R^F-bearing benzodiazepines **25** and quinoxalin-2-ones **26** (Scheme 10).



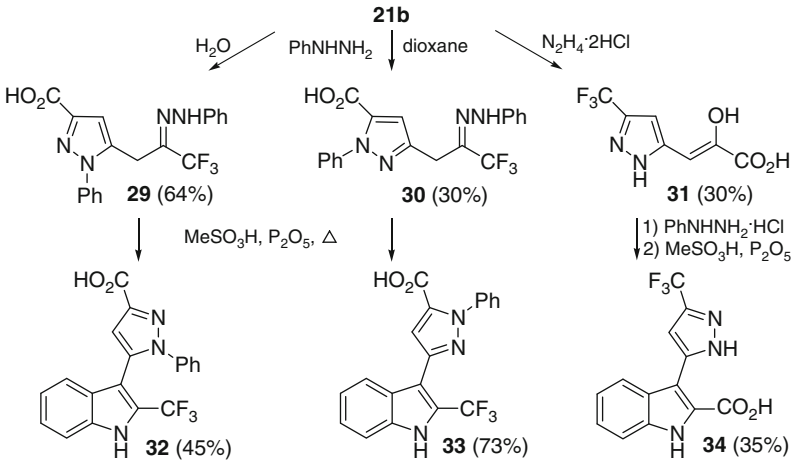
Scheme 10 Reactions of pyrones **21** with amines in the presence of an acid

In the absence of a strong acid, compounds **27** can be prepared as a mixture of two tautomers (R^F=CF_3, **27**: **27′** = 21: 79; R^F=CF_2H, **27**: **27′** = 65: 35) from the reaction of 6-R^F-comanic acids **21b,d** with *o*-phenylenediamine. To transform **27′** into more conjugated tautomers **27** the mixtures were heated in DMSO at 80–120 °C. Under the same conditions reaction of pyrone **21b** with *o*-aminophenol led to the formation of benzo[*b*][1,4]oxazin-2-one **28** [17] (Scheme 11).



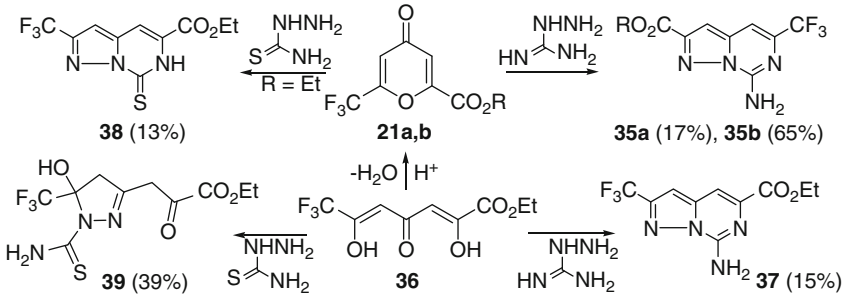
Scheme 11 Reactions of **21b,d** with amines in the absent of an acid

It was also reported that acid **21b** reacts regioselectively with phenylhydrazine in water to give 1-phenylpyrazole-3-carboxylic acid **29**. Similar reaction in dioxane leads to 1-phenylpyrazole-5-carboxylic acid **30**. A strong solvent influence on the reaction route was also found for 6-(trifluoromethyl)comanic acid derivatives **21a** and **22** [18]. The reaction of **21b** with $N_2H_4 \cdot 2HCl$ (2.2 equiv.) in water gave a mixture of regioisomeric pyrazoles from which 3-(trifluoromethyl)pyrazole **31** was isolated in 30 % yield. Phenylhydrazones **29** and **30** as well as phenylhydrazone from pyrazole **31** were converted into 3-(pyrazolyl)indoles **32** and **33**, and indole-2-carboxylic acid **34**, by heating in $MeSO_3H$ with P_2O_5 [19] (Scheme 12).



Scheme 12 Some reactions of pyrone **21b**

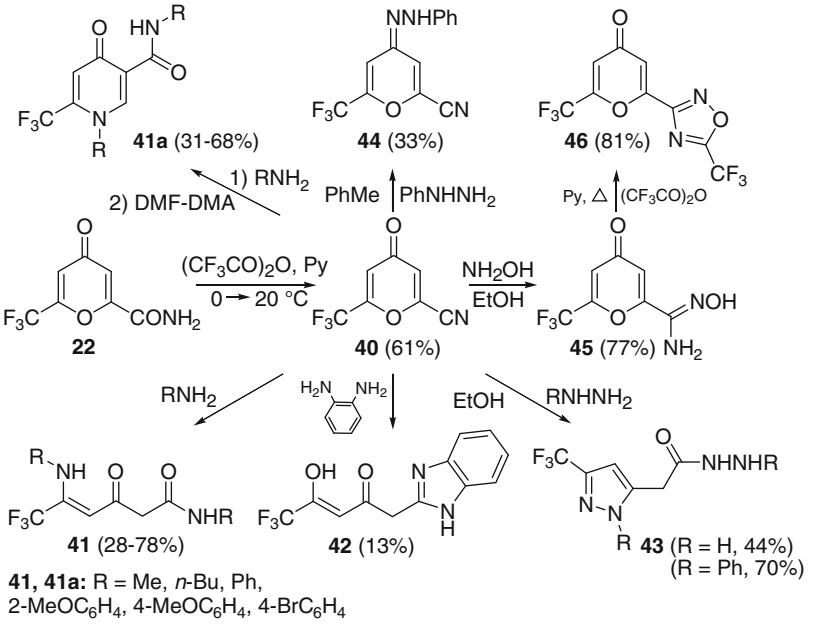
Pyrones **21a,b** react with aminoguanidine to give 5-CF_3-pyrazolo[1,5-*c*]pyrimidines **35a,b** as the major products, while the reaction of their precursor, ethyl 7,7,7-trifluoro-2,4,6-trioxoheptanoate (**36**), with the same polynucleophile gave regioisomeric 2-CF_3-pyrazolo[1,5-*c*]pyrimidines **37**. On the other hand, the reaction of **21a** and **36** with thiosemicarbazide affords **38** and **39** in low yield [20] (Scheme 13).



Scheme 13 Some reactions of **21a,b** and **36**

Dehydration of pyronecarboxamide **22** with trifluoroacetic anhydride in the presence of pyridine leads to the formation of 2-cyano-6-(trifluoromethyl)-4-pyrone (**40**) in 61 % yield. The reactions of this cyanopyrone with *N*-nucleophiles can proceed with or without substitution of the cyano group to give a wide range of novel trifluoromethylated compounds. Thus, cyanopyrone **40** easily reacted with aliphatic and aromatic amines in EtOH at −20 °C and *o*-phenylenediamine in

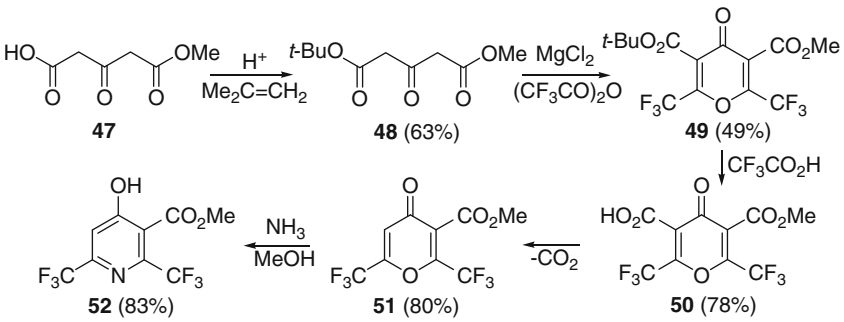
acetic acid to produce carbamoylated aminoenones **41** and benzimidazole **42**. Treatment of **41** with DMF-DMA in toluene under ambient conditions for 24 h gave 4-pyridone-3-carboxamides **41a** in 31–68 % yields. The regiochemistry of the reactions of **40** with hydrazine and phenylhydrazine in EtOH is similar to those observed in the case of the amine attack. These reactions afforded derivatives of 2-(3-trifluoromethylpyrazol-5-yl)acetic acid **43**, whereas the reaction with phenylhydrazine in toluene resulted in the formation of phenylhydrazone **44** in 33 % yield. The reaction between **40** and hydroxylamine in ethanol proceeds by the nucleophilic addition to the cyano group to give amidoxime **45**. Heating this compound with trifluoroacetic anhydride in the presence of pyridine gave pyrone **46** in high yield [21] (Scheme 14).



Scheme 14 Some reactions of pyrone **40**

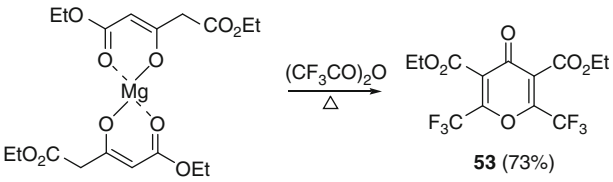
1.3 Synthesis and Reactions of 2,6-bis(Polyfluoroalkyl)-4-Pyrones

The first synthesis of 4-pyrone derivatives with two CF_3 groups was reported in 1988 by Lee and co-workers [22]. Acetone dicarboxylic acid monomethyl ester **47** reacted with isobutylene in sulfuric acid to form **48**. Subsequent reaction with $MgCl_2$ and trifluoroacetic anhydride led to pyrone **49**. This compound was converted to the monoester **50**, which gave pyrone **51**. The latter was reacted with ammonia in methanol to form 4-hydroxypyridine **52** [22] (Scheme 15).



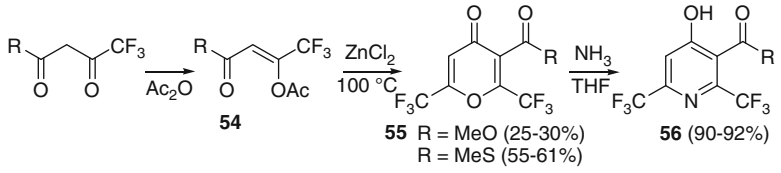
Scheme 15 Synthesis of compounds **49**–**52**

Diester **53** was obtained by the one-pot transformation of a magnesium diacetonedicarboxylate complex using trifluoroacetic anhydride [23] (Scheme 16).



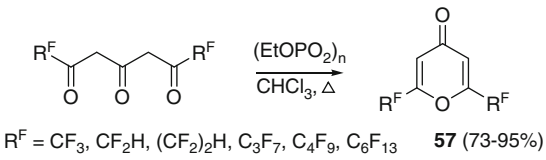
Scheme 16 Synthesis of pyrone **53**

Babu et al. reported that 3-acetoxy-4,4,4-trifluoro-2-butenoates (**54**) undergo self-condensation at 100 °C in presence of catalytic amounts of zinc chloride to yield 2,6-bis(trifluoromethyl)-4-pyrones **55**. These compounds were further converted to the corresponding pyridine derivatives **56** via ammonolysis [24] (Scheme 17).



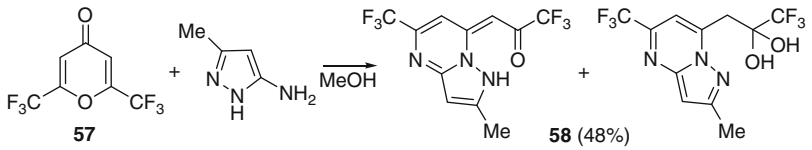
Scheme 17 Synthesis of pyrones **55**

A variety of procedures have been used to obtain the 2,6-bis(polyfluoroalkyl)-4-pyrones **57** from the corresponding 1,3,5-triketones [H_2SO_4, PPA, HCl/MeOH, $(Me_3SiO)_3PO$]. Ethyl polyphosphate appeared to be the most effective dehydrating agent with regard to the isolation and yield of products formed [25] (Scheme 18).



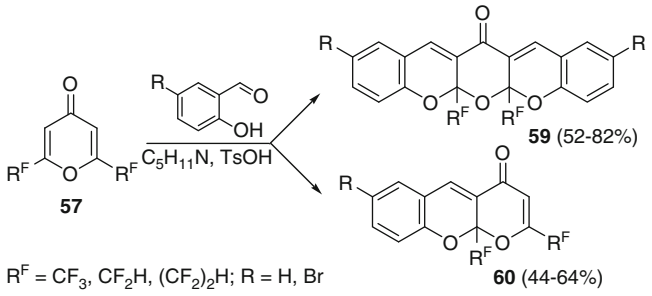
Scheme 18 Synthesis of pyrones **57**

Pyrazolo[1,5-*a*]pyrimidine **58** and its hydrated form were obtained by reaction of 5-amino-3-methylpyrazole with 2,6-bis(trifluoromethyl)-4-pyrone (**57**) [26] (Scheme 19).



Scheme 19 Synthesis of compounds **58**

Polyfluoroalkyl-substituted 4-pyrones **57** react with salicylaldehydes in the presence of piperidine and *p*-TsOH to give a wide variety of fused 2*H*-chromenes **59** and **60**. Compounds **59** were obtained as mixtures of the corresponding *trans*- and *cis*-isomers in variable proportions, depending on the nature of the starting materials and catalysts. This annulation proceeds by a tandem intermolecular oxa-Michael addition and subsequent intramolecular Mannich condensation [27] (Scheme 20).



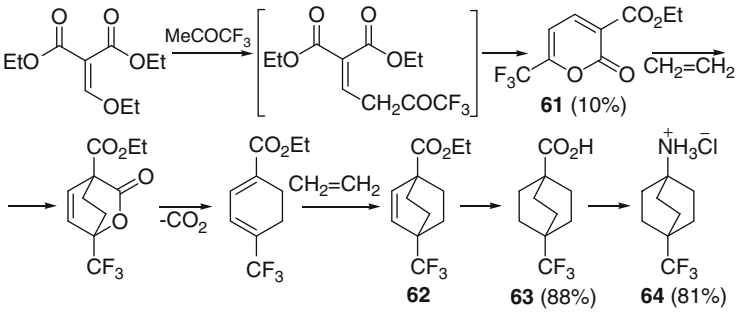
Scheme 20 Synthesis of compounds **59** and **60**

2 Fluorinated 2-Pyrones

Most reports concerning 2*H*-pyran-2-ones (α-pyrones) involve non-fluorinated derivatives, which perform important biological functions in nature and have unlimited synthetic potential for the construction of a variety of arenes and heteroarenes [28]. However, very few deal with 2-pyrones containing fluoroalkyl groups. It is evident that the C-2, C-4 and C-6 positions of the 2-pyranone ring are electrophilic in nature and prone to nucleophilic attack. The presence of polyfluoroalkyl substituents on the pyrone ring favours these reactions. At the same time, R^F-containing 2-pyrones behave as cyclic dienes in cycloadditions.

2.1 Synthesis and Reactions of 6-(Polyfluoroalkyl)-2-Pyrones

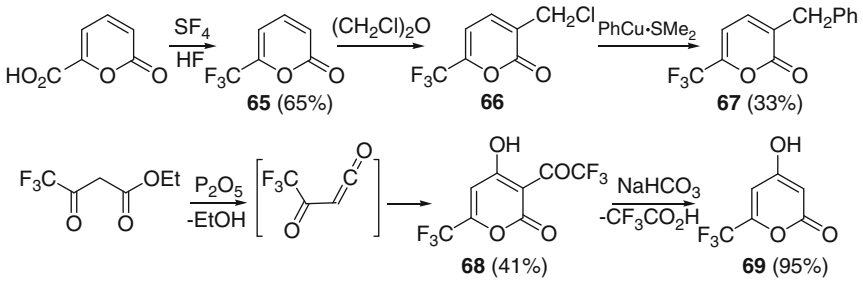
The ethyl 6-(trifluoromethyl)-2-pyrone-3-carboxylate (**61**) was prepared by condensation of trifluoroacetone with diethyl ethoxymethylenemalonate, followed by cyclization of intermediate diethyl β-acylethylidenemalonate. This pyrone was used for the preparation of cage derivatives to explore their usefulness as antiviral agents. Reaction of **61** with ethylene at high pressure afforded ester **62**. Hydrogenation of **62** yielded the corresponding alkyl bicyclo[2.2.2]octane-l-carboxylate, which was hydrolyzed to **63**. The latter was converted into bicyclo[2.2.2]octan-l-amine hydrochloride **64** via the Schmidt reaction [29] (Scheme 21).



Scheme 21 Synthesis of pyrone **61** and its derivatives

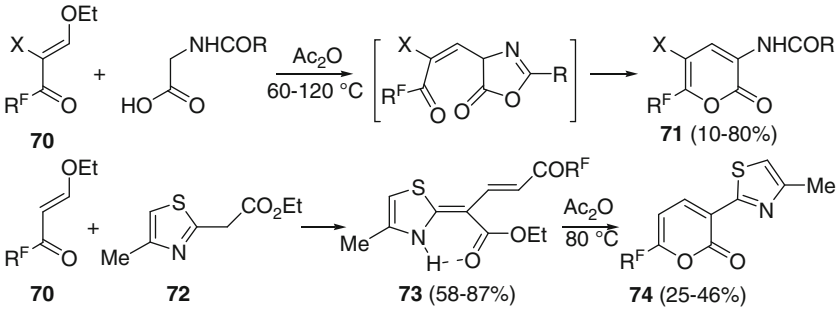
6-(Trifluoromethyl)-2-pyrone (**65**) was prepared in 65 % yield by reaction of 2-pyrone-6-carboxylic acid with SF_4–HF at 100 °C. Chloromethylation with bis(chloromethyl) ether and sulfuric acid at 75 °C gave an inseparable mixture of mono- and bis(chloromethyl)pyranones. However, when the mixture was treated with phenylcopper-dimethyl sulfide in THF at 35 °C, only **66** reacted, giving the desired pyrone **67** as one of the perspective inactivators of α-Chymotrypsin [30] (Scheme 22).

Dealkoxylation of trifluoroacetoacetic ester by P_2O_5 leads to trifluoroacetylketene, which quickly dimerizes to hexafluorodehydroacetic acid **68**. The reaction of **68** with $NaHCO_3$ leads to the formation of 2-pyrone **69** [31] (Scheme 22).



Scheme 22 Synthesis of pyrones **67**–**69**

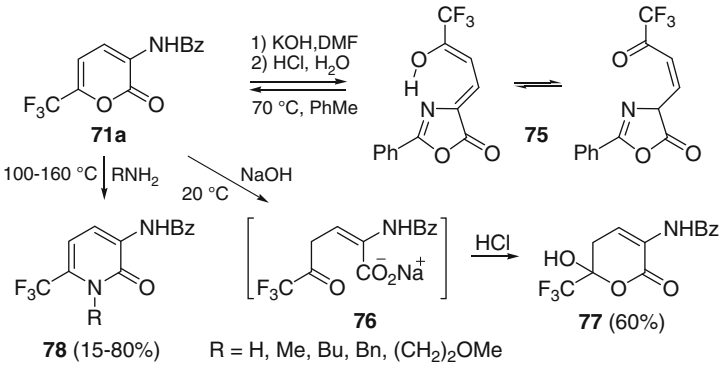
Gerus et al. reported that heating of β-alkoxyvinyl ketones **70** and *N*-acylglycines in acetic anhydride gave the corresponding 3-(acylamino)-6-(polyfluoroalkyl)-2*H*-pyran-2-ones (**71**) [32]. Reactions of thiazole **72** with enones **70** gave products **73** in good to high yields as a result of acylvinylation of the active methylene group. Products **73** were cyclized to pyrones **74** by heating in acetic anhydride [33] (Scheme 23).



Scheme 23 Synthesis of pyrones **71** and **74**

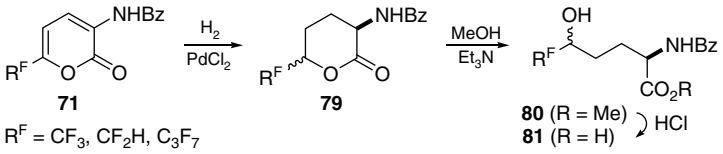
The reactions of 2*H*-pyran-2-one **71a** with *O*– and *N*-nucleophiles were studied and a series of trifluoromethyl-containing oxazolone and pyridone derivatives were synthesized. The oxazolone **75**, which can exist in two tautomeric forms, can be obtained by heating of **71a** with KOH in DMF and subsequent acidification. When **71a** was dissolved in aqueous 1N NaOH, a yellow solution of salt **76** was formed.

After acidification of the solution with HCl, hydroxypyrone **77** precipitated. The pyridones **78** were obtained by heating **71a** with ammonia or alkylamines [32, 34] (Scheme 24).



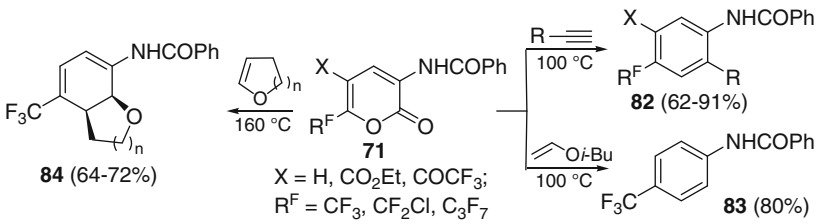
Scheme 24 Some reactions of pyrone **71a**

The key step of the synthesis of new δ-(polyfluoroalkyl)-δ-hydroxy-α-amino acids **81** was the hydrogenation of 2*H*-pyran-2-ones **71** to the tetrahydropyrones **79**, which were transformed into the corresponding benzoylamino acid esters **80** by methanolysis. In all cases mixtures of diastereomeric esters **80** were formed, careful treatment of which with 15 % HCl gave a mixture of the diastereomeric benzoylamino acids **81**. The latter are of interest as analogues of 2-amino-5-hydroxyvaleric acid and glutamic acid [35] (Scheme 25).



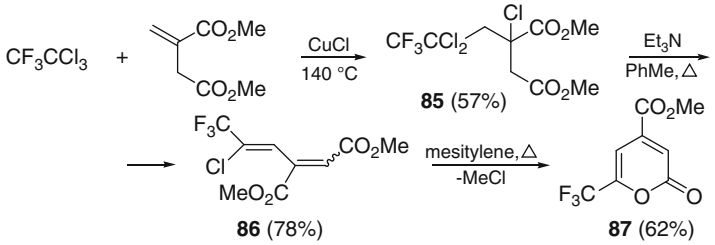
Scheme 25 Reduction of pyrones **71**

The propensity of α-pyrones to undergo the Diels-Alder reaction makes them useful for syntheses of highly substituted aromatics and biphenyls. A practical method for the regioselective synthesis of the *N*-benzoyl-4-(polyfluoroalkyl)anilines **82** by thermal Diels–Alder cycloaddition of **71** with fluorostyrenes and acetylenes was described. Free 4-(polyfluoroalkyl)anilines were smoothly formed in good yields by DBU-assisted deprotection. In the case of the reactions of pyrone **71a** with isobutyl vinyl ethers and cyclic vinyl ethers, compounds **83** and **84** were obtained, respectively [36] (Scheme 26).



Scheme 26 Diels-Alder reaction of pyrones **71**

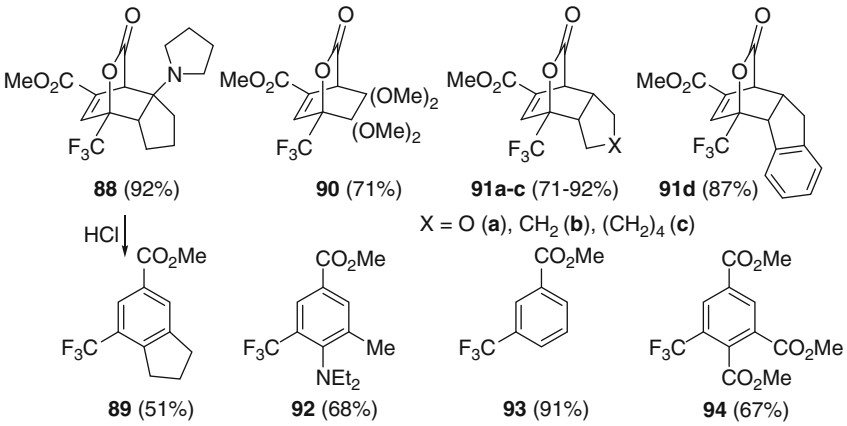
The Cu-catalysed (3–6 mol%) addition of 1,1,1-trichloro-2,2,2-trifluoroethane to methyl itaconate leads to the 1: 1 adduct **85** in 57 % yield. Double HCl elimination with triethylamine affords the diene **86** (*Z*/*E* = 17:83). Refluxing of **86** in mesitylene leads to elimination of MeCl and formation of **87** in 62 % yield [37] (Scheme 27).



Scheme 27 Synthesis of pyrone **87**

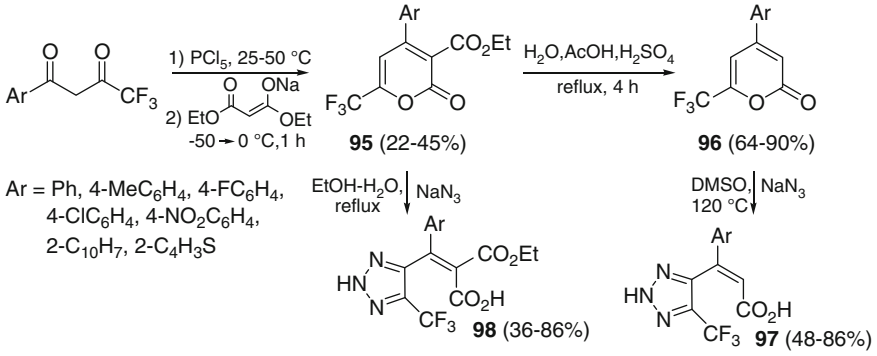
The presence of the carbomethoxy and trifluoromethyl groups in the diene system of the pyrone **87** increases its electrophilicity and its ability to undergo Diels-Alder reactions with inverse electron demand. The reaction of **87** with 1-(*N*-pyrrolidino)-1-cyclopentene at 30 °C gives rise to the tricyclic lactone **88**. When **88** is treated with HCl/dioxane, the indane derivative **89** is obtained. This compound was prepared directly in the reaction of **87** with l-(trimethylsilyloxy)cyclopentene at 180 °C in 90 % yield. More reactive tetramethoxyethylene adds at 100 °C to **87** to afford **90**. With 2,5-dihydrofuran at 130 °C, **91a** is formed as the sole isomer. Endo-adducts of this type result also with cyclopentene (**91b**, 120 °C), cyclooctene (**91c**, 150 °C), and indene (**91d**, 80 °C). All four possible regio- and stereoisomers can be identified in the reaction of **87** with vinylacetate at 150 °C (79 % yield) (Scheme 28).

Another feature of 2-pyrone **87** is its ability to undergo Diels-Alder reactions with acetylenes. The cycloadducts decarboxylate spontaneously to form benzene rings bearing the CF_3 group. The substitution pattern is determined by the regioselectivity of the [4 + 2] cycloaddition step. Thus, the reaction of **87** with 1-(*N*,*N-diethylamino*)-1-propyne takes place at 0 °C to produce **92** as a single isomer. Less electron rich acetylenes require heating at 140–200 °C. Treatment of **87** with acetylene at 200 °C leads to **93**, while with dimethyl acetylenedicarboxylate triester **94** is formed [37] (Scheme 28).



Scheme 28 Products obtained from pyrone **87**

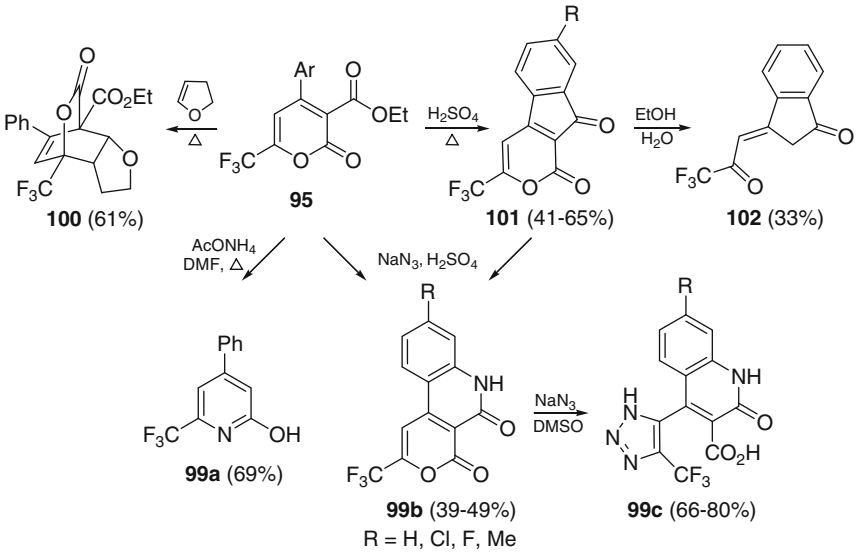
Our group reported that treatment of 1-aryl-4,4,4-trifluorobutane-1,3-diones with PCl_5 and then with sodium diethyl malonate afforded ethyl 4-aryl-6-(trifluoromethyl)-2-oxo-2*H*-pyran-3-carboxylates (**95**) in moderate yields. These compounds can be converted in high yields to 2*H*-pyran-2-ones **96** by refluxing in aqueous acetic acid with H_2SO_4 [38]. Pyrones **95** and **96** react with sodium azide to produce highly functionalized (*Z*)-CF_3-1,2,3-triazoles **97** and **98** [39a] (Scheme 29).



Scheme 29 Synthesis of pyrones **95** and **96** and their reaction with NaN_3

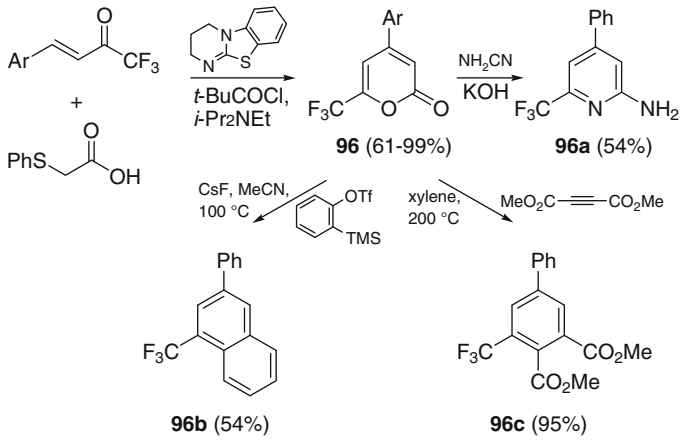
The reaction of **95** (Ar=Ph) with NH_4OAc in refluxing aqueous DMF, involving loss of the ethoxycarbonyl group at the 3-position, afforded the pyridinol derivative **99a**, while the solvent-free inverse electron-demand Diels-Alder reaction with 2,3-dihydrofuran gave bicyclic lactone **100** in 61 % yield. Treatment of **95** with H_2SO_4 at 110–125 °C afforded the intramolecular Friedel-Crafts acylation products **101**, which are the first representatives of a novel polynuclear fused heterocyclic system. Due to the presence of antiaromatic cyclopentadienone fragment compound **101** (R=H) showed high reactivity to weak nucleophiles such as water leading to the formation of **102** [38a]. 2-(Trifluoromethyl)-6*H*-pyrano[3,4-*c*]quinoline-4,5-diones

99b can be obtained from pyrones **95** and **101** via the Schmidt reaction in moderate yields. When pyranocarbostyrils **99b** were heated in DMSO with NaN_3 at 120 °C for 3 h, triazoles **99c** were obtained in good yields and presumably arise via ring-opening of the initially formed fused intermediate [38b] (Scheme 30).



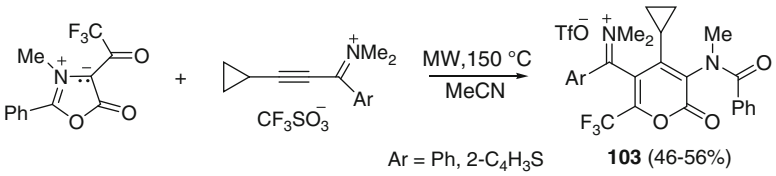
Scheme 30 Some reactions of pyrones **95**

Very recently, the concise synthesis of a range of disubstituted 2-pyrones **96** from (thiophenyl)acetic acids and readily available trifluoromethyl enones via an isothiourea mediated one-pot Michael addition/lactonization/thiol elimination sequence has been demonstrated. Derivatization of these reactive pyrones to generate additional high-value products was next investigated and compounds **96a–c** were prepared in good yields [39b] (Scheme 31).



Scheme 31 Synthesis and some reactions of pyrones **96**

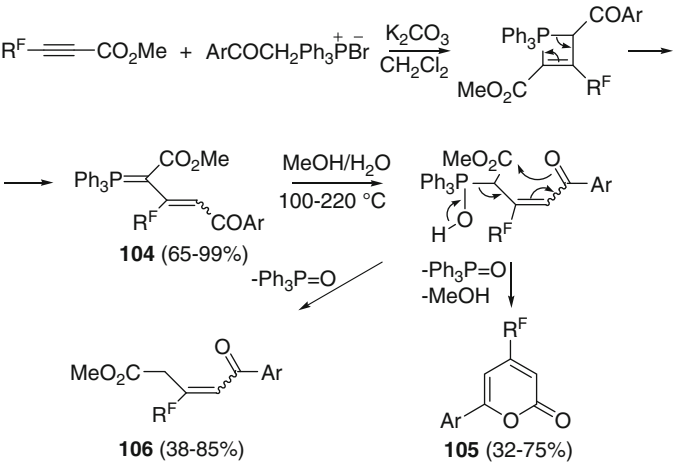
Gerster and Maas reported that heating 4-trifluoroacetyl-substituted münchnone and the propyne iminium triflates in acetonitrile solution at 150 °C (closed vessel) under microwave irradiation furnished the (6-oxo-2-trifluoromethyl-6*H*-pyran-3-yl) arylidene iminium salts **103** [40] (Scheme 32).



Scheme 32 Synthesis of pyrones **103**

2.2 *Synthesis of 4-(Perfluoroalkyl)-2-Pyrones*

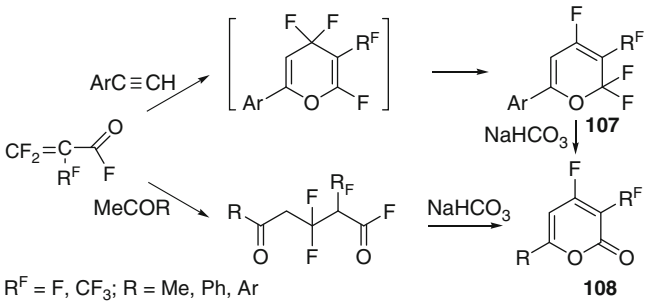
In contrast to 6-(perfluoroalkyl)-2-pyrones, only one method for the preparation of 4-(perfluoroalkyl)-2-pyrones has been described [41]. It was established that the reaction of methyl 2-perfluoroalkynoates with aroylmethyltriphenyl phosphonium bromide in the presence K_2CO_3 in dichloromethane at room temperature gave methyl 4-aroyl-2-triphenylphosphoranylidene-3-(perfluoroalkyl)-3-butenoates **104** in excellent yields. 6-Aryl-4-(perfluoroalkyl)-2-pyrones **105** and methyl 4-aroyl-3-(perfluoroalkyl)-3-butenoates **106** were obtained in moderate to high yield by hydrolysis of phosphoranes **104** with hot aqueous methanol in a sealed tube. The butenoates **106** were isolated chromatographically as mixtures of *Z* and *E* isomers, the ratios of which were estimated by ^{1}H NMR. Reaction mechanism was proposed to account for the formation of products **104–106** [41] (Scheme 33).



Scheme 33 Synthesis of pyrones **105**

2.3 Miscellaneous

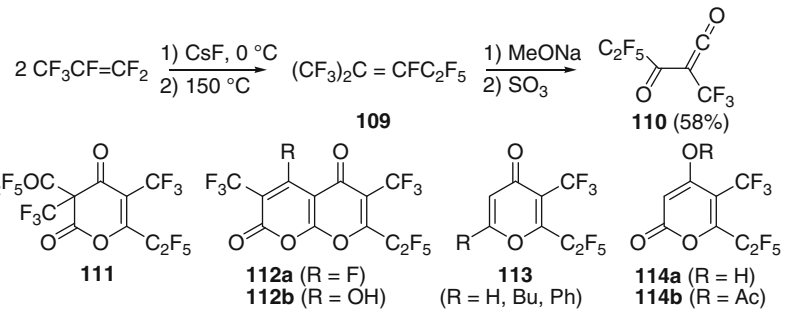
Fluorinated α-pyrones were obtained from perfluoroacryloyl fluoride and perfluoromethacryloyl fluoride by reaction with arylacetylenes and methyl ketones. The arylacetylene route involves a [4 + 2] cycloadduct, followed by a 1,3 fluoride ion shift to **107** and hydrolysis to the pyrone **108**. The methyl ketone route may involve addition of enols to the fluorinated double bond, ring closure through the enol form of the resulting 1,5-diketone, and loss of HF [42a] (Scheme 34).



Scheme 34 Synthesis of pyrones **108**

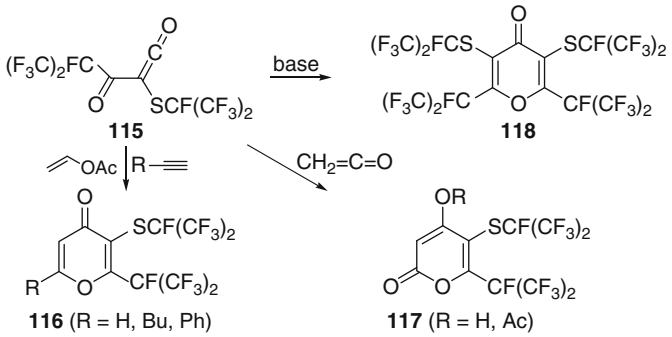
The synthesis and chemistry of perfluoroacylketene **110** are described by England [42b]. Hexafluoropropene dimerizes under CsF catalysis. Heating the resulting mixture in a sealed vessel to 150 °C yields the thermodynamic dimer **109**, from which compound **110** was prepared in good yield (Scheme 35).

Cesium fluoride catalyst in tetraglyme without heating caused the acylketene **110** to dimerize to **111**. When heated with catalytic amounts of cesium fluoride in tetraglyme **110** gave the pyronopyrone **112a** (from 3 mol of **110** with loss of 2 mol of C_2F_5COF). Hydrolysis of **112a** by sulfuric acid gave **112b**. The acylketene **110** also reacted with phenyl- and butylacetylenes to give pyrones **113**. Although acetylene was not reacted with **110**, the corresponding product **113** (R=H) was obtained by reaction with vinyl acetate with simultaneous loss of acetic acid. Compound **110** added readily to the C=C bond in ketene with proton migration to give a mixture of hydroxypyrone **114a** and the acetylated product **114b**. These products could be interconverted by hydrolysis of **114b** in sulfuric acid and by acetylation of **114a** with ketene [42b] (Scheme 35).



Scheme 35 Products obtained on the basis of acylketene **110**

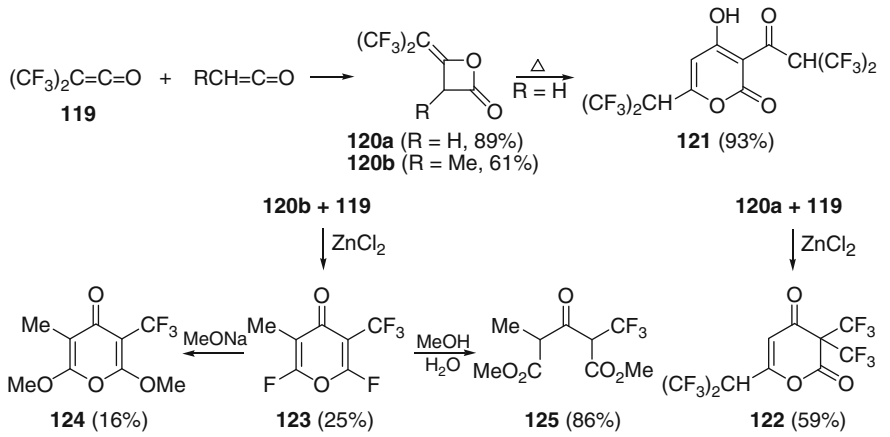
The chemistry of compound **115**, prepared from the reaction of hexafluoropropene with sulfur and potassium fluoride in DMF, is similar to **110**. Diels-Alder addition of **115** to vinyl acetate was accompanied by loss of acetic acid to give the parent pyrone **116** (R=H). The reaction of **115** with butyl- and phenylacetylenes gave **116** (R=Bu, Ph). Addition of **115** to the C=C bond of ketene was accompanied by a 1,3 hydrogen shift to produce the hydroxypyrone and its acetylated product **117**. In the presence of a weak base such as dimethylacetamide or dimethylpropionamide, **115** underwent a self-condensation reaction with loss of CO_2 to give the pyrone **118**; this reaction was not observed for **110** [43] (Scheme 36).



Scheme 36 Products obtained on the basis of acylketene **115**

England and Krespan reported that ketene **119** reacted exothermically with ketene at very low temperature to give β-lactone **120a**, which was readily dimerized by base to give α-pyrone **121**, a reaction analogous to the formation of dehydroacetic acid from diketene. Lactone **120a** also reacted with another equivalent of ketene **119** in the presence of zinc chloride as catalyst to give the insertion product **122**. Methylketene, like ketene, reacted with **119** to give a mixed lactone **120b**, the reaction of which with another mole of **119** in the presence of zinc chloride gave γ-pyrone **123**. Reaction of **123** with sodium methoxide replaced two fluorine atoms to give the dimethoxypyrone **124**, methanol gave the keto diester **125** [44] (Scheme 37).

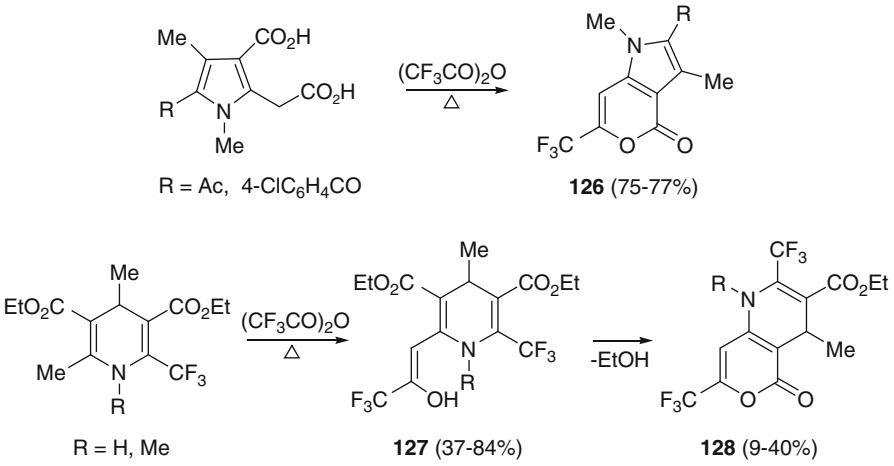
A synthetic entry to 2-acyl-1,3-dimethyl-6-(trifluoromethyl)-1*H*-pyrano[4,3-*b*]pyrrol-4-ones **126** in high yields has been developed via ring closure of pyrrole-2-acetic



Scheme 37 Products obtained on the basis of ketene **119**

acid derivatives with trifluoroacetic anhydride at reflux [45a]. Under the same conditions trifluoromethylated dihydropyridinecarboxylates were converted via compounds **127** into pyrano[4,3-*b*]pyridine-3-carboxylates **128** in low yields [45b] (Scheme 38).

The butenolide, 3-(trifluoromethyl)-2*H*-furo[2,3-*c*]pyran-2-one, was obtained by treatment of 3-iodo-2*H*-furo[2,3-*c*]pyran-2-one with trifluromethyltriethylsilane in the presence of copper iodide and potassium fluoride in 1-methyl-2-pyrrolidinone [45c].



Scheme 38 3,4-Fused pyrones **126** and **128**

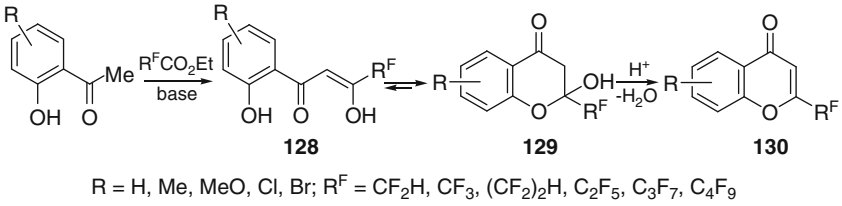
3 Fluorinated Chromones

Chromones (4*H*-chromen-4-ones, 4*H*-1-benzopyran-4-ones) are naturally occurring oxygen-containing heterocycles which perform important biological functions in nature [46]. Many chromone derivatives, including flavones and 2-(trifluoromethyl)

chromones, exhibit various types of biological activity and find use as valuable synthetic intermediates in the preparation of pharmacologically relevant products and new heterocyclic systems [47–49]. There are a number of methods available for preparing chromones, however, the most common methods involve Claisen condensation of 2-hydroxyacetophenones with esters or Baker-Venkataraman rearrangement of 2-acyloxyacetophenones. The ensuing diketone is then cyclized under strongly acidic conditions to furnish chromones. These compounds possess two strong electrophilic centers (carbon atoms C-2 and C-4) and their reactions with nucleophiles start predominantly with attack of the C-2 atom (1,4-addition) and are accompanied by pyrone ring-opening to form an intermediate capable of undergoing intramolecular heterocyclizations. Alternatively, the initial attack can also occur at C-4 (1,2-addition) [46].

3.1 Synthesis of 2-(Polyfluoroalkyl)Chromones

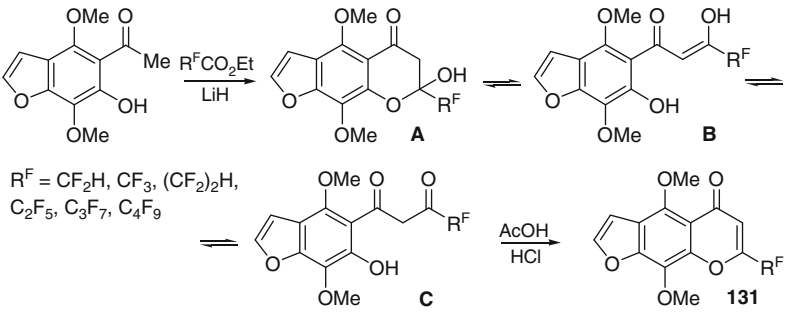
The first representatives of 2-(trifluoromethyl)chromones were obtained in 1951 by condensation of substituted 2-hydroxyacetophenones with ethyl trifluoroacetate in the presence of sodium followed by dehydration of the initially formed β-diketones in an acid medium [50]. It has long been considered [51] that these diketones have a linear keto-enol structure **129a**; however, subsequently, it has been found on the basis of ^{1}H NMR data [52] that they exist as cyclic semiketals **129b** both in solutions and in crystals. Cyclisation is facilitated by the presence of the electron-withdrawing trifluoromethyl group in the side chain and the hydroxy group in the *ortho*-position of the benzene ring. Refluxing of 2-hydroxychromanones **129b** in ethanol [50] or acetic acid [53, 54] in the presence of concentrated HCl results in 2-(polyfluoroalkyl)chromones **130** (Scheme 39).



Scheme 39 Synthesis of 2-R^F-chromones **130**

Modification of natural products by replacing an alkyl group by a polyfluoroalkyl group has long attracted the attention of researchers, because the electron-withdrawing effect of the fluorinated substituent entails electron density redistribution in the molecule and thus changes its reactivity with respect to nucleophilic reagents [55]. In this connection, of obvious interest is the synthesis of 7-(polyfluoroalkyl)norkhellins **131** [56, 57], which are fluorinated analogues of natural furochromone khellin (active substance of the plant *Ammi visnaga L.*, known for its therapeutic properties since antiquity), because it opens up the way for the

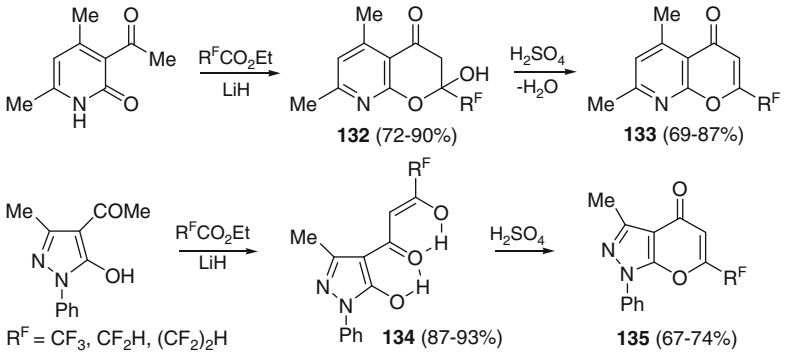
preparation of a broad range of fluorine-containing heterocycles that incorporate the benzofuran fragment and are potentially biologically active (Scheme 40).



Scheme 40 Synthesis of fluorokhellins **131**

Fluorokhellins **131** were prepared by the reaction of khellinone with R^FCO_2Et in the presence of LiH followed by dehydration of the condensation products, which exist as furochromanones **A** in crystals and in DMSO-d_6 solutions. In $CDCl_3$, these compounds (except for R^F=CF_3) are mixtures of tautomers **A–C**. Irrespective of length of the fluoroalkyl group, cyclic form **A** predominates (50–78 %), while the content of the diketone form **C** usually does not exceed 8 % [57].

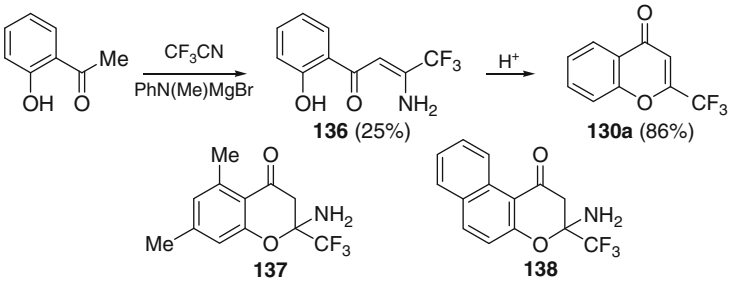
If 2-hydroxyacetophenone analogues such as 3-acetyl-4,6-dimethyl-2-pyridone and 4-acetyl-5-hydroxy-3-methyl-1-phenylpyrazole are used as the methylene component in the condensation with R^FCO_2Et in the presence of LiH in THF or dioxane, the reaction gives the corresponding R^F-containing β-diketones **132** and **134**, whose dehydration under the action of concentrated H_2SO_4 affords 8-aza-2-(polyfluoroalkyl) chromones **133** [58] and 6-(polyfluoroalkyl)-3-methyl-1-phenylpyrano[2,3-*c*] pyrazol-4(1*H*)-ones **135** [59] (Scheme 41).



Scheme 41 Synthesis of compounds **133** and **135**

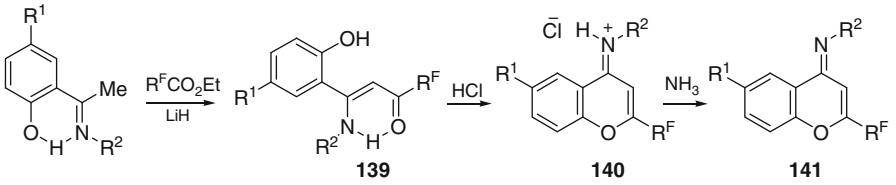
Recently, 2-(trifluoromethyl)chromones **130** have been prepared by the reaction of 2-hydroxyacetophenones with trifluoroacetic anhydride in pyridine (80 °C, 3 h, yields

79–98 %) [60]. Due to the low solubility of phenolates, derivatives hydroxylated at the benzene ring are synthesized using the Kostanecki–Robinson method. Thus, 7-hydroxy-2-(trifluoromethyl)chromone was obtained in 68 % yield by heating 2,4-dihydroxyacetophenone with trifluoroacetic anhydride and sodium trifluoroacetate [49]. In addition to these protocols, other methods for the synthesis of chromones **130** have also been developed. For example, the reaction of 2-hydroxyacetophenone with trifluoroacetonitrile affords aminoenone **136**. Unlike diketones **128**, this compound exists in the open form as *Z*-isomer having a coplanar *s-cis*-conformation stabilised by an intramolecular hydrogen bond [61]. However, the products of condensation of CF_3CN with sterically hindered 2-hydroxy-4,6-dimethylacetophenone and 1-acetyl-2-naphthol exist predominantly as 2-aminochroman-4-ones **137** and **138** due to unfavourable interactions between the vinylic hydrogen atom and the *ortho*-substituent in the benzene ring [62]. In an acid medium, compounds **136–138** are converted into **130** in high yields (Scheme 42).



Scheme 42 Precursors **136–138**

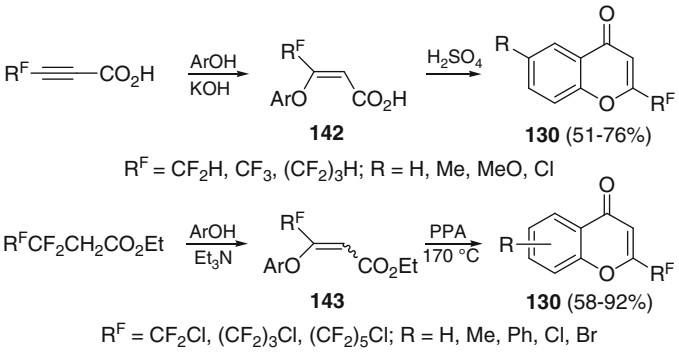
The condensation of ketimines, prepared from 2-hydroxyacetophenones and primary amines, with R^FCO_2Et in the presence of LiH yields aminovinyl ketones **139** with γ-arrangement of the NHR and R^F groups, which exist only in the open form. In an ethanol solution of HCl, these compounds cyclise to 2-(polyfluoroalkyl)-4*H*-chromene-4-iminium salts **140**, which can be neutralised with ammonia to form 2-(polyfluoroalkyl)-4*H*-chromene-4-imines **141**. On treatment with aqueous acetic acid, compounds **139** and **141** are hydrolysed to chromanones **129**, which can be easily converted into chromones **130** [63] (Scheme 43).



$R^F = CF_3, H(CF_2)_2$; R^1 = H, Me; $R^2 = CH_2Ph$, *i*-Pr, $(CH_2)_2OH$

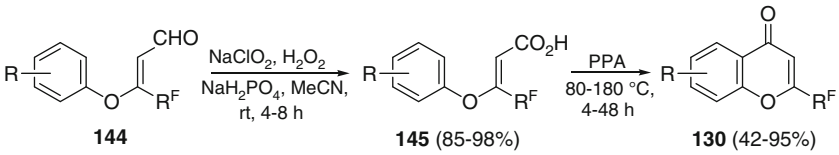
Scheme 43 Synthesis of chromone imines **141**

The reactions of polyfluoroalk-2-ynoic acids with a fivefold excess of ArOH and KOH in an aqueous solution are stereoselective and result in (*Z*)-β-(polyfluoroalkyl)-β-aryloxyacrylic acids **142**. On treatment with concentrated H_2SO_4, these compounds are converted into 2-R^F-chromones **130** [64]. A similar approach to the synthesis of 2-R^F-chromones **130** has been described in a study [65], in which ethyl 2,2-dihydropolyfluorocarboxylates were used as the starting substrates. They were made to react with phenols in the presence of Et_3N in MeCN at 60 °C, which gave ethers **143**, most often, as mixtures of *Z*- and *E*-isomers. When heated with polyphosphoric acid (PPA) at 170 °C, they were converted into chromones **130** in high yields (Scheme 44).



Scheme 44 Syntheses of chromones **130**

The oxidation of enals **144** using sodium chlorite and hydrogen peroxide under mild conditions gave the corresponding acids **145**. When acids **145** were treated with polyphosphoric acid at high temperatures, the desired chromones **130** were obtained in predominantly very high yields [66] (Scheme 45).



Scheme 45 Synthesis of chromones **130**

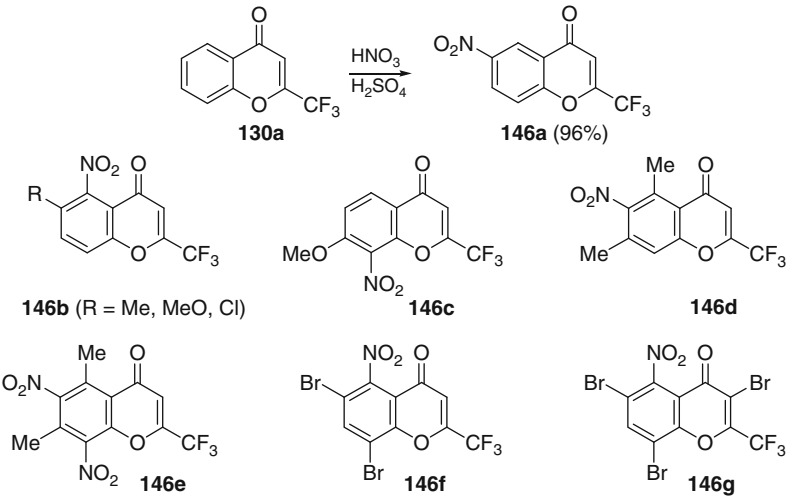
3.2 Reactions of 2-(Polyfluoroalkyl)Chromones

In recent years, our research group has examined the chemistry of 2-(polyfluoroalkyl) chromones **130** and a number of features of these compounds important from the synthetic standpoint have been found. This allowed chromones **130** to be

recommended as readily accessible highly reactive substrates for the synthesis of various heterocyclic derivatives including R^F-containing compounds with a potential biological activity [46b]. The NMR, vibrational, electronic, and structural properties of 6-nitro- and 6-amino-2-(trifluoromethyl)chromones were discussed and assigned with the assistance of DFT calculations [67a].

3.2.1 Nitration and Hydrogenation

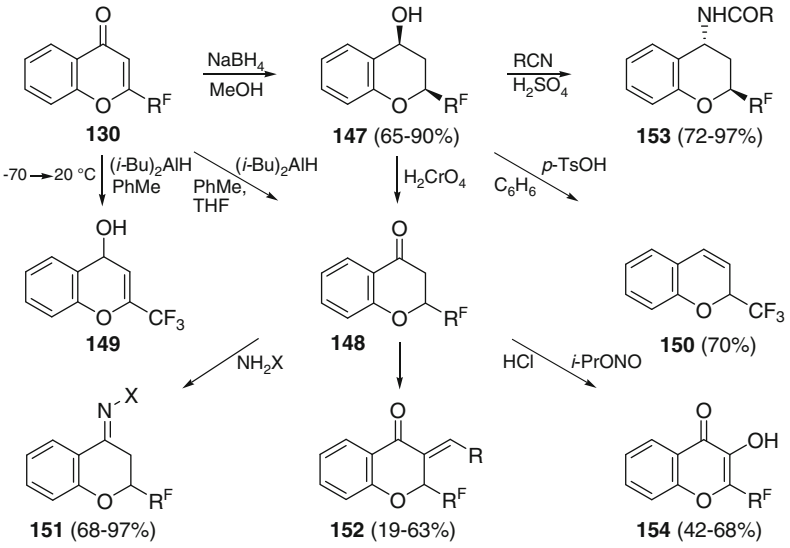
2-(Trifluoromethyl)chromone **130a** unsubstituted in the benzene ring, like its non-fluorinated analogues, is smoothly nitrated at the 6-position yielding 6-nitro-2-(trifluoromethyl)chromone (**146a**). On heating with a mixture of nitric and sulfuric acids, 6-, 7- and 8-substituted 2-(trifluoromethyl)chromones are nitrated into the positions, which is in line with the directing effect of substituents, giving rise to the corresponding nitro derivatives **146b–g** [54, 67–69] (Scheme 46).



Scheme 46 Some 2-CF_3-chromone derivatives

Reduction of 2-(polyfluoroalkyl)chromones **130** by sodium borohydride in methanol gives *cis*-2-(polyfluoroalkyl)chroman-4-oles **147** in high yields, which were easily oxidized under the action of chromic acid into 2-(polyfluoroalkyl) chroman-4-ones **148**. Selective reduction of chromone **130a** can be achieved by using of diisobutylaluminium hydride. In this case, 2-(trifluoromethyl)chroman-4-one (**148a**, R^F=CF_3) and 2-(trifluoromethyl)-4*H*-chromen-4-ol (**149**) were obtained. Dehydration of chromanol **147a** (R^F=CF_3) gave 2-(trifluoromethyl)-2*H*-chromene (**150**) [70]. Chromanones **148**, which easily react at both the carbonyl carbon atom and α-methylene group, are of interest as the starting materials for the preparation of novel R^F-containing chromans derivatives. Thus, they react with hydroxylamine,

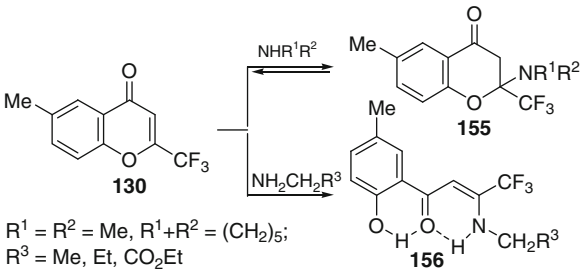
hydrazine hydrate, benzaldehyde on reflux in ethanol and with an excess of dimethylformamide dimethylacetal to give oximes and hydrazones **151** as well as methylidene derivatives **152** [70]. Application of the Ritter reaction conditions to chroman-4-ols **147** gave 4-(acylamino)-2-(polyfluoroalkyl)chromans (**153**) in excellent yields. This reaction was stereoselective and chromanes **153** were obtained as mixtures of *trans*- and *cis*-isomers (*trans*/*cis* = 84/16–94/6) without the formation of any side products [71]. Treatment of an alcoholic solution of **148** with an excess of isopropyl nitrite and concentrated hydrochloric acid at 0–80 °C for 3 h gave 3-hydroxychromones **154** in good yields [72] (Scheme 47).



Scheme 47 Some reactions of **130** and **148**

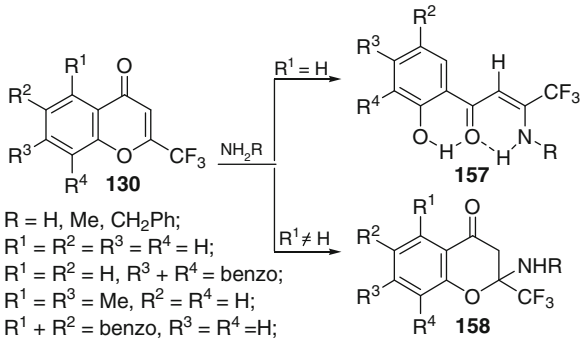
3.2.2 Reactions with Mono-, Di- and Triamines

In 1981, an attempt at using 6-methyl-2-(trifluoromethyl)chromone (**130**) as a protective group in the peptide synthesis was made, which showed for the first time that secondary amines (dimethylamine and piperidine) add reversibly to the C-2 atom without opening of the pyrone ring to give unstable compounds **155** (in the case of sterically hindered diethylamine, the reaction does not proceed). However, even mere mixing of 6-methylchromone **130** with primary amines (ethyl- and propylamines) induces opening of the pyrone ring to give aminoenones **156**. A similar transformation takes place for ethyl glycinate in MeCN [73]. Subsequently, the significance of the steric factor in the reactions of **130** with ammonia and primary amines was also demonstrated for other examples (Scheme 48).



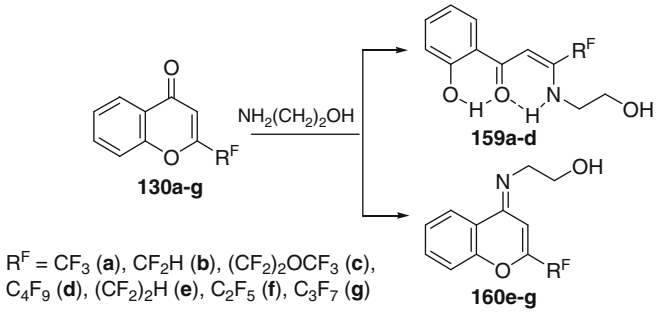
Scheme 48 Reactions of chromones **130** with amines

The nature of the substituent at the 5-position of the chromone system influences the form of existence of the reaction products, which can be either ring or open. The attack by the amine on the C-2 atom of **130** for R^1=H is accompanied by the pyrone ring opening and yields aminoenones **157**; when $R^1 \neq H$, the process stops after the nucleophilic addition of the amine to give stable chromanones **158** [74] (Scheme 49).



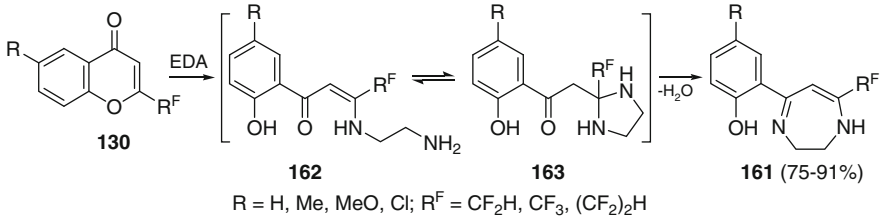
Scheme 49 Reactions with primary amines

A change in the direction of nucleophilic attack has been found in a study of the reaction between chromones **130a–g** unsubstituted in the benzene ring and 2-aminoethanol at room temperature. This amine easily yields aminovinyl ketones **159a–d**, however the reaction with **130e–g** leads to imines **160e–g** [75, 76] (Scheme 50).



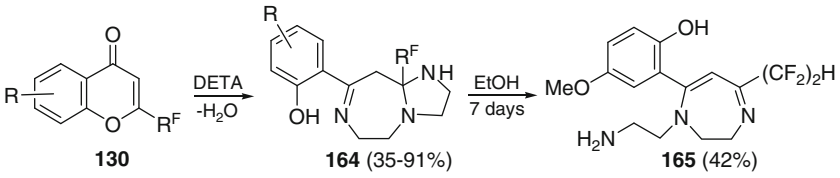
Scheme 50 Reactions with ethanolamine

Unlike non-fluorinated chromones, whose reactions with ethylenediamine (EDA) give complex mixtures of products [77], the reactions of 2-R^F-chromones **130** give rise to 5-(2-hydroxyaryl)-7-(polyfluoroalkyl)-2,3-dihydro-1*H*-1,4-diazepines (**161**) in excellent yields. The reaction is accompanied by opening of the pyrone ring with the initial formation of aminovinyl ketones **162** (in equilibrium with imidazolidines **163**) and cyclization to dihydrodiazepines **161** [78, 79]. Compounds **161** exist in $CDCl_3$ as the 1*H*-7-R^F-tautomers due to the formation of an intramolecular hydrogen bond between the phenolic proton and the imine nitrogen atom of the heterocycle. This conclusion was based on the values of the $^3J_{H,F}$ coupling constants, which are 2.8–4.5 Hz for molecules with the HCF_2CF_2–C(X)=C fragments, where X=O, N [80] (Scheme 51).



Scheme 51 Synthesis of dihydrodiazepines **161**

With diethylenetriamine (DETA), chromones **130** are converted into 5-(2-hydroxyaryl)-7-(polyfluoroalkyl)-1,4,8-triazabicyclo[5.3.0]dec-4-enes (**164**) (35–91 %), which represent the cyclic form of dihydrodiazepines containing a 2-aminoethyl group at the nitrogen atom located most closely to the fluorinated group. The first step is nucleophilic addition of the primary amino group to the C-2 atom accompanied by opening of the pyrone ring yielding *N*-substituted aminovinyl ketones, which further cyclise to triazabicyclic products **164** with participation of both electrophilic centres [81]. It should be emphasised that the formation of **164** is typical only of 2-R^F-chromones and R^F-aminovinyl ketones [82], where the R^F group substantially increases the reactivity of the carbon atom that carries this group. On keeping in ethanol for a week, compound **164** (R^F=$(CF_2)_2H$, R=MeO) isomerises into dihydrodiazepine **165** [83] (Scheme 52).

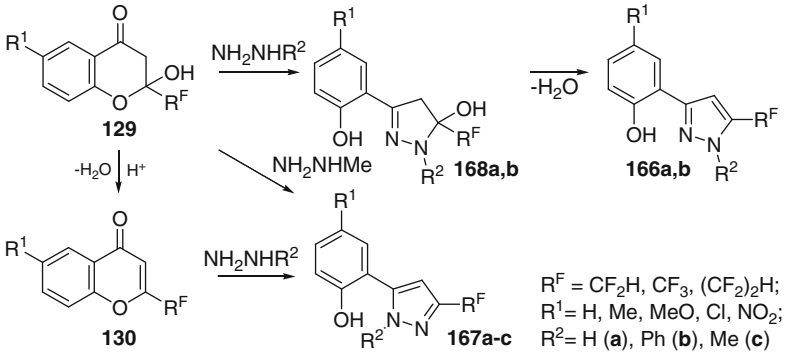


Scheme 52 Synthesis of compounds **164** and **165**

Thus, the reaction of 2-R^F-chromones with amines usually starts with the attack by the amino group on the C-2 atom. In the case of secondary amines or in the presence of a substituent at the 5-position, the reaction can stop after 1,4-nucleophilic addition; however, in most cases, it is accompanied by pyrone ring opening giving the corresponding aminovinyl ketones, whose structural features and subsequent transformations provide a variety of products. An exception is the reaction of 2-R^F-chromones with 2-aminoethanol pointing to the possibility of an attack by the amine on the carbonyl group.

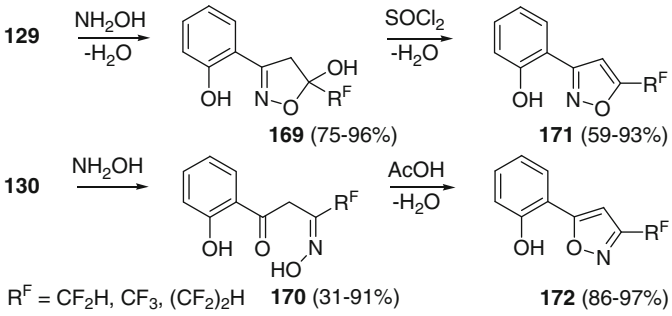
3.2.3 Reactions with Hydrazines, Hydroxylamine, Amidines and Sodium Azide

The reactions of chromanones **129** and chromones **130** with hydrazine hydrate resulted in the formation of 3(5)-(2-hydroxyaryl)-5(3)-polyfluoroalkylpyrazoles that have a planar conformation and mainly exist as 1*H*-5-R^F-tautomers **166a** in $CDCl_3$ and as 1*H*-3-R^F-tautomers **167a** in DMSO. The reaction with phenylhydrazine allows one to synthesise regioisomeric 5-R^F-pyrazole **166b** from **129** and 3-R^F-pyrazoles **167b** from **130**. With methylhydrazine, only the 3-R^F-regioisomers **167c** are formed. Under mild conditions, the reaction of **129** with hydrazines can be arrested after the formation of dihydropyrazoles **168** [84a]. Reactions of CF_3-pyrazole **166a** (R^1=H) with various 2-chloro-3-nitropyridines via nucleophilic aromatic substitution followed by denitrocyclization gave benzo[*f*]pyrazolo[1,5-*d*]pyrido[3,2-*b*][1,4]oxazepines in 50–60 % yields (Scheme 53).



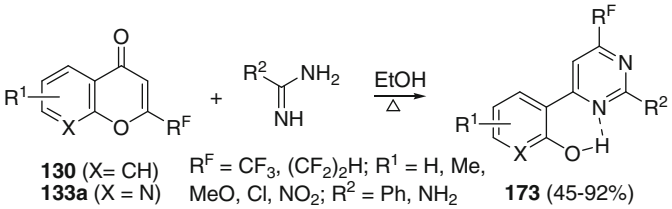
Scheme 53 Reactions with hydrazines

The reaction of chromanones **129** with hydroxylamine gave oximes existing in the ring isoxazoline form **169** [53]. Under similar conditions, chromones **130** react at the C-2 atom rather than at the oxo group and give isomeric oximes **170**, which do not tend to cyclise, unlike the aliphatic analogues [85]. The change in the direction of the nucleophilic attack on passing from **129** to **130** makes it possible to obtain regioisomeric 5-R^F-isoxazoles **171** (refluxing of **169** in toluene with $SOCl_2$) and 3-R^F-isoxazoles **172** (refluxing of **170** in AcOH with HCl) (Scheme 54). Azachromones **133** react with amines, hydrazines and hydroxylamine similarly [86].



Scheme 54 Reactions with hydroxylamine

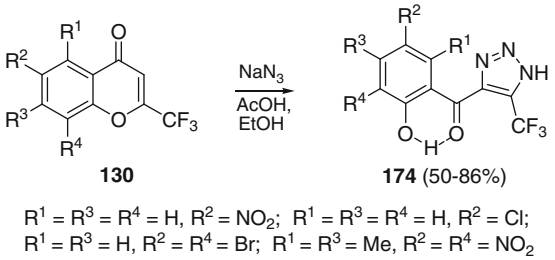
Substituted 2-R^F-chromones are effective in the reaction with amidines to create R^F-containing pyrimidine derivatives. Reflux of chromones **130** with benzamidine hydrochloride or guanidinium nitrate in the presence of KOH yielded the pyrimidines **173** in moderate to high yields [87] (Scheme 55).



Scheme 55 Reactions with amidines

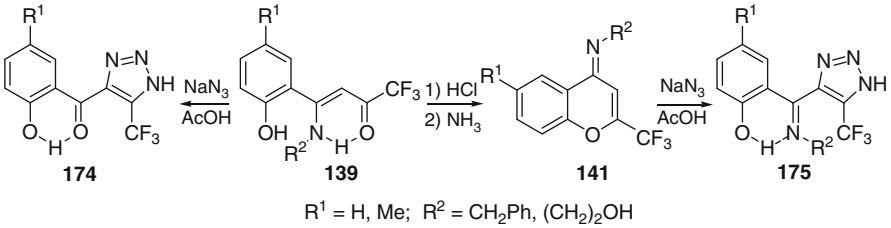
The reaction is applicable to the 8-aza-5,7-dimethyl-2-(trifluoromethyl)chromone (**133a**) to afford the corresponding pyrimidines with 2-pyridone substituent [87].

Salicyloyltriazoles **174** were prepared by the reaction of 2-CF_3-chromones **130** with sodium azide. It should be noted that on replacement of the CF_3 group by H, CF_2H or $(CF_2)_2H$, the reaction does not take place. Furthermore, without an electron-withdrawing group at the 6-position the reaction slows down to such an extent that 2-(trifluoromethyl)chromone **130a** is recovered unchanged [88] (Scheme 56).



Scheme 56 Reactions of chromones **130** with sodium azide

The reactivity of the pyrone ring with respect to NaN_3 can be increased by replacement of the C=O group by the C=NR group. It was shown [88] that the presence of an electron-withdrawing group in the benzene ring is not obligatory for chromene-4-imines **141**, and they easily react with NaN_3 in the presence of AcOH to give aryltriazolylketone imines **175** due to protonation of C=N bond (Scheme 57).

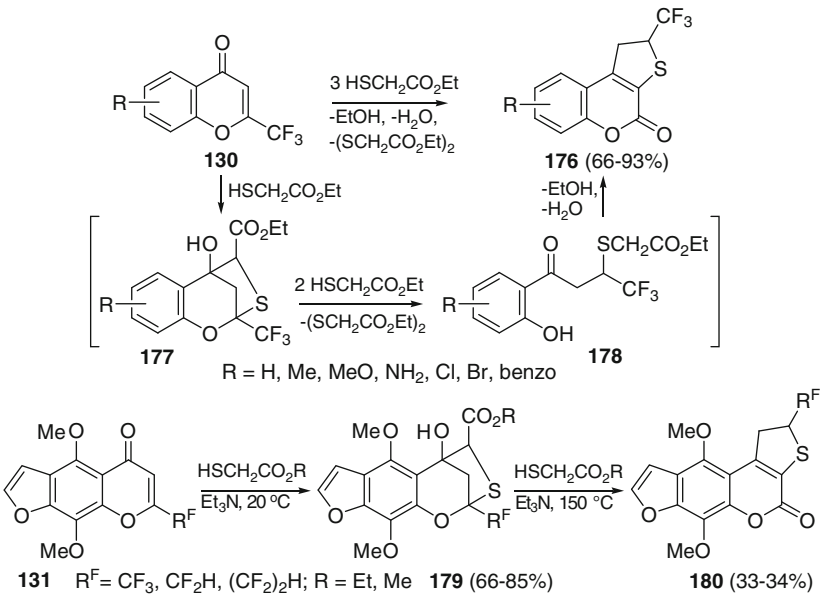


Scheme 57 Reactions with sodium azide

Hydrolysis of imines **175** affords triazoles **174**, which could not be synthesised from the corresponding 2-CF_3-chromones. Since the transformations **139** → **141** and **141** → **174** proceed via common iminium intermediate **140**, it comes as no surprise that aminovinyl ketones **139** are converted under these conditions into triazoles **174** as easily as chromene-4-imines **141** [88].

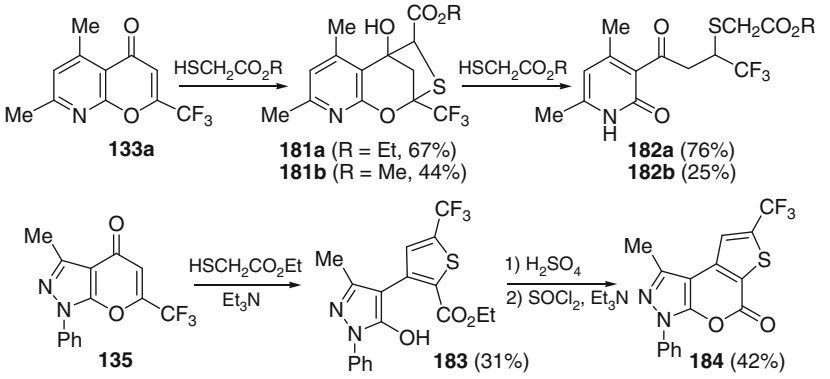
3.2.4 Reactions with Alkyl Mercaptoacetates

One of the most unexpected reactions of 2-CF_3-chromones **130** is the reaction with ethyl mercaptoacetate in the presence of Et_3N, which results in **176** and diethyl 3,4-dithiaadipate via redox process. This reaction can be accomplished only with 2-CF_3-chromones. Most likely, it starts with the formation of **177**, subsequent reductive opening leads to **178** cyclizing to dihydrothienocoumarin **176** [89]. The reaction of alkyl mercaptoacetates with fluorokhellins **131** stops after the formation of products **179**. Only under rigorous conditions (sealed tube, 150 °C), norkhellins **131** were converted into **180** [57, 90] (Scheme 58).



Scheme 58 Reactions of **130** and **131** with ethyl mercaptoacetate

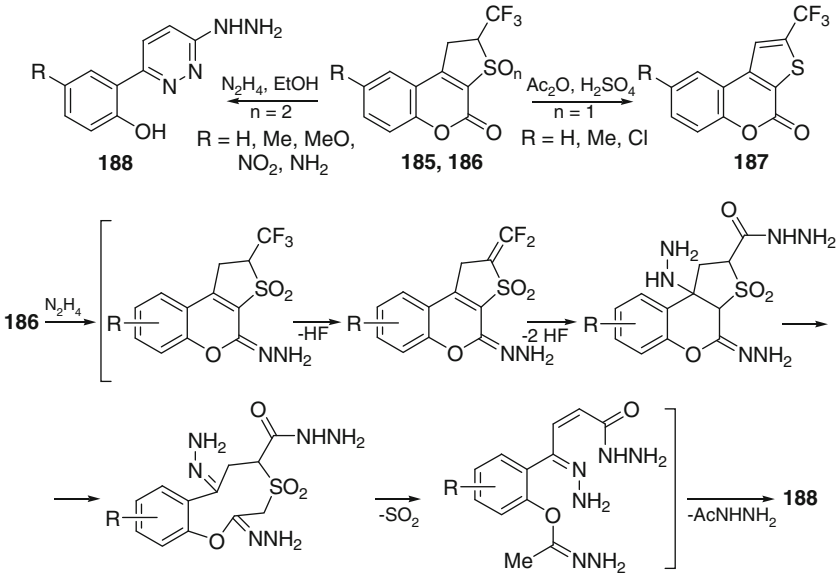
The reaction of 8-aza-5,7-dimethyl-2-(trifluoromethyl)chromone (**133a**) with alkyl mercaptoacetates afforded bicycles **181a**,**b**. When the reaction time and the amount of Et_3N were increased, acyclic derivatives **182a**,**b** were isolated [91]. A similar reaction of pyranopyrazole **135** proceeds at the C-6 atom followed by pyrone ring opening and intramolecular condensation of the aldol type to give compound **183**, from which heterofused coumarin **184** was obtained [59] (Scheme 59).



Scheme 59 Reactions of **133a** and **135** with ethyl mercaptoacetate

Selective oxidation of dihydrothienocoumarins **176** gives rise to highly reactive substrates, namely, sulfoxides **185** (NO_2, $CHCl_3$) and sulfones **186** (H_2O_2, AcOH). Under Pummerer rearrangement conditions, sulfoxides **185** produce thienocoumarins

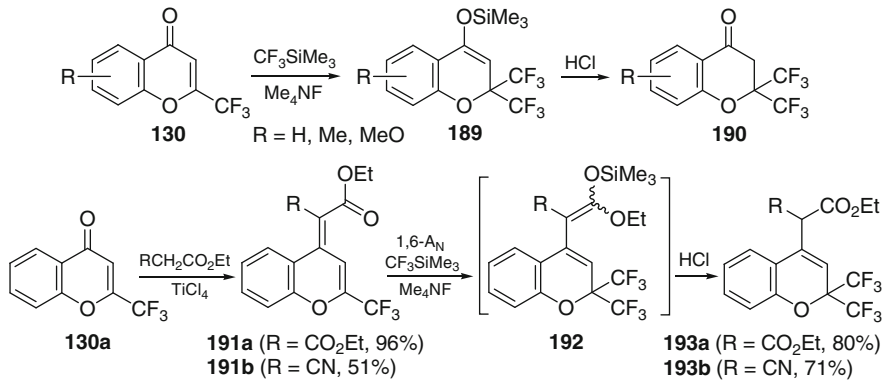
187 [89b]. Sulfones **186** are transformed into 3-hydrazino-6-(2-hydroxyaryl)pyridazines **188** by the action with hydrazine hydrate [92]. Previously, these pharmaceutically valuable products providing the basis for a series of 3-hydrazinopyridazine drugs [93], were synthesised in seven steps starting from phenols and succinic anhydride [94]. Multistep mechanism of this transformation is given below (Scheme 60).



Scheme 60 Synthesis of hydrazinopyridazines **188**

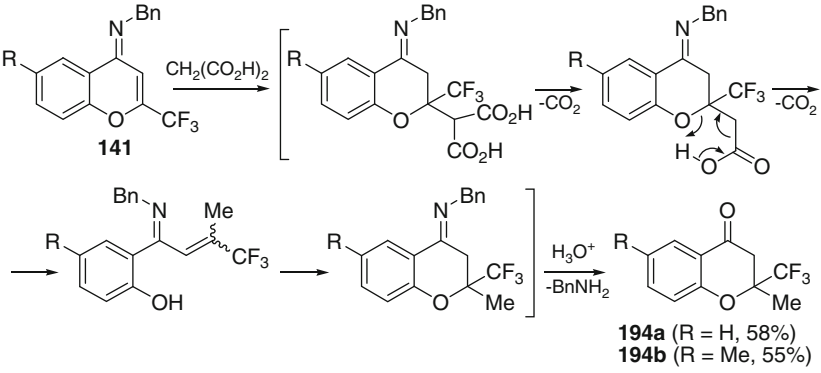
3.2.5 Reactions with *C*-Nucleophiles

Trimethyl(trifluoromethyl)silane (Ruppert's reagent) easily reacts with α,β-unsaturated carbonyl compounds yielding the corresponding trifluoromethylated alcohols [95]. The reaction of CF_3SiMe_3 with 2-CF_3-chromones **130** is the first example of preparative 1,4-trifluoromethylation of the α,β-enone system, which leads to trimethylsilyl ethers **189** giving after acid hydrolysis 2,2-bis(trifluoromethyl)chroman-4-ones **190** [96]. Chromone **130a** reacts with ethyl malonate and ethyl cyanoacetate to give methylidene derivatives of 4*H*-chromene **191a,b**. Subsequent reaction with CF_3SiMe_3 in the presence of Me_4NF involves nucleophilic 1,6-addition to the conjugated systems to produce, through acid hydrolysis of intermediate **192**, 2*H*-chromenes **193a,b** [97] (Scheme 61).



Scheme 61 Reactions with Ruppert's reagent

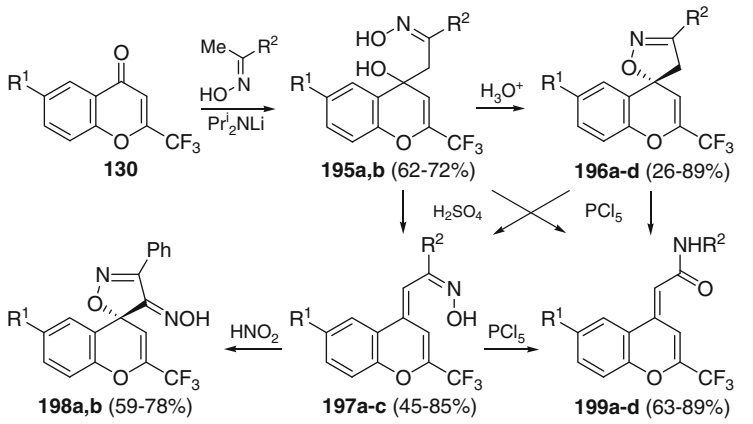
2-Methyl-2-(trifluoromethyl)chroman-4-ones **194a,b** were obtained in good yields by reaction of chromene-4-imines **141** with malonic acid, which acts as methylating agent via addition-decarboxylation-hydrolysis sequence [98] (Scheme 62).



Scheme 62 Reactions with malonic acid

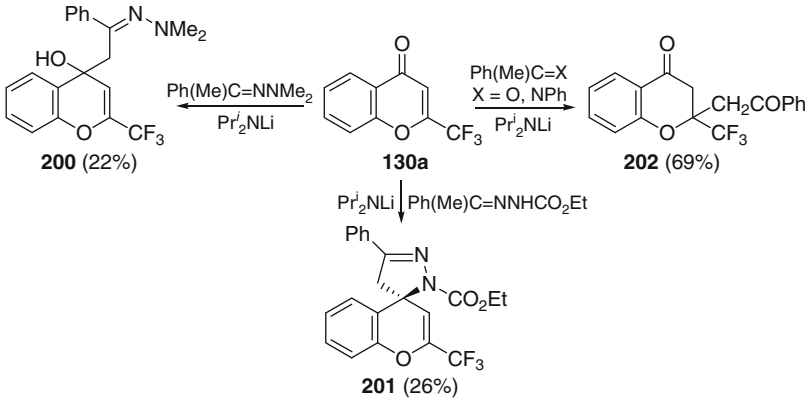
The reactions of 2-CF_3-chromones **130** with dilithiooximes proceed via nucleophilic 1,2-addition to give β-hydroxy oximes **195a–d** and, on acidification, 4*H*-chromene-4-spiro-5′-isoxazolines **196a–d**. The isoxazoline ring in **196** undergoes opening under the action of concentrated H_2SO_4, yielding oximes **197a–c**. Their nitrosation leads to **198a,b**, while the Beckmann rearrangement, to α,β-unsaturated amides **199**. The latter are also formed from **196** using PCl_5 [99] (Scheme 63).

Analogous reactions of acetophenone dimethylhydrazone and acetophenone ethoxycarbonylhydrazone with chromone **130a** gave β-hydroxy hydrazone **200** and spiropyrazoline **201**, which are also 1,2-adducts. In contrast, acetophenone and



Scheme 63 Products from **130** and dilithiooximes

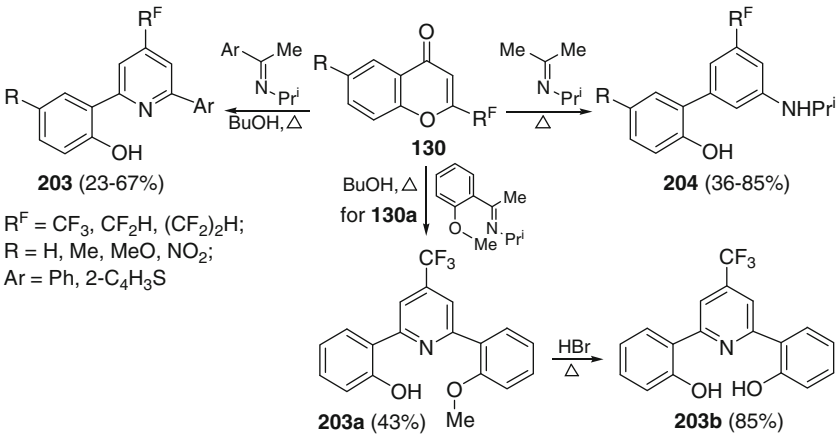
acetophenone anil behaved differently under the same conditions giving via 1,4-addition chromanone **202** [99, 100] (Scheme 64).



Scheme 64 Reactions of **130a** with hydrazones, acetophenone anil and acetophenone

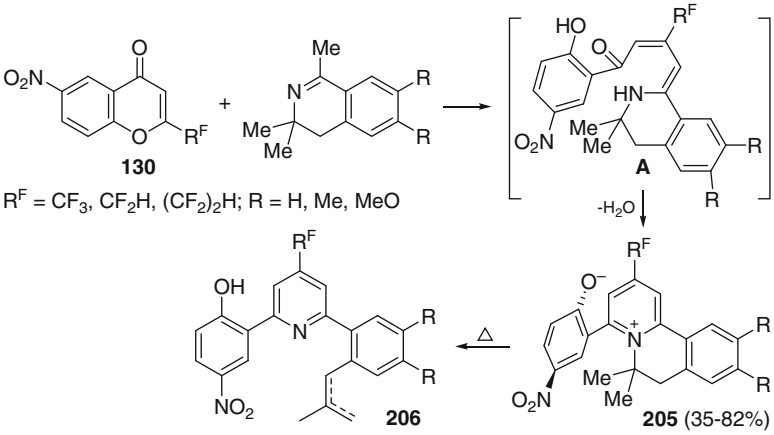
It was also found that 2-R^F-chromones **130** react with *N*-(1-arylethylidene)-2-propanamines to afford pyridines **203** in moderate yields. Using this reaction, pyridine **203a** was obtained, demethylation of which to 2,6-bis(2-hydroxyphenyl)-4-(trifluoromethyl)pyridine (**203b**) was achieved by heating with 48 % HBr at 200 °C [87]. When a mixture of chromones **130** with (isopropylidene)isopropylamine was refluxed without solvent for 10 h, anilines **204** were obtained [101] (Scheme 65).

The reaction of 6-nitro-2-R^F-chromones **130** with 1,3,3-trimethyl-3,4-dihydroisoquinolines affords chiral zwitter-ions **205** in 35–82 % yields. This reaction is typical only for 6-nitro derivatives and includes the nucleophilic attack of the



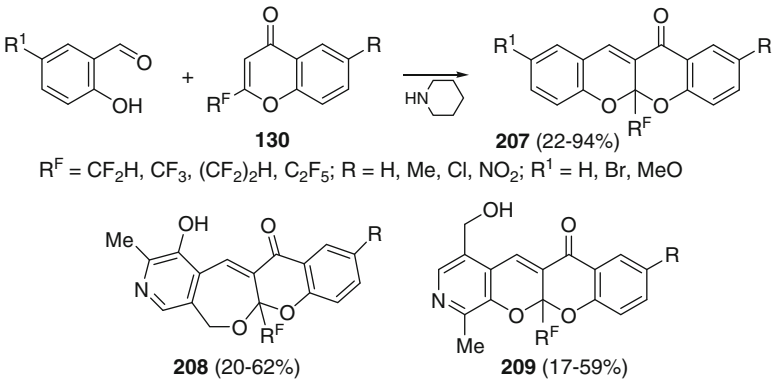
Scheme 65 Reactions of **130** with imines

enamine tautomer of dihydroisoquinoline to C-2 atom of **130** followed by ring opening and intramolecular cyclization at the keto group with elimination of H_2O. Cleavage of the Me_2C–N bond, resulting in the formation of isomers **206**, takes place on heating or in the presence of H_2SO_4 [102] (Scheme 66).



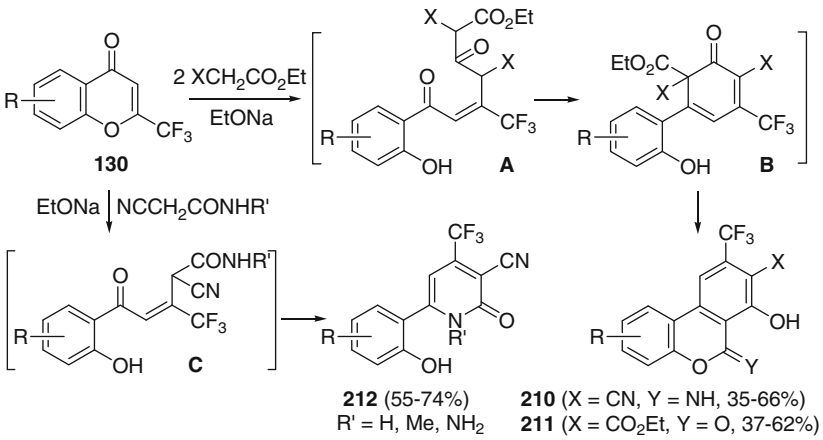
Scheme 66 Reactions of **130** with 3,4-dihydroisoquinolines

We also found that 2-R^F-chromones **130** react with salicylaldehydes in the presence of piperidine to afford **207** via oxa-Michael addition followed by intramolecular Mannich condensation [27]. Treatment of **130** with pyridoxal hydrochloride in the presence of NaOH (2.6 equiv.) gave oxepines **208** in moderate yields. In this case, the reaction proceeded at the alcoholic hydroxyl. Interestingly, using 1.3 equiv. of NaOH, it was possible to obtain **209** [103] (Scheme 67).



Scheme 67 Reactions of **130** with salicylaldehydes

Recently, Sosnovskikh et al. reported that 2-(trifluoromethyl)chromones **130** reacted with two molecules of ethyl cyanoacetate, yielding benzo[*c*]chromene-8-carbonitriles **210**. A similar base-mediated reaction of **130** with diethyl malonate gave carboxylates **211**. These products are formed through nucleophilic attack followed by Claisen condensation (intermediate **A**), intramolecular cyclization and dehydration (intermediate **B**), and then by aromatization (after hydrolysis and decarboxylation) through involvement of the phenolic hydroxy group. At the same time, chromone **130a** reacts with cyanoacetamide, *N*-methyl cyanoacetamide, and cyanoacetohydrazide in the presence of sodium ethoxide, affording 2-pyridones **212** in good yields [104] (Scheme 68).



Scheme 68 Reactions of **130** with active methylene compounds

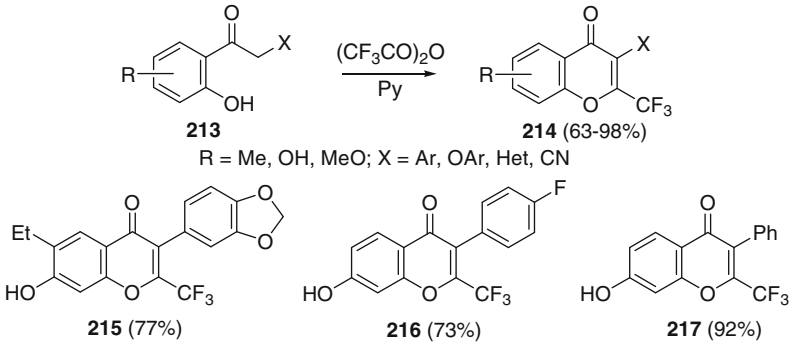
In conclusion, it should be noted that the trifluoromethyl group occupies a special place among polyfluorinated substituents, because the most interesting and peculiar transformations with *N*-, *S*- and *C*-nucleophiles can be carried out only for

2-CF_3-chromones and their derivatives. Most of the reaction described in this chapter are typical only for 2-R^F-chromones and does not occur when the R^F group is replaced by the methyl or trichloromethyl group [46b].

3.3 3-Substituted 2-(Polyfluoroalkyl)Chromones

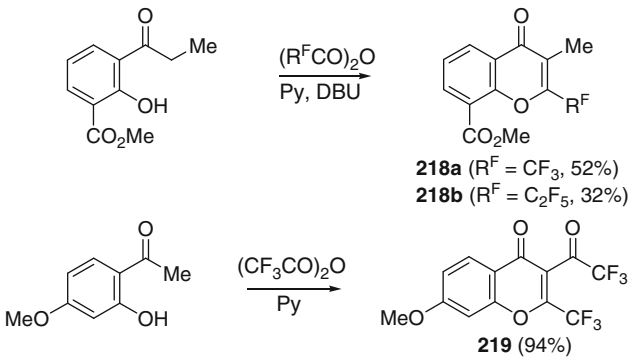
3.3.1 Synthesis of 3-Substituted 2-(Trifluoromethyl)Chromones

Preparation of 3-aryl and 3-hetaryl-2-(trifluoromethyl)chromones **214** was achieved by reaction of trifluoroacetic anhydride with pyridine solutions of ketones **213** [105]. This simple and effective procedure was also used for the synthesis of 7-hydroxy-2-(trifluoromethyl)chromone-3-carbonitrile (**214**, X=CN), from which 7-hydroxy-2-(trifluoromethyl)chromone-3-carboxamide (**214**, X=$CONH_2$) was obtained. These compounds are useful for preventing allergic and asthmatic symptoms [106]. The same procedure was employed for the preparation of isoflavones **215** and **216** which are potent dual PPARα and γ agonists [107]. By heating ω-phenylresacetophenone with $(CF_3CO)_2O$ and sodium trifluoroacetate isoflavone **217** was prepared with the intent to study antihypertensive activity [48]. The reactions of isoflavones containing a trifluoromethyl group at the 2-position have been reviewed previously [108] (Scheme 69).



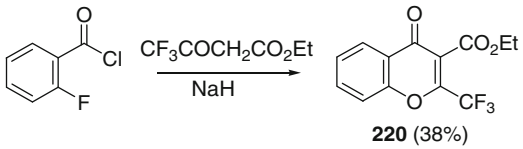
Scheme 69 Synthesis of 3-substituted 2-CF_3-chromones

2-Hydroxy-3-(methoxycarbonyl)propiophenone is easily converted into chromones **218a,b** through DBU assisted Baker-Venkataraman reaction with perfluoroalkanoyl anhydrides in pyridine [109]. The strength of the trifluoroacetic anhydride as acylating agent and the electron delocalization toward the carbonyl oxygen promoted by the *para*-methoxyl group favor the over trifluoracetylation of an intermediate, which ultimately produce **219** in excellent yield [60] (Scheme 70).



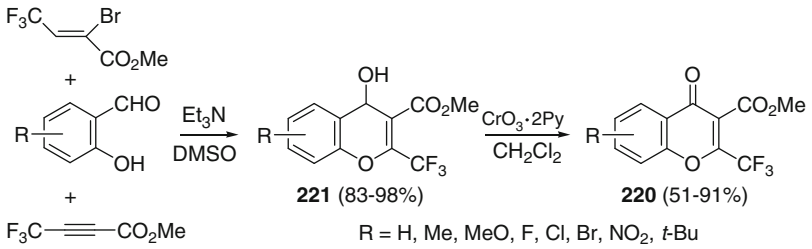
Scheme 70 Synthesis of 3-substituted 2-R^F-chromones

The reaction of *o*-fluorobenzoyl chloride with β-ketoesters in the presence of NaH has been proposed as a method for the synthesis of 2-methylchromone-3-carboxylic acid and its esters. In particular, this reaction proved to be suitable for the preparation of ethyl 2-(trifluoromethyl)chromone-3-carboxylate (**220**) [110] (Scheme 71).



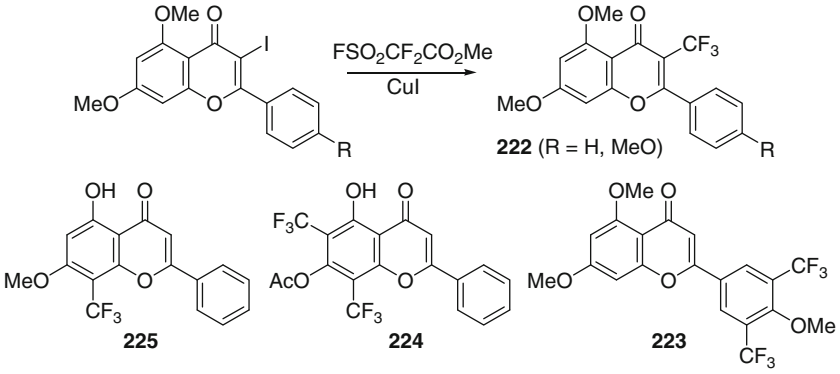
Scheme 71 Synthesis of chromone **220**

Derivatives of 4-hydroxy-2-(trifluoromethyl)-4*H*-chromene **221** were obtained via condensation of salicylaldehydes with methyl (*Z*)-2-bromo-4,4,4-trifluoro-2-butenoate [111] or methyl 2-perfluoroalkynoates [112]. Treatment of **221** with Sarrett reagent in CH_2Cl_2 generated chromones **220** in high yields [111] (Scheme 72).



Scheme 72 Synthesis of compounds **220** and **221**

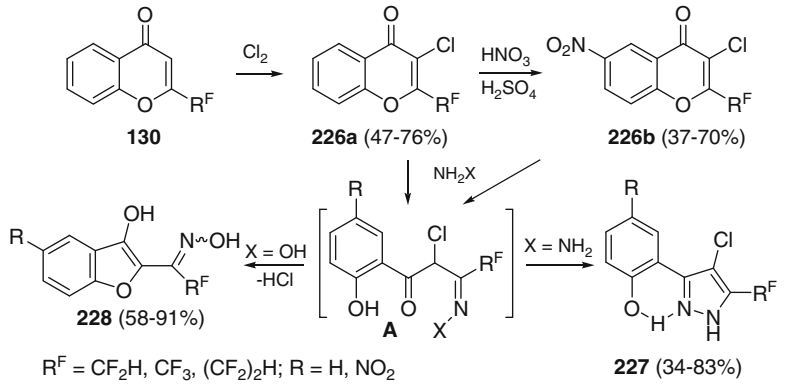
3-(Trifluoromethyl)flavonoid derivatives **222** were prepared by trifluoromethylation of 3-iodoflavonoids with $FSO_2CF_2CO_2Me$/CuI. Other C ring and B ring trifluoromethylated flavones were also prepared. All the compounds were tested for their effect on the U2OS cell cycle. Bistrifluoromethylated apigenin derivative **223** showed the strongest activity [113]. Chrysin derivatives **224** and **225** were tested in vitro against human gastric adenocarcinoma cell line (SGC-7901) and colorectal adenocarcinoma (HT-29) cells [114] (Scheme 73).



Scheme 73 Trifluoromethylated flavones

3.3.2 Reactions of 3-Substituted 2-(Polyfluoroalkyl)Chromones

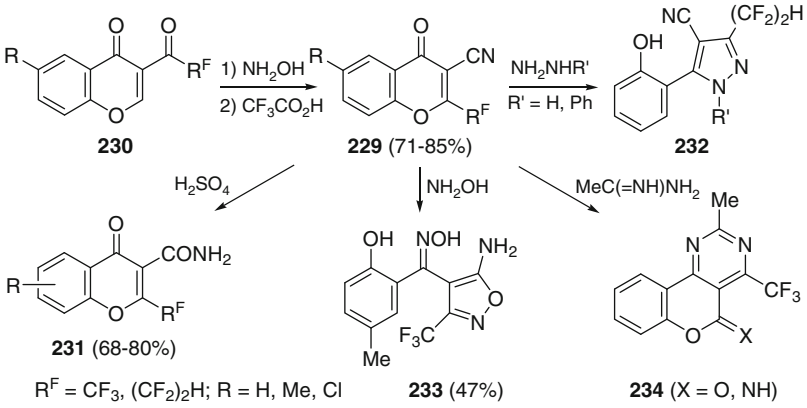
When treated with chlorine in the light (CCl_4, ~60 °C, 1 h), chromones **130** add a chlorine molecule at the double bond of the pyrone ring and, after elimination of HCl, they are converted into 3-chlorochromones **226a**, which are readily nitrated to give 3-chloro-6-nitrochromones **226b** [67, 115] (Scheme 74).



Scheme 74 Reactions of chromones **226** with hydrazine and hydroxylamine

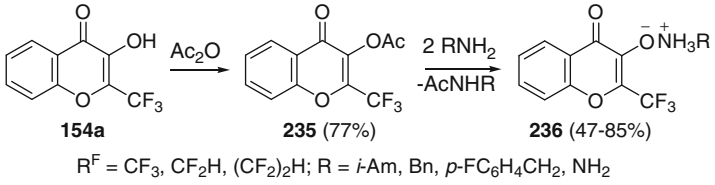
3-Chlorochromones **226** react with hydrazine dihydrochloride to give 4-chloropyrazoles **227** in good yields [115]. It is the first example of a reaction of 3-halochromone with a nucleophile with retention of the halogen atom in the reaction product. When chromones **226** are refluxed with hydroxylamine, contraction of the pyrone ring to the furan ring, typical of 2-unsubstituted 3-halochromones, takes place to give benzofurans **228** [116]. The reactions involve intermediate **A** resulting from the attack of the NH_2 group on the C-2 atom with the pyrone ring opening. This is followed by either an intramolecular Ad_N-E reaction between the C=O and NH_2 groups (X=NH_2) or nucleophilic substitution of the phenolic hydroxyl for the chlorine atom (X=OH) [116] (Scheme 74).

When 3-cyano-2-(polyfluoroalkyl)chromones **229**, prepared from 3-(polyfluoroacyl)chromones **230** (see Sect. 3.4.1), were treated with H_2SO_4, amides **231** were obtained in high yields. Heterocyclization of **229** with hydrazines, hydroxylamine and acetamidine resulted in pyrazoles **232**, 5-aminoisoxazole oxime **233**, and pyrimidin-5-ones **234** in variable yields [117] (Scheme 75).



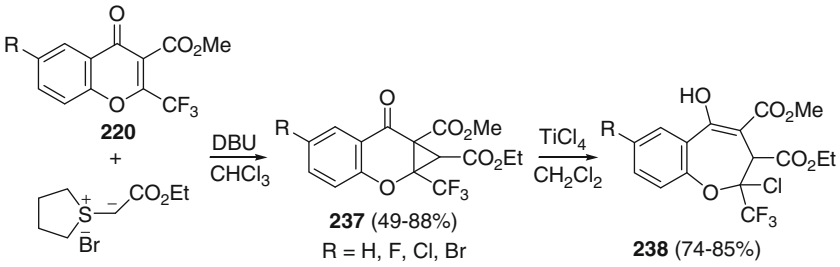
Scheme 75 Some reactions of chromones **229**

We found that **154a** smoothly reacts with an excess of MeI (refluxing acetone) and Ac_2O–Py to produce the expected 3-methoxy- and 3-acetoxy-2-(trifluoromethyl) chromones in high yields. Treatment of **235** with primary amines and hydrazine gave only the corresponding ammonium salts **236** [72] (Scheme 76).



Scheme 76 Acetylation of chromone **154a**

Chromones **220** were converted to 2-trifluoromethyl-substituted benzoxepins **238** through cyclopropanation and Lewis acid-catalyzed ring opening of **237** [111] (Scheme 77).

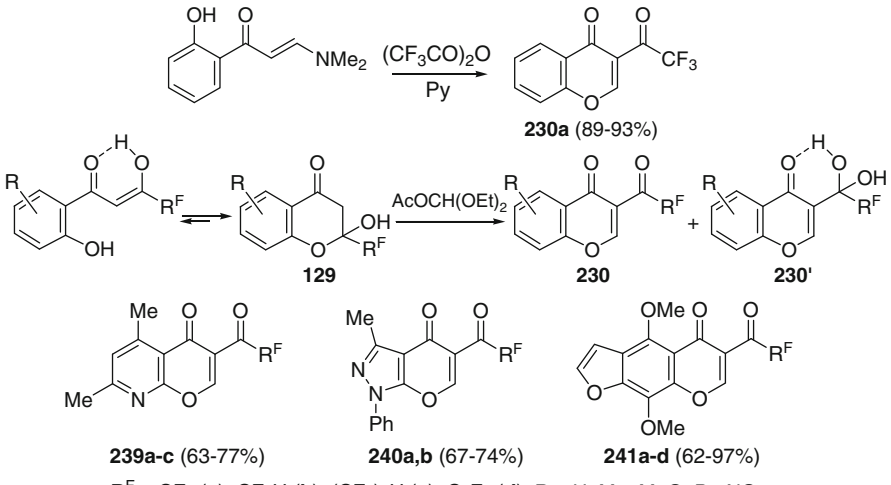


Scheme 77 Synthesis of compounds **237** and **238**

3.4 3-(Polyfluoroacyl)- and 2-(Trifluoroacetyl)Chromones

3.4.1 Synthesis and Reactions of 3-(Polyfluoroacyl)Chromones

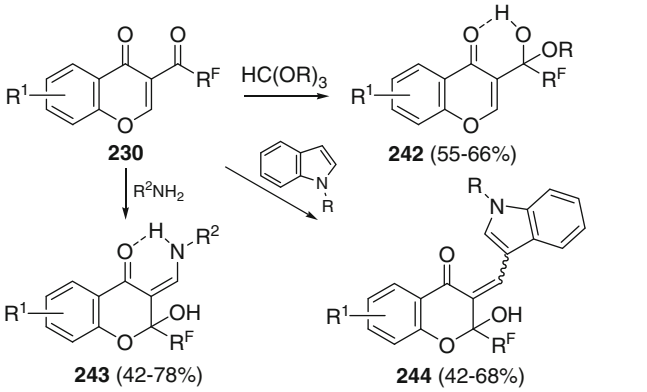
3-(Polyfluoroacyl)chromones **230** containing a β-dicarbonyl fragment and a masked formyl group are highly reactive R^F-containing building blocks [118]. There has been only two reports on the preparation of **230** by trifluoroacetylation of 3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one with trifluoroacetic anhydride or *N*-(trifluoroacetyl)imidazole [119] and by formylation of 2-hydroxy-2-(polyfluoroalkyl)chroman-4-ones **129** using diethoxymethyl acetate [120] (Scheme 78).



Scheme 78 Synthesis of 3-(polyfluoroacyl)chromones **230** and their heteroanalogs

It should be taken into account that these compounds easily add a water molecule at the carbonyl group and exist as a mixture with their hydrates **230′** [121]. Pure **230a** was obtained from a mixture of keto and hydrate forms using P_2O_5 [122]. Heteroanalogues **239–241** were obtained similarly in high yields [59, 121, 123].

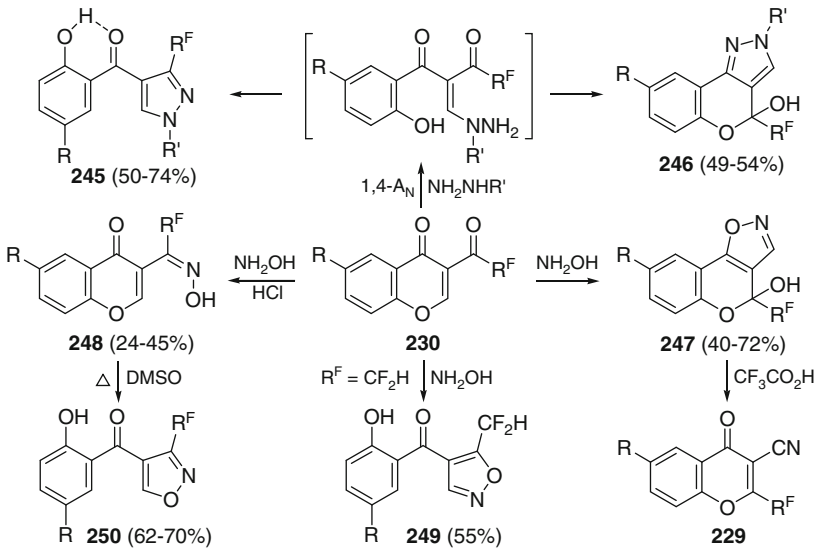
As expected, the reaction of chromones **230** with alkyl orthoformates catalyzed with HCl or *p*-TsOH resulted in the formation of hemiketals **242**. The reaction of **230** with primary amines afforded chromanones **243** in good yields [121] (Scheme 79).



Scheme 79 Reactions of **230** with amines and indoles

Chromones **230** smoothly react with indole and *N*-methylindole in refluxing pyridine resulting in the formation of **244** as mixtures of *Z*- and *E*-isomers [124]. These reactions include the nucleophilic 1,4-addition of the amine or indole with concomitant opening of the pyrone ring and subsequent intramolecular cyclization of the intermediate at the R^FCO group [125].

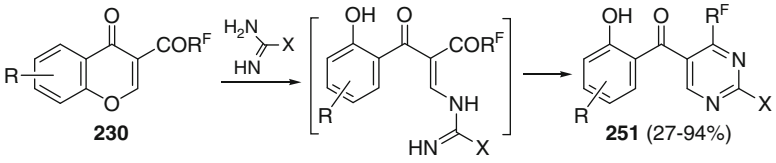
Reactions of 3-(polyfluoroacyl)chromones **230** with hydrazine hydrate and methylhydrazine proceed via nucleophilic 1,4-addition followed by opening of the pyrone ring and heterocyclization at polyfluroacyl group into 4-(2-hydroxyaroyl)-3-(polyfluoroalkyl) pyrazoles **245** or aroyl group into 4-(polyfluoroalkyl)-2,4-dihydrochromeno[4,3-*c*] pyrazol-4-oles **246** [126] (Scheme 80).



R^F = CF_2H, CF_3, $(CF_2)_2H$; R = H, Me, Cl, NO_2; R' = H, Me

Scheme 80 Reactions of **230** with hydrazines and hydroxylamine

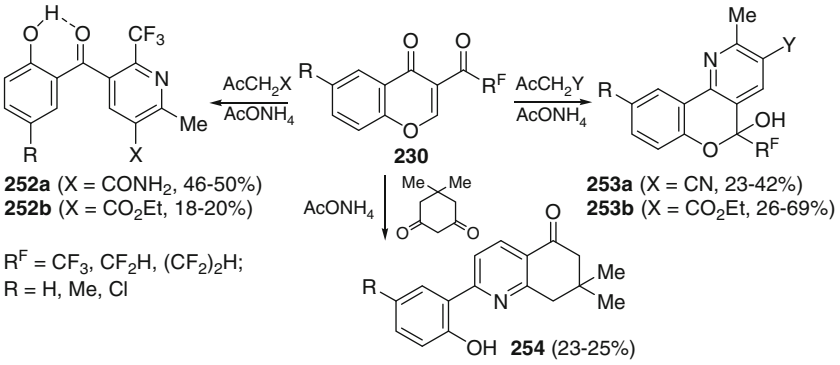
Similar reaction of **230** with hydroxylamine proceeds via 1,4-addition and subsequent cyclization to **247** in good yields. On treatment with trifluoroacetic acid, the isoxazole ring of this fused heterocyclic system opens to give 3-cyano-2-R^F-chromones **229** (see Sect. 3.3.2). On the other hand, oximation of **230** with hydroxylamine hydrochloride occurs either at the C=O group connected to the R^F group or at the C-2 atom to give chromones **248** and isoxazole **249**, respectively. The former were converted to isoxazoles **250** by heating in DMSO [127] (Scheme 80). Treatment of chromones **230** with amidine and guanidine gave 5-salicyloyl-4-(polyfluoroalkyl) pyrimidines **251** in variable yields, from which the corresponding 4-(trifluoromethyl) pyrimidine-5-carboxylic acids, a new class of potent ryanodine receptor activators, were obtained under Dakin reaction conditions [128] (Scheme 81).



R^F = CF_2H, CF_3, $(CF_2)_2H$, C_3F_7; R = H, Me, MeO; X = H, Me, Ph, NH_2, NMe_2

Scheme 81 Reactions of **230** with amidines

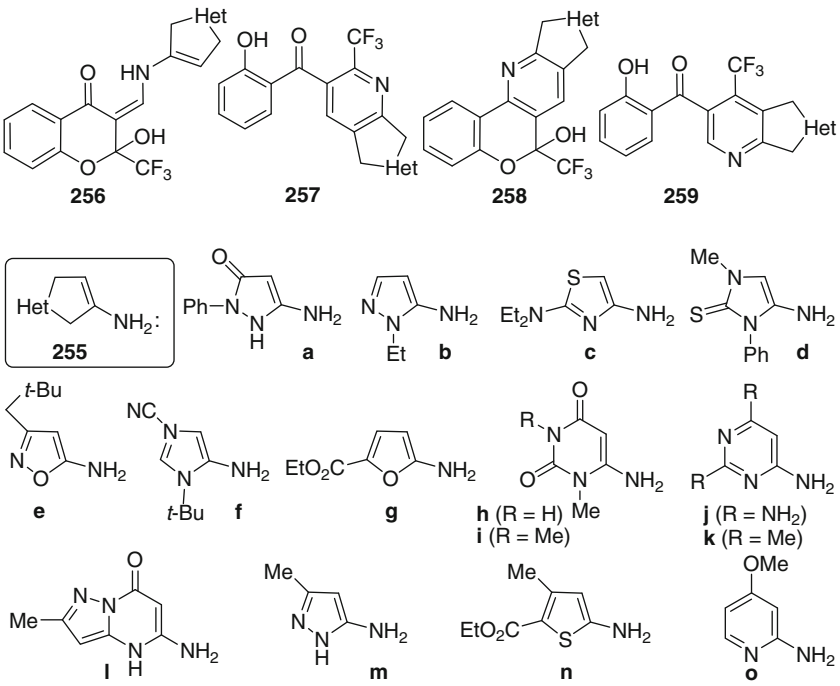
Reactions of chromones **230** with acetoacetamide and ethyl acetoacetate in ethanol in the presence of ammonium acetate proceed at the C-2 atom of the chromone system with pyrone ring-opening and subsequent cyclization to **252**. Similar reaction with β-aminocrotononitrile gave 5-hydroxy-2-methyl-5-(polyfluoroalkyl)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitriles (**253a**) [129]. Three-component reaction between chromones **230**, dimedone, and $AcONH_4$ is accompanied by detrifluoroacetylation and leads to **254** in low yields [130] (Scheme 82).



Scheme 82 Reactions of **230** with active methylene compounds

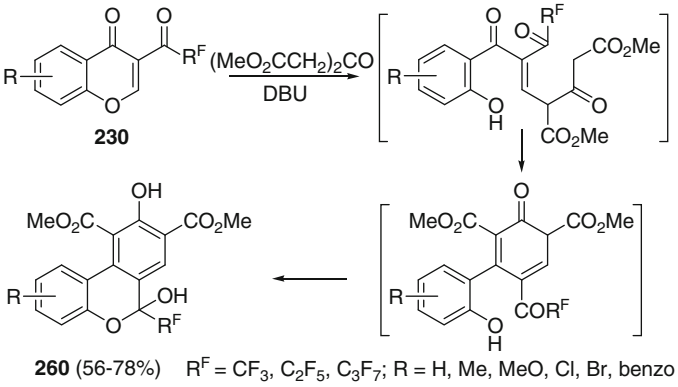
Chromone **230a** reacts with heterocyclic amines **255** giving four types of products, depending on the nature of the 1,3-*C,N*-dinucleophile and the solvent. The reaction of heterocycles **255a**,**i,j,l** with **230a** gave the corresponding fused pyridines **257** as the main products, while in the case of **255e–h** the formation of chromeno[4,3-b]pyridines **258** was preferred. At the same time, aminoheterocycles **255b,k,m–o** in DMF gave mainly chromanones **256**. Reactions of **255a–e**, performed in glacial acetic acid yielded preferably products **257** and **259**, which represent fused pyridines with a trifluoromethyl group located in the α- or γ-position. It clearly appears that the less aromatic heterocycles **255a–j,l** have a proclivity to form fused pyridines **257**–**259** [131] (Scheme 83).

While enamines react with chromones **230** mainly at the R^FCO group to produce pyridine derivatives, reactions of dimethyl acetonedicarboxylate with **230** took an entirely different course and gave a series of 6*H*-benzo[*c*]chromenes **260** in good yields. This heterocyclic system certainly is the product of the primary 1,4-addition



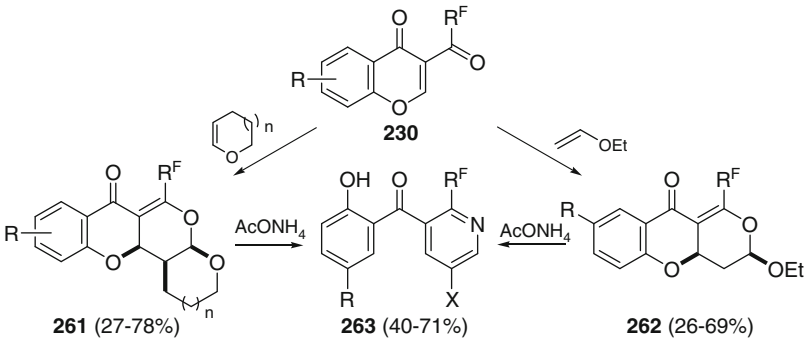
Scheme 83 Products **256**–**259** from chromones **230** and aminoheterocycles **255**

followed by the pyrone ring-opening, attack of the second CH_2 group to the carbonyl bound with the aromatic cycle, and ring-closure involving the phenolic hydroxyl and R^FCO group [132] (Scheme 84).



Scheme 84 Reaction of chromones **230** with dimethyl acetonedicarboxylate

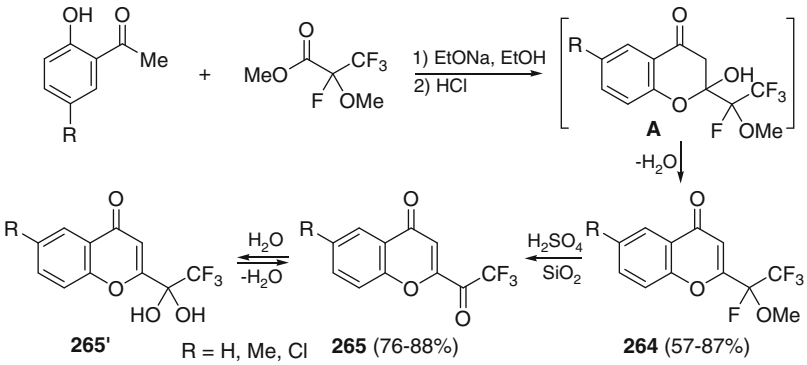
3-(Polyfluoroacyl)chromones **230** undergo heterodiene cycloaddition to 3,4-dihydro-2*H*-pyran, 2,3-dihydrofuran and ethyl vinyl ether under mild conditions, producing novel fused pyranes **261** and **262** with high stereoselectivity and in good yields. Some of these pyranes were transformed into 2-R^F-containing pyridines on treatment with ammonium acetate in ethanol [133] (Scheme 85).



Scheme 85 Hetero-Diels-Alder reaction of chromones **230**

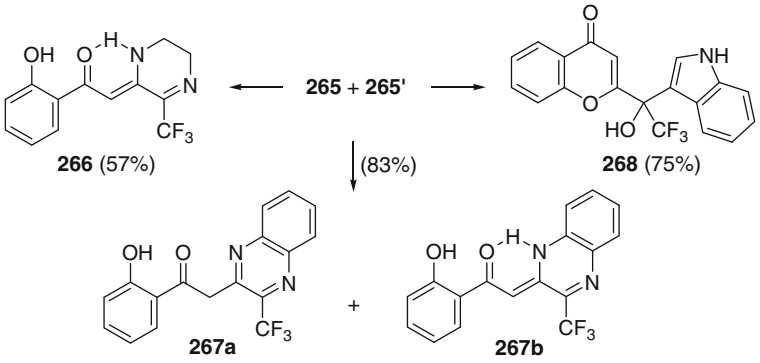
3.4.2 Synthesis and Reactions of 2-(Trifluoroacetyl)Chromones

We found that methyl 2-methoxytetrafluoropropionate reacted with 2-hydroxyacetophenones under Claisen reaction conditions (NaOEt or LiH) affording chromones **264** in high yields. Deprotection of chromones **265** was carried out using 96 % H_2SO_4 and SiO_2, to afford 2-(trifluoroacetyl)chromones **265**, which were prone to form hydrates [134] (Scheme 86).



Scheme 86 Synthesis of 2-(trifluoroacetyl)chromones **265**

Chromone **265** (R=H) behaves as a latent 1,2-diketone, having a masked aroyl fragment at the 3-position, and reacts with ethylenediamine and *o-phenylenediamine* to give **266** and **267a,b** (two tautomeric forms) in good yields. This chromone reacted smoothly with indole to produce the expected adduct **268**. These results clearly indicate that C-2 of **265**, due to the electron-withdrawing effect of the CF_3CO group, is very susceptible to nucleophilic attack [134] (Scheme 87).



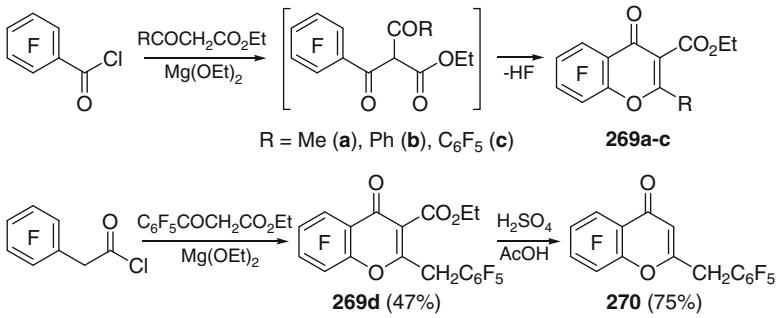
Scheme 87 Some reactions of 2-(trifluoroacetyl)chromones **265**

4 Ring-Fluorinated Chromones and Coumarins

4.1 Synthesis of Ring-Fluorinated Chromones and Coumarins

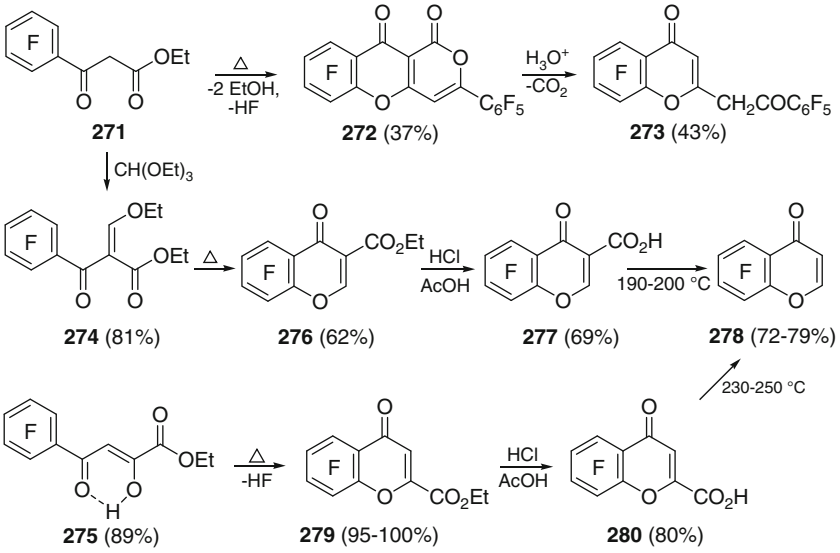
Ring-fluorinated chromone carboxylic acids are very interesting compounds being oxygen analogues of the fluoroquinolone antibiotics. It is well-known that polyfluoroaryl β-dicarbonyl compounds are useful in this area because the nucleophilic replacement of their *ortho*-fluorine atom leads to the formation of chromone structures. Such behaviour has been found in the reactions of pentafluoroaromatic β-ketoesters [135] and β-diketones [135, 136] and also in the synthesis of 2-substituted 3-ethoxycarbonyl-5,6,7,8-tetrafluorochromones **269a–d** through the reaction of pentafluorobenzoyl and pentafluorophenylacetyl chlorides with β-ketoesters in the presence of magnesium ethoxide. On hydrolysis, **269d** gave 2-pentafluorobenzyl-5,6,7,8-tetrafluorochromone (**270**) [135, 137] (Scheme 88).

Saloutin et al. reported [138] that the self-condensation of ethyl pentafluorobenzoylacetate (**271**) on refluxing without any catalyst leads to the formation of compound **272** in 37 % yield, acid hydrolysis of which gave 2-pentafluorobenzoylmethyl-5,6,7,8-tetrafluorochromone (**273**). Other routes for preparing some new ring-fluorinated chromones have been performed from the 2-ethoxymethylene pentafluorobenzoylacetic ester (**274**) and also via intramolecular cyclization of ethyl pentafluorobenzoylpyruvate (**275**). The reaction of ester **271** with ethyl orthoformate results in the



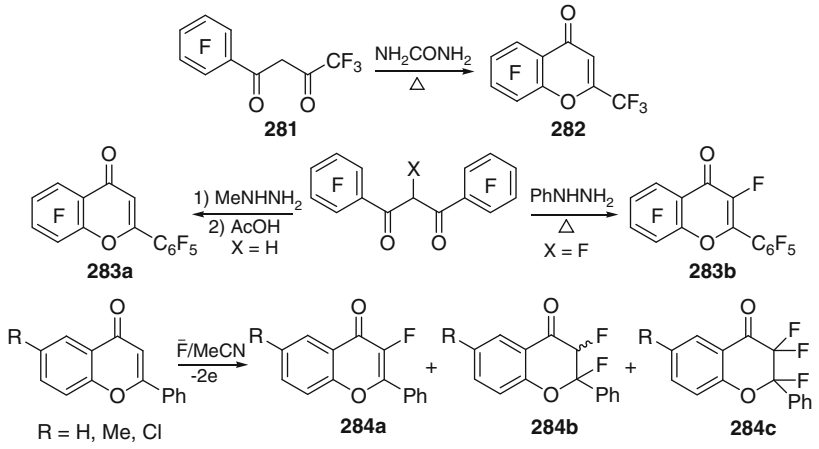
Scheme 88 Synthesis of chromones **269** and **270**

formation of compound **274**, which was refluxed with water to form 3-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (**276**). The latter was hydrolyzed under acidic conditions to give carboxylic acid **277**, sublimation of which produced 5,6,7,8-tetrafluorochromone (**278**). This compound was derived directly from ester **276** in boiling acetic acid [138]. Pentafluoroacetophenone reacts with diethyl oxalate in the presence of LiH to give ethyl pentafluorobenzoylpyruvate (**275**), which can be isolated through its copper(II) chelate. Ester **275** is stable at room temperature, but is converted by heat to give 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (**279**) in quantitative yield. The latter under acidic hydrolysis gave tetrafluorochromone (**280**), sublimation of which at 230–250 °C produced chromone **278** [138]. Pentafluoroacetophenone also reacts with Vilsmeier reagent to give chromone **278** and its 3-formyl derivative depending on the conditions [139] (Scheme 89).



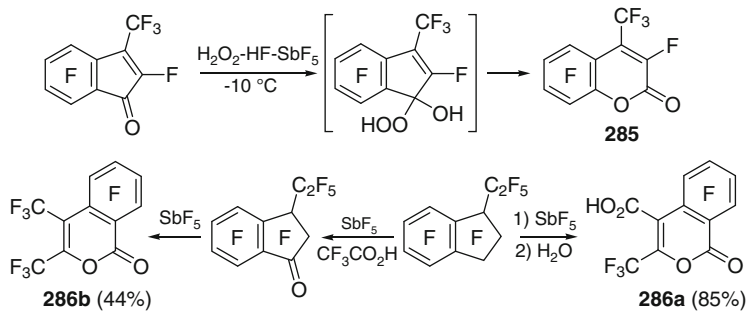
Scheme 89 Synthesis of chromones **273**, **278** and **280**

Heating diketone **281**, containing an easily replaceable fluorine atom in the *ortho*-position to the carbonyl group, with urea results in 2-(trifluoromethyl)-5,6,7,8-tetrafluorochromone (**282**) [140]. Perfluoroflavones **283a,b** were obtained from the reactions of bis(pentafluorobenzoyl)- and fluorobis(pentafluorobenzoyl)-methanes with methyl- and phenylhydrazines [136]. 3-Fluoroflavone **284a** and its 6-substituted derivatives were prepared from appropriate flavones by electrochemical fluorination with $Et_4NF \cdot 4HF$ or $Et_3N \cdot 3HF$. Anodic fluorination of flavones affords mono- (**284a**), di- (**284b**) and tri- (**284c**) fluoro derivatives, whose ratio depends on the type of salt used and the temperature of electrolysis. 3-Fluoroflavones **284a** are formed upon dehydrofluorination of **284b** under the action of Et_3N, while trifluoro derivatives **284c** are the products of further fluorination of **284a**. The yields of **284a** vary over a broad range (25–63 %) [141] (Scheme 90).



Scheme 90 Some ring-fluorinated chromones

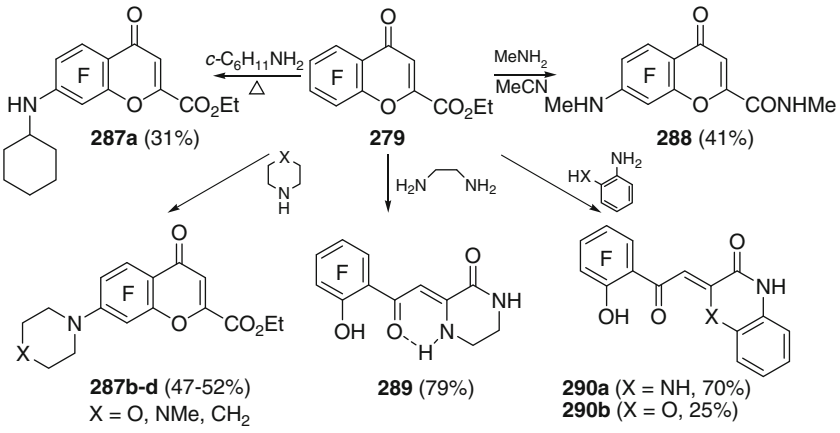
Formation of perfluoro-4-methylcoumarin **285** has been reported from perfluoro-3-methylindenone, in which the carbonyl group is involved in reaction with H_2O_2 in the HF–SbF_5 system [142a]. Perfluoro-1-ethylindan heated with excess of SiO_2 in SbF_5 at 75 °C and then treated with water, gives isocoumarin **286a** in high yield. Perfluoro-3-ethylindan-1-one is converted, under the action of SbF_5 at 70 °C, to perfluoro-3,4-dimethylisocoumarin **286b** [142b, c] (Scheme 91).



Scheme 91 Some ring-fluorinated coumarins

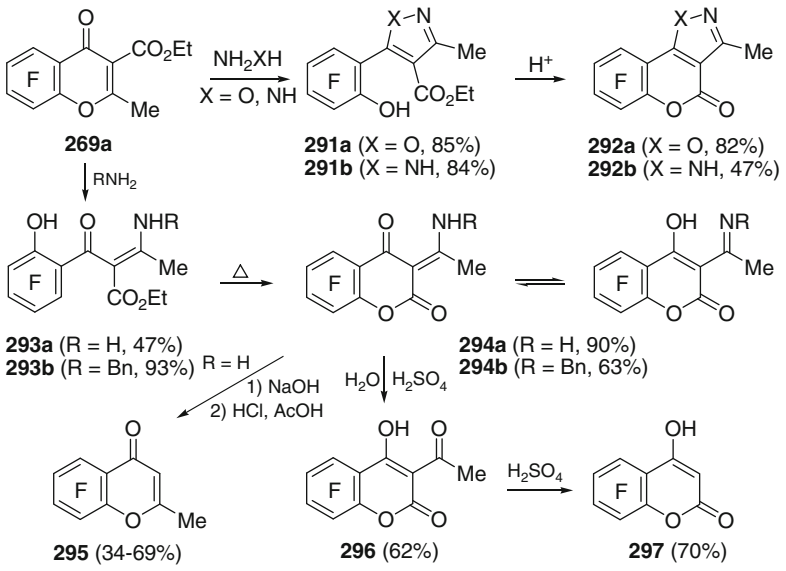
4.2 Reactions of Ring-Fluorinated Chromones and Coumarins

The reactions of chromones with amines is known to afford the corresponding aminoenones at the C-2 atom [46]. In contrast, chromone **279** reacts with cyclohexylamine, morpholine, *N*-methylpiperazine, and piperidine without pyrone ring opening to give compounds **287a–d**. Similar reaction with methylamine furnishes compound **288**, which results from reaction at the ethoxycarbonyl group and nucleophilic displacement of the fluorine atom at the 7-position of the heterocycle. At the same time, ammonia and aniline does not react with **279**. The reaction of **279** with ethylenediamine gave piperazinone **289** [143]. Refluxing of **279** with *o-phenylenediamine* in toluene for 18 h in the presence of $BF_3 \cdot Et_2O$ results in the formation of quinoxalinone **290a** [144]. On treatment with *o*-aminophenol chromone **279** gave benzoxazinone **290b** in low yield [145, 146] (Scheme 92).



Scheme 92 Reactions of chromone **279** with amines

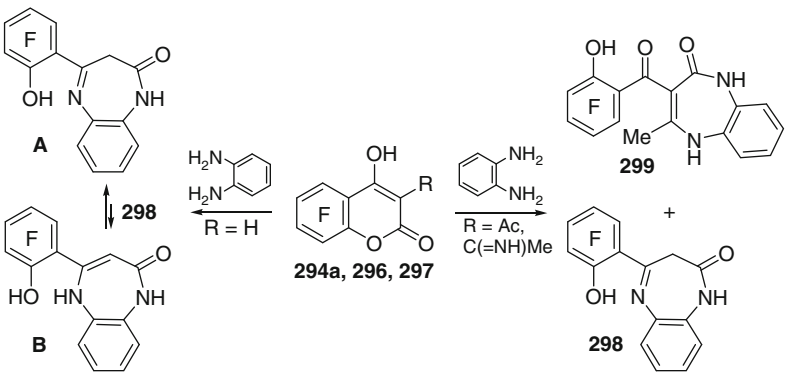
The reaction of chromone **269a** with hydroxylamine affords isoxazole **291a**, which could only arise from addition of the *N*-nucleophile at the C-2 position of the heterocycle. This compound was subjected to cyclization on refluxing under acidic conditions to give benzopyranoisoxazole **292a**. A similar reaction of chromone **269a** with hydrazine hydrate gave the corresponding pyrazole **291b**. When **291b** was heated with a boiling mixture of concentrated acetic and hydrochloric acids, benzopyranopyrazole **292b** was obtained [147a]. Chromone **269a** also reacts with ammonium hydroxide at room temperature to give a mixture of aminoenone **293a** and its cyclic derivative **294a**. The latter can be derived from **293a** by refluxing with ammonium hydroxide. When **269a** was heated with ammonium hydroxide, only **294a** was obtained. Similar reaction of **269a** with benzylamine also proceeds at the C-2 position and gives substituted aminoenone **293b**, which was then subjected to cyclization to produce coumarin **294b** without any catalyst or solvent at 100 °C. Both keto-enamino and imino-enol isomers are possible in structures **293** and **294**, however keto-enamino form is preferred [147b, c]. Under acidic conditions, aminoenone **293a** was hydrolyzed to give 2-methyl-5,6,7,8-tetrafluorochromone (**295**), which was also obtained from 3-carboxy-2-methyl-5,6,7,8-tetrafluorochromone and compound **294a** by alkaline and subsequent acidic treatment. When **294a** was treated with diluted H_2SO_4, coumarin **296** was obtained. The latter was treated with concentrated H_2SO_4 to give 4-hydroxy-5,6,7,8-tetrafluorocoumarin (**297**) [147a] (Scheme 93).



Scheme 93 Some derivatives of chromone **269a**

4-Hydroxycoumarin **297** was found to react with *o*-phenylenediamine on refluxing in toluene to form product **298** existing as a mixture of tautomers **A** and **B**. Under similar conditions, 3-acetyl-4-hydroxycoumarin **296** reacts with *o*-phenylenediamine

to form a mixture of products from which benzodiazepine-2-one **299** and compound **298** can be isolated. The former was also obtained in 65 % yield by the reaction of 3-acetimidoyl-4-hydroxycoumarin **294a** [148a] (Scheme 94).



Scheme 94 Reactions of 4-hydroxycoumarins with *o*-phenylenediamine

The reactions of 4-hydroxy-5,6,7,8-tetrafluorocoumarine derivatives with ammonia and morpholine involve aromatic nucleophilic substitution of fluorine atoms at the 7-position as the main process [148b].

5 Fluorinated Coumarins

Derivatives of 2*H*-1-benzopyran-2-one, also known as coumarins, are prominent natural products possessing a wide range of valuable physiological activities. Many coumarin derivatives exert anticoagulant, antitumor, antiviral, antiinflammatory and antioxidant effects, as well as antimicrobial and enzyme inhibition properties [47a, 149]. In addition, they represent useful synthetic building blocks in organic and medicinal chemistry, and have also found application as photosensitisers, fluorescent and laser dyes [150]. 7-Amino-4-(trifluoromethyl)coumarins, the important class of laser dyes for the "blue-green" region, are strongly fluorescent in polar solvents, and their fluorescence properties depend on the electron-donating ability of the 7-amino group [151].

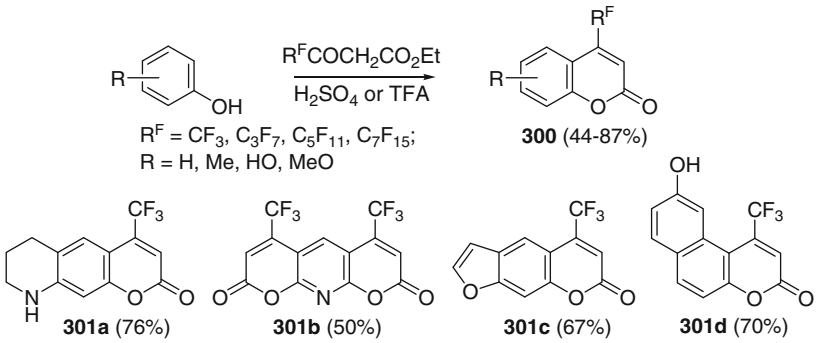
5.1 Synthesis and Application of Polyfluoroalkylated Coumarins

5.1.1 3-Unsubstituted 4-(Polyfluoroalkyl)Coumarins

Coumarins have been synthesized by several routes, including Pechmann, Perkin, Knoevenagel and Wittig reactions. The reaction of various phenols with β-ketoesters in the presence of an acid catalyst, an example of the Pechmann reaction, has been

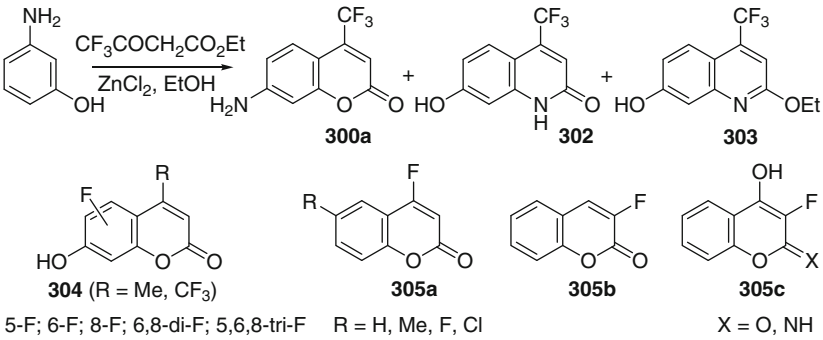
extensively used in the synthesis of 4-substituted coumarins. With ethyl 4,4,4-trifluoroacetoacetate [152] and electron-rich phenols, the reaction affords, almost invariable, 4-(trifluoromethyl)coumarins **300** bearing different electron-donating substituents at the benzene ring [50, 153, 154].

Various derivatives of 7-hydroxy- and 7-amino-4-(trifluoromethyl)coumarins **300** are readily prepared by the Pechmann reaction using zinc chloride as the condensing agent [155]. Recently, there have been reports on the use of $ZrCl_4$ [156], AgOTf and molecular iodine [157], $InCl_3$ [158], $Sc(OTf)_3$ [159] and $TiCl_4$ [160] as Lewis acids for the synthesis of 4-CF_3-coumarins **300**. A 30-membered library of 4-substituted coumarins has been synthesized in a microwave-assisted Pechmann reaction using neat trifluoroacetic acid both as an acidic reagent and a reaction medium [161]. Fused 4-(trifluoromethyl)coumarins **301a–d**, including 4-CF_3-psoralen **301c**, were obtained in the presence of an acid catalyst such as $ZnCl_2$, methanesulfonic acid or sulfuric acid [162–165] (Scheme 95).



Scheme 95 Some representatives of 4-(trifluoromethyl)coumarins

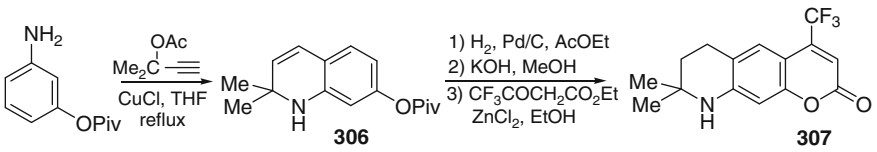
Synthesis and purification of 7-amino-4-(trifluoromethyl)courmarin (**300a**) (R = 7–NH_2, R^F=CF_3, Coumarin 151) from 3-aminophenol by the Pechmann reaction was first reported in 1980 [166]. Two byproducts, 7-hydroxy-4-(trifluoromethyl-2-quinolone (**302**) and 2-ethoxy-7-hydroxy-4-(trifluoromethyl)quinoline (**303**), were also isolated and identified. The synthesis of benzene ring fluorinated 7-hydroxy-4-methyl- and 7-hydroxy-4-(trifluoromethyl)coumarins **304** in 45–80 % yields was reported by Sun et al. by the condensation of fluorinated resorcinols with ethyl acetoacetate and ethyl trifluoroacetoacetate in methanesulfonic acid at ~20 °C [167]. 4-Fluorocoumarins **305a** were obtained from the corresponding 4-chlorocoumarins by a halogen-exchange reaction [168a]. The reaction of (*Z*)-2-fluoro-3-methoxyprop-2-enoyl chloride with phenol gave 3-fluorocoumarin **305b** [168b]. Dmowski reported facile preparation of 3-fluoro-4-hydroxycoumarins **305c** by treatment of *o*-hydroxy-2,3,3,3-tetrafluoropropiophenone with aqueous KOH and NH_3 [168c, d] (Scheme 96).



Scheme 96 Some representatives of fluorinated coumarins

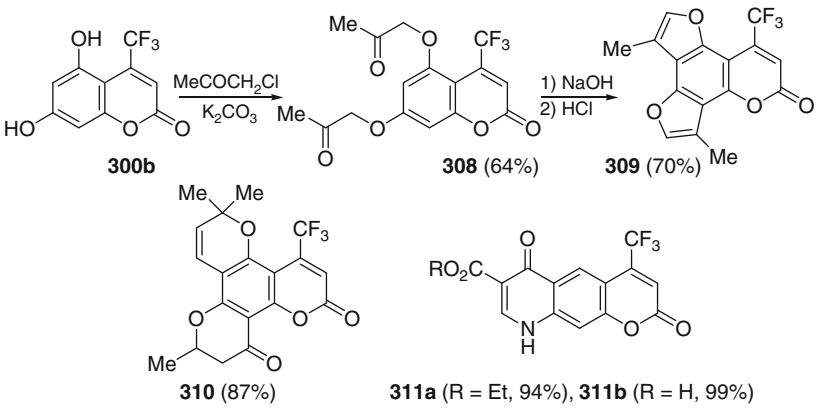
Reaction of 3-aminophenylpivalate with 3-acetoxy-3-methyl-l-butyne in the presence of CuCl afforded the corresponding propargyl aniline, which could be cyclized to **306** by treatment with catalytic CuC1 in refluxing THF. Reduction of the olefin by catalytic hydrogenation, deprotection of the phenol, and Pechmann cyclization using ethyl trifluoroacetoacetate mediated by zinc chloride in ethanol, afforded coumarin **307**, the 1-oxa version of 4-(trifluoromethyl)-2(1*H*)-piperidino[3,2-*g*]quinolinone, typified by the lead human androgen receptor antagonist LG120907. A series of 4-(trifluoromethyl)-2*H*-pyrano[3,2-g]quinolin-2-ones was prepared and tested for the ability to modulate the transcriptional activity of the human androgen receptor [169] (Scheme 97).

It was shown that the base-catalyzed cyclization of **308**, prepared from **300b** and chloroacetone, gave difurocoumarin **309** in high yield [170]. Coumarin **300b** was



Scheme 97 Synthesis of coumarin **307**

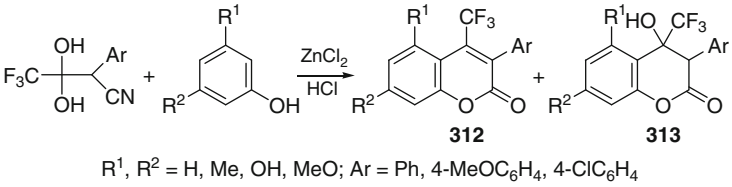
also reacted with crotonic acid in the presence of PPA to offer the corresponding angular chromanone, which was further condensed with 1,1-diethoxy-3-methyl-2-butene under microwave irradiation to produce the target tetracyclic dipyranocoumarin **310** as a potential anti-HIV-1 agent [171]. Reaction of 7-aminocoumarin **300a** with diethyl ethoxymethylenemalonate led to the condensation intermediate (the Gould-Jacobs reaction), thermal cyclization of which gave the desired tricyclic ester **311a**. This ester was hydrolyzed to the corresponding benzopyranopyridine carboxylic acid **311b**, which was found to possess high antimicrobial activity against Gram-positive microorganism [172] (Scheme 98).



Scheme 98 Some derivatives of 4-(trifluoromethyl)coumarin

5.1.2 3-Substituted 4-(Trifluoromethyl)Coumarins

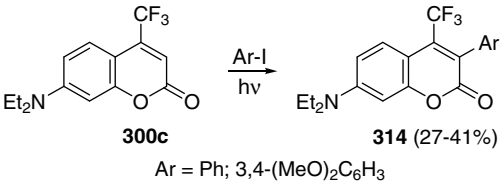
Resorcinol and 5-methylresorcinol react with 3-oxo-2-aryl-4,4,4-trifluorobutyronitrile using $ZnCl_2$ in dibutyl ether under the Hoesch reaction conditions to give a low yield of coumarins **312**. However, the related reaction with *m*-methoxyphenol was found to produce poor yields of **312** and **313** [173] (Scheme 99).



Scheme 99 Synthesis of coumarins **312**

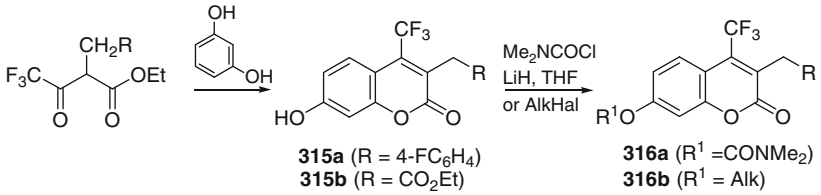
3-Aryl-7-(diethylamino)-4-(trifluoromethyl)coumarins **314** were synthesized as a result of the photoreaction of 7-(diethylamino)-4-(trifluoromethyl)coumarin (**300c**) with iodobenzene and 3,4-dimethoxyiodobenzene in acetonitrile. It was established that the electron-withdrawing CF_3 group and addition of triethylamine accelerate photosubstitution [174] (Scheme 100).

Ethyl 2-(*p*-fluorobenzyl)trifluoroacetoacetate reacted with resorcinol in 70 % sulfuric acid at 100 °C to provide coumarin **315a**. Upon treatment with *N,N-dimethylcarbamoyl* chloride in the presence of NaH, this compound was readily converted into the corresponding *N,N*-dimethylcarbamate **316a**, which was tested as a TNF-α inhibitor [175]. A similar reaction of resorcinol with diethyl



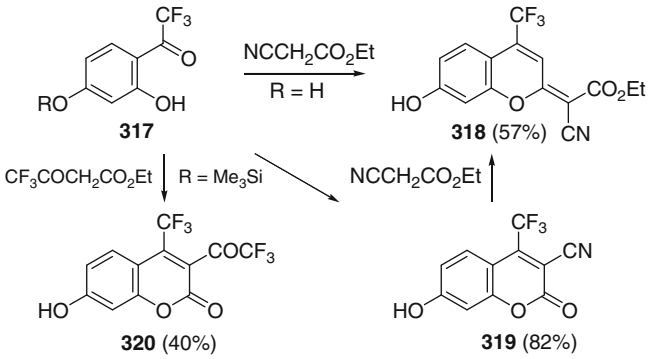
Scheme 100 Synthesis of coumarins **314**

trifluoroacetosuccinate in PPA gave compound **315b**, from which **316b** as CYP2C9 substrates responsible for the metabolism of drugs were obtained [176] (Scheme 101).



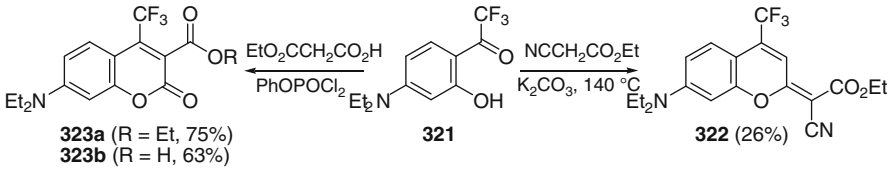
Scheme 101 Synthesis of coumarins **315** and **316**

Voznyi et al. reported that condensation of 4-(trifluoroacetyl)resorcinol **317** (R=H) with cyanoacetic ester occurs at 100–150 °C and is accompanied by closure of the pyrane ring and formation **318** as a result of condensation of **319** with cyanoacetic ester, followed by hydrolysis of the cyano group and decarboxylation [177]. When the trimethylsilyl derivative **317** (R=Me_3Si) was heated with cyanoacetic ester, it was possible to increase the yield of compound **319** from 10–12 % to 79–82 %. The synthesis of **320** was realized by a similar method [178] (Scheme 102).



Scheme 102 Synthesis of coumarins **318**–**320**

Similarly, reaction of **321** with cyanoacetic ester and potassium carbonate gave the benzopyrane **322**. When ketone **321** was treated with monoethyl malonate, triethylamine and phenyl phosphorodichloridate, the required coumarin **323a** was obtained and subsequent alkaline hydrolysis gave the acid **323b** [179] (Scheme 103).



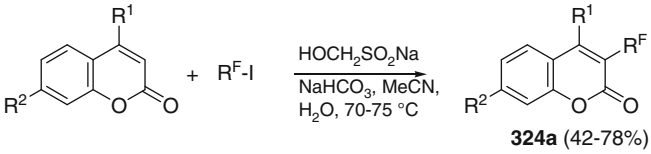
323a (R = Et, 75%)
323b (R = H, 63%)

321

322 (26%)

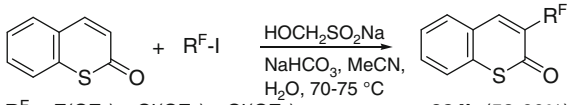
Scheme 103 Synthesis of coumarins **322** and **323**

Huang et al. reported that coumarins and thiocoumarin react with perfluoroalkyl iodides in the presence of sodium hydroxymethanesulfinate (Rongalite) to give 3-(polyfluoroalkyl)coumarins **324a,b** selectively and under mild conditions. A free-radical mechanism was proposed for the reaction [180]. The regioselective reaction of 3-unsubstituted coumarins with bis(perfluoroalkanoyl)peroxides also affords 3-(perfluoroalkyl)coumarins **324c**. Though the introduction of perfluoroalkyl groups into the 3-position of coumarins lowers the fluorescence intensities, the derivatives **324c** are much more stable towards UV irradiation than 3-unsubstituted coumarins [181] (Scheme 104).



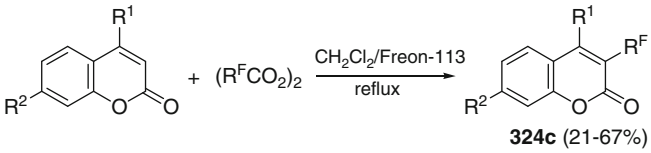
324a (42-78%)

R^F = $F(CF_2)_6$, $F(CF_2)_7$, $F(CF_2)_8$, $Cl(CF_2)_4$, $Cl(CF_2)_6$, $Cl(CF_2)_8$;
R^1 = H, Me; R^2 = H, OH, NEt_2



R^F = $F(CF_2)_6$, $Cl(CF_2)_4$, $Cl(CF_2)_6$

324b (53-60%)



324c (21-67%)

R^F = CF_3, C_3F_7, C_7F_{15}; R^1 = H, Me, CF_3; R^2 = H, Me, OH, MeO, NH_2, NMe_2, NEt_2

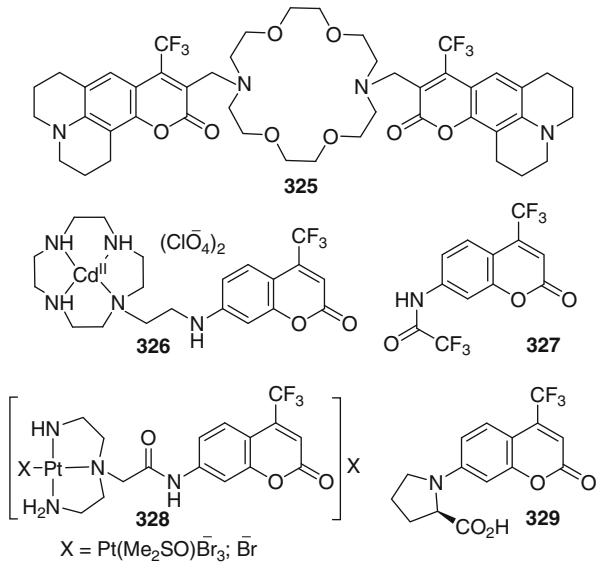
Scheme 104 Synthesis of 3-(polyfluoroalkyl)coumarins **324**

5.1.3 Applications of 7-Amino-4-(Trifluoromethyl)Coumarin Derivatives

7-Amino-4-(trifluoromethyl)coumarin (**300a**) is strongly fluorescent in polar solvents and its ^{19}F NMR spectrum shows only a singlet peak without any coupling to intramolecular protons. Thus, coumarin **300a** has been utilized as a reporter group that is active in both fluorescence measurement and ^{19}F magnetic resonance imaging [182].

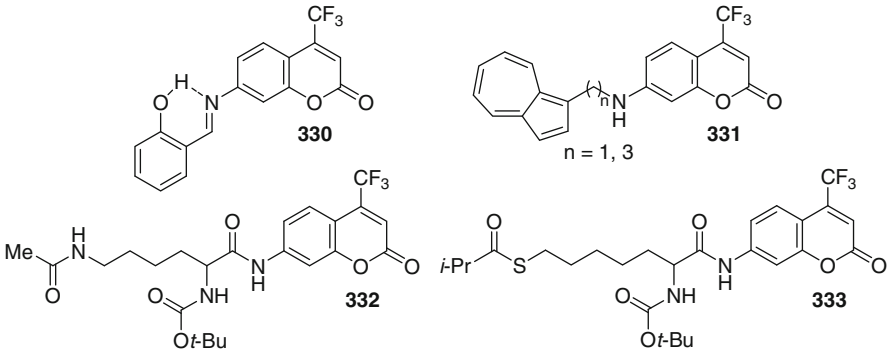
The photophysical properties of fluoroionophores composed of a laser dye, Coumarin 153, linked to azacrowns have been reported. The changes in the photophysical properties upon complexation with alkali and alkaline-earth metal cations are due to the direct interaction between the cation and the carbonyl group of the coumarin. Of particular interest is the bis-coumarin **325**, which exhibits specific changes in quantum yield according to the size of the cation [183]. Mizukami et al. reported a novel fluorescent anion sensor **326** that works in neutral aqueous solution for bioanalytical application. This molecule contains 7-amino-4-(trifluoromethyl)coumarin (**300a**) as a fluorescent reporter and Cd(II)-1,4,7,10-tetraazacyclododecane as an anion host. In neutral aqueous solution, Cd(II) of **326** is coordinated by the four nitrogen atoms of cyclen and the aromatic amino group of coumarin [184]. A colorimetric and fluorescent cyanide probe based on 4-(trifluoromethyl)coumarin **327** displays rapid response and high selectivity for cyanide over other common anions [185]. In order to develop coordination complexes that can be used as selective probes, fluorescent agents and inorganic medicinal agents, the design, synthesis, characterization and X-ray structure of new water-soluble monofunctional Pt(II) complexes with useful spectroscopic properties for assessing metal binding to biomolecules were investigated. Complex **328** was designed to allow the fluorophore group, coumarin **300a**, to be attached to metal centers through the diethylenetriamine moiety [186]. Proline-substituted coumarin derivatives, such as compound **329**, were prepared and used as environment-sensitive fluorescence probes. Phosphorylation and dephosphorylation of tyrosine derivatives labeled with the coumarin–proline conjugate induced marked changes in fluorescence intensity allowing phosphatase activity to be monitored [187] (Scheme 105).

A coumarin-based derivative **330**, a highly selective and sensitive turn-on fluorogenic probe for the detection of hydrosulfate anion in aqueous solution, has been designed and synthesized. This compound exhibits a unique fluorescence change in the presence of the HSO_4^- ion and with high selectivity over other anions [188]. Compounds **331** were synthesized from 1-azulenecarboxaldehyde and 7-amino-4-(trifluoromethyl)coumarin (**300a**) and a very fast vibrational cooling process of azulene was studied by the transient absorption method using molecular integrated systems with a molecular thermometer. This is the first attempt to use the



Scheme 105 Useful derivatives of 7-amino-4-(trifluoromethyl)coumarin

molecular heater–molecular thermometer integrated system for investigating the thermalization process from the solvent side [189] (Scheme 106).

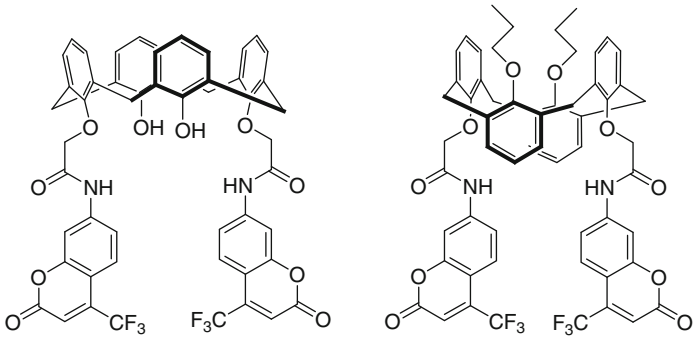


Scheme 106 Useful derivatives of 7-amino-4-(trifluoromethyl)coumarin

To probe the steric requirements for deacylation, lysine-derived small molecule substrates, including coumarin derivative **332**, were synthesized and their structure-reactivity relationships with various histone deacetylases were examined. It was found that compound **332**, prepared from the corresponding lysine derivative and coumarin **300a** in pyridine in the presence of $POCl_3$, is selectively deacetylated by HDAC6 in preference to HDAC1 and HDAC3. This indicated that the structure of

N-Boc and trifluoromethyl coumaryl amide of **332** is selectively recognized by HDAC6 [190]. Suzuki et al. have identified novel HDAC6-selective inhibitors whose designs were based on the structure of the HDAC6-selective substrate **332**. Thus, compound **333**, in which the acetamide of **332** is replaced by a thioester function, was obtained from the corresponding bromide and thioisobutyric acid under alkaline conditions [191] (Scheme 106).

Novel calix[4]arene-based anion sensor **334** with two coumarin units attached via amido functions acting also as binding sites was described. This compound may be considered as a potential fluorescent chemosensor for F^-. Reference calixarene **335** was also synthesized and its 1,3-alternate conformation was deduced from the ^1H NMR spectrum [192] (Scheme 107).

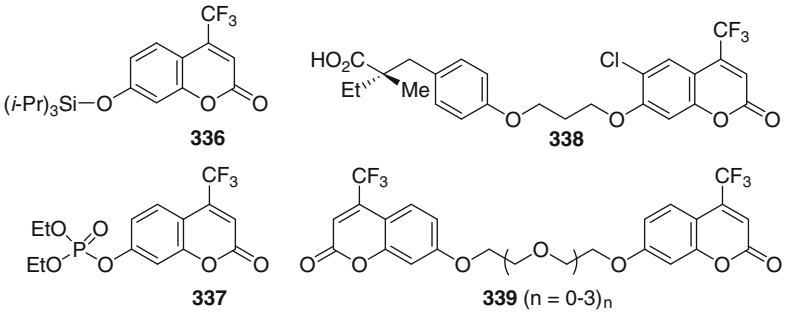


Scheme 107 Useful derivatives of 7-amino-4-(trifluoromethyl)coumarin

5.1.4 Applications of 7-Hydroxy-4-(Trifluoromethyl)Coumarin Derivatives

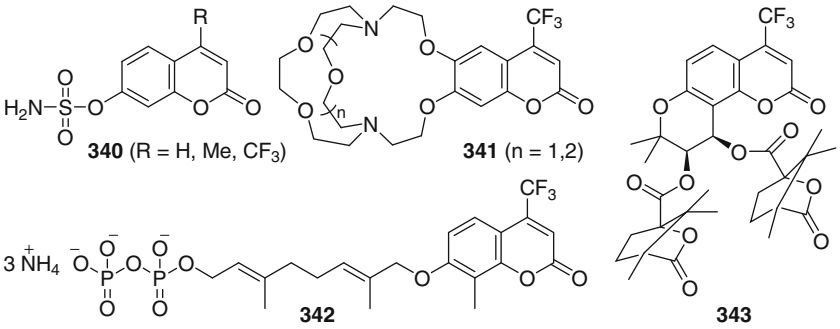
One-step reaction of 7-hydroxy-4-(trifluoromethyl)coumarin (**300c**) with TIPS-Cl provided compound **336** in 67 % yield, which was used to detect fluoride anions in organic and aqueous media, utilizing the specific affinity of fluoride anion to silicon [193]. Eighteen new fluorogenic analogues of organophosphorus nerve agents were synthesised and characterised. They included analogues of tabun, sarin, cyclosarin, and soman, with the 7-hydroxy-4-(trifluoromethyl)coumarin leaving group, for example, compound **337**. These analogues inhibited acetylcholinesterase effectively in vitro and therefore have potential as tools for the identification of novel organophosphatases in biological systems [194]. A series of potent and highly subtype-selective PPARα agonists was identified through a systematic SAR study. Based on the results of superior in vivo efficacy in the two animal models, coumarin **338** was

characterized in pharmacokinetic studies in three preclinical animal species. It exhibited low plasma clearance, good oral bioavailability, and no significant off-target activity was observed for **338**. Unfortunately, the results for the stability studies of compound **338** indicated the lactone ring stability issues [195]. Bis-4-(trifluoromethyl)-7-hydroxycoumarins **339** (n = 0, 1) ended mono and diethyleneglycols were prepared starting from bis(3-hydroxyphenyl)glycols by Pechmann condensation using ethyl trifluoroacetoacetate. Accordingly, coumarin **300c** was converted to bis-coumarin ended three and tetraethylenglycol derivatives **339** (n = 2, 3) by reacting with three and tetraethyleneglycols dichlorides in Na_2CO_3/DMF. The Li^+, Na^+ and Rb^+ metal/ligand selectivities of cation binding behaviour of products in acetonitrile were studied with steady state fluorescence spectroscopy [196] (Scheme 108).



Scheme 108 Useful derivatives of 7-hydroxy-4-(trifluoromethyl)coumarin

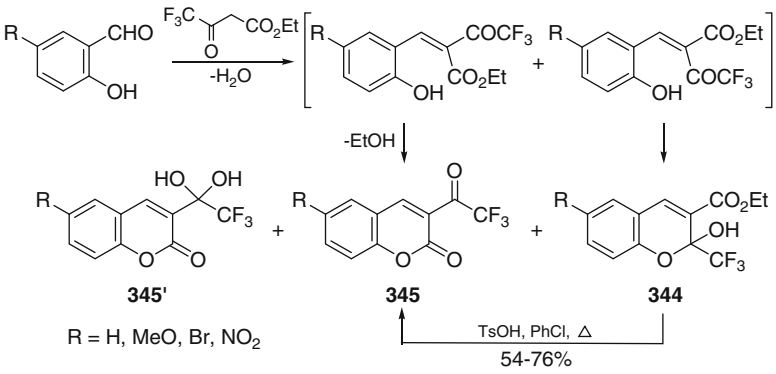
Woo et al. synthesized and examined coumarin sulfamates **340**, of which 4-methylcoumarin 7-*O*–sulfamate was found to be the most effective nonsteroidal E1-STS inhibitors [197]. The coupling between the fluorescence properties of the (trifluoromethyl)coumarino fluorophore and the protolytic state of the ion binding moiety of two fluorescent cryptands **341** is investigated. The experimental results obtained with **341** indicate that the diprotonated state of the fluorescent cryptands exhibit a comparatively high quantum yield around 0.6 and are characterized by a single lifetime around 5.4 ns [198]. Coumarin **342**, a fluorescent analogue of farnesyl pyrophosphate (FPP), was prepared and utilized to study ligand interactions with *E. coli* UPPs [199]. To explore the structural requirements of (+)-*cis-khellactone* derivatives as novel anti-HIV agents, 24 monosubstituted 3′,4′-di-*O*-(*S*)-camphanoyl-(+)-*cis*-khellactone derivatives, including compound **343**, were synthesized asymmetrically [200]. The metabolism of 7-benzyloxy-4-(trifluoromethyl)coumarin to 7-hydroxy-4-(trifluoromethyl)coumarin (**300a**) was studied in human liver microsomal preparations and in cDNA-expressed human cytochrome P450 (CYP) isoforms [201] (Scheme 109).



Scheme 109 Useful derivatives of 7-hydroxy-4-(trifluoromethyl)coumarin

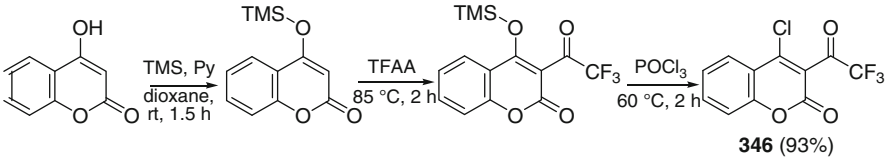
5.2 *Synthesis and Reactions of 3-(Trifluoroacetyl)Coumarins*

A series of ethyl 2-hydroxy-2-(trifluoromethyl)-2*H*-chromene-3-carboxylates (**344**) was obtained in high yields via the Knoevenagel condensation of salicylaldehydes with ethyl trifluoroacetoacetate in the presence of piperidinium acetate. The subsequent recyclization of these chromenes proceeds smoothly in refluxing chlorobenzene in the presence of *p*-toluenesulfonic acid affording 3-(trifluoroacetyl) coumarins (**345**) in good yields [202]. These compounds were also prone to the facile and reversible covalent hydrate formation [120] (Scheme 110).



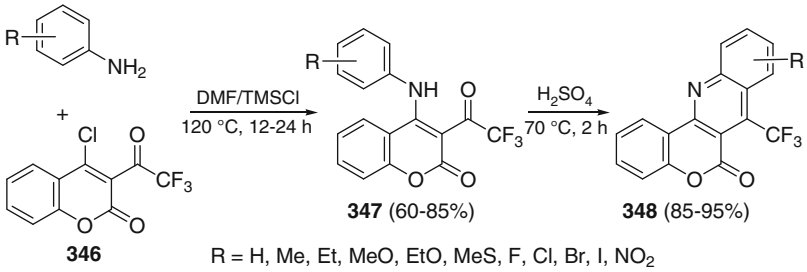
Scheme 110 Synthesis of 3-(trifluoroacetyl)coumarins **345**

4-Chloro-3-(trifluoroacetyl)coumarin (**346**) was synthesized via direct TMSCl-mediated acylation of 4-hydroxycoumarin with trifluoroacetic anhydride (TFAA) followed by the treatment with $POCl_3$ [203] (Scheme 111).



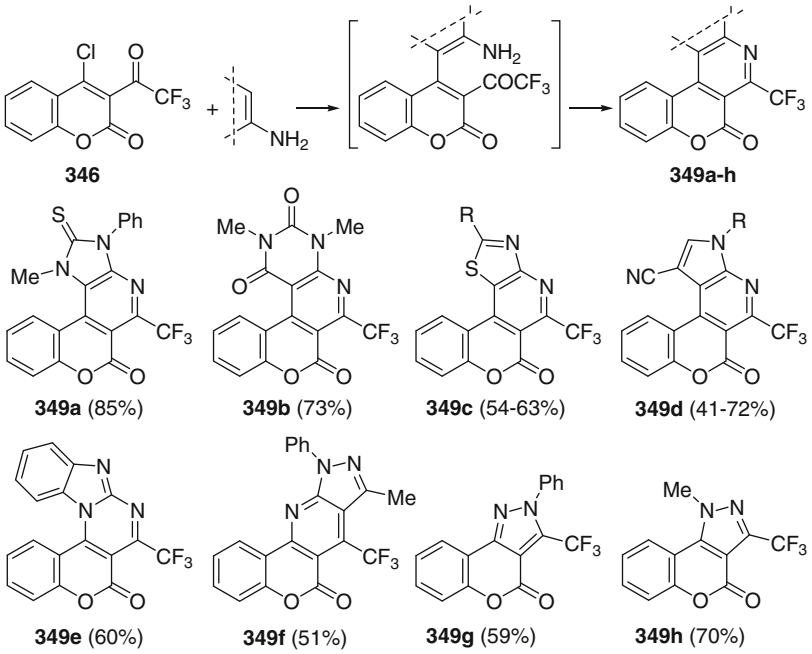
Scheme 111 Synthesis of 4-chloro-3-(trifluoroacetyl)coumarin **346**

Iaroshenko et al. reported that the reaction of **346** with anilines is a two-step method, which affords via substitution products **347** a set of 7-(trifluoromethyl)-6*H*-chromeno[4,3-*b*]quinolin-6-ones (**348**) in concentrated H_2SO_4 at 70 °C in high yields [203] (Scheme 112).



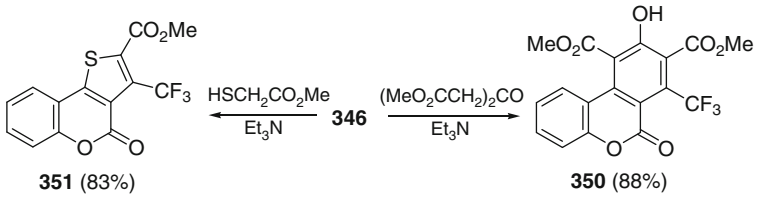
Scheme 112 Reaction of coumarin **346** with anilines

Coumarin **346** also reacts with electron-rich aminoheterocycles, dimethyl 1,3-acetonedicarboxylate, hydrazines, alkyl thioglycolates, and methyl sarcosinate to give a variety of 3,4-heteroannulated coumarins **349a–h** with an excellent regioselectivity and in moderate to high yields (41–85 %) [204] (Scheme 113).



Scheme 113 Products from coumarin **346** and aminoheterocycles

Treatment of **346** with dimethyl 1,3-acetonedicarboxylate in dioxane in the presence of triethylamine at reflux gave the expected benzo[*c*]coumarin **350**, whereas the reaction with methyl thioglycolate in dichloromethane at room temperature resulted in the formation of thienocoumarin **351** [204] (Scheme 114).



Scheme 114 Synthesis of compounds **350** and **351**

6 Conclusion

Analysis of the published data demonstrates that of the diverse fluorine-containing pyrones, chromones and coumarins, 2-(trifluoromethyl)-4-pyrones and 2-(polyfluoroalkyl)chromones, as well as 3-(polyfluoroacyl)chromones and chromones with the

perfluorinated benzene ring have now been studied most comprehensively. Data on 3-fluoro- and 3-(trifluoromethyl)chromones and coumarins are quite scarce. Despite the ready accessibility of polyfluoroalkylated pyrones and chromones, these compounds have long remained out of sight of chemists engaged in synthesis, and their systematic study has started only in recent years. Nevertheless, it is already clear that these compounds and, in particular, trifluoromethylated analogues of natural oxygen-containing heterocycles are valuable substrates for the synthesis of diverse partially fluorinated heterocycles with a potential biological activity. Indeed, a polyfluoroalkyl group present at the C-2 atom of the pyrone system entails dramatic changes in the reactivity of this ring, which is manifested as a bunch of new transformations uncharacteristic of non-fluorinated analogues. In addition, the introduction of a polyfluoroacyl group into the 3-position of the chromone system also changes crucially the reactivity of the pyrone ring with respect to nucleophiles and stipulates the broad synthetic potential of 2-unsubstituted 3-(polyfluoroacyl)chromones. The diversity of properties of these compounds is due to the fact that, being actually highly reactive geminally activated alkenes with a good leaving group at the β-carbon atom, they acquire the ability to undergo additional reactions related to opening and transformation of the γ-pyrone ring.

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Fluorine Containing Diazines. Synthesis and Properties

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V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 2: 6-Membered Heterocycles*, 291
DOI 10.1007/978-3-319-04435-4_6,

Abstract This review deals with general and significant developments in the area of chemistry of fluorinated pyrimidine, pyrazine and pyridazine. Diazines bearing fluoro or α-fluoroalkyl substituent at carbon atoms of the heterocyclic ring, as well as their fused derivatives are discussed. The literature data are divided into two parts, which describe synthesis and chemical behavior of ring- and chain-fluorinated diazines (RFD and CFD respectively).

Keywords Pyrimidine • Pyrazine • Pyridazine • Fluorine • Trifluoromethyl group • Synthesis • Chemical behaviour • Fluorinated heterocycles

Abbreviations

acac	Acetylacetone
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
Amphos	2-(2,4,6-*i*-Pr_3-C_6H_2)–C_6H_4-PCy_2
ANRORC	Addition of the nucleophile, ring opening, and ring closure in nucleophilic attack on ring systems
aq.	Aqua is the Latin word for water
Bmim	1-Butyl-3-methylimidazolium hexafluorophosphate
Bn	Benzil
Boc	tert-Butyloxycarbonyl
$(BPin)_2$	Bis(pinacolato)diboron
Bz	Benzoyl
CFD	Chain-fluorinated diazines
CNC	(N,N′-dimethylimidazolidino)tetramethylguanidinium chloride
COD	Cyclooctadiene
Cy	Cyclohexyl
DABCO	Dimethylbenzylamine
DAST	Diethylaminosulfur trifluoride
Dba	Dibenzylideneacetone
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicycloundec-7-ene
DCC	N,N′-Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Deoxo-Fluor	Bis(2-methoxyethyl)aminosulfur trifluoride
DEAD	Diethyl azodicarboxylate
DIPEA	Ethyl diisopropyl amine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMG	Dimethylglyoxime

DFMS	Zinc difluoromethanesulfinate
DMSO	Dimethyl sulfoxide
DNPG	Dinitrophenyl hydrazine
DoM	Direct *ortho*-methalation
Dppf	1,1′-bis(diphenylphosphino)ferrocene
EDG	Electron donating group
EWG	Electron withdrawing group
5-FU	5-Fluorouracil
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b] pyridinium 3-oxid hexafluorophosphate
HFA	Hexafluoroacetone
HIV	Human immunodeficiency virus
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide
HMTA	Hexamethylenetetramine
i-Am	Isoamyl
ihDA/rDA	Inverse-electron-demand hetero-/retro-Diels – Alder
KHMDS	Potassium Hexamethyldisilazane
LAH	Lithium aluminum hydride
LB	Lithium tertbutyl-(1-isopropylpentyl)amide
LDA	Lithium diisopropylamide
L-DBT	L-dibenzoyltartaric acid
LTMP	Lithium 2,2,6,6-tetramethylpiperidide
MeTFP	Methyl trifluoropyruvate
MW	Microwave
MNDO SCF MO	Modified Intermediate Neglect of Differential Overlap is a semi-empirical method
NaHMDS	Sodium Hexamethyldisilazane
NAS Ukraine	The National Academy of Sciences of Ukraine
NBS	N-Bromosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NMP	N-methylpyrrolidone
NOAc	N4-Octadecylcytosine β-D-arabinofuranoside
O-TBDMS	O-tert-butyldimethylsilyl
PEG-400	Polyethylene glycol 400
PES	Photoelectron spectroscopy
PET	Polyethylene terephthalate
Phen	Phenantroline
PhMe	Methylbenzene
PPA	Polyphosphoric acid
Ph	Phenyl
py	Pyridine
PM3	Parameterized Model number 3 (a semi-empirical method)

RCM	Ring-closing metathesis
RFD	Ring-fluorinated diazines
SSCS	Statistical substituent chemical shift
TBAF	Tetra-n-butylammonium fluoride
TBS	Tert-butyldimethylsilyl
TCBQ	Tetrachloro-1,4-benzoquinone
TDAE	Tetrakis(dimethylamino)ethylene
TEA	Triethylamine
TEBAC	Benzyltriethylammonium chloride
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TFMS	Zinc trifluoromethanesulfinate
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMSPP	Trimethylsilyl polyphosphate
TMSBr	Bromo(trimethyl)silane
Ts	Tosy

1 Introduction

Diazines, especially pyrimidines, are among most widespread six-membered heterocycles including both synthetic and natural compounds [1–3]. It is not surprising therefore that introduction of fluorine into the diazine core or side chain has been used extensively in various areas of chemistry. The first representative of the fluorinated diazines refer to late 1940s when Miller and co-workers described synthesis of 6-trifluoromethyl-2-thiouracil (1) (Fig. 1) [4]. In the next few years, several compounds of general formula 2 were prepared using Biginelli reaction [5]. In 1957, first representatives of ring-fluorinated diazines (e.g. 5-Fluorouracil (3) [6]), as well as fluorinated quinoxaline derivative 4 [7] were described.

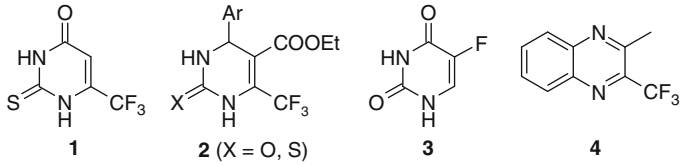


Fig. 1 The first representatives of fluorinated diazines

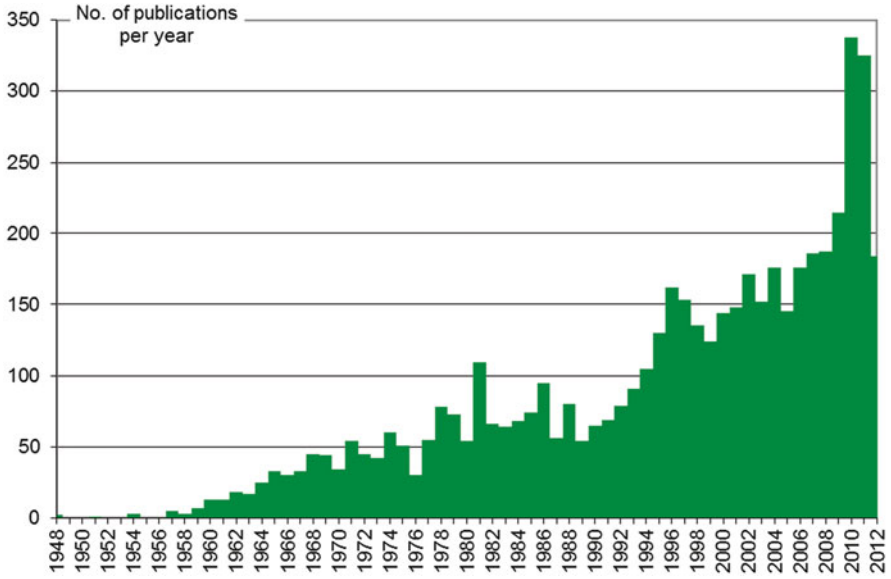


Fig. 2 Number of publications on fluorinated diazines per year (Reaxys® June 2012). The publications describing different types of the fluorinated diazines are counted several times (purine derivatives are excluded)

These pioneering works initiated an avalanche of publications on chemistry of fluorinated diazines, which have been intensified in recent years (Fig. 2).

It should be noted that different types of the fluorinated diazines are represented unequally among the known compounds (Table 1). In particular, nearly a half of literature references deals with 5-fluoropyrimidines (49.1 %). Other popular structural motifs include 2- and 4-fluoropyrimidines (2.9 and 4.3 %), 2-, 4(6)-, and 5-trifluoromethylpyrimidines (6.1, 16.2 and 5.0 %, respectively), and trifluoromethyl-substituted pyrazines (2.9 % of the literature references, the works on fused derivatives are included into numbers in all the above cases).

In this chapter, diazines bearing fluoro or α-fluoroalkyl substituent at any carbon atoms of the heterocyclic ring, as well as their fused derivatives are discussed. The literature data are divided into two parts, which describe synthesis and chemical behavior of ring- and chain-fluorinated diazines (RFD and CFD respectively). It should be noted that only chain-fluorinated diazines having the fluorine atom at α position of the alkyl substituent are discussed, since more distant fluorine atoms have lesser effect on the chemistry of the corresponding heterocycles. Chain-fluorinated diazines with fluorine atoms or fluorine-containing substituents linked to the aromatic ring via heteroatoms are also beyond the scope of this literature survey.

Both ring- and chain-fluorinated diazines are widely used in medicinal chemistry and agrochemistry (see Chap. 7). In fact, fluorinated diazines were used in drug discovery since the very first works on their synthesis. Other areas of application

Table 1 Distribution of the fluorinated diazines in the literature citations[a]

#	Atom	Substituent	Number of citations			
			Total	Total (%)	Papers	Patents
Pyrimidines and their fused derivatives						
1	2	F	**288**	**2.9**	**158**	**130**
2		CH_2F	51	0.5	22	29
3		CHF_2	28	0.3	8	20
4		CF_3	**597**	**6.1**	**228**	**369**
5		CF_2R[b]	66	0.7	25	41
6	4(6)	F	**421**	**4.3**	**180**	**241**
7		CH_2F	54	0.6	17	37
8		CHF_2	73	0.7	23	50
9		CF_3	**1589**	**16.2**	**562**	**1027**
10		CF_2R	143	1.5	95	48
11	5	**F**	**4801**	**49.1**	**2604**	**2185**
12		CH_2F	16	0.2	5	11
13		CHF_2	26	0.3	10	15
14		CF_3	**493**	**5.0**	**215**	**277**
15		CF_2R	28	0.3	21	7
Pyridazines and their fused derivatives						
16	3(6)	F	111	1.1	78	33
17		CH_2F	5	0.1	3	2
18		CHF_2	5	0.1	2	3
19		CF_3	184	1.9	91	93
20		CF_2R	18	0.2	11	7
21	4(5)	F	83	0.8	62	21
22		CH_2F	4	0.0	1	3
23		CHF_2	6	0.1	0	6
24		CF_3	88	0.9	36	52
25		CF_2R	15	0.2	12	3
Pyrazines and their fused derivatives						
26	any C	F	186	1.9	105	81
27		CH_2F	42	0.4	4	38
28		CHF_2	32	0.3	7	25
29		CF_3	**288**	**2.9**	**102**	**186**
30		CF_2R	38	0.4	27	11

[a]Reaxys® June 2012. The publications describing different types of the fluorinated diazines are counted several times

[b]R – any substituent attached via carbon atom

include dyes and liquid crystals. The 5-chloro-2,4-difluoropyrimidinyl radical acts as the reactive group in reactive dyes for cellulose and cotton fibers such as Levafix EA (Bayer) and Drimarene K (Sandoz) and for wool, e.g., Verofix (Bayer) and Drimalene (Sandoz) [8]. Both 2- and 4- fluoropyrimidine derivatives were used in liquid crystals engineering [9–11]. Also the ring fluorinated diazines were actively used as model compounds under investigation of different chemical transformation.

2 Ring Fluorinated Diazines

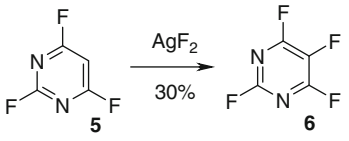
Ring-fluorinated diazines constitute an important family of organic compounds with a wide array of applications ranging from drugs to multi-ton industrial intermediates [12, 13]. The first representatives of RFDs, were synthesized in the 1960–1970s. Developments in this field were made during all this time. The main purpose of this review is not only to explore the field of chemistry of the ring-fluorinated diazines but also to identify the remaining gaps as opportunities for the future research effort.

3 Synthesis

3.1 Substitution Reactions

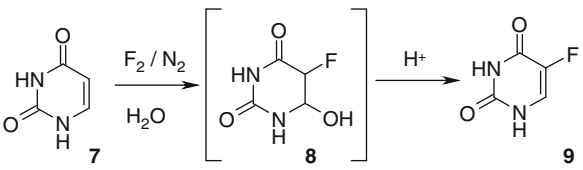
3.1.1 Electrophilic Fluorination. Replacement of H by F

Electrophilic fluorination is one of the most direct methods for selective introduction of fluorine into organic compounds. Historically first electrophilic fluorination of diazine derivatives was accomplished in 1960. Silver difluoride has been used in the final stage of an earlier synthesis of tetrafluoropyrimidine **6** from trifluoropyrimidine **5** [14]. Later the similar transformation was carried out using ClF_5 in 15 % yield and was found that side chlorination occurs in 9 % yield [15] (Scheme 1).



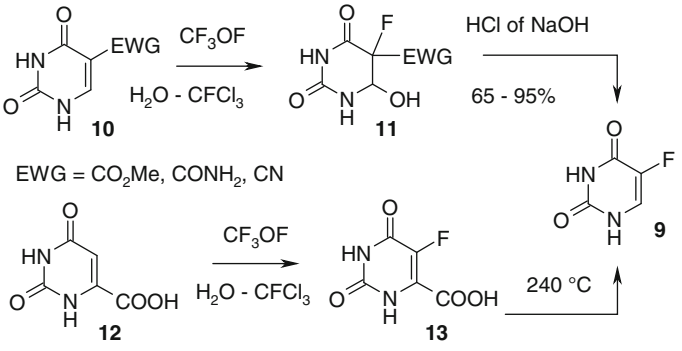
Scheme 1 Synthesis of tetrafluoropyrimidine

The most famous direct fluorination of diazine derivatives is fluorination of uracil by elemental fluorine affording 5-fluorouracil **9** (5-FU) [16] (Fig. 1). This is rare example of the use of fluorine gas in a successful commercial process developed by PCR Inc. in 1976. In spite of low yield of the process (~35 %), the original multistep synthesis of 5-FU was more expensive [17] (Scheme 2). The success of industrial fluorination of uracil was fixed in 1978 by Daikin Kogyo Co., Ltd. which increased the yield up to 85 % [18].



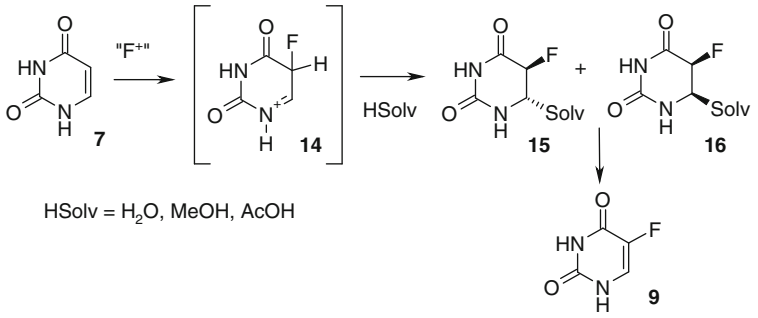
Scheme 2 Commercial synthesis of 5-FU

Uracil gave 5-fluorouracil when fluorine was passed into an aqueous suspension of the uracil. It is suspected, that fluorinating species of fluorine formed in water are HOF and/or F_2O, which reacted with uracil [19]. Besides elemental fluorine another reagents were used in the reaction. Among successful reagents are CF_3OF (ca. 90 %) [20], graphite intercalate, $C_{19}XeF_6$ (90 %) [21], AcOF (80–90 %) [22], $CsSO_4F$ (54 %) [23] and Selectfluore (82 %) [24]. Small-scale preparations involving direct fluorination of uracil with fluorine or trifluoroacetyl hypofluorite gave yields in the region 76–92 %, but scaling-up considerably reduced the efficiency [25]. Problems arising from difluorination of highly activated substrates [16, 26] have been overcome by incorporating an electron-withdrawing group in the ring. Direct fluorination of isoorotic esters, amides, or nitriles **10** in the presence of water, methanol, or acetic acid, followed by mild hydrolysis and decarboxylation of intermediate products gave up to 92 % yields of 5-fluorouracil [25] (Scheme 3). Also the fluorination of the orotic acid was investigated; the initially obtained fluoroorotic acid **13** was subjected to decarboxylation. The use of two-step reaction sequence was claimed to be advantageous due to simplified product isolation and purification [27] (Scheme 3).



Scheme 3 Synthesis of 5-FU based on orotic and isoorotic acid derivatives

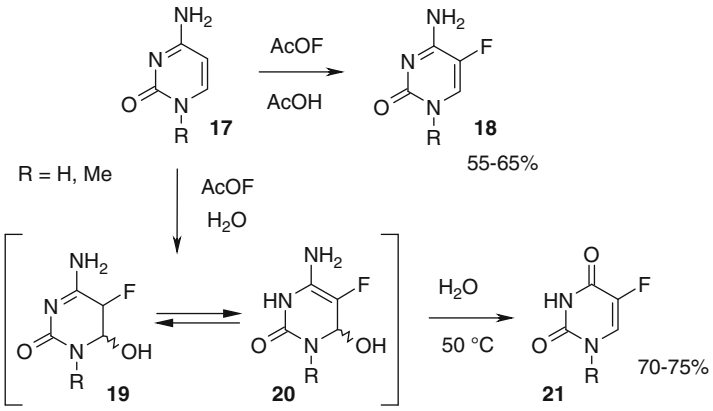
All of the direct fluorinations reported appear to be addition-elimination processes with solvent involvement (Scheme 4). A study of the mechanism and stereochemistry of uracil fluorination using F_2 and AcOF has implicated a radical-cation mechanism [28]. The effect of acetate ion on the products proved to be important. In its absence both *cis*- **16** and *trans*-isomers **15** were observed in the reaction mixture, but only *trans*- **15** in its presence. NMR studies have revealed that acetate originated from the solution containing acetate ion, rather than the residue from acetyl hypofluorite, binds to the 6-position of uracil to form the intermediates **15** and **16** (Solv=OAc). Acetate is a sufficiently strong base to induce *trans*-elimination of acetic acid from the *cis*-isomer **16** [29, 30].



Scheme 4 Proposed reaction scheme for the fluorination of uracil

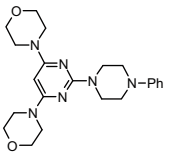
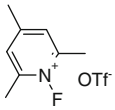
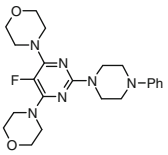
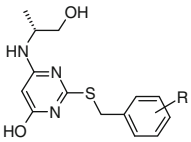
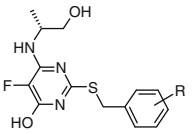
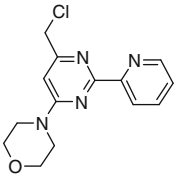
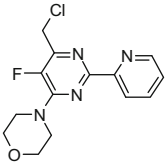
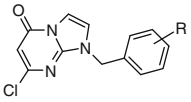
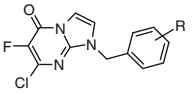
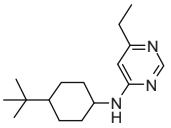
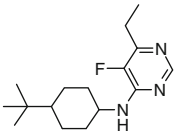
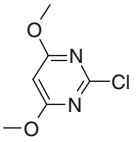
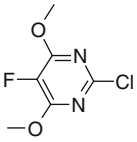
Due to the high importance of the 5-FU derivatives as anti cancer drugs a lot of different fluorinating agents were tested in the fluorination of the derivatives. The most important examples of the fluorination used in drug synthesis are listed in the next chapter of the book.

In a course of fluorination of uracil derivatives, the fluorination of cytosine derivatives **17** leading to 5-fluorocytosine **18** was investigated [28, 30]. In contrast to uracil some side process were disclosed. 1-Substituted cytosine intermediate adducts **19** rapidly deaminated in water to yield uracil analogues **21** [30] (Scheme 5). The corresponding NF_2-derivatives were detected during fluorination of cytosine in water by fluorine [31]. It should be noted, that occurrence only one electron-donating hydroxy(keto) group in pyrimidinone-2 is sufficient for direct fluorination. The corresponding pyrimidinone-2 and its N1-substituted derivatives give under fluorination by fluorine in HF or AcOH the corresponding 5-fluorinated derivatives in 38–61 % yields. In this case the fluorination proceeds also as addition-elimination process [32].



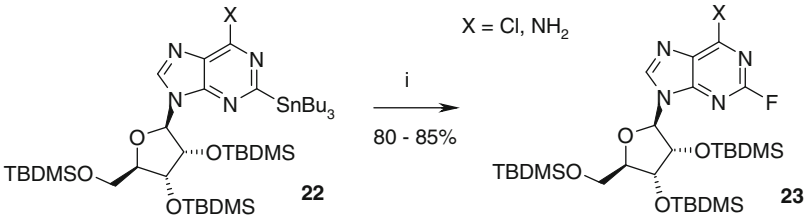
Scheme 5 Proposed reaction scheme for the fluorination of uracil

Table 2 Electrophilic fluorination of pyrimidine derivatives

#	Substrate	Conditions	Products	Yield (%)	Ref.
1		 DCM, rt, 30 min		31	[33]
2		Selectfluor, MeOH, rt, 3 days		19–25	[34]
3		Selectfluor, MeOH, 5 °C, 16 h		20	[35]
4		Selectfluor, DCM-MeOH, overnight, rt		33	[36]
5		F_2/N_2, TFA, 15 °C		41	[37]
6		1. LDA, THF, −78 °C, 1.5 h 2. NFSI, THF, −78÷−20 °C, 15 h		48	[38]

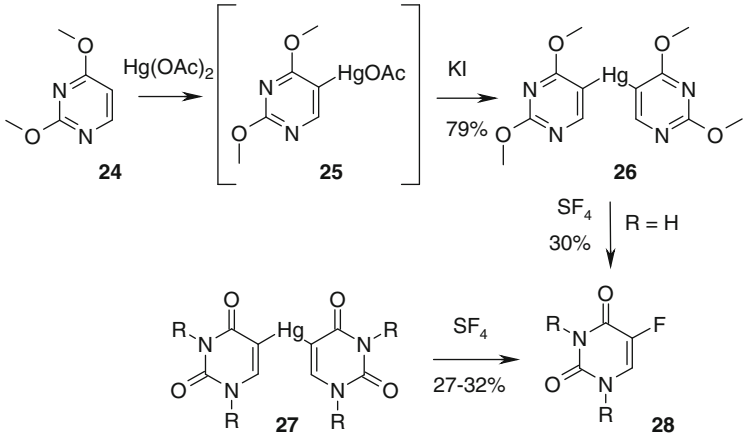
The intensive development of electrophilic fluorination reagents in last two decades leads to it's using both in academician and industrial investigation. Recent patents and papers directed to the early stage drug discovery are illustrated this trend. Some examples of such fluorinations based on electron rich pyrimidines are listed in Table 2.

As seen from the table for direct fluorination of monocyclic pyrimidine ring needs activation at least by one amino group. Activation of the ring by alkoxy groups is not sufficient. In this case of preliminary lithiation is used with subsequent fluorination with NFSI (Table 2, Entry 6). Besides fluorination of lithium derivatives, fluorinations of other organomethallic derivatives of pyrimidines are known. In a series of purines XeF_2 mediated fluorination of 8-tributylstannyl derivatives **22** was developed leading to 8-fluorinated derivatives **23** in high preparative yield (Scheme 6) [39, 40].



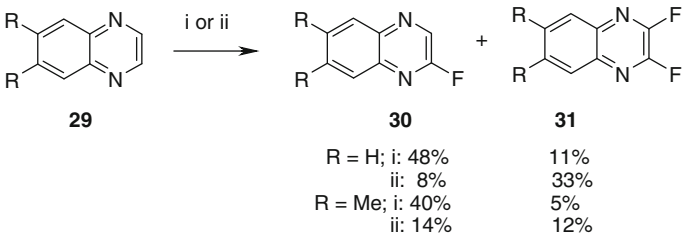
Scheme 6 Synthesis of F-containing pyrimidines via Sn–F exchange

Unusual approach to the 5-fluoropyrimidides through organomercury derivatives was elaborated by Polish scientists. 2,4-Dimethoxypyrimidine **24** was readily mercurated with a boiling aq. $Hg(OAc)_2$ solution acidified with AcOH for 2 h, and this hot solution containing **25** was applied at once in subsequent reactions with saturated aq. KI solution affording **26** in 79 % preparative yield. By analogous way uracil derivatives were synthesised. By successively reacting (at ca. −60 °C) these symmetric organomercurials with excess of neat liquid SF_4 (b.p. −40.4 °C) the corresponding monofluorinated products **28** were obtained in ca. 30 % yield. In this reaction SF_4 formally plays unusual role as F+ source (Scheme 7) [41].



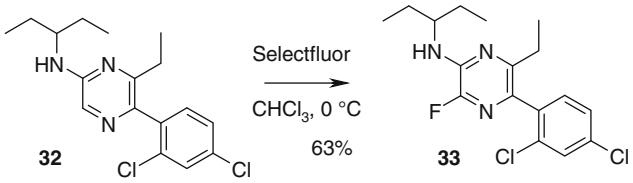
Scheme 7 Synthesis of F-containing pyrimidines via Hg–F exchange

Excluding pyrimidine derivatives electrophilic fluorination of other diazines was almost not studied. To the best of our knowledge there is no examples of electrophilic fluorination of pyridazines and only 1 paper and 1 patent devoted to fluorination of pyrazines and quinoxaline. Chambers and co-workers described fluorination of quinoxalines **29** in good yields using elemental fluorine–iodine mixtures at room temperature (Scheme 8). Mono- (**30**) and difluorinated products **31** were formed in different ratio depending on amount of fluorine used in the reaction. It should be noted that pyrazine, pyrimidine and pyridazine were recovered unchanged using similar condition [42].



Scheme 8 Fluorination of quinoxaline derivatives

Fluorination of pyrazine **32** activated by amino group using Selectfluor afforded fluoropyrazine **33**in 63 % preparative yield (Scheme 9) [43].



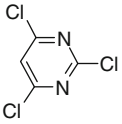
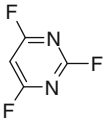
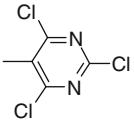
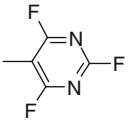
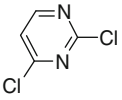
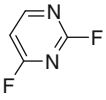
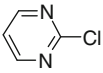
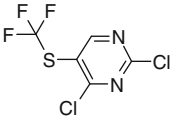
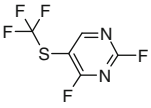
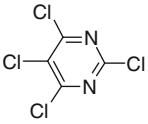
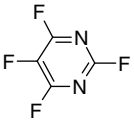
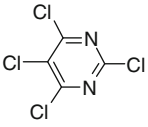
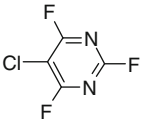
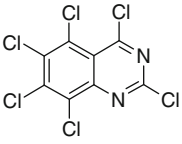
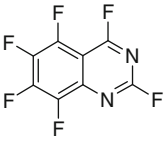
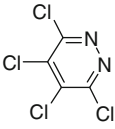
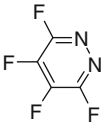
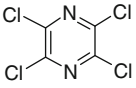
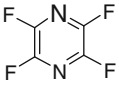
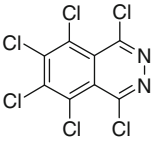
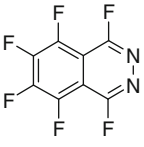
Scheme 9 Fluorination of pyrazine derivative

3.1.2 Nucleophilic Fluorination. Halogen Exchange Reactions

The most practicable and versatile laboratory and industrial route to ring-fluorinated diazines involves nucleophilic displacement of chloride by fluoride from systems activated towards nucleophilic attack. This is often referred to as the 'Halex' (halogen exchange) process [44]. Historically first electrophilic fluorination of diazine derivatives was accomplished in 1960 by silver fluoride [14]. Later different sources of fluoride ion included hydrogen, sodium, potassium, cesium, antimony, silver tetralkylammonium fluorides, and sulfur tetrafluoride have been used. Reactivity of the alkali metal fluorides decreases in the series CsF > KF >> NaF (i.e., with increasing lattice energy), and because the reactivity of fluoride as a nucleophile decreases sharply on solvation, dipolar aprotic solvents are often use. A lot of diverse ring fluorinated diazines were prepared by the manner. The rate determining step in nucleophilic aromatic fluorination by substitution, including the Halex process, is the addition of fluoride to form a Meisenheimer complex. Therefore, aryl chlorides are more suitable substrates in the Halex process than the corresponding aryl bromides and iodides, because chlorine is more electronegative than bromine and iodine.

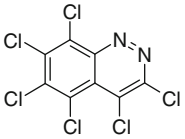
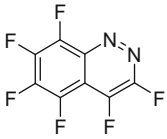
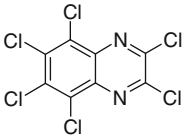
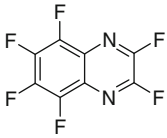
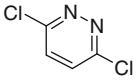
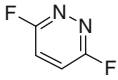
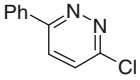
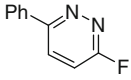
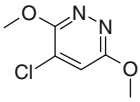
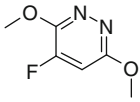
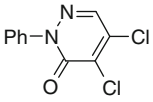
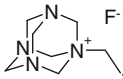
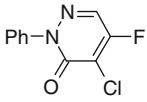
In the last decade phase-transfer catalysis and ionic liquid using become popular nucleophilic fluorination. The representative set of the reaction illustrated the methodology are listed in the Table 3.

Table 3 Nucleophilic fluorination of diazine derivatives

#	Substrate	Conditions	Products	Yield (%)	Ref.
1		AgF, neat, 98 °C		76	[14, 45]
2	-//-	KF, 300–310 °C	-//-	85	[46]
3	-//-	CsF, DMF, 150 °C, 2,5 h	-//-	53	[47]
4	-//-	3 eq. PS*HF, MeCN, 50 °C, 48 h	-//-	98	[48]
5	-//-	6 eq. $Bu_4P^+ HF_2^-$, 50 °C, 4 h	-//-	85	[49]
6		Et_3N*3 HF, 80 °C		93	[50]
7		SF_4, 150 °C, 9 h		70	[51]
8		CsF, NMP, 150 °C, 3,5 h		33	[47]
9		KF, SbF_3, 250 °C, 2 h		63	[52]
10		KF, 480 °C		85	[53]
11		NaF, 300 °C		85	[54]
12		KF, 350 °C		>60	[55]
13		KF, 300 °C		50–60	[56]
14		KF, 310 °C		95	[57]
15		KF, 290 °C		60	[58]

(continued)

Table 3 (continued)

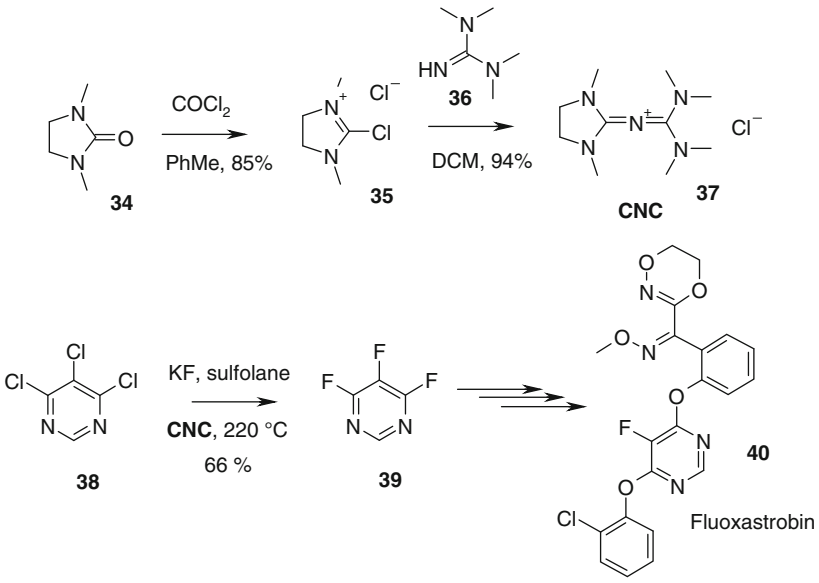
#	Substrate	Conditions	Products	Yield (%)	Ref.
16		KF, 290 °C		n.r.	[59]
17		KF, 380 °C		50	[60]
18		1.3 eq. TBAF, 1 h		>95	[61]
19		2.5 eq. TBAF, 30 min		>95	[61]
20		1.3 eq. KF, 10 % 18-crown-6, 200 °C, 1 h		100	[62]
21		KF, [bmim][BF_4], 120 °C, MW, 10 min		80	[63]
22		 , DMSO		93	[64]

The chlorine/fluorine exchange reaction is an equilibrium reaction and can be influenced by altering the pressure, time, temperature and the ratio of the reactants. Usually high-temperature/high-pressure autoclave technique was used for shifted the equilibrium to fluorinated product. Anhydrous potassium fluoride in tetraglyme with a catalytic amount of dicyclohexano-l8-crown-6 at 15–16 °C converted 2,4-dichloropyrimidine into 2,4-difluoropyrimidine. This process solved the problem of having to use an autoclave or dimethylformamide as solvent, because in tetraglyme (bp 275–276 °C) the more volatile fluoro products could be distilled directly from the reaction mixture uncontaminated by solvent. Under similar conditions 2-chloro-5-methoxypyrimidine was converted into the 2-fluoro analogue [65].

Contact time very much controls the degree of conversion of polychlorinated pyrimidines heated in sealed tubes with solid potassium fluoride (Entry 6) [66], and selectivity can also be achieved by careful control of reaction conditions and reagents. With 2,4,5-trichloropyrimidines, substituted at C–6 by chloro, methyl, chloromethyl, di- or tri-chloromethyl, sodium or potassium fluoride use only resulted in nuclear fluorination. Hydrogen fluoride can displace chlorines on either side chain or nucleus (especially 2-chloro), and antimony fluoride is specific for all chlorinated methyl groups. Sodium fluoride initially replaces a 4-chloro group [67]. Fluorination reactions on tetrachloropyridazine using sodium fluoride and potassium

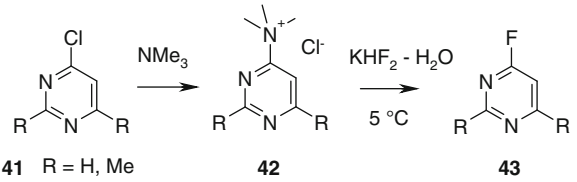
fluoride proceeds in 4 steps and produce mixtures of the various fluorinating stages (from 1 to 4) in each case, it being possible to separate the compounds from each other using distillation. The second and third fluorination stages are composed of the difluorinated trifluorinated isomers. In contrast to this, the chlorine/fluorine exchange using hydrogen fluoride proceeds selectively as this reaction only yields one isomer for each fluorination stage. In last case the 4(5)-positions were found to be less active than the 3(6)-positions [68]. (proceeding from)In going from tetrachloropyazine to trichloropyrazine 4-position becomes more active towards Halex process [63]. Some of these processes have been subjected to kinetic investigation, which demonstrated that in polar, aprotic solvents fluorine-chlorine exchange is a pseudo first-order, consecutive reaction [69]. Recently a few papers devoted to the selectivity in clorine-fluorine exchange in polychlorocompounds were published. Solvent-free PTC conditions (KF/18-crown-6) with MW activation or protone sponge (PS) hydrogen fluorides using leads to complete or selective fluorinations of certain dichloro(benzo)diazines in satisfactory yields. In some cases, the selectivity can be explained based on the difference between thermodynamic stability of the Meisenheimer complexes [48, 62].

Among different conditions for Halex process one of the most effective for low activated substrates is (N,N′-dimethylimidazolidino)tetramethylguanidinium chloride **37** (CNC) using as phase-transfer catalyst. The synthesis and using of the catalyst were developed in 2006 by LANXESS Deutschland GmbH in a course of Fluoxastrobin intermediate **39** development [70] (Scheme 10). It should be noted, that traditional phase-transfer catalysts does not work well in the transformation and in original Bayer synthesis stepwise fluorination was used [71].



Scheme 10 CNC catalyzed Halex process

Besides chlorine, another living group can be involved into nucleophilic fluorination. Preliminary transformation of chloropyrimidines **41** to trimethylammonium salts **42** facilitate further fluorination. In this case the reaction proceeds in very mild conditions – under 5 °C (Scheme 11) [72, 73]. This approach allows to fluorinate pyrimidines deactivated by electron-donated groups. When heated with potassium fluoride in ethylene glycol 2,6-dimethoxy-4-trimethylammoniopyrimidine salts were converted into the 4-fluoroderivatives in 42 % yield [74] Analogously fluorination can be accomplished in 2-d position, which was illustrated by preparation of 2-fluoro-4-phenyl-pyrimidine [75].



41 R = H, Me **42** **43**

Scheme 11 Fluorination of trimethylammoniopyrimidines

3.1.3 Nucleophilic Fluorination. The Balz–Schiemann Reaction

In this classical reaction the leaving group, molecular nitrogen, is lost on pyrolysis and the mechanism appears to involve formation of an aryl cation which then abstracts fluoride ion. In comparison with halogen exchange the Balz–Schiemann reaction is not widespread in diazine chemistry. But from early 1970 to recent times the method is actively used in laboratory scale (Table 4). Generally procedure includes the treatment of aminodiazine solution in aq. HBF_4 by $NaNO_2$ at ca −10 °C to −15 °C followed by neutralization with NaOH. Another procedure is based on $NaNO_2$ treatment in HF-Py media with subsequent heating. The last method gives better yields, especially for 4-fluoripyrimidines. The Balz–Schiemann approach allow to synthesized fluoropyrimidines bearing active chlorine atom, which are unacceptable via Halex process (Entry 5 and 6).

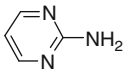
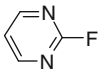
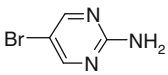
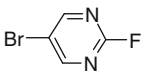
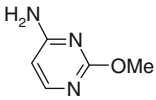
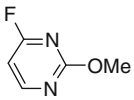
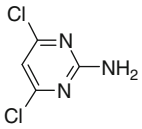
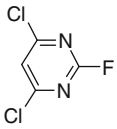
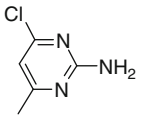
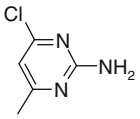
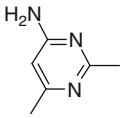
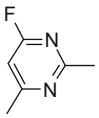
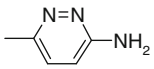
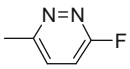
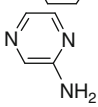
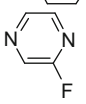
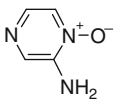
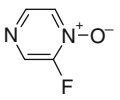
3.2 Cyclization Processes

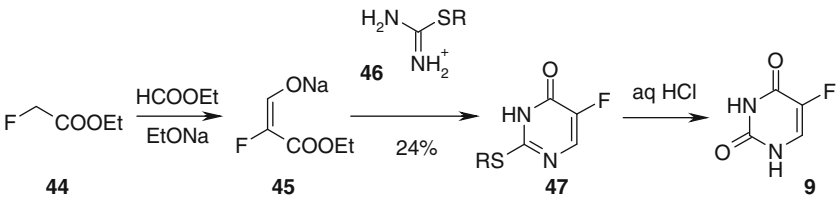
3.2.1 "Principal Synthesis" of Pyrimidines

The condensation of two acyclic reagents (with any preattached substituents), one to supply $N^1C^2N^3$ fragment and the other to supply $C^4C^5C^6$ fragment to form the resulting ring, is the most used procedure and is known accordingly as the "principal synthesis" of pyrimidines. The approach is important for the synthesis of C^5-F pyrimidine derivatives.

First synthesis of 5-FU was accomplished by Heidelberger in 1957 according the methodology [6, 81]. Ethyl fluoroacetate **44** was subjected to Claisen condensation with ethyl formate to give **45**. The salt **45** was introduced into reaction with *S*-alkylisothiourea derivatives **46** to give fluoropyrimidines **47**, which were hydrolysed to give **5-FU** (Scheme 12).

Table 4 The Balz–Schiemann reaction of diazine derivatives

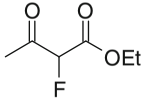
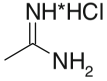
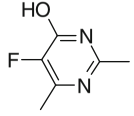
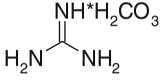
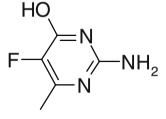
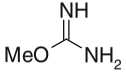
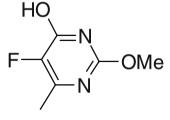
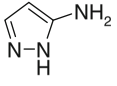
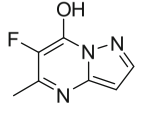
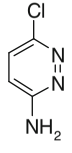
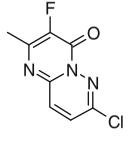
#	Substrate	Conditions	Products	Yield (%)	Ref.
1		1. $NaNO_2$ in aq. HBF_4, −10 °C 2. NaOH		30–41	[72, 76]
2	-//-	1. 1.1 eq. $NaNO_2$, 90 eq. HF-Py (X_{HF} = 0.86), 0 °C, 2° min 2. 20 °C, 1 h	-//-	55	[77]
3		1. $NaNO_2$ in aq. HBF_4, −10 °C 2. NaOH		38	[73]
4		1. $NaNO_2$ in aq. HBF_4, −10 °C 2. NaOH		1°	[65]
5		1. 1.1 eq. $NaNO_2$, 90° eq. HF-Py (X_{HF} = 0.86), 0 °C, 20 min 2. 40 °C, 1 h		8°	[77]
6		1. 1.1 eq. $NaNO_2$, 90 eq. HF-Py (X_{HF} = 0.86), 0 °C, 20 min 2. 20 °C, 1 h		72	[77]
7		1. 1.1 eq. $NaNO_2$, 90 eq. HF-Py (X_{HF} = 0.86), 0 °C, 20 min 2. 90 °C, 1 h		6°	[77]
8		1. $NaNO_2$ in aq. HBF_4, −10 °C 2. NaOH		n.r.	[78]
9		1. $NaNO_2$ in aq. HBF_4, −5 °C 2. NaOH		3°	[79]
10		1. $NaNO_2$ in aq. HBF_4, Cu, −5 °C 2. $NaHCO_3$		17	[80]



Scheme 12 Heidelberger synthesis of 5-FU

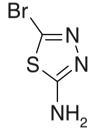
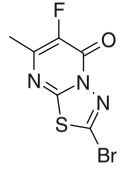
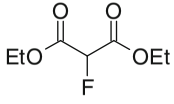
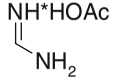
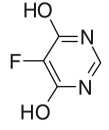
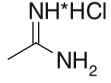
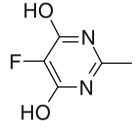
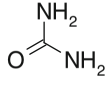
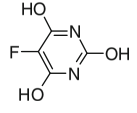
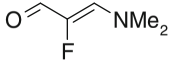
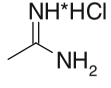
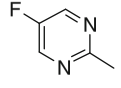
The cyclization of 2-fluoro-3-ketoesters derivatives with 1,3-*NCN*-bisnucleophiles is general approach to fluorinated pyrimidines. There are a lot of examples of such transformations in the literature. A representative set of the cyclization is listed in Table 5. Besides usual 1,3-*NCN*-bisnucleophiles, such as amidine, guanidine and

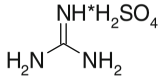
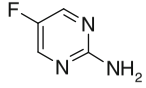
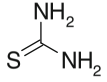
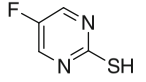
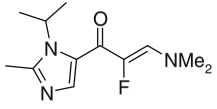
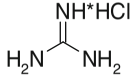
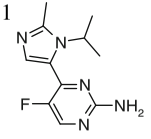
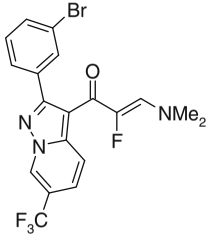
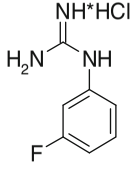
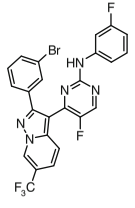
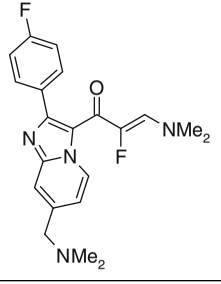
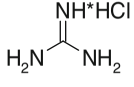
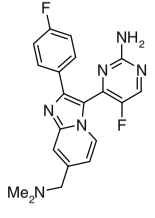
Table 5 "Principal synthesis" of pyrimidines

#	1,3-*CCC*-bielectrophile	1,3-*NCN*-binucleophile	Conditions	Products	Yield (%)	Ref.
1			MeOH, MeONa, rt		56	[82]
2	-//-		H_2O, KOH, reflux, 3 h		46	[82]
3	-//-		H_2O, EtOH, CaO		63	[83]
4	-//-		MeOH, reflux		84	[84, 85]
5	-//-		$PhCH_2OH$, refluxe, 24 h		n. r.	[86]

(continued)

Table 5 (continued)

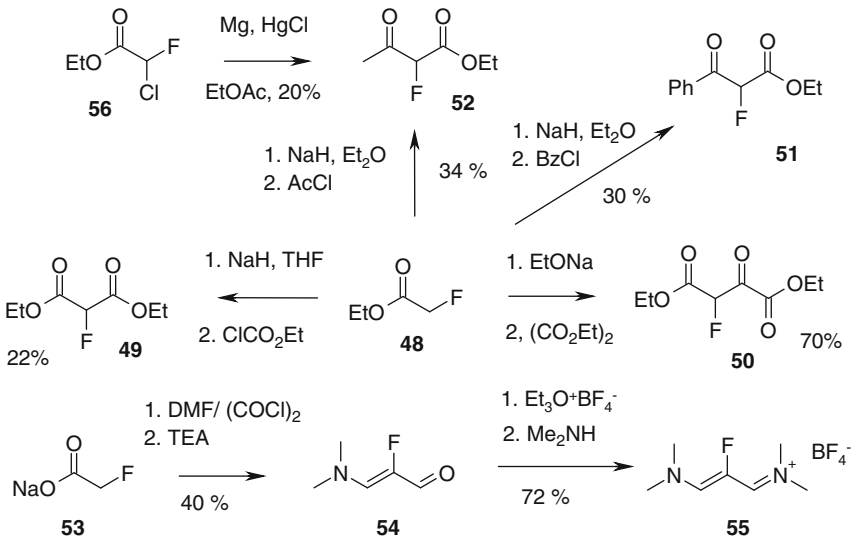
#	1,3-*CCC*-bielectrophile	1,3-*NCN*-binucleophile	Conditions	Products	Yield (%)	Ref.
6	-//-		PPA, 100 °C, 8 h		8°	[87]
7			EtOH, EtONa, reflux, 8 h		52	[88]
8	-//-		EtOH, EtONa, reflux, 3 h		64	[89]
9	-//-		EtOH, EtONa, reflux, 6°h		93	[90]
10			NMP, 170–190 °C, 3 h		26	[91]

11	-//-		MeOH, MeONa, reflux, 5 h		57	[91]
12	-//-		MeOH, MeONa, reflux, 5 h		54	[91]
13			BuOH, MeONa, MW, 140 °C, 1 min		71	[92]
14			K_2CO_3, DMA, 130 °C, 8 h		60	[93]
15			PrOH, MeONa, 80 °C, 2 h		13	[94]

urea derivatives in the reaction a set of appropriate aminoheterocycles (Entry 4–6) was used. In this case fused derivatives of 5-fluorineted pyrimidines were synthesised. It should be noted, that synthesis of fused heterocyclic pyrimidines could not be accomplished in basic conditions, in a case of aminopyrazole and aminopyrimidine neutral conditions were used, in a case of aminothiadiazole acidic catalysis works well. Fluorinated malonic acid derivatives were subjected also to the "Principal synthesis" of pyrimidines affording 4,6-dihydroxypyrimidine derivatives (Entry 7–9). Basic conditions in this case give final products in 5°–9°% yields.

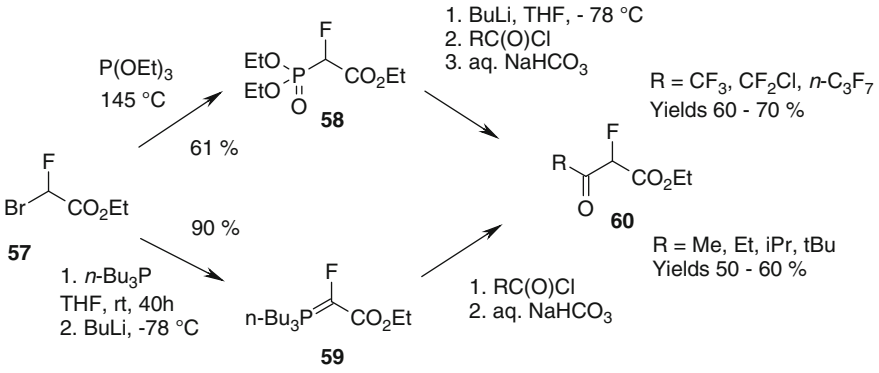
Latent dicarbonyl compounds, especially fluorinated "push-pull" enaminones also used as 1,3-*CCC*-bielectrophiles in the cyclization. In earlier examples based on 3-dimethylamino-2-fluoroacrolein both thermal and basic conditions were used for the synthesis of the corresponding pyrimidines in 26–57 % yields (Entry 10–12). Also 3-dimethylamino-2-fluoroacrolein gives parent 5-fluoropyrimidine in 52 % yield under heating at 190 °C in formamide. Recent works dealt with sophisticated fluorinated "push-pull" enaminones also referred basic cyclization conditions as well as thermal.

In many cases synthesis of the fluorinated 1,3-*CCC*-bielectrophile precursors is the most difficult part of the synthetic sequence and using "classical" methods is usually accomplished by the use of highly toxic fluoroacetic acid derivatives in Claisen condensation with ethyl formiate [81], ethyl chloroformate [95, 96], diethyloxalate [82, 97], acetyl, benzoyl chlorides [82] or Vilsmeier-type formylation [98, 99] (Scheme 13). The product of Vilsmeier-type formylation is 3-dimethylamino-2-fluoroacrolein **54** which reacts with triethyloxonium tetrafluoroborate and dimethylamine to give the vinamidinium salt **55** [91], which also can be used as 1,3-bielectrophile (see Scheme 19). Also Reformatsky-type synthesis of ethyl α-fluoroacetoacetate **52** starting from ethyl chlorofluoroacetate **56** was described in 20 % yield [82].



Scheme 13 Approaches to fluorinated 1,3-CCC-bielectrophiles

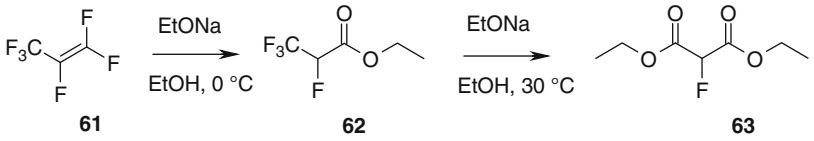
Wittig and Wittig-Horner reactions were used to prepare α-fluoro-β-keto esters from halofluoroacetates (Scheme 14). Triethyl phosphite and ethyl bromofluoroacetate **57** gave under thermal conditions (145 °C, 5 h) 150 g of fluorinated phosphonate **58** in one run in 61 % yield [100]. Tri-*n*-butylphosphine (Ph_3P also entered into the reaction, but further transformation described using *n*-Bu_3P) reacts with ethyl bromofluoroacetate in THF solution at rt during 4°h affording phosphonium salt in 9°% yield, which was converted into ylide **59** by BuLi treatment in THF at −78 °C and used in the solution for further transformation [101]. Both substrates are applicable for the synthesis of α-fluoro-β-keto esters using alkyl and aryl substituted acyl chlorides. Acylation of ylide **59** with perfluorinated and partially fluorinated acyl chlorides did not proceed cleanly, however the anion derived from phosphonate **58** undergo acylation with further hydrolysis affording desired products in good yields [102]. Further some modification of the procedure was reported using phosphonate **58** [103], which is now commercially available.



Scheme 14 Wittig and Wittig-Horner approach to fluorinated 1,3-*CCC*-bielectrophiles

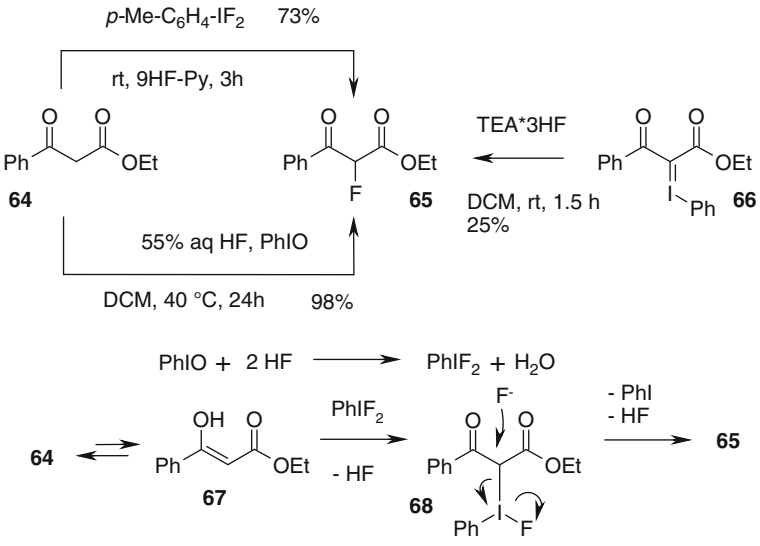
The further work devoted to the synthesis of fluorinated 1,3-*CCC*-bielectrophiles tries to avoid the use of fluoroacetic acid derivatives. These three general approaches to synthones gain commercial value:

– electrophilic fluorination of the corresponding dicarbonyl compounds (Tosoh F-Tech, Inc., F_2/N_2 [104]; Air Products and Chemicals, Inc. $CF_2(OF)_2$ [105];)
– nucleophilic fluorination of the corresponding chloro-derivatives (Bayer, TEA*3HF [106, 107])
– ethanolysis of hexafluoropropene **61** (E.R. SQUIBB and SONS, INC., Scheme 15 [108, 109])



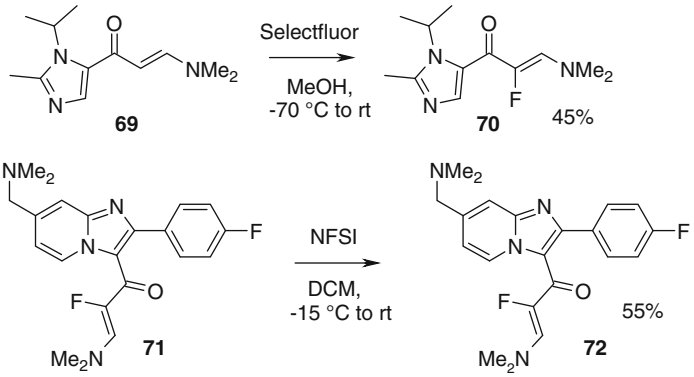
Scheme 15 Synthesis of monofluoromalonate from perfluoropropene

Lab scale synthesis of fluorinated 1,3-*CCC*-bielectrophiles based on electrophilic fluorination has disadvantage in difluoroproducts formation. This problem was solved recently by application of iodotoluene difluoride or iodosylbenzene – HF [110, 111]. A possible mechanism for a fluorination reaction of 1,3-dicarbonyl compounds is shown in Scheme 16. First, $PhIF_2$ should be formed in situ by reaction of PhIO with HF. The reaction of $PhIF_2$ with **64** is considered to proceed effectively after enolization of **64**. The resulting 2-iodanyl-1,3-dicarbonyl compound **68** readily undergoes displacement by a fluoride ion due to the high leaving ability of the phenyliodonium group, to give the fluorine-containing product **65**. Also the fluorinated product was formed through the *C*-protonation of the iodonium ylide, followed by displacement with fluoride ion [112].



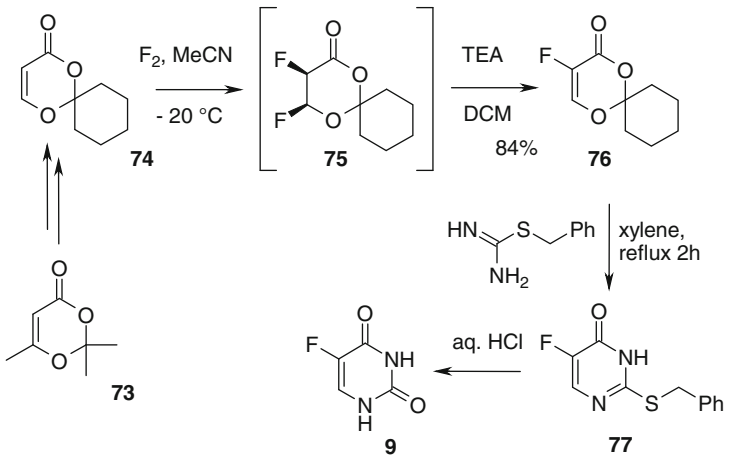
Scheme 16 Lab scale fluorination of β-dicarbonyl compounds

Another way to avoid the difluorination can be achieved by using of "push-pull" enamines and Selectfluor or NFSI as fluorine source (Scheme 17) [92, 94].



Scheme 17 Lab scale electrophilic fluorination of "push-pull" enamines

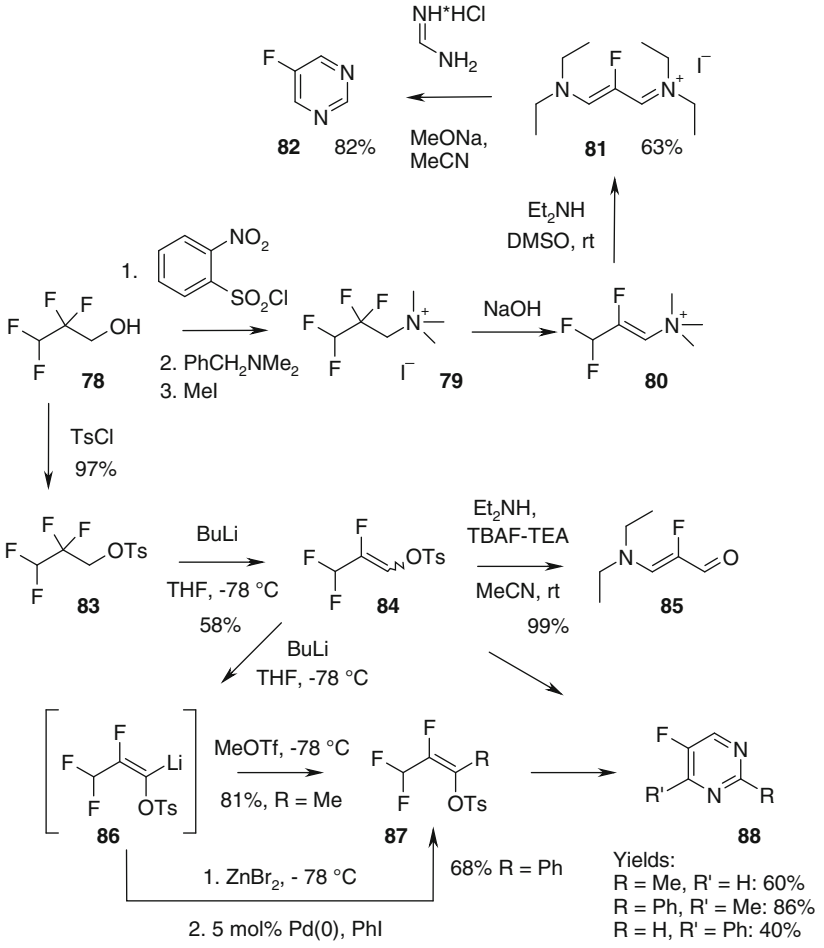
Electrophilic fluorination of formal formylacetic acid synthon was carried out through 5,6-unsubstituted 1,3-dioxin-4-ones **74** by fluorine followed by treatment with triethylamine. The fluorination proceeds via *cis*-addition – elimination in 84 % overall yield affording 5-fluoro-1,3-dioxin-4-one **76**. The compound could be transformed to 5-FU by analogy with Heidelberger synthesis of 5-FU but original paper doesn't refer yields for the transformations [113] (Scheme 18).



Scheme 18 5,6-unsubstituted 1,3-dioxin-4-ones fluorination

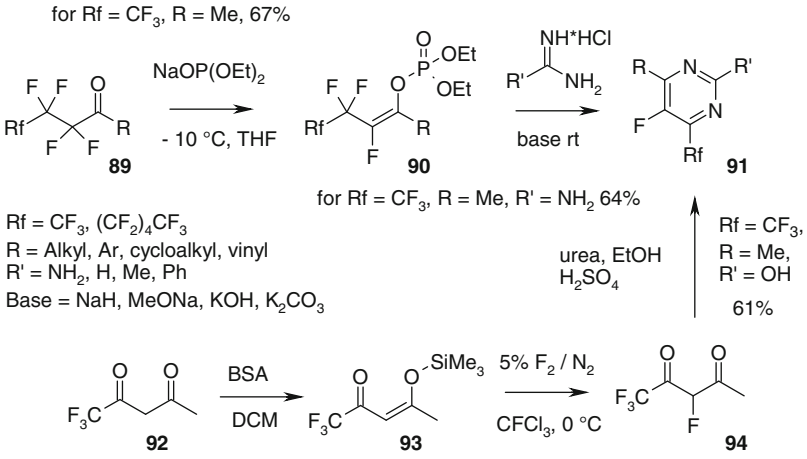
Alternative approaches to some fluorinated synthons were developed in 1990s by Yamanaka with co-workers starting from commercially available polyfluorinated alcohol. The corresponding quaternary ammonium salt **80** was prepared in four step

synthesis in 69 % total yield. **80** under treatment by secondary amines gave vinamidinium salts **81** similar to Vilsmeier-type sequence (see Scheme 13) [114]. The salts appear appropriate synthons for pyrimidine synthesis, for example the reaction with formamidine hydrochloride affords parent 5-fluoropyrimidine **82** in 82 % yield [115]. Same synthetic equivalent of fluoromalonic dialdehyde – 3-dialkylamino-2-fluoroacroleins **85** also acceptable from tetrafluoropropanol via 3-step sequence including tosylation [116], elimination of HF via lithiation [117, 118] and dialkylamino treatment. The overall yield of the sequence is 55 % [117]. Tosylate **84** directly can be subjected to cyclization with amidines and can be used for synthesis of 1-substituted sulfonates through additional lithiation – alkylation/Pd-catalyzed coupling with ArI [119] (Scheme 19).



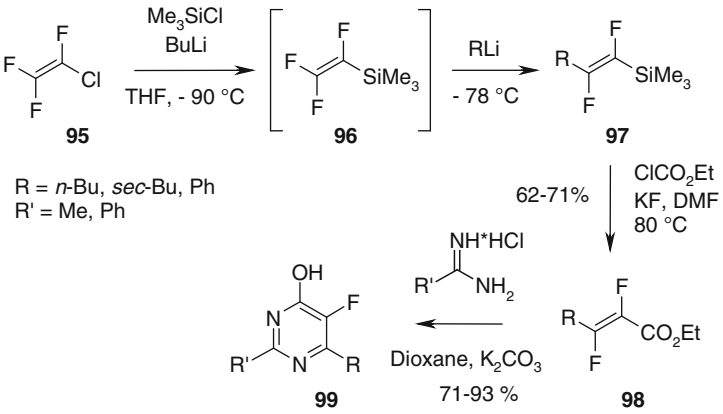
Scheme 19 Tetrafluoropropanol as starting material for synthesis of fluorinated pyrimidines

Another Japanese group of chemists in 1988 described the synthesis of fluorinated pyrimidines starting fluorinated ketones. The treatment of fluoroalkyl ketones **89** with sodium diethyl phosphate in THF at −10 °C gave 1-substituted fluoro-1-alkenyl phosphates **90**, which readily reacted with amidine derivative at room temperature afford corresponding pyrimidines **91** bearing fluorine at 5-th position as well as perfluoroalkyl fragment [120]. Another synthon able to incorporate both ring fluorine atom as well as perfluoroalkyl group was described by Sloop in 2002 via fluorination of silyl enol esters. This diketone **94** was converted to pyrimidinol **91** in acidic conditions in 61 % yield [121] (Scheme 20).



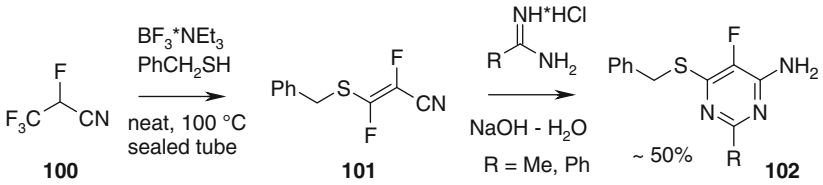
Scheme 20 Synthesis of ring and chain fluorinated pyrimidines

3-Substituted-*trans*-2,3-difluoro-2-acrylates **98** can be used as synthons for pyrimidine synthesis. Trifluorovinyltrimethylsilane **96**, prepared from trimethylsilyl chloride, chlorotrifluoroethylene **95** and n-butyl lithium in THF, reacted with a variety of lithium reagents to afford the corresponding addition–elimination products **97**. Ethyl chloroformate reacted with trans-(2-alkyl or 2-aryl-1,2-difluoroethenyl) trimethylsilanes **97** in presence of dry potassium fluoride (1.5–2°equiv.) in DMF at 80 °C to afford the corresponding esters **98** stereoselectively in good yields. Treatment of ethyl 3-substituted-trans-2,3-difluoro-2-acrylates with acetamidine hydrochloride and benzamidine hydrochloride, respectively, in presence of K_2CO_3 in 1,4-dioxane gave the corresponding 5-fluoropyrimidine derivatives **99** in good yield [122] (Scheme 21).



Scheme 21 Synthesis of fluorinated pyrimidines from 2,3-difluoro-2-acrylates

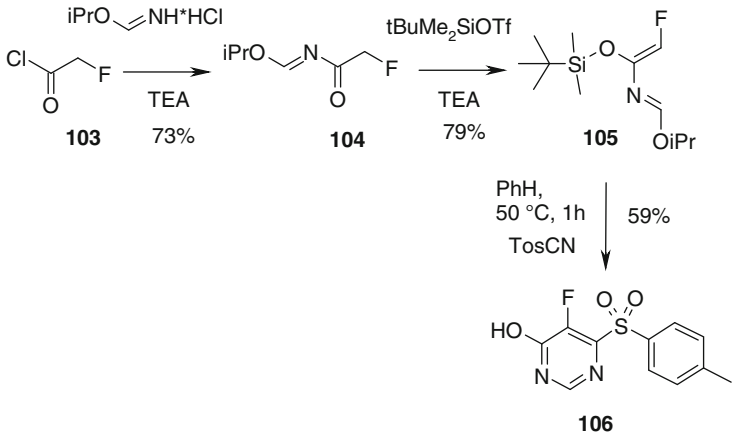
Similar approach (trough difluorinated vinyls) was developed by Sizov with co-workers in early 2000-th starting from commercially available tetrafluoropropionitrile **100**. The nitrile reacts with $PhCH_2SH$ in presence of 2 eq. of the BF_3*NEt_3 complex affording vinyl sulfide **101** in a preparative yield. Difluorobenzylthioacrylonitrile reacted with amidines to produce the corresponding 4-amino-5-fluoropyrimidines **102** [123, 124] (Scheme 22).



Scheme 22 Synthesis of fluorinated pyrimidines from difluorobenzylthioacrylonitrile

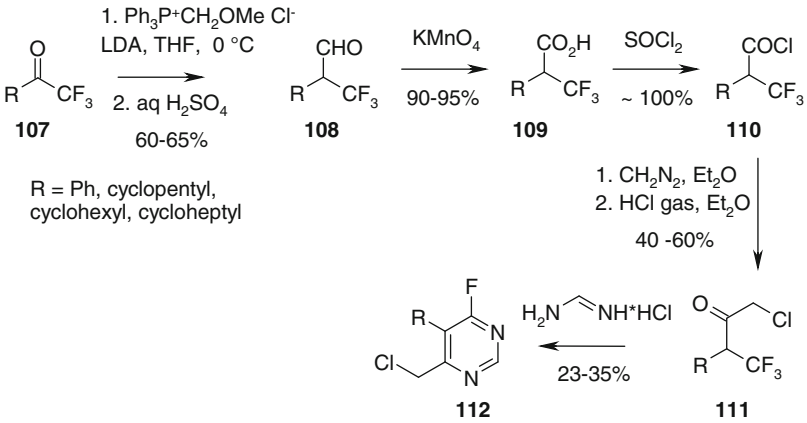
3.2.2 Miscellaneous Cyclization

5-Fluoropyrimidines **106** can be also synthesized using Diels-Alder reaction of fluorinated 2-aza-1,3-diene **105** with tosyl cyanide. The corresponding 2-aza-1,3-diene was easy synthesized from N-acylimldates **104** through silylation with t-butyldimethylsilyl triflate in a presence of triethylamine [125] (Scheme 23).



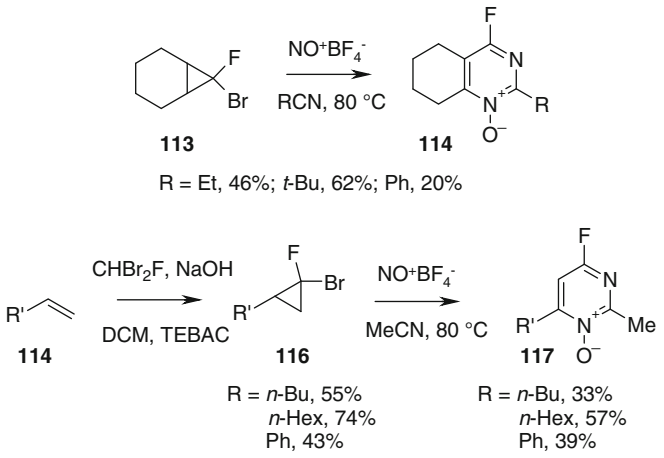
Scheme 23 Diels-Alder approach to fluorinated pyrimidines

Unusual approach to 4-fluoriopyrimidines was developed by de Nanteuil where CF_3-groupplaysaroleoffluorinesource.Thecorrespondingα-chloro-α'-trifluoromethyl ketones **111** were synthesised in 5 steps starting from **107**, which reacted with formamidine affording 5-substituted 4-fluoro-6-chloromethyl pyrimidines **112** in 23–35 % yield [126] (Scheme 24).



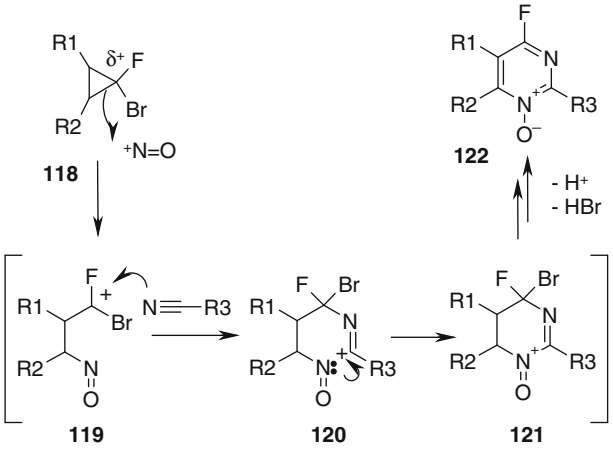
Scheme 24 Access to 4-Fluoropyrimidines from **α**-chloro-**α′**-trifluoromethyl ketones

Very recently unusual approach to 4-fluoropyrimidine N-oxides from alkenes was elaborated in Moscow State University. The method based on three-component heterocyclization involving gem-bromofluorocyclopropanes **113** or **116**, nitrosyl tetrafluoroborate, and a molecule of the solvent (nitrile) yielding previously unknown fluorinated pyrimidine N-oxides **114** or **117** (Scheme 25) [127].



Scheme 25 Heterocyclization of *gem*-Bromofluorocyclopropanes with $NOBF_4$ and nitriles

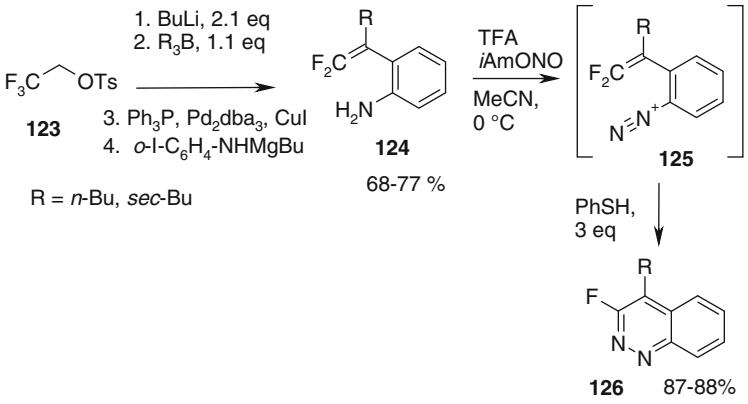
The first step of cyclization involves the electrophilic attack of NO^+ and the opening of the three-membered ring resulting in the formation of the intermediates type **119**. Than intermediate **119** is trapped by solvent, resulting in the formation of nitrilium species **120**, which undergo intramolecular cyclization into final pyrimidine N-oxides **122** (Scheme 26).



Scheme 26 Heterocyclization of *gem*-Bromofluorocyclopropanes with $NOBF_4$ and nitriles

Ichikawa and co-workers described in 2007 intramolecular cyclization leading to 3-fluoroccinnolines. *o*-Amino-β,β-difluorostyrenes **123**, prepared from CF_3CH_2OTs and o-iodoaniline, were treated with isoamyl nitrite (i-AmONO) for diazotization,

and then reduced with n-Bu_3SnH. The expected intramolecular substitution of the terminal diazenyl nitrogen (HN=N–) proceeded smoothly, to give 3-fluorocinnoline **126** (R=*n*-Bu) in 58 % yield. Then several other reducing reagents were tested, and it was found that benzenethiol raised the yield of **126** (R=*n*-Bu and *sec*-Bu) to 88 and 87 %, respectively (Scheme 27). In the reaction of **124**, diphenyl disulfide (PhSSPh) was obtained in 90 % yield based on PhSH, which implies that PhSH definitely acted as a reducing agent [128].



Scheme 27 Synthesis of 3-fluoroccinnolines

4 Properties and Chemical Transformation

4.1 General

RFDs without additional chromophores are either colorless liquids or white solids and, apart from having relatively high volatilities, no special handling procedures are required for their use. The boiling points of the perfluorinated diazines somewhat lower than those for the corresponding parent hydrocarbons in contrast to perfluorobenzenoid compounds which have boiling points that parallel those of the corresponding hydrocarbons (Table 6). This is attributed to the much lower intermolecular forces and the very low basicities of the fluorocarbon systems that compensate for the increase in mass upon replacing hydrogen by fluorine [129].

All the perfluoroheteroaromatic systems are very weak bases and, for instance, superacids are required to protonate pentafluoropyridine. Relative base strengths of the perfluorinated heteroaromatic systems have been determined by NMR competition experiments and the major influence is that of the fluorine atoms ortho to ring nitrogen that significantly decrease the basicity of the system (Fig. 3) [130]. Despite the fact that perfluoropyrimidine did no participate in experimental NMR competition CNDO/2 SCF-MO calculations of energy release on portonation in

Table 6 Comparison of boiling points of perfluoroheteroaromatics systems with the corresponding hydrocarbon systems

#	System	Boiling point (°C)	Boiling point of perfluorinated compound (°C)
1	Benzene	80.1	80.2
2	Toluene	110.6	102–103
3	Pyridine	115.5	83.3
4	Pyridazine	208	117
5	Pyrimidine	123.5	89
6	Pyrazine	115	54

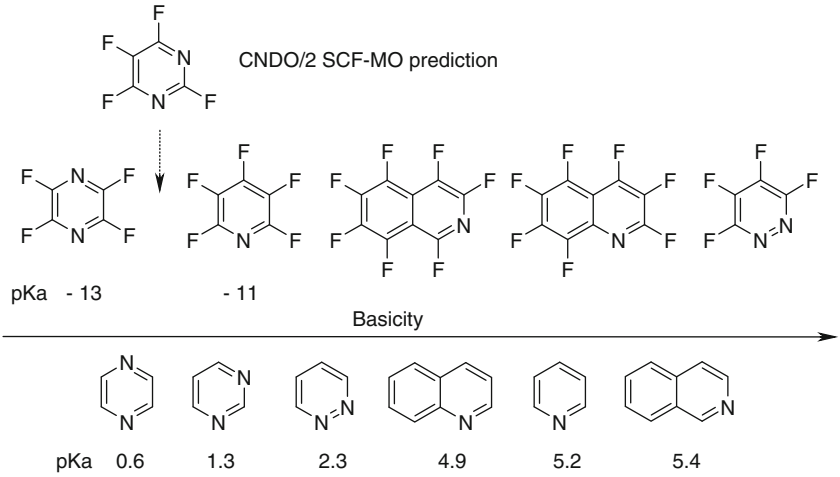


Fig. 3 Basicity of perfluoroheteroaromatic systems

gaseous phase (ΔE_g) predict that basicity of the compound are between perfluoropyridine and pefluoropyrazine [131].

The common method of securing information about electronic structure is photoelectron spectroscopy (PES), which permits a direct comparison with experiment of various quantum-chemical models used for the calculation of phischem characteristics. The fluorinated diazines have been investigated by the method [132]. By means of fluorine substitution the analysis of the HR HeI line PES of the parent compounds was made in details in Twente University, made it possible to refine the assignment of the bands in the PE spectrums of diazines. Especially in a case of aza- and diazaaromatics, where nitrogen "lone-pair" bands and π-bands lie in the same region of the spectrum, the use of the perfluoro effect is indispensable for a thorough analysis of the spectra. By the same scientists the electrochemical reduction of RFDs was studied [133]. The electrochemical reduction process of fluorinated aza-aromatics can well be described by the pattern which is normally postulated for aryl halogenides, i. g. fission of the carbon-halogen bond. However,

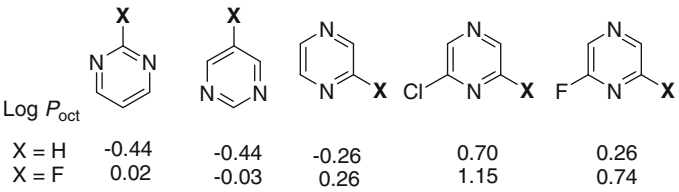


Fig. 4 Hydrophobicity of RFDs

the stability of the intermediate mono-negative ions is generally higher than for the comparable fluoro-substituted arenes. The half-wave reduction potentials of the first reduction wave can be related to the electron affinities of the molecules. These electron affinities have been correlated with those obtained by quantum-chemical calculation. Also recently the theoretical MP2 study was performed for the structural investigation of anion-binding involving π-acidic RFDs [134].

The hydrophobicity of molecules plays an important role in structure–activity relationship studies for various bioactive compounds. The introducing of the fluorine atom into diazine core increased hydrophobicity and selected experimental data is presented on Fig. 4 [135–137]

Despite of a lot of NMR data of RFDs the limited data available for simple RFDs allow one to see how the position of the fluorine substituent on a heterocycle can significantly affect its chemical shift [138]. To the best of our knowledge there are not literature data dealing with general analysis of NMR data of RFDs. Only a few reviewed papers just summarized the ^{19}F NMR data of RFDs described in 1968–1981 [139–142]. For the synthetic chemists one of the most important is ^{19}F NMR data, because the knowledge allows simple monitoring of the reaction mixtures by ^{19}F NMR of the reaction mixtures. This data also give possibilities to registrate of non-isolable intermediates in solutions, which significant simplify the mechanistic interpretation of the processes. Besides practical application the ^{19}F NMR data for RFDs, has been used to verify previously published statistical substituent chemical shift (SSCS) values for fluoroarenes. The data was allowed generation of a set of structure factors for aromatic nitrogen heterocycles which allows the signals for these compounds to be predicted from the same set of SSCS values as fluoroarenes [143].

In case of pyrimidines, large differences in chemical shift are observed for fluorines at the 2-, 4- (6-), and 5- positions with fluorines at the 2-position of pyrimidines being the most deshielded, and those at the 5-position being the most shielded. The chemical shifts for fluoropyrimidines and 5-fluorouracil are provided on Fig. 5. ^{13}C and ^{1}H NMR chemical shift and coupling constant data for some ring fluorinated pyrimidines are also given on Figs. 6 and 7. It should be noted, that in fluorinated pyrimidines, unlike with fluorinated benzenes, the values of coupling $^{3}J_{FH}$ constants are significant small (0.8–2.7 Hz), less then values of $^{5}J_{FH}$ constants in 5-fluorinated pyrimidines (~3.3 Hz) and than values of $^{4}J_{FH}$ constants in 4-fluorinated pyrimidines (~10 Hz).

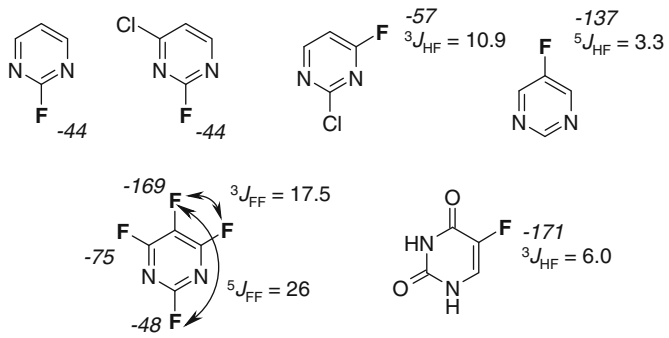


Fig. 5 ^{19}F NMR data of ring fluorinated pyrimidines

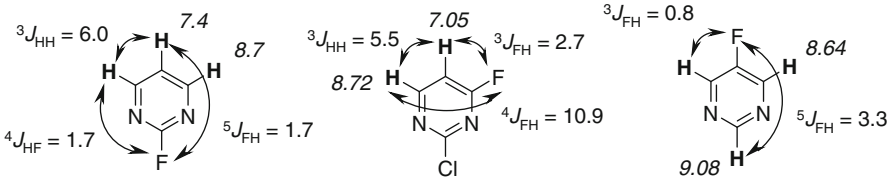


Fig. 6 ^{1}H NMR data of ring fluorinated pyrimidines

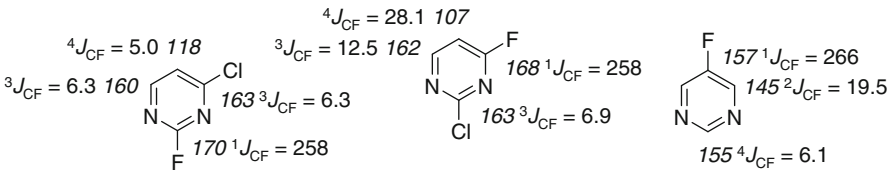


Fig. 7 ^{13}C NMR data of ring fluorinated pyrimidines

In pyridazine series like in pyrimidines large differences in chemical shift are observed for fluorines in 3-(6-)- and in 4-(5-) positions. The fluorines at the 3-(6-)-positions of pyridazine being more deshielded. The values of of fluorine-fluorine coupling constants one can easily find from NMR data of series fluorochloropyridazines [68] (Fig. 8). As in a case of pyrimidine a large value (ca. 30 Hz) of the $^5J_{FF}$ constant is noteworthy. Also on Fig. 9 ^{13}C and ^{1}H NMR chemical shifts and coupling constant of model 6-chloro-3-fuoropyridazine are provided. The values of coupling $^3J_{FH}$ constants are significantly small (~2 Hz) than values of $^4J_{FH}$ constants (~6–7 Hz).

^{19}F, ^{13}C and ^{1}H NMR chemical shift and coupling constant data for some ring fluorinated pyrazines are provided on Fig. 10.

The determination of substitution patterns in diazine compounds is particular important. One of the approaches to solve the problem is 2D ^{15}N NMR spectroscopy.

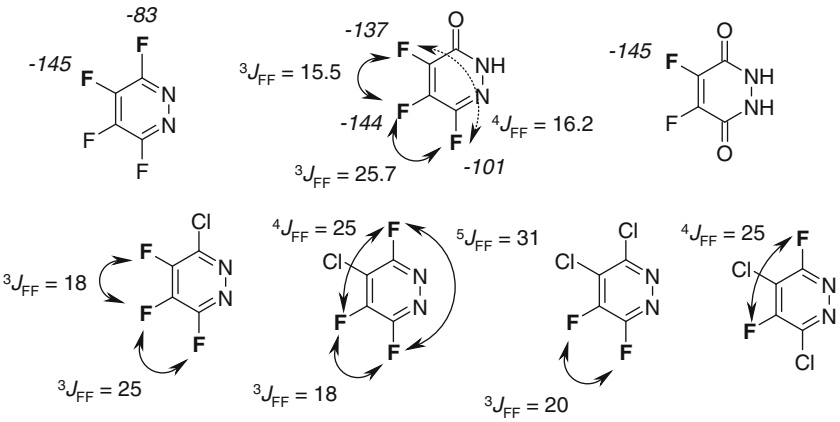


Fig. 8 ^{19}F NMR data of ring fluorinated pyridazines

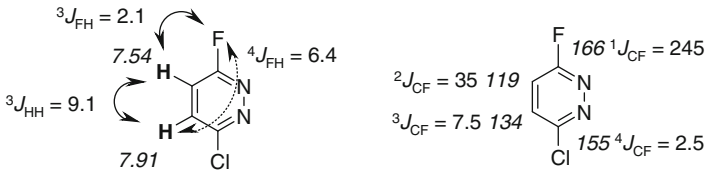


Fig. 9 ^{1}H and ^{13}C NMR data of ring fluorinated pyridazines

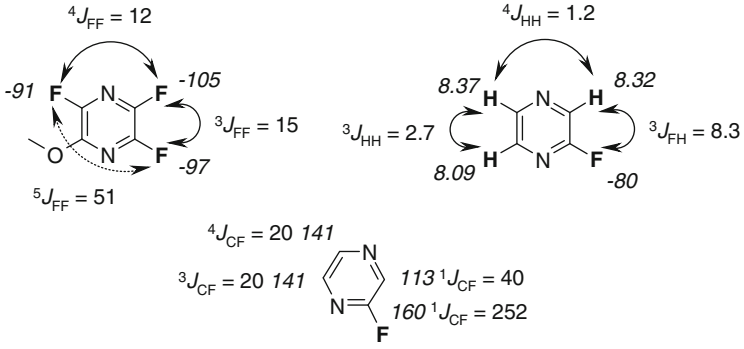


Fig. 10 NMR data of ring fluorinated pyrazines

Therefore in the literature there are some ^{15}N NMR data of ring fluorinated diazines. The ^{15}N NMR of perfluorinated diazines are summarized in Table 7 [144]. Also recently few works devoted to theoretical calculations of coupling constants in fluorinated azines were published [145, 146].

Table 7 Comparison of ^{15}N chemical shifts of perfluoroheteroaromatic systems with the corresponding hydrocarbons analogues (shifts relative to liq. NH_3)

#	System	δ(^{15}N) (ppm)	δ(^{15}N) (ppm)of the hydrocarbon analogue	$^{N}J_{NF}$ (Hz)	N
1	Pyridine	234	316	−51.7	2
				3.9	3
				1.2	4
2	Pyridazine	328	400	−50.0	2
3	Pyrimidine	228	195	−53.7	2
				2.9	3
4	Pyrazine	278	334	−45.1	2
5	Phtalazine	273	370	−59.5	2
				8.8	3
6	Quinoxaline	273	329	−54.5	2

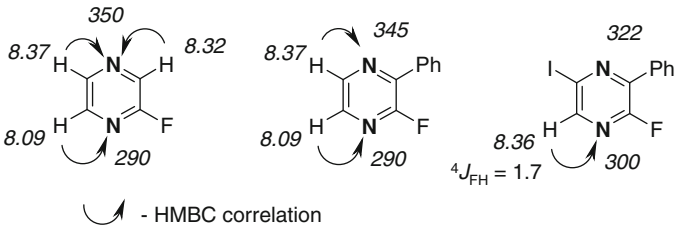


Fig. 11 Structure determination of 2-fluoro-3-phenyl-5-iodopyrazine

As an example of RFD structure determination based on long-range $^{1}H–^{15}N$ GHMBC spectra one can refer determination of structure of 2-fluoro-3-phenyl-5-iodopyrazine based on comparison of GHMBC spectra of fluorinated pyrazines (Fig. 11) [147].

4.2 Nucleophilic Aromatic Substitution

4.2.1 General Remarks: Orientation and Reactivity

A considerable number of ring-fluorinated diazines undergoes various nucleophilic aromatic substitution reactions. Nucleophilic aromatic substitution reactions follow the well-established two-step addition–elimination mechanism *via* a Meisenheimer intermediate. The destabilization of sp^2-C bound fluorine by p–π repulsion activates fluorinated aromatic compounds toward nucleophilic attack and subsequent substitution. The susceptibility of the carbon center toward nucleophiles is also enhanced by the negative inductive (*–Iσ*) effect of fluorine. Therefore the ease of nucleophilic halogen replacement – F>Cl>Br>I – is in the opposite order to that for aliphatic

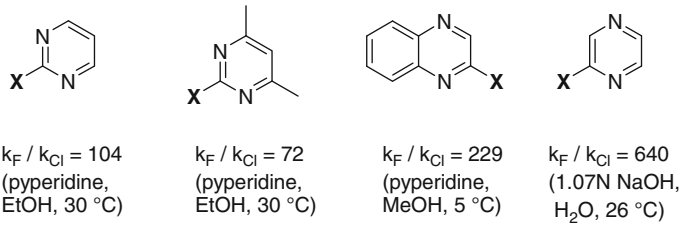
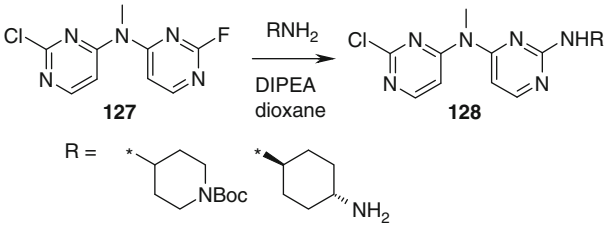


Fig. 12 Fluorine versus chlorine mobility in substitution reactions

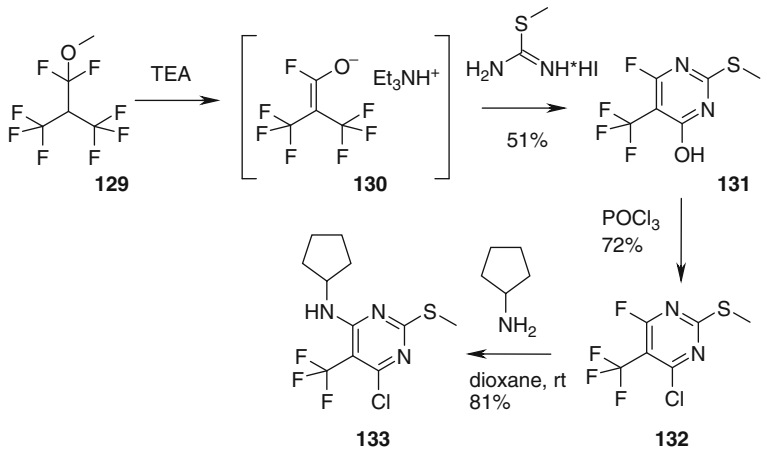
nucleophilic substitution. The kinetic data of pyperidinolysis in diazine series proof the assumption and k_F/k_{Cl} ratios are listed in Fig. 12 [72, 148]. Also the acid-promoted hydrolysis of the 2-fluoro derivatives of pyrimidine, 4-methylpyrimidine, and 4,6-dimethylpyrimidine have been studied in hydrochloric acid. The mechanism for hydrolysis of the pyrimidines as distinct from that of the less activated 2-fluoroquinoline and the 2-fluoropyridines by suggesting that nucleophilic attack takes place without proton transfer to a second water molecule in the reactions of the former compounds and with transfer in reaction of the latter [149]. Kinetic studies of basic hydrolysis of halogenopyrazines in aqueous NaOH also show that 2-fluoropyrazine in 640 times more active than 2-chloropyrazine [150] (Fig. 12).

The difference in fluorine/chlorine mobility was also practically illustrated by Amgen using bis-pyrimidine **127** for libraries construction [151]. In this case only the fluorine displacement is observed (Scheme 28).



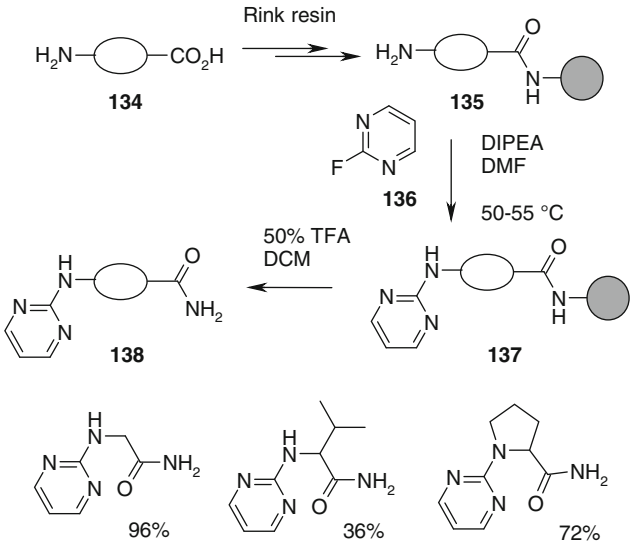
Scheme 28 Fluorine versus chlorine mobility in libraries constructions

Another example of fluorine/chlorine exchange selectivity one can find in Novartis patent were chlorofluoropyrimidine **132** react with cyclopentylamine leading to compound **133** (Scheme 29) [152]. It should be noted, that the synthesis of starting compound **131** is similar to approach shown on Scheme 24, where CF_3 group is a source of fluorine in pyrimidine nuclear.



Scheme 29 Fluorine versus chlorine mobility

High reactivity of 2-fluoropyrimidine was used for the amines, anilines and aminoacids decoration on solid support. In this case among halopyrimidines only 2-fluoropyrimidine is appropriate as reagent and in a case of aminoacids gave corresponding in high preparative yields (Scheme 30) [76, 153, 154]



Scheme 30 Solid-supported decoration of amino acids by 2-fluoropyrimidine

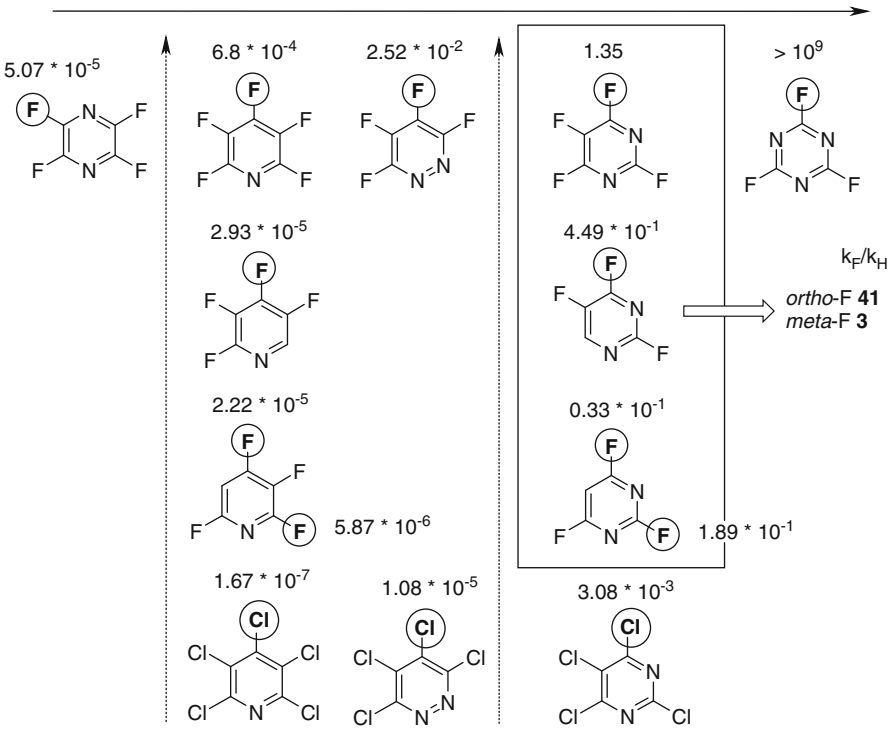
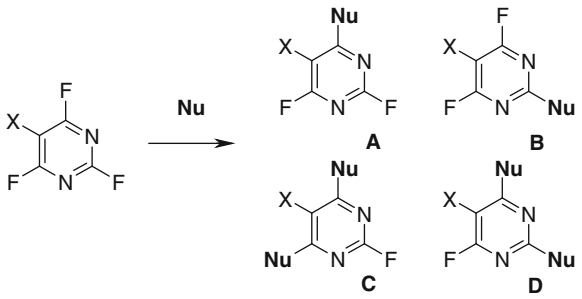


Fig. 13 Rate Constants for attack by ammonia in dioxane-water at 25 °C ($L \cdot mol^{-1} \cdot s^{-1}$)

The increasing of number of ring fluorine atoms in diazines leads to increasing of activity towards various nucleophiles. The results of comparative kinetic studies of various polifluorinated diazines in the reaction with ammonia in dioxane are shown on Fig. 13. Among perfluorinated azines the activities towards nucleophiles of pyrimidine and pyridazine are in the region between pyridine and triazine. Tetrafluoropyrazine is less active than pentafluoropyridine. The reduced reactivity of tetrafluoropyrazine compared to the other perfluorinated azines reflects the absence of highly activated sites in *para*-position to ring nitrogen. The increasing of activity in pyrimidine (trifluoro substituted to tetrafluoro substituted) series are in agreement with data obtained in pyridine series. Activating influences of fluorine in the pyrimidine ring system are k(*ortho*-F)/k(H) = 41 and k(*meta*-F)/k(H) = 3 respectively. This such big influence for *ortho* fluorine atom explains the loss of the regioselectivity in fluorine displacement in 2,4,6-trifluoropyrimidine [155, 156].

Besides fluorine the influences of another substituents such as Cl, CF_3, NO_2, CN on fluorine displacement in 2,4,6-trifluoropyrimidine were studied. The results (Table 8) can be satisfactory rationalized in terms of bimolecular additional-elimination S_NAr mechanism through Meisenheimer type complexes [157].

Table 8 Nucleophilic substitution in 2,4,6-trifluoropyrimidine



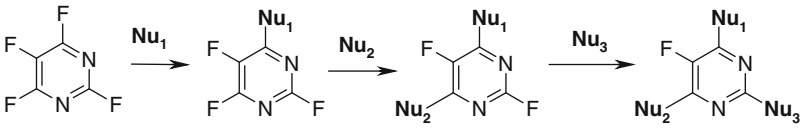
			Product				
				Composition			
X	Nucleophile	T (°C)	Yield (%)	A	B	C	D
H	MeOH–Na_2CO_3	>20	77	67	33	0	0
H	aq. NH_3	0	79	33	67	0	0
Cl	MeOH–Na_2CO_3	0–20	57	94	6	0	0
Cl	aq. NH_3	0	90	91	9	0	0
CF_3	MeOH–Na_2CO_3	−20 to +20	87	50	45	0	0
CF_3	MeCH=CHLi	−96 to −78	56	4	83	0	0
NO_2	aq. NH	−20	73	0	0	100	0
CN	MeOH–Na_2CO_3	−20 to +20	70	0	0	10	90
CN	aq. NH_3	−20 to +20	84	0	0	0	100

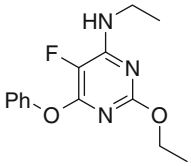
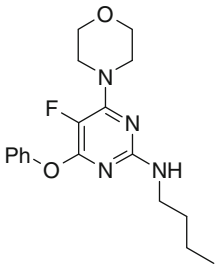
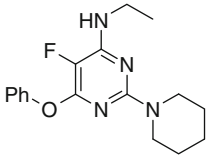
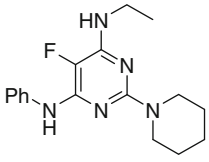
4.2.2 Application in Organic and Combinatorial Synthesis

The high selectivity in sequential nucleophilic substitution in perfluorodiazines made them attractive scaffolds for the synthesis of a diverse array of polysubstituted diazines. These approaches were recently developed by Stanford group. Thus, tetrafluoropyrimidine may be used as a scaffold for the synthesis of a range of 2,4,6-trisubstituted pyrimidine derivatives upon sequential displacement of the fluorine atoms attached to the strongly activated 4-, 6- and 2-positions (Table 9) [158]. The first two substitutions proceed in very mild conditioned (0 °C or room temperature). The last nucleophilic substitution of fluorine at 2-position proceeds in harsh conditions and needs MW heating.

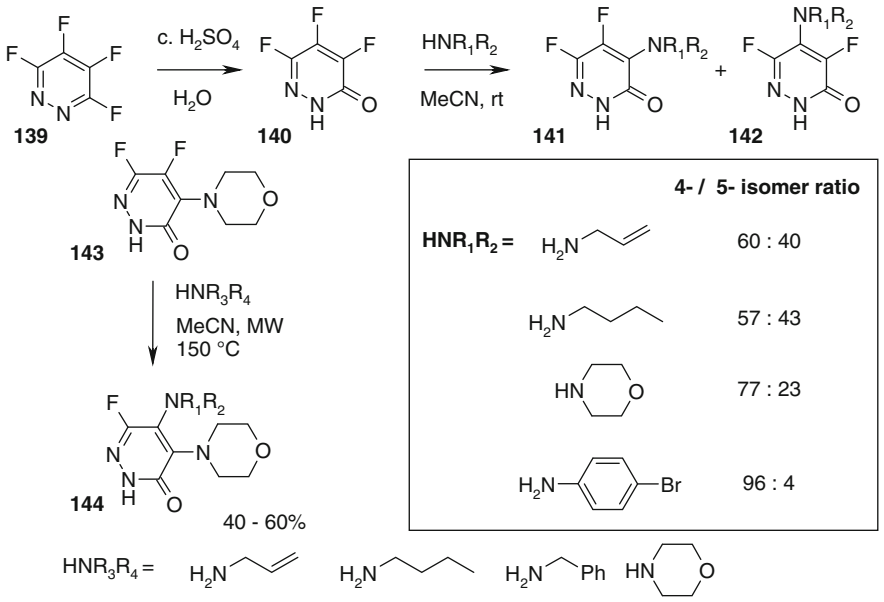
Similarly, trifluoropyridazinone **140**, readily synthesised by reaction of tetrafluoropyridazine **139** with sulfuric acid, may be used as the starting material for the synthesis of a variety of 4,5-diamino-fluoropyridazinone systems **144**. Reaction of trifluoropyridazinone gives a mixture of products **141** and **142** arising from dis-

Table 9 Tetrafluoropyrimidine as a core scaffold



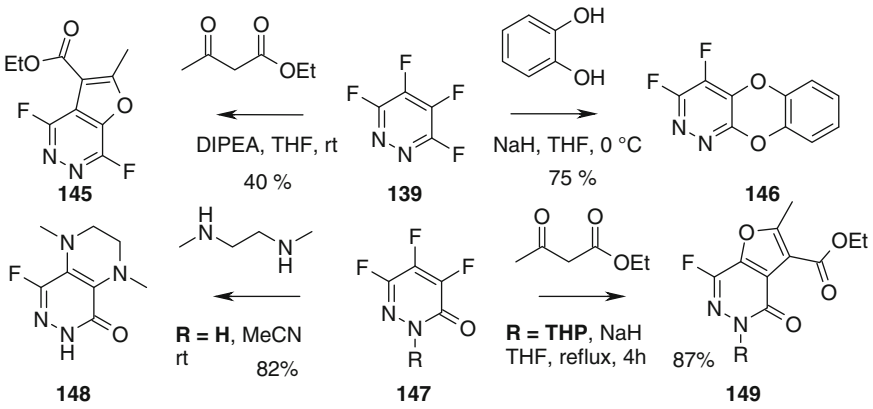
Nu_1	Nu_2	Nu_3	Product
$EtNH_2$, THF, DIPEA, 0 °C	PhONa, THF, rt	EtONa, THF, MW, 140 °C, 15 min	
 THF, DIPEA, 0 °C	PhONa, THF, rt	nBuNH$_2$, THF, MW, 140 °C, 15 min	
$EtNH_2$, THF, DIPEA, 0 °C	PhONa, THF, rt	 THF, MW, 140 °C, 15 min	
$PhNH_2$, THF, DIPEA, 0 °C	$EtNH_2$, THF, DIPEA, rt	 THF, MW, 140 °C, 15 min	

placement of fluorine from either 4- or 5-positions, both positions are activated by *para* ring nitrogen, but these isomers can be separated by column chromatography and used in subsequent S_NAr processes for the synthesis of a range of aminated pyridazinone derivatives. The predominant product formed in the reaction is product of 4-F substitution **141**. The first substitution with amines proceeds in room temperature whereas the next substitution, as in a case of tetrafluoropyrimidine, needs MW heating (Scheme 31) [159].

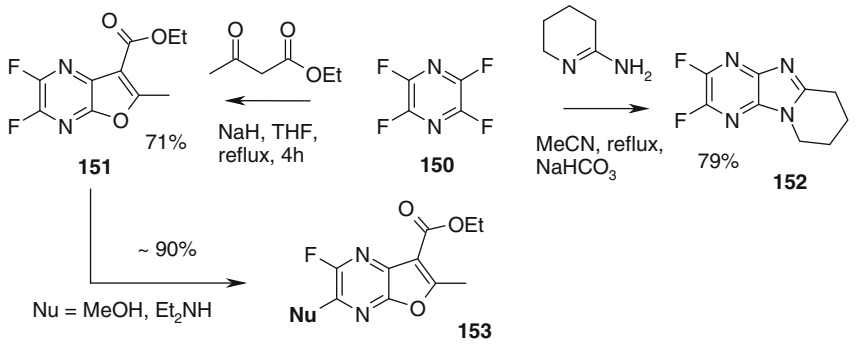


Scheme 31 Tetrafluoropyridazine as core for diaminated derivatives

Reactions of trifluoropyridazinone with highly basic sodium methoxide or phenoxide gave complex mixtures of products and tar derived, presumably, from deprotonation of the pyridazinone ring NH and subsequent polymerisation. Protection of the ring NH group as a tetrahydropyran derivative, however, allows the functionalization of the pyridazinone core scaffold by oxygen-centred nucleophiles extending the range of functional pyridazinone systems which may be accessed by this general strategy [160]. Also the reaction of polyfluorinated pyridazines with binucleophilic compounds leads firstly to intermolecular nucleophilic substitutions followed by cyclization to afford fused systems. This enhanced reactivity is reflected in the relative reactivity found in intramolecular nucleophilic substitution reactions compared to corresponding intermolecular processes. Among binucleophiles N,N′-dimethylethylene diamine, catechol and actoacetic ester derivatives were tested (Scheme 32). Besides tetratrifluoropyridazine derivatives, tetratrifluoropyrazine also entered into annelation reaction. In a case of acetoacetic ester furo[2,3-b]pyrazine derivative formed bearing two active fluorine atoms. But the additional nucleophile treatment showed regioselective displacement only at C-3 position (Scheme 33) [159–162].



Scheme 32 Annelation reaction based on polifluoropyridazines



Scheme 33 Annelation reaction based on perfluoropyrazine

In general, tetratrifluoropyrazine is less studied as core scaffold. Reactions of tetrafluoropyrazine with nucleophiles occur readily and, of course, there are no issues regarding regioselectivity of the first nucleophilic substitution process due to the symmetry of this system. The reduced reactivity of tetrafluoropyrazine compared to the other perfluorinated diazines reflects the absence of highly activated sites in *para* position to ring nitrogen. The regiochemistry of the reaction of trifluoropyrazine derivatives with nucleophiles is influenced by the nature of the substituent as well as the presence of the remaining fluorine atoms. If the substituent is either an alkoxy or amino group, the site of attack is generally *ortho* to the substituent, although steric effects can also influence the outcome of this reaction. In contrast, when the substituent is a hydrogen or alkyl group or chlorine, the site of attack is *para* – position to the substituent. (Fig. 14) [57, 163, 164].

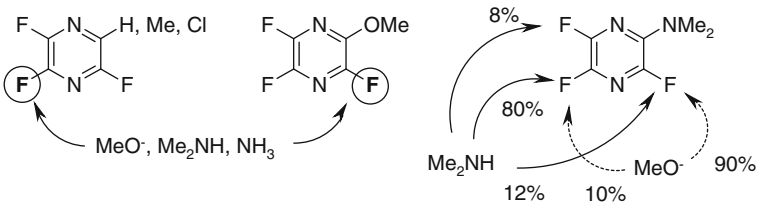
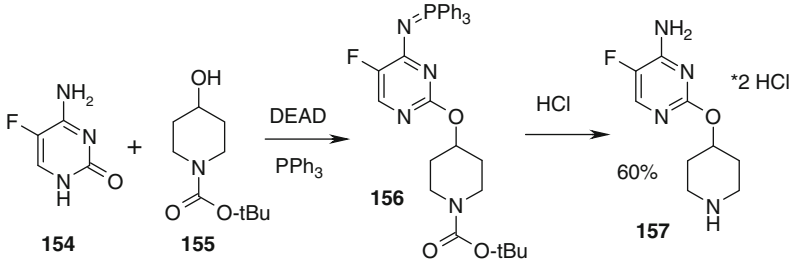


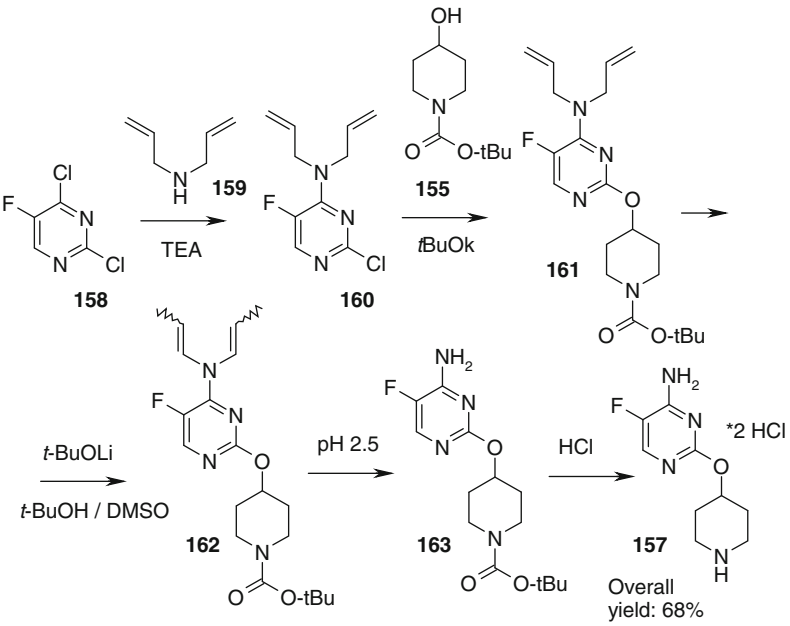
Fig. 14 Regiochemistry pattern for trifluoropyrazines

Of course in the academic and patent literature there are a lot of examples of nucleophilic substitution of fluorine by different *N*, *S*, *O* – nucleophiles. Also another halogens in appropriate positions are able to entered in substitution reaction. A recent example of using of nucleophilic substitution was described by Lexicon Pharmaceuticals in course of development of deoxycytidine kinase inhibitors. Key intermediate for this investigation was 5-fluoro-2-(piperidin-4-yloxy) pyrimidin-4-amine **157**. The medicinal chemistry group used a synthesis based on the Mitsunobu reaction of commercially available 5-fluorocytosine **154** and N-Boc-4-piperidinol **155** (Scheme 34). The resulting iminophosphorane **156** is then treated with HCl to give the 5-fluoro-2-(piperidin-4-yloxy)pyrimidin-4-amine dihydrochloride in about 60 % yield. While this synthesis worked well on small scale and provided rapid access to gram quantities of **157** for early investigations of SAR, it gave inconsistent yields on scale-up [165].



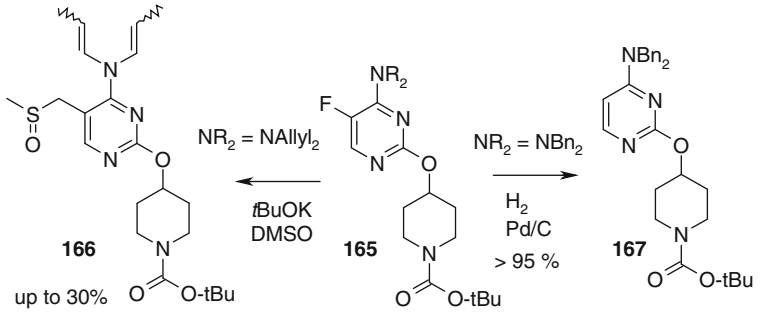
Scheme 34 Medicinal chemistry synthesis of 5-fluoro-2-(piperidin-4-yloxy)pyrimidin-4-amine

The R@D route to 5-fluoro-2-(piperidin-4-yloxy)pyrimidin-4-amine **157** was developed starting from readily available 2,4-dichloro-5-fluoropyrimidine **158**. This dichloroderivative, is one of the most frequently used building block among fluorinated diazines (198 reactions from 164 references in Reaxys® database). It was subjected to the reaction with bisallylamine and than with N-Boc-4-piperidinol affording compound **161**. The deprotection of amino group was carried out by isomerization using lithium tert-butoxide in DMSO/tert-butanol with subsequent hydrolysis leading to desired 5-fluoro-2-(piperidin-4-yloxy)pyrimidin-4-amine dihydrochloride **157** (Scheme 35).



Scheme 35 R@D route to 5-fluoro-2-(piperidin-4-yloxy)pyrimidin-4-amine

Such unusual chemical route to the target compound was developed due to the number of side process disclosed during investigation: fluorine substitution by dimsyl sodium of defluorination by catalytic hydrogenation (Scheme 36).



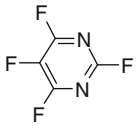
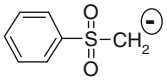
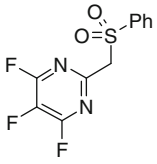
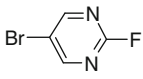
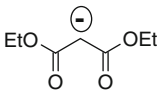
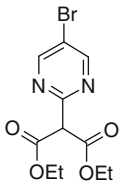
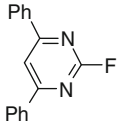
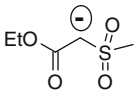
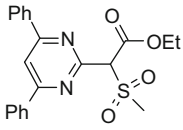
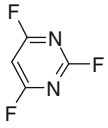
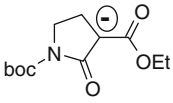
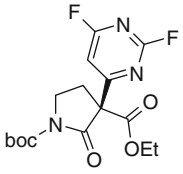
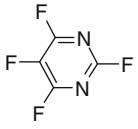
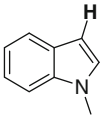
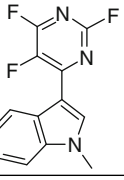
Scheme 36 Side process disclosed during 5-fluoro-2-(piperidin-4-yloxy)pyrimidin-4-amine synthesis

In this review we have no possibility to give comprehensive information about all types of these diverse transformations. Some of these transformations used for drug synthesis will be discussed in next chapter of this book. Another part of transforma-

tions has been partially reviewed early [166–169]. But in the next part of the section we would like to draw the reader's attention to less known nucleophilic substitutions such as with *C*-, *P*- and formally hydride nucleophiles and substitution of fluorine atom in 5-position of pyrimidine.

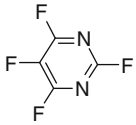
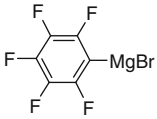
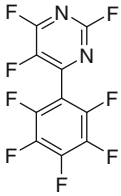
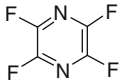
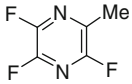
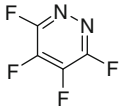
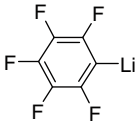
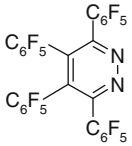
There are a few examples of fluorine substitution by *C*-nucleophiles. The reaction of fluorinated pyrimidines with stabilized carbanions affording the corresponding functionalized pyrimidines in low to moderate yields was described [170–176]. In all this cases the reactions do not have preparative value and was used for synthesis of model objects (Table 10, Entry 1–3). Recently such arylation was carried out

Table 10 Fluorine substitution with by *C*-nucleophile

#	Fluorinated diazine	*C*-nucleophile	Products	Yield (%)	Ref.
1[a]				26	[170]
2[b]				22	[171]
3				60	[172]
4[c]				65	[173]
5[d]				36	[174]

(continued)

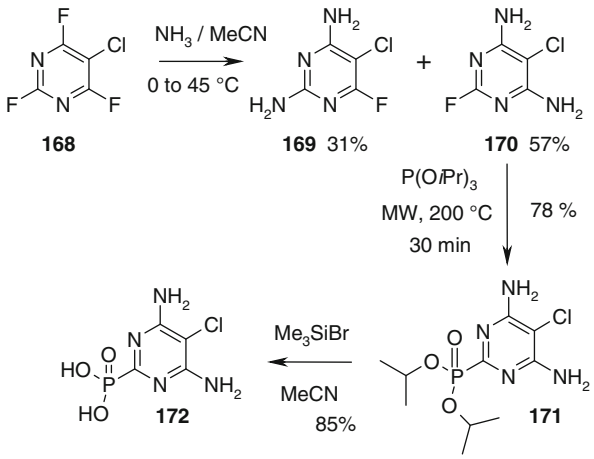
Table 10 (continued)

#	Fluorinated diazine	*C*-nucleophile	Products	Yield (%)	Ref.
6[e]				40	[175]
7[e]		MeLi		70	[57]
8[f]				86	[176]

[a]Carbanion was generated from corresponding sulphone and BuLi
[b]Potassium malonate in MeCN a presence of 18-crown-6
[c]ee 68 %, CsOH, PhMe/$CHCl_3$, −40 °C in *O*-benzoylated cinchona alkaloid
[d]MeCN, reflux
[e]Et_2O, − 70 – −50 °C
[f]Generated from C_6F_5H and BuLi in Et_2O-hexane at −78 °C

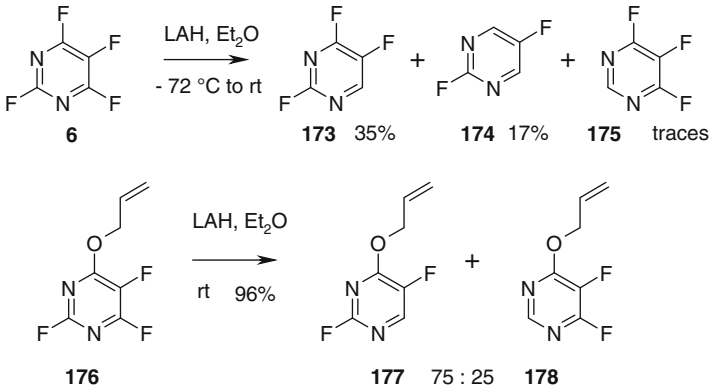
in asymmetric manner using an *O*–benzoylated cinchona alkaloid derivative as organocatalyst (Table 10, Entry 4). Besides arylation of stabilized carboanions the non catalytic hetarylation of π-electron reach indole was described by tetrafluoropyrimidine [174]. Also at the early step of pefluorinated diazines studies the reaction with Grignard reagents and alkyl lithium compounds were discovered by Banks and Chambers (Table 10, Entry 6–8). It should be noted, that the regiochemistry of the reaction of fluorinated diazines with *C*-nucleophiles are in accordance with *N*- and *O*– nucleophiles regiochemistry.

The reactions with *P*-nucleophiles are even more rare than with *C*-nucleophiles. Recently such reaction was used for the synthesis of polysubstituted pyrimidinylphosphonic acid **172**. Microwave-assisted Michaelis-Arbuzov reaction of triisopropyl phosphite with the corresponding 2-fluoropyrimidine **170**, followed by deprotection of the phosphonate group using TMSBr in acetonitrile gave the desired acid **172** in 66 % total yield. The derivative **172** exhibits anti-influenza virus A activity in the middle micromolar range (Scheme 37) [177].



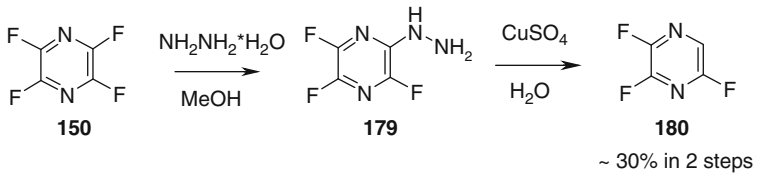
Scheme 37 Michaelis-Arbuzov type reaction with fluoropyrimidine

Another reaction discussed in this section is reduction of fluorinated pyrimidines by LAH. In this case LAH can be considered as strong hydride donor, which undergo nucleophilic substitution of fluorine. In a case of tetrafluoropyrimidine **6** the defluorination by LAH predominantly proceeds at 4-position. Double defluorination and defluorination at 2-position were detected as byprocess. Analogously allyloxy derivative **176** also undergo defluorination by LAH and major defluorination proceeds at 4-position (Scheme 38) [178, 179].



Scheme 38 Defluorination of polyfluoropyrimidines by LAH

But this simple defluorination methodology was found to be ineffective in a case of another diazines, therefore another approaches were elaborated. For example, tetrafluoropyrazine **150** was converted to trifluoropyrazine **180** in two steps – using

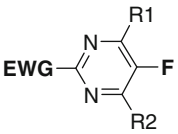
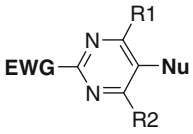
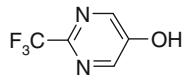
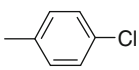
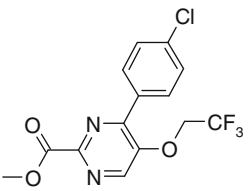


Scheme 39 Defluorination of pyrazines by NH_2NH_2–$CuSO_4$ sequence

hydrazine hydrate substitution – copper oxidation sequence (Scheme 39) [163]. Another defluorination strategy will be discussed in next sections.

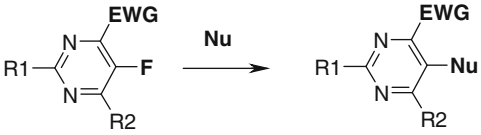
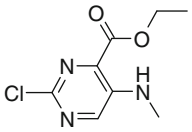
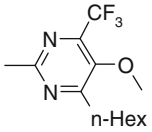
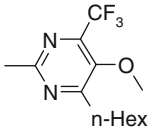
The most problematic nucleophilic substitution in fluorinated diazine series is substitution of fluorine at 5-position of pyrimidine due to the absence of highly activated sites *para* or *ortho* to ring nitrogen. The first example of fluorine exchange in 5-position was described simultaneously with tetrafluoropyrimidine. Heating at 220 °C in di-*n*-buthylamine leads to exhaustive fluorine exchange giving tetracis-di-n-butylaminopyrimidine [14]. But further publication showed that fluorine substitution in 5-position of pyrimidine needed activation by electron withdrawing groups or facilitating by intramolecular cyclization. Ester and CF_3 groups in 2-and 4-position of pyrimidine ring were used as electron withdrawing groups (Table 11). Interesting fact was disclosed recently that fluorine at 5-position activated by ester group is more reactive than chlorine atom at 2-position of pyrimidine (Table 11, Entry 3).

Table 11 Fluorine substitution in 5-th pyrimidine position activated by electron withdrawing group

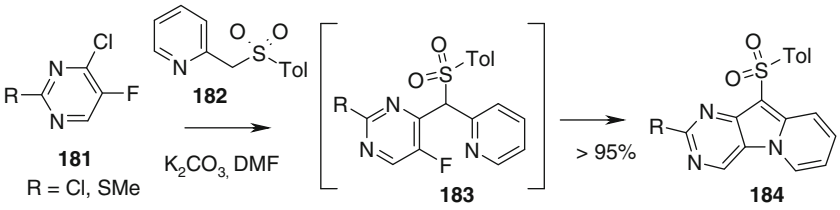
#	EWG	R1	R2	Nu	Product	Ref.
						
1	CF_3	H	H	NaOH, DME-H_2O, reflux, 2 h, 79 %		[180]
2	CO_2Me		H	CF_3CH_2OH, Cs_2CO_3, DMSO, 60 °C, 86 %		[181]

(continued)

Table 11 (continued)

#	EWG	R1	R2	Nu	Product	Ref.
						
3	CO_2Et	Cl	H	$MeNH_2$, TEA, DCM, rt, 80 %		[182]
4	CF_3	Me	*n*-Hex	MeONa, rt, 73 %		[120]
5	CF_3	Me	*n*-Hex	CF_3CH_2ONa, rt, 46 %		[120]

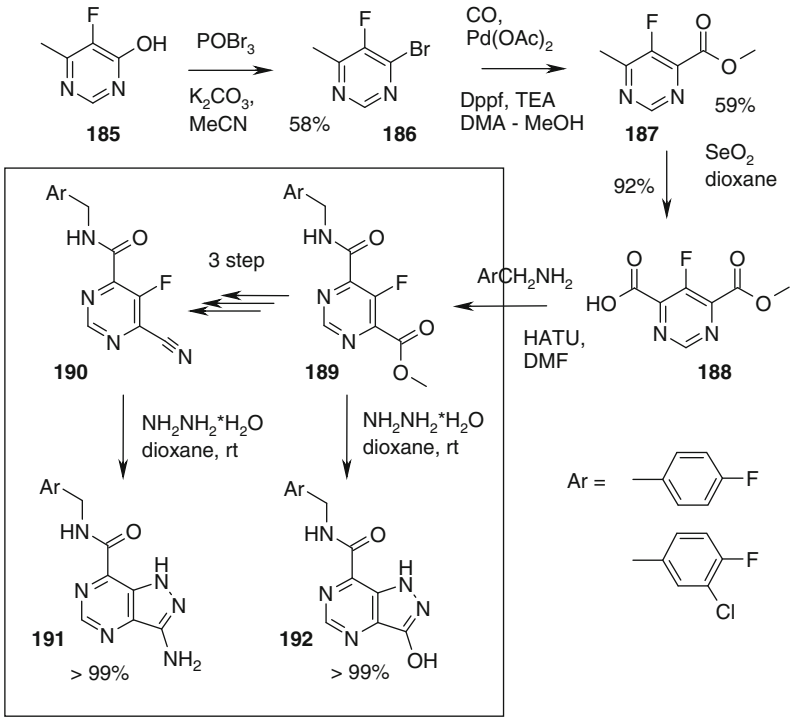
The first example of fluorine substitution in 5-position accomplished by intramolecular cyclization was described by Ukrainian chemist in 1991. The reaction of 4-chloro-5-fluoropyrimidines **181** with carbanions generated from 2-tosylmethylazahetarenes **182** in presence of K_2CO_3 in refluxing DMF does not stop at the step involving replacement of the chlorine atom (intermediate **183**) but concludes by cyclization to give triazafluorene **184** (Scheme 40) [183].



Scheme 40 Reaction of 4,5-dihalopyrimidines with 2-tosylmethylazahetarenes

Further annelation to pyrimidine ring based on substitution of fluorine at 5-position was used in patent literature. Alantos Pharmaceuticals in a course of matrix metalloprotease inhibitors development described an efficient pyrazole annelation to pyrimidine. The synthesis of key intermediate – pyrimidine dicarboxylic acid **188** was accomplished in 3 step bromination – carbonylation – oxidation sequence from pyrimidinone **185**. The acid was converted to the corresponding

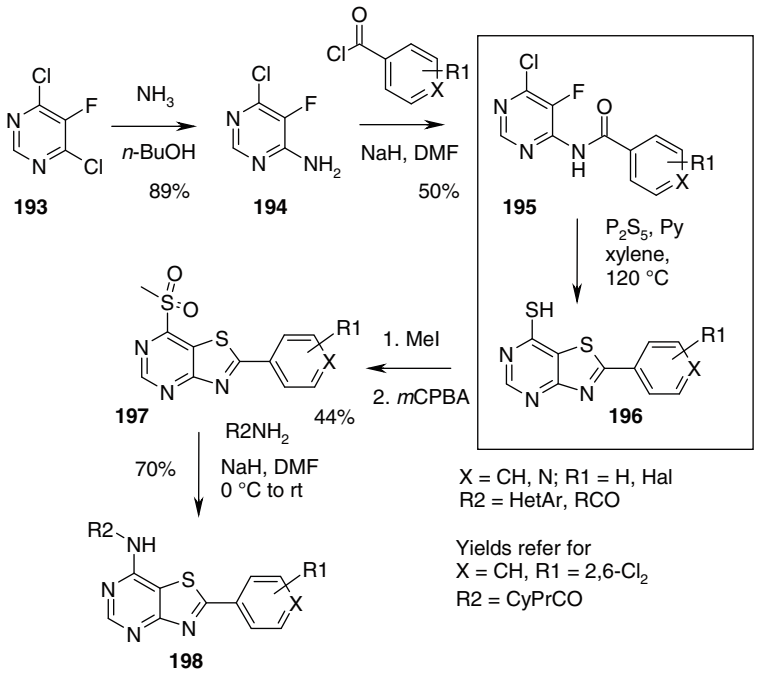
ester **189** and nitrile **190**. In both cases cyclization with hydrazine hydrate proceeds in mild conditions affording pyrazolo[4,3-d]pyrimidines **191** and **192** in nearly quantitative yields (Scheme 41) [184].



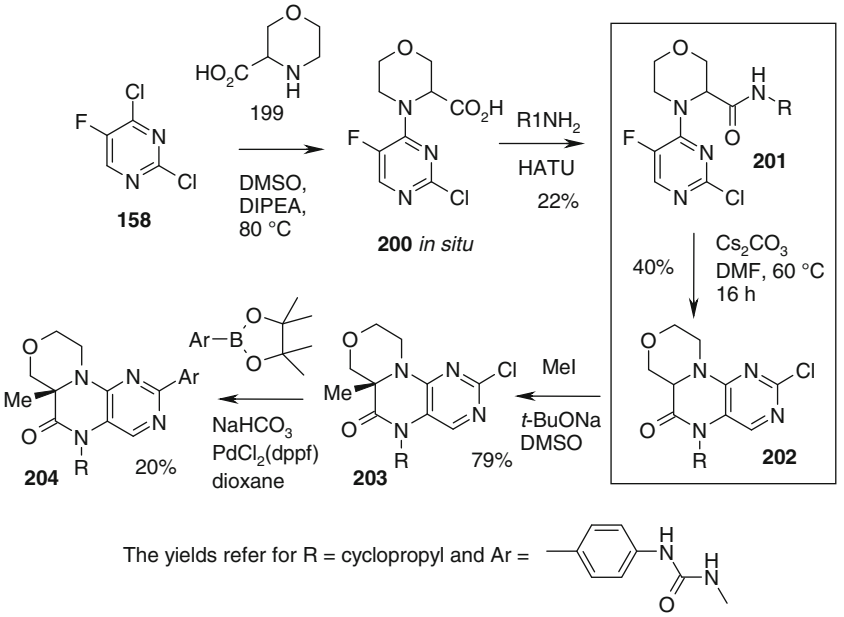
Scheme 41 Synthesis of pyrazolo[4,3-d]pyrimidines based on fluorine substitution

Another example of annelation was demonstrated by Hoffmann-La Roche at the thiazolo[4,5-d]pyrimidine scaffold synthesis and decoration. Under thionation with P_2S_5, the acylated 6-aminopyrimidine **195** gives the corresponding thioamide, which cyclised spontaneously into thiazolo[4,5-d]pyrimidine thione **196**. Thione **196** was used further transformation for synthesis of key building block **197** applied for the preparation of the library **198** (Scheme 42) [185].

The most interesting annelation example was recently described by Takeda during oxa-2,4,4b,10-tetraazaphenanthren-9-one scaffold **204** synthesis. Unlike above mentioned examples, in this case annelation does not proceed with aromatization. In compound **201** fluorine atom is formally deactivated by electron donating dialkylamino residue at 4-position. Despite both this factors the intramolecular fluorine substitution proceed in sufficiently mild conditions (DMF, Cs_2CO_3, 60 °C) affording fused compound **202** in moderate yield (Scheme 43) [186].



Scheme 42 Synthesis of thiazolo[4,5-d]pyrimidines based on fluorine substitution



Scheme 43 Synthesis of oxa-2,4,4b,1°-tetraazaphenanthren-9-ones

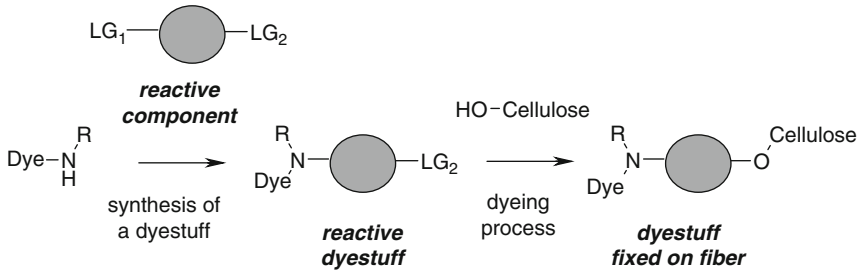


Fig. 15 Functioning of a reactive component in reactive dyes

4.2.3 Reactive Dyes

One of the most important application of fluorine nucleophilic substitution in diazines was found in reactive dyes industry. In a reactive dye a chromophore contains a substituent that is activated and allowed to directly react to the surface of the substrate. Reactive dyes have good fastness properties owing to the bonding that occurs during dyeing. Reactive dyes are most commonly used in dyeing of cellulose like cotton or flax, but also wool is dyeable with reactive dyes.

Detailed reviews of this subject are now available [187–189]. In reactive dyes with halogen as a leaving group, these two partial structures nearly always linked by an amino function in the chromophore, which makes an important contribution to the chromophore conjugated π-electron system. In practical terms, this means that the *reactive component* must have at least two reactive groups, one of them reacts with dye base affording *reactive dyestuff* and another one reacts with cellulosic fiber (Fig. 15).

The development of reactive components based on azines started in 1956 with the launch of chlorotriazine dyes by ICI. The immediate success of the triazine based reactive dyes led to an intensive search for alternative reactive systems by the various dyestuff firms. Much efforts has been expended on the synthesis and evaluation of several related fluoropyrimidinyl derivatives. Out of all the patented components only 5-chloro-2,4,6-trifluoropyrimidine and 5-chloro-2,4-difluoro-6-methylpyrimidine have attained notable technical and economic significants. Figure 16 shows the relevant dyestuffs and their manufacturers.

4.2.4 Acid-Induced Processes

Although ring-fluorinated compounds are only weak bases, nucleophilic substitution can be induced by proton or Lewis acids and interesting contrasts in orientation can sometimes be achieved because attack to *ortho-position* to nitrogen is often preferred under these conditions. Among perfluorinated diazines pyridazine **139** is the most basic and and protonation of ring nitrogen by strong acids or alkylation is

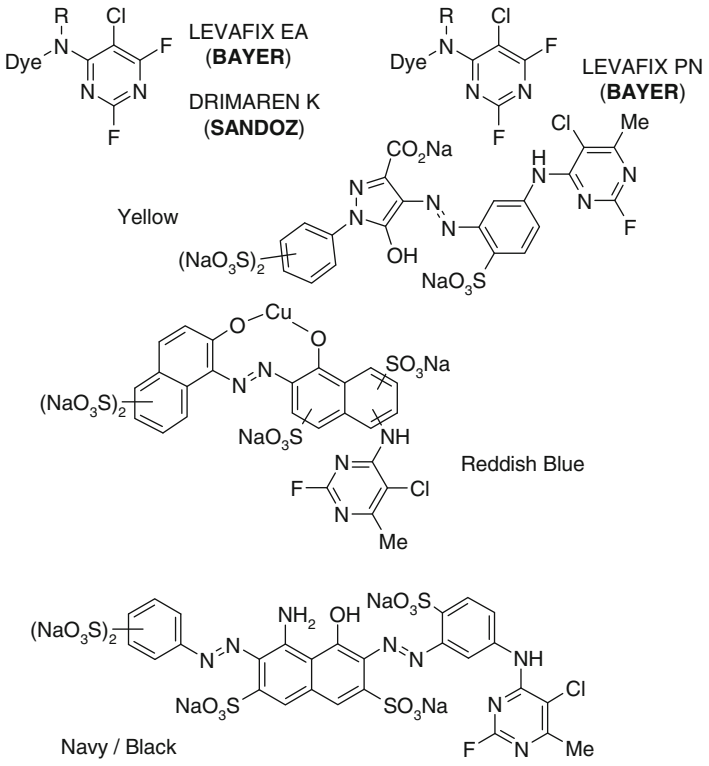
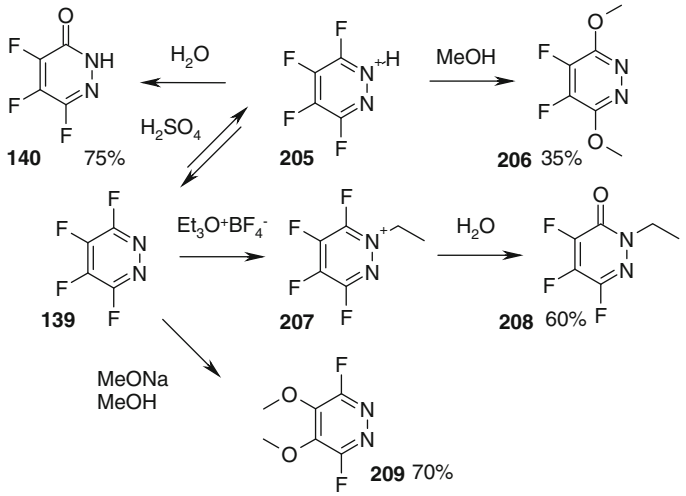


Fig. 16 Industrially significant dyestuff based on fluorinated pyrimidines

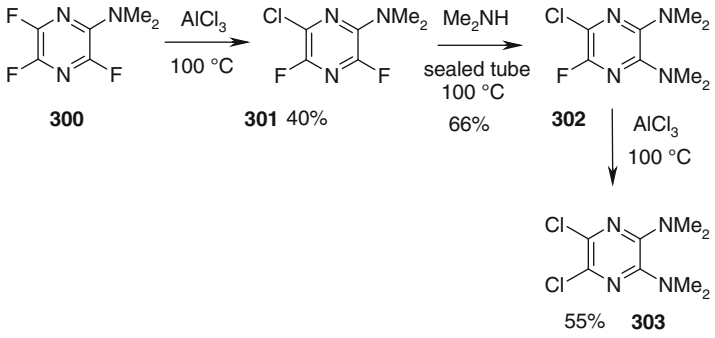
possible if a strong alkylating agent is used. It is clear from the striking tendency for the protonated systems, as shown in Scheme 44, to give *ortho*-attack to nitrogen that, again, polar influences are extremely important in governing the reactivity of a



Scheme 44 Switching of regiochemistry under protonation of tetrafluoropyridazine

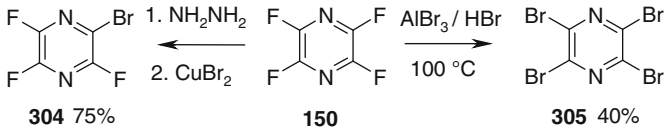
C-F bond, at least with hard nucleophiles. In both of the examples contained in Scheme 44, the orientation of entry of the nucleophile is changed in comparison with reaction with the neutral system [56, 190].

Another important acid-induced process in fluorinated diazine chemistry is fluorine-halogen exchange promoted by Lewis acids. In some cases the switching of regiochemistry also observed. Thus in a case of dimethyl-(3,5,6-trifluoro-pyrazin-2-yl)-amine **300** treatment with $AlCl_3$ leads to exchange of fluorine at 6-th position unlike with Me_2NH substitution (compare with Fig. 14). Subsequently dialkylamino – $AlCl_3$ treatment leads to dichloropyrazine **303**, which unavailable by selective manner from tetrachloropyrazine (Scheme 45) [164].



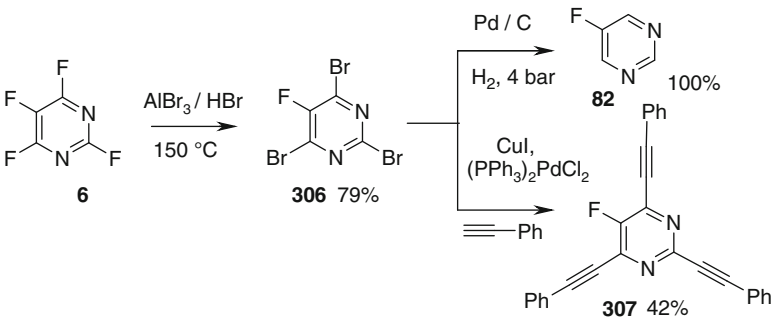
Scheme 45 $AlCl_3$ induced chlorine-fluorine exchange

Like with $AlCl_3$, $AlBr_3$ promote bromine-fluorine exchange. In a case of perfluoropyrazine **150** $AlBr_3$ treatment leads to exhaustive bromination affording perbromopyrazine **305**. For single fluorine exchange to bromine atom another approaches were used (Scheme 46, compare with Scheme 39) [57]

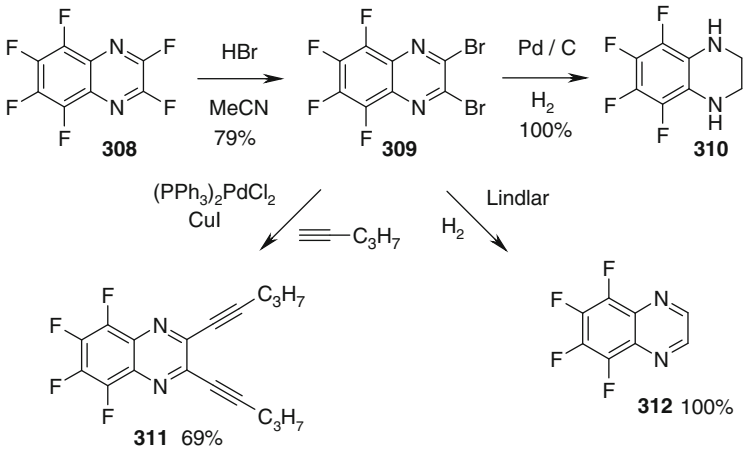


Scheme 46 $AlBr_3$ induced bromine-fluorine exchange

These bromine-fluorine exchanges are important processes because introduction of bromine by these simple procedures allows access to the powerful range of palladium chemistry that is now available (see next section). Also bromine introduction – Pd catalyzed hydrogenation gives an excess to fluorinated nitrogen heterocycles with unusual substitution patterns (Schemes 47 and 48) [191].



Scheme 47 Synthesis of fluorinated heterocycles with unusual substitution patterns



Scheme 48 Synthesis of fluorinated heterocycles with unusual substitution patterns

4.2.5 Fluoride-Ion-Induced Reactions

Reactions of perfluorinated alkenes, such as hexafluoropropene, with fluoride ion give perfluoroalkylcarbanions which can act as nucleophiles in S_NAr reactions with perfluoroheteroaromatic systems (Fig. 17). These reactions are example of "mirror-image" chemistry and reflect well-known Friedel–Crafts reactions of hydrocarbon systems that proceed by reaction of the corresponding electrophile and carbocationic intermediates. Reactions involving chlorotrifluoroethene and bromotrifluoroethene introduce further complexities. Direct substitution may occur giving halofluorosubstituent, but this is frequently accompanied by loss of Cl or Br from the side chain to give a pentafluoroethyl derivative. The almost complete list of the reaction with polifluorinated heterocycles was earlier reviewed by Brooke in 1997 [166].

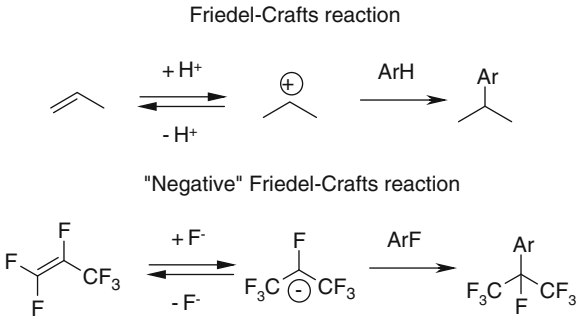
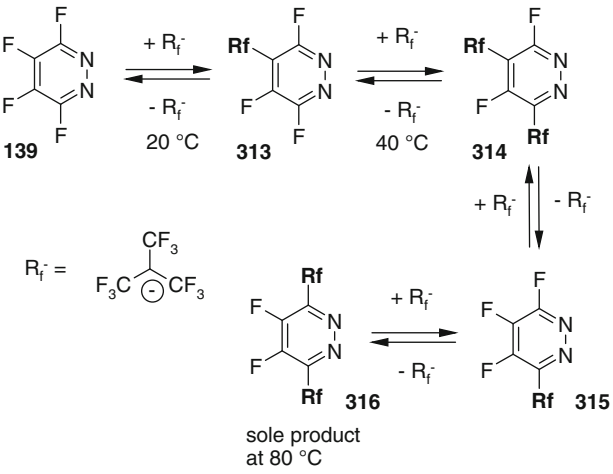


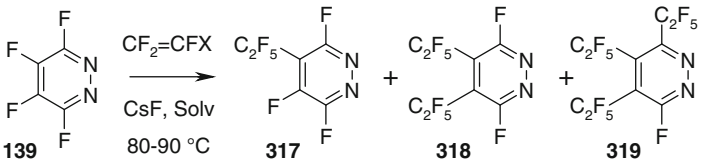
Fig. 17 "Mirror-image" chemistry, negative Friedel–Crafts reactions

As an example, the discovering of kinetic and thermodynamic control in nucleophilic substitution in fluorinated diazines can be shown. The use of MeO^-/MeOH is routinely used to test for possible nucleophilic substitution of fluorine in polyfluoroheteroaromatic compounds and identifies sites for kinetically controlled reactions because of the irreversibility of the reaction. Tetrafluoropyridazine **139** forms only the 4,5-dimethoxy isomer **209** (Scheme 44) whereas the variability in the orientations of dipolyfluoroalkylations of tetrafluoropyridazine and other systems is a manifestation of the interplay between kinetic and thermodynamic control of the reaction products (Scheme 49) [192]. In a case of octafluoroisobutene the reaction with tetrafluoropyridazine **139** in a presence of CsF in sulpholan at 20 °C leads to perfluoro-4-t-butylpyridazine **313**. Heating the reaction mixture to 40 °C showed formation of perfluoro-3,5-di-*t*-butypyridazine **314**, which under heating to 80 °C intermolecular rearrange to the least crowded perfluoro-3,6-di-*t*-butypyridazine **316** through perfluoro-3-*t*-butylpyridazine **315**. Meanwhile, less hindered pentafluoroethyl anion



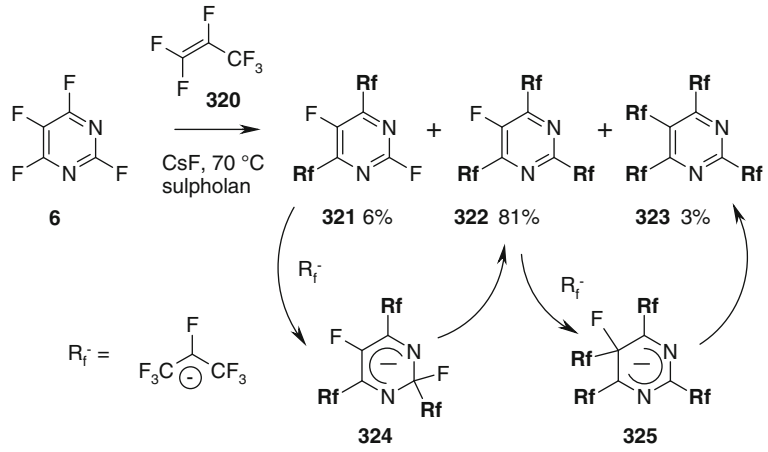
Scheme 49 Kinetic vs thermodynamic control in fluoride-ion-induced reactions

in similar conditions gives the products arise exclusively from kinetic control (Scheme 50) [193, 194]. Hexafluoropropene in this investigation occupies an intermediate position and gives more complicate number of products. Therefore the variation in the observed products is consistent with the ease of formation as well as the steric requirements increasing in the series CF_3-CF_2^- < $(CF_3)_2CF^-$ < $(CF_3)_3C^-$ and these results provide a striking example of the interplay of kinetic and thermodynamic control of reaction products in nucleophilic aromatic substitution.



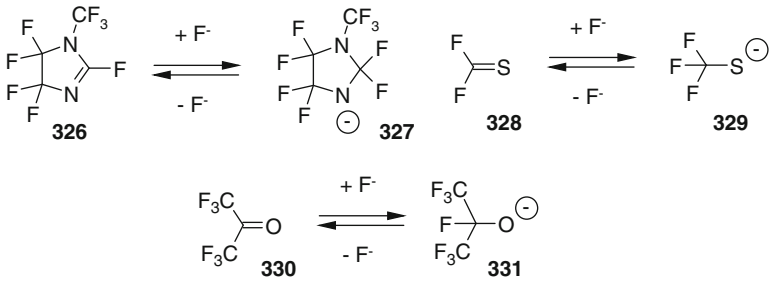
Scheme 50 Fluoride-ion-induced pentafluoroethylation of perfluoropyridazine

Besides tetrafluoropyridazine **139,** tetrafluoropyrimidine **6** was investigated in the fluoride induced reactions. These reactions also have specificity. For example, the reaction of tetrafluoropyrimidine **6** with hexafluoropropene **320** induced by CsF in sulpholan gives mixture of perfluoro-2,4,6-triisopropylpyrimidine **322**, perfluoro-4,6-diisopropylpyrimidine **321** and perfluoro-2,4,5,6-traisopropylpyrimidine **323** were detected (Scheme 51) [195]. This is unusual pattern of nucleophilic attack on tetrafluoropyrimidine where formation of the highly hindered **323** (with displacement of inactivated fluorine in 5-position) occurs when the reaction mixture still contained some of the disubstituted compound **321**, which offers an unhindered fluorine atom at the 2-position. It may be interpreted by formation of possible intermediates **324** and **325** and reversibility of the reaction.



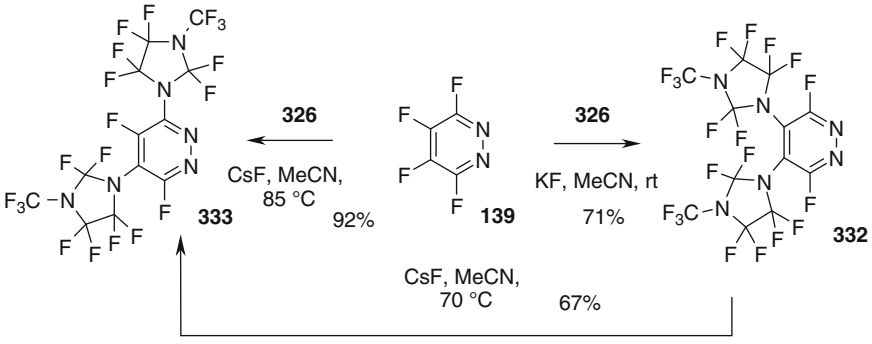
Scheme 51 The reaction of tetrafluoropyrimidine with hexafluropropene induced by CsF

An extension of the idea for generating other anionic nucleophiles by F^- addition to unsaturated precursors has been realised for nitrogen, sulphur and more recently for oxygen (Scheme 52). High reaction ability of tetrafluoropyridazine and tetrafluoropyrimidine towards nucleophiles made it useful in "trapping experiments" for anions **327**, **329** and **331** [196–199].

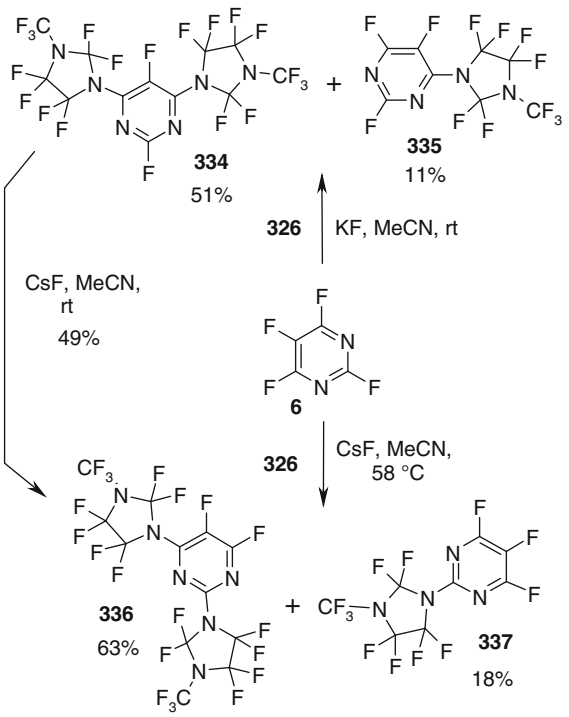


Scheme 52 An extension of fluorine-induced approach to N-, S- and O-nucleophiles

Moreover investigation of nitrogen anion **327** leads to another fundamental result. It was found, that **327** generated by KF at room temperature gives kinetically controlled products **332** whereas **327** generated by CsF at higher temperatures produced thermodynamically controlled products **333**, which was confirmed by experiments in pyridazine series (Scheme 53). Applying the experiment to tetrafluoropyrimidine leads to discovery of kinetic and thermodynamic control under nucleophilic substitution in pyrimidine (Scheme 54) [196].



Scheme 53 Kinetic vs thermodynamic control in fluoride-ion-induced reactions



Scheme 54 Kinetic vs thermodynamic control in fluoride-ion-induced reactions

4.3 Metalation Reaction

Moving from benzene via azines to the diazines, a decrease of aromaticity can be observed, this being attributed to the weaker overlap of the p orbitals in the rings. In consequence, the acidity of hydrogens is increased in the same order. A selection of calculated pKa values of nitrogen-containing heterocycles of interest is given in Fig. 18 [200]. Introducing into heterocycle of inductively electron-withdrawing fluorine atom increase the thermodynamic acidity of the heteroaromatic hydrogen atoms. These hydrogen atoms can be abstracted by strong bases leading to metalated compounds. The metal atom – usually lithium – is also stabilized by favorable electrostatic and electron-donating interactions with the lone electron pairs of fluorine. The observed *ortho* selectivity of the metalation of suitably substituted heteroaromatic compounds is, therefore, usually kinetically induced. Fluorine is highly effective as a strongly *ortho*-directing, acidity-enhancing substituent. Whereas many aryl lithium species are stable up to room temperature and above, *ortho*-fluoro lithio hetarenes are stable at low temperatures only [201, 202]. Based of this general consideration we can conclude that ring fluorinated diazines bearing *ortho-unsubstituted* position are good objects for direct ortho-methalation (DoM) reaction.

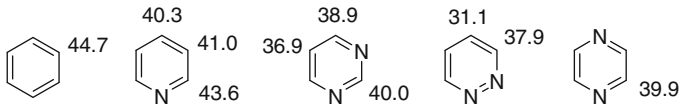
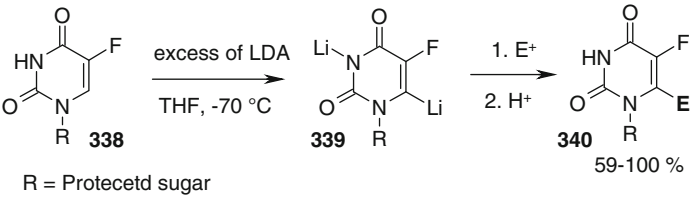


Fig. 18 Calculated pKa values of various N-heterocycles

4.3.1 Fluoropyrimidines

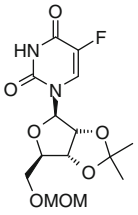
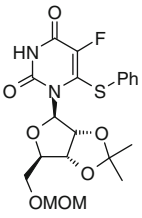
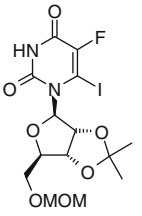
First lithiated fluorodiazines were described in early 1980 by Tanaka. These derivatives were prepared by deprotonation of fluorouracils with excess of LDA. The reaction proceeds though dilithiated species of type **339**, which after reaction with an electrophile and subsequent acidic treatment gave substituted uracils **340** in high yields (Scheme 55). The approach was used in synthesis of antileukemic nucleosides [204] and anti HIV agents [204–206]. (Table 12)

Recently this transformation was applied for synthesis of orotidine-5′-monophosphate decarboxylase inhibitors [207]. Unexpected results was obtained during the methylation



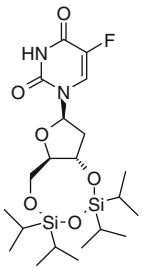
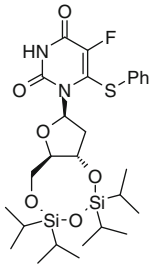
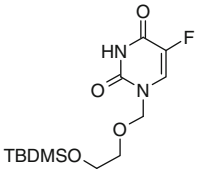
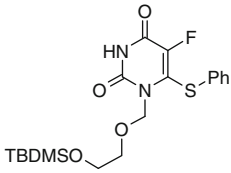
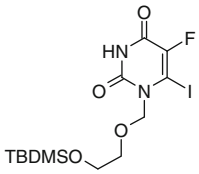
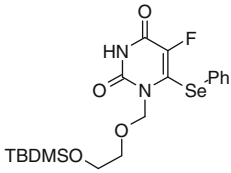
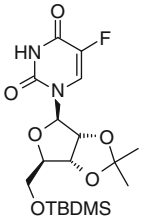
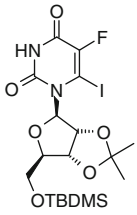
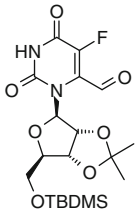
Scheme 55 DoM reaction of fluorouracile derivatives

Table 12 DoM reaction of fluorouracile derivatives

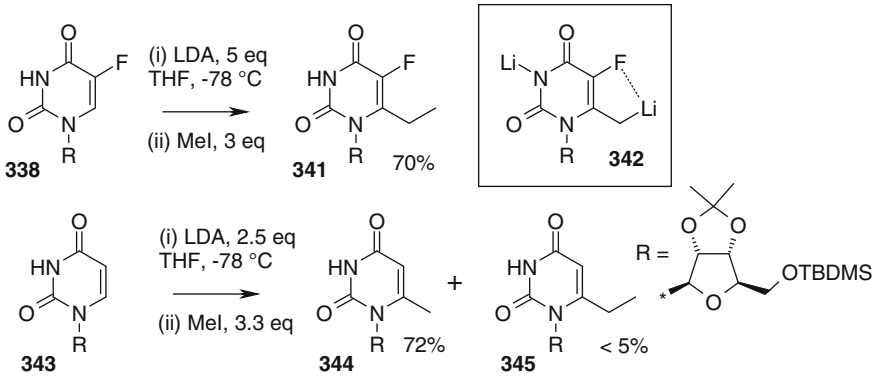
#	Substrate	Conditions	Product	Yield (%)	Ref.
1		i. LDA 2.5 eq., THF, −70 °C, 1 h ii. PhS-SPh		100	[203]
2	-//-	i. LDA 2.5 eq., THF, −70 °C, 1 h ii. I_2		92	[203]

(continued)

Table 12 (continued)

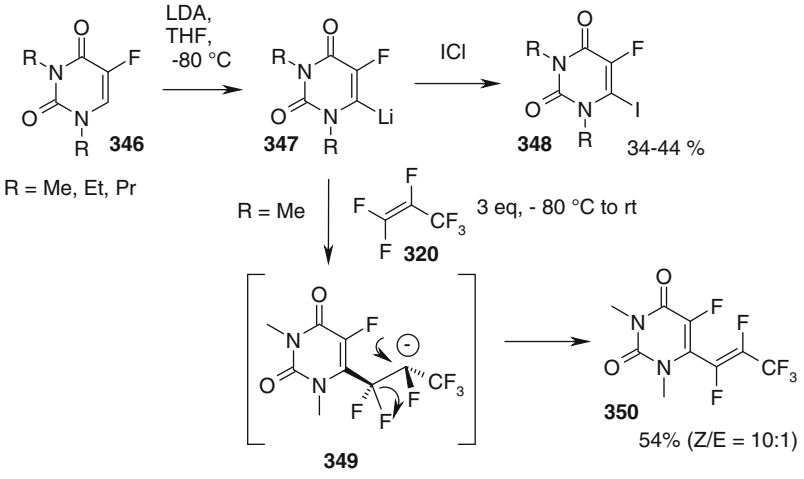
#	Substrate	Conditions	Product	Yield (%)	Ref.
3		i. LDA 5 eq., THF, −78 °C, 1 h ii. PhS-SPh		59	[204]
4		i. LDA 2.5 eq., THF, −70 °C, 1 h ii. PhS-SPh		81	[205]
5	-//-	i. LDA 2.5 eq., THF, −70 °C, 1 h ii. I_2		79	[205]
6	-//-	i. LDA 2.5 eq., THF, −70 °C, 1 h ii. PhSe-SePh		85	[206]
7		i. LDA 3 eq., THF, −70 °C, 1 h ii. I_2		95	[207]
8	-//-	i. LDA 5 eq., THF, −70 °C, 1 h ii. HCO_2Me 1.5 eq.		70	[207]

of lithium species by MeI. Earlier Tanaka has observed that lithiation of uridines at C-6 followed by methylation can be accompanied with undesired α-methylation of the newly attached substituent [208]. Bello et al. in 2009 [207] turned the fact to good account and smoothly ethylated substrate **341** *via* a two-stage methylation. In absence of fluorine, the second methylation is a bit more tricky and under similar conditions (2.5 equiv. LDA, followed by 3.3 equiv. MeI at −78 °C) a mixture of 6-methyluridine **344** (44 %) and 6-ethyluridine **345** (<5 %) was isolated (Scheme 56) [209]. Therefore, assistance of the neighboring fluorine (**342**) facilitates alkylation.



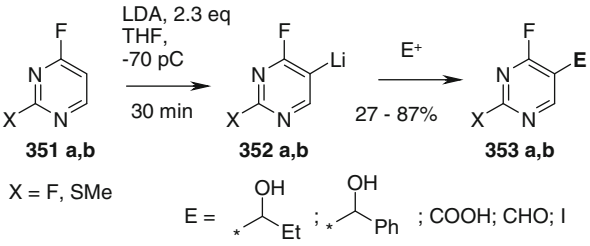
Scheme 56 Double alkylation of C-6 lithiated uridines

In 1990 Tanaka obtained lithiated 1,3-dialkyl-5-fluorouracils **347** [210], which were iodinated with ICl to afford **348**. Later lithiated 1,3-dimethyl-5-fluorouracils **347** were reacted with hexafluoropropene **320** [211] to form intermediate carbanion **349** giving after fluoride elimination vinylated products **350** as a mixture of E and Z isomers (Scheme 57).



Scheme 57 Reactions of 6-lithio-1,3-dialkyl-5-fluorouracils

4-Fluoropyrimidines **351a,b** were also metallated with LDA affording the functionalized compounds **353a,b** in moderate to good yields (Scheme 58) [212]. When LTMP was used as a metalating agent under the same conditions a loss of regioselectivity in the *ortho*-position of the fluorine atom is observed. Besides compounds **352a,b** 7–8 % of metalation at the C-6 position were observed.



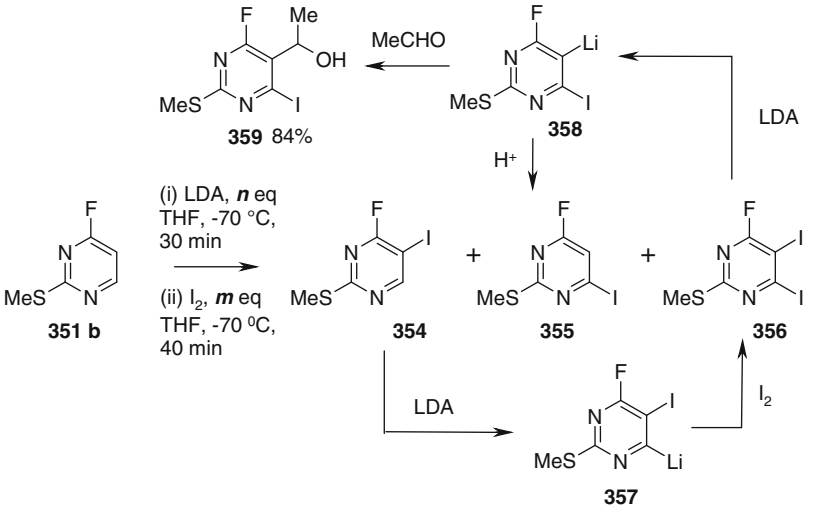
Scheme 58 Lithiation of 4-fluoropyrimidines

When iodine was used as an electrophile the results were quite dependent on the experimental conditions (amounts of metalating agents and iodine) (Scheme 59, Table 13). Metalation of **351b** with 1.1 eq. of LDA followed by reaction with iodine in excess led to the C(5) iodo derivative **354** (Table 13, Entry 1). The diiododerivative **356** was the major product when the metalating agent and iodine were in excess (entry 2). It can be assumed that the reaction of **351b** with 1.1 eq. of LDA led to the C(5) lithioderivative which reacted with iodine affording compound **354**. In a presence of an excess of metalating agent, compound **354** underwent a further lithiation at the C(6) position and after the reaction with another equivalent of iodine afforded the diiodo derivative **356**. The unexpected C(6) iodo derivative **355** was observed when LDA was in excess (2.3 eq.) and when iodine was in stochiometric amounts (entry 3). Such as unusual regioselectivity can be explained by formation of diiodo derivative **356**, which underwent halogen-lithium exchange affording C(5) lithium derivative **358**, which gave after hydrolysis the C(6) monoiodo derivative **355**. The formation of the C(5) lithio derivative **358** from the reaction of **356** with LDA was proved by trapping of the lithio derivative with acetic aldehyde affording **359** in 84 % yield.

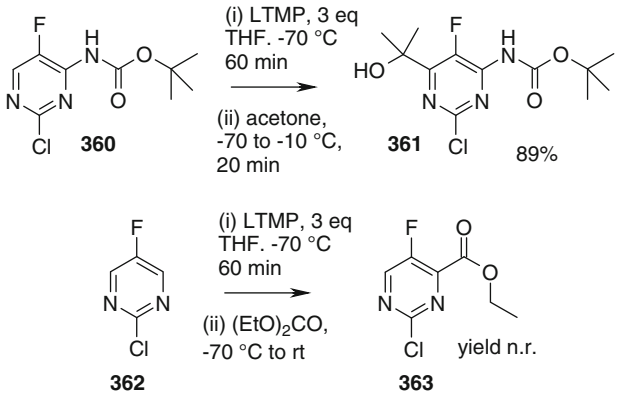
Boc-protected aminofluoropyrimidine **360** was subjected to lithiation with LTMP followed by acetone addition to form **361** in 89 % yield. It was used in synthesis of as gaba-A alpha 2/3 ligands for depression [213]. The ethyl ester **363** was synthesized by similar way by lithiation of pyrimidine **362** [182] (Scheme 60).

Table 13 Lithiation/iodination of 4-fluoropyrimidine **351**

#	n	m	**354**	**355**	**356**
1	1.2	3	87 %	–	6 %
2	2.3	3	10 %	–	70 %
3	2.3	1	–	77 %	3 %



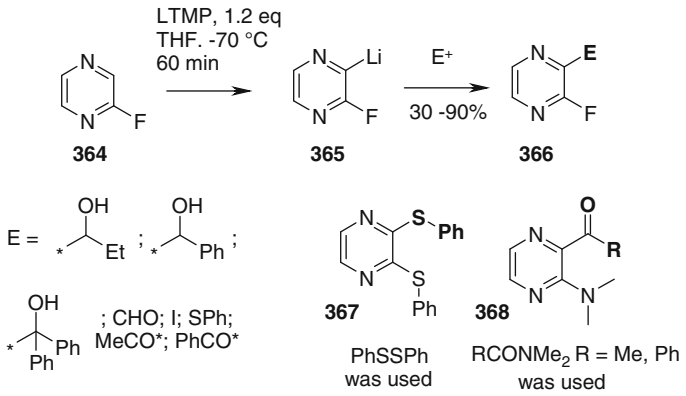
Scheme 59 Lithiation/iodinationof 4-fluoropyrimidines



Scheme 60 C(6) lithiation of 5-fluoropyrimidines

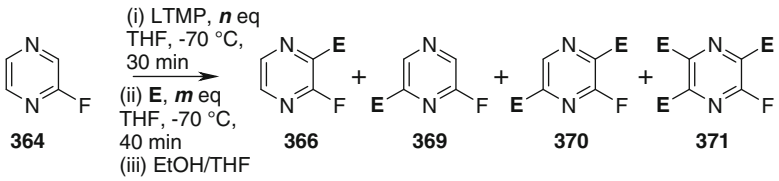
4.3.2 Fluoropyrazines

Metalation of fluoropyrazine **364** has been achieved in 1998 by Queguiner with LTMP as metalating agent at −75 °C with a short reaction time (5 min) leading to a wide range of 2,3-disubstituted fluoropyrazines **366**. Pyrazine derivatives are well known to be good electrophiles, when they are substituted by a good leaving group such as fluorine, a further nucleophilic substitution is observed by the released species coming from the electrophile used during the trapping step. For example, during functionalization of fluoropyrazine, formation of 2,3-diphenylthiopyrazine **367** (89 % yield) and the 2-acetyl and 2-benzoyl-3-dimethylamino pyrazines **368** have been observed besides the expected disubstituted fluoropyrazines when diphenylsulfide or N,N-dimethylacetamide or N,N-dimethylbenzamide have been used as electrophiles (Scheme 61) [214].



Scheme 61 Lithiation of 2-fluoropyrazine

Starting from fluoropyrazine, a regioselective synthesis of iodo- and tributylstannyl substituted fluoropyrazines has been elaborated. Lithiation of fluoropyrazine with stoichiometric amounts of LTMP and iodine afforded the 2-fluoro-3-iodopyrazine **366** (E=I) as sole product otherwise a mixture of mono-, di-, and triiodo derivatives were formed (Scheme 62, Table 14) [147]. In a similar manner, use of tributyltin chloride as electrophile led to mono and di-stannylpyrazines [215]. Formation of compounds **369**, **370** and **371** is a result of metalation at the position adjacent to the nitrogen atom without assistance of the fluorine atom as DMG. Such a metalation without a DMG has been previously reported during direct metalation of bare pyrazine by use of an excess of LTMP (4 equiv.) with very short reaction time (5 min) at low temperature −78 °C [216].

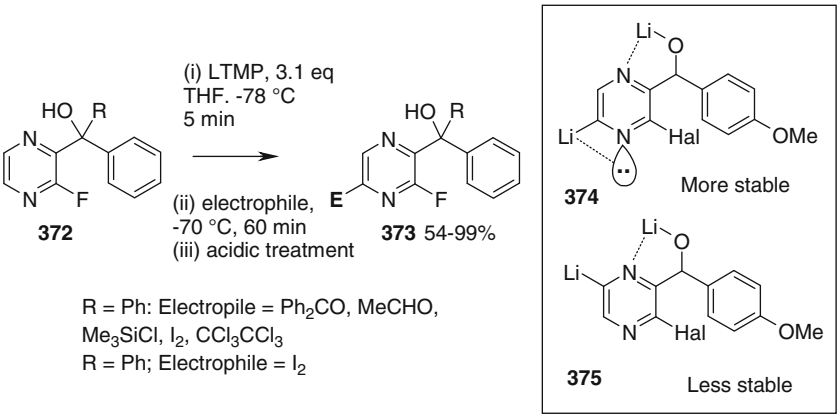


Scheme 62 Lithiation of 5-fluoropyrazine

Table 14 Lithiation of 2-fluoropyrazine

#	E	n	m	T (°C)	**366**	**369**	**370**	**371**
1	I	1.1	1.1	−78	50	–	6	4
2	I	2.0	2.0	−78	11	–	35	15
3	I	4.0	4.0	−78	–	–	–	65
4	Bu_3SnCl	1.1	1.5	−78	11	26	–	–
5	Bu_3SnCl	1.1	1.5	−100	54	–	–	–
6	Bu_3SnCl	2.0	1.5	−100	15	10	52	–
7	Bu_3SnCl	4.0	1.5	−100	–	20	–	53

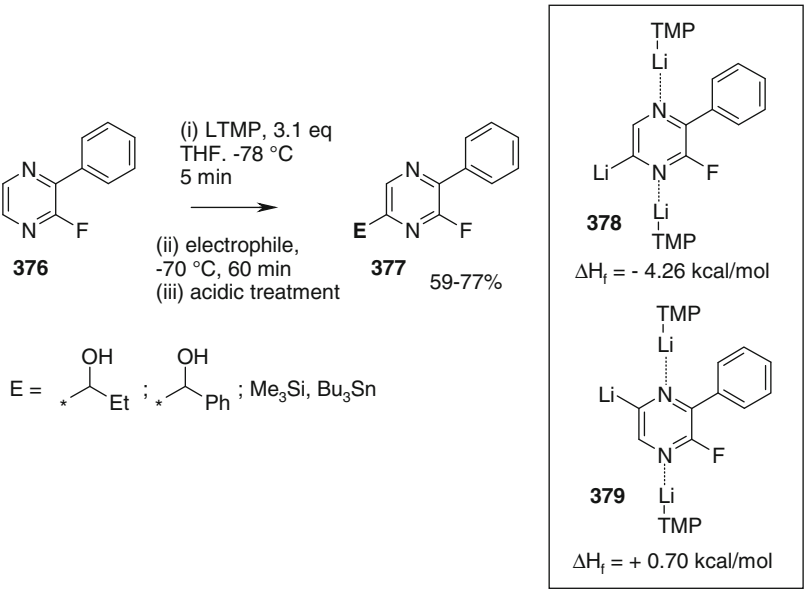
Lithiation of 2-fluoro-1-hydroxymethylpyrazines **372** with LTMP (3 equiv.) in THF at −78 °C occurred at the C(6) position (Scheme 63). With iodine as the electrophile, the 6-iodo derivative has been obtained. This iodide was used in Negishi and Suzuki cross couplings to access a natural products analogues and liquid crystals [147, 217]. When alkylamides such as LTMP are used as metalating agent, the deprotonation is considered as thermodynamically controlled. The heats of formation of the lithio compound could be examined as a simple approach to estimate the regioselectivity. Considering that the hydrogen of the hydroxyl group is first abstracted by LTMP, a lithium atom could form a chelate between the oxygen of the alcoholate and the neighboring nitrogen. The lithium at the C(6) position may coordinate with the adjacent free nitrogen N(1) whereas such coordination cannot be observed when the lithium is at the C(5) position since the nitrogen N(4) is already chelated. This assumption is in agreement with the calculation of heats of formation of two lithio derivatives (Hal=Cl) by Li/PM3. C(6)-lithioderivative **374** is more stable than **375** with a difference of $\Delta(\Delta H_f) = 6.8$ kcal/mol [217].



Scheme 63 Lithiation of 2-fluoro-3-hydroxymethylpyrazines

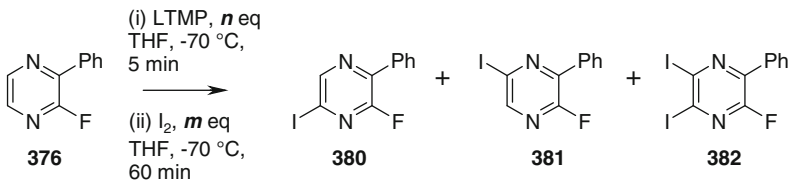
A regioselective functionalization at the C(6) position has also been achieved when the 2-fluoro-3-phenylpyrazine **376** reacted with an excess of LTMP (3 equiv.) followed by reaction with various electrophiles leading to compounds **377** (Scheme 64) [147]. To explain this regioselectivity which occurs exclusively at the C(6) position, theoretical calculations using Li/PM3 semiempirical method have been performed [147]. A complexation between the lithium of LTMP and the two nitrogen atoms of the pyrazine moiety, which behaves as a complexing agent, has been taken into account (Scheme 64). The values calculated indicated that the C(6)-lithio derivative **378** is clearly more stable than the 5 one **379**. This result could explain the complete regioselectivity at C(6) position.

However, when compound **376** was reacted with 3 eq. of LTMP at −78 °C for 5 min followed by reaction with 1 eq. of iodine, a C(5) monoiodo derivative **381** was formed in 64 % yield beside traces of diiododerivative **382**. In this case, as in a case of 5-fluoropyrimidine (Scheme 59), the lithiation of **376** followed by reaction with iodine as an



Scheme 64 Lithiation of 2-fluoro-3-phenylpyrazine

electrophile was investigated under various experimental conditions (Scheme 65, Table 15) [147]. In the reaction with 1.1 eq. of LTMP and excess of iodine the C(6) derivative was obtained in good yield (entry 1). An excess of LTPM and of iodine leads to diiodo derivative **382** (entries 3,5). When the metallating agent was in excess in relation to iodine the C(5) iodo derivative **381** was obtained as a sole product (entries 2,4 and 6). These results are in agreement with results obtained in pyrimidine series (see Scheme 59) and could be assumed by the similar way. The reaction of **376** with 1–4 eq.



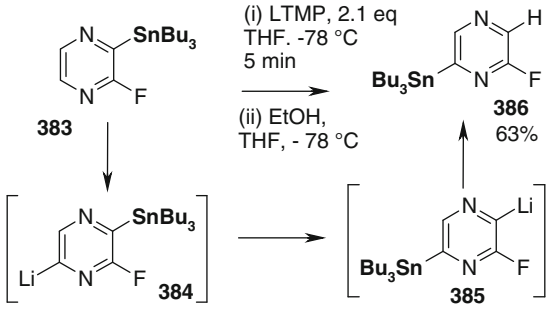
Scheme 65 Lithiation/iodinationof 2-fluoro-3-phenylpyrazine

Table 15 Lithiation / iodination of 2-fluoro-3-phenylpyrazine

#	n	m	**380**	**380**	**382**
1	1.1	2.0	73	–	–
2	2.1	1.0	–	59	–
3	2.1	2.0	–	–	80
4	3.1	1.0	–	64	–
5	3.1	3	–	–	68
6	4.1	1.0	–	57	–

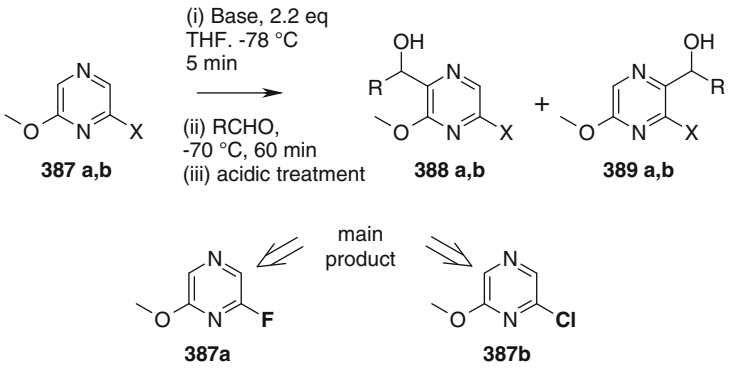
of LTMP led first to C(6)-lithio derivative which reacted with iodine to give C(6) iodo derivative. This compound underwent a further isomerisation involving iodine atom migration leading to C(5) iodo derivative **381**. Such isomerisation resulting from a halogen migration is known as a "halogen-dance" reaction.

Besides iodine migration in fluoropyrazine serie the migration of the tributylstannyl group is known. When metalation of 2-fluro-3-tributylstannylpyrazine **383** was performed with 2.1 equiv. of LTMP with a short reaction time and was followed by protonation of the lithio derivative, compound **386**, resulting from intramolecular tin/lithium exchange, was isolated in 63 % yield (Scheme 66) [215].



Scheme 66 The migration of the tributylstannyl group in pyrazine

To establish a comparison between the ortho directing power of fluoro, chloro, and methoxy groups, the lithiation of 2-halo-6-methoxypyrazines **387a,b** has been investigated using various alkylamides as metalating agent at −78 °C with a short reaction time (5 min) (Scheme 67, Table 16) [218]. The main isomer has the substituent at the ortho position relative to the fluorine atom as in **387a**, contrary to what is observed with the chlorine atom as in **387b**. When LDA is used as metalating agent, the metalation is more regioselective than with more bulky bases such as LTMP or LB (lithium tertbutyl-(1-isopropylpentyl)amide). These results allowed to estimate the relative ortho directing power as F > OMe > Cl.



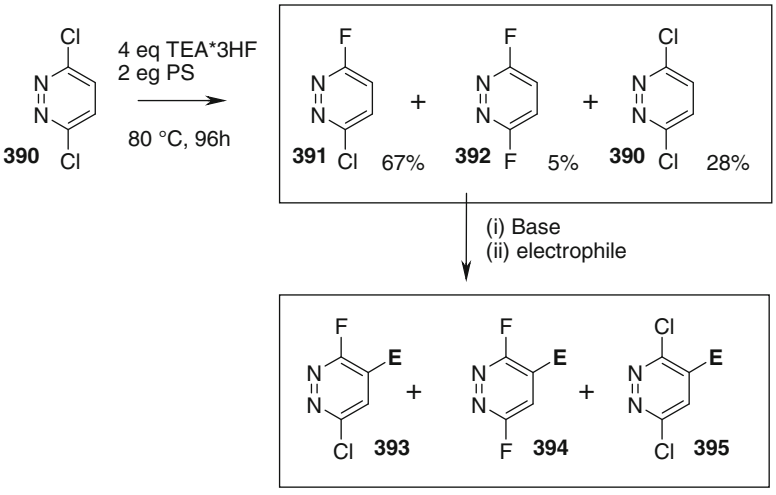
Scheme 67 Lithiation of 2-halo-6-methoxypyrazines

Table 16 Lithiation of 2-halo-6-methoxypyrazines

Entry	X	R	Base	Yield (%)	**388:389**
1	F	Me	LDA	72	4:96
2	F	Me	LTMP	78	12:88
3	F	Me	LB	71	12:88
4	F	C_5H_{11}	LDA	74	4:96
5	F	C_5H_{11}	LTMP	65	14:86
6	F	C_5H_{11}	LB	8°	14:86
7	Cl	Me	LDA	91	88:12
8	Cl	Me	LTMP	80	68:32
9	Cl	Me	LB	71	62:38
10	Cl	C_5H_{11}	LDA	74	88:12
11	Cl	C_5H_{11}	LTMP	82	67:33
12	Cl	C_5H_{11}	LB	79	61:39

4.3.3 Fluoropyridazines

To the best of our knowledge only one paper deals with metalation of ring fluorinated pyridazines [218]. In order to compare directly the *ortho* directing power of two halogens Quenguiner et al. in 2003 tried to synthesise 3-chloro-6-fluoro-pyridazine by nucleophilic fluorination of 3,6-dichloropyridazine. However the reaction of 3,6-dichloropyridazine **390** with TEA*3 HF in a presence of proton sponge gave a mixture of products. The monofluoro compound **391** was the main product beside 28 % of starting material and a small amount (5 %) of difluoro derivative **392** (Scheme 68). Subsequent metalation of this mixture was performed with three electrophiles (Table 17). The proportions of the functionalized products **393–393** were constant with the electrophiles, the metalating agent and the time and reflected the proportion of the starting material; this showed a similar behavior of the three compounds (393–395) with regard to the metalation reaction. The most important result was



Scheme 68 Lithiation of mixture of pyridazines

Table 17 Lithiation of 2-fluoropyrazine

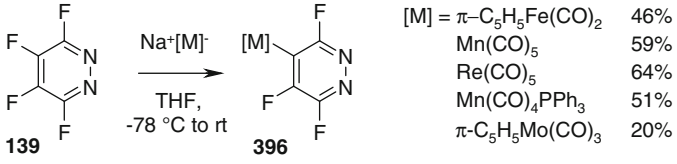
Entry	Base	Time, min	E-phile	Yield (%)	Product **393+394** (%)[a]	Product **395** (%)[b]
1	LDA	5	MeCHO	46	77	23
2	LTMP	5	MeCHO	44	72	28
3	LTMP	2°	MeCHO	48	74	26
4	LTMP	9°	MeCHO	63	77	23
5	LTMP	9°	PhCHO	55	72	28
6	LTMP	9°	I_2	37	77	23

[a]The amount of difluorocompounds 394 was too low to be quantified
[b]% determined by NMR

that the metalation of **391** was regioselective in *ortho* position relative to the fluorine atom, leading to the conclusion that the fluorine atom was a much better *ortho*-directing group than the chlorine.

4.4 Organometallic Compounds and Transition Metals Catalyzed Process

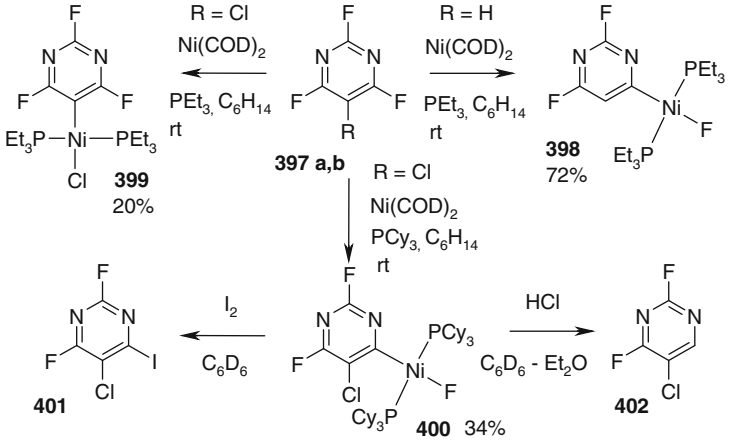
The most obvious feature of the chemistry of highly fluorinated aromatic compounds which can be exploited is their susceptibility to nucleophilic attack. Therefore, reactions with anionic species containing metals can be useful and the most significant examples of this type involve transition-metal carbonyl anions. Francis Gordon Albert Stone in 1968 described the reaction of carbonyl metal anions derived from Fe, Mn, Re and Mo with tetrafluoropyridazine leading to organometallic complexes wherein 4-trifluropyridazine group is σ-ligand to transition metals (Scheme 69) [219]. Compound **396** with [M] = π-$C_5H_5Mo(CO)_3$ was one of the first molibdenium complex obtained by nucleophilic displacement with [π-$C_5H_5Mo(CO)_3$]$^-$, and their isolation further illustrates the reactivity of perfluoropyridazine, since the anion is a relatively weak nucleophile tolerated towards hexafluorobenzene and pentafluoropyridine.



Scheme 69 Reaction of tetrafluoropyridazine with transition-metal carbonyl anions

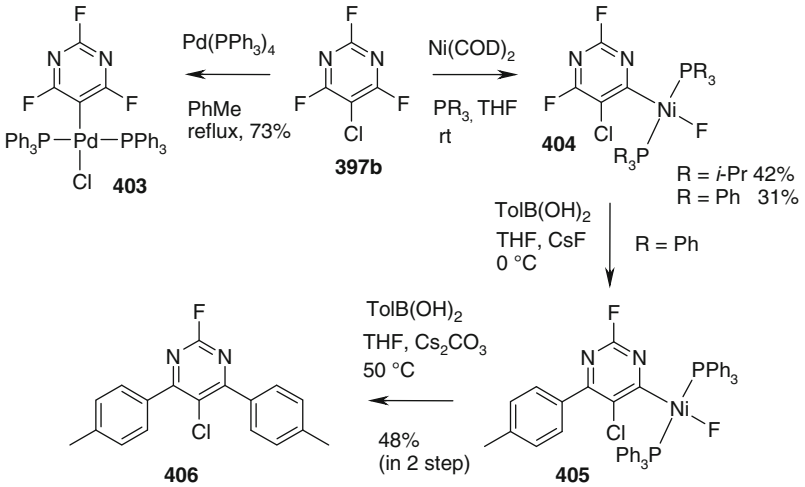
But due to the extraordinary strength of the carbon–fluorine bond, transition metal-mediated activation of fluoroalkanes and arenes is not easy to achieve. Nevertheless, Braun disclosed in 1999 activation of the C–F bond in highly electron-deficient compounds such as 2,4,6-trifluoropyrimidine **397a** (R=H), with stoichiometric amounts of bis(triethylphosphano) nickel(0) giving activated complex **398** (Scheme 70) [220]. Later it was found that the transition from 2,4,6-trifluoropyrimidine to 5-chloro-2,4,6-trifluoropyrimidine **397b** (R=Cl) in similar conditions ($Ni(COD)_2$, PEt_3) leads to C-Cl

activation. But using PCy_3 instead of PEt_3 exclusive activation of the C–F bond takes place affording *trans*-[NiF(4-$C_4N_2ClF_2$)(PCy_3)$_2$] **400**. The treatment of the complex **400** by HCl led to 5-chloro-2,4-difluoropyrimidine **402** meanwhile reaction with iodine gives 5-chloro-2,6-difluoro-4-iodopyrimidine **401** (Scheme 70) [221].

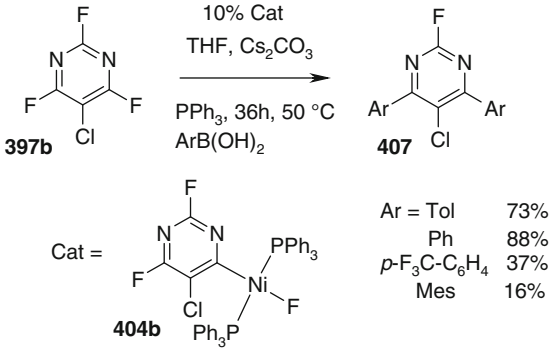


Scheme 70 Nickel mediated activation of the aromatic carbon–fluorine bond and subsequent reactions

In 2005 the same scientist showed that treatment of $Ni(COD)_2$ with 5-chloro-2,4,6-trifluoropyrimidine **397b** in presence of P*i*-Pr_3 or PPh_3 effects the formation of the fluoro complexes *trans*-[NiF(4-$C_4N_2ClF_2$)(PR_3)$_2$] **404**. In contrast, a reaction of **397b** with $Pd(PPh_3)_4$ leads to the insertion of a {$Pd(PPh_3)_2$} unit into the C-Cl bond yielding *trans*-[PdCl(5-$C_4N_2F_3$)(PPh3)$_2$] **403**. Treatment of **404** with an excess of $TolB(OH)_2$ results in the slow formation of *trans*-[NiF(4-C_4N_2TolClF)(PPh_3)$_2$] **405** and subsequently 5-chloro-2-fluoro-4,6-ditolylpyrimidine **406** (Scheme 71) [222].



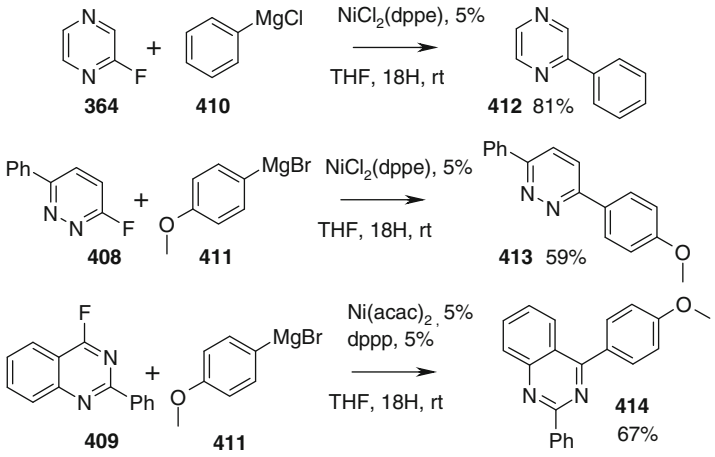
Scheme 71 Activation of 5-Chloro-2,4,6-trifluoropyrimidine at Palladium and Nickel



Scheme 72 Catalytic cross-coupling reactions of 5-Chloro-2,4,6-trifluoropyrimidine

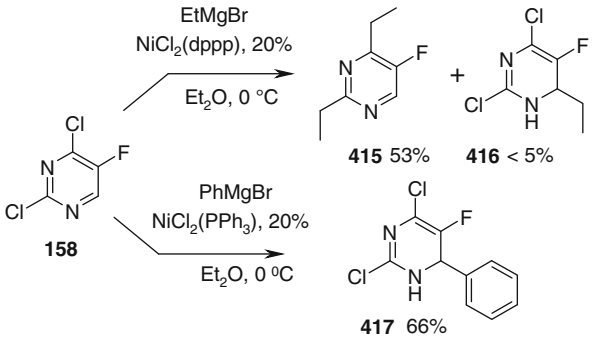
In catalytic experiments **397b** is converted with the set of boronic acids into **407** when 10 % of **404b** is employed as catalyst (Scheme 72) [222].

Meanwhile Queguiner with co-workers in 2002 disclosed Kharasch cross-coupling reactions of phenylmagnesium halides with fluorodiazines. The nickel-catalyzed cross-coupling reactions between aryl Grignard reagents and fluorodiazines **364**, **408** and **409** occurred in THF at rt using commercially available 1,2-bis(diphenylphosphino) ethane, 1,3-bis(diphenylphosphino)propane, or 1,1′-bis(diphenylphosphino)ferrocene as ligands (Scheme 73) [223].



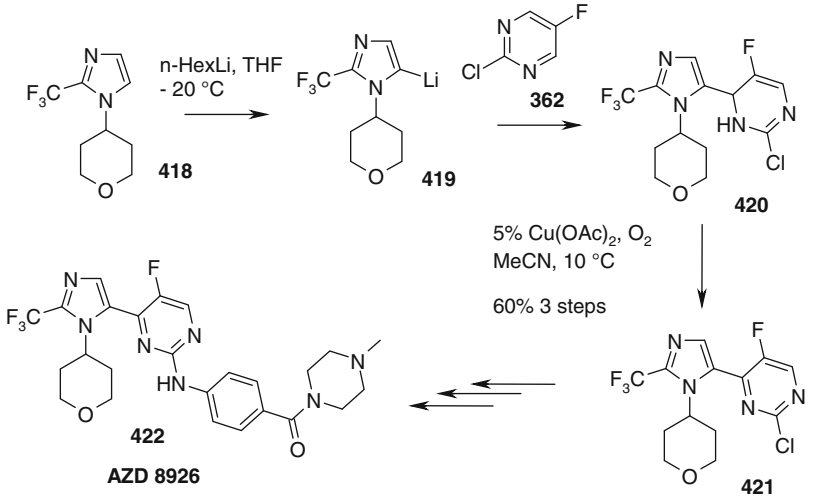
Scheme 73 Nickel mediated cross-coupling of Grignard reagents with Fluorodiazines

Earlier in 1983 Norwegian chemists tried to applied the similar cross-coupling conditions to 2,4-dichloro-5-fluoropyrimidine **158**. In a case of EtMgBr the diethylated product **415** formed in 53 % yield with small amount of C(6) addition product **416** [224]. But when PhMgBr was used the dihydropyrimidine **417** formed as a sole product (Scheme 74) [225].



Scheme 74 Reactions of Grignard reagents with 2,4-dichloro-5-fluoropyrimidine

Recently such type of transformation was used for the scalable process to the GSK3β Inhibitor AZD8926 **422** (Scheme 75). The process include a lithiation of 1-(pyran-4-yl)-2-trifluoromethyl-imidazole **418**, a Ziegler-type coupling of lithiated **419** with commercially available 2-chloro-5-fluoropyrimidine **362** *via* 1,2-addition over the 3,4-C–N bond and a copper-catalyzed dehydrogenative aromatization



Scheme 75 Scalable process to the GSK3β inhibitor AZD8926

using oxygen as the stoichiometric oxidant giving imidazopyrimidine **421** in 60 % total yield [226].

Although aryl fluorides are very unreactive toward oxidative addition of palladium, whether the electron-deficient pyrimidine ring coupled with the strong electron-withdrawing effect of fluorine would allow 2,4,6-trifluoropyrimidine to function as a suitable partner in a Suzuki coupling process. Unfortunately, when 2,4,6-trifluoropyrimidine was treated in a manner similar to the other halogenated

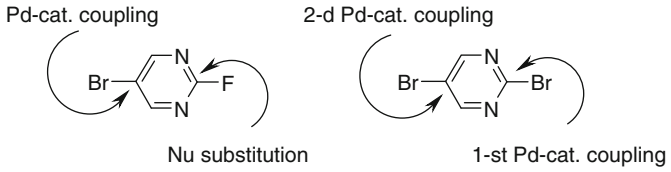
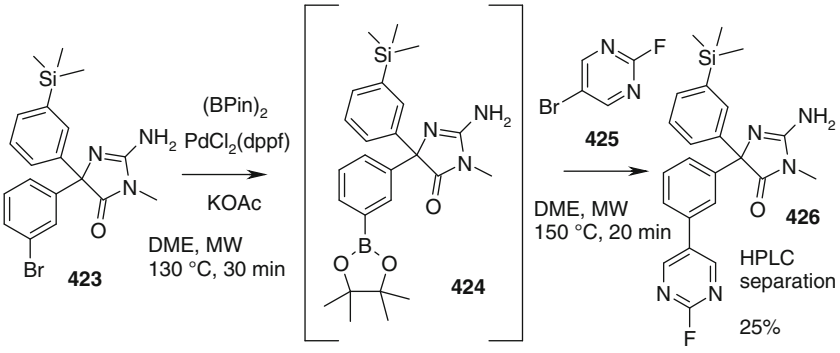


Fig. 19 Reactivity of 2-fluoro-5-bromopyrimidine and 2,5-dibromopyrimidine

pyrimidines no arylation was observed. The major reaction appeared to be hydrolysis of one or more of the fluorine substituents [227]. But this tolerance of fluorine atom towards Pd-catalyzed coupling reactions can be used in organic synthesis. In can be illustrated by reactivity comparison of 2-fluoro-5-bromopyrimidine and 2,5-dibromopyrimidine (Fig. 19).

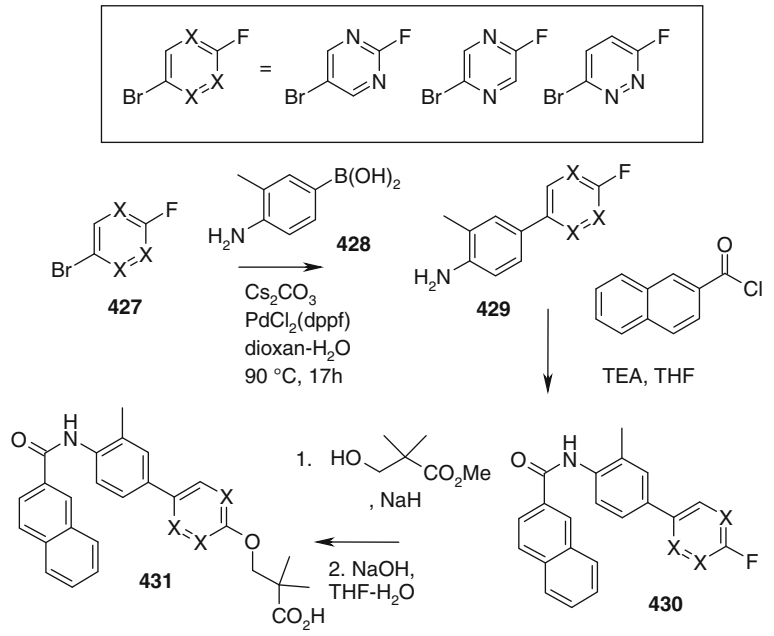
In a case of 2,5-dibromopyrimidine Suzuki coupling with boronic acids proceeds selectively at 2-position leaving 5-bromine atom intact [228, 229] meanwhile Sonogashira coupling with terminal alkynes proceeds unselectively by both position [230]. But in a case of 2-fluoro-5-bromopyrimidine the selectivity pattern of Pd-catalyzed couplings is switched off. Thus 2-fluoro-5-bromopyrimidine **425** entered in Suzuki coupling with boronic species **424** exclusively in 5-th brominated position leaving fluorine intact giving compound **426** – BACE inhibitor, potential drug for the prevention of treatment of neurodegeneration [231] (Scheme 76).



Scheme 76 Suzuki reaction of 2-fluoro-5-bromopyrimidine

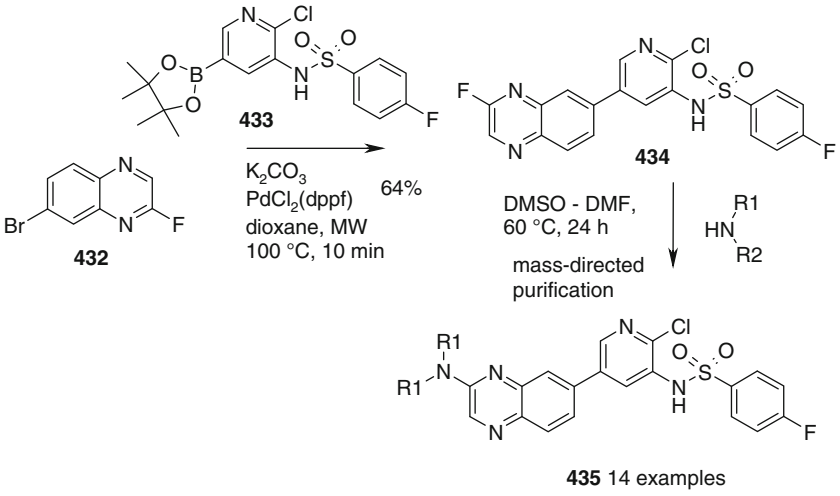
The selectivity pattern is general for fluoro-bromo diazines. In course of diacylglycerol acyltransferase 1 (DGAT1) inhibitors **431** design and synthesis this assumption was proved. All fluoro-bromo diazine derivatives **427** undergo Suzuki coupling only with bromine participation. Moreover, after the transformations the fluorine atom in compounds **430** remains active towards nucleophilic substitution [232] (Scheme 77).

Another example of such differentiation of activity using was described during phosphoinositide 3-kinase (PI3K) inhibitors **435** development. In this case the core compound for the library construction was 7-bromo-2-fluoroquinoxaline **432**. First the quinoxaline **432** was subjected to coupling reaction with boronic acid pinacol



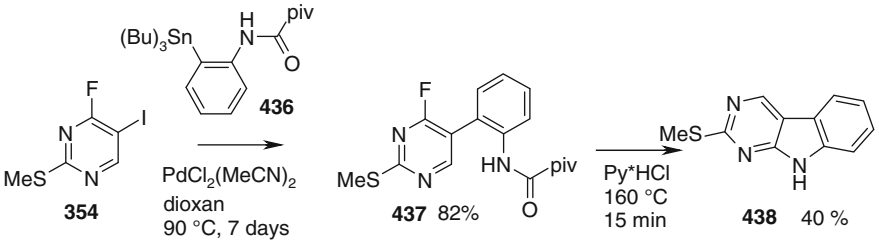
Scheme 77 Suzuki reaction of fluoro-bromo diazines

ester **433** in MW condition giving corresponding key building block **434** in 64 % yield [233]. Than the **434** was used in parallel synthesis based on fluorine substitution in DMSO solution with a list of 14 aliphatic amines with subsequent mass-directed purification [234] (Scheme 78).



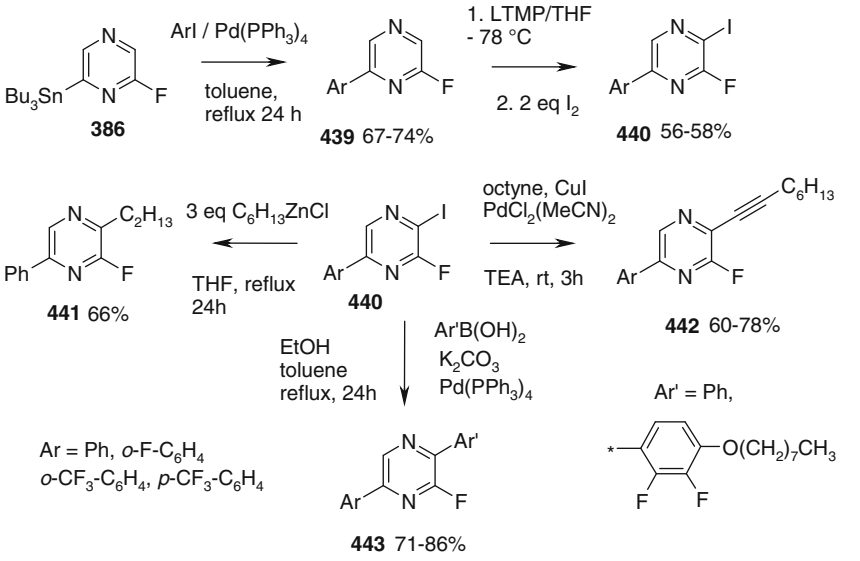
Scheme 78 Library of PI3K inhibitors obtained from 7-bromo-2-fluoroquinoxaline

The similar situation was observed with fluoro-iodo diazines. Fluoro-iodo pyrimidine **354** (see Scheme 59) was subjected to Stille coupling followed by intramolecular cyclization into targeted azacarboline **438** [212] (Scheme 79).



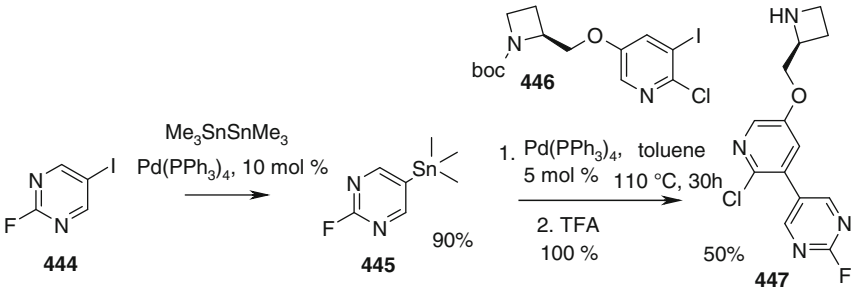
Scheme 79 Azacarboline synthesis based on fluorinated pyrimidines

In 2003 the same group of scientists shown wide applicability of Pd-catalyzed coupling – metalation sequences in various pyrazine synthesis. Starting from 2-fluoro-6-tributhylstannanyl-pyrazine **386** (Scheme 66) as building block a general synthetic route to access to various alkylaryl or diaryl pyrazines with multiple fluorosubstituents in strategic lateral position to generate a wide range of molecules was elaborated. The Stille, Suzuki, Sonogashira and Negishi couplings gave yields in range 50–80 % [215] (Scheme 80).



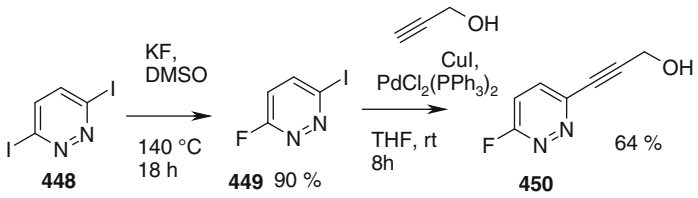
Scheme 80 2-Fluoro-6-tributhylstannanylpyrazine as key building block

Later the different iodo/fluoro activity was used in nicotinic acetylcholine receptor (nAChR) PET ligand **447**. On the early step of the synthesis starting from 2-fluoro-5-iodopyrimidine **444** the corresponding trialkyltin heteroaromatic intermediate **445** was obtained based on "stanno-Stille" coupling in 90 % yield. Further the fluorinated stannate was entered in reaction with iodopyridine **446** leading to cross-coupled pyridine-pyrimidine in 50 % yield. The final step of the synthesis was Boc-deprotection by TFA affording **447** [235] (Scheme 81).



Scheme 81 Synthesis of acetylcholine receptor PET ligand

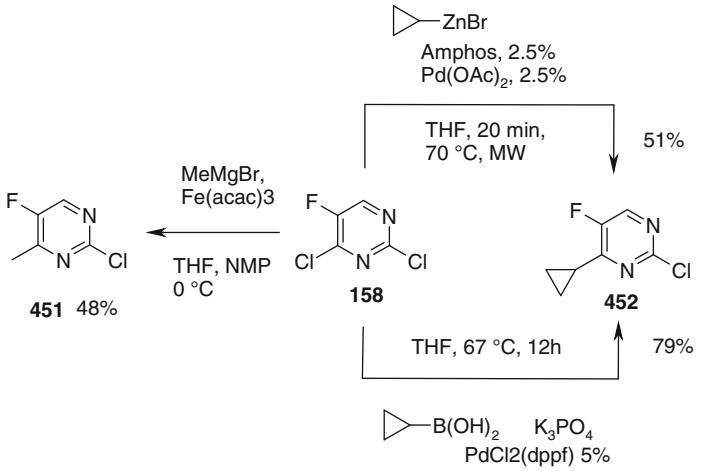
In 1995 selective Sonogashira reaction with 3-fluoro-6-iodopyridazine **449** was described leading to selective substitution of iodine by propargyl alcohol in 64 % yield [236] (Scheme 82).



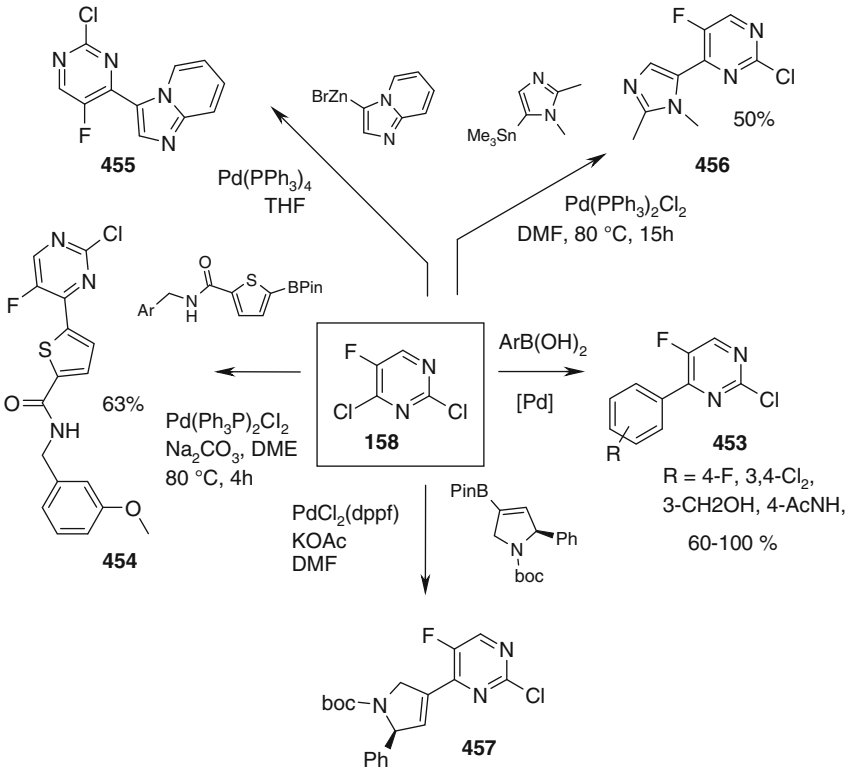
Scheme 82 Sonogashira reaction with 3-fluoro-6-iodopyridazine

A lot of cross couplings were described for 2,4-dichloro-5-fluoropyrimidine **158**. In a case of this substrate the exclusive substitution of chlorine in 4-position occurs leaving chlorine in 2-position intact. Iron-catalyzed coupling with Grignard reagent was used for introduction of alkyl group instead chlorine atom in 2,4-dichloro-5-fluoropyrimidine leading to 2-chloro-5-fluoro-4-methylpyrimidine in 48 % yield [237]. Alternative approaches to 2-chloro-5-fluoro-4-alkylpyrimidines include Negishi coupling with organozinc derivatives and Suzuki coupling with alkyl boronic acids [238, 239] (Scheme 83).

Different variants of Suzuki reaction were used for introduction of aryl and hetaryl group into 5-fluoropyrimidine core. In majority cases the yield of reaction remains high and some functionality such as protected amino group or free alcohol function could be introduced together with benzene ring [240–243]. Also the reaction allows introduction of different heterocyclic moieties [244, 245] via Stille reaction [246] and Negishi coupling [247] using **158** (Scheme 84).

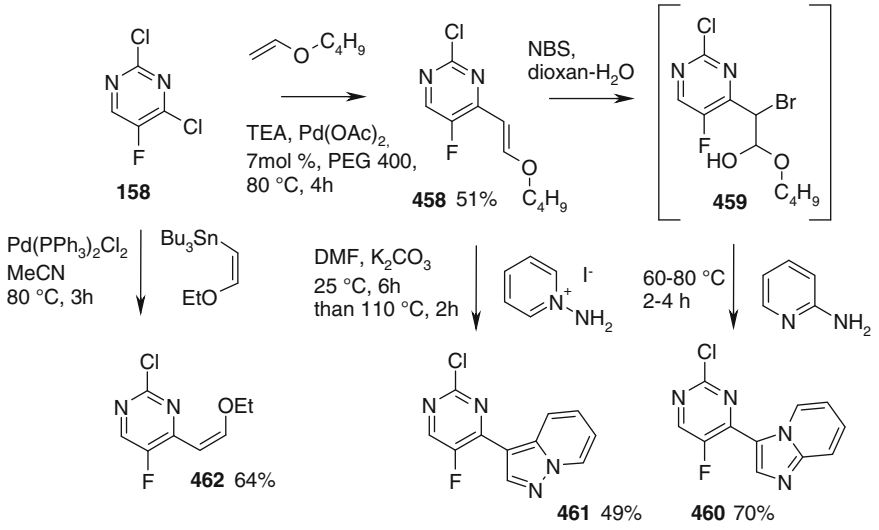


Scheme 83 Cross-couplings of 158 (Amphos = 2-(2,4,6-*i*-Pr_3-C_6H_2)–C_6H_4-PCy_2)



Scheme 84 Cross-coupling reactions of 2,4-dichloro-5-fluoropyrimidine

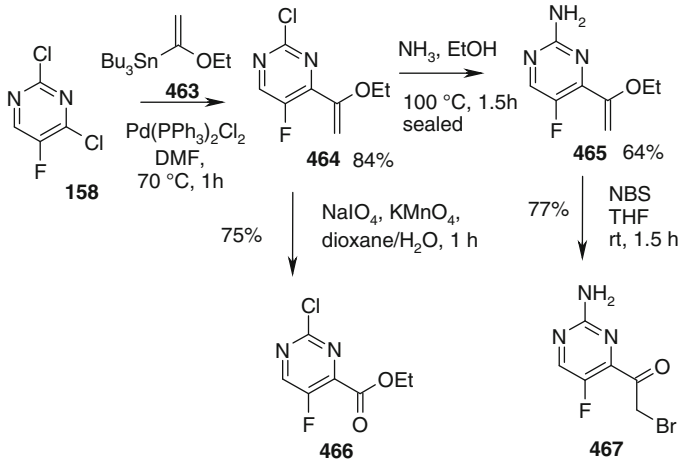
More unusual transformation based on 2,4-dichloro-5-fluoropyrimidine were described during development of inhibitors of the insulin-like growth factor-1 receptor tyrosine kinase [248]. In a course of the project selective β-arylation of vinyl ethers by 4-chloropyrimidines could be achieved using a phosphine-free Heck reaction in polyethyleneglycol. The reaction of **158** with butyl vinyl ether (3 equiv.) in the presence of Et_3N (1 equiv.) and $Pd(OAc)_2$ (7 mol %) using PEG-400 as a solvent provided vinyl ether **458** in 51 % yield. Bromination of the vinyl ether **458** with NBS in dioxane–water followed by a cyclocondensation with 2-aminopyridine provided the imidazopyridine **460** in 7 % yield, presumably *via* the α-bromo hemiacetal **459**. With the aim of the replacement of the imidazopyridine ring by a pyrazolo[1,5-a]pyridine the 1,3-dipolar cycloaddition between vinyl ethers **458** and the azomethine imine formed by deprotonation of a 1-amino-pyridinium ion, followed by an oxidative aromatization was carried out affording **461** in 49 % yield [249]. Alternative stereoselective approach to β-arylatated vinyl ethers **462** was described by Banyu Pharmaceutical starting from *cis*-l-ethoxy-2-tri-*n*-butylstanylethylene [250] (Scheme 85).



Scheme 85 Cross-coupling reactions of 2,4-dichloro-5-fluoropyrimidine

Another useful Stille coupling was performed based on tributyl(1-ethoxyvinyl) stannane **463** which allowed to obtain additional function in pyrimidine ring. The reaction of stannane **463** with **158** in presence of bis(triphenylphosphine) $PdCl_2$ in DMF leads to corresponding 4-vinyl ether **464** in 84 % yield. The amino group was introduced at position 2 upon treatment with aqueous concentrated ammonia in ethanol under heating with microwaves, and bromination of the resulting vinyl ether **465** to α-bromo-ketone **466** was accomplished with N-bromosuccinimide in aqueous

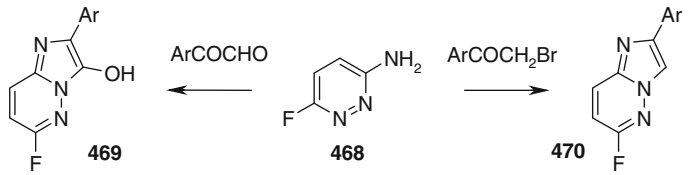
tetrahydrofuran [251]. Also the 2-ethoxyvinyl moiety of **464** was subsequently converted into ethyl ester **466** by oxidative cleavage using $NaIO_4$-$KMnO_4$ system [182] (Scheme 86).



Scheme 86 Cross-coupling reactions of 2,4-dichloro-5-fluoropyrimidine

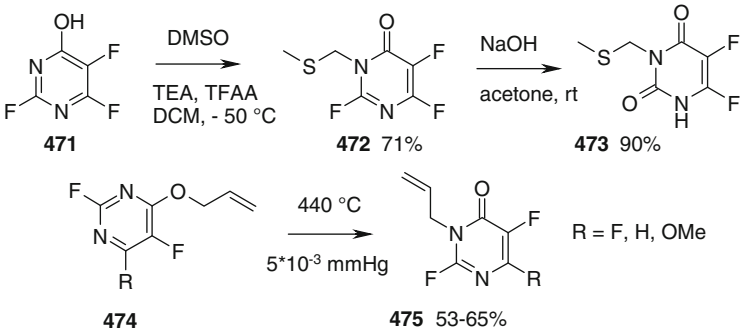
4.5 Miscellaneous Cyclizations and Rearrangements

In the literature there are a lot of cyclization reaction were fluorine in diazine core does not play significant role. As an example the cyclizations of 6-fluoropyridazin-3-ylamine **468** were shown [252–254] (Scheme 87).



Scheme 87 Cyclizations based on 6-fluoropyridazin-3-ylamine

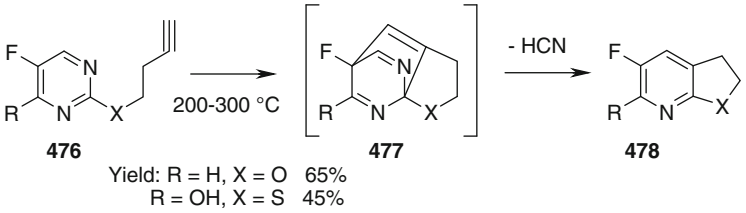
But in the section we would like to draw the reader's attention to the more rare reaction, which results are not always clear from general considerations. For example the reaction of 2,5,6-trifluoropyrimidin-4-ol **471** with DMSO in presence of TFAA proceeds with 2,3-sigmatropic rearrangement leading to pyrimidine **472**, which was hydrolyzed to 5-fluorouracil derivative **473** [255] The same scientists described the Claisen rearrangement of 4-allyloxy fluoropyrimidines **474** in which N(3) is the migration terminus [181] (Scheme 88). 5-Fluoro-4,6-dimethoxypyrimidine



Scheme 88 Sigmatropic rearrangement of fluorinated pyrimidines

in reaction with activated DMSO also gave 2,3-sigmatropic rearrangement leading to 5-fluoro-4,6-dimethoxymethylthiomethylpyrimidin-2(1H)-one in 59 % yield.

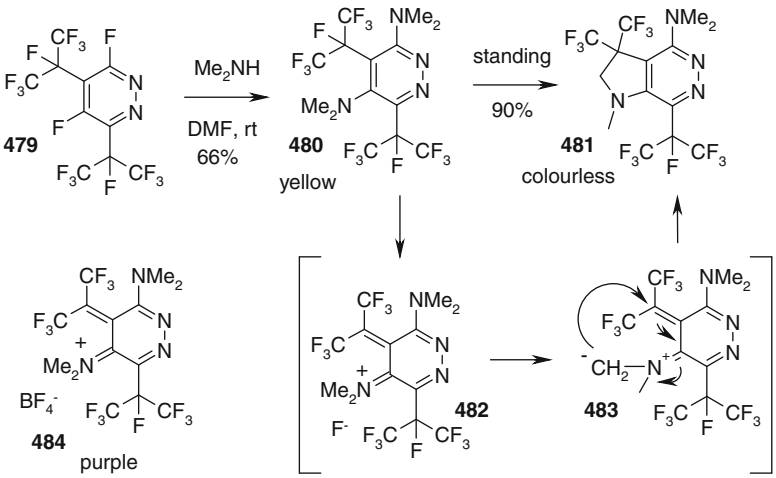
Recently pyrimidine substituted alkynes **476** were subjected to intramolecular inverse-electron-demand hetero-Diels-Alder reaction with extrusion of HCN affording fused fluorinated pyridines **478**. The reaction proceeds at high temperatures in sealed tubes for small amount of the starting materials [256] or as scalable flow process [257] (Scheme 89)



Scheme 89 Intramolecular inverse-electron-demand hetero-Diels-Alder reaction

Unusual *tert*-amino reaction was found under investigation of nucleophilic substitution in 3,5-bisheptafluoroisopropyl-4,6-difluoropyridazine **479** with dimethylamine. The reaction gives bis(dimethy1amino) derivative **480** which then undergoes spontaneous cyclisation by a displacement of fluorine from a perfluoroisopropyl group. This process is accelerated by water in DMF to give the colourless compound **481** in 90 % yield. The cyclization proceeds trough the loss of 'tertiary' fluorine and formation of purple intermediate compound **482**, which was proved by isolation of a purple solid **484** (87 % yield) by adding boron trifluoride-dietliyl ether to **480** [258] (Scheme 90).

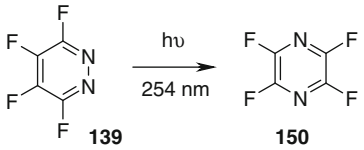
Historical developments of the structure of benzene is important part of history of chemistry. Structures considered were Dewar benzene **486**, Ladenberg's prismane **487** and benzvalene **488** (Fig. 20). Photochemistry of fluorinated aromatic systems has made an important contribution to the study of valence isomers because it has been possible to isolate and characterize some species on which there had previously only been speculation.



Scheme 90 Tert-reaction with perfluoroisopropyl group participation

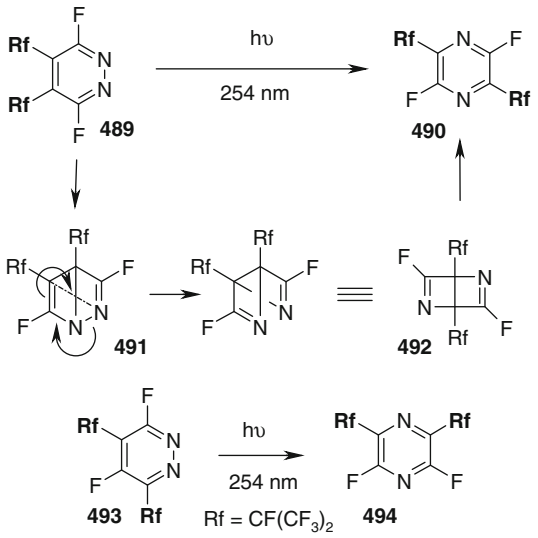
Fig. 20 Valence isomers of benzene

The fluorinated diazines plays important role as model object for the investigation. Tetrafluoropyridazine has been converted photochemitally into tetrafluoropyrazine via formal 1,3-shift of nitrogen [259] (Scheme 91).



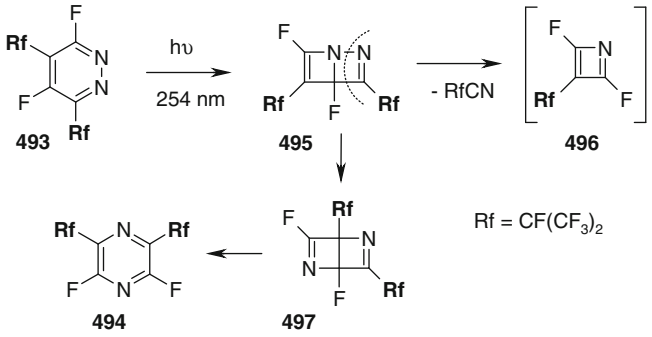
Scheme 91 Photoizomerization of perfluorinated pyridazine

The use of polyfluoroalkyl substituents in positions 4 and 5 (compound **489**), however, enabled a mechanistic pathway to pyrazine **490** substituted at positions 2 and 5, to be suggested (Scheme 92) Individual para-bonded species **491** and **492** have been isolated in this and other cases, and converted into the next component along the reaction pathway by photo or thermal reactions [260]. In a case of 4,6-disubstituted pyridazine **493** only pyrazine substituted at positions 2 and 6 **494** was observed. A very unusual mechanistic pathway may be drawn from the structures of the isolated and characterised valence isomers (Scheme 92). This appears to be the first case where substituent labelling has allowed each stage in a photochemical aromatic rearrangement to be identified through various intermediate valence isomers.

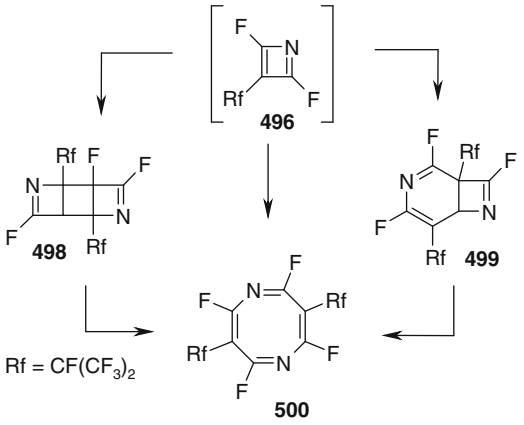


Scheme 92 Substituent labeled photoizomerization of fluorinated pyridazines

Also during the investigation of photolysis of 4,6-disubstituted pyridazine **493** have been established that by-products are formed in the reaction through the intermediacy of an azacyclobutadiene derivative **496** [261] (Scheme 93). The azacyclobutadiene **496** was not isolated but the products of its dimerization **498**–**500** were isolated and characterized. From all characterized dimers the 1,5-diazocine derivative **500** appears most thermodynamically stable (Scheme 94).

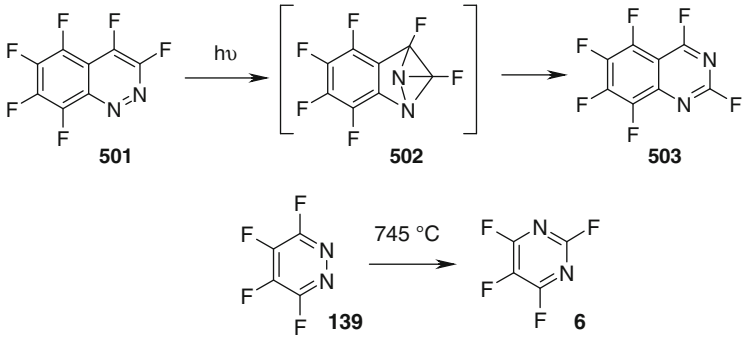


Scheme 93 Generation of by-product azacyclobutadiene



Scheme 94 Dimers of azacyclobutadiene

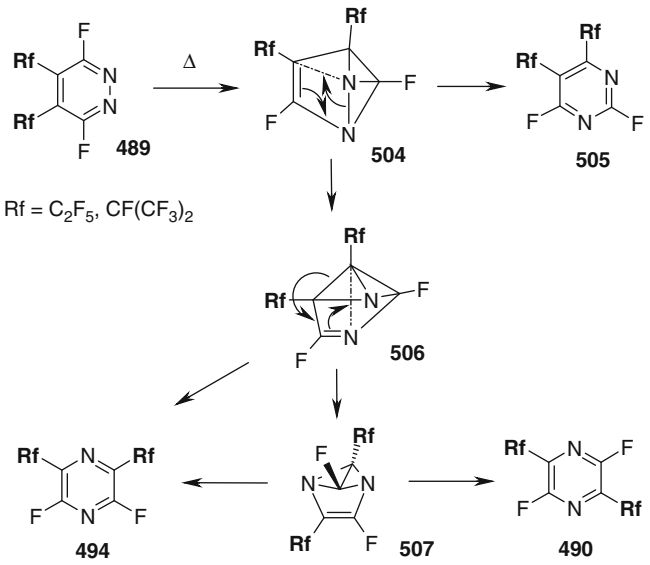
A benzodiazabenzvalene derivative **502** has been proposed to account for the photochemical rearrangement of perfluorocinnoline **501** to the quinazoline **503** [59] (Scheme 95).



Scheme 95 Izomerization of fluorinated pyridazines to pyrimidines

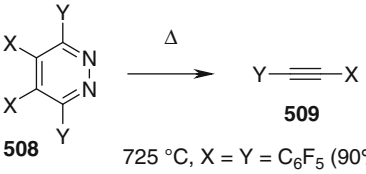
A remarkable series of transformations has been discovered with fluorinated pyridazines, giving pyrimidines and small amounts of pyrazines on pyrolysis. The pyrolysis of tetrafluoropyridazine **139** gave the isomer tetrafluoropyrimidine **6** as the major product (30 %) (Scheme 95) [262], though at 815 °C tetrafluoropyrazine was among the products.

Once again, the use of 4,5-di(polyfluoroalkyl) derivatives **489** and the orientation of the substituents in the products enabled the reaction pathway to be rationalised on the basis of the formation and rearrangement of three intermediate diazabenzvalenes **504**, **506** and **507**. For Rf=C_2F_5, the major component **505** was accompanied by a small amount of the 2,6-substituted pyrazine **494**, whereas for Rf=$(CF_3)_2CF$, is formed with a smaller amount of the 2,5-substituted pyrazine **490** [263] (Scheme 96). Despite of no valence isomers have actually been isolated. Cycloaddition processes have been ruled out by N-15 labelling experiments. Furthermore, rearrangement is encouraged by free-radical promotors, leading to the conclusion that these processes involve free-radicals formation [264].



Scheme 96 Substituent labeled pyrolysis of fluorinated pyridazines

After investigation of Chambers group made in late 70-th in 1984 Clark and co-worker investigated plasma polymerization of the isomeric perfluorodiazines. The studies showed that plasma polymers are produced by rearrangement mechanisms. A comparison of rates of formation of plasma polymer films reveals distinctive differences between the isomeric diazines that suggest that equilibration of valence isomers occurs on a substantially slower time scale than for isomeric fluorinated benzenes [265]. Also extensive MNDO SCF MO calculations were made to determine the heats of formation of the ground state of geometry-optimized perfluorodiazabenzenes (pyridazine, pyrimidine, and pyrazine) and some of their structural isomers (Dewar benzene, benzvalene, prismane, fulvene and hexadienyne) [266]. From these calculations it is readily apparent that perfluoropyridazine could eliminate nitrogen without further rearrangement with a heat of reaction of 27 kcal/mol. Despite of known pyrolyses of perfluoroalkylpyridazines leads to rearrangements to pyrimidines and pyrazines, rather than loss of nitrogen, the pyridazines bearing perfluoroaryl substituents loss the nitrogen under termolysis. Thermal elimination presents a route to fluorinated alkyne derivatives [267] (Scheme 97).

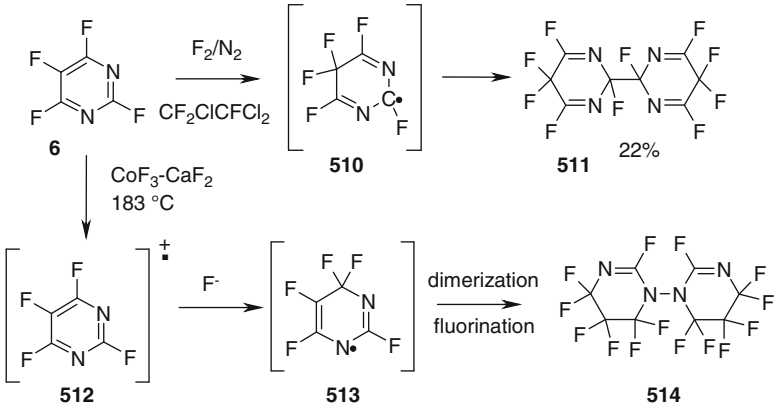


725 °C, X = Y = C_6F_5 (90%)
720 °C, X = C_2F_5, Y = C_6F_5 (88%)
680 °C, X = $CF(CF_3)_2$, Y = C_6F_5 (84%)
700 °C, X = $CF(CF_3)_2$, Y = 4-C_5F_4N (82%)

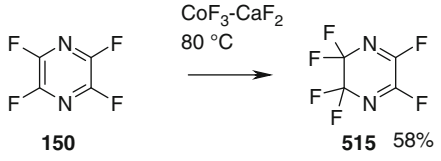
Scheme 97 Termolysis of perfluoroaryl substituted pyridazines

4.6 Fluorination Reactions

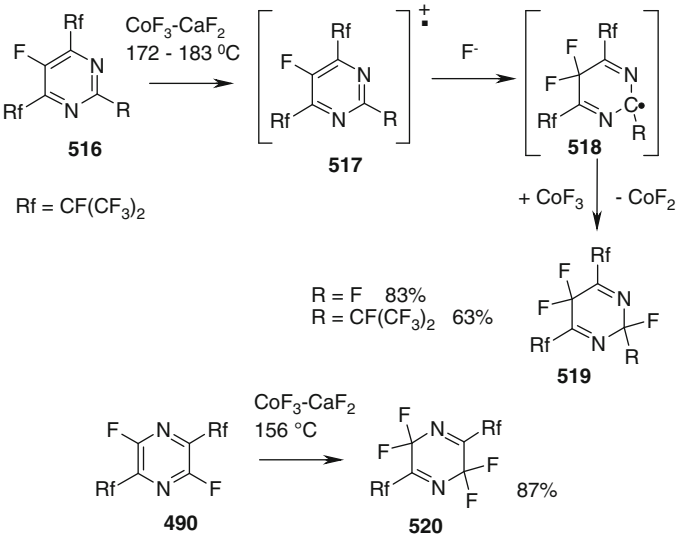
Chambers and coworkers studied direct fluorination of perfluoropyrimidine by elemental fluoride. The formation of the dimeric compound **511** in the reaction indicated the radical nature of the process [267]. Addition of highly electrophilic fluorine atom at a position meta to nitrogen in followed by dimerisation of **510** is easily understandable. Meanwhile the fluorination of perfluoropyrimidine by cobalt (III) fluoride with calcium fluoride leads to another product. In this case the reaction proceeds trough cation radical **512**, which after fluoride anione additional formed radical **513**. Dimerization of the radical **513** followed by fluorination leads to bispyrimidine **514** in 25 % isolated yield [268] (Scheme 98). Whereas perfluoropyrazine under CoF_3-CaF_2 fluorination gives 1,3-diene **515** in 58 % yield with ~50 % conversion of starting materials (Scheme 99). Bulky perfluoroisopropyl group in 4- and 6-positions of pyrimidine prevent dimerisation under CoF_3-CaF_2 fluorination and reaction results in formation of 1,4-dienes **519** in high yield. Similar situation is observed with fluorination of perfluoro-2,5-diisopropylpyrazine **490** (Scheme 100). But the pyridazine derivatives **489** and **493** each lost nitrogen on fluorination. However, this provides a novel synthetic approach to some unusual fluorinated alkenes (Scheme 101).



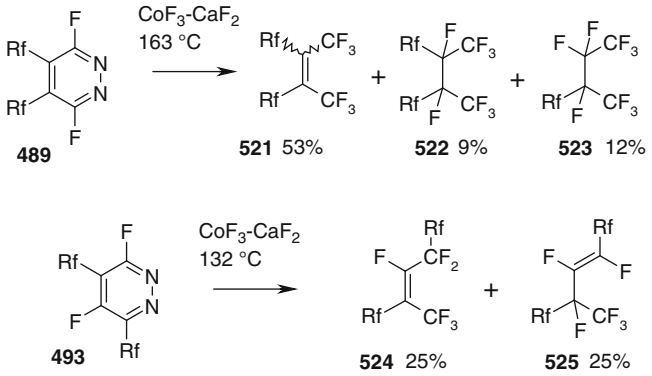
Scheme 98 Fluorination of perfluoropyrimidine



Scheme 99 Fluorination of perfluoropyrazine



Scheme 100 1,4-Dienes formation under CoF_3-CaF_2 fluorination of diazines



Scheme 101 CoF_3-CaF_2 fluorination of pyridazines

5 Side Chain Fluorinated Diazines

Chain-fluorinated diazines is another family of organofluorine compounds which is of great importance for synthetic, medicinal and agricultural chemistry [12, 13]. The first representatives of this class, namely, chain-fluorinated pyrimidines and quinoxalines were obtained in late 1950s. Since then, over a thousand papers dealing with synthesis and chemistry of chain-fluorinated diazines were published.

Due to a huge number of the data, this chapter gives a general review of synthetic methods and chemical properties of chain-fluorinated diazines. Only selected (sometimes deliberately) literature examples are given to illustrate them.

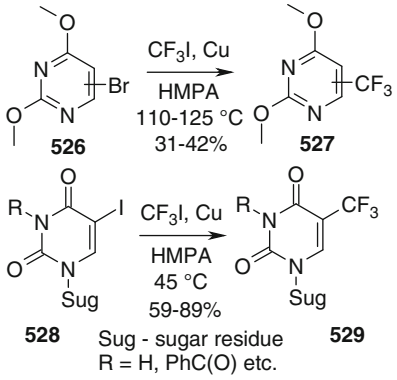
Known approaches to the synthesis of chain-fluorinated diazines are subdivided into two categories: the methods, which rely on introduction of fluorine or fluorine-containing substituents into diazine core (i.e. direct (per)fluoroalkylation and nucleophilic substitution with fluoride), and construction of the diazine core starting from fluorine containing building blocks. Chemical properties of the chain-fluorinated diazines are discussed in a separate section.

6 Introduction of Fluorine-Containing Substituents into Diazine Core

6.1 Direct (Per)Fluoroalkylation

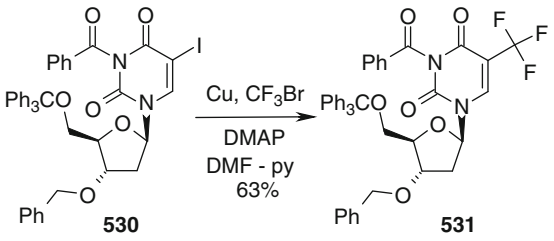
6.1.1 Perfluoroalkylcopper Reagents

Perfluoroalkylation with perfluoroalkyl copper species is one of the most known "direct" method for introducing CF_3 group and other fluorinated alkyl substituents into aromatic cores. One of the first reports in this area was made in 1977 [269] and later in 1980 – as a full paper [270]. In these works, Kobayashi and co-workers used CF_3I–Cu – HMPA system to generate CF_3Cu solution, which reacted with 5-bromo- **526** and 5-iodouracil derivatives **528** to give 5-trifluoromethylpyrimidines **527** and **529** (Scheme 102). The method was used for the synthesis of Trifluridine and its analogues (see Chap. 20) [269–271].



Scheme 102 Trifluoromethylation of pyrimidine derivatives using the method of Kobayashi and co-workers

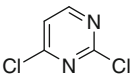
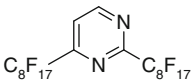
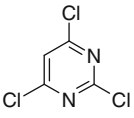
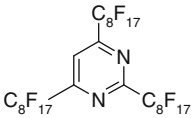
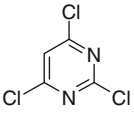
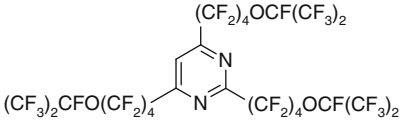
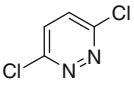
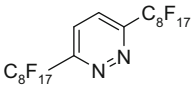
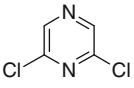
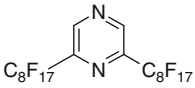
A related procedure employed less expensive but less reactive CF_3Br instead of CF_3I as the source of the trifluoromethyl group [272]. In this case, CF_3Cu was generated by heating CF_3Br and copper powder in DMF – pyridine at 115 °C in a sealed tube. It was found that addition of 4-dimethylaminopyridine (DMAP) substantially accelerated formation of the complex. The preformed CF_3Cu reacted with pyrimidine **530** at to give **531**. This procedure was used for the preparation of FTC-092, an investigational anti-cancer drug (Scheme 103, see Chap. 20).



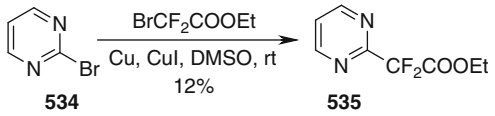
Scheme 103 Trifluoromethylation step in the synthesis of FTC-092

The method was extended to other perfluoroalkyl iodides, *i.e.* *n*-$C_8F_{17}I$ (**532**) or $(CF_3)_2CFO(CF_2)_4I$ (**533**) (Table 18) [273]. In this case, the reaction was performed in C_6F_6 as the solvent at *ca.* 85 °C; DMSO and 2,2′-bipyridyl were used as additives to accelerate formation of perfluoroalkyl copper reagents. The method was effective only for the primary perfluoroalkyl iodides.

Table 18 Perfluoroalkylation of diazines with iodides 3 and 4. Conditions: 532 or 533, Cu, 2,2′-bipy, DMSO, C_6F_6, *ca.* 85 °C

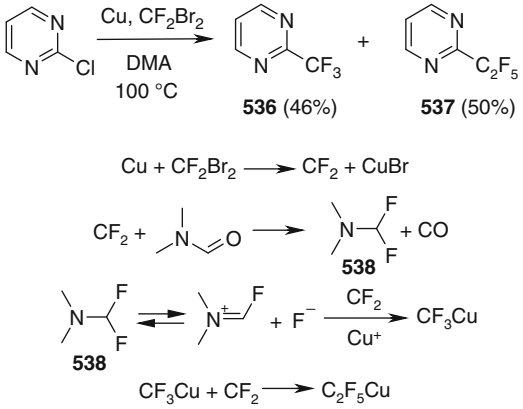
#	Substrate	Reagent	Product	Yield (%)
1		**532**		70
2		**532**		59
3		**533**		56
4		**532**		68
5		**532**		89

Analogous reaction of ethyl dibromofluoroacetate with 2-bromopyrimidine **534** gave the corresponding product **535** in low yield (12 %) (Scheme 104) [274].



Scheme 104 Coupling of 2-bromopyrimidine with ethyl dibromofluoroacetate

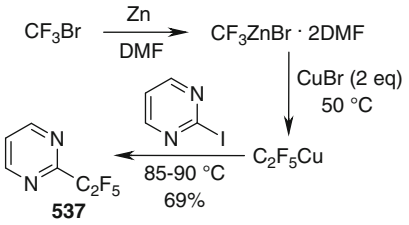
Burton's conditions (*i.e.* Cu–CF_2Br_2 – DMA [275]) were also checked for trifluoromethylation of diazines (namely, 2-chloropyrimidine). Despite high conversion of the substrate, the method gave nearly equimolar mixture of 2-perfluoroalkylpyrimidines **536** and **537** was obtained (Scheme 105) [276, 277]. The mechanism of the reaction included reduction of CF_2Br_2 with copper to give difluorocarbene, which reacted with dimethylacetamide to give the adduct **538**. The latter acted as a source of fluoride ion and reacted with difluorocarbene to give CF_3Cu species. In case of low activated substrates (*i.e.* 2-chloropyrimidine), CF_3Cu slowly reacted with difluorocarbene to give C_2F_5Cu, which also took part in the transformation.



Scheme 105 Trifluoromethylation of 2-chloropyrimidine under Burton's conditions

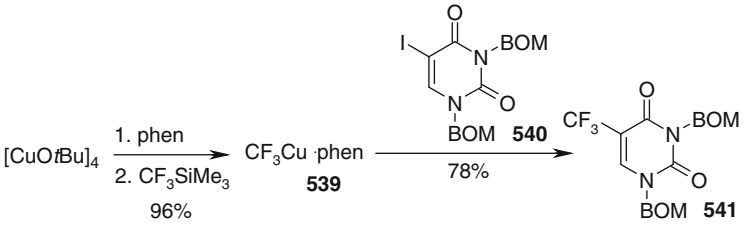
Recently, several novel methods for the generation of perfluoroalkyl copper species were used for direct perfluoroalkylation of diazines, e.g. transmetallation reactions involving $(CF_3)_2Hg$ [278] and $CF_3ZnBr \cdot 2DMF$ [279]. In both cases, the procedure did not require special laboratory equipment such as autoclaves or steel tubes, which were necessary in the case of using CF_3Br or CF_3I as the source of trifluoromethyl group. The first method ($(CF_3)_2Hg$–Cu – dimethylacetamide, 110–140 °C) was successfully applied for trifluoromethylation of 5′-iodouridine derivatives;

the corresponding products were obtained in more than 90 % yields. In the second procedure, C_2F_5Cu species were generated selectively (from $CF_3ZnBr \cdot 2DMF$ and CuBr), which reacted with 2-iodopyrimidine to give the product **537** in 69 % yield (Scheme 106).



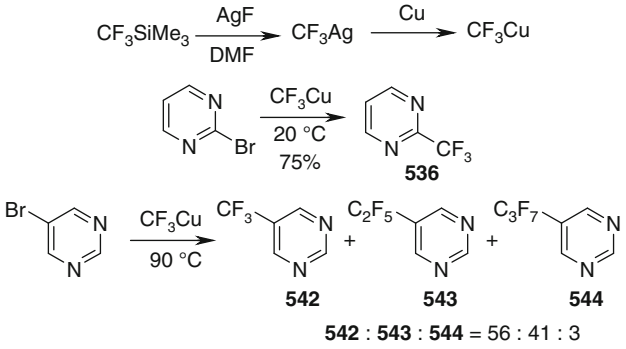
Scheme 106 Pentafluoroethylation of 2-iodopyrimidine

An alternative source for the generation of trifluoromethyl copper species, which gained momentum in the last years, is Ruppert – Prakash reagent (CF_3SiMe_3). Hartwig and co-workers used this reagent to obtain stable complex $CF_3Cu \cdot phen$ (**539**) [280]. The latter was obtained in 96 % yield on a gram scale by reaction of copper (I) *tert*-butoxide with 1,10-phenantroline (phen) and then – with CF_3SiMe_3 in benzene at rt (Scheme 107). The complex **539** is called Trifluoromethylator™, which is an easily handled, thermally stable, single-component reagent for the trifluoromethylation of aryl iodides and now is available from Aldrich. Reaction of **539** with uracil derivative **540** gave the product **541** in 78 % yield.



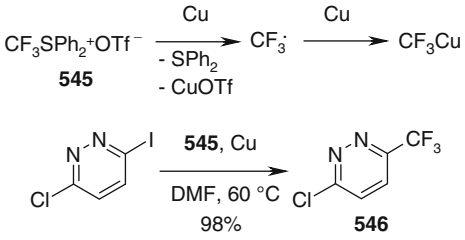
Scheme 107 Trifluoromethylation of iodouracile with Trifluoromethylator™

One more method relied on reaction of CF_3SiMe_3 with AgF in DMF, which led to CF_3Ag species [281]. The latter was treated with copper to obtain the trifluoromethyl copper reagent, which was rather effective for the trifluoromethylation of 2-bromopyrimidine (75 % yield) (Scheme 108). In case of 5-bromopyrimidine, a mixture of perfluoroalkylation products **542**–**544** was formed at 56:41:3 ratio, respectively.



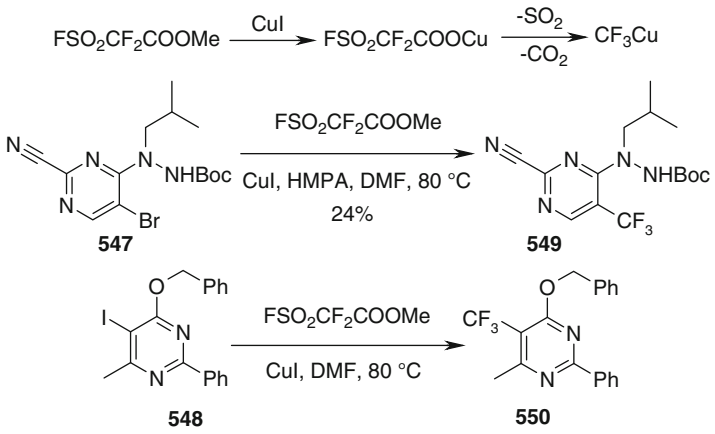
Scheme 108 Trifluoromethylation with CF_3SiMe_3 –AgF–Cu

In a recent paper, *S*-(trifluoromethyl)diphenylsulfonium triflate (**545**) in the presence of copper was proposed as an efficient reagent for trifluoromethylation of heteroaromatic compounds [282]. In particular, 3-chloro-6-iodopyridazine smoothly reacted with this reagent to give the product of the iodine selective substitution (**546**) in 98 % yield (Scheme 109). The proposed mechanism for the formation of active species included reduction of **545** leading to trifluoromethyl radicals, which in turn reacted with copper to give CF_3Cu.



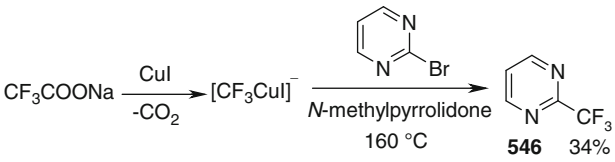
Scheme 109 Trifluoromethylation with $CF_3SPh_2^+OTf^-$–Cu

It was found that $FSO_2CF_2CO_2Me$ readily eliminates CO_2 and SO_2 in the presence of CuI in DMF at 60–80 °C to produce $CuCF_3$ species that can be used for aromatic trifluoromethylation [283]. The method was used for trifluoromethylation of pyrimidines **547** [284] and **548** [285] (Scheme 110).



Scheme 110 Trifluoromethylation with $FSO_2CF_2CO_2Me$–CuI

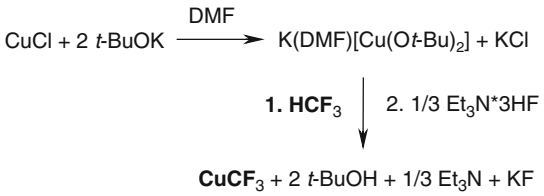
An analogous idea was implied in an older method which used CF_3COONa–CuI – *N*-methylpyrrolidone system for trifluoromethylation of 2-bromopyrimidine (Scheme 111) [286]. The corresponding product **546** was obtained in 34 % yield. The authors proposed $[CF_3CuI]^-$ species as the active trifluoromethylation agent.



Scheme 111 Trifluoromethylation with CF_3COONa–CuI

The most recent methodology for CF_3Cu generation based on CF_3H was elaborated by Grushin [287]. The method is based on a novel ate complex reagent, [K(DMF)][(*t*-BuO)$_2$Cu], that is formed quantitatively upon treatment of CuCl with 2 equiv. of t-BuOK. This dialkoxycuprate, generated in situ or preisolated, reacts with CHF_3 at room temperature and atmospheric pressure within minutes to give rise to $CuCF_3$ in >90 % yield. Stabilization of thus produced trifluoromethyl copper(I) with a source of HF such as Et_3N*3HF furnishes the reagent that is stable at room temperature for days (Scheme 112). Prior to the stabilization, fluoroform-derived $CuCF_3$ reacted with haloarenes to give the corresponding arenetrifluorides. The conditions were also checked for trifluoromethylation of diazines [288]. Due to the cupration occurs within seconds at room temperature and is not mediated

by CF_3^- or CF_2, which accounts for its remarkably high selectivity, the reaction leads only to trifluoromethyl derivatives without C_2F_5 derivatives side-formation, unlike to above-mentioned procedures (Table 19).

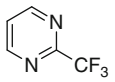
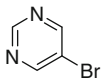
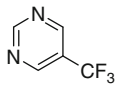
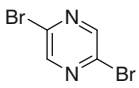
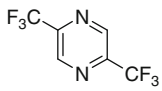


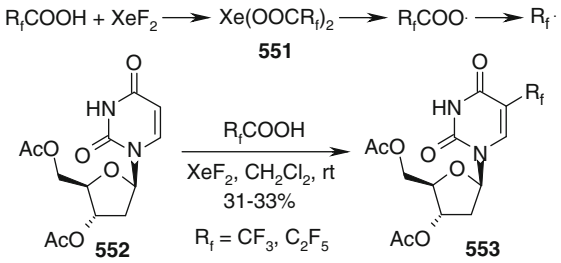
Scheme 112 Fluoroform-derived $CuCF_3$ generation

6.1.2 Perfluorocarboxylic Acids or Their Derivatives

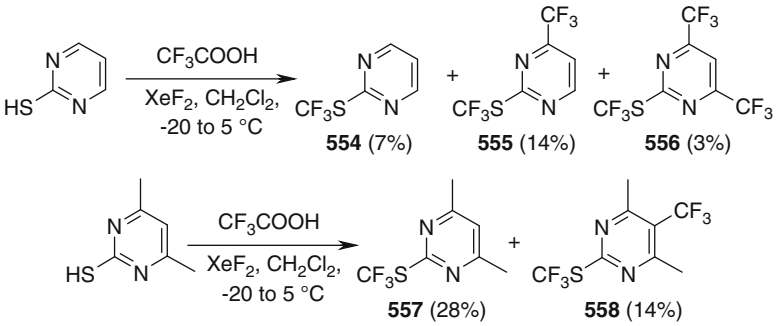
Perfluorocarboxylic acids, in particular CF_3COOH, are probably the most accessible sources of perfluoroalkyl fragments. It is not surprisingly, therefore, that some efforts were put to develop the methods for direct perfluoroalkylation of diazines using perfluorocarboxylic acids or their derivatives. One of such methods was already mentioned in the previous section, namely, decarboxylative trifluoromethylation using CF_3COONa–CuI system reported in 1988 [286]. An alternative procedure used XeF_2 to generate active species from perfluorocarboxylic acids [289]. In particular, intermediate xenon (II) perfluocarboxylate **551** decomposed to give perfluoroacyl radical. The latter eliminated CO_2 to form the corresponding perfluoroalkyl radicals (*i.e.* CF_3 or C_2F_5). These active species reacted with aromatics (in particular, pyrimidine derivative **552**) (Scheme 113) at rt. The procedure was used for the synthesis of antiviral drug Trifluridine (see Chap. 20). The reagent was also applied for trifluoromethylation of 2-mercaptopyrimidines; in this case, mixtures of products (**554**–**558**) was obtained (Scheme 114) [290].

Table 19 Trifluoromethylation of diazine bromides with fluoroform-derived $CuCF_3$

#	Substrate	Conditions	Product	Yield (%)
1		1.5 eq. $CuCF_3$, 23 °C, 18 h		95
2		1.5 eq. $CuCF_3$, 50 °C, 18 h		24
3		3 eq. $CuCF_3$, 23 °C, 24 h		94

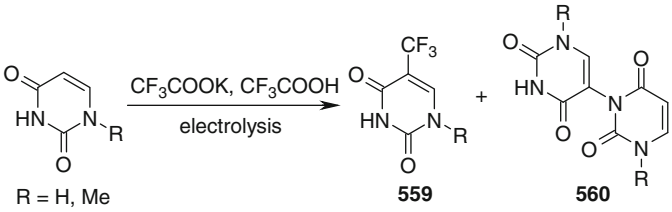


Scheme 113 Trifluoromethylation with $R_fCOOH–XeF_2$



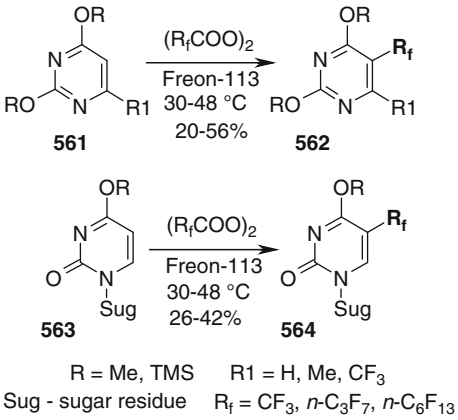
Scheme 114 Reaction of 2-mercaptopyrimidines with $CF_3COOH–XeF_2$

Electrochemical generation of trifluoroacetyl (and hence trifluoromethyl) radicals in the presence of uracil derivatives was studied [291]. Electrolysis of CF_3COOK/CF_3COOH solutions of N-1- and N-3-methylated uracils provided mixtures of 5-trifluoromethyl derivatives **559** and N–C uracil dimers **560** (Scheme 115). In case of 1,3-dimethyluracil, N-1 demethylathion was also observed.



Scheme 115 Electrolytic trifluoromethylation of uracil derivative

The reaction of bis(perfluoroacyl)peroxides and various *O*–protected uracils is a valuable method for the introduction of perfluoroalkyl group at C-5 atom of uracil [292]. The corresponding products were obtained in 20–56 % yields (Scheme 116). Substitution at C-6 of uracil did not interfere with reaction. The method could be extended for unprotected uracils and uridine derivatives (26–42 %).

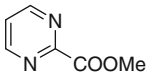
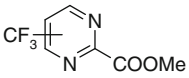
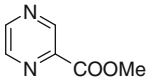
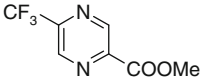
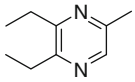
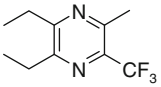
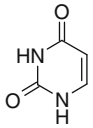
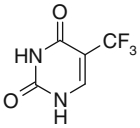
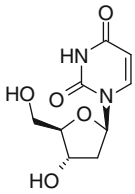
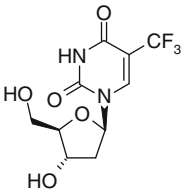


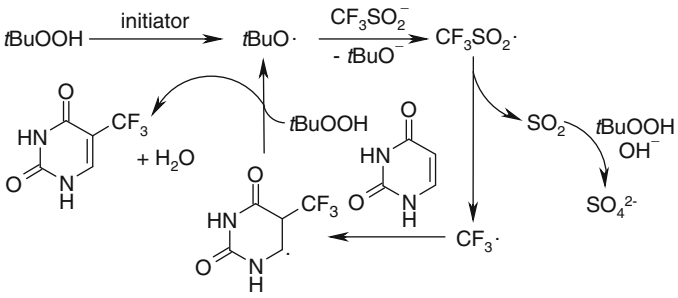
Scheme 116 Trifluoromethylation of uracil derivatives with bis(perfluoroacyl)peroxides

6.1.3 (Per)Fluoroalkylsulfinates

Although perfluorocarboxylic acids are readily available sources for of perfluoroalkyl groups, their use for direct perfluoroalkylation often requires higher temperatures, transition-metal additives, or strongly oxidizing conditions. (Per)fluoroalkylsulfinic acids are alternative reagents, which can also deliver (per)fluoroalkyl radicals. In particular, a method for trifluoromethylation of heterocycles (including diazines) reported by Baran and co-workers in 2011 used CF_3SO_2Na–*t*BuOOH system (Table 20) [293]. A putative mechanism of the transformation included reaction of *tert*-butoxy radical, generated from *t*BuOOH and trace metal or another initiator, with $CF_3SO_2^-$ to produce $CF_3SO_2\cdot$ radical (Scheme 117). This intermediate decomposed to release SO_2 and $CF_3\cdot$. The trifluoromethyl radical was then trapped with heterocyclic substrate; the intermediate formed was oxidized to the final product with *t*BuOOH, concomitantly generating another molecule of *t*BuO·.

Table 20 Trifluoromethylation of diazines with CF_3SO_2Na–tBuOOH. Conditions: CF_3SO_2Na (3 eq.), tBuOOH (5 eq.), CH_2Cl_2–H_2O, rt

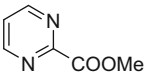
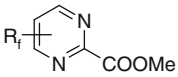
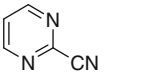
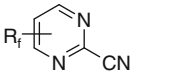
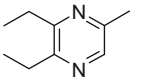
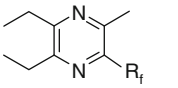
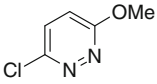
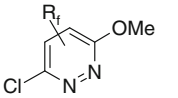
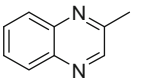
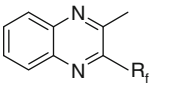
#	Substrate	Product	Yield (%)
1		 4- and 5-, 1 : 1	37
2			50
3			57
4			87
5			57



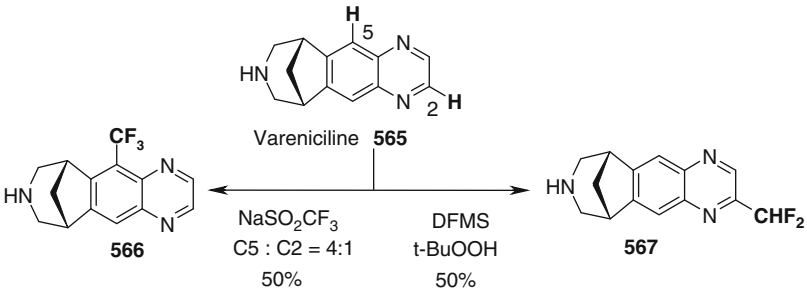
Scheme 117 Putative mechanism of uracil trifluoromethylation with CF_3SO_2Na–*t*BuOOH

Later, it was found that zinc sulfinates are superior reagents for the (per)fluoroalkylation of heterocycles in terms of both stability and reactivity [294]. A toolkit of zinc sulfinates (Baran reagents), most of which are now commercially available from Sigma-Aldrich, was developed [295], including $(CF_3SO_2)_2Zn$ (TFMS), $(CHF_2SO_2)_2Zn$ (DFMS), and $(CH_2FSO_2)_2Zn$ (Table 21). Although in many cases the yields in the transformations using zinc (per)fluoroalkylsulfinate – *tert*-butyl hydroperoxide were moderate, these reactions can be conducted open to the air on unprotected.

Table 21 (Per)fluoroalkylation of diazines with $(R_fSO_2)_2Zn$–*t*BuOOH. Conditions: $(R_fSO_2)_2Zn$, *t*BuOOH, organic solvent – H_2O, rt – 50 °C

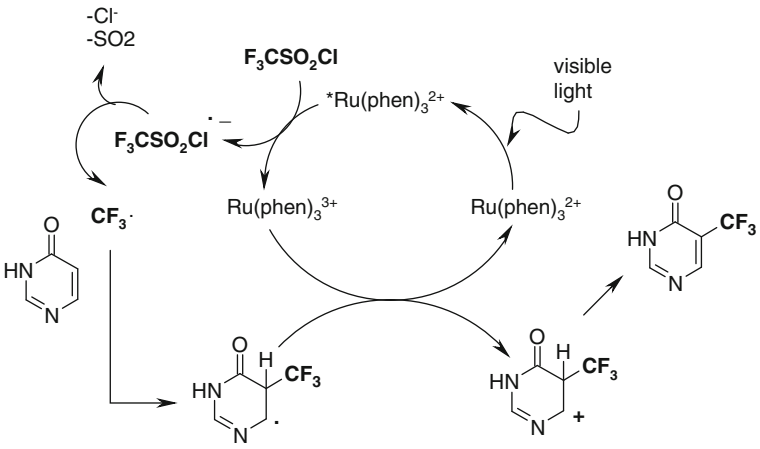
#	Substrate	Product	Yield (%), R_f =		
			CF_3	CHF_2	CH_2F
1			–	62 4- and 5- 4:1	–
2			42 4- and 5- 1.6:1	21 4- and 5- 1.6:1	–
3			–	66	–
4			45 4 only	57 4- and 5- 6:1	–
5			75 5 products	50	56

Site-selectivity of (per)fluoroalkylation depends on combined electronic properties of the reacting π-system and incoming radical species. This point is illustrated through a comparison between CF_3 and CF_2H radical additions to Varenicline (marketed in the U.S. as the prescription medication Chantix by Pfizer). In this case, high levels of selectivity are observed for CF_3 and CF_2H radical addition, in spite of the multiple potentially reactive sites (Scheme 118). For Varenicline, innate radical C–H trifluoromethylation takes place at the most electron rich position within the arene rings (C5, giving **566**). Conversely, difluoromethylation occurs exclusively at electron-poor sites adjacent to heteroatoms within the heteroarene rings (C2, giving **567**).



Scheme 118 Regiochemical comparison of innate difluoro- and trifluoromethylations

Taking the advantage of photoredox catalysis, Nagib and MacMillan developed in 2011 a $Ru(phen)_3Cl_2$-catalyzed trifluoromethylation reaction of arenes and heteroarenes by the use of trifluoromethanesulfonyl chloride (CF_3SO_2Cl) as trifluoromethyl group source (Scheme 119) [296]. The relatively low cost and ease of handing of CF_3SO_2Cl as well as the mild reaction conditions led this method to become particular interesting. The absorption of one photon by the photocatalyst $Ru(phen)_3^{2+}$ will generate a high energy excited species $*Ru(phen)_3^{2+}$. The reaction is initiated by the reduction of triflyl chloride with $*Ru(phen)_3^{2+}$ (called oxidative quench) via one-electron transfer. The triflyl chloride rapidly collapses to trifluoromethyl radical when it ensues an electron from $*Ru(phen)_3^{2+}$.



Scheme 119 $Ru(phen)_3Cl_2$-catalyzed trifluoromethylation reaction of diazines

The addition of the trifluoromethyl radical to (het)arenes would form a new cyclohexadienyl like radical species, which would give trifluoromethylate (het)aryl compounds by the oxidation of $Ru(phen)_3^{3+}$ followed by deprotonation. The reaction has wide substrate scope. Different types of diazines gave good to excellent yields of trifluoromethylated products under treatment by 1–4 eq. of CF_3SO_2Cl in MeCN in a presents of 1–2 % of $Ru(phen)_3Cl_2$ and K_2HPO_4 as a base with irradiation by 26 W light source (Fig. 21).

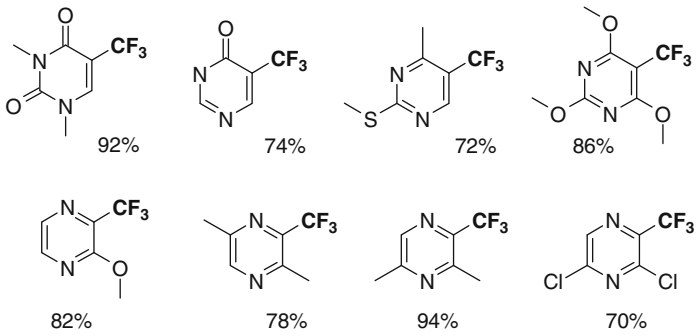
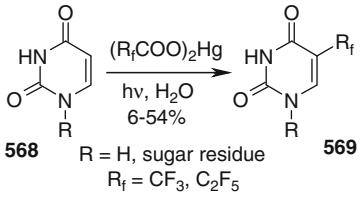


Fig. 21 Radical trifluoromethylation of diazines via photoredox catalysis

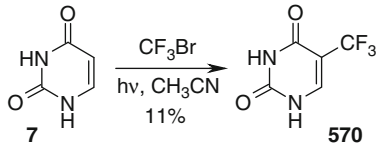
6.1.4 Other Methods

There are several other methods for generation of (per)fluoroalkyl radicals in reactions with diazines. In particular, photochemical decomposition of perfluoroalkyl mercury derivatives was used for perfluoroalkylation of uracils **568** (Scheme 120) [297]. Whereas for the parent uracil the method gave satisfactory results (30–54 % yields), the procedure was unfruitful for the sugar-modified derivatives (6–11 % yields).



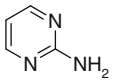
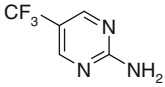
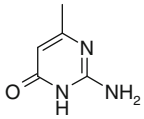
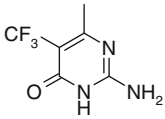
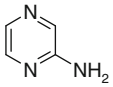
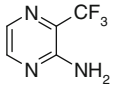
Scheme 120 Photochemical perfluoroalkylation of uracils with bis(perfluoroalkyl)mercury

Photochemical reaction of uracil **7** with CF_3Br also gave the corresponding 5-trifluoromethyl derivative, although in this case, the yield was unsatisfactory (11 %, 56 % conversion) (Scheme 121) [298].



Scheme 121 Photochemical trifluoromethylation of uracil with CF_3Br

Table 22 Fe(II)-catalyzed trifluoromethylation of diazines with CF_3I

#	Substrate	Conditions	Product	Yield (%)
1		CF_3I (3 eq.), $FeSO_4$ (0.3 eq.), H_2O_2 (2 eq.), H_2SO_4 (1 eq.), DMSO, rt		22
2		CF_3I (3 eq.), $FeSO_4$ (0.3 eq.), H_2O_2 (2 eq.), DMSO, rt		86
3		CF_3I (3 eq.), $FeSO_4$ (0.3 eq.), H_2O_2 (2 eq.), H_2SO_4 (1 eq.), DMSO, rt		57

Yamakawa with co-workers reported in 2010 Fe-catalyzed trifluoromethylation of various aromatics (including diazines) with CF_3I (Table 22). The method used $FeSO_4$–H_2O_2 system to generate active species from CF_3I. Since the reaction was of electrophilic nature, only diazines with electron-donating substituents were used as the substrates [299].

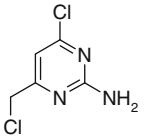
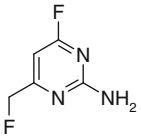
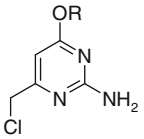
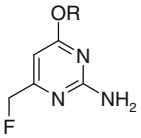
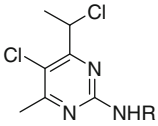
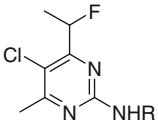
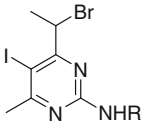
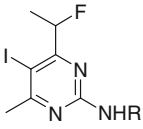
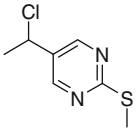
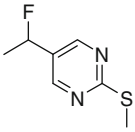
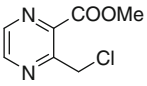
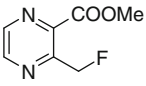
Several methods for the preparation of chain-fluorinated pyridazines relied on the so-called "anionic Friedel – Crafts" reactions (*i.e.* aromatic nucleophilic substitution with perfluoroalkyl anions or their synthetic equivalents) with tetrafluoropyridazine, which was discussed in the corresponding section on chemistry of ring-fluorinated diazines.

6.2 Nucleophilic Substitution with Fluoride

6.2.1 Substitution of Other Halogens

Nucleophilic substitution of halogen atoms with fluoride ion was relatively rarely used for the preparation of chain-fluorinated diazines. The method was applied for the preparation of monofluoroalkyl and trifluoromethyl diazines, and various reaction conditions were used in these two cases. Monofluoroalkyl diazines were obtained by reaction of the corresponding benzyl-type halides with CsF in DMF [300–304] or HMPA – DMSO [307] (Table 23). This approach was successfully

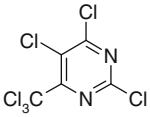
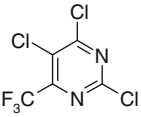
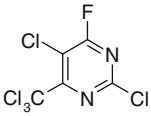
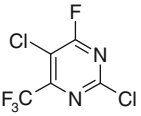
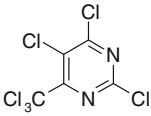
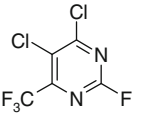
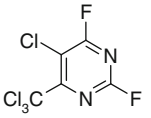
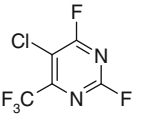
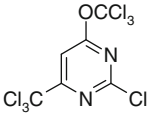
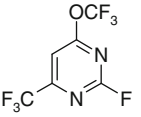
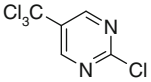
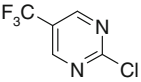
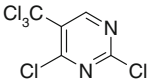
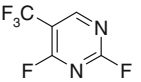
Table 23 Preparation of monofluoroalkyl diazines using nucleophilic substitution

#	Substrate	Conditions	Product	Yield (%)	Ref.
1		CsF, DMF, reflux		n/a	[300]
2		CsF, DMF, reflux (R=Me, Et, *n*-Bu)		n/a	[300]
3		CsF, DMF, 120–140 °C (R=$PhCH_2$, 4-$MeOC_6H_4(CH_2)_2$)		35–49	[301, 302]
4		CsF, DMF, 120–130 °C (R = 4-$FC_6H_4(CH_2)_2$)		75	[303]
5		CsF, DMF, 100 °C		17	[304]
6		CsF, HMPA, DMSO, 140 °C		9	[305]

used for the preparation 2-(fluoroalkyl)pyrimidines; the only literature example with pyrazine derivative reported low yield (9 %) [305].

For the synthesis of trifluoromethyl substituted diazines, the corresponding trichloromethyl derivatives were treated with HF [306], SbF_3 – cat. $SbCl_5$ [67, 307], or SbF_5 [308] at elevated temperatures (Table 24). Notably, the latter two reagents allowed selective fluorination of the side chain in the presence of chlorine substituents in the heteroaromatic ring [67, 308]. Contrary, in case of fluorination using HF the chlorine atoms in the diazine core were substituted first [67].

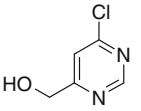
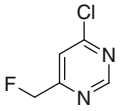
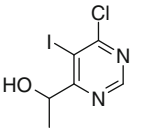
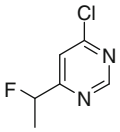
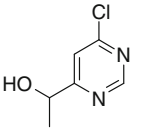
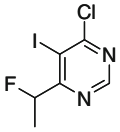
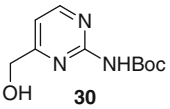
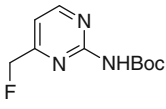
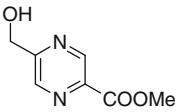
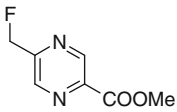
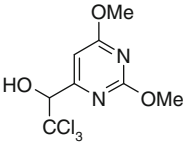
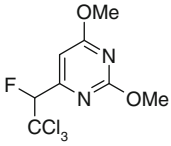
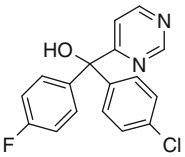
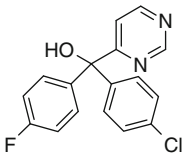
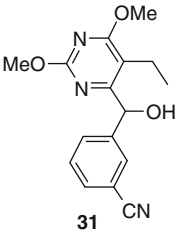
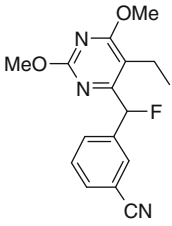
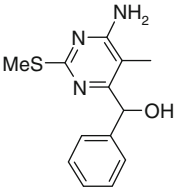
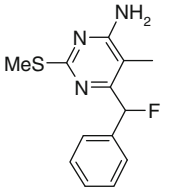
Table 24 Fluorination of trichloromethyl diazines

#	Substrate	Conditions	Product	Yield (%)	Ref.
1		SbF_3, $SbCl_5$, 175 °C		52	[67]
2		SbF_3, $SbCl_5$, 165 °C		38	[67]
3		SbF_3, $SbCl_5$, 150 °C		42	[67]
4		SbF_3, $SbCl_5$, 135 °C		65	[67]
5		SbF_3, $SbCl_5$,		72	[307]
6		SbF_5, 150 °C		51	[307]
7		HF, 10 bar, 142 °C		90	[306]

6.2.2 Deoxofluorination

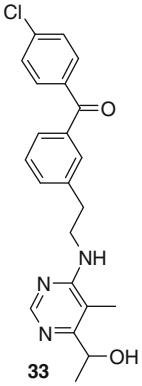
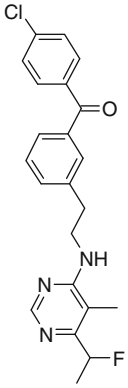
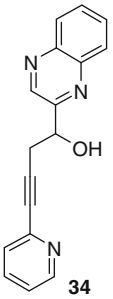
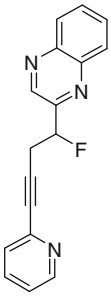
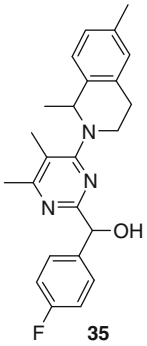
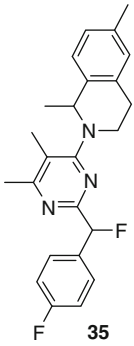
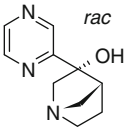
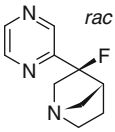
Reaction of alcohols, aldehydes and ketones with fluorinating agents (*i.e.* deoxofluorination) is a well-established method for the synthesis of chain-fluorinated diazines. Mono- and difluoroalkyl substituted diazines were obtained in moderate to good yields using this method (Tables 25 and 26). A common reagent used to achieve this type of transformations is diethylaminosulfur trifluoride (DAST) (**571**). Bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor™) (**572**), which is of higher thermal stability and therefore more amenable to large-scale use [309], is an alternative reagent for deoxofluorination. Both reagents work under mild conditions and are tolerant to a number of functional groups; they were successfully used for the fluorination of many functionalized diazines. In the case of chiral alcohols (Table 25, Entry 12–15), the reaction proceeded with inversion of the configuration (Fig. 22).

Table 25 Deoxofluorination of diazine-derived alcohols

#	Substrate	Conditions	Product	Yield (%)	Ref.
1		**571**, CH_2Cl_2, −78 °C to rt		30	[310]
2		**571**, CH_2Cl_2, −78 °C to rt		38	[310]
3		**571**, CH_2Cl_2, 0 °C to rt		79	[310]
4	 **30**	**571**, CH_2Cl_2, 0 °C		32	[311]
5		*n*-$C_4F_9SO_2F$, Et_3N, $Et_3N \cdot 3HF$, 0 °C to rt		15	[312]
6		**571**, CH_2Cl_2, −78 °C to reflux		53	[313]
7		**571**, CH_2Cl_2, rt		41	[314]
8	 **31**	**571**, CH_2Cl_2, −5 °C to rt		60	[315]
9	 **32**	**571**, CH_2Cl_2, 0 °C to rt		N/A	[316]

(continued)

Table 25 (continued)

#	Substrate	Conditions	Product	Yield (%)	Ref.
9	 **33**	**571**, CH_2Cl_2, 0 °C to rt		50	[302]
10	 **34**	**571**, CH_2Cl_2, −78 °C		33	[317]
11	 **35**	**571**, CH_2Cl_2, −78 °C	 **35**	73	[318]
12	 **41**	**571**, CH_2Cl_2, −65 °C		18	[319]

(continued)

Table 25 (continued)

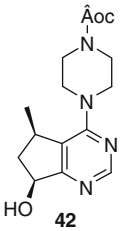
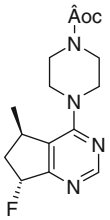
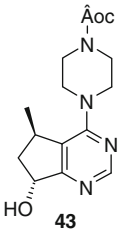
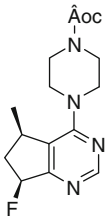
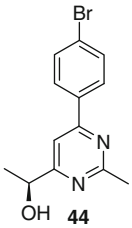
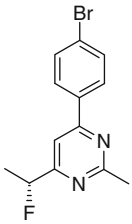
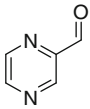
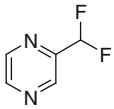
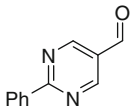
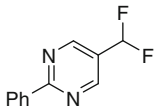
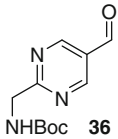
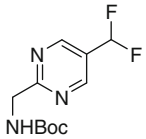
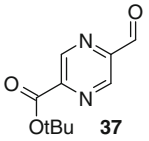
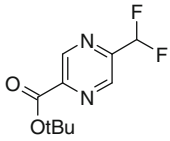
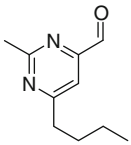
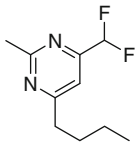
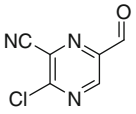
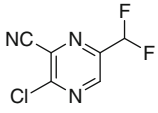
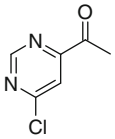
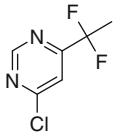
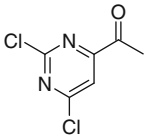
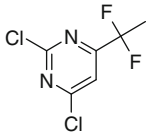
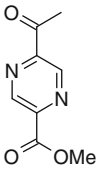
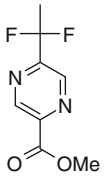
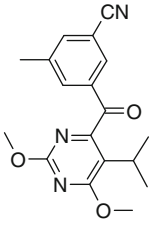
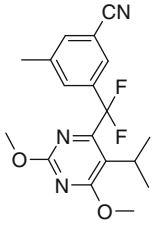
#	Substrate	Conditions	Product	Yield (%)	Ref.
13	 **42**	**571**, CH_2Cl_2, –20 °C		72	[320]
14	 **43**	**571**, CH_2Cl_2, –20 °C		61	[320]
15	 **44**	**571**, CH_2Cl_2, –10 °C		87	[321]

Table 26 Deoxofluorination of diazine-derived aldehydes and ketones

#	Substrate	Conditions	Product	Yield (%)	Ref.
1		**571**, $CFCl_3$, 20 °C		39	[322]
2		**571**, CH_3CCl_3, heating		61	[323]
3	 **36**	**28**, CH_2Cl_2, 0 °C		23	[324]

(continued)

Table 26 (continued)

#	Substrate	Conditions	Product	Yield (%)	Ref.
4	 **37**	**571**, THF, 0 °C to rt		68	[325]
5		**571**, $CDCl_3$, 35 °C		95	[321]
6	 **38**	**571**, CH_2Cl_2, cat. EtOH, rt		N/A	[326]
7		**571**, CH_2Cl_2, −78 °C to rt		24	[310]
8		**571**, CH_2Cl_2, rt		94	[327]
9	 **39**	**572**, CH_2Cl_2, 0 °C to rt		52	[311]
10	 **40**	**572**, 110 °C		73	[328]

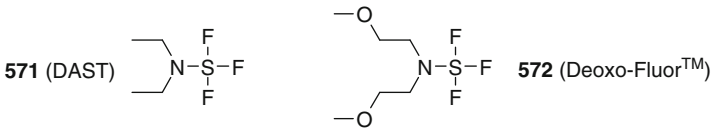
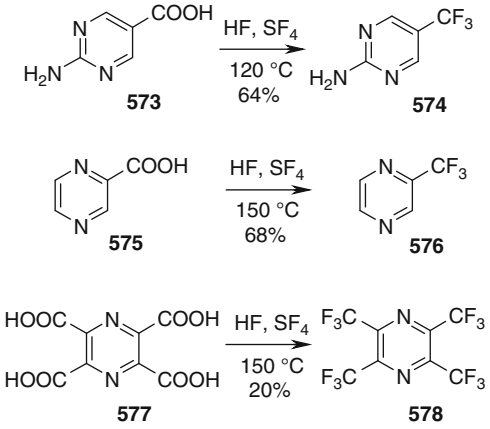


Fig. 22 Structure of DAST and Deoxo-Fluor

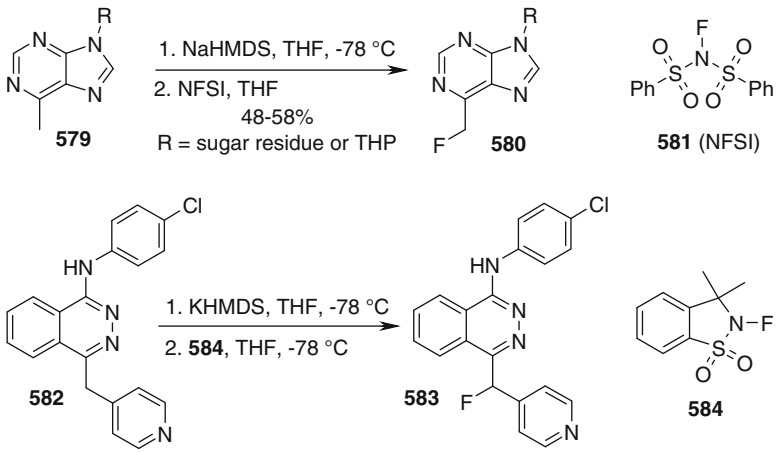
Exhaustive deoxofluorination of carboxylic group in diazines was studied scarcely: only a few examples included reaction of 2-aminopyrimidine-5-carboxylic acid (**45**), pyrazine mono- (**575**) and tetracarboxylic acids (**577**) with HF–SF_4 at 120–150 °C, giving the corresponding trifluoromethyl derivatives **547, 576** and **578** respectively in 20–68 % yield (Scheme 122) [329–331]. Under milder reaction conditions (*e.g.* with DAST), deoxofluorination of carboxylic acids stops at the formation of the corresponding acyl fluorides.



Scheme 122 Deoxofluorination of the carboxylic acids

6.3 Electrophilic Fluorination

In principle, fluorine atom can be introduced into the side chain of heterocycles by reaction of the corresponding α-hetarylcarbanions with electrophilic fluorinating reagents. Nevertheless, this approach was rarely used for diazines. In particular, 6-fluoromethylpurines **580** were obtained in 48–58 % yields by deprotonation of purine derivatives **579** with NaHMDS followed by reaction with *N*-fluorobenzenesulfonimide (NFSI, **51**) (Scheme 123) [332]. A phthalazine derivative **583** was prepared by an analogous approach, using *N*-fluoro-2,α-cumenesultam (**584**) as the fluorinating agent [333].



Scheme 123 Electrophilic fluorination of diazines

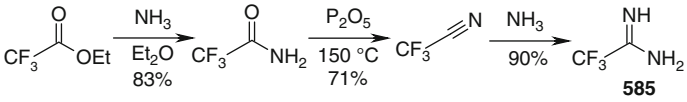
7 Construction of Diazine Core Using Fluorine-Containing Building Blocks

7.1 Synthesis from α-Fluorocarboxylic Acids and Their Derivatives

7.1.1 CCC+NCN Approach to Pyrimidines (Principal Synthesis)

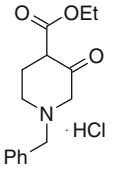
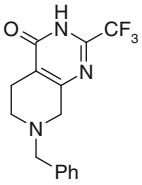
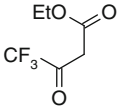
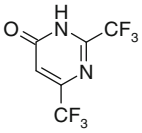
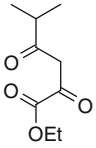
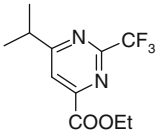
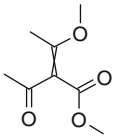
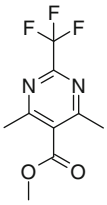
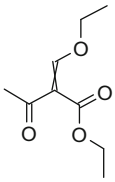
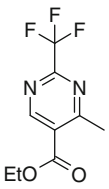
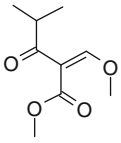
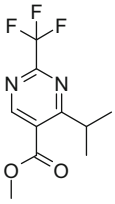
Because of its wide applicability, the method that involves the reaction of a binucleophile to supply the three-atom fragment (NCN) with a bis-electrophile to provide the three-carbon fragment (CCC), *i.e.* CCC+NCN or [3+3] approach to pyrimidines, is known as the principal synthesis [334]. Among the NCN binucleophiles, only amidines provide possibility to introduce the fluorinated side chain into the pyrimidine core.

Trifluoroacetamidine (**585**) is most widely used for the principal synthesis of pyrimidines. Compound **585** can be prepared from ethyl trifluoroacetate by ammonolysis, followed by dehydration with P_2O_5 and reaction with ammonia (Scheme 124) [335, 336]. Amidine **585** has been introduced into reaction with various β-dicarbonyl compounds and their synthetic equivalents (Table 27), including β-ketoesters (Entries 1–6), in particular β-ketopyruvates (Entry 3) and α-alkoxymethylene-β-ketoesters (Entries 4–6), β-enaminocarbonyl compounds (Entries 7–9), malonic acid derivatives (Entry 10), fluorinated β-diketones (Entry 11), vinamidinium salts (Entry 12), α,β-unsaturated nitriles with leaving group at β position (Entries 13–15) and other bis-electrophiles (Entries 16, 17). Usually, the reaction gives moderate yields of the target 2-CF_3-pyrimidines (*ca.* 50 %).



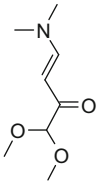
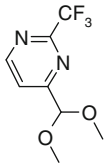
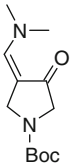
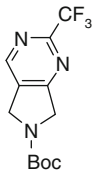
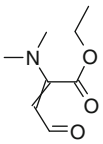
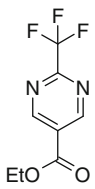
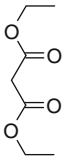
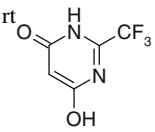
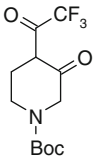
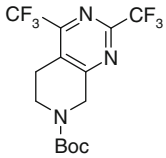
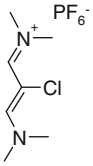
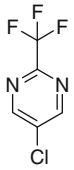
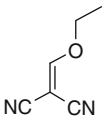
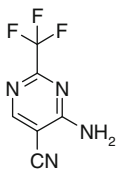
Scheme 124 Synthesis of trifluoroacetamidine (**585**)

Table 27 Syntheses of fluorinated diazines using trifluoroacetamidine (**585**)

#	Substrate	Conditions	Product	Yield (%)	Ref.
1		**585**, EtONa, EtOH, rt		78	[337]
2		**585**, EtONa, EtOH, rt		24	[338]
3		**585**, HCl, EtOH, 0 °C		65	[339]
4		**585**, MeOH, acetone 0 °C to rt		45	[340]
5		**585**, EtONa, EtOH, reflux		55	[341]
6		**585**, MeONa, MeOH, reflux		50–60	[342]

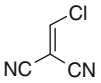
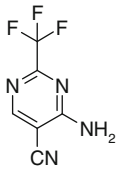
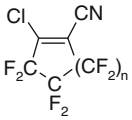
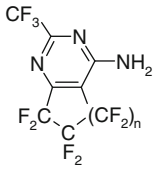
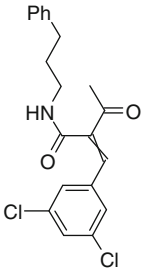
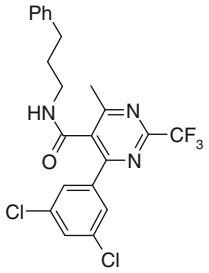
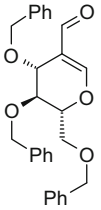
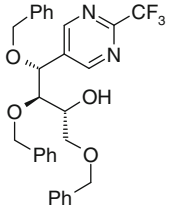
(continued)

Table 27 (continued)

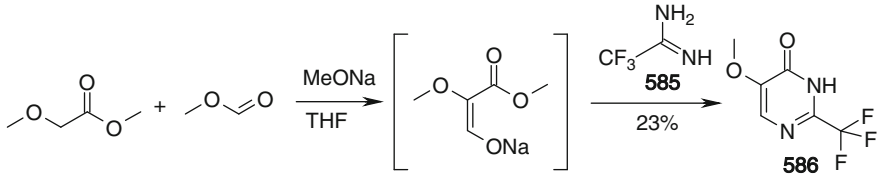
#	Substrate	Conditions	Product	Yield (%)	Ref.
7		**585**, EtOH, reflux		44	[343]
8		**585**, EtONa, EtOH, reflux		N/A	[344]
9		**585**, EtOH, reflux		44	[341]
10		**585**, MeONa, MeOH, 0 °C to rt		N/A	[345]
11		**585**, py, 80 °C		87	[346]
12		**585**, Et_3N, MeCN, rt		36	[347]
13		**585**, EtONa, EtOH, rt		72	[348]

(continued)

Table 27 (continued)

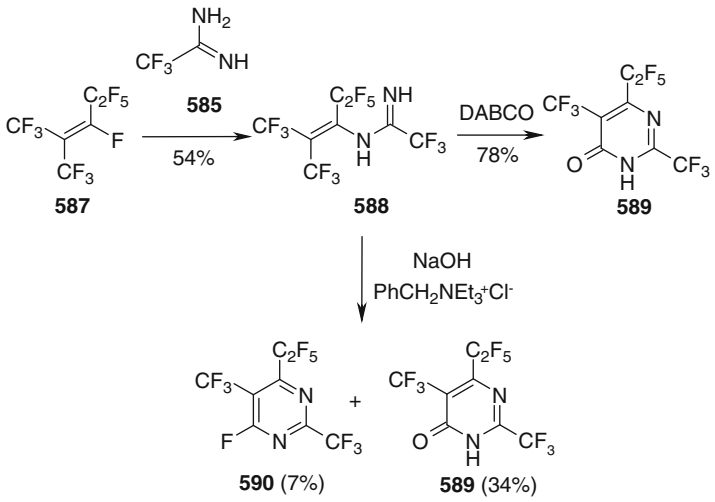
#	Substrate	Conditions	Product	Yield (%)	Ref.
14		**585**, Et_2O, rt		79	[349]
15		**585**, Et_2O, rt; n = 1, 2		76–90	[350]
16		**585**, AcONa, DMF, 80 °C		25	[351]
17		**585**, EtONa, 90 °C, MW		70	[352]

A three-component one-pot reaction of **585**, methyl formate, methyl methoxyacetate in presence of sodium methoxide was also studied (Scheme 125) [353]. Obviously, in this case Claisen condensation occurred first, followed by heterocyclization with **585** to give pyrimidine derivative **586**.



Scheme 125 A three-component reaction involving **585**

Reaction of amidine **585** with perfluorinated alkene **587** led to the formation of amidine **588**, which upon heating with alkali gave a mixture of pyrimidines **590** (7 %) and **589** (34 %) (Scheme 126) [354]. Pyrimidine **589** was obtained in 78 % yield when the second step of this sequence was performed using DABCO.



Scheme 126 Synthesis of pyrimidines starting from alkene **587**

Apart from **585**, another fluorinated amidines were used for the principal synthesis of pyrimidines including compounds **591–594** (Fig. 23).

Since the corresponding nitrile **595** does not react with ammonia directly, preparation of **591** starting from **595** used several steps (Scheme 127), including isolation of ethyl 2-fluoroacetimidate (as hydrochloride **596**) [355, 356] or ethyl 2-fluorothioacetimidate [357]. In some literature sources the step including reaction of **592** with ammonia was omitted [358]. Compound **592** was prepared in 48 % yield from methyl difluoroacetate **597** by reaction with NH_4Cl–Me_3Al in toluene at 80 °C [359]. Synthesis of **59** is analogous to that of trifluoroacetamidine **585** [360], and **594** – of fluoroacetamidine **591** [361].

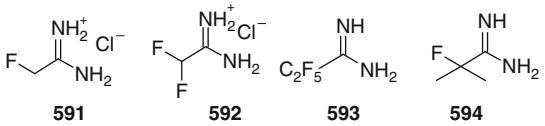
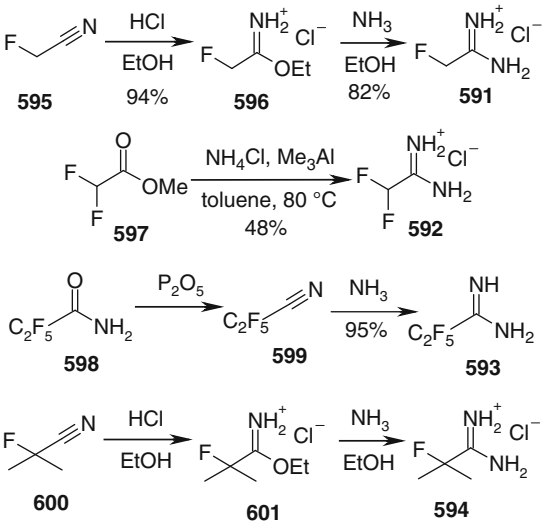


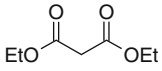
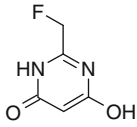
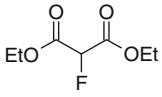
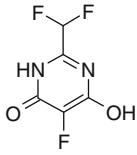
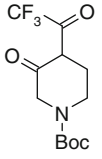
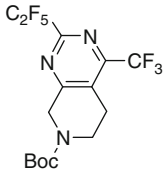
Fig. 23 Structure of **α**-fluorinated amidines



Scheme 127 Synthesis of fluorinated acetamidines **591**–**594**

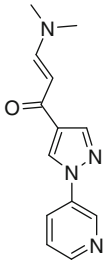
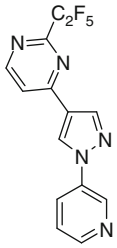
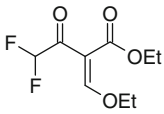
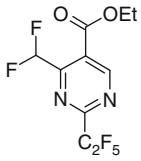
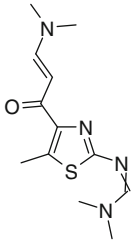
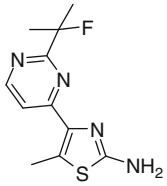
Only a few examples of principal synthesis of pyrimidines involving amidines **591**–**594** were described to date (Table 28), including reaction of **591** and **592** with malonic acid derivatives (Entries 1 and 2), **593** – with β-diketone, enamino ketone and ethyxymethylene derivative of a β-ketoester (Entries 3–5), and **594** – with enamino ketone (Entry 6).

Table 28 Syntheses of fluorinated diazines using amidines **591**–**594**

#	Substrate	Conditions	Product	Yield (%)	Ref.
1		**591**, MeONa, MeOH, reflux		96	[355]
2		**592**, MeONa, MeOH, 80 °C		61	[359]
3		**593**, *i*PrOH, cat. $BF_3{\cdot}Et_2O$, 120 °C		59	[362]

(continued)

Table 28 (continued)

#	Substrate	Conditions	Product	Yield (%)	Ref.
4		**593**, MeONa, MeOH, 55 °C		44	[363]
5		**593**, EtONa, EtOH, reflux		40	[364]
6		**594**, $MeO(CH_2)_2OH$, rt, then NaOH, 125 °C		N/A	[361]

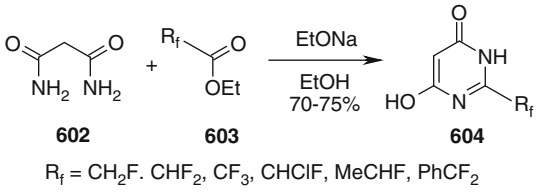
7.1.2 Other Approaches to Pyrimidines

Apart from the principal synthesis of pyrimidines (*i.e.* CCC+NCN or [3+3] approach), several other methods involve the use of fluorinated carboxylic acid derivatives:

– NCCCN+C or [5+1] approach;
– CC+2CN or [2+2+2] approach;
– NCCCC + N or [5 + 1] approach;

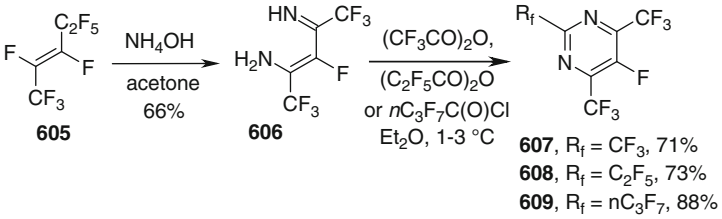
One of them (NCCCN+C approach) is a common method for the preparation of quinazolines and their hetero-analogues (see the next section). Nevertheless, malonamide **602** was shown to react with various fluorinated esters **603** to give pyrimidine derivatives **604** in good yields (70–75 %) (Scheme 128) [365] (in some patents,

lower yield of the product was reported, *e.g.* 29 % for the difluoromethyl derivative [356]). Excess of sodium alcoxide was used in the reaction, therefore, sodium salt of malonamide was likely an active species, which allowed retaining nitrogen atoms of the amide fragment in the final product. In the case of ethyl trifluoroacetate, the reaction was performed on a kilogram scale (conditions: NaH, *n*BuOH, toluene, 100 °C, then 23–25 °C, 44 %) [366].



Scheme 128 NCCCN+C approach to pyrimidines using fluorinated esters

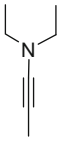
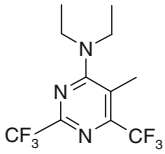
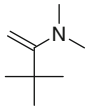
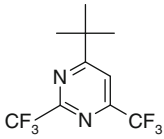
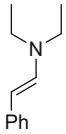
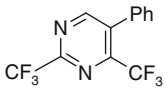
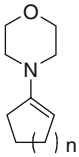
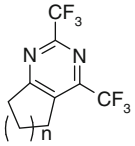
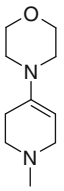
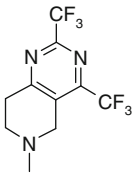
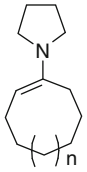
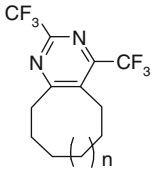
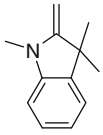
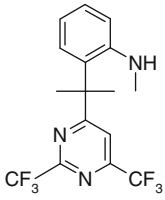
One more method relying on NCCCN+C approach was used for the synthesis of perfluorinated pyrimidine derivatives. It relied on acylation of β-diimine **606** – a product of reaction of alkene **605** (an analogue of **587** mentioned in the previous section) with ammonia – with perfluorinated anhydrides or acyl chlorides (Scheme 129) [367]. Pyrimidines **607**–**609** were obtained in 71–88 % yields.



Scheme 129 Synthesis of pyrimidines starting from alkene **66**

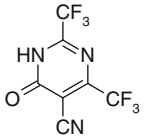
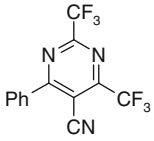
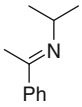
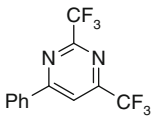
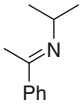
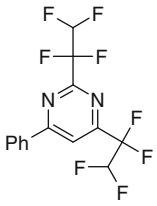
Several methods for the preparation of chain-fluorinated pyrimidines involve reactions of fluorinated nitriles. One of such methods relies on reaction of two trifluoroacetonitrile molecules with one molecule of a substrate, *i.e.* CC+2CN or [2+2+2] approach. This approach was used for several types of substrates (Table 29), including ynamines (Entry 1), enamines (Entries 2–7), imines and methylene active compounds (Entries 8, 9).

Table 29 CC+2CN approach to chain-fluorinated pyrimidines

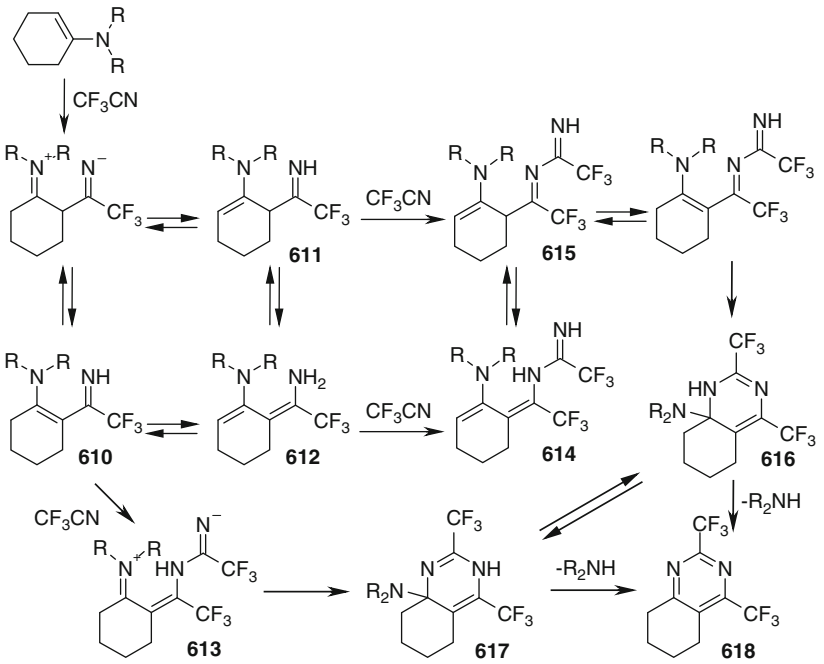
#	Substrate	Conditions	Product	Yield (%)	Ref.
1		CF_3CN, hexane, −15 °C		75	[368]
2		CF_3CN, hexane, 40 °C		78	[369]
3		CF_3CN, hexane, 40 °C		72	[369]
4		CF_3CN, hexane, 40 °C; n = 1, 2		77–87	[369]
5		CF_3CN, hexane, 40 °C		52	[369]
6		CF_3CN, hexane, 40 °C; n = 1, 5		71–78	[369]
7		CF_3CN, hexane, 40 °C		81	[369]

(continued)

Table 29 (continued)

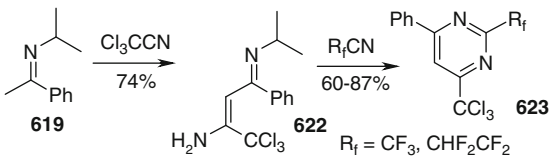
#	Substrate	Conditions	Product	Yield (%)	Ref.
8		*t*BuOK, THF, rt; then CF_3CN		84	[370]
9		NaH, THF, rt; then CF_3CN		63	[371]
10	 **619**	CF_3CN, rt	 **620**	78	[372]
11	 **619**	CHF_2CF_2CN, 65 °C	 **621**	90	[372]

Stepwise mechanism was proposed for the reaction of CF_3CN with enamines including formation of tautomeric 1:1 adducts **610–612** (Scheme 130) [369]. Each of these adducts can react further with CF_3CN to give 1:2 adducts **613–615**, which can undergo cyclization to dihydropyrimidines **616** and **617**, either directly or *via* tautomerization. Both **616** and **617** give the final product **618** upon elimination of a secondary amine. In case of enamines lacking β′-hydrogen atom, only one of the pathways mentioned above is possible, namely, *via* adducts of the type **610** and **613**.



Scheme 130 Reaction of enamines with CF_3CN: a proposed mechanism

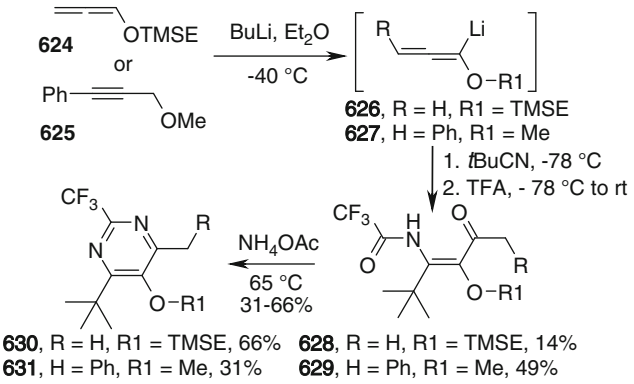
Ketimines (*e.g.* **619**) were also introduced into reaction with fluorinated nitriles (CF_3CN and CHF_2CF_2CN) to give 2:1 adducts (Table 29, Entries 10 and 11) [374]. In case of **619**, pyrimidines **620** and **621** were obtained in 78–90 % yields, whereas for the 2-thienyl analogue of **619**, the yields of the corresponding products were moderate (26–45 %). Notably, the method allowed to use two different electron-deficient nitriles, if CCl_3CN was used in the first step of the reaction (Scheme 131). In this case, intermediate **82** could be isolated.



Scheme 131 Two-step reaction of imines with electron-deficient nitriles

Recently, an interesting approach to chain-fluorinated pyrimidines was described (CF_3COOH as the source of CF_3 group). The method relied on CCCCN+N ([5+1]) cyclization of enamides **628** and **629** with NH_4OAc to give pyrimidines **630** and **631** in 66 and 31 % yields respectively (Scheme 132) [373]. Compounds **628** and **629** were prepared by generation of the corresponding lithiated allene derivatives **626**

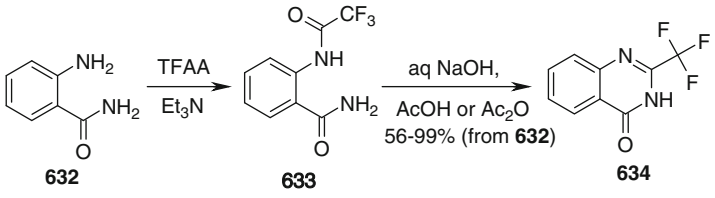
and **627**, followed by reaction with nitrile and subsequent acylation with CF_3COOH. In case of **628**, the synthesis was complicated by partial removal of the trimethylsilylethyl protecting group (TMSE) to result in low yield of the product (14 %).



Scheme 132 CCCCN+N ([5+1]) approach to chain-fluorinated pyrimidines

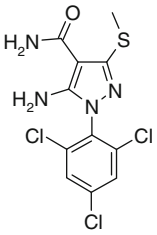
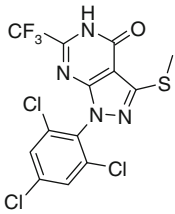
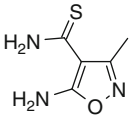
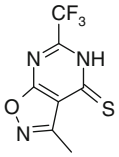
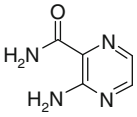
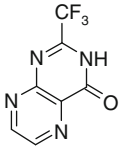
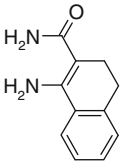
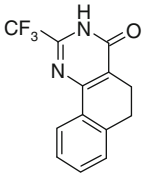
7.1.3 Construction of Pyrimidine Ring of Quinazolines and Their Hetero-analogues

A classical method for the synthesis of quinazolines is reaction of anthranilamides (*i.e.* NCCCN-binucleophiles) with carboxylic acids or their derivatives (*i.e.* C_1-electrophiles) [374]. The reaction proceeds in two steps: acylation of aromatic amino group followed by heterocyclization. For example, reaction of anthranilamide **632** or its derivatives with trifluoroacetic anhydride afforded amide **633**, which underwent cyclization upon action of aqueous NaOH [375], AcOH [376] or Ac_2O [377] to give quinazolone **634** (56–99 % from **632**) (Scheme 133). The reaction sequence was also performed in one-pot manner by heating of anthranilamides and CF_3COOH at 300 °C upon MW irradiation; in this case moderate to good yields of the products were obtained (29–75 %) [378]. Alternatively, **634** was obtained by heating of **632** and ethyl trifluoroacetate [379]. Several modifications of the method were applied for the synthesis of fused quinalozolones and hetero-analogues, *e.g.* pyrazolo[3,4-*d*]pyrimidine (Table 30, Entry 1), isoxazolo[5,4-*d*]pyrimidine (Entry 2), pteridine (Entry 3), or benzoquinazoline (Entry 4) derivatives.



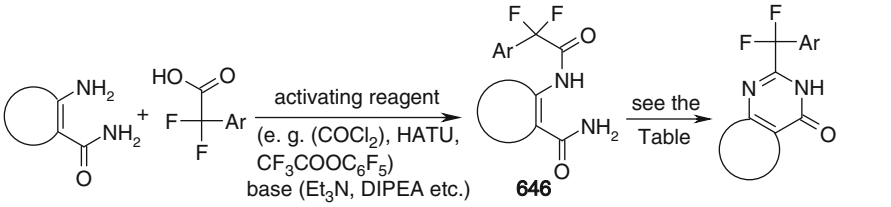
Scheme 133 Synthesis of quinazolone **634**

Table 30 Synthesis of hetero-analogues of chain-fluorinated quinalozolones

#	Substrate	Conditions	Product	Yield (%)	Ref.
1		CF_3COOEt, EtONa, EtOH, reflux		100	[380]
2		TFAA, TFA, rt		40	[381]
3		TFAA, TFA, 90 °C		90	[382]
4		TFAA, $CHCl_3$, reflux		93	[383]

The above mentioned approach was used extensively for the preparation of 2-(aryldifluoromethyl)quinazolin-4-ones and their hetero-analogues. In particular, anthranilamides, as well as their thiophene or pyrazole analogues **635–642** were coupled with (het)aryldifluoroacetic acids **643–645** to give amides **646** (Table 31). For the activation of the carboxylic acid, a number of common reagents were used, including $(COCl)_2$, HATU, and pentafluorophenyl trifluoroacetate. Cyclization of **103** was performed by heating with Me_3SiCl/Et_3N in 1,2-dichloroethane (DCE) at 80–85 °C (Entries 1–5), as well as by refluxing in AcOH or Ac_2O/AcOH (Entries 6 and 7). One-pot reaction of **637–642** and **643–645** was also developed by using of trimethylsilyl polyphosphate (TMSPP) at 115–130 °C (Table 32).

Table 31 Two-step synthesis of 2-(aryldifluoromethyl)quinazolin-4-ones and their hetero-analogues



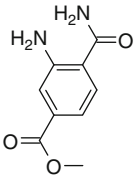
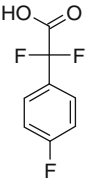
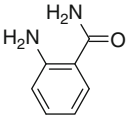
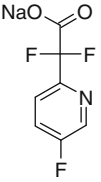
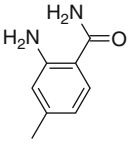
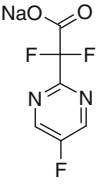
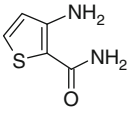
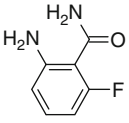
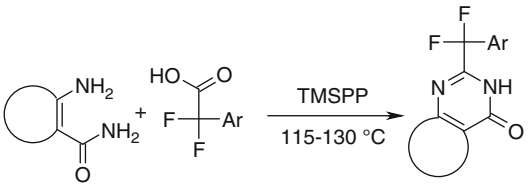
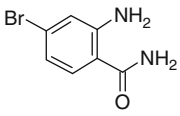
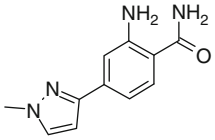
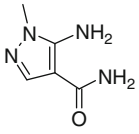
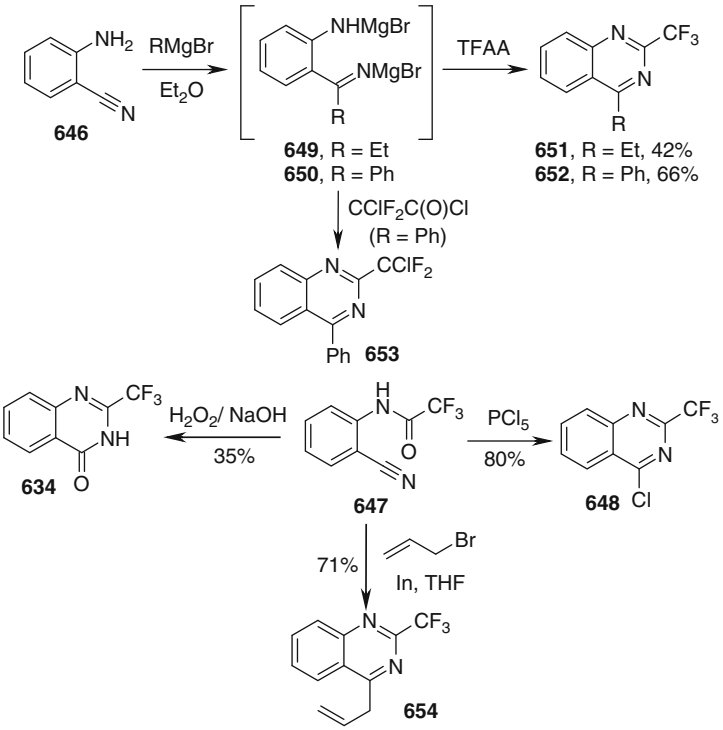
#	Substrate	Acid	Cyclization step: Conditions	Yield (%)	Ref.
1	 **635**	 **643**	Me_3SiCl, Et_3N, DCE, 85 °C	89	[384]
2	 **636**	 **644**	Me_3SiCl, Et_3N, DCE, 85 °C	91	[385]
3	 **637**	**643**	Me_3SiCl, Et_3N, DCE, 85 °C	37	[386]
4	**636**	 **645**	Me_3SiCl, Et_3N, DCE, 85 °C	69	[385]
5	 **638**	**643**	Me_3SiCl, Et_3N, DCE, 85 °C	83	[385]
6	 **639**	**643**	AcOH, 120 °C	61	[386]
7	**638**	**643**	AcOH, reflux, then Ac_2O, AcOH, reflux	85	[384]

Table 32 One-pot synthesis of 2-(aryldifluoromethyl)quinazolin-4-ones and their hetero-analogues



#	Substrate	Acid	Yield (%)	Ref.
1	 **640**	**643**	79	[384]
2	 **641**	**643**	91	[384]
3	**640**	**644**	77	[385]
4	**637**	**644**	66	[385]
5	**638**	**644**	43	[384]
6	 **642**	**644**	44	[387]

A convenient precursor of quinazoline derivatives is anthranilic acid nitrile **646**. It should be noted that in order to introduce the substituent at C4 position of the quinazoline core starting from **646** or its derivatives, a nucleophile is necessary for the cyclization – a feature which can be advantageous since additional diversity point appears in the synthesis. In particular, reaction of *N*-trifluoroacetyl derivative of **646** – compound **647** – with PCl_5 in sulfolane gave 4-chloro derivative **648** in 80 % yield (Scheme 134) [388]. Upon heating of **646** with H_2O_2/NaOH at 35–45 °C, quinazolone **634** was obtained; in this case, amide **633** was an intermediate in the reaction [393]. Reaction of **646** with Grignard reagents gave intermediates **649** and

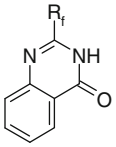
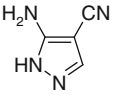
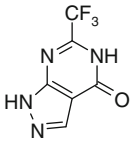
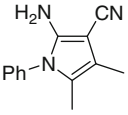
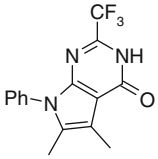
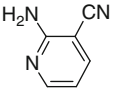
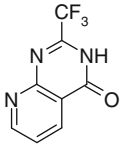
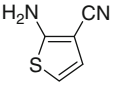
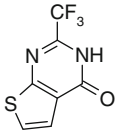


Scheme 134 Anthranilic acid nitrile (**104**) and its amide **105** as a quinazoline precursors

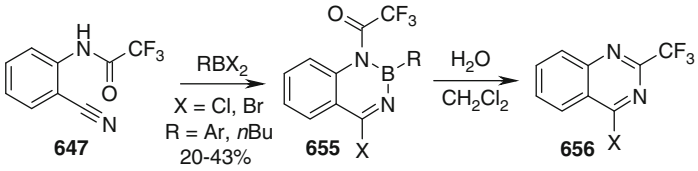
650, which upon acylation with TFAA or $CClF_2C(O)Cl$ gave quinazolines **651**–**653** in 42–90 % yields [390]. Indium-promoted version of the latter method was also developed for the synthesis of 4-allylquinazolines, which could be illustrated by reaction of compound **47** with allyl bromide in a presence of indium [391].

Compound **646** and the corresponding heterocyclic nitriles were used in the synthesis of other perfluorinated quinazolines (Table 33, Entry 1) and their hetero-analogues, *e.g.* pyrazolo[3,4-*d*]pyrimidine (Entry 2), 7-deazahypoxanthine (Entry 3), pyrido[2,3-*d*]pyrimidine (Entry 4), or thieno[2,3-*d*]pyrimidine derivatives (Entry 5). In all these cases, the corresponding amides (*e.g.* **633**) can be proposed as the intermediates in the reaction.

Table 33 Synthesis of chain-fluorinated quinalozolones and their hetero-analogues of quinalozolones from the corresponding nitriles

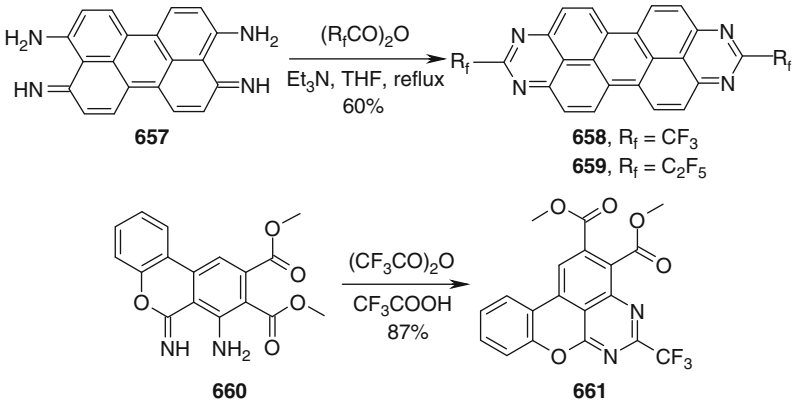
#	Substrate	Conditions	Product	Yield (%)	Ref.
1	**646**	1. $R_fC(O)Cl$, py, 60 °C 2. NaOH, H_2O_2, H_2O, dioxane, 35–40 °C; R_f=C_3F_7, C_5F_{11}, C_7F_{15}		20–62	[389]
2		1. TFAA, 40 °C 2. KOH, H_2O_2, H_2O, 10–15 °C 3. 210–260 °C		61	[392]
3		1. TFAA, TFA, reflux, 20 min 2. P_2O_5, DMCA, H_2O, 200 °C, 3 h		27	[393]
4		1. TFAA, py, 0 °C to rt 2. NaOH, H_2O_2, EtOH, H_2O, reflux then rt		74	[394]
5		TFA, $POCl_3$, MW, 70 °C		N/A	[395]

An unusual (although scarcely preparative) variation of using nitrile **647** for the synthesis of quinazolines was described in late 1970s [396]. Compound **647** reacted with organoboron derivatives to give bora-heterocycles **655**, which upon hydrolysis rearranged to quinazoline derivatives **656** (Scheme 135).



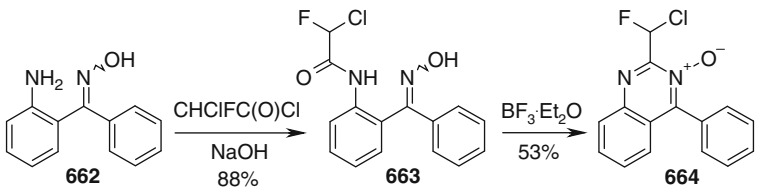
Scheme 135 Boron-mediated synthesis of quinazolines from **647**

Certain *peri*-substituted aromatic diamines can act as NCCCN binucleophiles in reaction with fluorinated acid derivatives to give pyrimidines. In particular, fused pyrimidine derivatives **658, 659** and **661** were obtained from amines **657** [397] and **660** [398] by reaction with fluorinated anhydrides (Scheme 136).



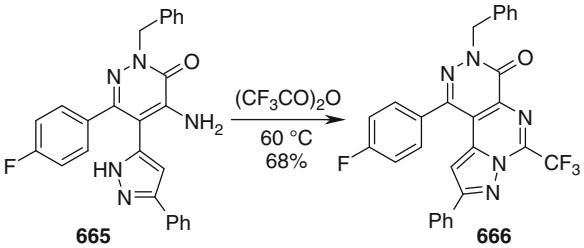
Scheme 136 Synthesis of fused pyrimidines from *peri*-substituted aromatic diamines

An unusual reaction sequence, which also falls into category of NCCCN+C approaches, was described in 1980 [399]. In particular, oxime **662** reacted with chlorofluoroacetyl chloride to give acyl derivative **663**, which underwent cyclization to quinazoline *N*-oxide **664** upon action of $BF_3 \cdot Et_2O$ (Scheme 137).



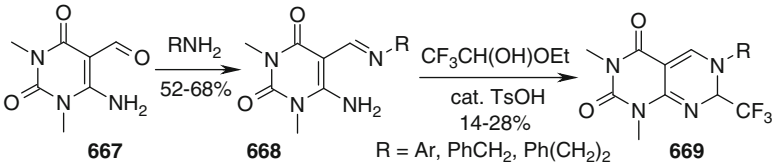
Scheme 137 Synthesis of quinazoline *N*-oxide **121**

One more example of an uncommon NCCCN binucleophile, compound **122**, was used recently in the synthesis of human A_1 adenosine receptor ligands (Scheme 138) [400]. In this case, a pyrazole nitrogen atom was one of the nucleophilic centers in the reaction, which led to the formation of tricyclic fused aromatic ring system (compound **666**).



Scheme 138 Synthesis of a tricyclic fused aromatic ring system (compound **123**)

NCCCN+C approach was also used for the preparation of fused dihydropyrimidines. In particular, reaction of imines **668** with trifluoroacetaldehyde ethyl hemiacetal in the presence of acidic catalyst gave pyrimido[4,5-*d*]pyrimidine derivatives **669**, although in low yields (14–28 %) (Scheme 139) [401].

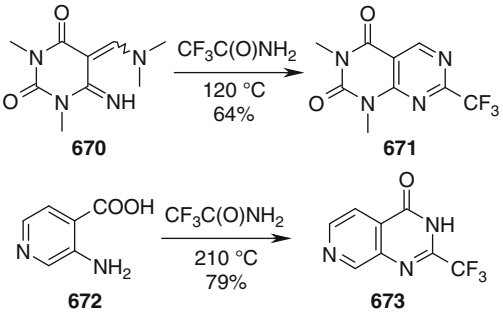


Scheme 139 NCCCN+C approach in the synthesis of fused dihydropyrimidines

Apart from NCCCN+C ([5+1]) approach discussed in all syntheses of chain-fluorinated quinazolines and their hetero-analogues described above, other methods were also developed, in particular:

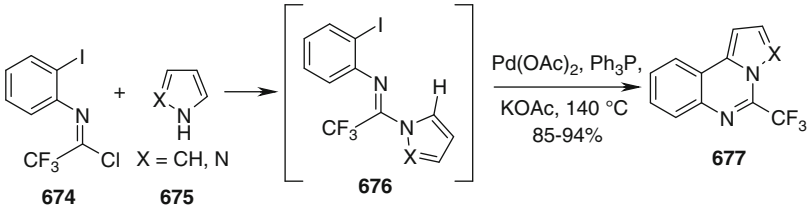
– CCCN+CN ([4+2]) approach;
– intramolecular cyclizations of alkynes;
– other heterocyclizations.

An example of using CCCN+CN ([4+2]) approach includes preparation of chain-fluorinated pyrimido[4,5-*d*]pyrimidine derivative **671** (Scheme 140) [402]. In this method, enamine **670** reacted with trifluoroacetamide at 120 °C to give **671** in 64 % yield. Analogously, reaction of trifluoroacetamide and pyridine derivative **672** led to the formation of pyrido[3,4-*d*]pyrimidine **673** [403].



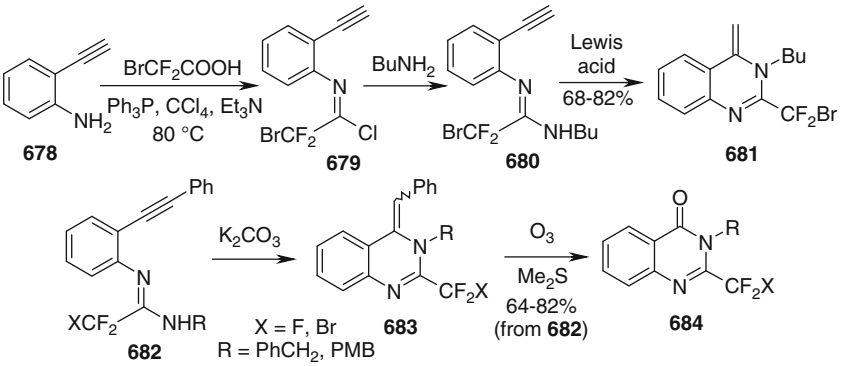
Scheme 140 CCCN+CN ([4+2]) approach to fused trifluoromethyl pyrimidines

A different example of using [4+2] approach described formation of tricyclic trifluoromethyl-substituted pyrimidine derivatives **677** *via* direct C–H bond functionalization in azoles (Scheme 141) [408]. In this case the trifluoromethyl group arrived to the final products from CCNC reactants.



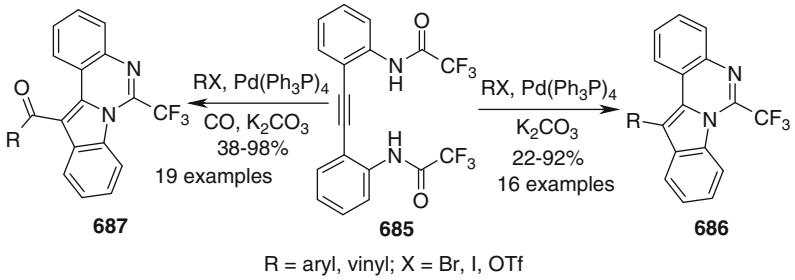
Scheme 141 CCNC+NC ([4+2]) approach to fused trifluoromethyl pyrimidines

Several methods for the preparation of chain-fluorinated quinazolines relied on using properly functionalized alkynes. In particular, upon treatment with a Lewis acis (*i.e.* $ZnCl_2$, $BF_3{\cdot}Et_2O$, $InCl_3{\cdot}3H_2O$, $CuSO_4$ or $Cu(OTf)_2$), amidine **679** (prepared in two steps from aromatic amine **678**) gave quinazoline derivative **681** in 68–82 % yield (Scheme 142) [405]. Furthermore, amidines **682** underwent analogous reaction upon treatment with K_2CO_3 in CH_3CN at 80 °C. Products **683** (obtained as mixtures of *E*/*Z* isomers) were subjected to ozonolysis to give quinazolones **684** in 64–82 % overall yield.



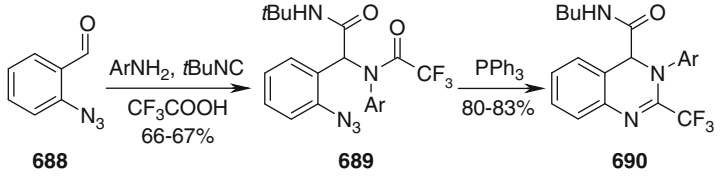
Scheme 142 Syntheses of chain-fluorinated quinazolines from alkynes **132** and **134**

Palladium-catalyzed reaction of bis(*o*-trifluoroacetamidophenyl) acetylene **685** with various aryl and vinyl halides and triflates led to the formation of indolo[1,2-*c*] quinazolines **686** (Scheme 143) [406]. If the reaction was performed in presence of CO, the corresponding acyl derivatives **687** were obtained [407]. In both cases, the indole heterocyclic system was formed first; the subsequent pyrimidine ring closure resulted in construction of the tetracyclic ring system.



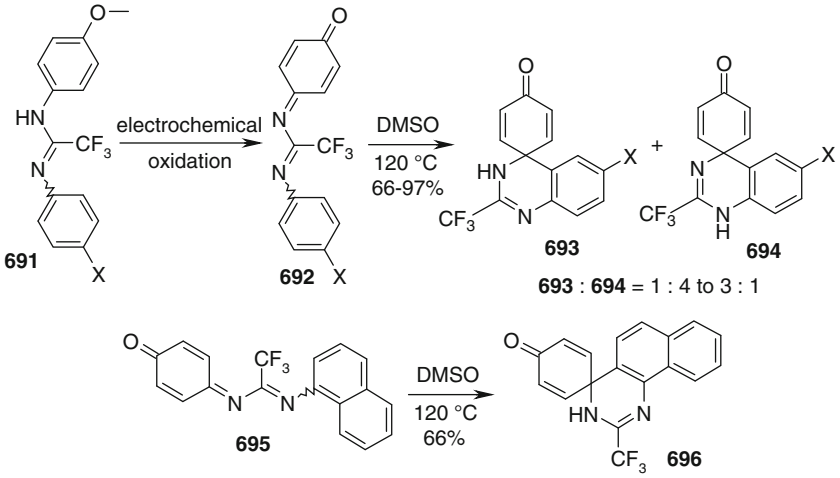
Scheme 143 Syntheses of chain-fluorinated quinazolines from alkyne **137**

3,4-Dihydroquinazolines **690** were obtained by intramolecular Staudinger – aza-Wittig tandem sequence from azides **689**, which in turn were synthesized from aldehyde **688** using a four-component Ugi reaction (Scheme 144) [408].



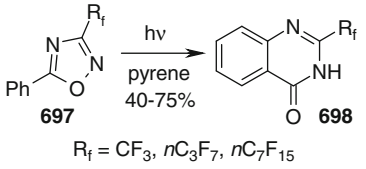
Scheme 144 Syntheses of chain-fluorinated dihydroquinazolines **140**

Tautomeric trifluoromethyl-substituted spirocyclic quinazolines **693** and **694** were formed when *p*-benzoquinone imines **692** (synthesized by electrochemical oxidation of the corresponding *p*-anisidine derivatives **691**) were heated in DMSO at 120 °C (Scheme 145) [409]. The reaction was affected by solvent (DMSO giving the highest yields) and nature of the substituents in **692**. In the case of naphthalene derivatives (e.g. **695**), the cyclization gave single tautomers (e.g. **696**). A synchronous mechanism was proposed for this transformation.



Scheme 145 Syntheses of spirocyclic quinazolines from *p*-benzoquinone imines

An interesting approach to chain-fluorinated quinazolines relied on photochemical recyclization of 1,2,4-oxadiazole derivatives **697** (Scheme 146) [410]. The corresponding quinazolones **698** were obtained in 40–75 % yields when pyrene was used as a sensitizer. This is contrary to the data obtained for simple alkyl-substituted oxadiazoles, which gave highest yields of the products upon irradiation in the presence of triethylamine.



Scheme 146 Photochemical recyclization of 1,2,4-oxadiazole derivatives

7.2 *Principal Synthesis from Fluorinated β-Dicarbonyl Compounds and Their Analogues*

In the previous section, synthesis of pyrimidine derivatives bearing fluorinated alkyl substituent at C-2 atom was discussed. Derivatives of fluorinated carboxylic acids and related compounds were used as the fluorine sources. The most important method for the preparation of other chain-fluorinated pyrimidines is the principal synthesis from fluoroalkyl-substituted three-carbon bis-electrophiles (*e.g.* β-dicarbonyl compounds). A huge number of fluorinated bis-electrophiles were introduced in the principal synthesis of pyrimidines bearing fluoroalkyl substituent at C-4 atom of the heterocyclic ring (Fig. 24), including fluorine-containing:

- β-dicarbonyl compounds **699**, *i.e.* β-diketones, β-ketoesters, β-ketoamides (385 reaction hits in Reaxys®);
- β-alkoxy-substituted enones **700** (202 hits), β-enaminones **701** (32 hits), (thio) acetals **702** (9 hits), as well as other enones **703** (52 hits);
- chromone derivatives and hetero-analogues **704** (23 hits) and **705** (22 hits);
- β-halosubstituted α,β-unsaturated carbonyl compounds **706** (33 hits), as well as corresponding nitriles **707** (16 hits);

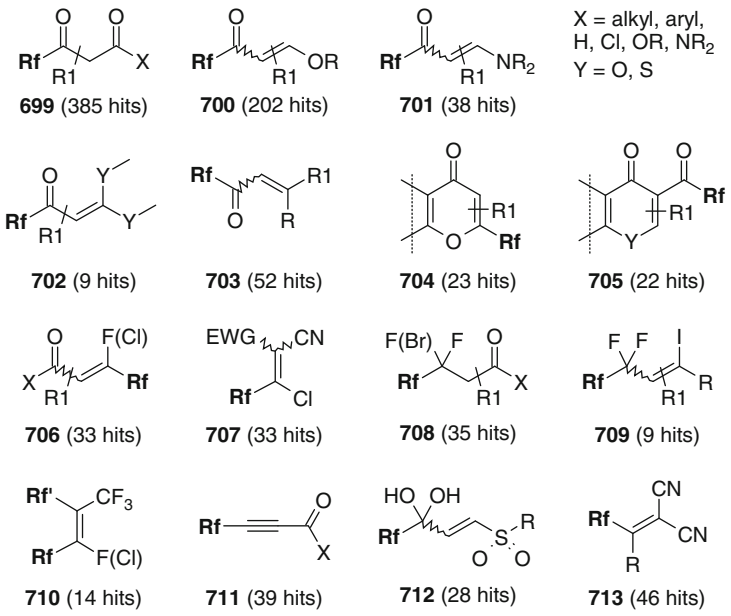


Fig. 24 Fluorinated bis-electrophiles used in synthesis of pyrimidines bearing fluorinated substituent at C-4 (in brackets a number of hits in Reaxys®)

– β,β-dihalosubstitutes carbonyl compounds **708** (35 hits) and the corresponding vinyl iodides **709** (9 hits);
– perfluorinated alkenes **710** (14 hits);
– ynones **711** (39 hits);
– α,β-unsaturated sulfones **712** (28 hits);
– methylenemalonodinitrile derivatives **713** (46 hits).

An overview of these reactions is given in the further sections; due to the huge number of data, only selected examples are provided. A separate section is related to principal synthesis of pyrimidines bearing fluorinated substituent at C-5 atom.

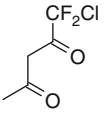
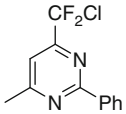
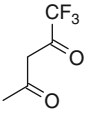
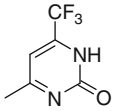
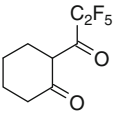
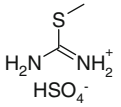
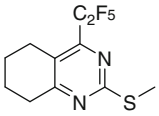
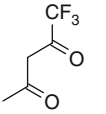
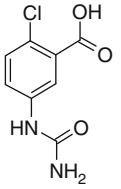
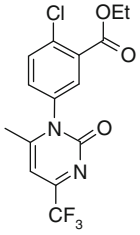
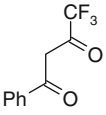
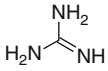
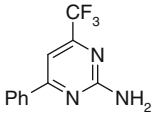
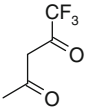
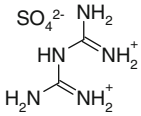
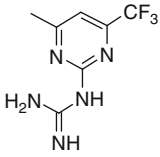
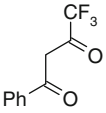
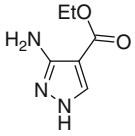
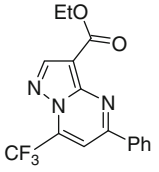
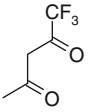
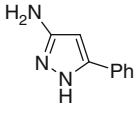
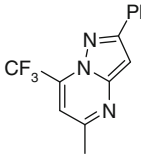
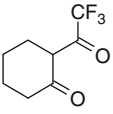
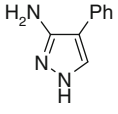
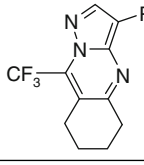
7.2.1 Pyrimidines with Fluorinated Alkyl at C-4 from β-Dicarbonyl Compounds

More than a third part of all the described principal syntheses of pyrimidines bearing fluorinated alkyl at C-4 atom commences from fluorinated β-dicarbonyl compounds **699**. The chemistry of these bis-electrophiles was reviewed recently [411, 412]; therefore, their preparation is not discussed herein. This synthesis of pyrimidines is fairly general (Table 34); it allows for introducing aliphatic, alicyclic and aromatic β-diketones (Entries 1–10), β-ketoesters (Entries 11–16), and cyclic β-ketoamides (Entry 17). Presence of some functional groups, such as additional ester moiety (Entry 15), is more or less tolerated, whereas increasing steric hindrance results in lowered yields of the products (Entry 10). A scope of common NCN binucleophiles include amidines (Entries 1, 11, 12, 17), (thio)urea and its derivatives (Entries 2–4), guanidines (Entries 5, 16) and biguanides (Entry 6). Electron-rich amino heterocycles (*e.g.* aminoazoles and even 2,6-diaminopyridine) are excellent NCN binucleophiles for the principal synthesis of fused pyrimidine derivatives (Entries 7–10, 13–15).

Although there are examples of uncatalyzed principal synthesis of pyrimidines using **699** as the starting material, the reaction usually requires acid or base as a promoter. Typical reaction conditions are reflux of the starting materials in AcOH or in alcohol in presence of alcoxide. Whereas AcOH is a common solvent for the reactions of (thio)ureas and amino heterocycles, the latter conditions are preferable if amidine or guanidine salts are used as the source of NCN binucleophiles, since the active species are liberated as the free bases in this case. Other reaction promoters include H_2SO_4, polyphosphoric acid (PPA), TsOH, $BF_3{\cdot}Et_2O$, AcONa and K_2CO_3 (see Table 34).

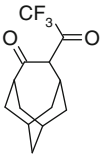
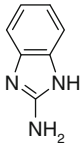
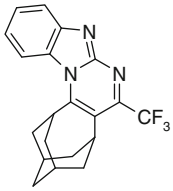
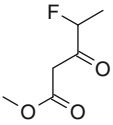
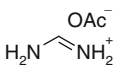
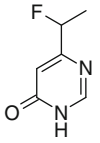
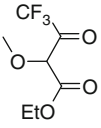
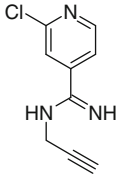
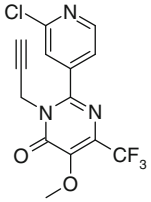
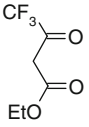
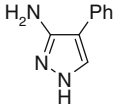
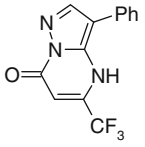
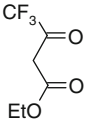
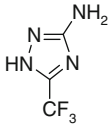
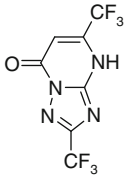
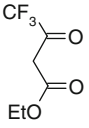
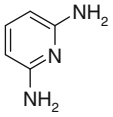
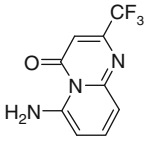
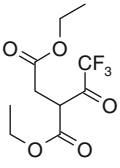
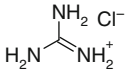
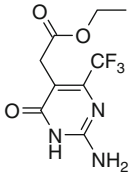
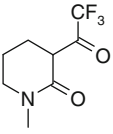
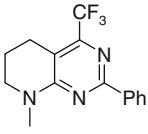
In case of non-symmetrical binucleophiles, the reaction with **699** is regioselective (although not always 100 %). Normally, it should start with attack of more nucleophilic nitrogen atom of the nucleophile at the fluoroalkyl-substituted carbonyl group of the electrophile (see, for example, Table 34, Entries 4 and 12). Nevertheless, the available data, reported mainly for the reactions of aminoazoles,

Table 34 Principal synthesis of pyrimidines with fluorinated **β**-dicarbonyl compounds 699

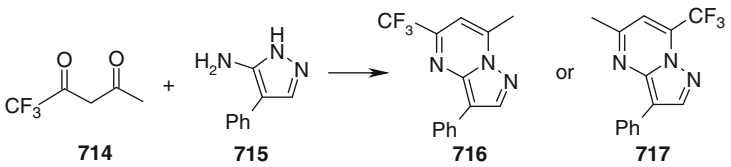
#	Reactants		Product	Conditions (yield)	Ref.
1				AcONa, xylene, 139 °C (71 %)	[413]
2				*cat.* H_2SO_4, EtOH, reflux (83 %)	[121]
3				$BF_3{\cdot}Et_2O$, Et_3N, *i*PrOH, reflux (81 %)	[414]
4				EtOH, H_2SO_4, 85 °C (9 %)	[415]
5				EtOH, reflux (72 %)	[416]
6				NaOH, EtOH, rt, then reflux (100 %)	[417]
7				AcOH, reflux (79 %)	[418]
8				AcOH, reflux (84 %)	[419]
9		 **165**		AcOH, 15 °C (89 %)	[420]

(continued)

Table 34 (continued)

#	Reactants		Product	Conditions (yield)	Ref.
10				K_2CO_3, EtOH, reflux (18 %)	[421]
11				MeONa, MeOH, 40 °C (65 %)	[422]
12				CH_2Cl_2, reflux (45 %)	[423]
13		 **165**		AcOH, reflux	[424]
14				TsOH, toluene, reflux (50 %)	[425]
15				PPA, 80 °C (78 %)	[426]
16				EtONa, EtOH, reflux (82 %)	[427]
17				neat, 100–180 °C (51 %)	[428]

are somewhat controversial. For example, reaction of 1,1,1-trifluoro-2,4-pentanedione **714** and pyrazole **715** afforded a single product, assigned to structures **716** [429] and **717** [419] by two groups of authors (Scheme 147). Although different reaction conditions were used in these two works (piperidine – EtOH and AcOH, respectively), a more thorough NMR study confirmed the second structure, **717**, for both cases [430]. Further evidences for such regioselectivity, including X-Ray crystallographic data, were obtained for analogous substrates [431] (see Table 34, Entries 7–9 for additional examples).

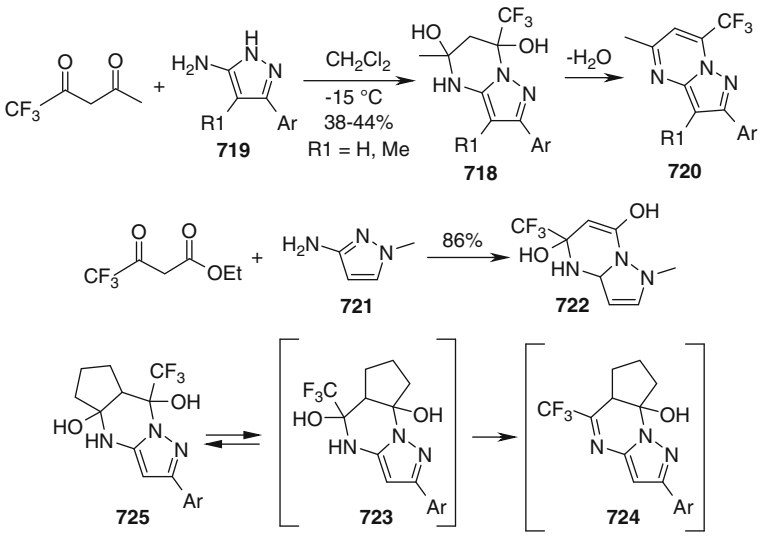


714 **715** **716** **717**

Scheme 147 Regioselectivity in the reactions of 1,1,1-trifluoro-2,4-pentanedione and aminopyrazole **715**

It should be noted that the reaction outcome depended strongly on the solvent. In particular, a mixture of **716** and **717** was obtained by heating the starting materials in EtOH instead of AcOH, **717** still being the major isomer (**717**:**716** = 70:30) [419]. These data show that the structures of the products in the reactions of fluorinated β-diketones **699** with amino azoles should be checked carefully in each particular case, especially for the early reports in this area. It is interesting to note, that opposite regioselectivity (confirmed by X-Ray) was observed in the case of fluorinated β-ketoesters (Table 34, Entries 13–15) [432].

Recently, intermediates **718** were isolated in the reaction of 1,1,1-trifluoro-2,4-pentanedione and aminopyrazoles **719** (Scheme 148) [433]. Compounds **718** were formed in CH_2Cl_2 below 10 °C in several minutes. Upon heating to 50 °C or standing at ambient temperature, they underwent dehydration to form the expected aromatic products **720**. An analogous intermediate **722** was isolated in the reaction of ethyl trifluoroacetoacetate and aminopyrazole **721** [434]. Intermediates **723** and **724**, which correspond to isomerization and partial dehydration of an analogue of **718** – compound **725** – were also detected by NMR [431]. Obviously, formation of these intermediates is responsible for the diminished regioselectivity of the process, which is observed at elevated temperatures or upon change of the solvent.



Scheme 148 Isolation of intermediates in the principal syntheses of chain-fluorinated pyrimidines from β-dicarbonyl compounds **699**

7.2.2 Pyrimidines with Fluorinated Alkyl at C-4 from Enones

Fluoroalkyl-substituted enones represent another important class of CCC bis-eletrophiles widely used for the preparation of pyrimidines with fluorinated alkyl at C-4. Their chemistry has been reviewed recently [435, 436], therefore, preparation of these bis-electrophiles is not discussed herein. Several subtypes of β-enones are amendable for the synthesis of chain-fluorinated pyrimidines. The most common group include compounds with a leaving group at β position (**700**–**702** and **706**). (Fig. 24). A special case of these bis-electrophiles is chromone derivatives and their hetero-analogues (704, 705). Other β-enones **703** (*i.e.* non-functionalized) and **712** (β-sulfonyl, hydrates) are also used.

β-Alkoxy-substituted enones **700** were used as the starting materials in nearly quarter of all the principal syntheses of pyrimidines with fluorinated alkyl at C-4. The structures of the compounds of general formula **700** are summarized in Fig. 25. Quite expectedly, most of them contain trifluoromethyl substituent, although compounds with difluoromethyl (**727** [239], **749** [437, 438]), chlorodifluoromethyl (**728** [413]), 1,1,2,2-tetrafluoroethyl (**750** [437, 439, 4406]), pentafluoroethyl (**729** [441]),

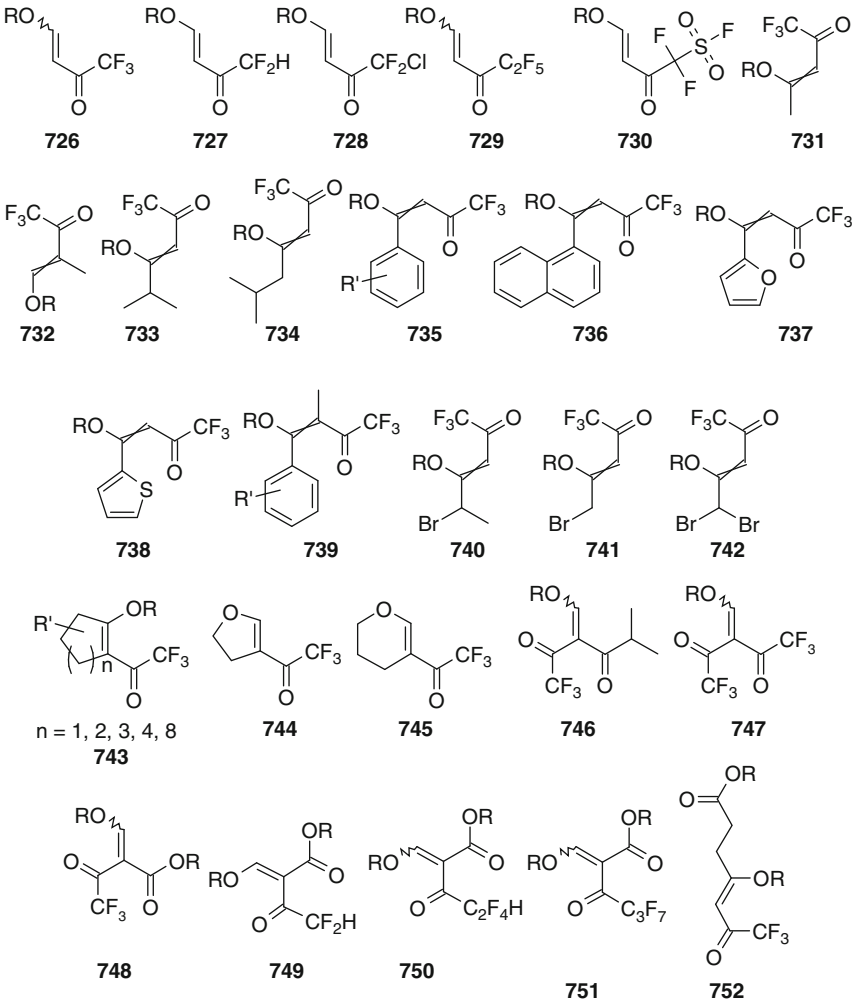
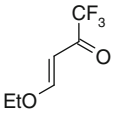
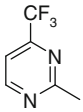
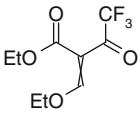
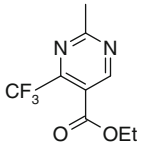
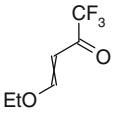
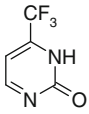
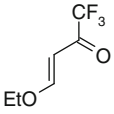
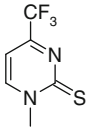
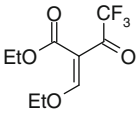
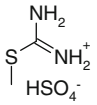
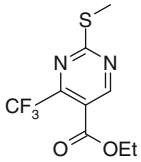
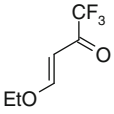
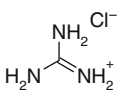
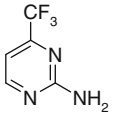
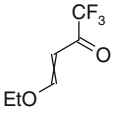
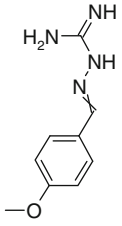
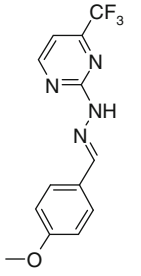
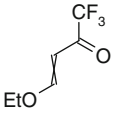
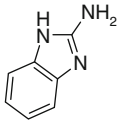
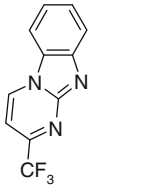


Fig. 25 Structures of biselectrophiles used (R=Me, Et, iPr, iBu)

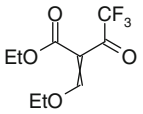
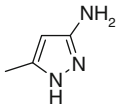
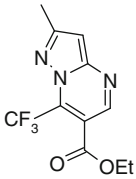
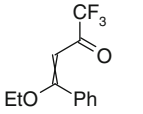
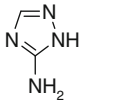
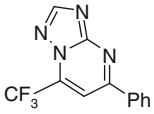
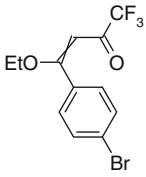
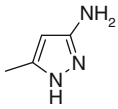
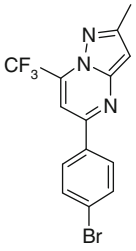
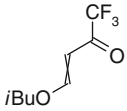
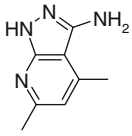
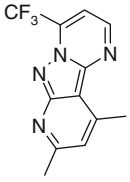
heptafluoropropyl (**751** [432, 433, 440]), and difluoro(fluorosulfonyl)methyl (**730** [441]) groups were also involved. Apart from the parent trifluoromethyl-substituted β-alkoxyenones **726** (Table 35), compounds with alkyl (**731** [442–448], **732** [443], **733** [449], **734** [450]), aryl (**735** [442, 444, 447, 451–455], **736** [454], **739** [449, 451]) and hetaryl (**737** and **738** [442, 449, 455]) substituents were used in the synthesis of 4(6)-trifluoromethylpyrimidines. Cyclic enones **743** [449, 454–456], **744** [445–448], and **745** [445, 446, 452] can be outlined. Among functionalized β-alkoxy-substituted enones, the derivatives containing an ester moiety at α-position (**748**–**751**) are most important (Table 35); other examples include allyl bromides **740** [457, 458], **741** [457, 458], and **742** [458], β-diketones **746** [459] and **747** [447, 454], and ζ-ketoester **752** [442].

Table 35 Principal synthesis of pyrimidines with **β**-alkoxy-substituted enones

#	Reactants		Product	Conditions (yield)	Ref.
1				NaOMe, MeOH, 0 °C (77 %)	[445]
2				EtONa, EtOH, reflux (58 %)	[455]
3				conc. HCl, MeOH, 60 °C (85 %)	[461]
4			 **760**	HCl, MeOH, 10 °C (68 %)	[341]
5				AcONa, DMF, 80–90 °C (60 %)	[463]
6				NaOH, EtOH, rt (64 %)	[464]
7				EtOH, rt (96 %)	[444]
8				Et_3N, toluene, reflux (95 %)	[452]

(continued)

Table 35 (continued)

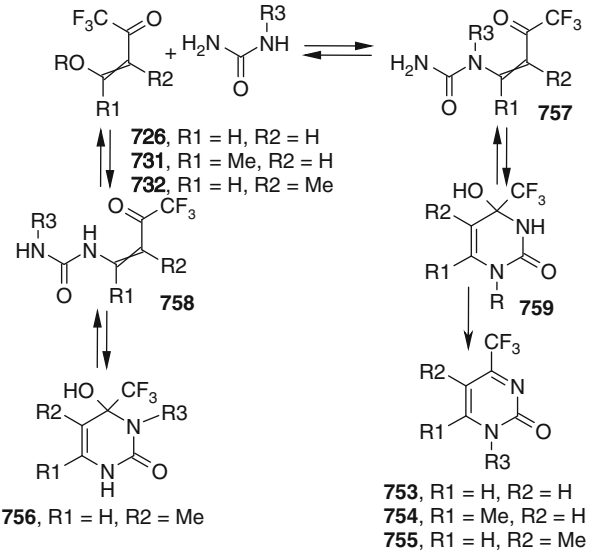
#	Reactants	Product	Conditions (yield)	Ref.
9	 		conc. HCl, EtOH, 70 °C (42 %)	[465]
10	 		MeCN, rt, then reflux (79 %)	[453]
11	 		AcOH, rt (86 %)	[466]
12	 		xylene, MW (82 %)	[460]

A range of NCN binucleophiles introduced into reaction with **700** is similar to that for fluorinated β-dicarbonyl compounds discussed in the previous section and includes amidines (Table 35, Entries 1, 2), (thio)urea and its derivatives (Entries 3–5), guanidines (Entry 6), semicarbazide derivatives (Entry 7), and electron-rich amino heterocycles (Entries 8–12).

As in case of fluorinated β-diketones, in most cases reactions of **700** with NCN binucleophiles were promoted by either acids (e.g. HCl, AcOH, $BF_3{\cdot}Et_2O$, $Ti(O\mathit{i}Pr)_4$) or bases (RONa, Et_3N, AcONa) (see Table 35). Again, basic conditions were preferred when the binucleophile was used in a salt form; in cases of urea derivatives and amino heterocycles the reaction was either promoted by acids or non-catalyzed.

The reaction of **700** with unsymmetrical NCN binucleophiles demonstrated regioselectivity, which was influenced by the nature of binucleophile, substituents in **700**, and even catalyst loading. In particular, reaction of N-alkylureas with β-alkoxyenones **726** and **731** in the presence of conc. aq HCl in refluxing MeOH led

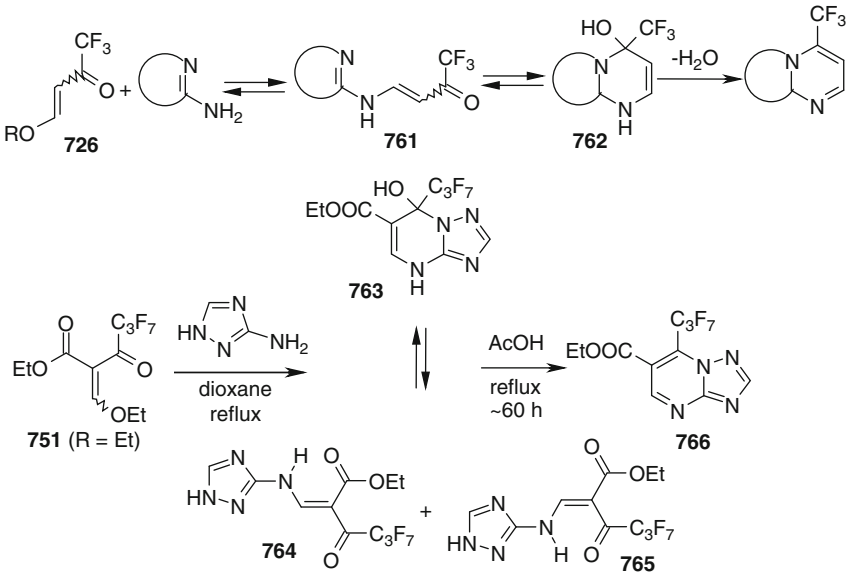
to the formation of pyrimidines **753** and **754** in 65–90 % yields [443] (Scheme 149). In the case of **732**, analogous products **755** were obtained when high concentration of HCl were used; upon lower acidity of the reaction medium, the products of alternative regioselectivity – compounds **756** – were obtained. Presumably, the reaction starts with the Michael addition of the amino groups of the *N*-alkylurea at the β-carbon atom of the enone, followed by elimination of an alcohol molecule to give enaminones **757** or **758**. Formation of **758** is faster due to higher steric accessibility of the primary amino group of the *N*-alkylurea. Cyclization of **758** furnishes compounds of the type **756**. In the case of R2=Me and low concentration of acid, **756** is stable, probably due to the steric effect of the methyl substituent on the trifluoromethyl and hydroxyl groups. When R2=H or the reaction is carried out at high concentration of acid, compounds of type **756** can equilibrate back to the starting compounds and then – to enaminone **757**. Cyclization of **757** followed by dehydration leads to the formation of pyrimidinones **753–755**. It should be noted that an intermediate **758** was isolated in the reaction of **726** with *N*-methylthiourea [462]. Again, upon prolonged reaction time this kinetic product rearranged to give enaminone of the type **757**, which underwent heterocyclization to give **760** (Table 35, Entry 4).



Scheme 149 Regioselectivity in the reaction of **726**, **731**, and **732** with *N*-alkylureas

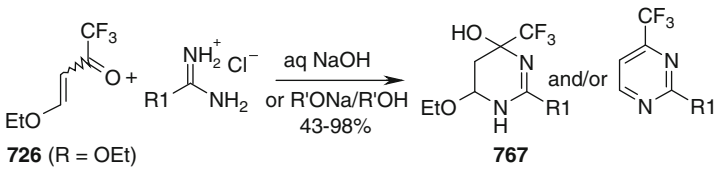
Most reaction of enones **700** with amino azoles have analogous mechanism, *i.e.* formation of enaminones **761**, followed by their cyclization and subsequent dehydration of intermediates **762** (Scheme 150) (Table 35, Entries 9–12). In many cases, hydrates **762** and/or enones **761** are reasonably stable and can be isolated

[437–439, 453]. For example, reaction of **751** and 3-amino-1*H*-[1, 2, 4]triazole in dioxane gives hydrate **763**, which exists in equilibrium with its open forms **764** and **765** in solution (DMSO, **763**:**764**:**765** = 80:11:9; acetone, **763**:**764**:**765** = 28:41:31) [438]. Dehydration of these species to obtain pyrimidine **766** requires prolonged reflux (~60 h) in AcOH. It should be noted that for all examples mentioned in the above paragraph, the reaction started with substitution of alkoxy group in the enone molecule with amino group of the amino azole (*via* addition – elimination mechanism). Therefore, the perfluoroalkyl group was in the neighboring position to the fusion nitrogen atom in the final product. Opposite regioselectivity was reported for the reaction of enones **700** with 2-aminobenzimidazole (Table 35, Entry 8). It was postulated that in this case, the reaction started with attack of endocyclic nitrogen at β-carbon of the enone [452].



Scheme 150 Reaction of enones **700** with amino azoles

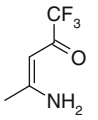
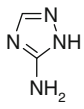
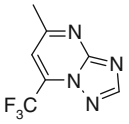
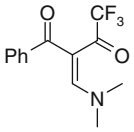
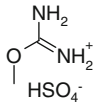
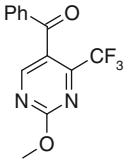
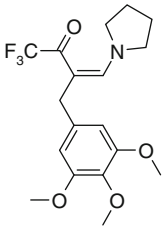
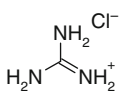
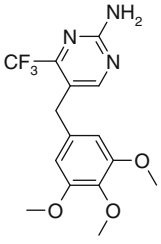
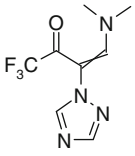
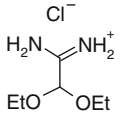
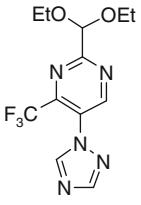
Interesting intermediates of the type **767** were obtained in the reaction of enones **700** with amidines (Scheme 151) [445]. Formation of these intermediates cannot be rationalized using the mechanistic schemes discussed above.



Scheme 151 Intermediates in the reaction of enones with amidines

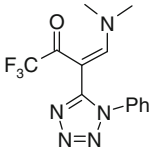
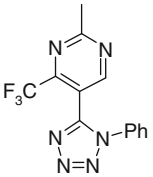
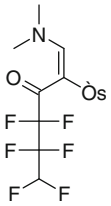
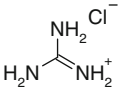
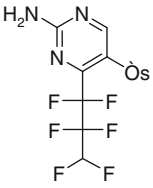
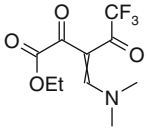
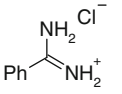
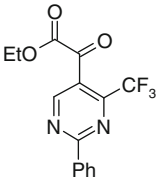
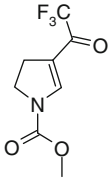
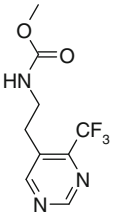
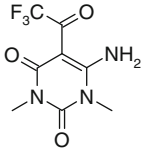
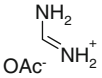
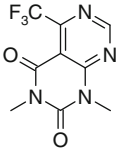
Enaminones **701** demonstrated similar behavior in the reactions with NCN binucleophiles compared with β-alkoxy-substituted enones **700** (Table 36). It should be noted, however, that rather unusual substituents were introduced into the molecules of the target pyrimidines using reagents **701** (Entries 3–9). In particular, the enaminone fragment of **701** can be a part of aminouracil moiety (Entry 9), although in this case, CCCN+CN mechanism for the pyrimidine ring formation is possible.

Table 36 Principal synthesis of pyrimidines with fluorinated β-enaminones

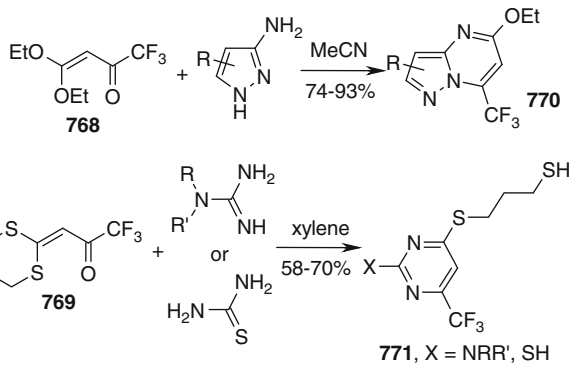
#	Reactants		Product	Conditions (yield)	Ref.
1				AcOH, 40 °C (65 %)	[467]
2				K_2CO_3, MeCN, 25 °C (63 %)	[468]
3				K_2CO_3, MeCN, 65 °C (88 %)	[469]
4				EtONa, EtOH, reflux (27 %)	[470]

(continued)

Table 36 (continued)

#	Reactants		Product	Conditions (yield)	Ref.
5				EtONa, EtOH, reflux (97 %)	[471]
6				K_2CO_3, MeCN, reflux (95 %)	[472]
7				K_2CO_3, MeCN, reflux (50 %)	[473]
8				*n*-hexanol, reflux (74 %)	[474]
9				DMF, 140 °C (66 %)	[401]

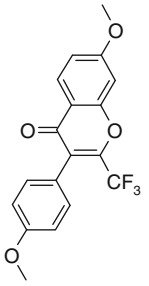
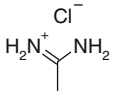
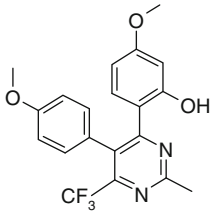
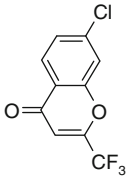
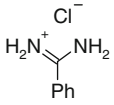
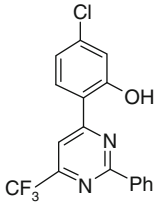
Two enones of general formula **702** were introduced into reaction with NCN binucleophiles, namely, **768** [453] and **769** [475] (Scheme 152). In case of **768**, one of the ethoxy groups can be retained in the final structure. Reactions with **769** were accompanied with the dithiane ring opening to give thiols **771**.



Scheme 152 Synthesis of pyrimidines with fluorinated β-enones **702**

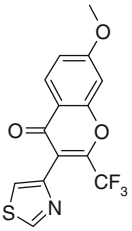
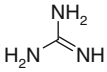
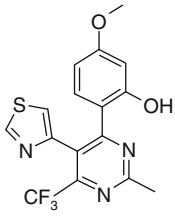
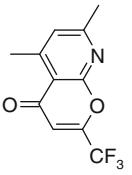
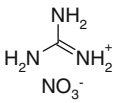
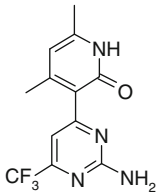
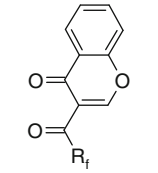
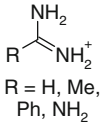
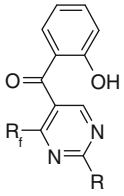
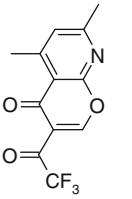
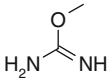
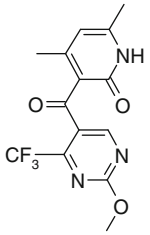
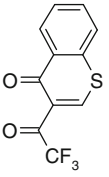
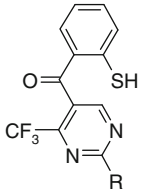
Chromone derivatives and their analogues **704** and **705** were used for synthesis of 4-fluoroalkylpyrimidines. In both cases, reaction with NCN binucleophiles was accompanied with recyclization of the γ-(thia)pyrone ring to give (2-(thio) hydroxyphenyl)-substituted pyrimidines or their analogues (Table 37).

Table 37 Synthesis of pyrimidines with fluorinated chromones and their hetero-analogues

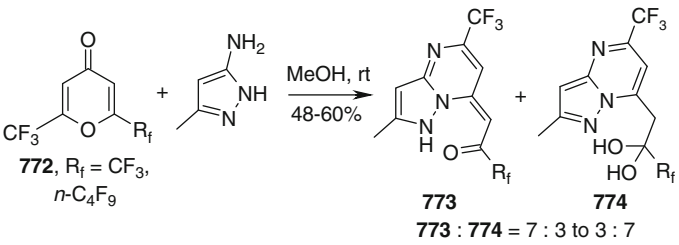
#	Reactants		Product	Conditions (yield)	Ref.
1				K_2CO_3, DMF, 75–80 °C (74 %)	[476]
2				KOH, EtOH, reflux (71 %)	[477]

(continued)

Table 37 (continued)

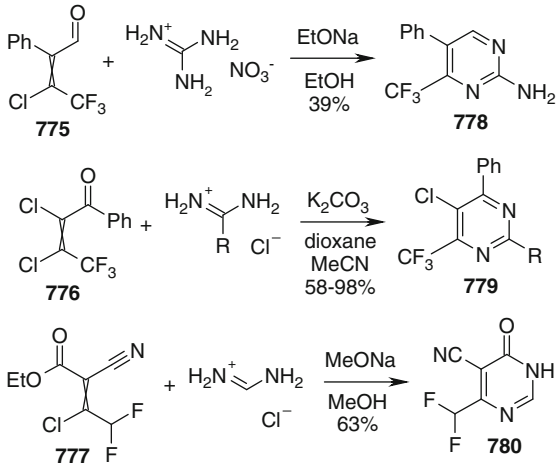
#	Reactants		Product	Conditions (yield)	Ref.
3				EtONa, EtOH, reflux, (78 %)	[478]
4				KOH, EtOH, reflux (58 %)	[477]
5	 R_f = CHF_2, CF_3, CHF_2CF_2, *n*-C_3F_7	 R = H, Me, Ph, NH_2		AcONa, DMF, 80 °C (52–92 %)	[479]
6				KOH, EtOH, reflux (38 %)	[479]
7				AcONa, DMF, 100 °C (57 %)	[479]

The method was extended to 2,6-bis(perfluoroalkyl)-substituted γ-pyrones **772**; in this case, equilibrium mixtures of products **773** and the corresponding hydrates **774** were obtained (Scheme 153) [480].



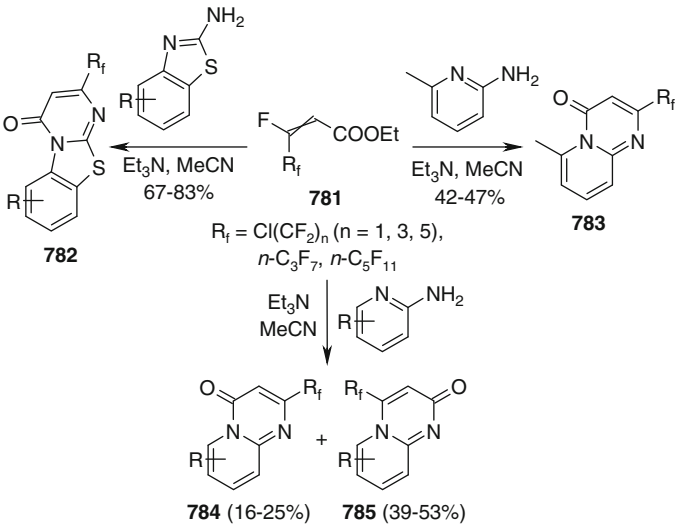
Scheme 153 Reaction of γ-pyrones **772** with amino azole

Apart from α,β-unsaturated carbonyl compounds having O–, N- and S-leaving groups at the β-position, compounds **706** with halogen nucleofuges (*i.e.* Cl, F) were also used in the synthesis of 4-fluoroalkylpyrimidines. In particular, reaction of aldehyde **775** [481], ketone **776** [482], or ester **777** [483] with amidines or guanidines gave pyrimidines **778–780** in 39–98 % yields (Scheme 154).



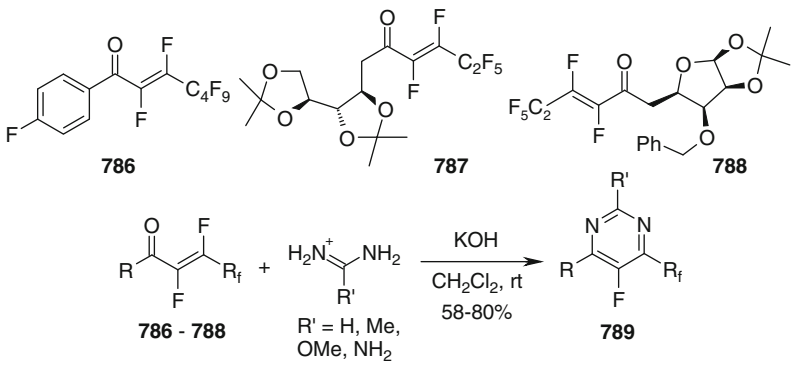
Scheme 154 Syntheses of pyrimidines with **775–777**

Reaction of fluorinated α,β-unsaturated esters **781** with 2-aminobenzothiazole derivatives resulted in a regioselective pyrimidine ring fusion and led to the tricyclic compounds **782** in 67–83 % yields (Scheme 155) [484]. On the contrary, reaction of **781** with 2-aminopyridines was not regioselective and led to the mixtures of isomers **784** and **785**. Similar results were obtained with 2-aminothiazole. In the case of 6-methyl-2-aminopyridine, only one regioisomer **783** was formed, presumably due to the steric effect of the methyl group which prevented attack of the β carbon of **781** at the endocyclic nitrogen atom.



Scheme 155 Principal syntheses of pyrimidines with **781**

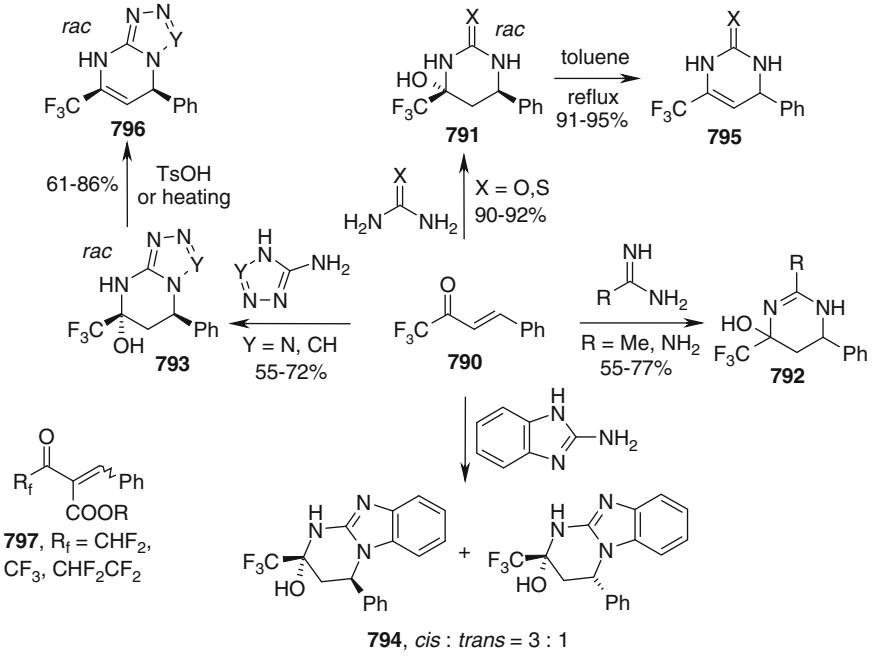
Aromatic (**786**) and xylose-derived (**787**, **788**) fluorinated enones were successfully introduced into reaction with amidines or analogous NCN binucleophiles to give pyrimidines **789** in 58–80 % yields (Scheme 156) [485].



Scheme 156 Principal syntheses of pyrimidines with **786**–**788**

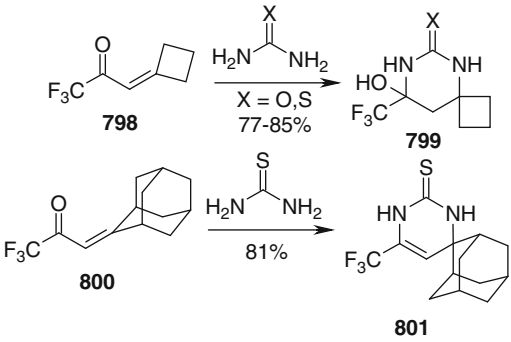
In principle, enones without a leaving group in β-position **703** can also react with NCN binucleophiles; in this case, partially hydrogenated pyrimidine derivatives are obtained. In particular, reaction of β-trifluoroacetylstyrene (**790**) with urea and

thiourea gave tetrahydropyrimidines **791** with more than 30:1 *dr* (Scheme 157) [486]. Analogous products **792** were obtained in case of acetamidine and guanidine. In case of aminotriazole and aminotetrazole, fused pyrimidine derivatives **793** were obtained as single diastereomers, whereas 2-aminobenzimidazole gave a 3:1 mixture of diastereomers **794** [487]. It should be noted that in both cases, the reactions were regioselective. Tetrahydropyrimidine derivatives **791** and **793** were subjected to dehydration to give **795** and **796**, respectively. Similar results were obtained in the reactions of urea and thiourea [488], as well as amino azoles [489, 490] with enones **797**.



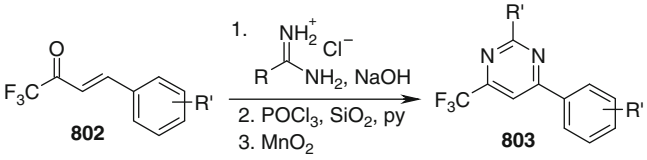
Scheme 157 Principal syntheses of di- and tetrahydropyrimidines with **790**

Analogously, reaction of enone **798** with thiourea gave tetrahydropyrimidines **799**, whereas in the case of enone **800**, dihydropyrimidine **801** was obtained (Scheme 158) [486].



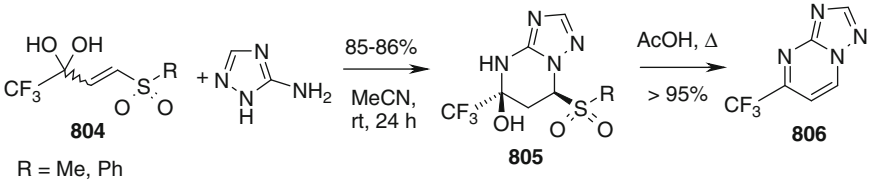
Scheme 158 Syntheses of di- and tetrahydropyrimidines with enones **798** and **800**

One-pot procedure for the synthesis of aromatic pyrimidine derivatives **803** from β-aryl-enones **802** was developed (Scheme 159) [491]. It included reaction of **802** with amidines, followed by dehydration with $POCl_3$ and oxidation with MnO_2.



Scheme 159 One-pot synthesis of aromatic pyrimidine derivatives **803** from **802**

Reaction of β-sulfonyl-enone hydrates **804** with aminotriazoles in acetonitrile at room temperature led to the formation the 5-CF_3 isomer of tetrahydropyrimidines **805**, which were transformed to their aromatic counterparts (*e.g.* **806**) by reflux in AcOH (Scheme 160). The reaction of **804** with **805** in other conditions (heating in water or acetic acid) lead to losing of the regioselectivity [492].

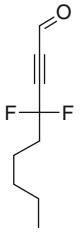
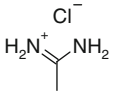
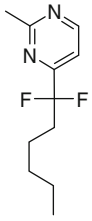
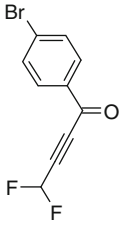
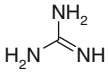
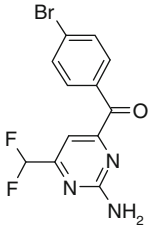
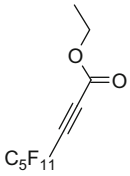
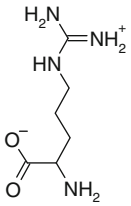
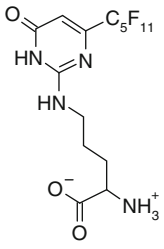


Scheme 160 Principal syntheses of pyrimidines with **163**

7.2.3 Other CCC Bis-electrophiles

Apart from fluorinated β-dicarbonyl compounds and β-enones, CCC bis-electrophiles used for the synthesis of 4-(per)fluoroalkylpyrimidines include alkynes **711**, α,β-unsaturated nitriles **707** and **713**, as well as compounds in which the fluorine atoms of the perfluoroalkyl substituent act as leaving group (**708**–**710**). Reactions of alkyne-derived aldehydes, ketones and esters of general formula **711** were analogous to that of β-enones discussed in the previous section (Table 38). Due to presence of triple bond, neither leaving group at β position nor using the oxidizing reagents were necessary to obtain aromatic derivatives. The method was used successfully for amidines (Entry 1), guanidines (Entries 2 and 3), aminopyridines and their fused analogues (Entry 4), and 2-aminooxazolidines (Entry 5) as NCN binucleophiles.

Table 38 Synthesis of pyrimidines with alkyne derivatives **711**

#	Reactants		Product	Conditions (yield)	Ref.
1				Na_2CO_3, MeCN, reflux (51 %)	[493]
2				Na_2CO_3, $CHCl_3$, MeCN, reflux	[321]
3				aq HCl, MeOH, reflux (30 %)	[494]

(continued)

Table 38 (continued)

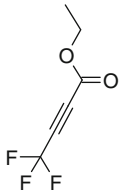
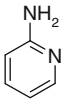
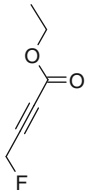
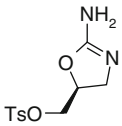
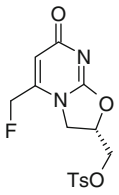
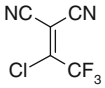
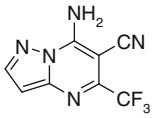
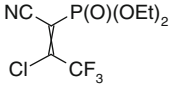
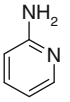
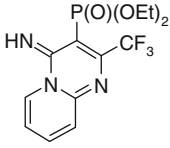
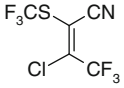
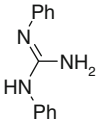
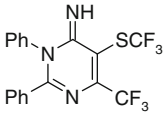
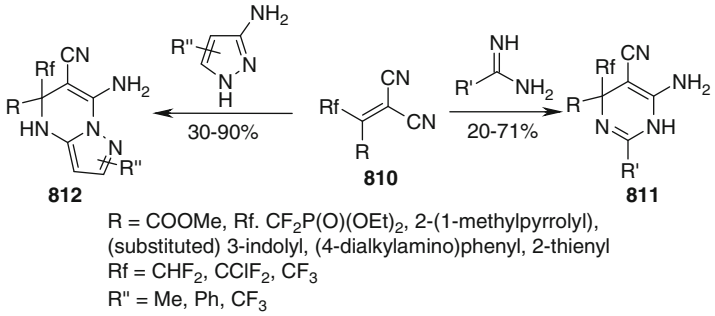
#	Reactants		Product	Conditions (yield)	Ref.
4				EtOH, rt (98 %)	[495]
5				EtOH, reflux (33 %)	[496]

Table 39 Principal synthesis of pyrimidines with nitriles of general formula **707**

#	Reactants		Product	Conditions (yield)	Ref.
1	 **807**			$CHCl_3$, rt (68 %)	[501]
2	 **808**			MeCN, rt (40 %)	[502]
3	 **809**			Et_2O (78 %)	[349]

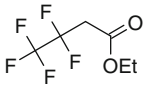
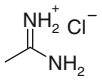
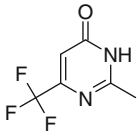
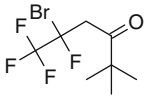
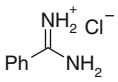
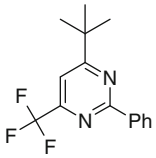
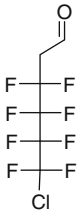
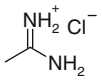
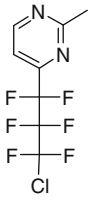
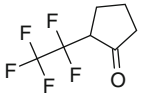
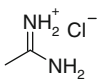
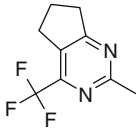
Malonodinitrile derivative **807**, as well as compounds with phosphonate (**808**) and trifluoromethylthio (**809**) groups were used in reactions with NCN binucleophiles, including *N*-alkylamidines, 3-aminopyrazoles and 2-aminopyridines to form **707** (Table 39). Activated alkenes **807–809,** unlike the compound **777** containing COOMe group, gave amino or imino derivatives of pyrimidines, which arose from attack of the nucleophile at the nitrile group. Analogous reaction was observed in case of **810**; as a result dihydropyrimidine derivatives **811** or **812** were formed (Scheme 161) [497–500].



Scheme 161 Syntheses of pyrimidines with **810**

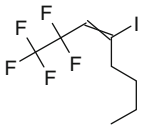
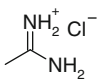
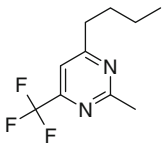
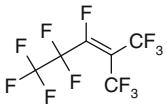
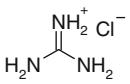
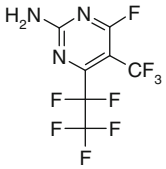
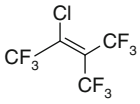
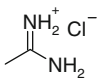
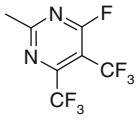
Aldehydes, ketones and esters of general formula **708** reacted with amidines to give pyrimidine derivatives (Table 40, Entries 1–4). Analogous methods were developed for (per)fluorinated vinyl halides **709** (Entry 5) and **710** (Entries 6, 7). Analogous reaction was successful with enol phosphate **814**, obtained from ketone **813** and sodium diethyl phosphite (Scheme 162) [120]. In all these cases, nucleophilic substitution of two fluorine atoms at α-carbon of the perfluoroalkyl group occurred.

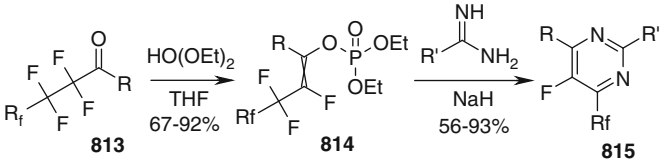
Table 40 Synthesis with compounds type **708–710** (see Fig. 24)

#	Reactants		Product	Conditions (yield)	Ref.
1				Na_2CO_3, dioxane, 60 °C (75 %)	[502]
2				Na_2CO_3, EtOH, rt (89 %)	[502]
3				Na_2CO_3, EtOH, rt (77 %)	[502]
4				Na_2CO_3, EtOH, rt (77 %)	[502]

(continued)

Table 40 (continued)

#	Reactants		Product	Conditions (yield)	Ref.
5				NaH, THF, rt (60 %)	[503]
6				Et_3N, MeCN, rt (83 %)	[504]
7				NaOH, BTEA, F-113, H_2O, rt (47 %)	[354]



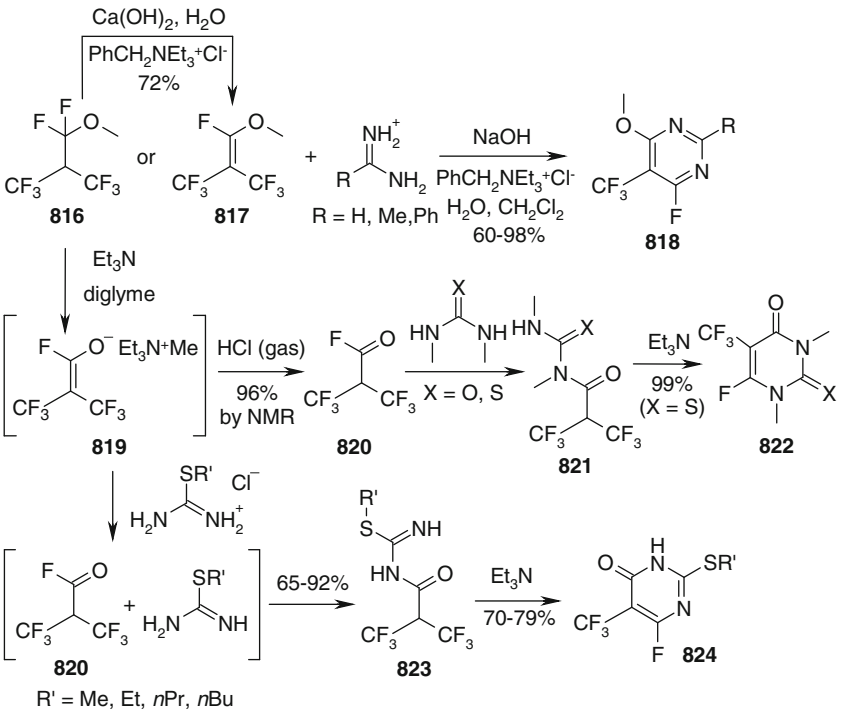
Rf = CF_3, *n*-C_5F_{11}; R = Alkyl, Ph; R' = H, NH_2, Me, Ph

Scheme 162 Synthesis pyrimidines using enol phosphate **814**

7.2.4 Pyrimidines with Fluorinated Group at C-5 Position

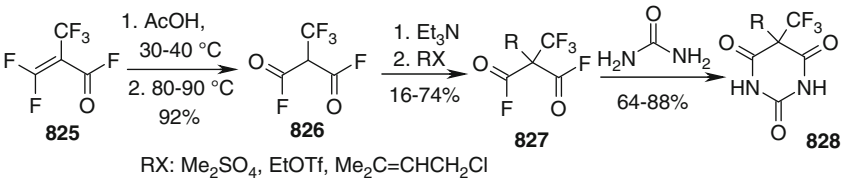
Unlike their C-2 and C-4-substituted counterparts, pyrimidines with fluorinated alkyl at C-5 were rarely prepared using reaction of NCN binucleophiles and CCC bis-electrophiles. Several examples of such transformations were already mentioned in previous section (reactions with **710** leading to 4,5-bis-perfluoroalkylpyrimidines, see Table 40, Entries 6,7). Analogous reactions with alkene **817**, as well as its precursor **816** (a stable adduct of methanol and 2-(trifluoromethyl)-1,1,3,3,3-pentafluoropropene), led to the formation of 5-trifluoromethylpyrimidines **818** (Scheme 163) [505, 506]. Pyrimidines **822** and **825** were also prepared from **816**. Reaction of **816** with triethylamine resulted in formation of enolate **819** (Scheme 163) [507]. When *in situ* generated **819** was treated with HCl, acyl fluoride **820** was formed. Reaction of **820** with *N*,*N*′-dimethyl(thio)urea resulted in the formation of adduct **821**, which underwent cyclization to **822** upon

treatment with triethylamine. Reaction of **819** with *S*-alkyl isothiouronium salts resulted in generation of **820**, which reacted with *S*-alkyl isothiourea base to give adduct **2823** [508]. Cyclization of **823** led to formation of pyrimidine **824**. Synthesis of **824** from **817** was also performed in one-pot manner.



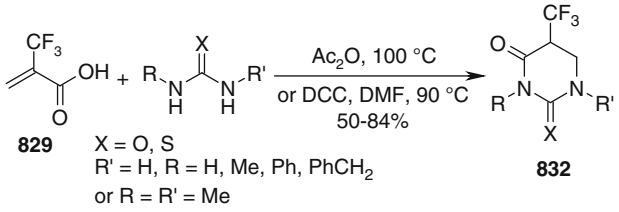
Scheme 163 Synthesis of pyrimidines from **816**

2-Trifluoromethylmalonic acid derivatives were used in the synthesis of 5-trifluoromethyl-substituted pyrimidines. In particular, acyl fluorides **827** were obtained by alkylation of trifluoromethylmalonyl fluoride (**826**), in turn prepared from acyl fluoride **825** (Scheme 164) [509]. Reaction of **827** with urea led to the formation of fluorinated barbiturates **828**.



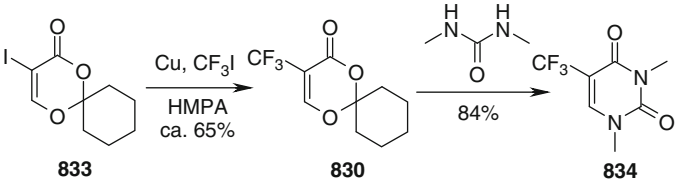
Scheme 164 Synthesis of pyrimidines from 2-trifluoromethylmalonic acid derivatives

α-Trifluoromethylacrylic acid (**829**), as well as and its derivatives **830** and **831** are valuable building blocks which can be used for preparation of 5-trifluoromethylpyrimidines. In particular, reaction of **829** with ureas in acetic anhydride led to the formation of 5-trifluoromethyl-5,6-dihydrouracils (**832**) in 67–84 % yields (Scheme 165) [510]. In case of unsymmetrical ureas, the reaction was regioselective (except *N*-methylurea, which gave a mixture of regioisomers). An alternative method was more effective for thioureas (DCC, DMF, 90 °C, 50–55 % yields), since S-acetylation occurred when Ac_2O was used.



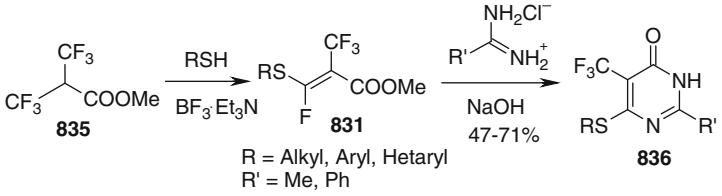
Scheme 165 Synthesis of pyrimidines from α-trifluoromethylacrylic acid **829**

The reaction of 5-iodo-1,3-dioxin-4-one **833** with trifluoromethyl iodide in the presence of copper powder in HMPA led to formation of 1,3-dioxine derivative **830** (Scheme 166) [511]. Compound **830** reacted with *N*,*N*′-dimethylurea in refluxing toluene to give pyrimidine **834** in 84 % yield.



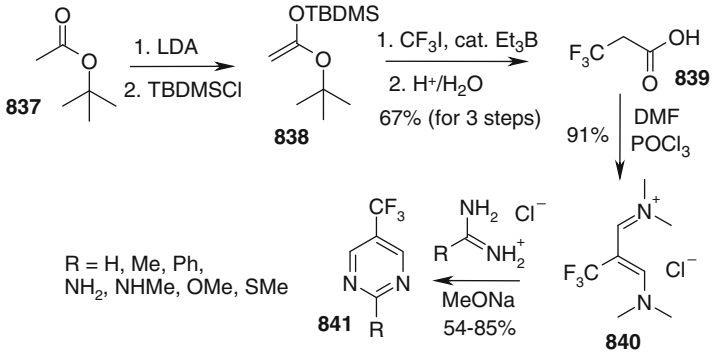
Scheme 166 Synthesis of pyrimidines from **830**

α,β-Unsaturated esters **831** were prepared by reaction of bis(trifluoromethyl) acetates **835** with various thiols in presence of $BF_3{\cdot}Et_3N$ complex (Scheme 167) [124]. Reaction of **831** with amidines led to pyrimidines **836** in 47–71 % yield.

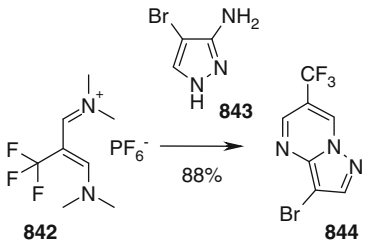


Scheme 167 Synthesis of pyrimidines from **831**

Vinamidinium salt **840** is a promising reagent for the synthesis of 5-trifluoromethylpyrimidines **841**, unsubstituted at positions C-4 and C-6. Compound **840** was prepared from 2,2,2-trifluoropropanoic acid (**839**). Acid **839** was obtained *via* radical addition of trifluoromethyl iodide to TBS-enolate **838** of *tert*-butyl acetate **837**, followed by acidic hydrolysis (Scheme 168) [512]. Reaction of **840** with amidines and their analogues led to formation of the corresponding pyrimidines **841** in 54–85 % yields. Additional examples of such transformations were described [347, 513], including also reaction with aminopyrazole **843** (Scheme 169) [514]



Scheme 168 Synthesis of pyrimidines from vinamidinium salt **840**



Scheme 169 Synthesis of fused pyrimidines from vinamidinium salt **842**

7.3 CNC+CCN Approach to Fluoroalkyl-Substituted Pyrimidines

A group of methods for the preparation of fluoroalkyl-substituted pyrimidines relied on CNC+CCN connection of the aromatic ring. A variety of fluorinated 1,3-dielectrophiles was used for the annulations of CNC triade to CCN binucleophiles (*i.e.* anilines, enamines and electron-rich amino heterocycles). The most widely used among such 1,3-CNC-dielectrophiles are functionalized heterocumulenes **845**–**847** (Fig. 26); trifluoromethyl substituted imine derivatives **848**, **849** and **850** can be also mentioned.

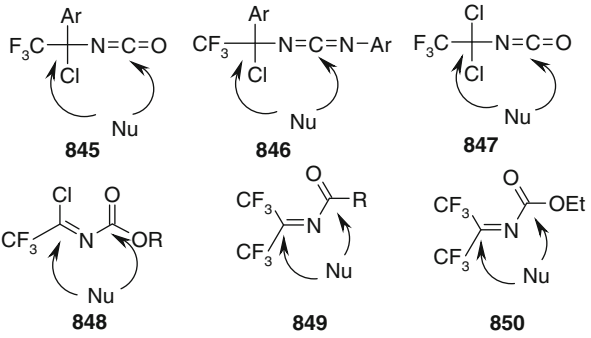
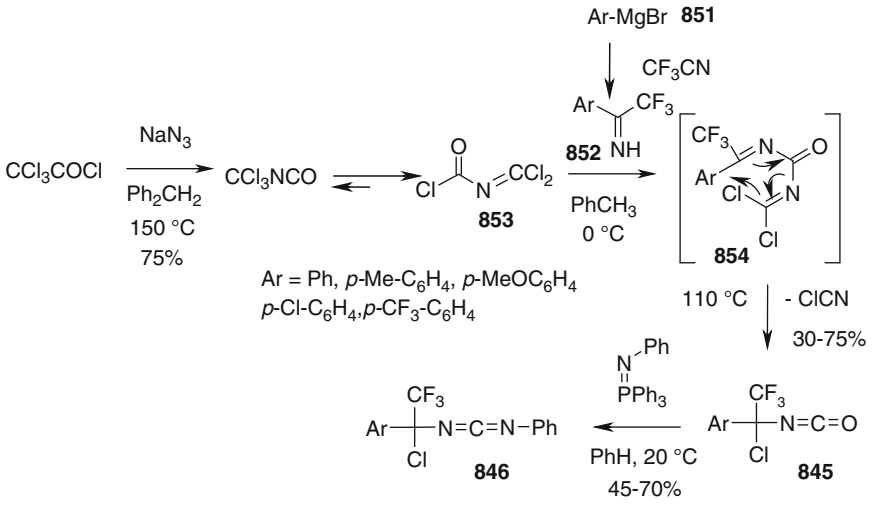


Fig. 26 Fluorinated CNC bis-electrophiles used for the synthesis of pyrimidines

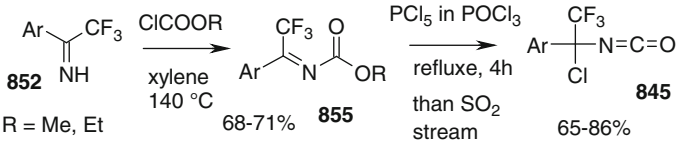
Most of these building blocks are not commercially available, since their preparation requires quite expensive fluorine-containing starting compounds, and the procedures leading to their formation cannot be classified as easy-to-perform. This may be the reason why their chemical behaviour has not been documented to a full extent. Only few research groups (mainly at the Institute of Organic Chemistry NAS Ukraine) deal with these CNC fluorine-containing bis-electrophiles [515].

Isocyanates **854** were first synthesized in Kiev by Samarai and co-workers in 1975 using the synthetic pathway described in the Scheme 170 [516, 517]. The starting aryl Grignard reagent was coupled with trifluoroacetonitrile to give of 2,2,2-trifluoro-1-arylethanimine **851**. The subsequent treatment of **851** with trichloromethyl isocyanate, which exists predominantly in the iminocarbonyl chlonde form **853** [518] led to the formation of the isocyanate **854**. The reaction proceeds through intermediate **854**, which undergo thermal extrusion of cyanogen chloride. Heterocumulenes **846** can be prepared in satisfactory yields from isocyanate **845** using aza-Wittig protocol with arylphosphinimines [519].



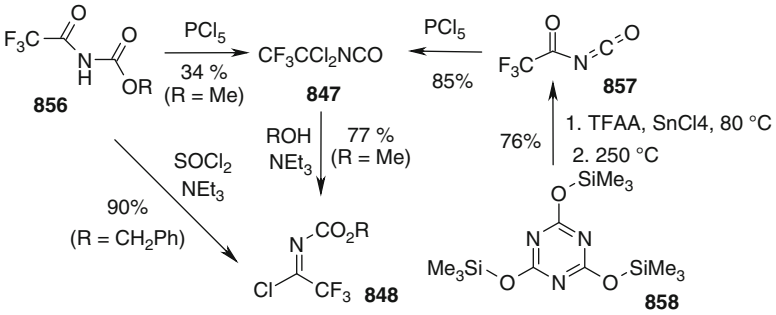
Scheme 170 Samarai synthesis of **845** and **846**

The above mentioned approach to isocyanates **854** has considerable disadvantages: the necessity of using highly toxic and difficultly accessible trichloromethyl isocyanate and excretion of highly toxic cyanogen chloride. In 2008 Vovk and co-workers propose a more convenient approach to 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanates. Acylation of imines **852** with alkyl chloroformates gives the corresponding carbamates **855** (Scheme 171) [520]. The subsequent reaction of **855** with phosphorus pentachloride in boiling phosphoryl chloride leads to the formation of target isocyanates **845** in 65–86 % yield. But in spite of visible benefits, the Vovk approach to isocyanates **854** has not been scaled up jet and Samarai method is still in use for multigram synthesis.



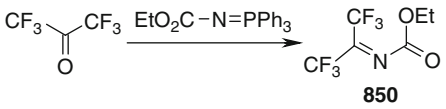
Scheme 171 Vovk synthesis of **845**

1,1-Dichloro-2,2,2-trifluoro-1-isocyanatoethane **286** [521] was also first synthesized in Kiev by Boiko and co-workers *via* chlorination of N-trifluoroacetylcarbamate **856** with phosphorus pentachloride at 170 °C. The method gives no more than 34 % of the target product. The same scientists optimized in 2002 the synthesis of trifluoroacetylisocyanate **857** [522], which is available from tris(trimethysilyl)cyanurate **858** [523]. Compound **847** readily reacts with alcohols in presence of triethylamine to give alkyl 1-chloro-2,2,2-trifluoroethylidenecarbamates **848** [524]. Alternatively, **848** were prepared by Osipov using the reaction of **856** with $SOCl_2$ in presence of Et_3N [525], this method was effective only for benzyl derivative (Scheme 172).



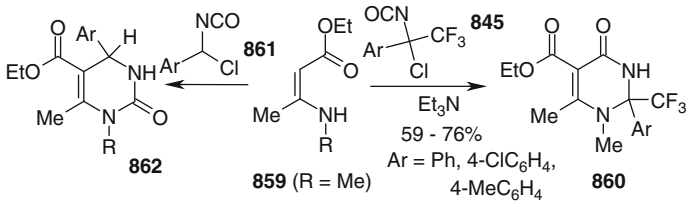
Scheme 172 Synthesis of **847** and **848**

Finally, acyl imines of hexafluoroacetone (*e.g.* **850**, Scheme 173) can be prepared using aza-Wittig reaction [526].



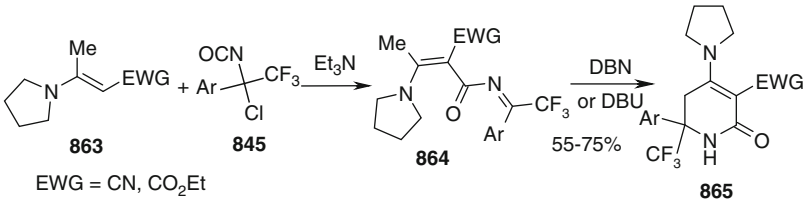
Scheme 173 Synthesis of hexafluoroacetone imines

Reactions of fluorinated alkylheterocumulenes **845**–**847** with CCN binucleophiles were studied for more than 30 years by Vovk laboratory. Initial reports in this area, however, were limited to reactions with (1-cyclohexenyl)dialkylamines [527, 528] and ethyl β-*N*-methylaminocrotonate (**859**) [529]. For example, reaction of **859** with isocyanates **845** led to the formation of dihydropyrimidines **860** (Scheme 174). Remarkably, the regioselectivity observed was opposite to that for the reaction of **859** with isocyanates **861** lacking trifluoromethyl group [530, 531].



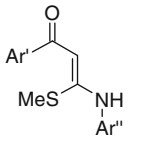
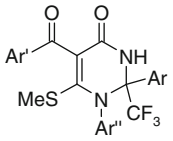
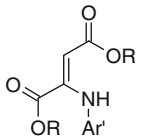
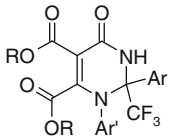
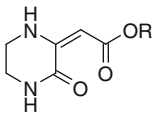
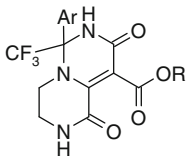
Scheme 174 Reaction of α-chloroisocyanates with enaminones

Tertiary enamines **863** also undergo reaction with isocyanates **283** in presence of triethylamine as a base, but the reaction products are dihydropyrimidones (Scheme 175) [532]. The reaction gives the corresponding carbamoyl derivatives **864**. Treatment of the adducts **864** with strong bases like DBU or DBN results in cyclization to pyrrolidin-1-yl-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-ones **300**. The reaction is faster if enaminoesters rather than enaminonitriles were used as the starting compounds of the type **863**; on the other hand, donor substituents in the aryl fragment of **845** reduced the reaction rate. Other enamines studied in the reaction with **845** are shown in Table 41. It should be noted that in all these cases, the regioselectivity of the reaction with **845** was opposite to that observed for isocyanates **861** lacking the trifluoromethyl group.

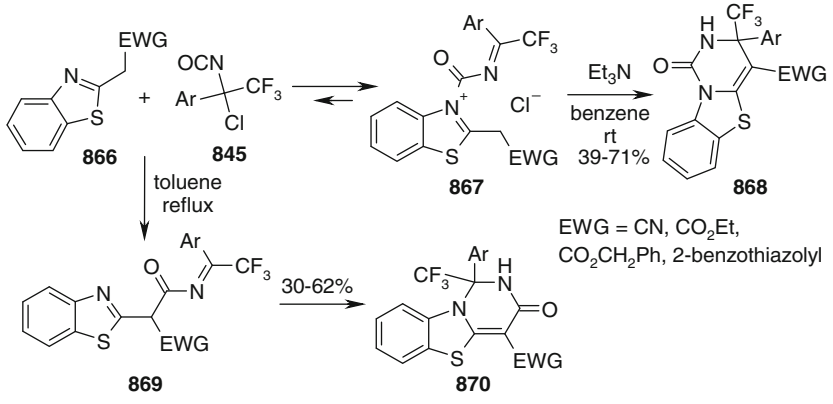


Scheme 175 Reaction of **283** with enamines **297**

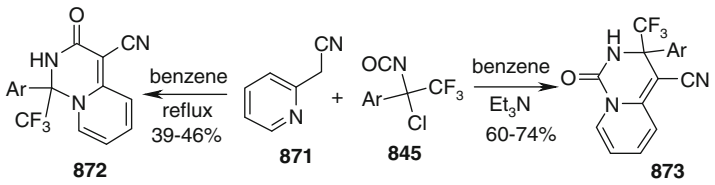
Table 41 Reaction of **845** with enamines

#	Enamine	Product	Conditions	Yield, %	Ref.
1			**845**, Et_3N, benzene, rt	56–73	[533]
2			**845**, Et_3N, benzene, rt, then reflux	20–22	[534]
3			**845**, toluene, reflux	39–62	[535]

It was found that benzothiazole derived acetonitriles **866** react with **845** in benzene in presence of triethylamine at room temperature to give adducts **868**, whereas reaction in toluene without a base at reflux led to the formation of isomeric compounds **870** via **869** (Scheme 176) [536]. These results were explained by reversible formation of intermediate **867**. Analogous results were obtained in reaction of **845** with 2-pyridylacetonitrile **871** as CCN binucleophile (Scheme 177) [537].



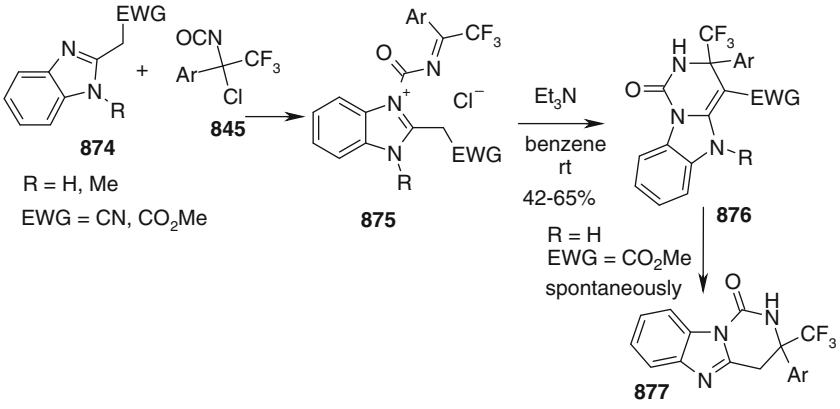
Scheme 176 Reaction of **845** with benzothiazole derivatives **866**



Scheme 177 Reaction of **845** with 2-pyridylacetonitrile **871**

Detailed investigation of the reaction of **845** with benzimidazole derivative **874** demonstrated that the process carried out both in presence of a base at room temperature or without base at heating resulted in a single type of compounds **876**.

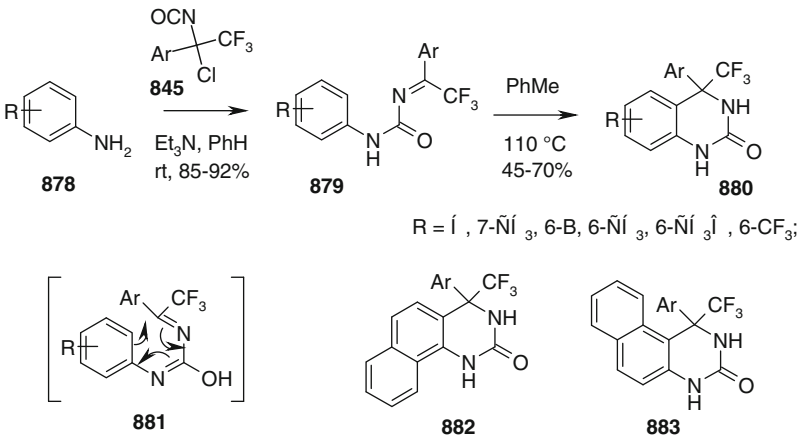
The result is obviously due to the enhanced basicity of the benzimidazole ring compared to those of benzimidazole and pyridine. Therefore the adduct **875** is more stable than its pyridine and benzothiazole analogues and does not dissociate into starting reagents under heating. Also when benzimidazolyl acetate with R=H, EWG=CO_2Me was used, the corresponding compounds **876** was found unstable to give decarboxylated compounds **877** (Scheme 178) [538].



Scheme 178 Reaction of **845** with benimidazole derivatives **874**

Besides cyclizations of hetaryl acetonitriles, the reactions of isocyanate **845** with anilines were studied. In presence of base the reaction leads to N-alkylidene-N-arylureas **879**. The compounds **879** bearing the C=N bond activated by trifluoromethyl group undergo thermal intramolecular cyclization to give 4-trifluoromethyl-1,2,3,4-tetrahydroquinazolin-2-ones **880** in good yields. A wide range of anilines

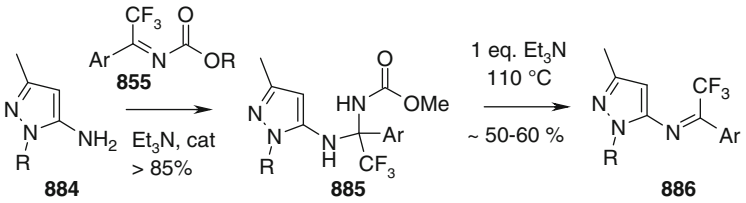
bearing EDG as well as EWG enters into cyclization. This fact is indirect proof that the reaction proceeds as synchronic process through 6-membered transition state **881**. Aminonaphthalenes afforded angular tricyclic compounds **882** and **883** (Scheme 179) [539].



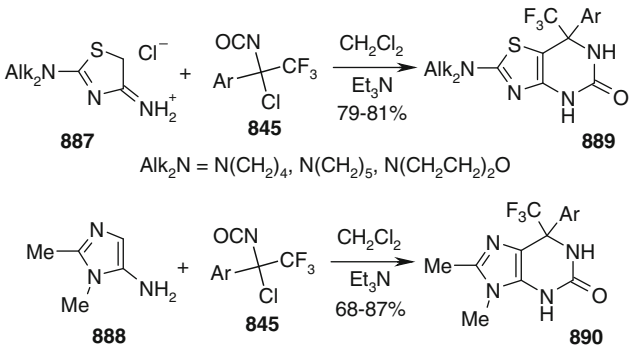
Scheme 179 Reaction of **845** with anilines

In order to establish scope and limitation of the method the set of electron-rich aminoheterocycles [540, 541] were reacted with isocyanates **845**. Unexpectedly it was found that the reaction resulted in complex mixture of products. For increasing of reaction selectivity the less electrophilic acyl imine **855** was used. But in this case the reaction proceeds at nitrogen atom of aminoheterocycle and further thermal treatment resulted in trifluoromethyl-containing hetarylimines (Scheme 180) [542].

Only aminothiazoles generated *in situ* from **887** and aminoimidazoles **888** were appropriate CCN binucleophiles to provide thiazolo[4,5-*d*]pyrimidones **889** and fluorinated dihydropyrines **890** (Scheme 181) [543]. The optimal reaction conditions were: Et_3N, CH_2Cl_2, ambient temperature.

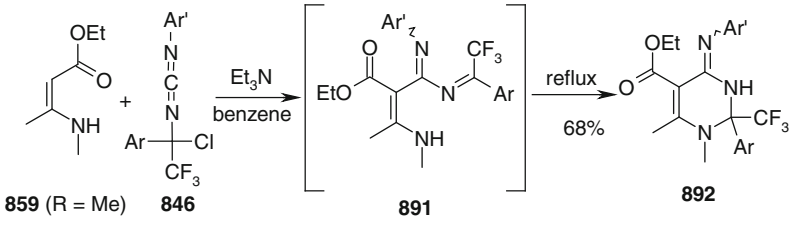


Scheme 180 Reaction of **855** with aminopyrazole



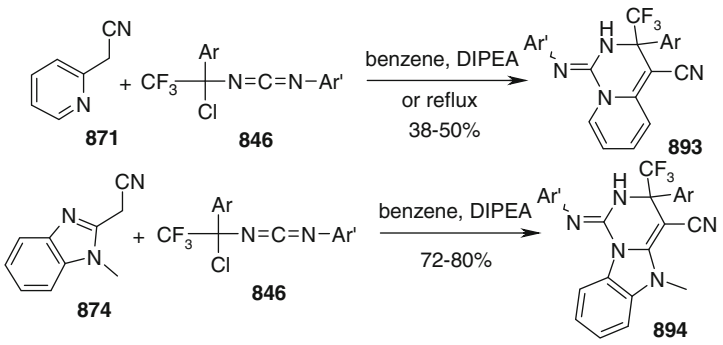
Scheme 181 Reaction of **845** with amino heterocycles

In many cases, reactions of carbodiimide **846** with binucleophiles were analogous to that of **845** in terms of regioselectivity. In particular, **846** reacted with enamine **859** to provide adduct **891**, which was transformed to pyrimidine derivative **892** upon heating (Scheme 182) [544].



Scheme 182 Reaction of **846** with enamine **859**

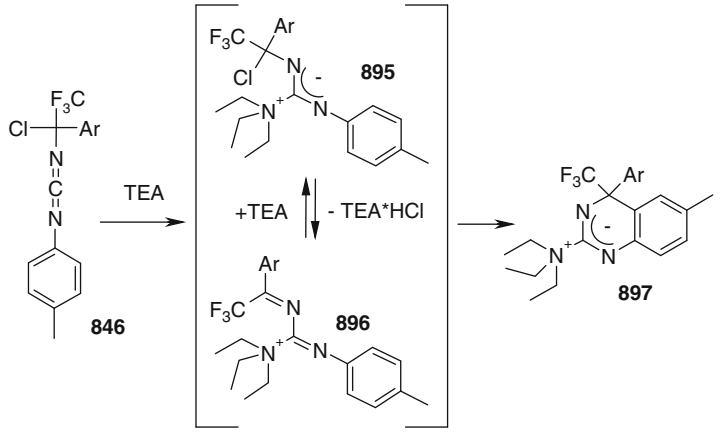
On the contrary, reaction of **846** with 2-pyridylacetonitrile (**871**) showed some differences compared to **845**. Unlike **846**, the same products **893** were formed either upon action of tertiary amines or heating without bases (Scheme 183) [553]. The reaction of **846** with benzimidazole derivatives **874** proceeds in a similar way to afford tricyclic compounds **894** (Scheme 183) [538].



Scheme 183 Reaction of **846** with hetaryl acetonitriles

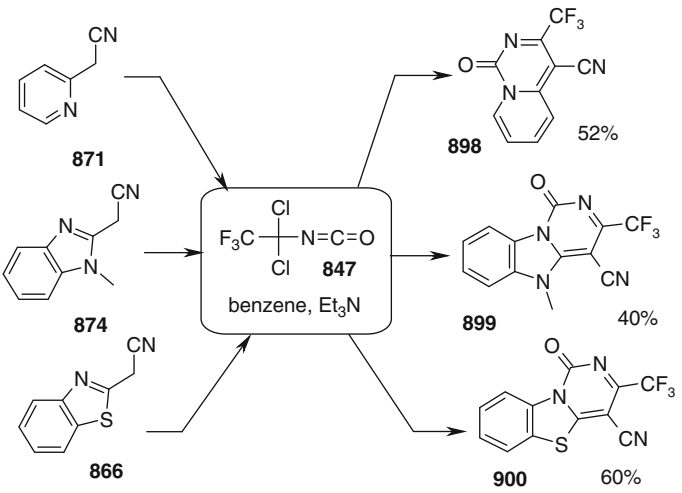
The feature of chemical behavior of carbodiimides **846** is ability to undergo intramolecular cyclization into dihydroquinazolidenes **897** in a presence of TEA. In absence of proton donating nucleophiles TEA attacks the highly electrophilic carbon of heterocumulene **846** providing intermediate **895**. The bond between a chlorine and a α-carbon in the latter is strongly polarized, and therefore these intermediates may exist in equilibrium with diazadiene **896** (compare with **881**, Scheme 179).

The presence of triethylamonium moiety considerably increases the electrophilicity of the α-carbon in the **895** as well as the carbon in the N-ethylidene fragment in **896**. As a result a ring closure at the ortho-position of the N-tolyl moiety becomes possible (Scheme 184) [545]. The structure of unusual zwitterionic compounds was confirmed by X-ray.



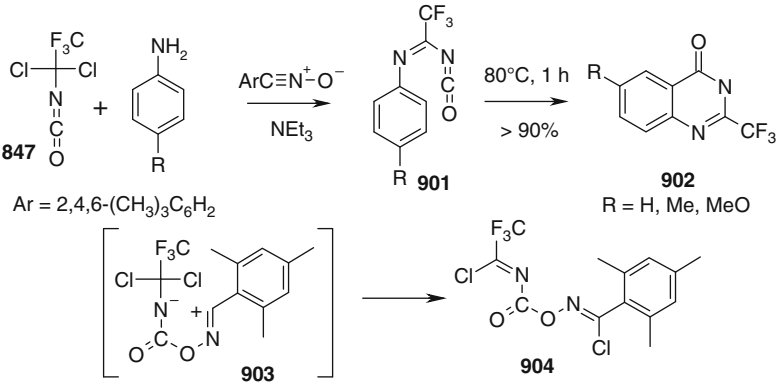
Scheme 184 Intramolecular cyclization of carbodiimides **846**

Besides the reactions of **845** and **846** with hetaryl acetonitriles interaction of these compounds with α,α-dichloroisocyanate **847** was studied. In all cases annelation of pyrimidine ring affording compounds **898–900** (Scheme 185) [536–538].



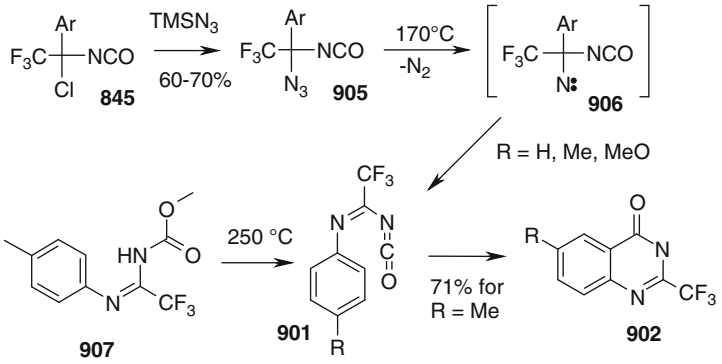
Scheme 185 Cyclization of isocyanate **847** with hetaryl acetonitriles

Also the reaction of α,α-dichloroisocyanate **847** with anilines was studied by Samarai and Vovk in presence of equimolar amounts of 2,4,6-trimethylbenzonitrile oxide [546]. The role of nitrile oxide consists in its unique blocking of the initial stage of the reaction to form **904** [547]. Nitrile oxide can be recovered in almost quantitative yield after completion of the process. It was established by IR spectroscopy that the reaction actually proceeds through isocyanates **901**, which undergo intramolecular cyclization (Scheme 186).



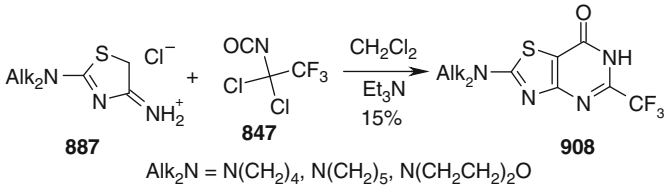
Scheme 186 Cyclization of isocyanate **847** with anilines

It should be noted, that isocyanates **901** can be generated by another ways. Samarai in 1977 described thermal nitrogen elimination from α-azidoisocyanates **905** followed by rearrangement to **901** [548]. Uneyama described in 1990 dehydromethoxylation at 250 °C of **907** to form ketenimide **901**, which afforded finally **902** in 71 % yield (Scheme 187) [549].



Scheme 187 Generation of isocyanates **901**

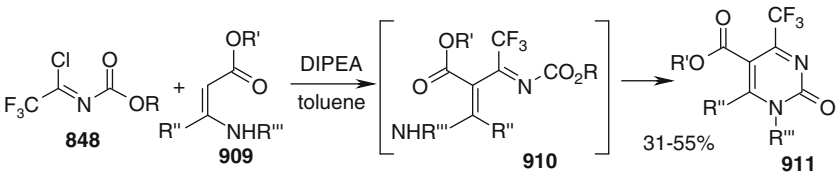
Reaction of **847** with aminothiazole precursors **887** was also studied; although the corresponding products of pyrimidine ring annelation **315** were obtained, their yields (15 %) were too low (Scheme 188; note the different regioselectivity compared to that observed for **283**, Scheme 181) [543].



Scheme 188 Reaction of **847** with aminothiazole precursors **887**

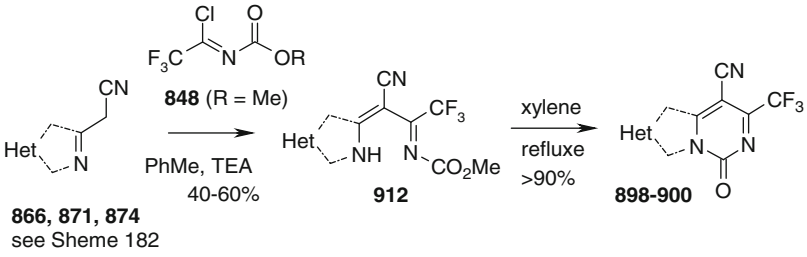
Imines **848** are promising reagents for the synthesis of fluoroalkyl-substituted pyrimidinines and their fused analogues since they lead to functionalized low-molecular-weight compounds which are of special interest for medicinal chemistry. Many CCN binucleophiles discussed in this section were also introduced into reaction with **848**. In particular, formation of pyrimidine derivatives **911** in reaction of **848** and enamines **909** (including compounds **859** discussed above) was described recently. The most likely initial step is the imidoylation of the nucleophilic carbon

atom in the enamine moiety of **909**. The resulting intermediate **910** appears to cyclize to compounds **911** already at room temperature (Scheme 189) [550].



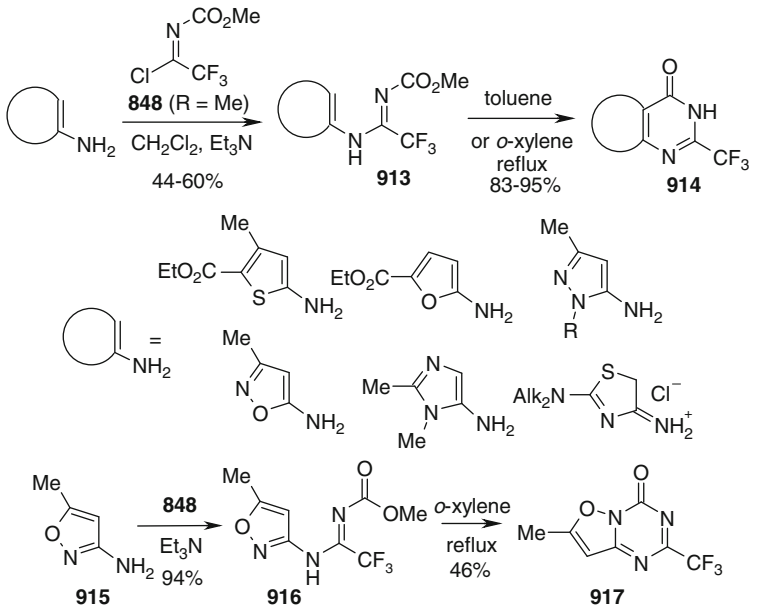
Scheme 189 Reaction of **848** with enamines **909**

Reaction of **848** with hetaryl acetonitriles in presence of triethylamine also proceeds through first *C*-imidoalkylation step as it confirmed by isolation of a stable compounds **912**. Compounds **912** were quantitatively converted into annelation products **898–900** by heating in boiling *o*-xylene (Scheme 190) [536–538]. It should be noted that the yields of **898–900** were somewhat lower than in the case of isocyanate **847** (see Scheme 185).



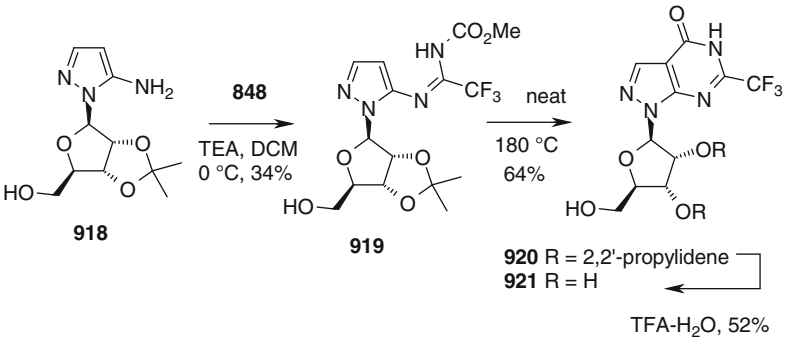
Scheme 190 Cyclization of imine **848** with hetaryl acetonitriles

Reaction of **848** with amino heterocycles is a valuable approach to chain-fluorinated purines and their bioisosteres. It was found that cyclocondensation of **848** with electron-rich aromatic and heteroaromatic amines proceeded in two steps (Scheme 191) [543, 551–554]. First, amidines **913** were formed under mild conditions (Et_3N, CH_2Cl_2, ambient temperature) in moderate yields (44–60 %). Cyclization of **913** occurred under harsh conditions (toluene or xylene, reflux); however, the yields of the products **914** in this step were high (83–96 %). It should be noted that in the case of 5-methylisoxazol-3-amine **915**, triazine derivative **917** was formed instead of the corresponding pyrimidine [555].



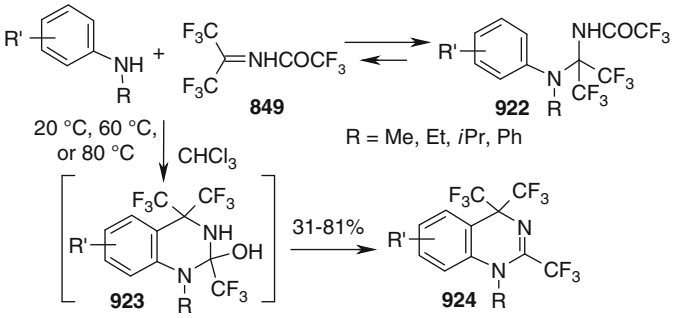
Scheme 191 Reaction of **848** with electron-rich aromatic and heteroaromatic amines

This approach was recently used for the synthesis of 2-trifluoromethyl allopurinol riboside. Aminopyrazole **918** reacts with two equivalents of imine **848** under mild conditions affording the product bearing two methyl 1,1,1-trifluoropropan-2-ylidenecarbamate groups, which was detected by HPLC. During the elution with EtOAc 1,1,1-trifluoropropan-2-ylidenecarbamate group on the 5-th position of the sugar residue was removed to give intermediate **919**. Amidine **919** appeared to be stable to the ring cyclization and required heating at 180 °C during 1 h. Removing the protecting group by acidic treatment leads to target 2-trifluoromethyl allopurinol riboside **921** (Scheme 192) [556].



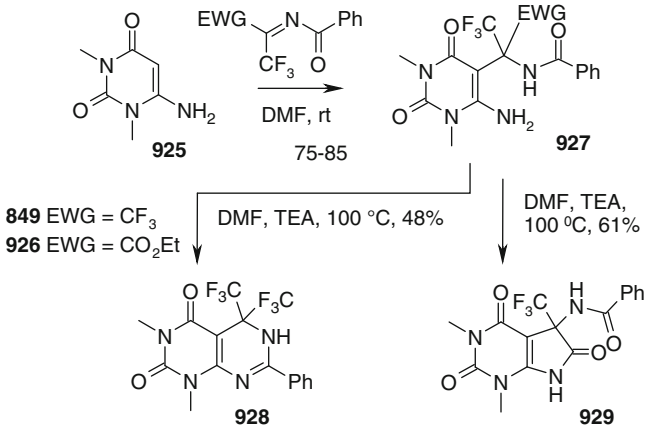
Scheme 192 Synthesis of 2-trifluoromethyl allopurinol riboside **921**

The chemistry of imines of hexafluoroacetone **849** and **850** as CNC bis-electrophiles was elaborated by Chkanikov and than developed by Sokolov group. Dihydroquinazoline derivatives **924** were obtained by reaction of imine **849** and *N*-alkylanilines (Scheme 193) [557, 558]. Initially, *N*-alkylation product **922** was formed, which is in equilibrium with starting materials. This intermediate rearranged to the product of C-alkylation to give **924** upon further dehydration. The water liberated in this reaction caused hydrolysis of the imine **849** as a side reaction. The rate of heterocyclization depends on stability of **922**, which decreases with increasing steric effect at the nitrogen atom of aniline. Indeed, *N*-methyl derivative of the type **922** is stable enough under reaction conditions and is converted to dihydroquinazoline only by heating, whereas in the case of *N*-isopropyl derivative, the heterocyclization product is formed already at 20 °C.



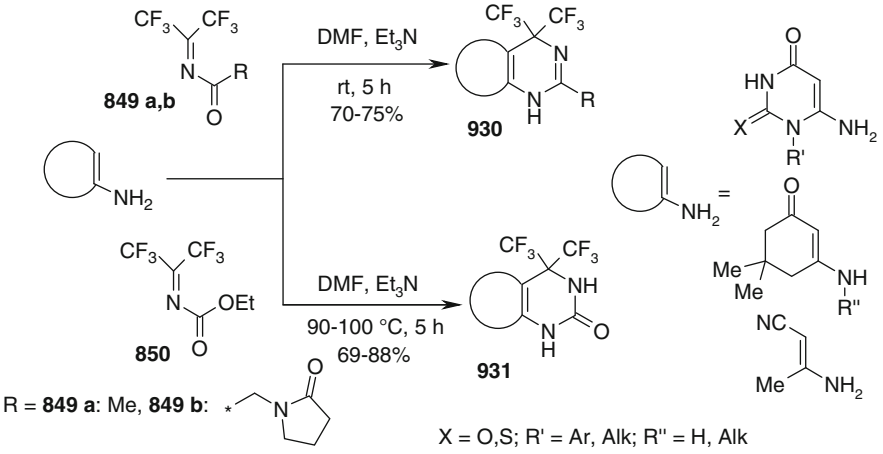
Scheme 193 Reaction of **849** with *N*-alkylanilines

In 2001 Sokolov with co-workers extended the reaction to aminouracil. In a case of benzoyl imine **849** the reaction with uracil **925** gives C-aminoalkylated product **927** cyclized into fused pyrimidine derivative **928** (compare with amopyrazole behaviour, see Scheme 180). It should be noted, that similar sequence with imine of trifluoropyruvate **926** leads instead of **849** to pyrrolo[2,3-d]pyrimidine derivative **929** (Scheme 194) [559].



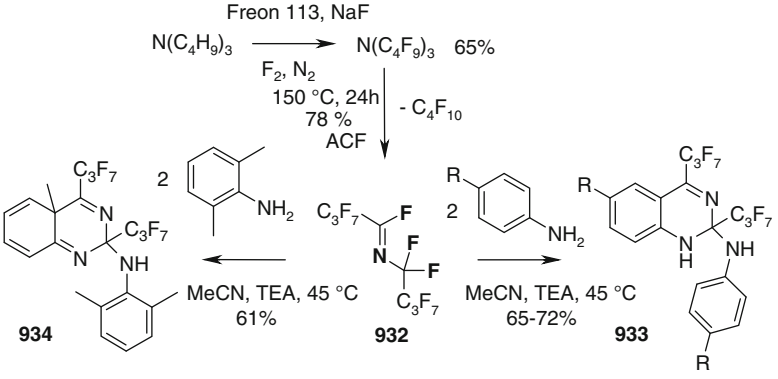
Scheme 194 Reaction of **849** with *N*-alkylanilines

Puch-pull enamines and more complicated hexafluoroacetone acyl imines **849b** afforded pyrimidines **930** (Scheme 195) [560, 561]. Ethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethylidenecarbamate **850** is another CNC bis-electrophile, which has been used for pyrimidine ring assembly. Aminouracil, aminocrotononitrile and 3-amino-5,5-dimethylcyclohex-2-en-1-one react readily with **850** to give pyrimidines **931** (Scheme 195) [562] as a single regioisomer.



Scheme 195 Reaction of **849** and **850** with CCN binucleophiles

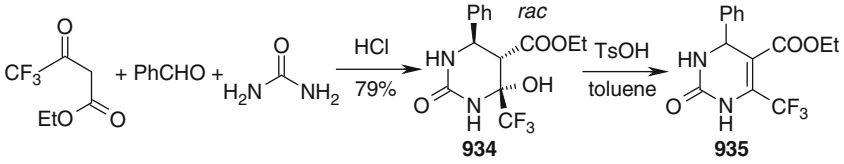
The reaction of anilines with perfluorinated imine **932** can be considered also as CNC+CCN approach to fluoroalkyl-substituted pyrimidines. Imine **932** was synthesized by perfluobutane elimination from perfluorotributylamine [563] under ACF (Aluminium chlorofluoride, $AlCl_xF_{3-x}$, $x \approx 0.05$–0.25) catalyzed thermolysis [564]. This imine have been found to react smoothly with 2 equivalents of anilines in presence of 3 equivalents of TEA in MeCN to give the fused pyrimidines **933** in good yields. In a case of 2,6-dimethylaniline the reaction leads to the dihydroquinazoline derivative **934** (Scheme 196) [565].



Scheme 196 Reaction of perfluoroimine **932** with anilines

7.4 Multicomponent Synthesis of Fluorinated Pyrimidines

Due to their productivity, high yields, convergence and facile execution multicomponent reactions are widely used in the synthesis of heterocycles. Surely, the most known multicomponent reactions in the field of pyrimidines is Biginelli reaction – a three-component condensation of aldehyde, methylene active compound and urea [566]. The use of fluorinated β-dicarbonyl compounds as methylene components in Biginelli reaction was documented first in 1950s [5]. In this work, formation of the structure **935** was reported in the reaction of ethyl trifluoroacetoacetate, benzaldehyde and urea (Scheme 197). Reinvestigation of these results, made in late 1990s, showed that stable hydrate **934** (most thermodynamically stable stereoisomer) was formed at these conditions [567]. Elimination of water from **934** occurred only in presence of a strong acid (TsOH, reflux in toluene).



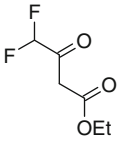
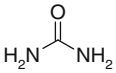
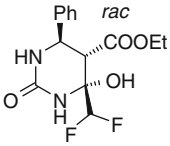
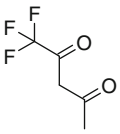
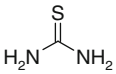
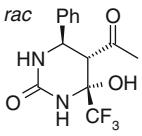
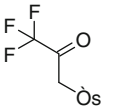
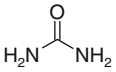
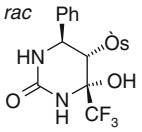
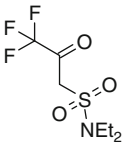
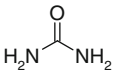
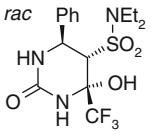
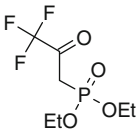
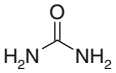
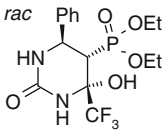
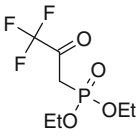
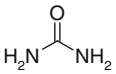
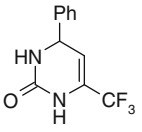
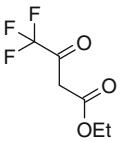
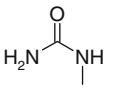
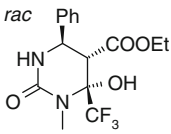
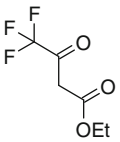
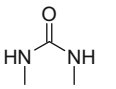
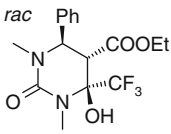
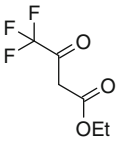
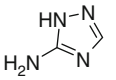
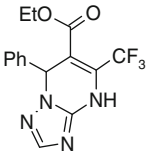
Scheme 197 The first Biginelli reaction with fluorinated β-dicarbonyl compounds

The method was extended to other classes of fluorinated β-dicarbonyl compounds, including β-ketoesters (Table 42, Entry 1), β-diketones (Entry 2), β-ketosulphones (Entry 3), β-ketosulphamides (Entry 4), and β-ketophosphonates (Entries 5 and 6). It should be noted that in case of some β-diketones (*i.e.* 1,1,1,5,5,5-hexafluoroacetylacetone), the products of principal pyrimidine synthesis were formed instead of Biginelli adducts under reaction conditions [568]. Apart from urea and thiourea, other classes of NCN binucleophiles were also introduced, including *N*-alkylureas (Entries 7 and 8, note different stereochemistry of the products), aminotriazoles (Entries 9 and 10), aminotetrazole (Entry 11), and 2-aminobenzimidazole (Entry 12).

A huge number of the reaction promoters were used for the preparation of structures of both types **934** and **935** in a selective manner. Apart from those mentioned in the Table 42, these include:

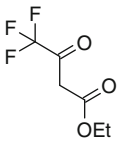
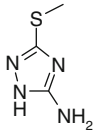
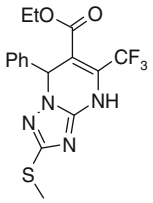
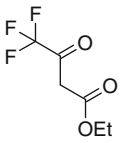
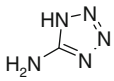
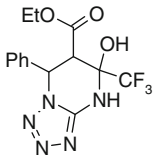
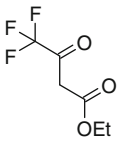
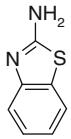
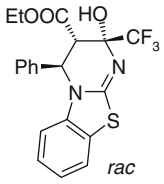
- for hydrates **934**: $Yb(OTf)_3$ [576], $ZrCl_4$ [577], ionic liquids [578], $LiCl–CuCl_2$ [579], $LiCl–SnCl_2$ [580], SmI_2 [581], $K_5CoW_{12}O_{40}·3H_2O$ [582], *p*-dodecyl benzenesulfonic acid [583], TsOH with grinding [584].
- for dihydropyrimidines **935**: ytterbium (III) perfluorooctanoate [585], $Bi(OTf)_3$ [586], $TaBr_5$ [587], bioglycerol-based sulfonic acid functionalized carbon catalyst [588], cerium ammonium nitrate with ultrasound activation [589], citric acid [590].

Table 42 Biginelli reaction with fluorinated **β**-dicarbonyl compounds

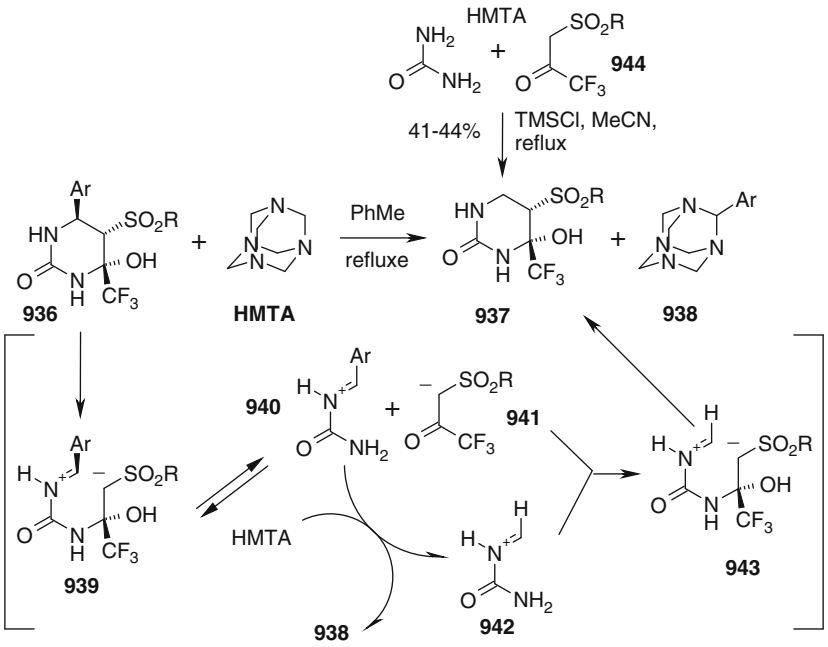
#	Reactants		Product	Conditions	Yield	Ref.
1				PhCHO, cat. HCl, EtOH, reflux	75	[569]
2				PhCHO, cat. HCl, EtOH, reflux	22	[569]
3				PhCHO, Ac_2O, AcOH, 80 °C	85	[570]
4				PhCHO, Ac_2O, AcOH, 80 °C	76	[570]
5				PhCHO, TMSCl, MeCN, rt	60	[571]
6				PhCHO, AcOH, 80 °C	70	[571]
7				PhCHO, TMSCl, DMF, rt	73	[572]
8				PhCHO, TMSCl, DMF, rt	52	[572]
9				PhCHO, cat. HCl, EtOH, reflux	55	[573]

(continued)

Table 42 (continued)

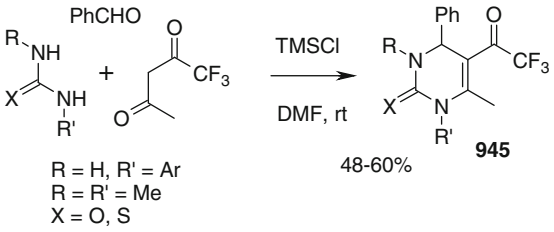
#	Reactants		Product	Conditions	Yield	Ref.
10				PhCHO, EtOH, MW, 150 °C	79	[574]
11				PhCHO, cat. HCl, EtOH, reflux	47	[574]
12				PhCHO, 80 °C	84	[575]

Some interesting results were found recently by Shermolovich with co-authors upon investigation of 2-oxo-2-polyfluoroalkylethane-1-sulfones and -sulfamides in Biginelli reaction (Table 42, Entry 3). The corresponding Biginelli compounds undergo 'retro-Biginelli' reaction by treatment with hexamethylenetetramine (HMTA) under thermal conditions involving replacement of 6-aryl substituent of the pyrimidinone cycle with a hydrogen atom donated by HMTA (Scheme 198) [570]. The formation of **937** proceeds through acyclic intermediate **940**, generated via thermal cleavage of **936**. In this intermediate the carbanion adjacent to the sulfonyl substituent is stabilized strong electron-withdrawing group, while the iminium cation is postulated as an intermediate in the condensation of aldehydes with urea in the classical Biginelli reaction. The arylidene group is transferred to HMTA releasing the methylidene moiety to afford the intermediate **942**, subsequent cyclization of which results in the 6-unsubstituted tetrahydropyrimidinone **937**. When ketones **944** were directly subjected to the Biginelli reaction with urea and HMTA using TMSCl as promoter the expected tetrahydropyrimidinones **937** were obtained in ca. 40 % yield (Scheme 198).



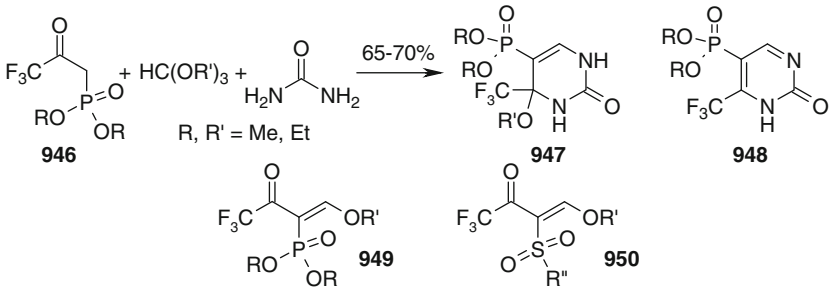
Scheme 198 'Retro-Biginelli' reactions

In another paper dealing with TMSCl promoted by Biginelli reaction unusual results were obtained in a case of trifluoroacetyl acetone and N-substituted (thio) ureas. In this case the cyclization leads to compounds **945** bearing CF_3CO group at 5th positions. To the best of our knowledge this reaction is the only example of Biginelli reaction with fluorinated unsymmetrical β-dicarbonyl compounds were CF_3CO groups leaves intact and compounds **945** are the only representatives of Biginelly compounds bearing CF_3CO groups at the 5th positions (Scheme 199) [572].



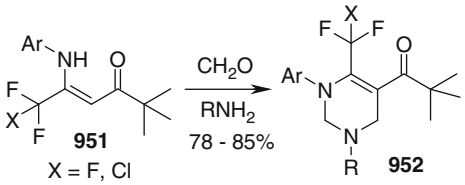
Scheme 199 The Biginelli reaction with 'abnormal' regioselectivity

Apart from the Biginelli reaction, several additional three-component condensations are worth mentioning in this section. In particular, a transformation closely related to Biginelli reaction was described by Shermolovich and coworkers, namely, reaction of β-ketophosphonates **946**, urea and orthoformates, which leads to adducts **947** (Scheme 200) [571]. The corresponding aromatic compounds **948** were not isolated, presumably due to high electrophilicity of C=N bond in their molecules. Evidently, the reaction occurs via intermediate formation of **946**, which has been reported by same scientists in the reaction of 3-arylsulfonyl-1,1,1-trifluoropropan-2-ones **944** with orthoformates [591].



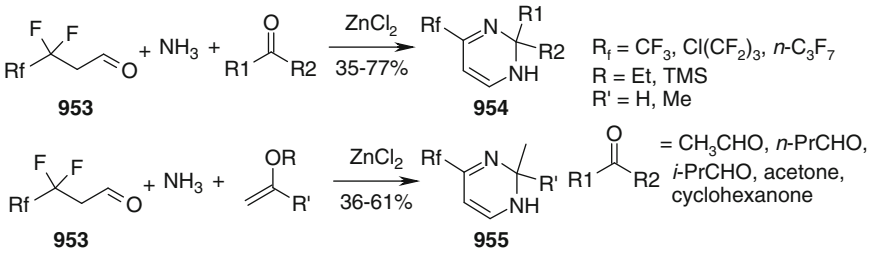
Scheme 200 Reaction of β-ketophosphonates **946**, urea and ortoformates

Reaction of fluorinated β-enaminones **951** with formaldehyde and primary amines resulted in tetrahydropyrimidines **952** in 78–85 % yields (Scheme 201) [592].



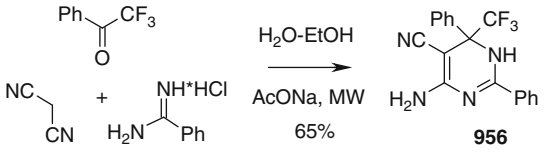
Scheme 201 Reaction of β-enaminones **951**, formaldehyde and primary amines

Dihydropyrimidines **954** or **955** were the products of the reaction of 2,2-dihydro polyfluoroalkylaldehydes **953** with ammonia and aldehydes, ketones or enol ethers (Scheme 202) [593].



Scheme 202 Three-component reactions with aldehydes **953**

One more three-component condensation leading to formation of chain-fluorinated pyrimidines **956** was microwave-assisted reaction of malononitrile, 2,2,2-trifluoro-1-phenylethanone and amidine in water (Scheme 203) [594]. Attempts to perform this reaction under thermal conditions were unsuccessful.

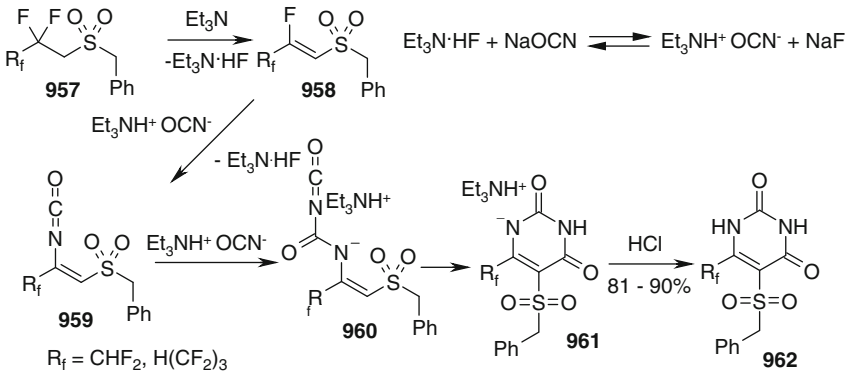


Scheme 203 Synthesis of pyrimidine **956** by three-component reaction

7.5 Miscellaneous Methods for the Preparation of Pyrimidines

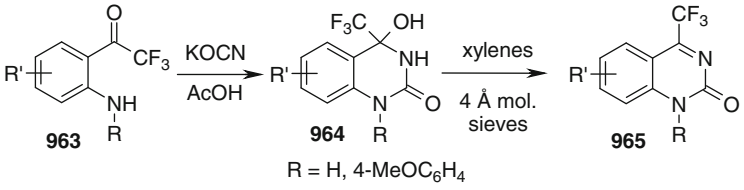
Several methods for construction of diazine core of chain-fluorinated pyrimidines do not fall into any of the mentioned above categories. One of such approaches is discussed in Sect. 7.8, namely, inverse-electron-demand Diels-Alder reactions with fluorinated *sym*-triazines. Other methods that fall into category "miscellaneous" are too different to discuss them systematically; therefore, selected examples of them are listed in this section.

An unusual method for the preparation of fluorinated uracil derivatives **962** relied by Shermolovich with co-workers on reaction of fluorinated sulphones **957** with sodium cyanate in presence of triethylamine, followed by acidification (Scheme 204) [595]. The mechanism of the reaction included base-catalyzed elimination of HF, followed by addition of two cyanate ions to the formed alkene **958**.



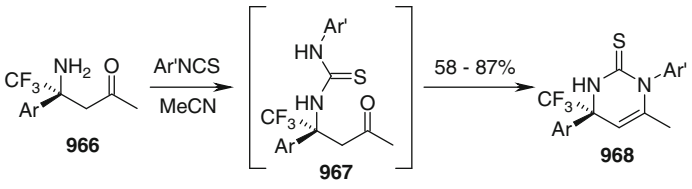
Scheme 204 Reaction of fluorinated sulphones **957** with sodium cyanate

Another cyanate-based method was used in the synthesis of reverse transcriptase inhibitors, namely, reaction of trifluoroacetophenones **963** with sodium cyanate, affording hydrate **964**, followed by dehydration in xylene (Scheme 205) [596].



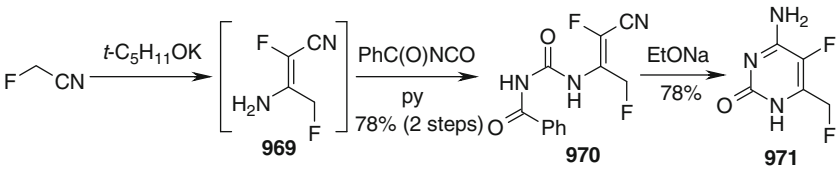
Scheme 205 Reaction of trifluoroacetophenones **963** with sodium cyanate

One more method relied on reaction of chiral fluorinated amino ketones **966** and aryl isothiocyanates to give pyrimidine derivatives **968** in 58–87 % yields and optical purity of 88–96 % (Scheme 206) [597].



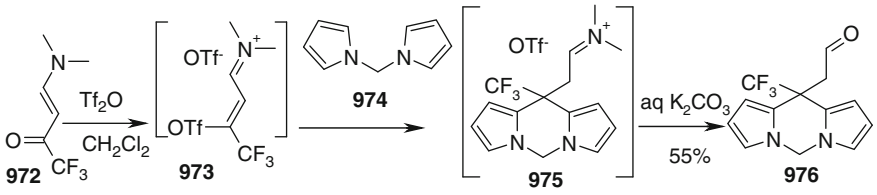
Scheme 206 Reaction of fluorinated amino ketones **441** with aryl isothiocyanates

A method which relied on the use of benzoyl isocyanate was developed for the synthesis of 5-fluoro-6-fluoromethylcytosine (**971**) (Scheme 207) [598]. Thorpe condensation of fluoroacetonitrile generated unstable enamine **969**, which reacted with benzoyl isocyanate in presence of pyridine to give urea derivative **970**. Cyclization of **970** upon action of NaOEt led to the formation of **971**.



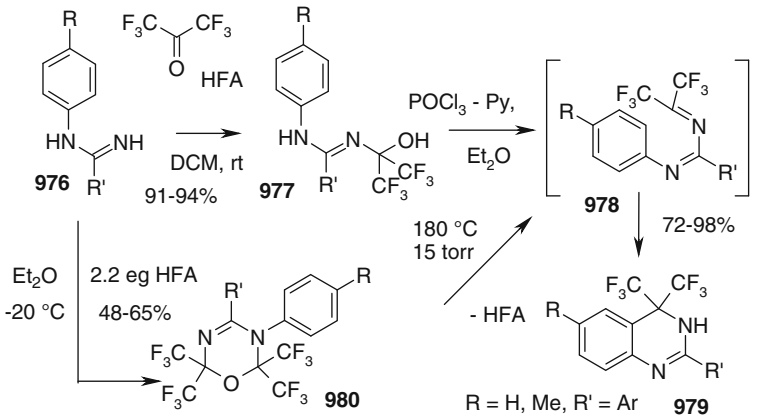
Scheme 207 Synthesis of 5-fluoro-6-fluoromethylcytosine

Tricyclic pyrimidine derivative **976** was obtained in the reaction of bis(pyrrolyl) methane (**974**), enaminone **972** and Tf_2O (Scheme 208) [599]. This is an example of quite unusual reactivity of enaminones (as C_1 synthons) in the synthesis of pyrimidines. This reactivity can be explained by preferential formation of the six-membered ring over eight-membered.



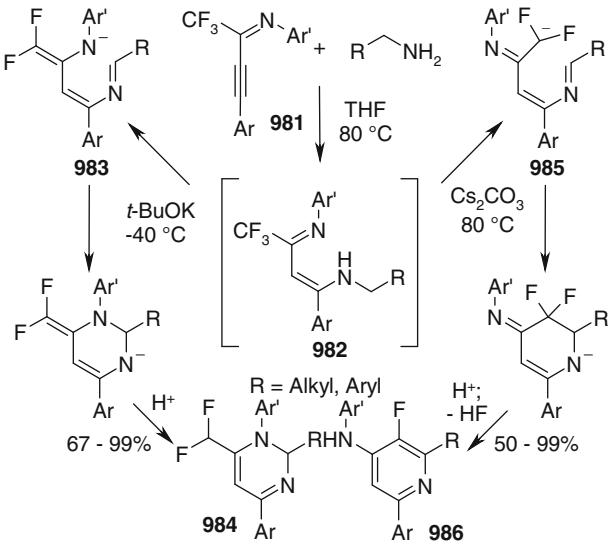
Scheme 208 Enaminone **972** as C_1 synthon in pyrimidine synthesis

Another example of fluorinated pyrimidine synthesis via [5+1] approach using fluorinated C_1 synthon was described by Burger in 1980. Amidines **976** react with hexafluoroacetone (HFA) affording adduct **977**, which under treatment with $POCl_3$-Py generating diazabuta-1,3-dienes **978** spontaneously cyclized into 3,4-dihydro-quinazolines **979** (compare with Schemes 179, 184, 193 and 194). If the firs step of the cyclization proceeds in ether with an excess of HFA the chemistry becomes more complicated. In this case 5,6-dihydro-2H-1,3,5-oxadiazines **980** are formed, which undergo retro Diels Alder reaction on thermolysis. Elimination of hexafluoroacetone leads to diazabuta-1,3-dienes **978** transformed into final 3,4-dihydro-quinazolines **979** (Scheme 209) [600]



Scheme 209 Fluorinated dihydroquinazolines **979** synthesis based on HFA

Recently Chinese chemists elaborated unusual cyclization based on alkynylimines **981**. Reaction of **981** (prepared by CuI-catalyzed coupling of terminal alkynes with fluoroalkylimidoyl chlorides) and primary amines led to formation of enamines **982**, which were not isolated but treated with *t*-BuOK at −40 °C to give dihydropyrimidines **984** (Scheme 210) [601].



Scheme 210 Synthesis of pyrimidines from alkynylimines **981**

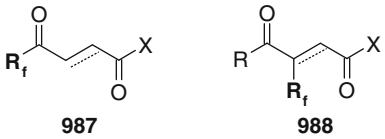


Fig. 27 1,4-Dicarbonyl compounds for the synthesis of chain-fluorinated pyridazines

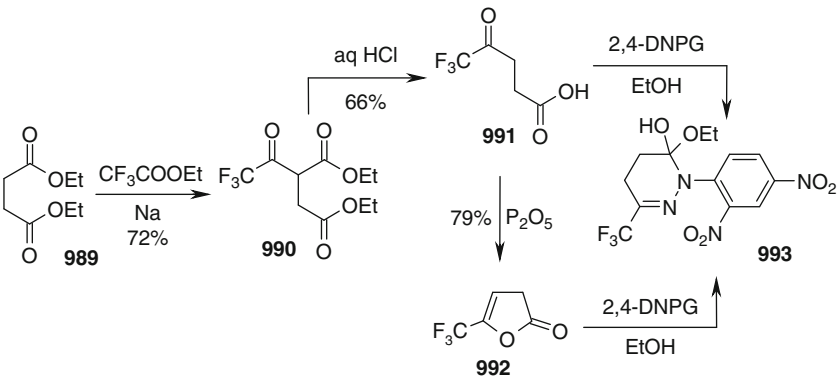
On the contrary, reaction in presence of Cs_2CO_3 at 80 °C provided pyridines **986**. A possible explanation of these results included formation of **982**, followed by generation of anion **983** upon action of base. When the reaction was carried out at a low temperature with a soluble base (*t*-BuOK), intramolecular *N*-nucleophilic cyclization of **983** was observed immediately to form dihydropyrimidine **984** through a kinetically controlled pathway. However, *C*-nucleophilic addition became an option upon elevated temperatures and/or with the use of an insoluble base (Cs_2CO_3), providing 1,2-dihydropyridine ring under thermodynamic control. The subsequent proton migration, β-fluoro elimination and final aromatization to form the pyridine ring of **986** also provided a driving force for this pathway.

7.6 Synthesis of Chain-Fluorinated Pyridazines

7.6.1 Synthesis from Fluorinated 1,4-Dicarbonyl Compounds and Their Analogues

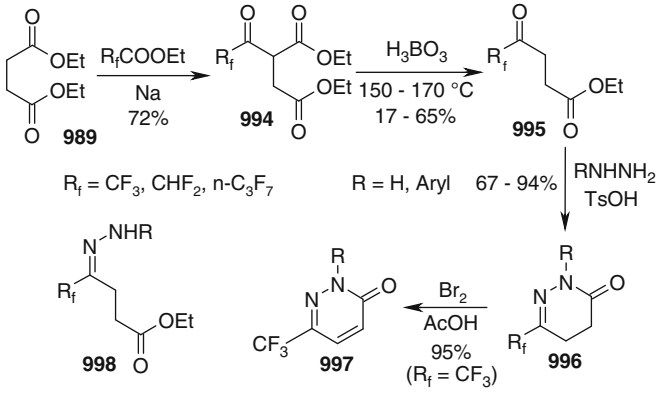
The reaction of 1,4-dicarbonyl compounds or their synthetic equivalents with hydrazines is one of the most significant methods for the construction of the diazine ring of chain-fluorinated pyridazines. Two subtypes of fluorinated 1,4-dicarbonyl compounds can be used for this aim (**987** and **988**) (Fig. 27), leading to formation of 3(6)- and 4(5)-fluoroalkyl-substituted pyridazines, respectively.

Formation of pyridazine ring by reaction of 1,4-dicarbonyl compounds of the type **987** was reported first in 1960, when characterization of 5,5,5-trifluorolevulinic acid (**991**) and its lactone **992** was performed (Scheme 211) [602]. Upon their reaction with 2,4-dinitrophenyl hydrazine (2,4-DNPG) in ethanol, a product **993** was obtained instead of 2,4-dinitrophenyl hydrazones. The starting compound **991** was obtained by hydrolysis of a Claisen adduct **990**, prepared from ethyl trifluoroacetate and diethyl succinate **989**.



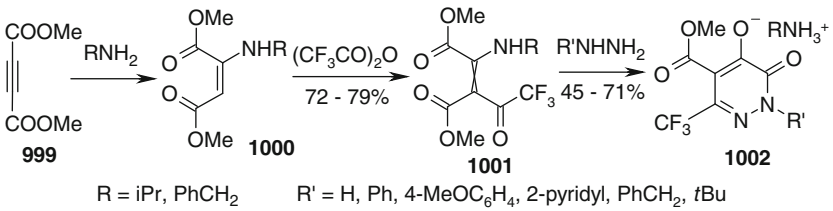
Scheme 211 Synthesis of pyridazines from 5,5,5-trifluorolevulinic acid (**991**)

Recently, a modification of this approach was developed by chemists from China [603]. In this method, esters **995** were prepared from **994** by heating with H_3BO_3 (Scheme 212). Compound **995** reacted with various hydrazines in presence of TsOH to produce dihydropyridazines **996** (although in the case of aryl hydrazines with EWG (*e.g.* 2,4-DNPG), the corresponding hydrazones **998** did not or only partially underwent cyclization to **996**). Aromatization of **996** could be performed by action of bromine in acetic acid to give products of the type **997**.



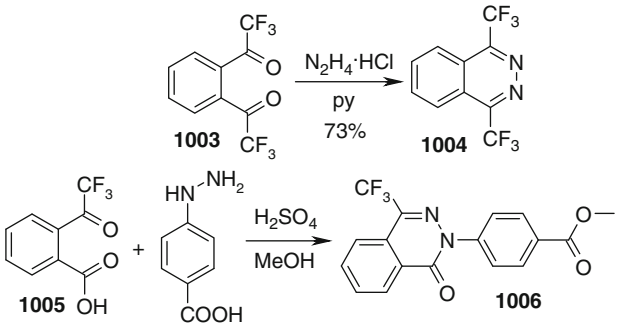
Scheme 212 Synthesis of pyridazines from esters **339**

Reaction of functionalized enamines **1001** with hydrazines assumed a slightly anomalous course leading to pyridazine derivatives **1002** (Scheme 213) [604]. The starting compounds **1001** were obtained in two steps from dimethyl acetylenedicarboxylate **999**.



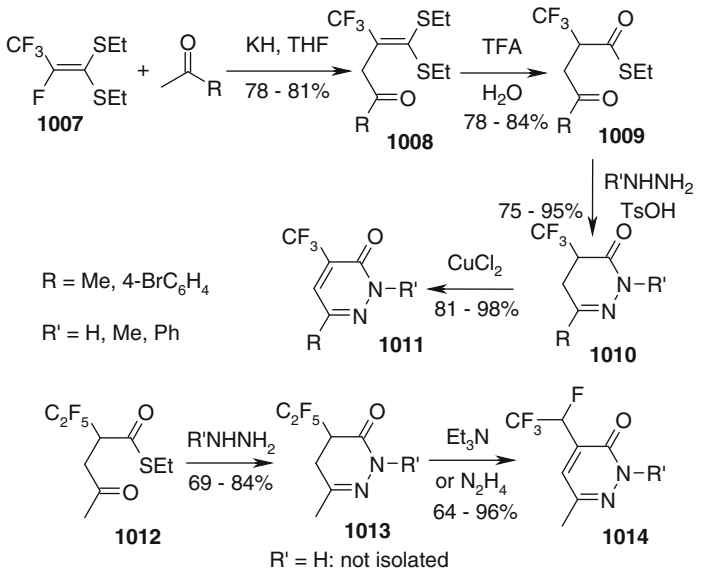
Scheme 213 Synthesis of pyridazines **345**

Fluorinated 1,4-dicarbonyl compounds of the type **987**, which carbonyl groups are mounted on an aromatic core, are common starting materials for the preparation of chain-fluorinated phthalazines and their analogues. Apart from benzene derivatives **1003** [605] and **1005** [606] (Scheme 214), derivatives of azulene [607], indene [608] and furane [609] were introduced into these transformations.



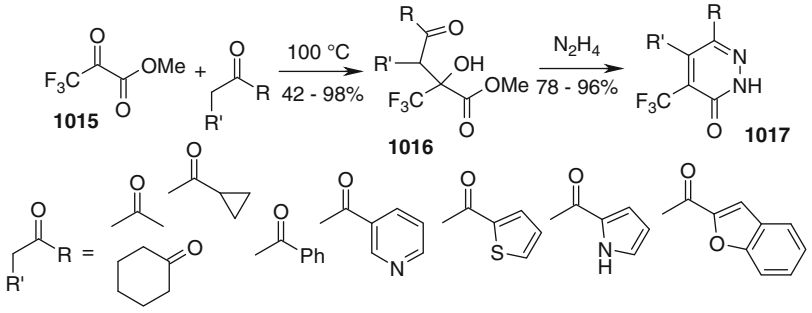
Scheme 214 Synthesis of chain-fluorinated phthalazines

Thioesters **1009** are examples of fluorinated compounds of the type **987**, which give 4(5)-fluoroalkyl-substituted pyridazines upon reaction with hydrazine. Compounds **1009** were prepared by reaction of ketene dithioacetal **1007** with the corresponding enolate anion, followed by hydrolysis (Scheme 215) [610]. Reaction of **1009** with hydrazines led to the formation of dihydropyridazines **1010** in a regioselective manner. Aromatization of **1010** was achieved by heating with $CuCl_2$ in acetonitrile. Analogous reaction sequence with thioester **1009** led to formation of dihydropyridazines **1013**, which underwent easily elimination of HF upon action of a base affording pyridazine **1014**. In case of hydrazine hydrate, compound of the type **1013** was not isolated; HF elimination occurred upon reaction conditions. The drawback of the approach is poor availability of commercially unavailable ketene dithioacetals **1007**. As in a case of above mentioned CNC-biselectrophiles, preparation of these compounds requires quite expensive fluorine-containing starting compounds, and the procedures leading to their formation cannot be classified as easy to perform [611].



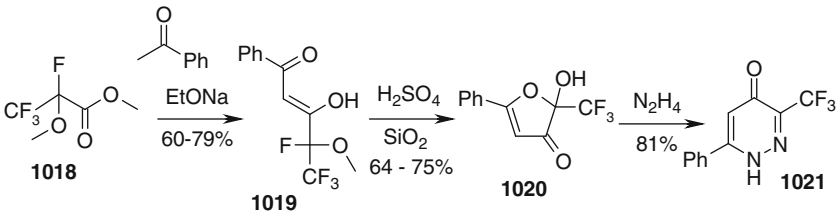
Scheme 215 Synthesis of pyridazines from thioesters **1007** and **1012**

A convenient two-step methodology for the preparation of 4-trifluoromethyl-(2*H*)-pyridazin-3-ones starting from methyl trifluoropyruvate MeTFP (**1015**) was developed (Scheme 216) [612]. The approach relied on aldol condensation of **1015** with various ketones, followed by reaction of the adducts **1016** with hydrazine. Recently, this methodology was used for the preparation of γ-secretase modulators [613].



Scheme 216 Synthesis of pyridazines from MeTFP **1015**

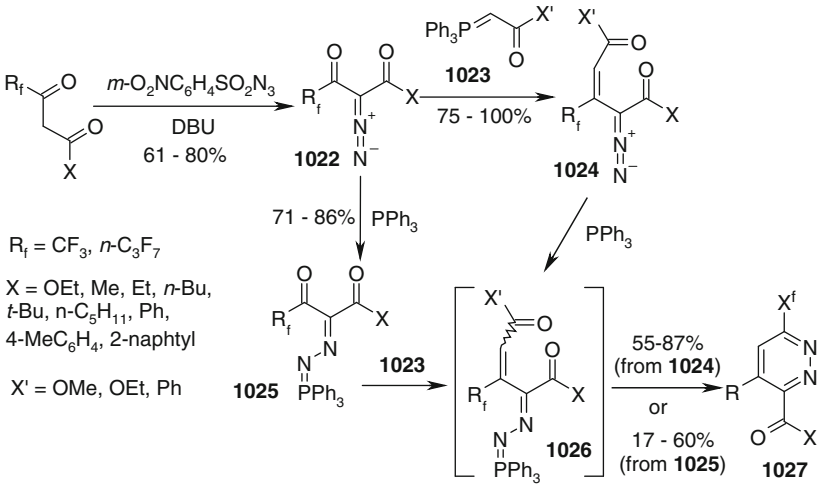
An unusual synthetic equivalent of trifluoromethyl substituted 1,4-dicarbonyl compounds is furanone **1020**, which can be obtained by condensation of acetophenone and methyl 2-methoxytetrafluoropropionate **1018** (synthetic equivalent of MeTFP in Claisen condensation), followed by acidic dehydration (Scheme 217) [614]. Reaction of **1020** with hydrazine led to the formation of pyridazine derivative **1021** in 81 % yield.



Scheme 217 Synthesis of pyridazines from **1018**

7.6.2 Diaza-Wittig Reactions

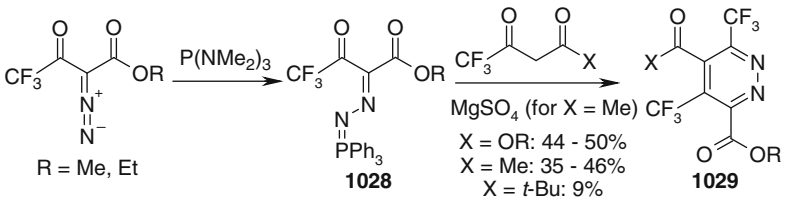
An interesting approach to pyridazine derivatives was described in 1998 by Guillaume and others [615] and studied later by Nikolaev and co-workers [616, 617]. The key idea of the method is implemented in the final step of sequence – intramolecular cyclization of intermediates **1026** – the so-called "diaza-Wittig" reaction (Scheme 218). Two alternative pathways for the generation of **1026** were used, both commencing from diazo-β-dicarbonyl compounds **1022**, in turn obtained by diazo transfer reaction. Compounds **1022** were subjected to Wittig reaction with stabilized ylides **1023**; the reaction proceeded in a stereoselective manner, so that *E*-isomer of product **1024** was formed. Reaction of **1024** with triphenylphosphine resulted in generation of **1026**, which underwent cyclization to give pyridazines **1027** in good yields. In an alternative scheme, compound **1022** was treated with triphenylphosphine to give Staudinger adducts **1025**. Wittig reaction of **1023** and **1025** resulted in generation of **1026**, which spontaneously underwent cyclization to give **1027**, although in moderate yields.



Scheme 218 Synthesis of pyridazines using intramolecular diaza-Wittig reactions

A closer look into stereochemical aspects of the diaza-Wittig reaction discussed above revealed that only one isomer of **1026** (*E* or *cis*) undergoes spontaneous cyclization to give pyridazine derivatives **1027** [618, 619]. The other isomer (*Z* or *trans*) can be isolated and in some cases even characterized by X-Ray data.

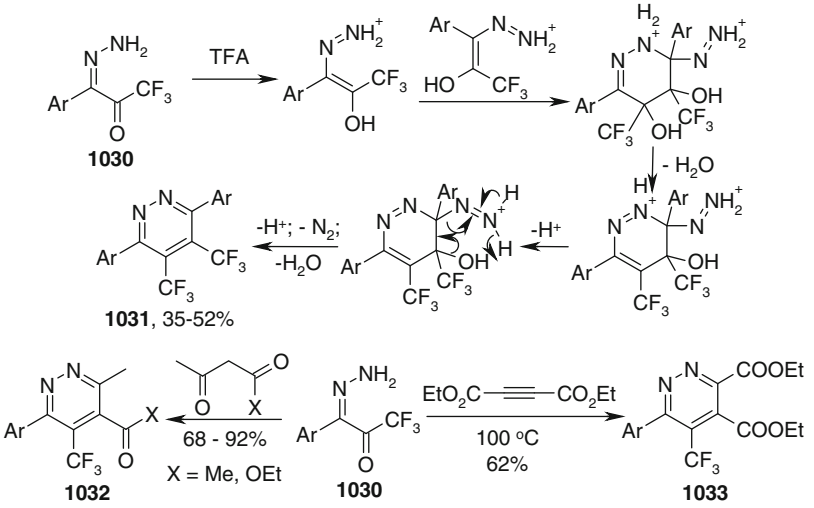
It was found that compounds **1025** (*i.e.* **1028**) react with β-dicarbonyl compounds to give pyridazine derivatives **1029** (Scheme 219) [620]. In this case, intermolecular diaza-Wittig reaction occurred, followed by intramolecular heterocyclization. The reaction was sensitive to steric factors: in case of β-diketone possessing bulky *tert*-butyl group, **1029** was isolated in low yield (9 %).



Scheme 219 Synthesis of pyridazines using intramolecular diaza-Wittig reactions

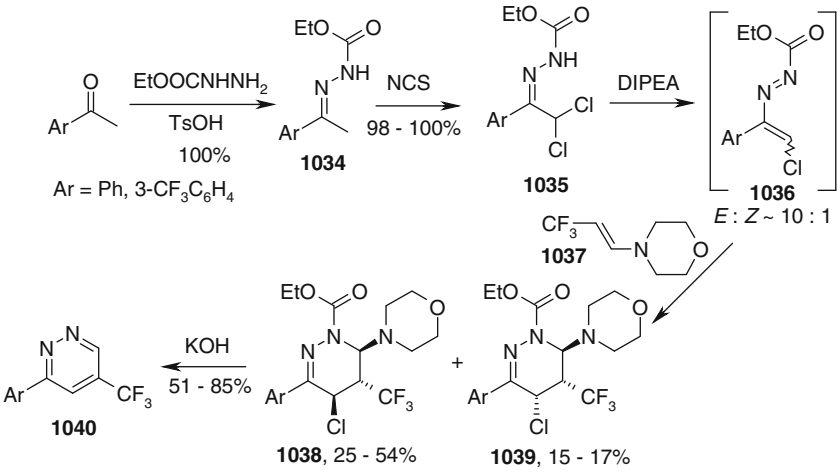
7.6.3 NNCC+CC Approaches

3-Hydrazono-1,1,1-trifluoroalkan-2-ones **1030** are NNCC units that have found use in synthesis of pyridazine derivatives. In particular, they undergo dimerization upon treatment with trifluoroacetic acid to give pyridazines **1031** (Scheme 220) [621]. Mechanistic study of this transformation showed that a key step of the reaction is concerted [4+2] cycloaddition of protonated **1030** [622]. Pyridazines (*i.e.* **1032** and **1033**) were the products in other reactions of hydrazones **1030** with acetylene dicarboxylates [621] and β-dicarbonyl compounds [623].



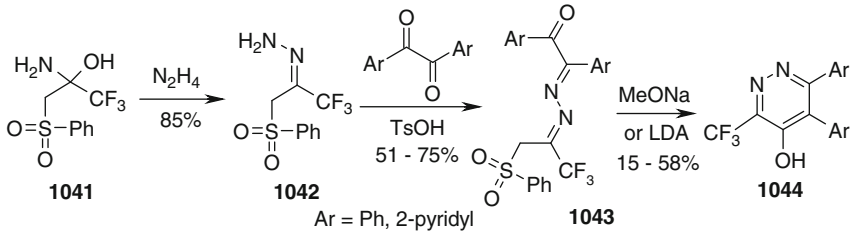
Scheme 220 Synthesis of chain-fluorinated pyridazines from hydrazones **1030**

Another fluorinated NNCC building blocks which give pyridazines through [4+2] cycloadditions are dichlorohydrazones **1035** (Scheme 221) [624, 625]. In this case, the fluoroalkyl substituent arrives from the CC partner of the reaction. Upon treatment with Hünig's base, 4-chloroazodienes **1036** are generated from **1035**, which undergo reaction with fluorinated enamines **1037** to form a mixture of diastereomers **1038** and **1039**. This mixture can be transformed to their aromatic counterparts **1040** by action of a strong base.



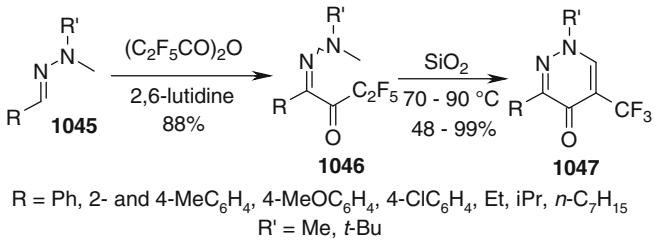
Scheme 221 Synthesis of chain-fluorinated pyridazines from hydrazones **1034**

Hydrazone **1042** (prepared from 2-amino-1,1,1-trifluoro-3-phenylsulfonyl-2-propanol) is one more NNCC binucleophile for the synthesis of chain-fluorinated pyridazines (Scheme 222) [626]. In this case, two-step reaction of **1042** with α-diketones is used, including acid-catalyzed hydrazone formation and base-promoted heterocyclization.



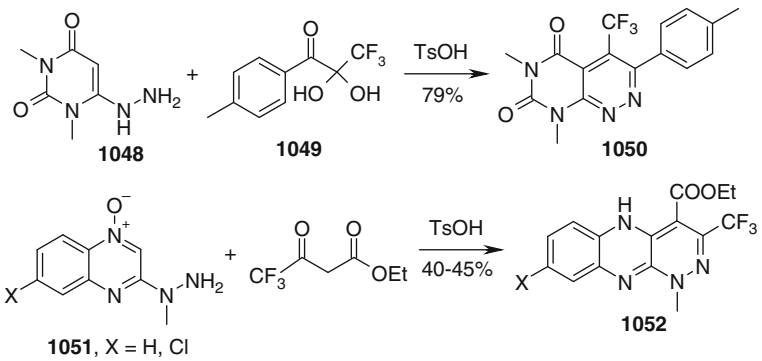
Scheme 222 Synthesis of chain-fluorinated pyridazines from hydrazone **1041**

In another two-step NNCC+CC strategy, acylation of hydrazones **1045** with perfluoropropionic anhydride led to the formation of **1046**, which underwent cyclization to pyridazines **1047** upon heating with silica gel (Scheme 223) [627].



Scheme 223 Synthesis of chain-fluorinated pyridazines from hydrazones **1045**

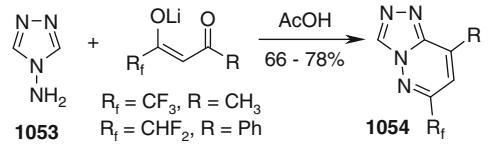
Heteroaromatic hydrazines were used as NNCC building blocks For the preparation of fused pyridazines. In particular, hydrazine **1048** reacted with hydrate of fluorinated α-diketone **1049** to give 4-trifluoromethylpyrimido[4,5-*c*]pyridazine derivative **1050** (Scheme 224) [628]. Furthermore, reaction of hydrazines **1051** with ethyl trifluoroacetoacetate led to the formation of pyridazino[3,4-*b*]quinoxaline derivatives **1052** [629].



Scheme 224 NNCC+CC approach to fused chain-fluorinated pyridazines

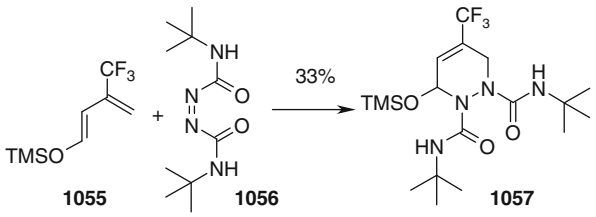
7.6.4 Other Methods

Reaction of 4-aminotriazole (**1053**) with fluorinated β-diketones is a method for the preparation of triazolopyridazines **1054** (Scheme 225) [630]. The method can be considered as NNC+CCC approach to the construction of the pyridazine ring.



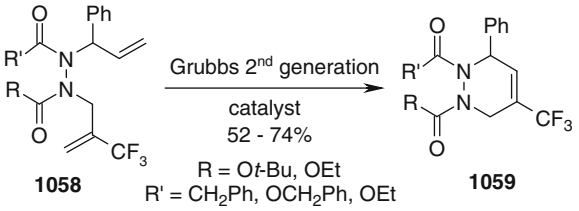
Scheme 225 NNC+CCC approach to chain-fluorinated triazolopyridazines

[4+2] cycloaddition of fluorinated diene **1055** and azo compound **1056** provided tetrahydropyridazine derivative **1057** – an example of CCCC+NN disconnection of chain-fluorinated pyridazine ring (Scheme 226) [631].



Scheme 226 CCCC+NN approach to chain-fluorinated pyridazines

Analogous pyridazine derivatives **1059** were prepared from diene precursors **1058** using metathesis reaction (Grubbs II catalyst, toluene, 100 °C). The corresponding trifluoromethyl-substituted cyclic hydrazines **1059** were obtained in reasonable to good yields. In almost all cases, 20 mol% of catalyst had to be added over a period of approximately 1 h in order to reach full conversion. (Scheme 227) [632].



Scheme 227 Synthesis of chain-fluorinated pyridazines using metathesis reaction

7.7 Synthesis of Chain-Fluorinated Pyrazines

7.7.1 Synthesis from 1,2-Diamines and Fluorinated 1,2-Bis-Electrophiles

A common method for the preparation of chain-fluorinated pyrazines relies on reaction of NCCN binucleophiles (*i.e.* 1,2-diamines) and fluorinated CC bis-electrophiles. This approach is especially valuable for the synthesis of quinoxalines and their hetero-analogues, since aromatic system is formed directly under reaction conditions. Therefore, most of the literature data concern heterocyclization with *o*-phenylenediamines, as well as the corresponding heterocyclic 1,2-diamines.

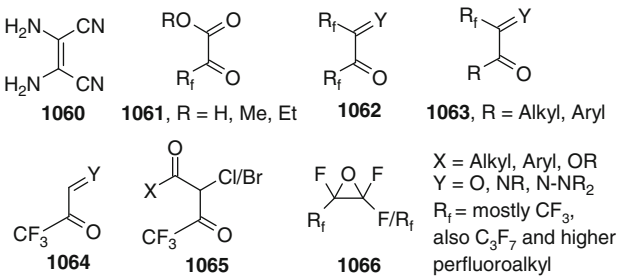


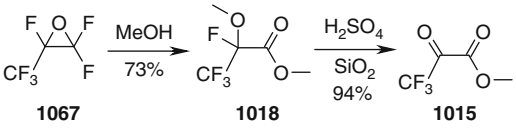
Fig. 28 Common substrates for NCCN+CC approach to pyrazines

Aliphatic diamines (mostly 1,2-ethylenediamine) are much less studied and often give poor results in the reaction with fluorinated 1,2-bis-electrophiles; possibly the only exception is diaminomaleonitrile (**394**), which also gives aromatic systems in these transformations.

The range of fluorinated 1,2-bis-electrophiles (some of these reagents (*e.g.* trifluoropyruvic acid) are available as hydrates) used for the construction of pyrazine core is vast (Fig. 28) and includes:

– trifluoropyruvic acid, its esters and higher homologues (**1061**);
– hexafluorobiacetyl, its derivatives and its higher homologues (**1062**);
– perfluoroalkyl-substituted α-diketones and their derivatives **1063**;
– trifluoromethyl glyoxal and its synthetic equivalents **1064**;
– fluorinated α-halo-β-dicarbonyl compounds **1065**;
– perfluorinated epoxides **1066**;
– other fluorinated 1,2-bis-electrophiles.

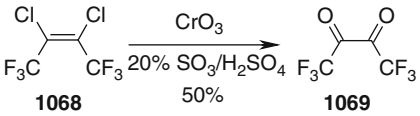
Preparations of these 1,2-bis-electrophiles share some common features. In particular, esters of trifluoropyruvic acid (like MeTFP **1015**) are available commercially, but they can be prepared in two steps from an epoxide **1067** (namely, hexafluoropropylene oxide, which is available on industrial scale) [633] (Scheme 228). In turn, epoxides **1067** are obtained by oxidation of the corresponding perfluorinated alkenes, *e.g.* with hypochlorite [634].



Scheme 228 Synthesis of methyl trifluoropyruvate

Hexafluorobiacetyl can be prepared in a reproducible manner in satisfactory yield (50 %) by oxidation of commercially available alkene **1068** (Scheme 229) [635]. Due to highly inhalation toxicity (LC_{50} inhalation – rat – 4 h – 16 ppm) the purchase

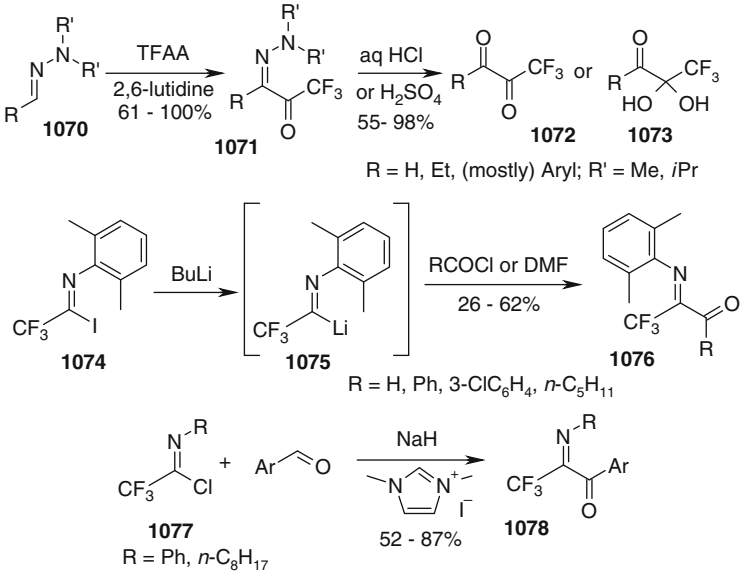
and transport of compound **1068** has some restriction, but the alkene can be prepared in laboratory by SbF_5 fluorination of hexachlorobutadiene [636].



1068 **1069**

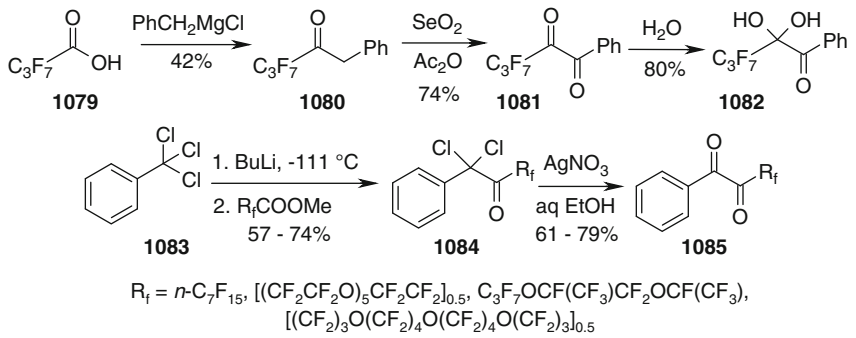
Scheme 229 Synthesis of hexafluorobiacetyl

Although generation and reactions of 1,1,1-trifluorobiacetyl was reported as early as in 1957, the compound was not isolated in this work [637]. Trifluoromethyl-substituted derivatives **1071** were obtained *via* trifluoroacetylation of hydrazones **1070** [638, 639], acylation of (trifluoroacetimidoy1)lithium derivatives **1075** [640], or condensation of trifluoroacetimidoyl chlorides **1077** with aromatic aldehydes in presence of sodium hydride [641] (Scheme 230). These methodologies were also used for the synthesis of trifluoromethyl glyoxal equivalents **1064** [640, 642].



Scheme 230 Synthesis of trifluoromethyl-substituted derivatives of the type **397** and **398**

Higher perfluoroalkyl homologues of the type **1063** were prepared *via* oxidation of benzyl-substituted ketones (*i.e.* **1080**) with SeO_2 [643] or hydrolysis of α,α-dichloroketones **1084** [644] (Scheme 231).

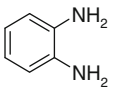
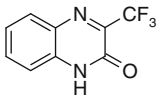
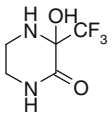
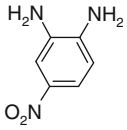
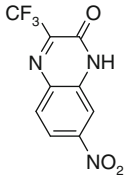
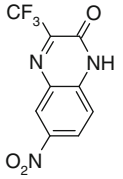
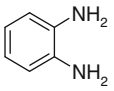
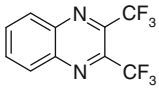
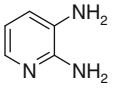
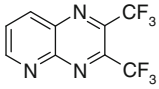
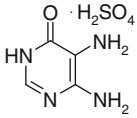
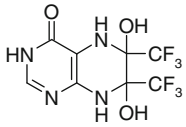
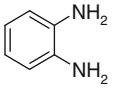
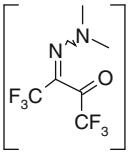
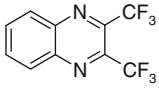
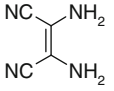
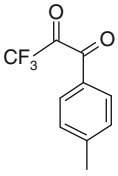
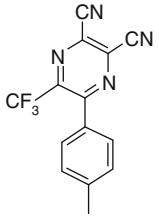
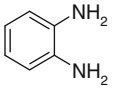
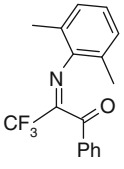
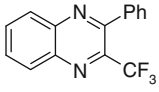


Scheme 231 Synthesis of higher perfluoroalkyl-substituted derivatives of the type **1063**

Synthesis of fluorinated α-halo-β-dicarbonyl compounds **1065** was straightforward and relied on halogenation of the corresponding fluorinated β-dicarbonyl counterparts (*e.g.* with NBS), which could be performed even in one-pot manner [645].

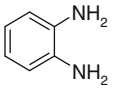
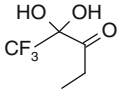
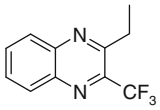
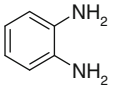
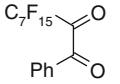
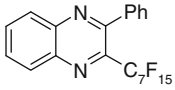
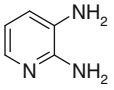
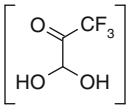
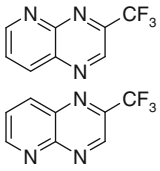
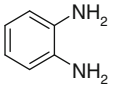
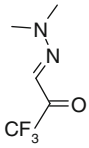
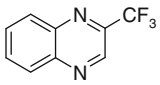
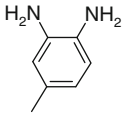
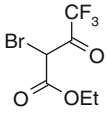
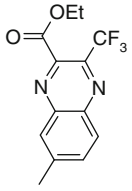
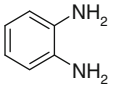
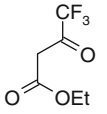
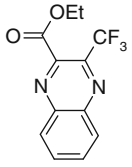
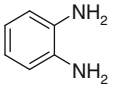
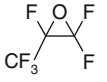
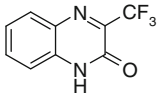
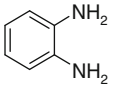
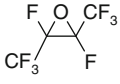
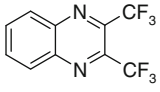
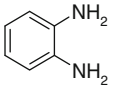
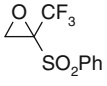
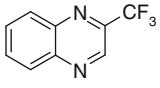
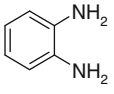
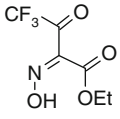
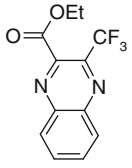
Selected examples of reactions of 1,2-bis-electrophiles **1061**–**1066** with 1,2-diamines are given in Table 43. The method gives good to excellent results when at least one of the starting components is symmetric; otherwise, the reaction is usually regioselective (see Entries 3, 12 and 14). Isolation of hydrates is a common feature in case of aliphatic 1,2-diamines (Entry 2), with a few exceptions (Entry 6), they are not observed in case of aromatic binucleophiles or diaminomaleonitrile **1060**. In a number of cases, the reactive 1,2-bis-electrophile is generated *in situ* or using one-pot procedure (Entries 7, 9, 12 (see also earlier work [646]), 13, 15). Apart from **1061**–**1066**, other fluorinated 1,2-bis-electrophiles were involved into reactions with 1,2-diamines (Table 24, Entries 18–26). Some of these bis-electrophiles can be considered as synthetic equivalents of **1061**–**1066**. In particular, epoxide **1086** can be used instead of trifluoromethyl glyoxal **1064** (Entry 18), whereas oxime **1087** – as a replacement for fluorinated α-halo-β-dicarbonyl compounds **1065** (Entry 19). Other 1,2-bis-electrophiles give an access to rather unusual pyrazine-derived structures. For example, adduct **1089** is obtained upon reaction of malonodinitrile derivative **1088** with *o*-phenylenediamine (Entry 20) (upon prolonged reaction times, however, malonodinitrile is eliminated from **1089**). In the reaction of imine **1090** with ethylenediamine, double formation of the pyrazine rings occurs (Entry 21), whereas in the case of chromone derivative **1091**, recyclization is observed (Entry 24). Another recyclization – a variation of Yur'ev reaction – was found in the case of ethylenediamine and furane derivative **1092** (Entry 25).

Table 43 Synthesis of pyrazines from 1,2-diamines and fluorinated 1,2-bis-electrophiles

#	Reactants		Product	Conditions	Yield	Ref.
1				H_2O, 50 °C	82	[647]
2				Neat, 0 °C	80	[648]
3			 	EtOH, reflux	20 70	[649]
4				Neat, 0 °C	N/A	[650]
5				DMF, 50 °C	66	[651]
6				$NaHCO_3$, DMF, H_2O, rt	47	[651]
7				$EtNMe_2$, $CHCl_3$, rt[a]	74	[652]
8				MeCN, rt	74	[638]
9				aq HCl, MeOH, rt	100	[640]

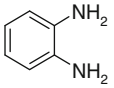
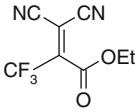
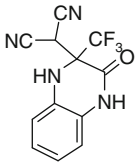
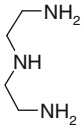
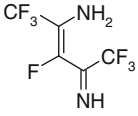
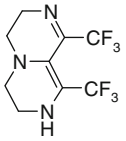
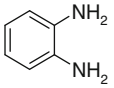
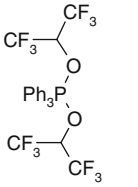
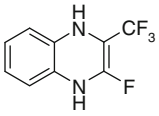
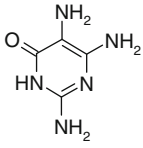
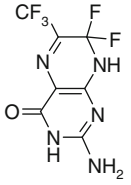
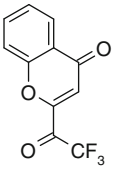
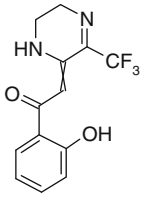
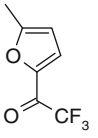
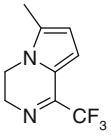
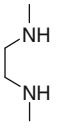
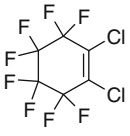
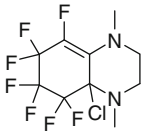
(continued)

Table 43 (continued)

#	Reactants		Product	Conditions	Yield	Ref.
10				MeCN, rt	52	[639]
11				*m*-cresol, rt	59	[644]
12				MeOH, 70 °C[b]	74 4	[653]
13				AcOH, MeCN, rt	75	[642]
14				Ionic liquid, rt	89	[654]
15				NBS, H_2O, 70 °C	80	[645]
16				$NaHCO_3$, Et_2O, rt	84	[655]
17				Dioxane, 100 °C	51	[656]
18		 **1086**		EtOH, rt, then reflux	45	[657]
19		 **1087**		MeOH, reflux	70	[658]

(continued)

Table 43 (continued)

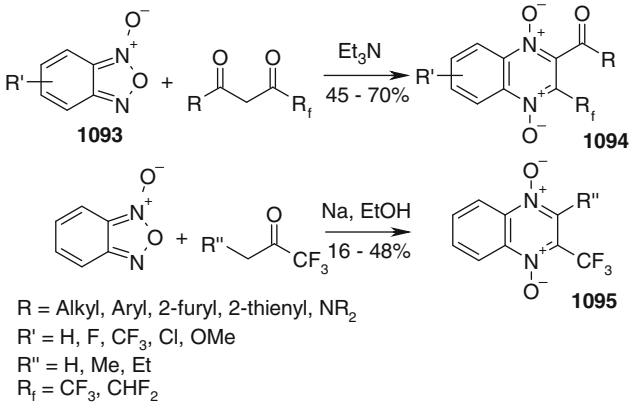
#	Reactants		Product	Conditions	Yield	Ref.
20		 **1088**	 **1089**	Et_2O, –20 °C to 20 °C	98	[659]
21		 **1090**		EtOH, reflux	44	[660]
22				CH_2Cl_2, Et_2O, rt, then Et_3N, THF, reflux	45	[661]
23				Et_3N, EtOH, reflux	71	[662]
24		 **1091**		MeOH, acetone, rt	57	[632]
25		 **1092**		Benzene, rt, then reflux	68	[663]
26				Et_3N, benzene, 25 °C	60	[664]

[a]The bis-electrophile is generated *in situ* from trifluoroacetaldehyde dimethylhydrazone and trifluoroacetic anhydride

[b]The bis-electrophile is generated prior the reaction from 1,1-dibromo-3,3,3-trifluoroacetone by heating with NaOAc in H_2O at 98 °C

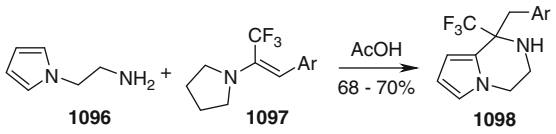
7.7.2 Other Methods

An interesting method for preparation of fluorinated quinoxaline *N*,*N*′-dioxides **1094** relies on reaction of benzofuroxanes **1093** with fluorinated β-dicarbonyl compounds – a fluoro version of the so-called Beirut reaction (named after the city where it was discovered) (Scheme 232). The reaction has attracted some attention due to the products **1094** revealed high antitumor and anti-trypanosomatid activity [665–667]. The method gave satisfactory results when at least one of the starting components was symmetric; otherwise, the reaction was not always regioselective. The approach was also used for simple fluorinated ketones; in this case, the corresponding products **1095** were obtained in low to moderate yields (16–48 %) [668].



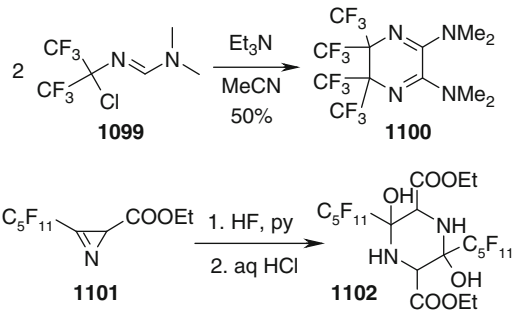
Scheme 232 Synthesis of fluorinated quinoxaline *N*,*N*′-dioxides **412** using Beirut reaction

Pictet-Spengler-type reaction of pyrrole-derived amine **1096** and enamines **1097** was used recently for the preparation of pyrrolo[1,2-*a*]pyrazine derivatives **1098** – a [5+1] approach to the construction of pyrazine ring (Scheme 233) [669].



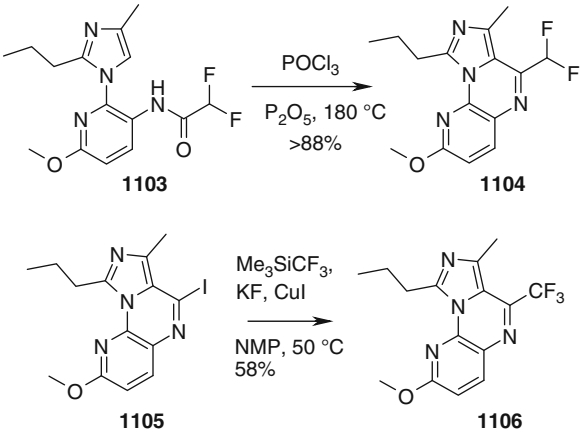
Scheme 233 Synthesis of fluorinated pyrrolo[1,2-*a*]pyrazines

A rare example of [3+3] retrosynthetic disconnection of fluorinated pyrazine ring was implemented by dimerization of fluorinated formamidine **1099** (Scheme 234) [670]. Another example is dimerization of azirine derivative **1101** [671].



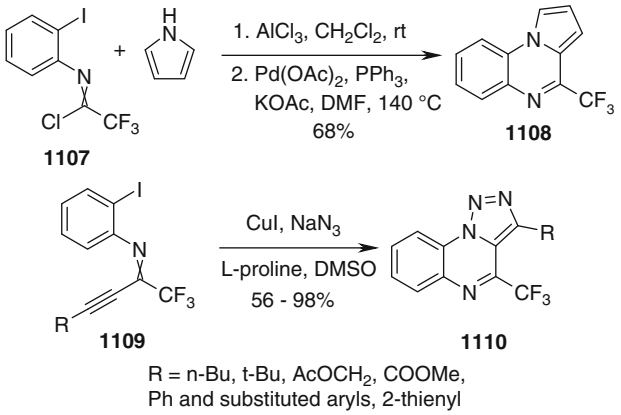
Scheme 234 [3+3] approach to fluorinated pyrazines

Fused tricyclic pyrazine derivative **1104** was prepared by intramolecular cyclization of amide **1103** under rather drastic conditions (P_2O_5, $POCl_3$, 180 °C in autoclave) (Scheme 235) [672]. It should be noted that for the synthesis of trifluoromethyl analogue **1106**, direct trifluoromethylation was used instead of this cyclization (see Sect. 6.1.1).



Scheme 235 Synthesis of fused tricyclic pyrazine derivatives

o-Iodoaniline derivatives **1107** and **1109** were the key intermediates for the preparation of fused tricyclic pyrazines **1108** and **1110**. To obtain **1108**, Friedel-Crafts acylation was used, followed by intramolecular cyclization based on Pd-catalyzed arylation (Scheme 236) [404]. A tandem azide click reaction – Ullman-type intermolecular coupling allowed for the construction of tricyclic system **1110** [673]. Bromo and chloro analogues of **1109** were also used to synthesize **1110**, but they were less effective.



Scheme 236 Synthesis of fused tricyclic pyrazines from *o*-iodoaniline derivatives

7.8 Inverse-Electron-Demand Diels – Alder Reaction with Fluorinated Building Blocks

An unusual approach to the synthesis of chain-fluorinated diazines relies on the inverse-electron-demand hetero-/retro-Diels – Alder (*ihDA/rDA*) sequence. The background of this method for the preparation of nitrogen-containing heterocycles in general has been reviewed recently [674]. Typical dienes used for the synthesis of chain-fluorinated diazines are given in Fig. 29. Since electron-deficient dienes are necessary for the first step of the sequence – inverse-electron-demand hetero-Diels – Alder reaction, fluoroalkyl substituents of tri- and tetrazines **1111**–**1112** are favorable for the process. Typical electron-rich dienophiles for the reactions with **1111**–**1112** are enamines (including amino heterocycles) and alkynes, although other examples are also known.

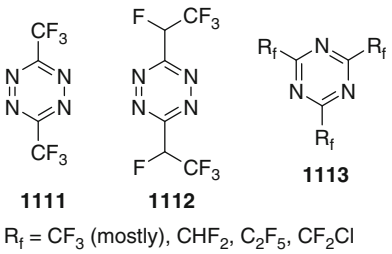
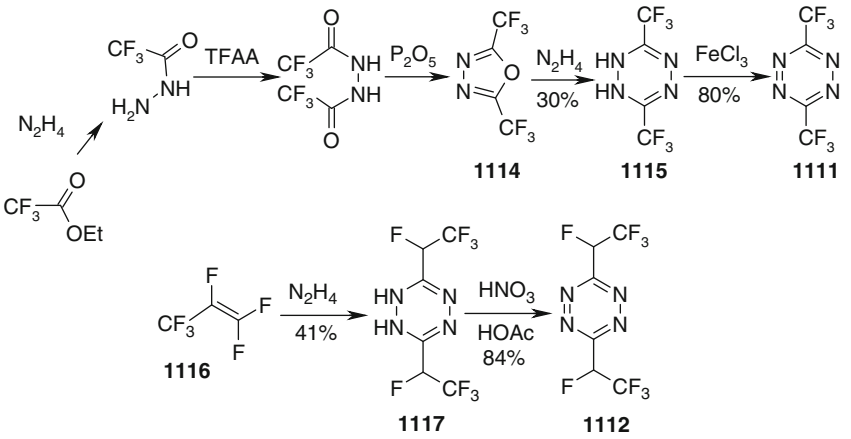


Fig. 29 Hetero-dienes used for the synthesis of chain-fluorinated diazines via *ihDA/rDA*

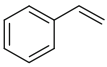
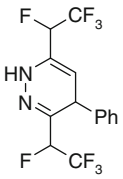
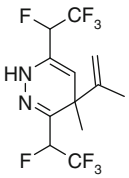
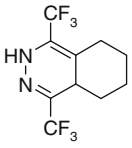
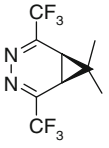
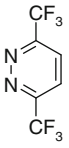
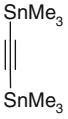
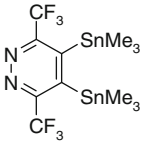
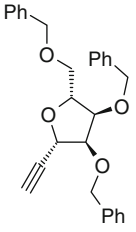
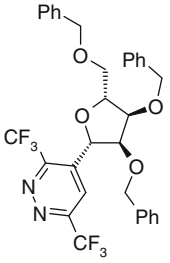
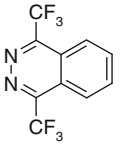
3,6-Bis(trifluoromethyl)-1,2,4,5-tetrazine (**1111**) and its homologue **1112** are extremely reactive hetero-dienes towards Diels – Alder reaction. Compounds **1111** and **1112** were prepared by reaction of oxadiazole **1114** [675] or perfluoropropene **1116** [676], respectively, with hydrazine, followed by oxidation (Scheme 237).



Scheme 237 Synthesis of *sym*-tetrazines **1111** and **1112**

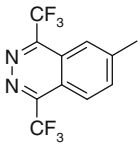
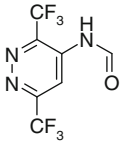
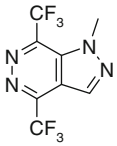
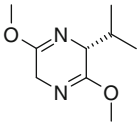
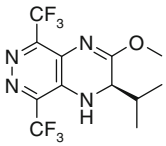
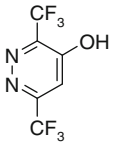
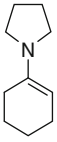
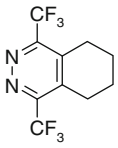
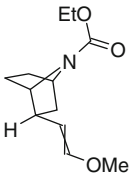
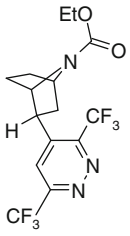
ihDA/rDA sequence with **1111** or **1112** and CC-dienophiles is accompanied with elimination of molecular nitrogen and results in formation of pyridazine derivatives – a process which is known in 1,2,4,5-tetrazine chemistry as Carboni – Lindsey reaction [677]. In fact, this reaction was discovered by Carbony and Lindsey when they studied chemical properties of **1112** (among some other *sym*-tetrazines) [678]. The method worked effectively with various non-functionalized alkenes (Table 44, Entries 1–3), including strained ones (Entry 4), to give dihydropyridazines. Aromatic pyridazine derivatives were formed in reactions with alkynes (Entry 5); the procedure showed high functional group tolerance (Entry 6) and was used for the preparation of nucleoside analogues (Entry 7). Even benzene underwent [4+2] cycloaddition with **1111**, although under harsh conditions (Entry 8); notably, in the case of substituted and fused benzene derivatives, the reaction demonstrated regioselectivity (Entry 9). Analogous results were obtained in the case of heteroaromatic compounds (Entries 10 and 11), although in some cases, ring opening of the aromatic ring occurred. Enol ethers and enamines are especially good dienophiles, which were used in a number of preparative syntheses (Entries 13–15). Unlike usual alkenes, these dienophiles gave aromatic pyridazines due to elimination of the leaving group (alkoxy or dialkylamino) under reaction conditions.

Table 44 Carboni – Lindsey reactions of **426** and **427**

#	Dienophile	Product	Conditions	Yield	Ref.
1			**1112**, Et_2O, pentane, rt	60	[678]
2			**1112**, rt	62	[678]
3			**1111**, 0 °C	88	[675]
4			**1111**, CCl_4, rt	95	[679]
5			**1111**, 0 °C	79	[675]
6			**1111**, 0 °C	78	[675]
7			**1111**, toluene, heating	77	[680]
8			**1111**, 140 °C, O_2 (air)	87	[681]

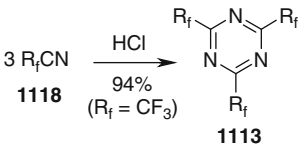
(continued)

Table 44 (continued)

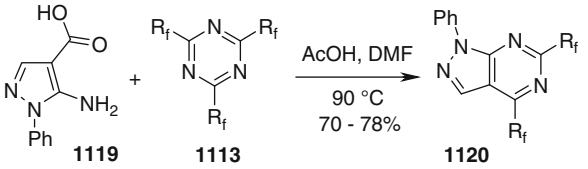
#	Dienophile	Product	Conditions	Yield	Ref.
9			**1111**, 140 °C, O_2 (air)	40	[681]
10			**1111**, toluene, heating	80	[682]
11			**1111**, toluene, heating	60	[682]
12			**1111**, toluene, heating	94	[683]
13			**1111**	70	[684]
14			**1111**, CH_2Cl_2, rt	78	[685]
15			**1111**, toluene, reflux	88	[686]

Sym-triazine derivatives of general formula **1113** can be prepared by trimerization of the corresponding perfluorinated nitriles **1118** (Scheme 238) [687]. Compounds **1113** are much less reactive towards cycloaddition reactions than **1111** or **1112**; it is not surprising therefore that the first reports on such transformations were made in early 2000s. In particular, reaction of 5-amino-1-phenyl-4-pyrazolecarboxylic

acid (**1119**) with **1111** resulted in a tandem decarboxylation – *ihDA/rDA* sequence with formal elimination of the perfluorinated nitrile **431** and ammonia to give pyrazolo[3,4-*d*]pyrimidine derivatives **1120** (Scheme 239) [688].



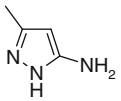
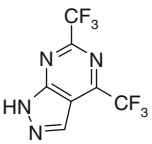
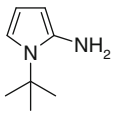
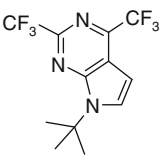
Scheme 238 Synthesis of fluorinated sym-triazines **1113**



Scheme 239 An early report on *ihDA/rDA* sequence with **1111**

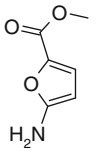
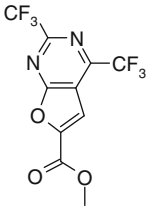
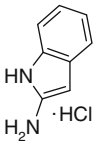
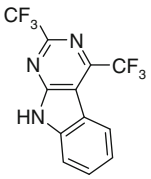
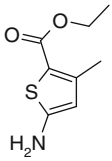
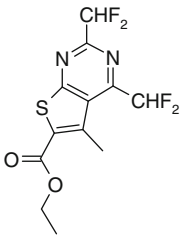
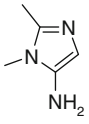
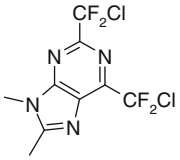
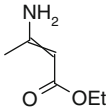
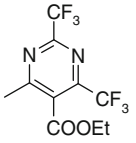
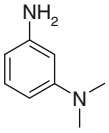
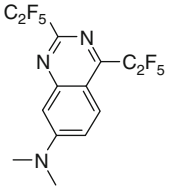
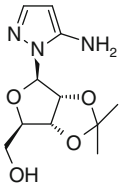
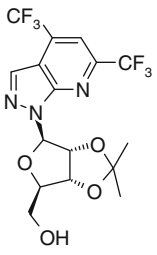
A wide range of amino heterocycles was introduced into reaction with **1111** (Table 45), including pyrazoles (Entry 1), pyrroles (Entry 2), furans (Entry 3), indoles (Entry 4), thiophenes (Entry 5), imidazoles (Entry 6), push-pull enamines (Entry 7) and even anilines (Entry 8). The method was also used for the synthesis of nucleoside analogues (Entry 9). Moreover, it was shown that amino imidazoles can be generated in situ in the reaction mixture containing **1111** for the preparation of fluorinated purines (Scheme 240) [689]. The latter procedure worked well for aliphatic amines and hydrazines (including those containing additional basic center); by using TMSOTf catalyst, it was also extended to aromatic and heteroaromatic amines.

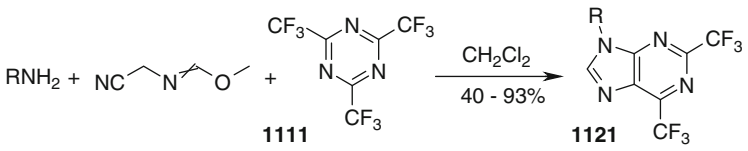
Table 45 *ihDA/rDA* sequence with **428**

#	Dienophile	R_f in **1111**	Product	Conditions	Yield	Ref.
1		CF_3		AcOH, CH_2Cl_2, rt	95	[689]
2		CF_3		Et_3N, THF, rt	61	[690]

(continued)

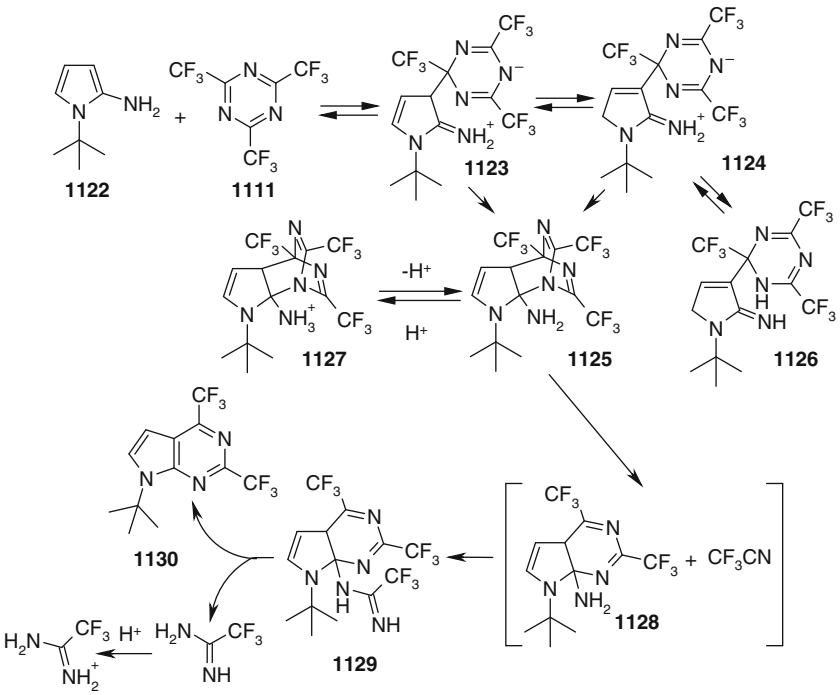
Table 45 (continued)

#	Dienophile	R_f in **1111**	Product	Conditions	Yield	Ref.
3		CF_3		DMSO, 100 °C	75	[691]
4		CF_3		MeOH, 50 °C	94	[692]
5		CHF_2		AcOH, CH_2Cl_2, rt	91	[693]
6		CF_2Cl		AcOH, CH_2Cl_2, rt	93	[693]
7		CF_3		AcOH, CH_2Cl_2, rt	100	[693]
8		C_2F_5		AcOH, CH_2Cl_2, rt	89	[693]
9		CF_3		AcOH, CH_2Cl_2, rt	97	[556]



Scheme 240 Three-component synthesis of fluorinated purines via *ihDA/rDA* sequence

The mechanism of *ihDA/rDA* reaction of **1111** with aminoheterocycles was studied extensively in the pyrrole series (Scheme 241) [694, 695]. It was shown that formation of "Diels – Alder" adduct of the type **1125** is nonconcerted; instead, the reaction starts as aromatic nucleophilic substitution to give Meisenheimer complex **1123** as an initial intermediate. Then, cyclization of **1123** leads to the formation of **1125**. Decomposition of **1125** occur as *retro*-[4+2] cycloaddition to form intermediate of the type **1129**. Aromatization of **1123** occurs via elimination of perfluorinated amidine, which was detected among the products of the reaction.



Scheme 241 The mechanism of *ihDA/rDA* sequence with **1111**

8 Properties and Chemical Transformation of CFD

In this part of the chapter, chemical properties of chain-fluorinated diazines are discussed. Since both diazine ring and fluoroalkyl group are electron-withdrawing, it is not surprising that most of the transformations discussed herein are reactions with nucleophiles. Diazine rings, namely, carbon atoms of the C=N double bonds, are common centers of the nucleophilic attack. Depending on the nucleophile and presence of the nucleofuge, the result of the reaction can be nucleophilic addition, or nucleophilic substitution. The reaction can occur not only with common nucleofuges like halogens, but with fluoroalkyl group itself. Fluoroalkyl substituent can also act as electrophilic center; in this case, nucleophilic substitution of fluorine occurs, which is promoted by electron-withdrawing diazine ring. Other reactions to be discussed are electrophilic substitution, metallation, reduction, oxidation and recyclization of the diazine ring, transition metal-catalyzed cross-couplings, photochemical cycloadditions as well as electron-demanding Diels-Alder reactions. Most of the examples will be taken from pyrimidine series since their chemistry is studied more thoroughly; chemical transformation of other side-chain fluorinated diazines will be discussed occasionally.

8.1 Addition of Nucleophiles to C=N Double Bond

8.1.1 Formation of Hydrates and Other Solvates

In the previous sections discussing synthesis of chain-fluorinated diazines by heterocyclizations, there were many examples of formation of di-, tetra- and hexahydropyrimidines – so-called hydrates (or other solvates) – instead of the corresponding aromatic products. This situation was quite common for the preparation of chain-fluorinated pyrimidinones or fused pyrimidines possessing an additional electron-withdrawing group, as well as Biginelli-type adducts (Fig. 30, see also Sect. 7 of this chapter).

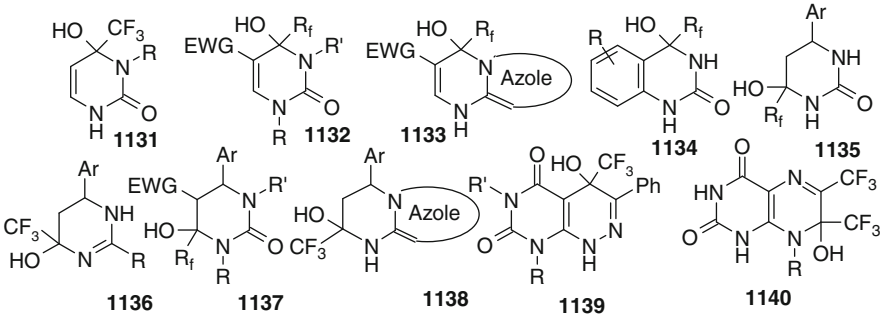
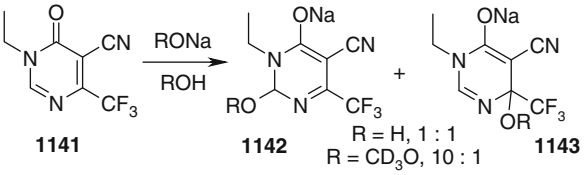


Fig. 30 Stable diazine hydrates (see Sect. 7 of this chapter)

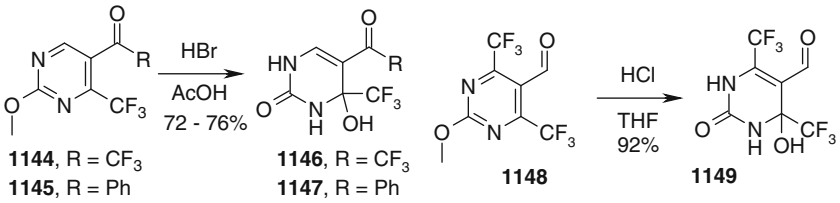
Moreover, these adducts were often so stable that they underwent water elimination only upon heating and/or action of dehydration agents. Nevertheless, in most cases the stability of these covalent hydrates was kinetic rather than thermodynamic, and the corresponding reverse reaction, *i.e.* formal addition of water or alcohols to the C=N bonds of the diazine ring are not common. The first observation of this type was made in 1990 by Lee and Sing, who noticed surprisingly high solubility of pyrimidine **1143** in aqueous alkali. More detailed investigations showed that a mixture of two adducts **1144** and **1145** were formed from **1143** in either aqueous sodium hydroxide or methanolic sodium methoxide-d_3 solutions (Scheme 242) [696]. Whereas with OH^-, a 1:1 mixture was formed, in the case of CD_3O^- ion, regioselectivity of the reaction was observed, presumably due to its higher steric volume.



1141 1142 1143

Scheme 242 Reaction of pyrimidine **1141** with anionic O-nucleophiles

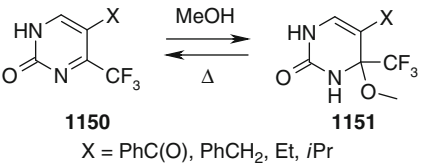
Another example was also found serendipitously: upon demethylation of pyrimidine derivative **1144** with HBr/AcOH, covalent hydrate **1146** was obtained in 72 % yield (Scheme 243) [468]. The method was extended to some other substrates (**1145** and **1148**).



1144, R = CF_3
1145, R = Ph
1146, R = CF_3
1147, R = Ph
1148
1149

Scheme 243 Formation of covalent hydrates upon demethylation of CFD

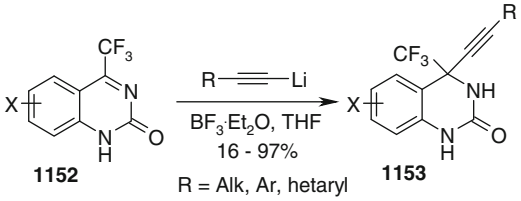
Formation of adducts with solvent was observed for the pyrimidine derivatives **1150** upon their recrystallization from methanol (Scheme 244) [697]. Unlike the previous example, in this case the reaction was reversible, since the adducts **1151** gave pyrimidines **1150** upon heating.



Scheme 244 Reversible formation of adducts of pyrimidines 6 with methanol

8.1.2 Addition of C-Nucleophiles

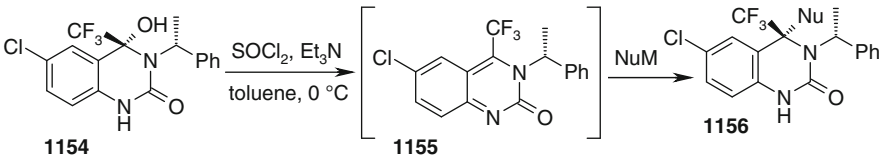
Addition of carbanions to C=N bond in chain-fluorinated diazines received considerable attention in the quinazoline series, since the products obtained in this reaction are intermediates in the synthesis of HIV 1 reverse transcriptase inhibitors (see Chap. 20). In particular, quinazolines **1152** react with acetylenides in the presence of $BF_3{\cdot}Et_2O$ in THF to give adducts **1153** in moderate to excellent yields (Scheme 245) [698–700].



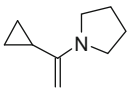
Scheme 245 Addition of *C*-nucleophiles to C=N bond of quinazolines **1152**

The method was extended for the preparation of optically pure compounds. In the first strategy, chiral auxiliary approach was used; namely, camphanoyl and α-phenyletylamine auxiliaries were introduced, the latter being more productive (Table 46) [701, 702]. Although quinazoline **1155** had limited stability, they could be generated *in situ* prior the reaction with the nucleophile. Notably, a wide range of nucleophiles was studied in this reaction, including organolithium, organomagnesium compounds and even methanol; nevertheless, lower chemical yields and/or diastereoselectivities were observed in many cases. The method was amendable to kilogram preparations.

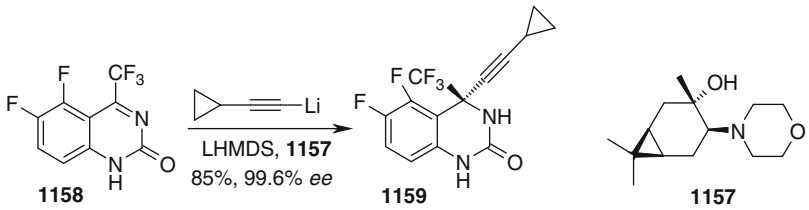
Table 46 Diastereoselective addition of nucleophiles to C=N bond of quinazoline **1155**



1154 **1155** **1156**

#	NuM	T, °C	Conversion, %	de, %
1		−70	95	85
2		−60	95	92
3		−10	97	80
4	MeOH	−5	95	80
5	CH_2=CHMgBr	−60	88	95
6	PhMgCl	−60	35	95
7	PhLi	−20	40	40
8	$PhCH_2MgCl$	−60	93	<10
9	MeMgI	−60	90	55
10	MeZnI	−5	94	95
11	$LiAlH(OtBu)_3$ (Nu=H)	–	94	85
12		−60	89	95

Alternative strategy for the preparation of enantiopure quinazolines of the type **9** relied on enantioselective moderation. It was found that in the presence of carene-derived chiral moderator **1157**, addition of cyclopropylethynyl lithium to quinazoline **1158** occurs in high yield and good enantioselectivity (Scheme 246) [703]. It should be noted that a number of other amino alcohols were evaluated as chiral additives in this reaction [704]. The mechanism of this transformation includes formation of mixed aggregates of the type **1160–1162** (Fig. 31) [704]. Even more complex aggregates are formed upon reaction of **1160–1162** with lithium salt of the quinazoline substrate [705].



1158 **1159** **1157**

Scheme 246 Enantioselective addition of *C*-nucleophiles to C=N bond of quinazoline 12

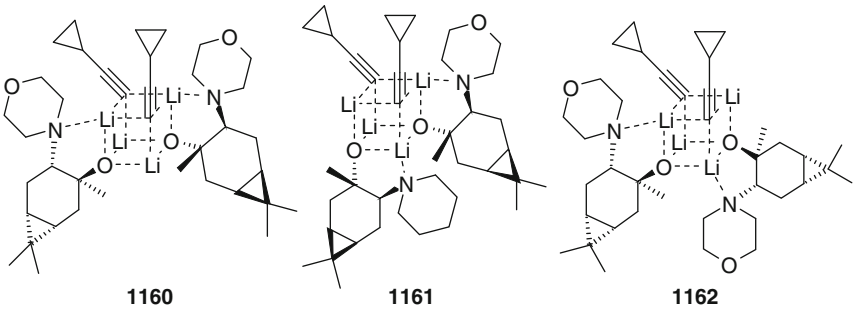
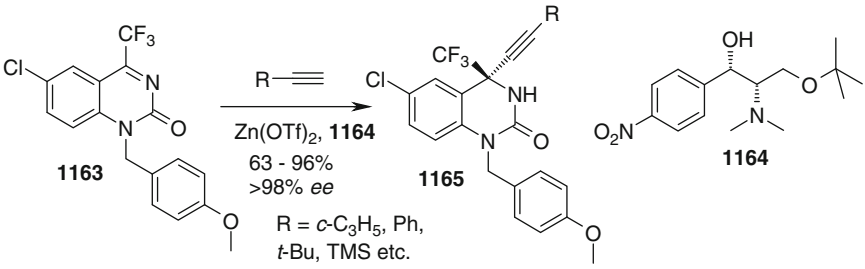
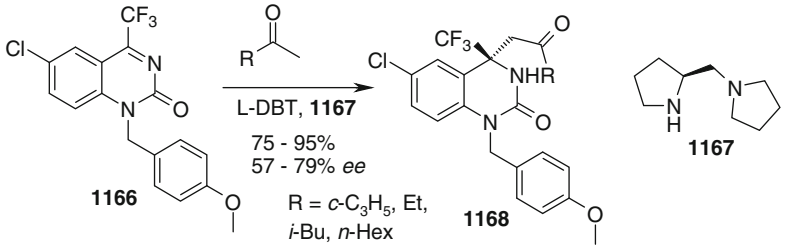


Fig. 31 Mixed cyclopropylethynyl lithium aggregates

Completely different reaction conditions for the synthesis of enantiopure quinazolines **1153** relied on Lewis acid catalysis. In particular, treatment of quinazoline **1163** with cyclopropyl acetylene and $Zn(OTf)_2$ in the presence of chiral additive **1164** (Scheme 247) [706] was extended to enantioselective diynylation of quinazolines [707]. An example of using organocatalysis included enantioselective Mannich-type reaction of **1166** or its analogues with ketones in the presence of chiral diamine **1167** and L-dibenzoyltartaric acid (*L*-DBT) (Scheme 248) [708]. In the latter case, the enantioselectivity was moderate, it might be improved to >99 % by a single recrystallization of the product.

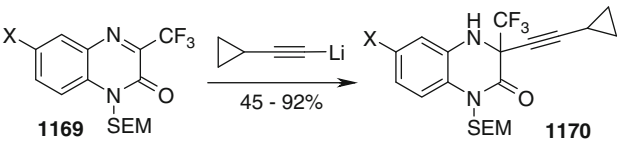


Scheme 247 Enantioselective addition of *C*-nucleophiles to C=N bond of quinazoline **1163**



Scheme 248 Enantioselective addition of *C*-nucleophiles to C=N bond of quinazoline **1166**

Apart from quinazolines, quinoxalines **1169** were successfully introduced into the reaction with lithium acetylenides to give adducts **1170** (Scheme 249) [709].



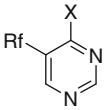
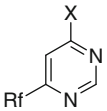
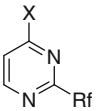
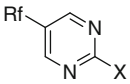
Scheme 249 Addition of *C*-nucleophiles to C=N bond of quinoxalines **1169**

8.2 Nucleophilic Substitution at the Diazine Ring

8.2.1 Substitution of Common Nucleofuges

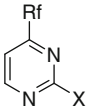
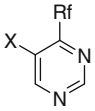
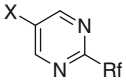
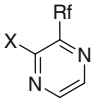
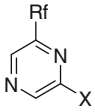
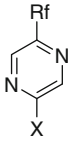
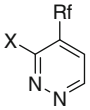
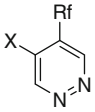
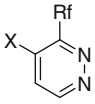
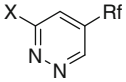
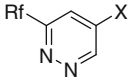
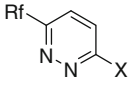
Nucleophilic substitution of common nucleofuges such as halogenes is one of the most well-studied reactions in the chain-fluorinated diazine series. Analysis of the literature data shows that nearly 90 % examples of chain-fluorinated halodiazine reactions with *N*-, *S*-, and *O*–nucleophiles refer to pyrimidine derivatives (Table 47). Only 2- and 4-fluoroalkyl-5-halopyrimidines have received almost no attention in these transformations. Data on nucleophilic substitution of halogens in chain-fluorinated diazines correlates with the accessibility of the corresponding substrates, and to a lesser extent – with their reactivity towards nucleophiles.

Table 47 Reactions of chain-fluorinated halodiazines with nucleophiles (Reaxys®)

#	Substrate[a]	No. of hits	No. of citations		
			Total	Papers	Patents
Pyrimidines and their fused derivatives					
1		194	80	15	65
2		356	87	26	61
3		267	97	36	61
4		252	82	15	67

(continued)

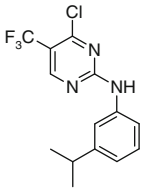
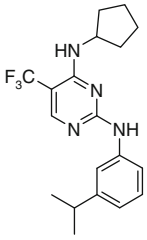
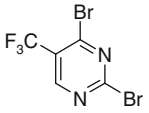
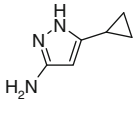
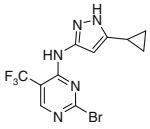
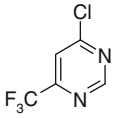
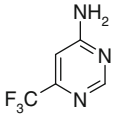
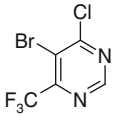
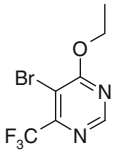
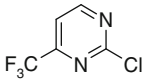
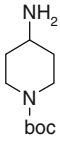
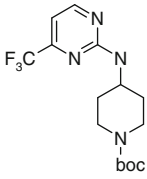
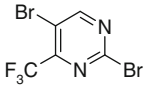
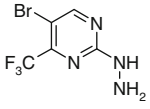
Table 47 (continued)

#	Substrate[a]	No. of hits	No. of citations		
			Total	Papers	Patents
5		218	114	37	77
6		2	1	1	0
7		7	7	1	6
Pyrazines and their fused derivatives					
8		24	10	4	6
9		5	4	1	3
10		13	12	1	11
Pyridazines and their fused derivatives					
11		11	8	4	4
12		1	1	1	0
13		5	1	0	1
14		5	5	0	5
15		1	1	0	1
16		28	23	4	19

[a]X=F, Cl, Br, I

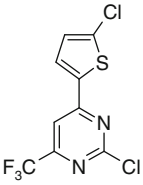
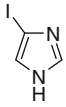
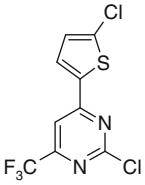
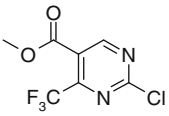
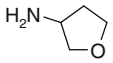
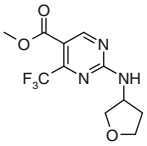
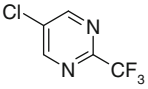
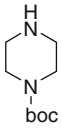
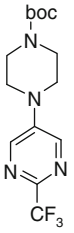
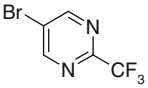
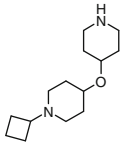
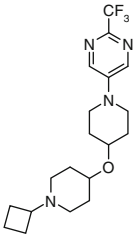
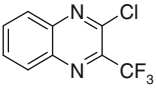
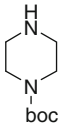
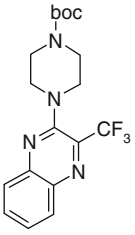
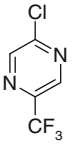
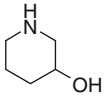
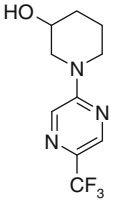
The reactivity of the chain-fluorinated halodiazines towards nucleophiles is to a considerable extent similar to that of the corresponding non-fluorinated analogues. In particular, chain-fluorinated 2(6)- and 4-halopyrimidines are the most reactive substrates for the nucleophilic attack, so that very mild reaction conditions are possible (Table 48, Entries 1–4, 6, 8). In the case of less reactive substrates, very harsh reaction conditions (*e.g.* heating or MW irradiation at 140–180 °C) still can promote "classical" nucleophilic substitution (Entries 9, 11, 13, 14, 16, 18), although using palladium or copper catalysts might be more convenient (Entries 10, 12).

Table 48 Typical reaction conditions for the nucleophilic substitution in CFD

#	Reactants		Product	Conditions	Yield	Ref.
1				K_2CO_3, MeCN, 50 °C, 5 h	78	[710]
2				EtOH, rt, 8 h	85	[711]
3		28 % aq NH_3		MeCN, rt, 12 h	98	[712]
4		EtONa		EtOH, rt	83	[713]
5				TEA, DMF, 100 °C, 3 h	85	[714]
6		NH_2NH_2		EtOH, rt	95	[715]

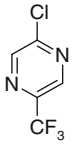
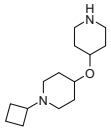
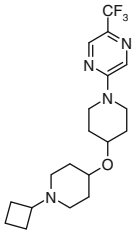
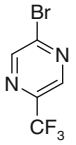
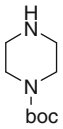
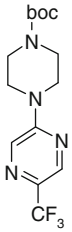
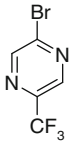
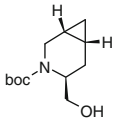
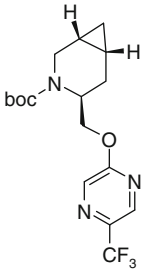
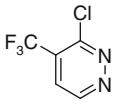
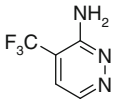
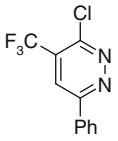
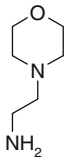
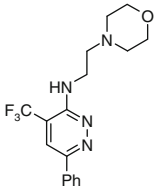
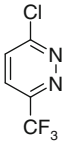
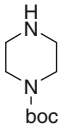
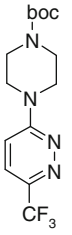
(continued)

Table 48 (continued)

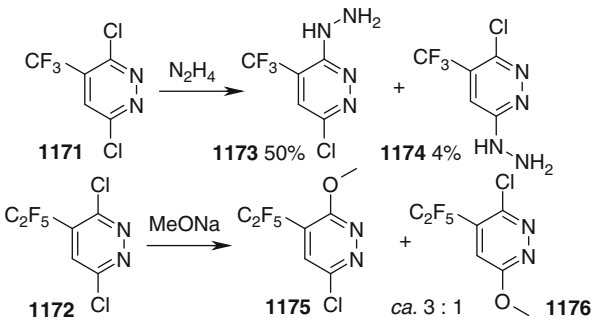
#	Reactants		Product	Conditions	Yield	Ref.
7				K_2CO_3, DMF, 130 °C, 1 h	97	[716]
8				DIPEA, THF, rt, 16 h	91	[717]
9				isobutyramide, 180 °C, MW, 20 min	55	[347]
10				*t*BuONa, DavePhos, Pd_2dba_3, dioxane, 120 °C, MW, 1 h	25	[718]
11				140 °C, MW, 45 min	47	[719]
12				CuI, K_2CO_3, *L*-proline, DMSO, 65 °C, 48 h	94	[720]

(continued)

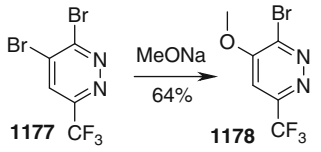
Table 48 (continued)

#	Reactants		Product	Conditions	Yield	Ref.
13				K_2CO_3, DMSO, 140 °C, MW, 45 min	83	[718]
14				isobutyramide, 180 °C, MW, 20 min	32	[347]
15				NaH, DMSO, rt, 1 h	50	[721]
16		28 % aq NH_3		DME, sealed reactor, 180 °C, 8 h	36	[722]
17				butan-1-ol, reflux, 48 h,	94	[723]
18				DIPEA, MeCN, 180 °C, MW, 30 min	99	[724]

Due to their electron-withdrawing inductive effect, the fluoroalkyl substituents activate substitution at α- and γ-positions. Although this activation does not overcome the effect from the nitrogen atoms of the diazine ring, it may define regioselectivity of the reaction in certain cases. In particular, reaction of 3,6-dichloro-4-fluoroalkylpyridazines **1171, 1172** with hydrazine or sodium methoxide results in nucleophilic substitution at C-4 (Scheme 250) [723, 725]. On the contrary, reaction of 3,4-dibromo-6-trifluoromethylpyridazine **1177** with NaOMe leads to the formation of 4-substituted derivative **1178** – a usual regioselectivity observed for the non-fluorinated analogues (Scheme 251) [727].



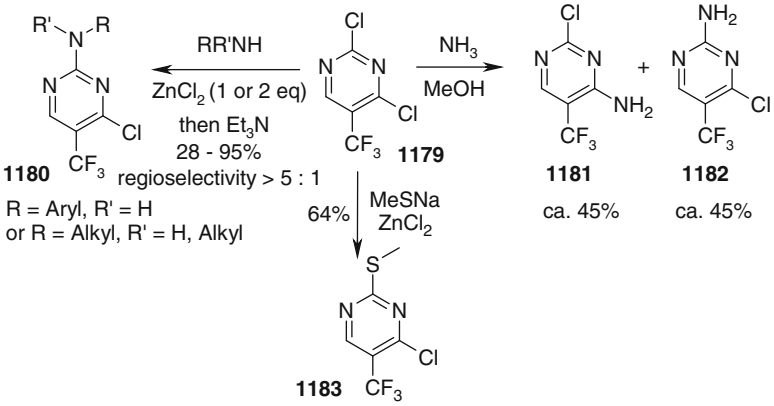
Scheme 250 Nucleophilic substitution in 3,6-dichloro-4-fluoroalkylpyridazines



Scheme 251 Nucleophilic substitution in 3,4-dibromo-6-trifluoromethylpyridazine

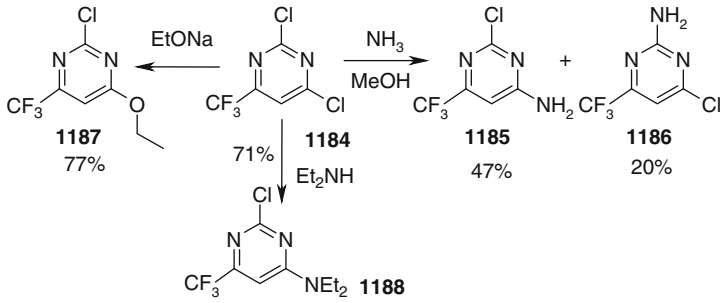
Several reports deal with nucleophilic substitution in chain-fluorinated 2,4-dichloropyrimidines. It is widely accepted that reaction of 2,4-dichloropyrimidines with nucleophiles occurs first at C-4 atom of the diazine ring, and the corresponding products can be obtained with high regioselectivity. In the case of 2,4-dichloro-5-trifluoromethylpyrimidine **1179**, nearly 1/1 mixtures of the corresponding regioisomers are obtained (Scheme 252) [728, 729]. The situation is changed if the reaction is carried out in the presence of a Lewis acid ($ZnCl_2$); in this case, substitution at C-2 atom occurs regioselectively. These features were addressed to the increased steric demands at C-4 provided by the fluoroalkyl group. Both aromatic and aliphatic amines [728], as well as thiolates were successfully introduced into the latter transformation [730], although in the case of aromatic amines capable of zinc coordination, as well as aliphatic amines, 2 equivalents of $ZnCl_2$ were necessary to

ensure high regioselectivity. However, the latter conditions in most cases led to the diminished yields of the products (28–33 % instead of 72–95 %) and prolonged reaction times.



Scheme 252 Nucleophilic substitution in 2,4-dichloro-5-trifluoromethylpyrimidine

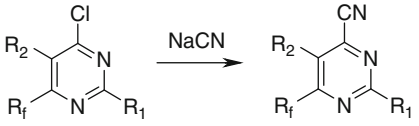
For 2,4-dichloro-6-trifluoromethylpyrimidines, usual regiselectivity was observed in nucleophilic substitution reactions, namely, preferential attack of the nucleophile at C-4 atom (Scheme 253) [731, 732].



Scheme 253 Nucleophilic substitution in 2,4-dichloro-6-trifluoromethylpyrimidine

The reactions of the halogenated chain-fluorinated diazines with *C*-nucleophiles are less studied in comparison with *N*, *S*, *O*– derivatives. The most actively used transformation is chlorine-cyanide exchange in a case of 4-chloro substituted pyrimidines (Table 49). In a case of nucleophilic catalysis by DMAP or DABCO the yields are in region 50-93 %. Without nucleophilic catalysis the yields of the cyanation decreased extremely (Table 49, Entry 11).

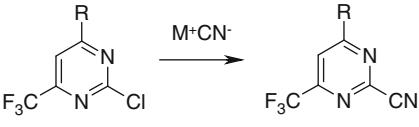
Table 49 Chlorine-cyanide exchange in 4-chloro chain-fluorinated pyrimidines



1189 **1190**

#	R_f	R_1	R_2	Conditions	Yield (%)	Ref.
1	CF_3	SMe	I	DMAP, EtCN, rt, 3 h	51	[733]
2	CF_3	Me	H	DABCO, DMSO-H_2O, rt, 2 h	81	[338]
3	CF_3	H	Br	-//-	93	[338]
4	CF_3	SMe	H	-//-	64	[338]
5	CF_3	H	H	-//-	75	[338]
6	CHF_2	H	H	-//-	83	[338]
7	C_2F_5	H	H	-//-	61	[338]
8	C_3F_7	H	H	-//-	51	[338]
9	CF_3	CF_3	H	-//-	93	[338]
10	CF_3	MeO	H	-//-	50	[338]
11	CF_3	H	H	MeCN, reflux, 20 h	18	[734]

In a case of 2-chloro substituted chain-fluorinated pyrimidines the cyanation is also described on two examples in "classical" variant as well as palladium catalyzed conditions (Scheme 254) [735, 736].

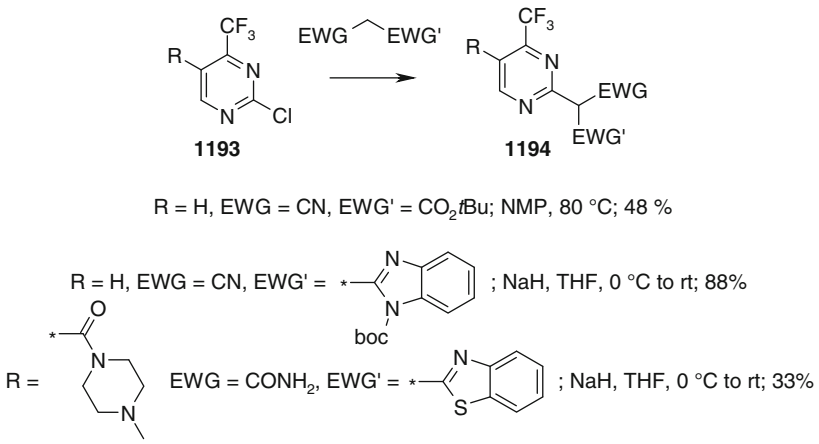


1191 **1192**

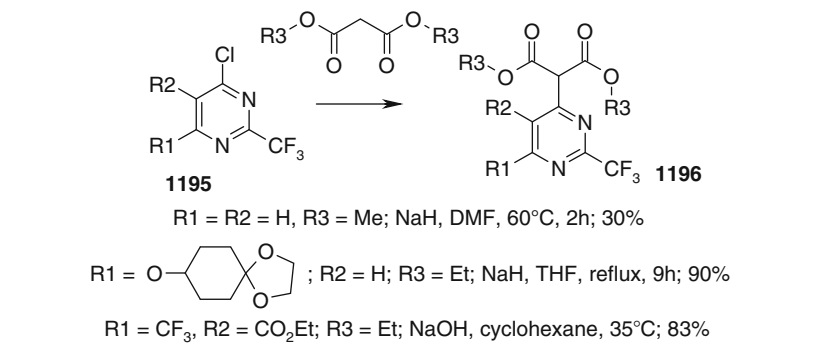
R = H, M^+ = Na, DMSO, rt, 30 min, 40%
R = Ph, M^+ = K, DMF, $Pd(PPh_3)_2Cl_2$, 67%

Scheme 254 Cyanation of 2-chloro substituted chain-fluorinated

Among other common *C*-nucleophiles only malonate and hetarylacetonitriles derivatives were used. 2-Chloro as well as 4-chloro chain-fluorinated pyrimidines **1193** and **1195** gave the corresponding pyrimidinylacetic acid derivatives **1194** and **1196** depicted on Schemes 255 [737, 738] and 256 [738–740].

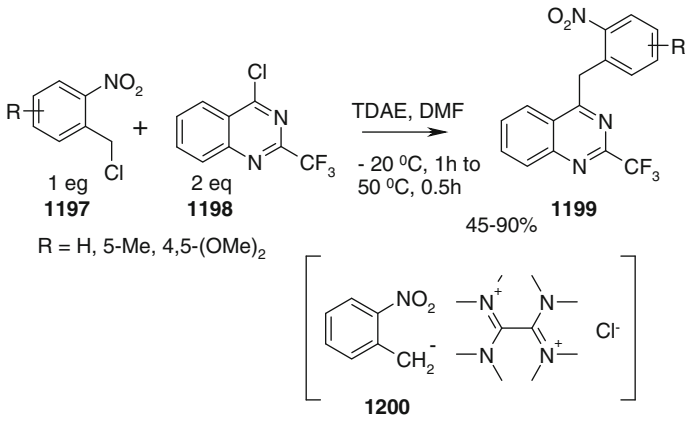


Scheme 255 Reaction of 2-chloro chain-fluorinated pyrimidines with C-nucleophiles



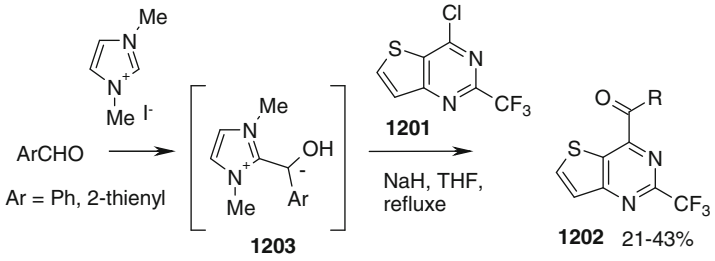
Scheme 256 Reaction of 4-chloro chain-fluorinated pyrimidines with C-nucleophiles

Recently Vanelle reported the first example of a S_NAr reaction using TDAE-initiated carbanions in fluorinated quinazoline series. The *o*-nitrobenzyl carbanion **1200**, formed by the action of TDAE on *o*-nitrobenzyl chloride **1197**, reacts with 4-chloro-2-trifluoromethylquinazoline **1198** via a S_NAr mechanism affording 4-benzyl-2-trifluoromethylquinazolines **1199**. The reaction as electron withdrawing group-dependent and in a case of non-fluorinated analogue of **1198** does no work (Scheme 257) [741].



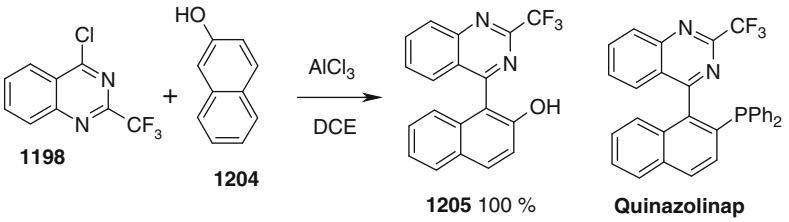
Scheme 257 S_NAr reaction using TDAE-initiated carbanions

Another unusual S_NAr reaction of fused trifluoromethylchloropyrimidines was disclosed in a course of human adenosine A_{2A} receptor antagonists discovery [742]. This is the reaction of aroylation of 2-chloro-4-trifluoromethylthieno[3,2-d]pyrimidine **1201** by aldehyde incorporation catalyzed by N,N-dimethylimidazolium chloride affording the ketoaryl compound **1202**. The process based on S_NAr reaction of zwitterionic intermediate **1203** with followed dimethylimidazolium elimination. Unfortunately the exact procedures does not refer in original paper but reported in Vernalis patent (Scheme 258) [743].



Scheme 258 Aroylation of **1201** by aldehyde incorporation

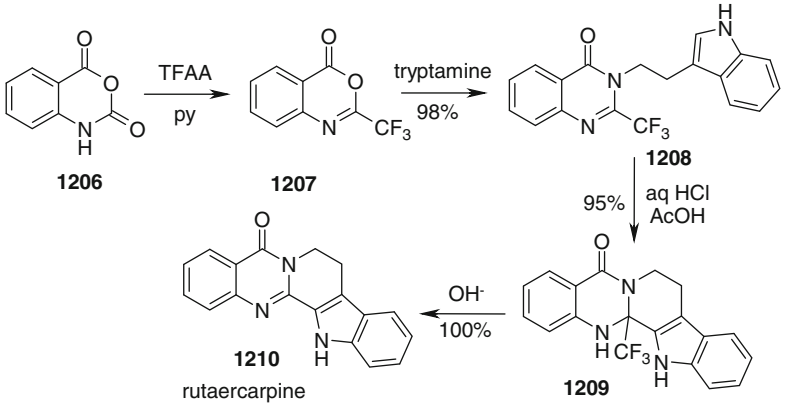
Also Friedel–Crafts-type reaction of 2-naphthol with 4-chloro-2-trifluoromethylquinazoline **1198** was recently reported Guiry. The reaction conditions employed 3 equiv. of $AlCl_3$ at 80 °C in DCE for 3.5 h. In the condition quinazoline **1198** gives 4-(2-hydroxynaphthalen-1-yl)quinazoline **1205** in quantitative yield. The latest compound is useful intermediate for the synthesis of atropisomeric P–N ligand, Quinazolinap, which has been successfully applied to the rhodium-catalyzed hydroboration of vinylarenes and palladium-catalyzed allylic alkylation (Scheme 259) [744].



Scheme 259 Friedel–Crafts-type reaction of 2-naphthol with **1198**

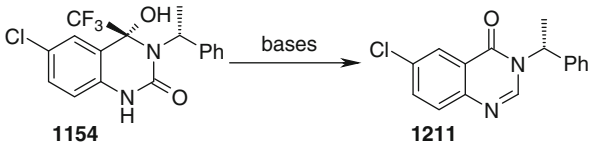
8.2.2 Addition with Elimination of the Fluoroalkyl Substituent

In principle, addition of a nucleophile to the C=N bond of the diazine ring can be accompanied by elimination of fluoroalkyl substituent. Two-step version of this reaction was used in the synthesis of alkaloid rutaecarpine (**1210**). In particular, reaction of anhydride **1206** with trifluoroacetic anhydride and then – with tryptamine led to the formation of quinazoline **1208**, which was transformed to **1210** with elimination of trifluoromethane upon acid-catalyzed cyclization, followed by alkaline hydrolysis (Scheme 260) [744].



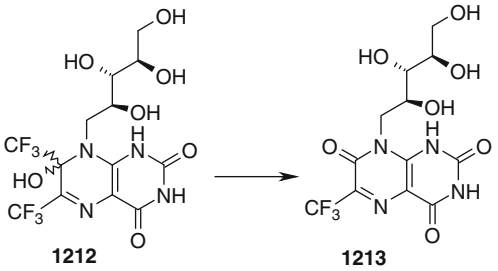
Scheme 260 Synthesis of rutaecarpine

Elimination of trifluoromethane was undesirable reaction which was observed during attempted stereoselective synthesis of HIV 1 reverse transcriptase inhibitors via intermediate **1154**; it occurred upon treatment of **1154** with bases (Scheme 261) [702].



Scheme 261 Elimination of trifluoromethane from **1154**

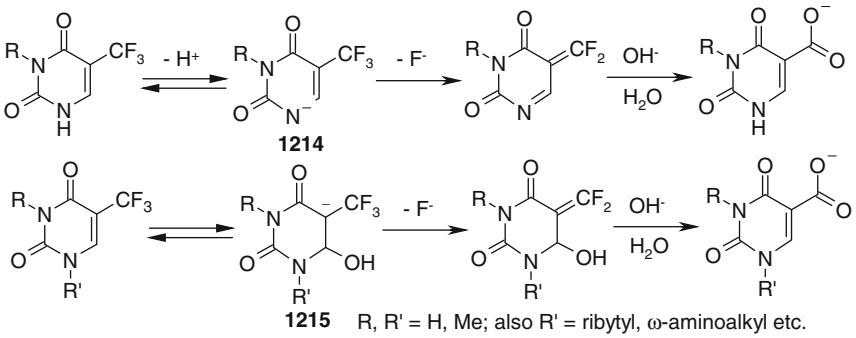
The reaction is particularly illustrative in the case of 6,7-bis(trifluoromethyl)-8-ribityllumazines **1212**, which were evaluated as potential inhibitors of lumazine synthase. It was found that both diastereomers of **1212** slowly eliminate trifluoromethane in neutral aqueous solutions above 37 °C giving 6-(trifluoromethyl)-7-oxo-8-ribityllumazine **1213**; at 60 °C, half-life of **1212** was 15 min (Scheme 262) [745]. Interestingly, the reaction was catalyzed by lumazine synthase, but only for one diastereomer (**1212**). A mechanistic rationale for this stereoselectivity was proposed from the data obtained by 2D NMR data [746].



Scheme 262 Elimination of trifluoromethane from **1212**

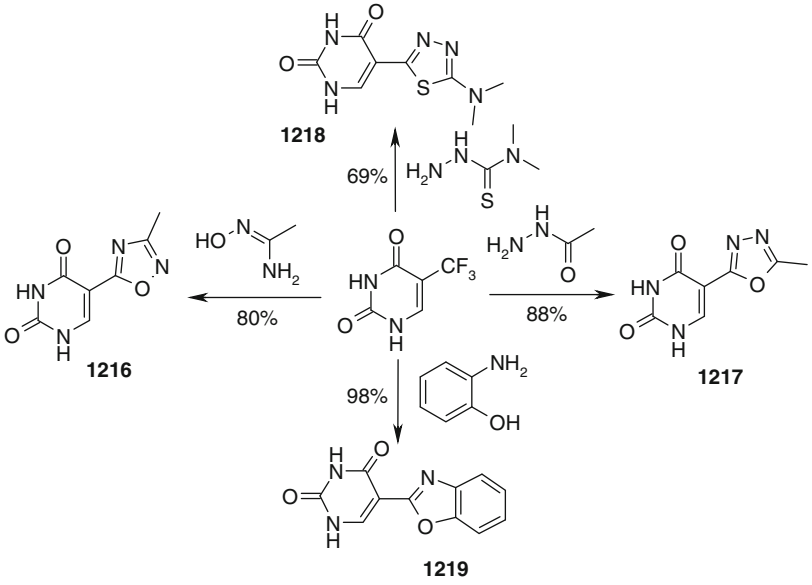
8.3 Transformation of Fluoroalkyl Substituent in CFD

Despite the widely accepted opinion that fluoroalkyl substituents in aromatic rings are chemically stable and rarely susceptible towards nucleophilic attack, a number of reactions of chain-fluorinated diazines at α-carbon of the fluoroalkyl moiety can be found. In fact, the first examples of such transformations were reported in 1960s [747]; they concerned an unusually easy hydrolysis of 5-trifluoromethyluracil and its derivatives upon warming in alkaline media (Scheme 263). Mechanism of the reaction was proposed, which included elimination of fluoride from anionic species **1214** and **1215**, formed either by deprotonation of the substrate or addition of hydroxide ion [748]. Additional (but similar) reaction pathways were also possible if more acidic NH protons were present in the molecule of the substrate.



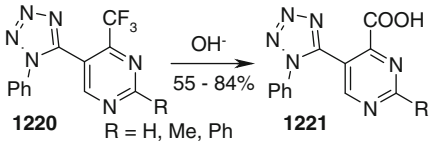
Scheme 263 Hydrolysis of 5-trifluoromethyluracil and its derivatives

It was shown that other nucleophiles can undergo analogous reactions with 5-trifluoromethyluracil or its derivatives, *e.g.* amines (methoxyamine [749]), bisulfite [750], and NH_4OH (to form 5-cyano-2′-deoxyuridine) [751]. Recently, this reaction was used for the synthesis of various heterocycles containing uracil moiety **1216–1219** (Scheme 264) [752].



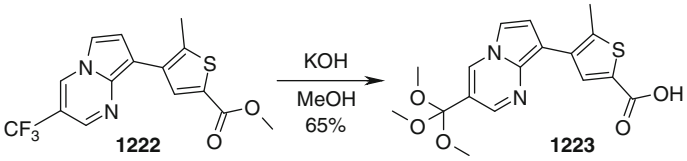
Scheme 264 Synthesis of heterocycles from 5-trifluoromethyluracil

Hydrolysis of trifluoromethyl group was accomplished in a different type of substrates, namely, tetrazolyl-substituted pyrimidines **1220** affording pyrimidine carboxylic acids **1221** (Scheme 265) [471]. Although support from the tetrazolyl moiety was stated, no explanation for this effect was proposed by the authors.



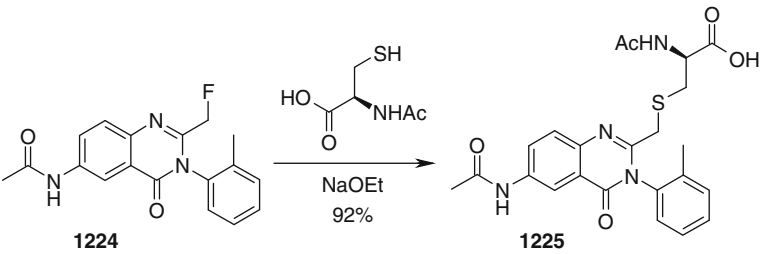
Scheme 265 Hydrolysis of the trifluoromethyl moiety in tetrazolylpyrimidines

Methanolysis of trifluoromethyl group in fused pyrimidine derivative **1222** was reported; in this case, orthoester **1223** was obtained (Scheme 266) [753].



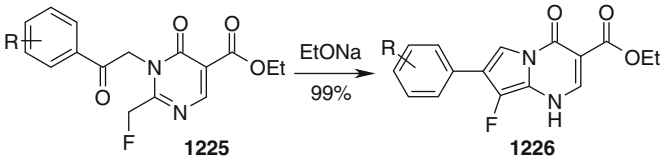
Scheme 266 Methanolysis of the CF_3-moiety in fused pyrimidine **1222**

Apart from nucleophilic substitution in the trifluoromethyl-substituted diazines discussed above, transformations related to mono- and difluoromethyl groups were also mentioned in the literature. In particular, hydrolysis of 5-difluoromethyluracyl and its derivative to form 5-formyl uracils was described [754]; the proposed mechanism reaction was analogous for the corresponding trifluoromethyl analogue. Nucleophilic substitution in fluoromethyl derivative **1224** was reported; in this case, *N*-acetylcysteine was acting as *S*-nucleophile (Scheme 267) [755].



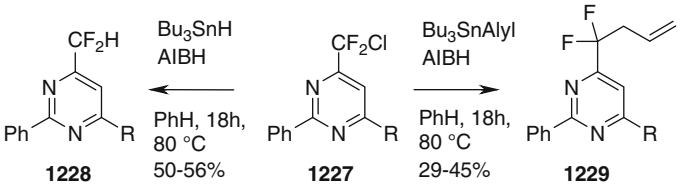
Scheme 267 Nucleophilic substitution in Afloqualone derivative **1224**

In another work, fluoromethyl group in pyrimidines **1225** acted as CH-acid in an intramolecular condensation with carbonyl compound, leading to the formation of 8-fluoro-pyrrolo[1,2-*a*]pyrimid-4-one derivatives **1226** (Scheme 268) [358, 756].



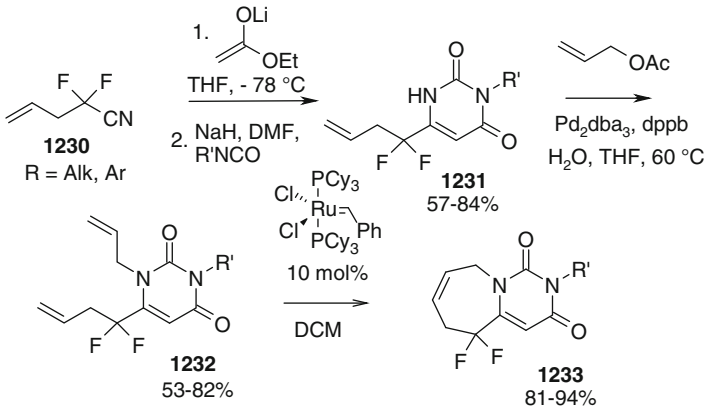
Scheme 268 Synthesis of 8-fluoro-pyrrolo[1,2-a]pyrimid-4-one derivatives **1226**

Another type of reactivity was disclosed for difluorochloro group in pyrimidine series. Recently Iaroshenko, Langer and co-workers shown that difluorochloro substituted pyrimidines **1227** can be converted into corresponding difluoromethyl pyrimidines **1228** by radical reduction with tributyltin hydride in the presence of AIBN in moderate yields. In addition, CF_2Cl-substituted pyrimidines **1227** were transformed to the corresponding 1,1-difluorobut-3-enyl pyrimidines **1129** by reaction with allyltributyltin and AIBN. In this case the yields of transformation are lower in comparison with tributyltin hydride reduction (Scheme 269) [412].



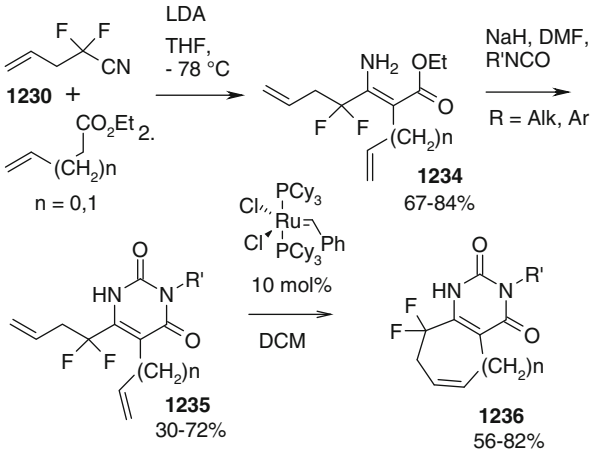
Scheme 269 Radical reaction of CF_2Cl-substituted pyrimidines **1227**

1,1-Difluorobut-3-enyl substituent is useful fragment for further transformation. Fustero with co-workers used the fragment for RCM reactions in synthesis of fused fluorinated uracils. Starting uracils in this case were synthesized not by CF_2Cl function transformation but by cyclization based on α,α-difluoro-4-pentenenitrile **1230** served as the starting materials. Nitrile **1230** reacted with ester enolates at −78 °C to afford intermediate β-enaminoesters, which could then be reacted with several isocyanates in the presence of sodium hydride in DMF-THF as solvent. In this way, several intermediate uracils **1231** were prepared in good yields. Than allyl acetate was used as alkylating agent in the presence of Pd(0) as catalyst to provide the N-allyl derivatives **1232**. Finally, these dienes reacted with the first generation Grubbs catalyst to afford the bicyclic seven-membered derivatives **1233** in excellent yields (Scheme 270) [757, 758].



Scheme 270 Synthesis of N1-C6 fused bicyclic uracils

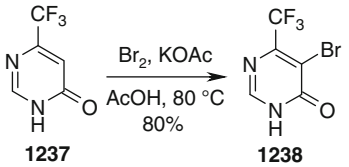
A slightly different strategy was used for the synthesis of the C5-C6 fused bicyclic uracils. The reaction of pentenoic and butenoic ester enolates with nitrile **1230** initially provided β-enamino esters **1234**, which then reacted with isocyanates to afford C5-C6 disubstituted uracils **1235** in variable yields. These uracils were transformed into the new family of fused bicyclic six- and seven-membered uracils **1236** by means of treatment with first generation Grubbs catalyst under the same conditions as described above, also in good yields (Scheme 271). These new families of uracils **1233** and **1226** were tested on acaricidal activity against *Tetranychus urticae*. Preliminary results showed that the best results for these compounds were slightly inferior than those for Tehufenpyrad [757, 758].



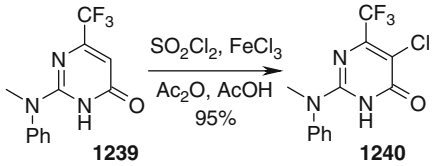
Scheme 271 Synthesis of C5-C6 fused bicyclic uracils

8.4 Electrophilic Substitution and Metalation at the Diazine Ring

Electrophilic substitution at the aromatic ring of chain-fluorinated diazines is rather unfavourable due to their electron-deficient nature. It is possible however when electron-donating substituents are also present in the diazine ring. For example, Shlösser reported successful bromination of pyrimidone **1237** with molecular bromine (Scheme 272) [715]. Halogenation of chain-fluorinated pyrimidine **1239** with SO_2Cl_2–$FeCl_3$ was also reported (Scheme 273) [759].



Scheme 272 Bromination of pyrimidone **1237**

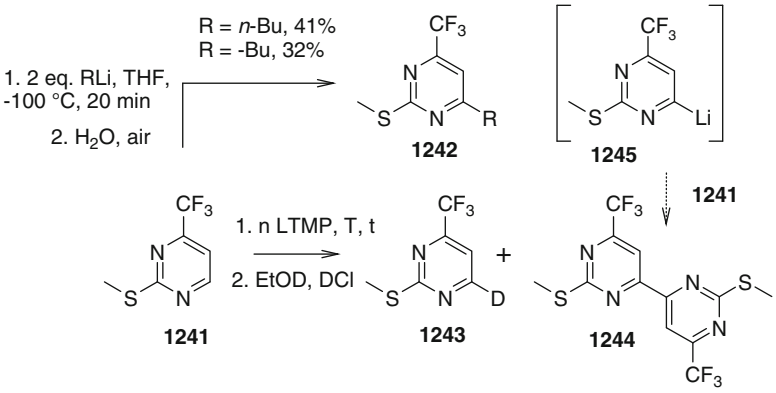


Scheme 273 Chlorination of chain-fluorinated pyrimidone with SO_2Cl_2–$FeCl_3$

An alternative approach for introducing electrophilic species into diazine ring relies on metalation. The first report about metalation CFD was made in 1997 by Queguiner using 2-thiomethyl-4-trifluoromethylpyrimidine **1241** [760]. In case of alkyllithium as metalating agent in THF at −100 °C, only 6-alkyl derivatives **1242** were obtained as a result of the nucleophilic addition at C6. To avoid the nucleophilic addition, lithium alkyl amides were tested in the reaction. In spite of electron-withdrawing effect of CF_3-group which favors *ortho*-lithiation, the steric hindrance of the group alters the orientation in this case. With excess of LTMP in THF at −100 °C metalation occurs at the C6, whereas with weaker base LDA in similar conditions only starting material was recovered. In a case of using 1.1 equivalent of LTMP the starting material was recovered with dimeric product **1244**. The formation of **1244** assumed that the metalation is slow or incomplete and **1241** underwent the nucleophilic attack from **1245**. To prevent the competitive reaction 4-fold excess of LTMP was used, so deuteriated compound **1243** was obtained without starting material, but small amounts of dimer **1244** were always present (Scheme 274, Table 50).

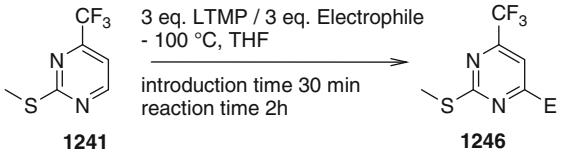
Table 50 Lithiation of 4-trifluoromethylpyrimidine

#	n	T (°C)	t(min)	**1241**	**1243**	**1244**
1	1.1	−78	30	24	–	17
2	2.2	−78	30	26	–	19
3	4	−78	15	–	33	10
4	4	−78	60	–	42	12
5	4	−100	60	–	22	30
6	4	−78	105	–	46	11



Scheme 274 Lithiation of 4-trifluoromethylpyrimidine

To avoid nucleophilic addition, a metalation/*in situ* trapping was used with a set of electrophiles. The simultaneous introduction of the electrophile and the compound **1241** prevent the dimer formation. Reaction of the lithioderivative **1245** with iodine or hexachloroethane as electrophiles gave 6-halopyrimidines in low yield whereas moderate or good yields observed for carbonyl compounds trimethylsilyl chloride and diphenyl sulphide (Scheme 275, Table 51) [760].

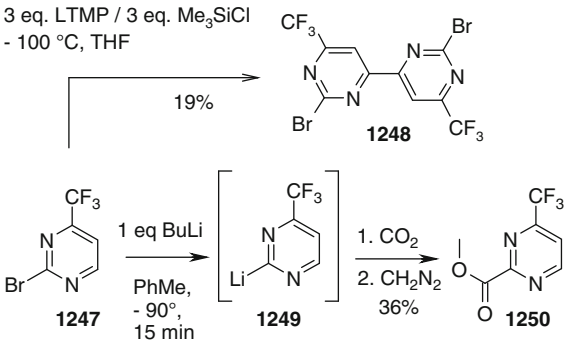


Scheme 275 Lithiation of 4-trifluoromethylpyrimidine by *in situ* trapping method

Table 51 Lithiation of 4-trifluoromethylpyrimidine by *in situ* trapping method

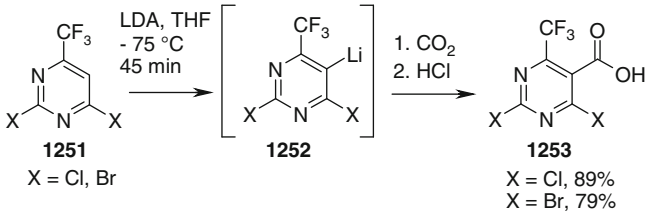
#	Electrophile	E	Yield (%)
1	PhCHO	PhCH(OH)	69
2	Ph_2CO	$Ph_2C(OH)$	77
3	I_2	I	26
4	C_2Cl_6	Cl	19
5	Me_3SiCl	Me_3Si	96
6	PhSSPh	SPh	98

Nine years after Queguiner paper the Shlösser group have studied lithiation of another trifluoromethyl-substituted pyrimidines [761]. According to *in situ* trapping method for pyrimidine **1247** with trimethylsilyl chloride no silylated pyrimidine was detected in the reaction mixture, only dimer **1248** was isolated in low yield. But consecutive treatment of **1247** with butyllithium in toluene at −90 °C leads to bromo/lithium permutation. Subsequent reaction with carbon dioxide followed by neutralization and esterification with diazomethane afforded methyl 4-(trifluoromethyl)pyrimidine-2-carboxylate **1250** in 36 % yield (Scheme 276).



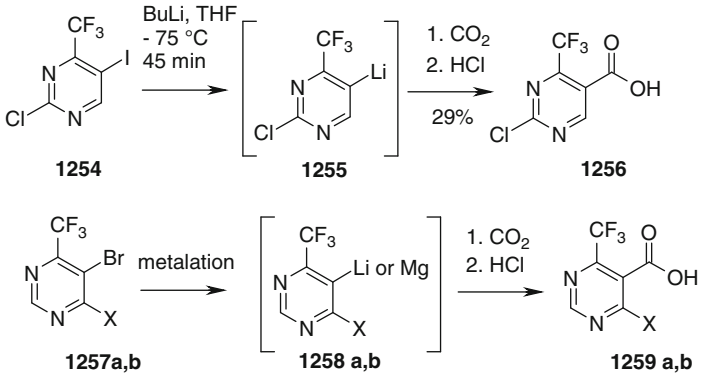
Scheme 276 Bromo/lithium permutation for 2-bromo-4-(trifluo-romethyl)pyrimidine

On the other hand, excellent results were achieved with 2,4-dihalo-6-(trifluoromethyl)pyrimidines **1251**. The corresponding pyrimidine-5-carboxylic acids **1253** were isolated in good preparative yields (Scheme 277).



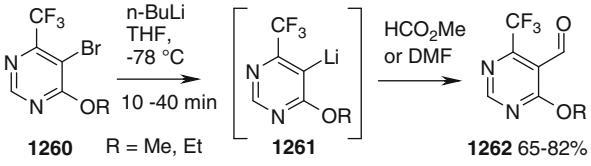
Scheme 277 Metalation and subsequent carboxylation of 2,4-hal--6-(trifluoromethyl)pyrimidines

Another 5-metalated 4-trifluoromethylpyrimidines could be generated by halogen-lithium exchange. The corresponding derivative **1254** was lithiated at 5-th position *via* iodine-lithium exchange affording intermediate **1255**, which was converted to acid **1256**, but the yield was low. In contrast, clean reactions were encountered with 5-bromo-4-chloro-6-(trifluoromethyl)pyrimidine **1257a** and 4,5-dibromo-6-(trifluoromethyl)pyrimidine **1257b** as the substrates when isopropylmagnesium chloride in diethyl ether and, respectively, butyllithium in toluene were employed as the exchange reagents. 4-Chloro and 4-bromo substituted 6-(trifluoromethyl)pyrimidine-5-carboxylic acids were isolated in 73 and 54 % yield respectively. The rigorous discrimination between the two bromine atoms by the Grignard reagent is observed (Scheme 278) [761]. Notably, the halogen atoms in the molecules of **1259 a,b** could be removed by catalytic hydrogenation.



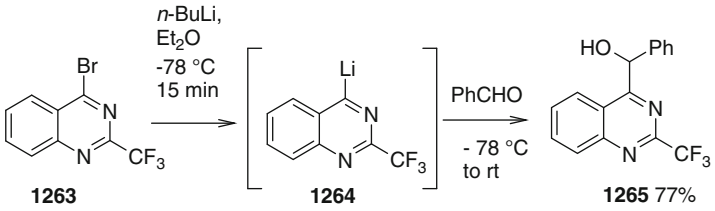
Scheme 278 Carboxylation of 4-trifluoromethylpyrimidines via halogen/metal exchange

The bromine-lithium exchange by butyllithium in CFD began to find industrial application. Kumiai Chemical Industry and Syngenta used the lithiation-formylation sequence for the synthesis of the corresponding aldehydes in herbicides development programs (Scheme 279) [713, 762]. Both methyl formate and DMF were used as formilating agents to afford aldehydes **1262** in good yields.



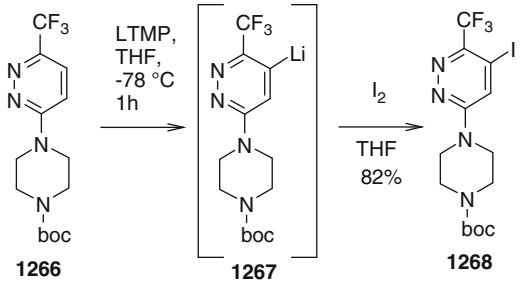
Scheme 279 Synthesis of **1262**

Also the bromine-lithium exchange in 4-bromo-2-trifluoromethylquinazoline **1263** was described using butyl lithium. The corresponding litho-derivative **1264** was entered into reaction with benzaldehyde to give alcohol **1265** (Scheme 280) [742]



Scheme 280 Synthesis of **1265**

Besides pyrimidine derivative, as to the best of our knowledge, only one example is described for another CFD. Janseen in 2008 described DoM reaction of pyridazine **1266** with LTMP followed by iodination affording iodo-derivative **1268** in 82 % preparative yield (Scheme 281) [724].

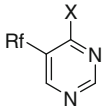
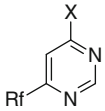
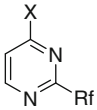
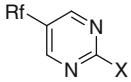
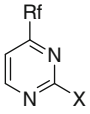
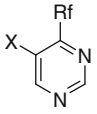
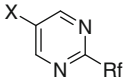
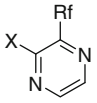
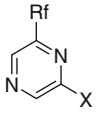
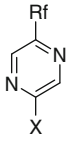


Scheme 281 DoM lithiation-iodination of pyridazine **1266**

8.5 Transition Metal-Catalyzed Cross-Couplings

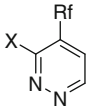
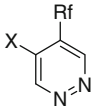
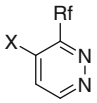
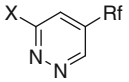
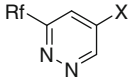
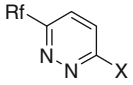
Unlike nucleophilic substitution with *N*-, *S*-, and *O*–nucleophiles discussed in Sect. 8.2.1 of this chapter, transition metal-catalyzed C–C couplings are not well-documented in chain-fluorinated diazine series. Almost all examples deal with palladium-catalyzed cross-coupling involving chain-fluorinated halodiazines and the corresponding organoelement compounds (*e.g.* Suzuki, Stille, Negishi or Kumada reactions), alkenes (*i.e.* Heck reaction), or alkynes (*i.e.* Sonogashira reaction) (Table 52). The reaction conditions are quite common for the analogous transformations involving aryl halides (Table 53).

Table 52 Reaxys® data for the C–C cross-couplings of chain-fluorinated halodiazines

#	Substrate[a]	No. of hits	No. of citations		
			Total	Papers	Patents
Pyrimidines and their fused derivatives					
1		23	5	2	3
2		11	9	3	6
3		14	15	3	12
4		2	2	0	2
5		12	10	4	6
6		16	5	1	4
7		6	5	1	4
Pyrazines and their fused derivatives					
8		7	6	1	5
9		1	1	0	1
10		6	5	1	4

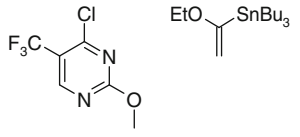
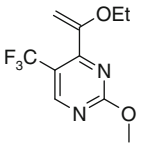
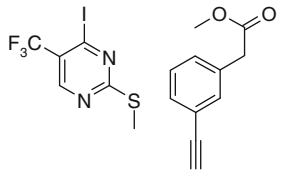
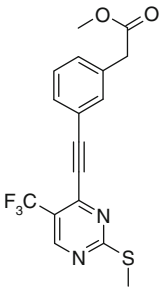
(continued)

Table 52 (continued)

#	Substrate[a]	No. of hits	No. of citations		
			Total	Papers	Patents
Pyridazines and their fused derivatives					
11		7	4	2	2
12		–	–	–	–
13		4	2	–	2
14		–	–	–	–
15		–	–	–	–
16		12	8	0	8

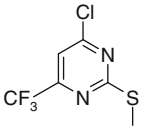
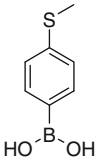
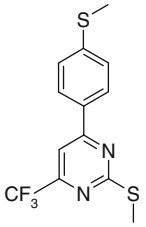
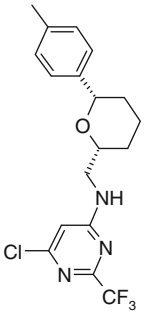
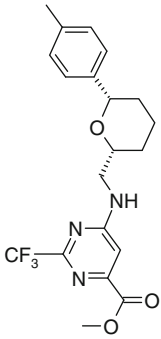
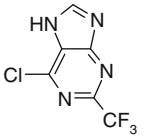
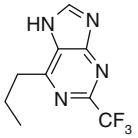
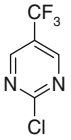
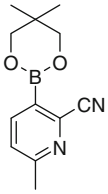
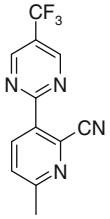
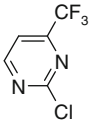
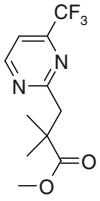
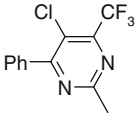
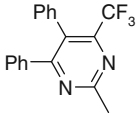
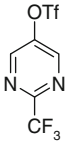
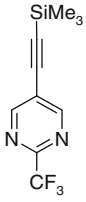
[a]X=F, Cl, Br, I

Table 53 Typical reaction conditions for the C–C couplings in chain-fluorinated diazines

#	Reactants	Product	Conditions	Yield	Ref.
1			$Pd(PPh_3)_4$, toluene, 110 °C	N/A	[763]
2			$Pd(PPh_3)_2Cl_2$, Et_3N,DMF, MW, 120 °C	69	[764]

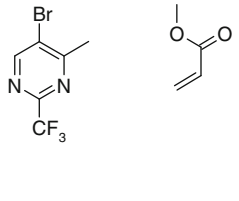
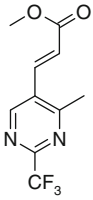
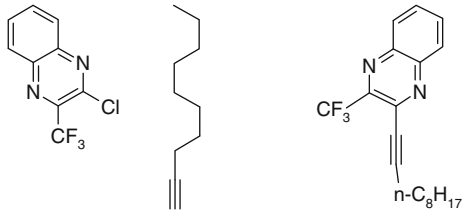
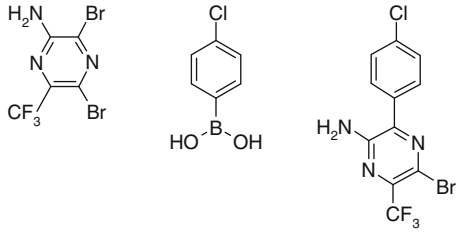
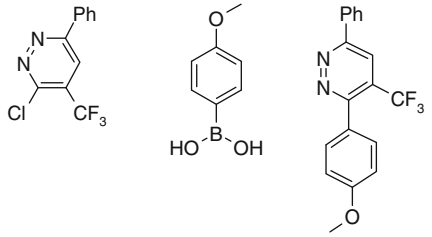
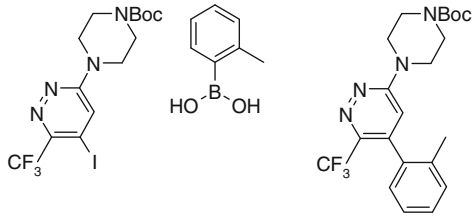
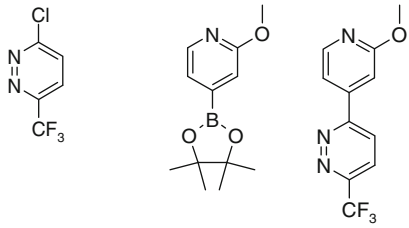
(continued)

Table 53 (continued)

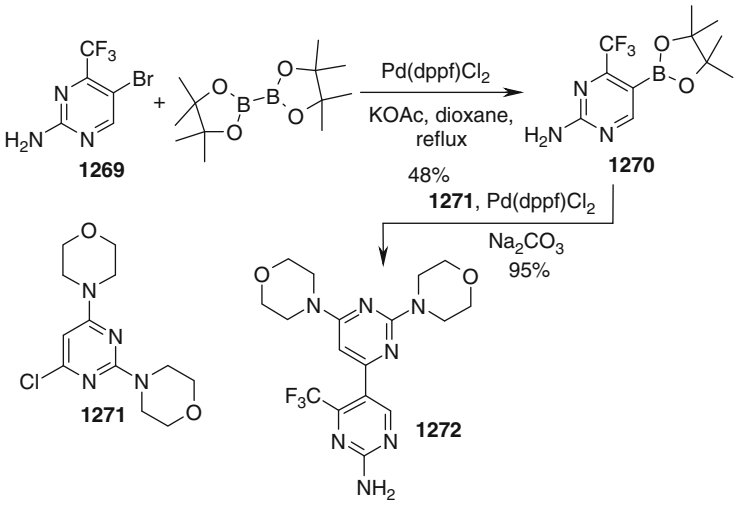
#	Reactants		Product	Conditions	Yield	Ref.
3				$Pd(PPh_3)_4$, Na_2CO_3, DME–H_2O, reflux	82	[765]
4		CO, MeOH		$Pd(OAc)_2$, dppf, DMF, 70 °C	60	[766]
5		*n*-PrMgBr		$Ni(dppp)Cl_2$, THF, 50 °C	30	[767]
6				$Pd(PPh_3)_4$, CuI, CsF, dioxane, 65 °C	42	[768]
7				Zn/Cu, $MeCONMe_2$, toluene, then $Pd(PPh_3)_4$, 70 °C	78	[769]
8		$PhSnBu_3$		$Pd(PPh_3)_4$, MeCN, MW, 180 °C	98	[482]
9				$Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 80 °C	95	[770]

(continued)

Table 53 (continued)

#	Reactants	Product	Conditions	Yield	Ref.
10			$Pd(OAc)_2$, Et_3N, 110 °C	72	[771]
11			$[t\text{-}Bu_2(4\text{-}Me_2NC_6H_4)P]_2Pd$, Cs_2CO_3, MeCN	87	[772]
12			$Pd(PPh_3)_4$, Na_2CO_3, DME– H_2O, reflux	66	[773]
13			$Pd(PPh_3)_4$, K_2CO_3, EtOH–H_2O, reflux	95	[774]
14			$Pd(dppf)Cl_2$, dppf, K_3PO_4, dioxane, 80–110 °C	48	[775]
15			$Pd(dppf)Cl_2$, K_2CO_3, DMSO, 80 °C	60	[776]

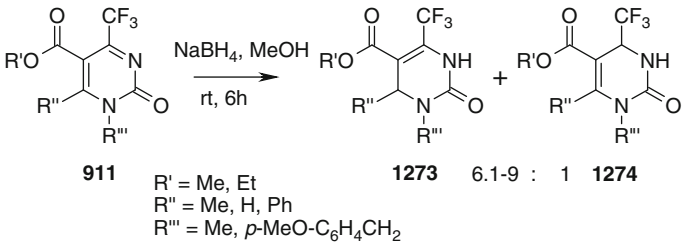
So far, the only reported example of organoelement compound derived from chain-fluorinated diazines used in C–C couplings is boronate **1270**, prepared from bromo derivative **1269** (Scheme 282) [787]. Compound **1270** was successfully introduced intro Pd-catalyzed coupling with chloride **1272** to give the product **1273** in good yield (95 %).



Scheme 282 Synthesis and Pd-catalyzed coupling of **1270**

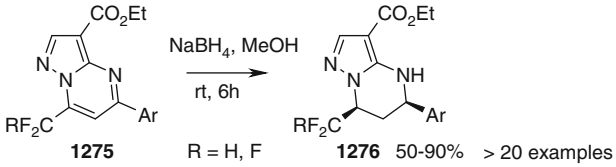
8.6 Reduction and Oxidation of the Diazine Ring

Usually nuclei of CFD are stable to common reduction agent such as complex metal hydride ($NaBH_4$, LAH etc.) and metals in low oxidation state ($SnCl_2$, Fe etc.) which allow to made different transformation of functional groups in these compounds leaving the ring of CFD intact. But in literature there are rare examples of reduction of the CFD nuclear by $NaBH_4$. Recently Vovk with co-workers shown that due to the alternation of bonds in the ring pyrimidones **911** (see Scheme 189) react with $NaBH_4$ in methanol at room temperature to give quantitatively a mixture of two stable isomeric tetrahydropyrimidines, **1274** and **1273**, with the predominance of the latter product as a result of 1,4-reduction of the endocyclic conjugated double bonds. 2-Oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **1273** can be isolated in pure form by double recrystallization from ethanol (Scheme 283) [550].



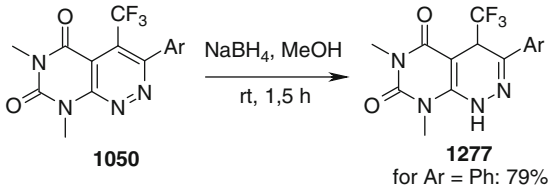
Scheme 283 Reduction of pyrimidones **911** with $NaBH_4$

Also the $NaBH_4$ reduction of fused pyrazolo[1,5-a]pyrimidines was disclosed in a course of discovery of antitubercular agents and novel structural class of potent calcium-sensing receptor antagonists. The reduction proceeds also in mild condition giving diastereoselectively desired tetrahydropyrazolo[1,5-a]pyrimidines in good preparative yields (Scheme 284) [418, 778].



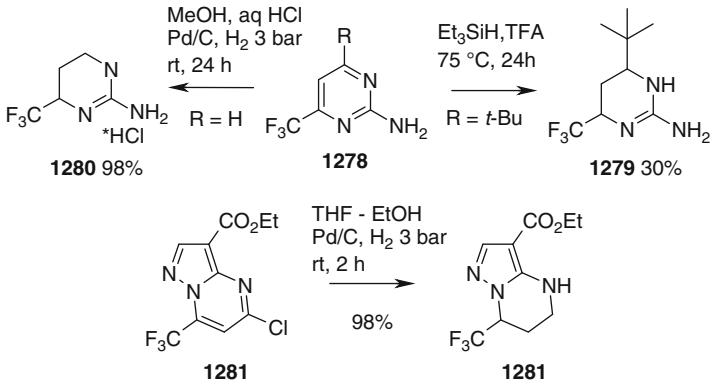
Scheme 284 Reduction of fused pyrimidines **1275** with $NaBH_4$

Besides pyrimidines one example of $NaBH_4$ reduction described for 4-trifluoromethylpyrimido[4,5-c]pyridazines **1050** (see Scheme 224), which reacted with $NaBH_4$ giving corresponding dihydroderivatives **1277** in good yields (Scheme 285) [628].



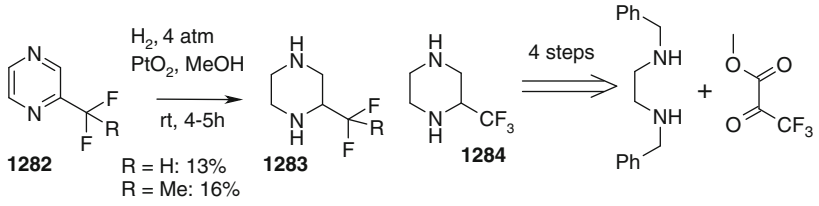
Scheme 285 Reduction of fused pyridazines **1050** with $NaBH_4$

Another agent used for CFD nuclear reduction is triethylsilane in the presence of trifluoroacetic acid. In a case of pyrimidine **1278** (R=*t*-Bu) the reaction leads to cyclic guanidine **1279** in 30 % yield [789]. The better result in similar transformation gives catalytic hydrogenation over palladium. In this case the preparative yield of guanidine **1280** is near to quantitative [780] (Scheme 286). In should be noted, that formation of cyclic guanidines under aminopyrimidines reduction is typical also for non-fluorinated analogues using triethylsilane as well as catalytic hydrogenation. The latest method also was used for tetrahydropyrazolo[1,5-a]pyrimidine **1281** synthesis. In this case dechlorination and pyrimidine reduction occurs by one step (Scheme 286) [418].



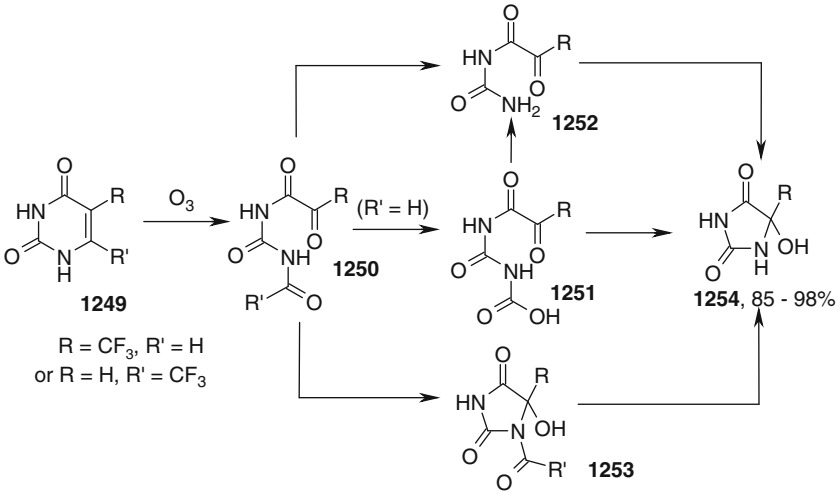
Scheme 286 Reduction of chain fluorinated pyrimidines with Et_3SiH and hydrogen

Reduction of fluoroalkylpyrazines could be a promising method for the synthesis of chain-fluorinated piperazines. This method was used for the synthesis of difluoromethyl- and (1,1-difluoroethyl)piperazines **1283**; nevertheless, it was obtained in low yield [322, 781]. Therefore the synthesis of "parent" (trifluoromethyl) piperazine **1284** is based on 4 steps synthesis started from methyl trifluoropyruvate and N,N′-dibenzyl ethylenediamine (Scheme 287) [782].



Scheme 287 Synthesis of chain-fluorinated piperazines

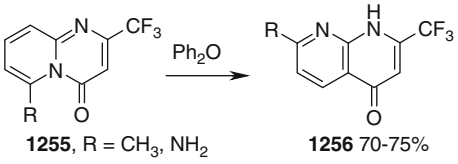
Among oxidation of the diazine ring in CFD the major part of the reports deal with the oxidation of the partially unsaturated diazines. Thus, tetrachloro-1,4-benzoquinone (TCBQ) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [611, 815], copper (II) halides [593, 784] and bromine [603, 785] were used as oxidizing agents. Also ozonolysis of chain-fluorinated diazines was reported. In particular, reaction of 5- and 6-trifluoromethyluracils with ozone led to the formation of hydantoins **1254** (Scheme 288) [786]. It was assumed that oxidative cleavage occurs at C5–C6 bond of the diazine ring, followed by hydrolysis and cyclization of the intermediate formed.



Scheme 288 Ozonolysis of trifluoromethyluracils

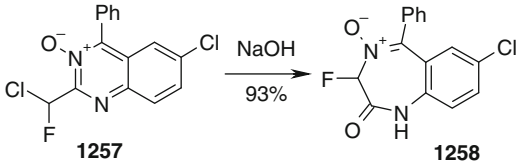
8.7 *Recyclizations*

Since ANRORC-type processes are characteristic for pyrimidine series, it is not surprising that there are some examples of recyclizations with chain-fluorinated pyrido[1,2-a]pyrimidin-4-ones **1255**. In particular, heating of fused pyrimidines **1255** in diphenyl ether resulted in the formation of 1,8-naphtyridine derivatives **1256** (Scheme 289) [787, 788].



Scheme 289 Recyclization of chain-fluorinated pyrido[1,2-a]pyrimidin-4-ones

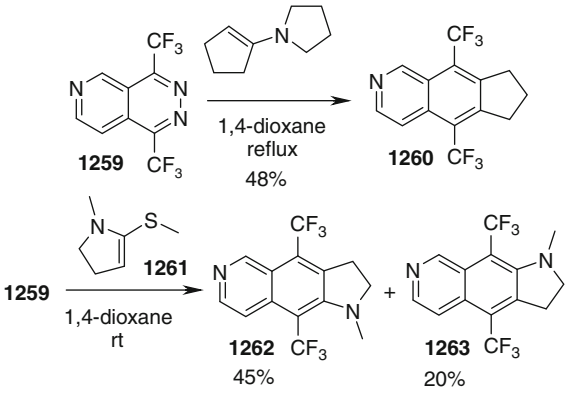
Another example includes rearrangement of quinazoline derivative **1257** into benzodiazepine **1258**, described in a patent (Scheme 290) [789].



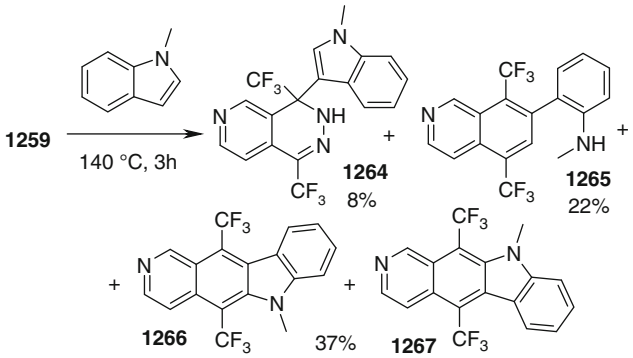
Scheme 290 Recyclization of fused pyrimidine **1257**

8.8 Inverse-Electron-Demand Diels-Alder Reaction

It was described in Sect. 7.8 of this chapter that chain-fluorinated diazines can be synthesized using inverse-electron-demand Diels-Alder reactions. Some of the fused pyridazines can also undergo analogous reactions with electron-rich alkenes. In particular, Diels-Alder reactions of pyridopyrazine **1259** were studied. It was found that **1259** reacted with enamines to give quinoline derivatives (*e.g.* **1260**) (Scheme 291) [790]. Reaction of **1259** with ketene N,S-acetal **1261** led to a mixture of regioisomers **1262** and **1263**, whereas reaction with *N*-methylindole gave complex mixture of products **1264**–**1267** (Scheme 292) [791].

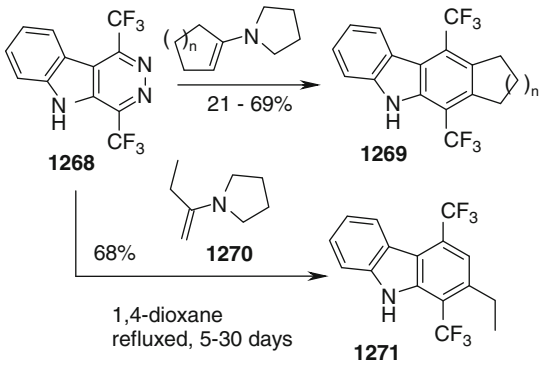


Scheme 291 Diels-Alder reactions of pyridopyrazine **1259** with enamines



Scheme 292 Diels-Alder reactions of pyridopyrazine **1259** with *N*-methylindole

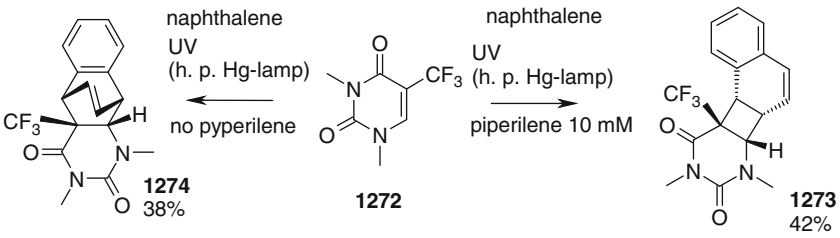
Pyridazino[4,5-*b*]indole **1268** is another example of aza-diene which was successfully introduced into inverse-electron-demand Diels-Alder reactions with enamines. The reaction proceeds upon prolonged refluxing in 1,4-dioxan (Scheme 293) [792]. Notably, reaction of **1268** with acyclic enamine **1270** proceeded in a regioselective manner.



Scheme 293 Diels-Alder reactions of pyridopyrazine **1268**

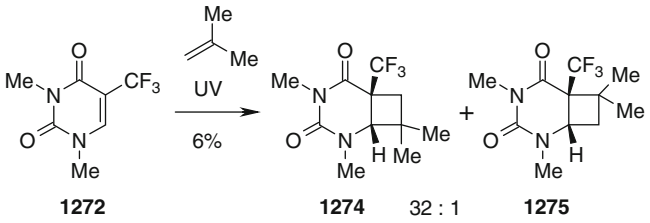
8.9 Photochemical [2+2] Cycloadditions

Chain-fluorinated diazines can undergo photochemical [2+2] cycloaddition with alkenes to give cyclobutane or azetidine derivatives. In particular, 1,3-dimethyl-5-trifluoromethyluracil **1272** reacted with naphthalene under UV-irradiation in the presence of piperylene preferentially underwent 1,2-cycloaddition to give cis-tetrah ydronaphthocyclobutapyrimidine **1273** in high stereoselectivity [793]. It should be noted that similar reaction without piperylene pass through 1,4-cycloaddition affording an ethenobenzoquinazoline derivative **1274** as sole product of the reaction [794] (Scheme 294).



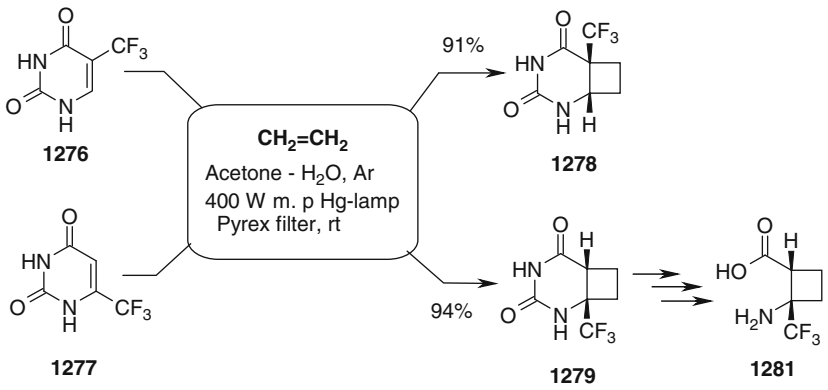
Scheme 294 Photochemical reaction of 5-trifluoromethyluracil **1272** with naphthalene

Also the reaction of 1,3-dimethyl-5-trifluoromethyluracil **1272** with isobutylene was studied. In this case nearly exclusively the head to-tail adducts **1274** formed, but the yield of transformation was extremely low (Scheme 295) [795].



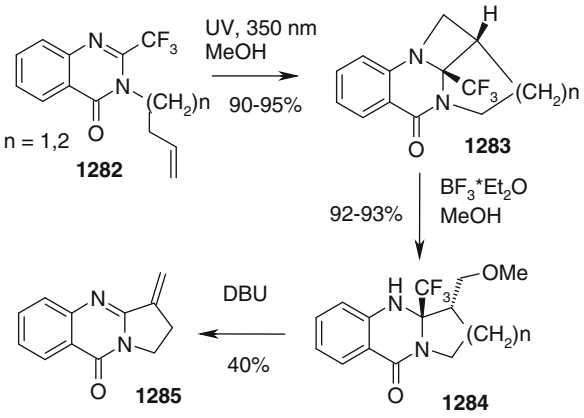
Scheme 295 Photochemical reaction of 5-trifluoromethyluracil **1272** with isobutylene

In 2006 Aitken with co-workers developed a procedure of [2+2] cycloaddition, which in a case of trifluoromethyluracils and ethylene gave excellent preparative yields (Scheme 296). Based on cycloaddition product **1279** the synthesis of cyclobutane derived amino acid **1281** was elaborated [796].



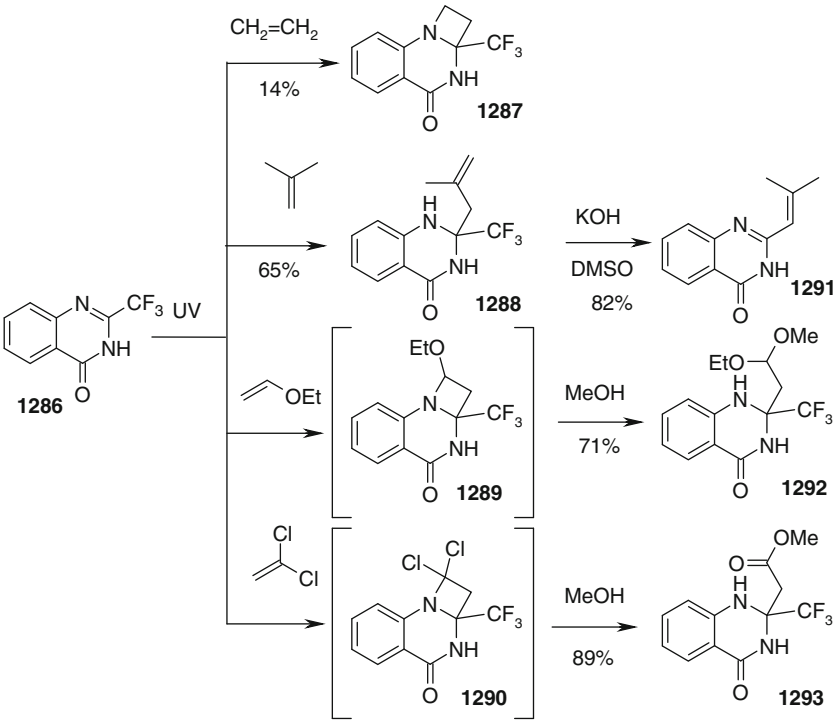
Scheme 296 Photochemical [2+2] cycloaddition of trifluoromethyluracils with ethylene

Intramolecular [2+2] photochemical cycloaddition based on 2-trifluoromethylquinazolines was studied. Compounds **1282** afforded the corresponding [2+2] adducts **1283** in 90–95 yields even on irradiation at 350 nm. Treatment of the adducts **1283** by methanol containing borontrifluoride etherate leads to cleavage of the azetidine cycle leading to fused compounds **1284**. In a case of treatment of the compound **1284** (n = 1) with DBU elimination of the CF_3-group occurs affording compound **1285** (see Sect. 8.2.2 of this chapter) (Scheme 297) [797].



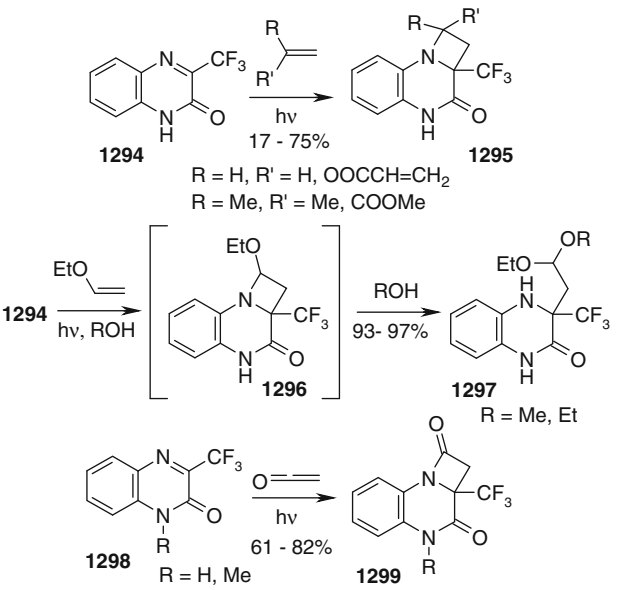
Scheme 297 Intramolecular photochemical [2+2] cycloaddition of **1282**

Also itermolecular photochemical [2+2] cycloaddition based on 2-trifluoromethylquinazoline **1286** was studied. In a similar conditions the reaction with ethylene gives compound **1287** in 17 % yield as a sole product probably due to low solubility of ethylene in methanol. Ene-type product **1288** was isolated in 65 % yield when isobutylene was used in the reaction, showing that biradical intermediate is involved in the transformation. In a case of ethyl vinyl ether acetal **1292** was formed as product of methanolysis of intermediate azetidine **1289**. Similarly was used intermediate azetidine **1290** was not isolated when dichloroethylene and its formation was proved by isolation of methanolysis product **1293** in 89 % yield. It should be noted, that treatment of product **1288** with base leads to elimination of CF_3-group as in a case of **1284** (Scheme 298) [797]



Scheme 298 Intermolecular photochemical [2+2] cycloaddition of **1286**

The same group of Japanese authors studied the photochemical reaction of fluorinated quinoxalines. Photochemical cycloadditions with quinoxaline derivative **1294** occurred and C=N double of the diazine ring, leading to the formation of azetidine derivatives (Scheme 299). The presence of trifluoromethyl group in the molecule of **1294** activated the substrate towards cycloaddion, so that even electron-deficient methyl methacrylate was introduced in the reaction [797]. In the case of ethyl vinyl ether as the alkene, the adduct **1296** also as in a case with **1289** was not stable and underwent azetidine ring-opening upon action of the solvent. Ketene was also successfully introduced in [2+2] cycloaddition with trifluoromethyl-substituted quinoxaline derivatives [797]



Scheme 299 Photochemical [2+2] cycloadditions with quinoxaline **1294**

9 Conclusions and Outlook

Since discovery of the first fluorinated diazine – antineoplastic agent 5-fluorouracil more than 20 compounds from the class were introduced into the pharmaceutical and crop protection market. Also these compounds find industrial application as reactive component for the synthesis of reactive dyestaff in textile industry and as a component of liquid crystals. Besides industrial application fluorinated diazines appear excellent objects for theoretical investigations. Starting from Halex process and electrophilic fluorination of uracil fluorinated diazines still attract the attention of chemists working in different industries as interesting objects of study. Undoubtedly the success was achieved due to joint progress of medicinal chemistry, agrochemistry as well as synthetic methods of heterocyclic and fluoroorganic chemistry. But despite really the huge number of articles and patents in this field the chemical space covered by fluorinated diazines remains "white spots". Thus, diazine scaffold decorated by important for medicinal chemistry and agrochemistry fluorinated fragments such as -CHF_2, -CH_2CF_3, -OCF_3, -SCF_3, -SF_5 were not investigated because the synthetic chemistry of these compounds is still on development phase or not developed at all. For example only in this year Yagupolskii with co-workers developed the first method of synthesis of 5-OCF_3 substituted pyrimidines [798]. Also the chemistry of organoelement (B, Si, Sn) derivatives of fluorinated diazines, able to transition metal catalyzed coupling reaction still

remains almost unexplored, especially in a case of CFD. Therefore the comprehensive investigations in the field of fluorinated diazines still are interesting both for academic and industrial scientists.

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Fluorine-Containing Diazines in Medicinal Chemistry and Agrochemistry

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V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 2: 6-Membered Heterocycles*, 577
DOI 10.1007/978-3-319-04435-4_7,

Abstract The combination of a fluorine atom and a diazine ring, which both possess unique structural and chemical features, can generate new relevant building blocks for the discovery of efficient fluorinated biologically active agents. Herein we give a comprehensive review on the biological activity and synthesis of fluorine containing, pyrimidine, pyrazine and pyridazine derivatives with relevance to medicinal and agrochemistry.

Keywords Pyrimidine • Pyrazine • Pyridazine • Fluorine • Bioactive compounds • Medicinal chemistry • Agrochemistry

Abbreviations

AHAS	acetohydroxy acid synthase
ATP	adenosine triphosphate
$B_2(Pin)_2$	Bis(pinacolato)diboron
BCR	B-cell receptor
Boc	*tert*-butoxycarbonyl
BOP	benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate
Bu	Butyl
CDK	cyclin-dependent kinase
CDMT	2-chloro-4,6-dimethoxy-1,3,5-triazine
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CSA	camphorsulfonic acid
CyJohnPhos	2-(dicylohexyl¬phosphino)biphenyl
DAST	diethylaminosulfur trifluoride
Dba	Dibenzylideneacetone
DHFU	Dihydrofluorouracil
DIC	diisopropyl carbodiimide
DIBAL	diisobutylaluminium hydride
DIPEA	ethyl diisopropyl amine
DMF	Dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dppe	bis(diphenylphosphino)ethane
Dppf	1,1′-bis(diphenylphosphino)pherocene
DPP-4	dipeptidyl peptidase
dTMP	deoxythymidine monophosphate
dUMP	deoxyuridine monophosphate
EPA	environmental protection agency
FDA	Food and Drug Administration
FdUDP	fluorodeoxyuridine diphosphate

FdUMP	fluorodeoxyuridine monophosphate
FdUTP	fluorodeoxyuridine triphosphate
FMDV	foot-and-mouth disease virus
FUDP	fluorouridine diphosphate
FUDR	Floxuridine
FUMP	fluorouridine monophosphate
FUR	Fluorouridine
FUTP	fluorouridine triphosphate
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
GIP	gastric inhibitory peptide
GLP-1	glucagon-like peptide-1
HIV	Human immunodeficiency virus
HOBT	Hydroxybenzotriazole
HPLC	high-performance liquid chromatography
JAK	Janus kinase
JAK–STAT	Janus kinase – signal transducer and activator of transcription
L-DOPA	L-3,4-dihydroxyphenylalanine
Me	Methyl
NADH	Nicotinamide adenine dinucleotide
NMM	N-methylmorpholine
PDC	pyridinium dichromate
Ph	Phenyl
py	Pyridine
RNA	ribonucleic acid
(S,S)-Et-DuPhos	1,2-bis[(2S,5S)-2,5-diethylphospholano]benzene
TBAF	tetra-n-butylammonium fluoride
TBDPS	tert-butyl diphenyl silyl
TFA	trifluoroacetic acid
TMSNCO	Trimethylsilylisocyanate
TMSO	Tetramethylenesulfoxide
TMSOTf	trimethylsilyl trifluoromethanesulfonate
WNV	West Nile virus
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
YFV	yellow fever virus

1 Introduction

Diazines are aromatic six-membered heterocycles that contain two sp^2-hybridized nitrogen atoms in the ring. The three diazine isomers are pyridazine (1,2-diazine), pyrimidine (1,3-diazine) and pyrazine (1,4-diazine). The most important naturally occurring diazines are the pyrimidine bases uracil, thymine, and cytosine, which comprise the fundamental nucleoside building blocks in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Pyrazines occur frequently as

constituents in foodstuffs and are responsible for their flavor and strong aroma. Although being present in very small amounts, they are highly odiferous and can be detected at extremely low concentrations. Unlike other heterocycles found in many important natural products, pyridazines were discovered only after 1970, and relatively few pyridazines have thus far been isolated from natural sources. As synthetic compounds, all diazines constitute an important pharmacophoric moiety present in many drugs acting on various pharmacological targets as well as agrochemicals.

Inspite of organofluorine compounds are almost absent as natural products, ~25 % of drugs in the pharmaceutical pipeline and ~15 % of agrochemicals contain at least one fluorine atom. One of the earliest synthetic fluorinated drugs is the antineoplastic agent 5-fluorouracil, derivative of pyrimidine, an antimetabolite first synthesised in 1957. Since the advent of 5-fluorouracil, fluorine substitution is commonly used in contemporary medicinal and agrochemistry to improve metabolic stability, bioavailability and protein–ligand interactions. In this review only compound bearing fluoro or fluoroalkyl substituent in diazine ring are discussed. Among fluorine containing diazines now 12 drugs and 10 agrochemicals are presented on the market. This review provides an information about fluorinated diazines as drugs or agrochemicals and their mode of action as well as synthesis. The review is divided in two parts. First part dedicated to the medicinal and synthetic chemistry of fluorinated diazines that have reached at least clinical development phase. The second one dedicated to the biological role and the chemistry of the marketed agrochemicals based on fluorinated diazines.

2 Fluorine-Containing Diazines in Medicinal Chemistry

It is widely accepted that compounds containing fluorine atoms have a remarkable record in medicinal chemistry and play a continuing role in providing lead compounds for potential therapeutic applications. The reasons for that have been discussed extensively in a number of books and reviews [1, 2]. In this view, fluorine-containing diazines are not the exception; they have attracted attention of medicinal chemists since 1950s when Fluorouracil (**1**) was introduces as anti-cancer drug. Analysis of MDDR (MDL Drug Data Report) data retrieved 1,150 hits derived from fluorine-containing diazines [3]. Nearly a third part of them is represented by anti-cancer agents (Fig. 1); other important classes (more than 100 examples) include compounds with antiviral (mainly anti-HIV) and antiarthritic activity.

According to MDDR, 106 compounds containing a fluorinated diazine moiety have entered pre-clinical studies, 40 of them have reached clinical phase, and 12 of these have become drug substances (Fig. 2). In the following sections, fluorine-containing diazine derivatives that have reached at least clinical development phase will be discussed, focusing on their aspects related to medicinal and synthetic organic chemistry.

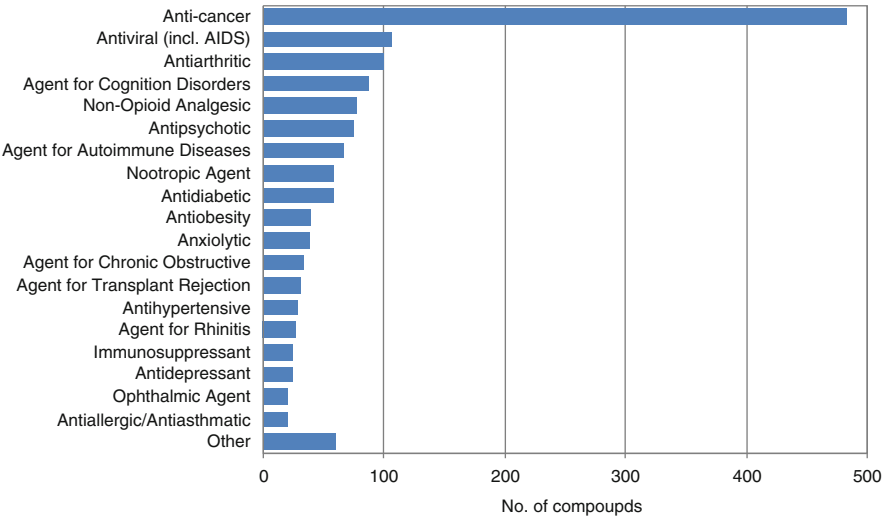


Fig. 1 Distribution of biological activity for fluorine-containing diazines in MDDR

3 Anti-cancer Agents

3.1 Fluorouracil and Floxuridine

The use of fluorinated diazines as anti-cancer agents is the major field of their application in medicinal chemistry. The first representative of this class, Fluorouracil (**1**) was developed by Charles Heidelberger and co-workers in 1957 [4]. It was approved by U.S. FDA [5] in 1962 as antineoplastic agent in the treatment of advanced colorectal cancer. Fluorouracil represents a class of rationally designed anticancer agents which act as antimetabolites. The observation that rat hepatomas utilized radiolabeled uracil more avidly than normal tissues [6] implied that the enzymatic pathways for utilization of uracil or its close analogs differed between malignant and normal cells – a feature which might provide a target for antimetabolite chemotherapy. A minimal modification of uracil by introducing a single fluorine atom allowed for implementation of cellular uptake and metabolic activation of **1** via the same transport processes and enzymes involved in the case of uracil. However, in the case of essential biological targets, remarkable differences are observed due to unique properties of the fluorine atoms, which result in inhibition of the metabolic and signal pathways involved. Although all the details of the mechanism by which Fluorouracil gives its biological effect are not elucidated, a remarkable progress has been made over the past half a century in elucidating its cellular and clinical pharmacology [7, 8].

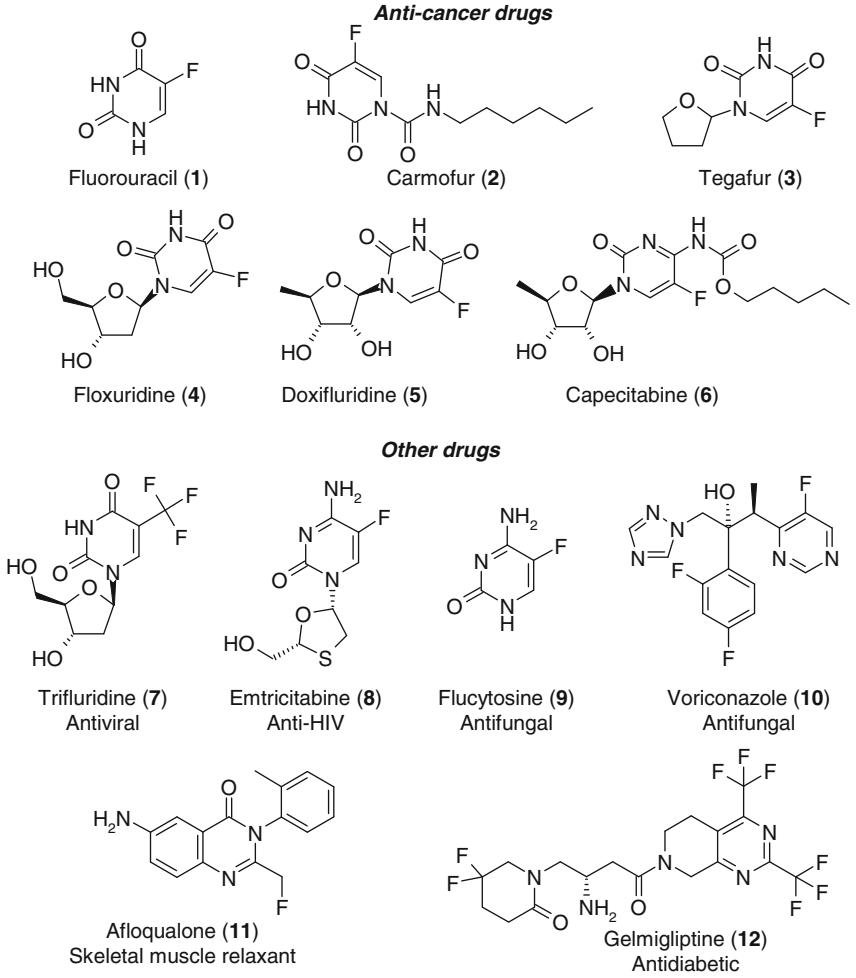
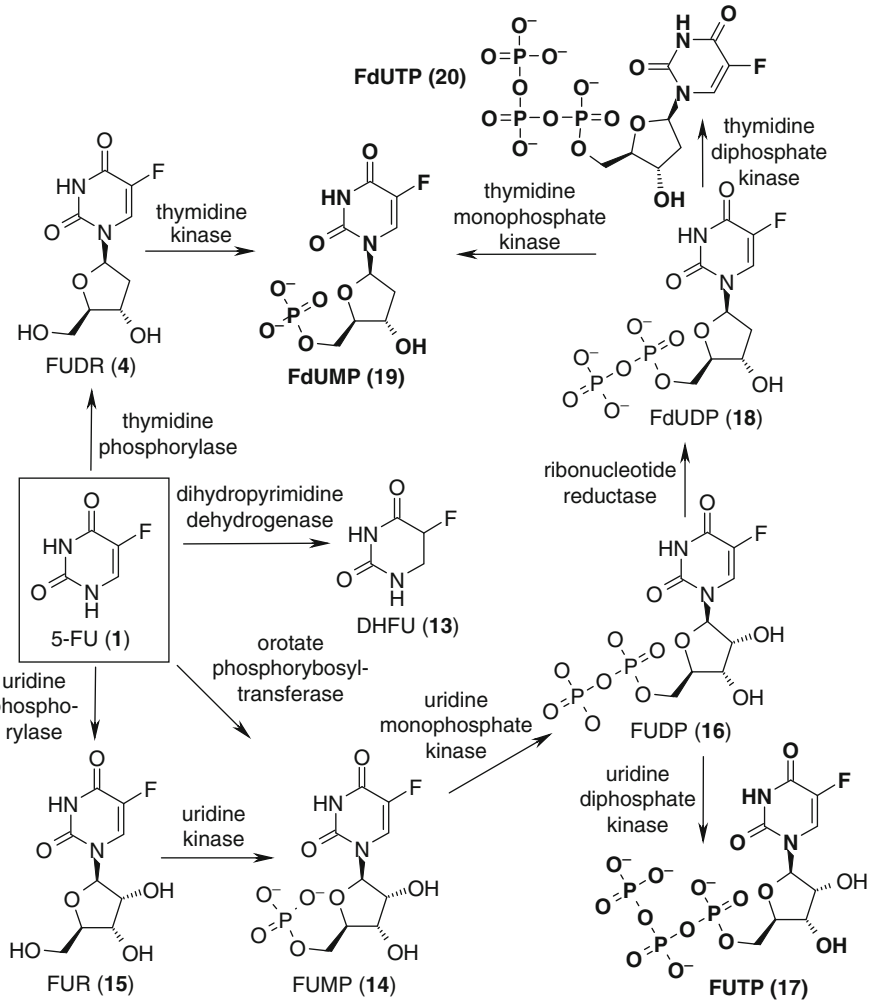


Fig. 2 Drug substances derived from fluorine-containing diazines

The key steps in Fluorouracil metabolism are shown in Scheme 1. Up to 80 % of **1** administered as injection is transformed to dihydrofluorouracil (DHFU, **13**) by dihydropyrimidine dihydrogenase (mostly in liver tissues). However, this metabolite is not involved into antineoplastic activity; instead, **13** itself and its further metabolites are responsible for most of the toxic effects of **1**. The main mechanism of activation of Fluorouracil is conversion to fluorouridine monophosphate (FUMP, **14**), either directly by orotate phosphoribosyltransferase, or *via* fluorouridine (FUR, **15**) through the sequential action of uridine phosphorylase and uridine kinase. **14** is then phosphorylated to give fluorouridine diphosphate (FUDP, **16**), which can be either phosphorylated again to the active metabolite fluorouridine triphosphate (FUTP, **19**), or reduced to fluorodeoxyuridine diphosphate (FdUDP, **18**) by ribonucleotide reductase. In turn, **18** can either be dephosphorylated or phosphorylated to generate

the active metabolites fluorodeoxyuridine monophosphate (FdUMP, **19**) and fluorodeoxyuridine triphosphate (FdUTP, **19**), respectively.

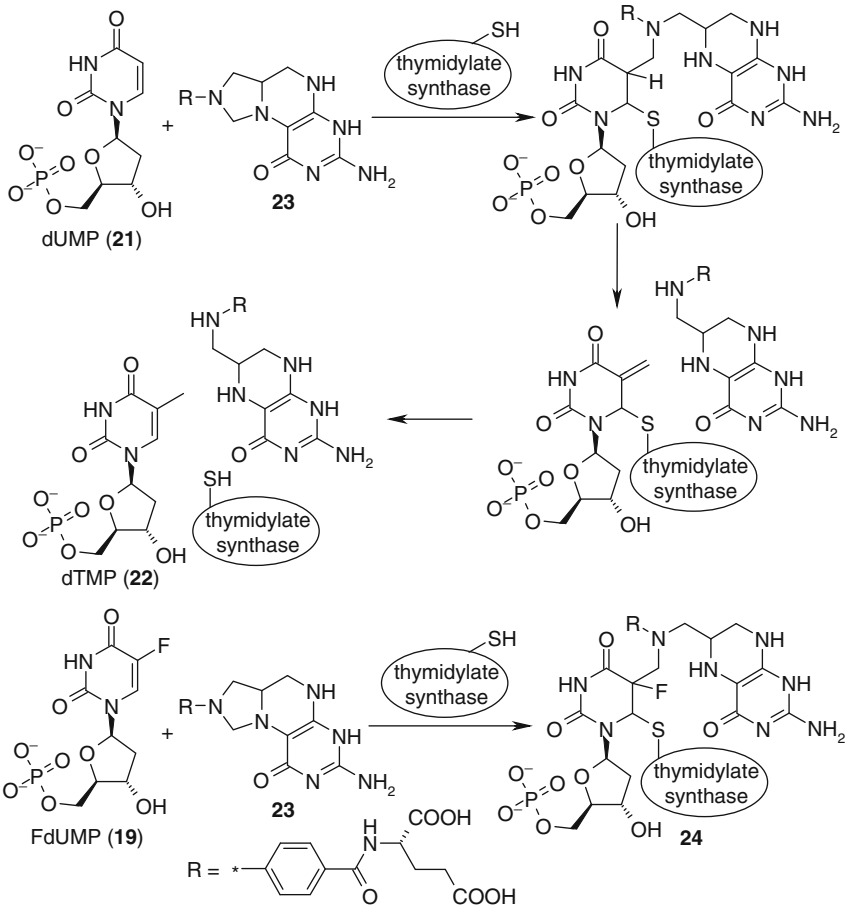


Scheme 1 Metabolism of Fluorouracil (active metabolites are shown in *bold*)

An alternative activation pathway involves the thymidine phosphorylase catalysed conversion of **1** to Floxuridine (FUDR, **4**), which is then phosphorylated by thymidine kinase to give **19**. The metabolite of **1** – Floxuridine – is itself used as an anti-cancer agent [9]. It was launched in 1970 by Hospira Inc [5]. Upon rapid injection, most of Floxuridine is catabolized to Fluorouracil; hence similar effects on the organism are obtained in this case. On the contrary, when **4** is slowly administered into the arterial blood, it is mostly transformed to **19**; thus toxic effects are diminished comparing to **1** [10].

It has long been recognized that one of the main mechanisms underlying Fluorouracil action is inhibition of thymidylate synthase by fluorodeoxyuridine monophosphate

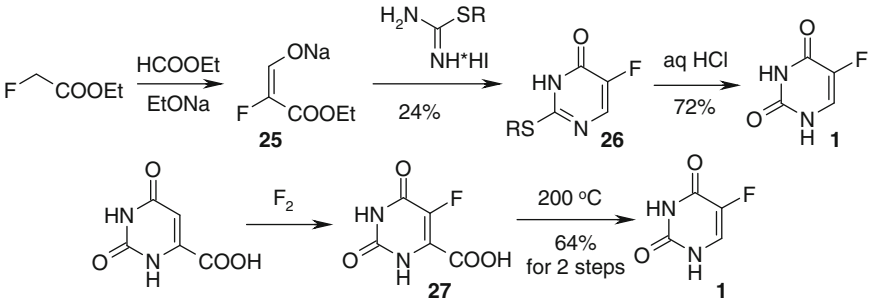
(**19**) [11]. Thymidylate synthase belongs to a class of enzymes required for DNA replication, and its activity is higher in rapidly proliferating cells. In particular, thymidylate synthase is responsible for methylation of deoxyuridine monophosphate (dUMP, **21**) to deoxythymidine monophosphate (dTMP, **22**) with the use of 5,10-methylenetetrahydrofolate (**23**) as a cofactor (Scheme 2) [12]. With fluorodeoxyuridine monophosphate, a slowly-reversible ternary complex **24** is formed instead. Inhibition of thymidylate synthase leads to deoxyribonucleotide imbalance, and hence to interference with DNA synthesis and repair. Alternative mechanism of DNA-directed Fluorouracil effect is misincorporation of fluorodeoxyuridine triphosphate (**20**) into DNA. Analogously, fluorouridine triphosphate (**17**) is extensively incorporated into different RNA species, disrupting their normal processing and function [7, 8, 11].



Scheme 2 Thymidylate synthase inhibition by fluorodeoxyuridine monophosphate (**19**)

Two principal approaches were used for the preparation of Fluorouracil (Scheme 3). One of the first methods [13, 14] commenced from ethyl fluoroacetate which was subjected to Claisen condensation with ethyl formate to give **25**. The salt **25** was

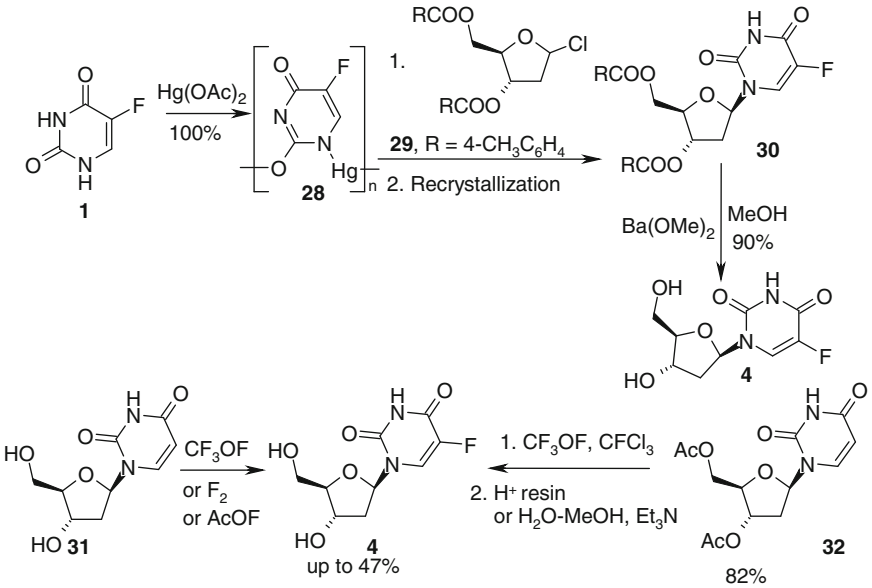
introduced into reaction with *S*-alkylisothiourea to give fluoropyrimidines **26**, which were hydrolysed to give **1**. Several variations of this method were also described; their common drawback was the use of highly toxic fluoroacetic acid derivatives.



Scheme 3 Syntheses of Fluorouracil (**1**)

In an alternative approach, Fluorouracil was prepared by direct fluorination of different pyrimidine derivatives, including uracil [15], cytosine [16], and orotic acid [17]. In the latter method, the initially obtained fluoroorotic acid **27** was subjected to decarboxylation. The use of two-step reaction sequence was claimed to be advantageous due to simplified product isolation and purification.

Early synthesis of Floxuridine commenced from Fluorouracil (**1**) which was transformed into its mercury salt **28** and then allowed to react with 2-deoxy-D-ribofuranosyl chloride derivative **29** (Scheme 4) [18]. The product **30** was subjected to alkaline hydrolysis to give Floxuridine (**4**).



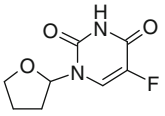
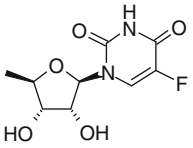
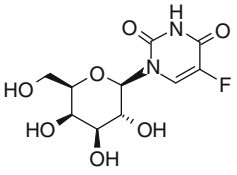
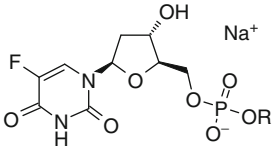
Scheme 4 Syntheses of Floxuridine (**4**)

As in the case of Fluorouracil, newer syntheses of Floxuridine relied on direct fluorination of uracil derivatives. Fluorination of uridine **31** was done using fluorine [19], acetyl fluoride [20], and CF_3OF [21]. The latter reagent gave good but still moderate yield of the product **4** (47 %). The use of a two-step reaction sequence, *i.e.* fluorination of diacetoxy derivative **32** and hydrolysis, improved the yield of **4** to 82 % over two steps [21, 22].

3.2 *Prodrugs of Fluorouracil*

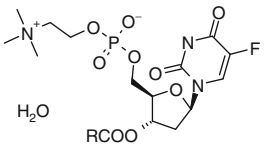
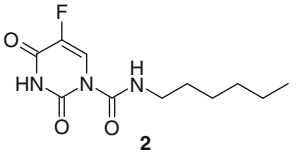
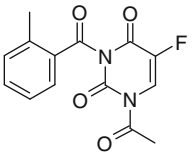
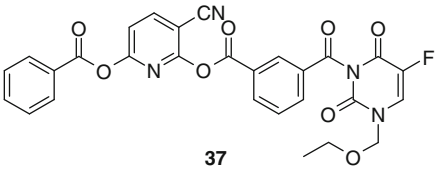
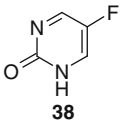
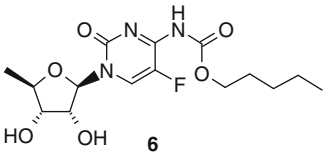
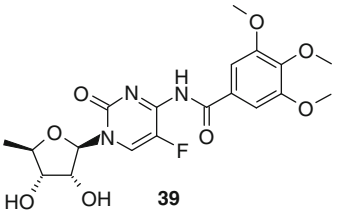
Despite Fluorouracil remains the main agent for the treatment of certain cancer types (*i.e.* colorectal) [23], it displays various side effects due to its nonspecific cytotoxicity, poor distribution to tumor sites, and serious limitations in effectiveness due to drug resistance. Apart from modulation of Fluorouracil biological action through combination therapies [7, 24], a number of drugs and clinical candidates acting as prodrugs of **1** and/or **4** were developed (Table 1).

Table 1 Fluorouracil/Floxuridine prodrugs [3, 5]

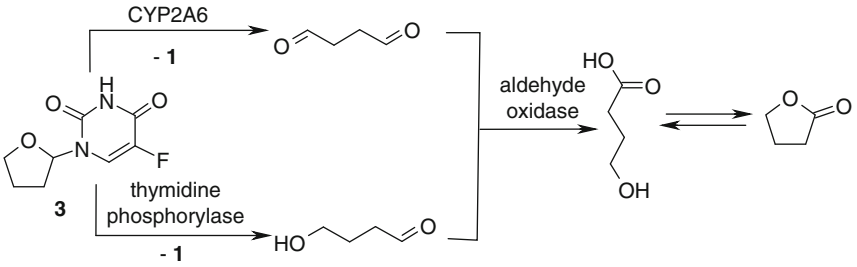
Structure	INN or ID, development phase	Company
 **3**	Tegafur Launched (1979)	Latvian institute of organic synthesis
 **5**	Doxifluridine Launched (1987)	Hoffmann –La Roche, Chugai Pharmaceutical
 **33**	OGT 719 Phase I	Oxford GlycoSciences
 **34**, R = *n*-$C_{14}H_{29}$	TT-62 Phase II	Teijin Pharma

(continued)

Table 1 (continued)

Structure	INN or ID, development phase	Company
 **35**, R = (*Z*)-pentadec-7-en-1-yl	T-506 Phase II	Toyama Chemical
 **2**	Carmofur Launched (1981)	Yamanouchi Pharmaceutical, Mitsui Chemicals
 **36**	Atofluding Phase III	Xian Lijun Pharmaceutical
 **37**	Emitefur, BOF-2A Phase III	Otsuka Pharmaceutical
 **38**	5-FP Phase I	Astex Pharmaceuticals, Yale University
 **6**	Capecitabine Launched (1998)	Hoffman La Roche
 **39**	Galocitabine Phase II	Hoffman La Roche

The first example of Fluorouracil prodrug is Tegafur (**3**) developed in 1960s in Latvia [25, 26]. Tegafur is an oral slow-release prodrug formulation of Fluorouracil which is readily absorbed through the gastrointestinal tract. The major pathway of metabolic activation of **3** includes hydroxylation by hepatic cytochrome P450 enzymes, mostly CYP2A6 (Scheme 5) [27].



Scheme 5 Metabolic activation of Tegafur (**3**)

Apart from Fluorouracil, 4-hydrohybutyraldehyde and succinic dialdehyde are also formed, which are further transformed into γ-butyrolactone and 4-hydrohybutyric acid [28]. Tegafur was shown to be 2–5 times more potent and less toxic than **1**; hence lower doses of **3** can be utilized, resulting in decreased neurotoxicity without compromising the antitumor effects.

Another prodrug of Fluorouracil – Doxifluridine (**5**), which also implies the idea of attachment of sugar-like moiety to the molecule of **1**, was launched in Japan in 1987 [29]. The mechanism of metabolic activation of **5** is rather simple and includes hydrolysis to Fluorouracil by thymidine phosphorylase [299]. Since the level of thymidine phosphorylase is significantly higher in several types of solid tumours (in particular, colorectal, breast, and kidney cancers) as compared with normal tissues, Doxifluridine possesses a higher therapeutic index for these types of cancers. The use of **5** is somewhat limited by gastrointestinal toxicity after oral administration due to release of **1** by intestinal pyrimidine nucleoside phosphorylase [30].

Yet another sugar-modified Fluorouracil derivative – OGT 719 (**33**), in which galactose is incorporated onto the fluoropyrimidine moiety, was developed by Oxford GlycoSciences and had reached Phase I clinical study [31]. In 1999, the company decided to discontinue development of **33** as the results of Phase I/II clinical study were not sufficiently strong to justify large scale Phase II studies. OGT 719 was rationally designed to reduce the systemic toxicity normally associated with Fluorouracil while retaining activity against tumors localized in the liver, in which it may be preferentially localized through the asialoglycoprotein receptors [32]. These receptors are present on the surface of hepatocytes and recognise various sugar-containing biomolecules through terminal galactose and *N*-acetylgalactosamine residues. The metabolic activation of OGT 719 occurs once the compound enters hepatocytes, where the galactose molecule is cleaved from the Fluorouracil residue.

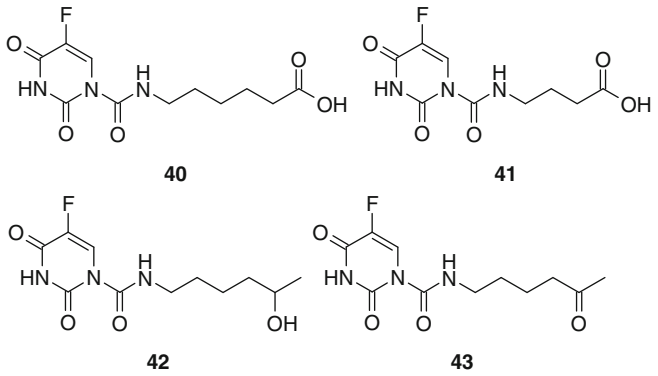
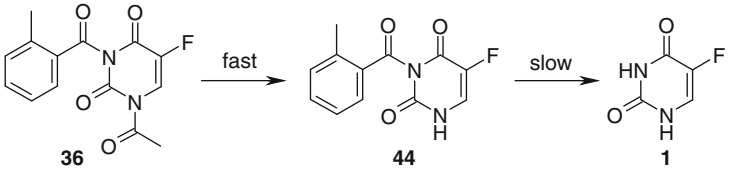


Fig. 3 Metabolites of Carmofur (**2**)

Two derivatives of Floxuridine – TT-62 (**34**) and T-506 (**35**) have reached Phase II clinical trials in Japan [3]. The compounds showed significant antitumor activity by oral administration; moreover, they slowly released Floxuridine, and the effective level of **4** was prolonged [33, 34]. The gastro-intestinal disturbances and loss of body weight were serious side effects of **34** and **35**.

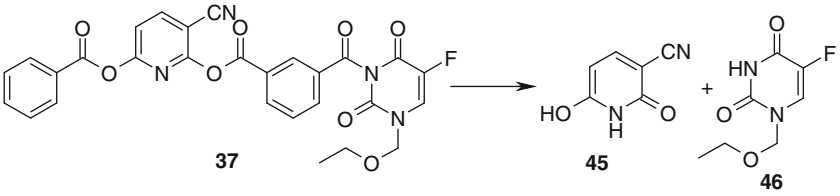
Several prodrugs of Flourouracil were obtained by acylation or carbamoylation of N-1 and/or N-3 atoms of the pyrimidine ring of **1**. In particular, an oral drug Carmofur (**2**) which is 1-hexylcarbamoyl derivative of **1** was launched in Japan in 1981 and later – in other countries [35]. The carbamate moiety in **2** decomposes gradually in neutral water or in basic conditions, but it is strongly resistant to acidic hydrolysis and hence can survive acid in the stomach. The 1-hexylcarbamoyl moiety also facilitates the rapid uptake of **2** through the cell membrane [36]. The metabolic activation of Carmofur involves oxidation and scission of the side-chain with slow release of **1** [37]. Two main routes of the side chain transformation are ω-oxidation and (ω–1)-oxidation: metabolites **40**–**43** were detected after administration of Carmofur (Fig. 3) [38]. Non-enzymatic hydrolytic decomposition of **2** and its metabolites also contributes to release of **1**.

Another oral prodrug of Fluorouracil, Atofluding (**36**) is a diacyl derivative of **1**. Atofluding has reached Phase III clinical trials in China [39]. The activation of **36** includes its fast non-enzymatic hydrolysis to 3-*o*-toluyl-5-Fluorouracil (**44**) following oral administration; **44** is then slowly metabolized to **1** (Scheme 6) [40]. Since the acetyl group of Atofluding is not stable and prone to decompose, impairing quality control for the preparation, a possibility of direct application of **44** was also considered [41].



Scheme 6 Metabolic activation of Atofluding (**36**)

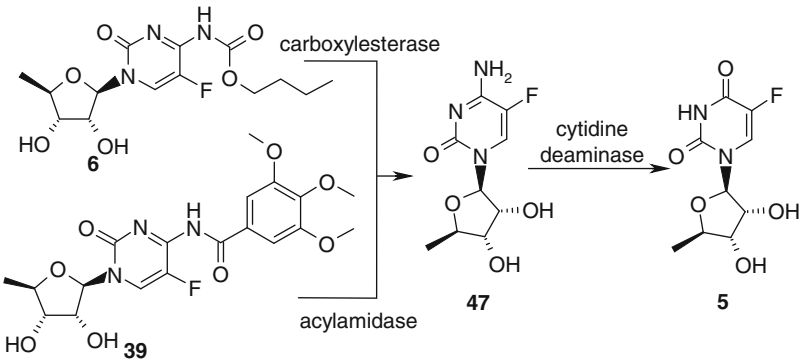
An interesting idea was behind design of Emitefur (**37**), a prodrug of Fluorouracil which was developed by Otsuka Pharmaceutical and has reached Phase III clinical trials in Japan [3, 42, 43]. The structure of **37** contains the fragments of two biologically active components: Fluorouracil (**1**) and 3-cyano-2,6-dihydroxypyridine (**45**), which is a potent inhibitor of dihydropyrimidine dehydrogenase. Therefore, **37** is a double prodrug which not only delivers Fluorouracil but also prevents its enzymatic biotransformation to the dihydropyrimidine derivative **12**. Metabolic activation of **37** occurs *via* rapid cleavage of the ester bonds by esterase to give **45** and 1-ethoxymethyl-5-fluorouracil (**46**) (Scheme 7). The intermediate **46** is further metabolized to **1** by microsomal enzymes in the liver [44].



Scheme 7 Metabolic activation of Emitefur (**37**)

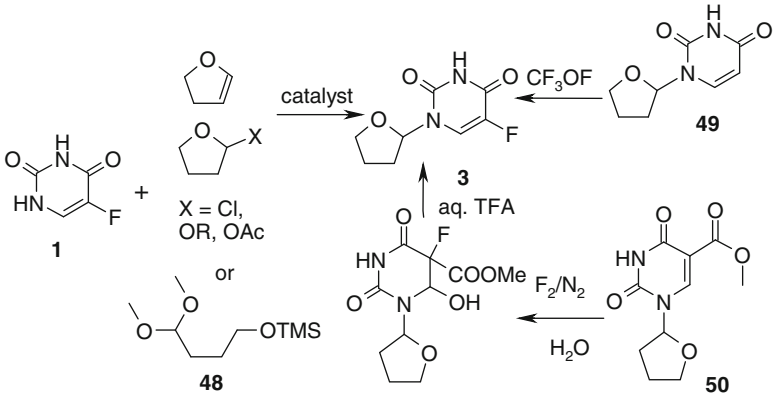
All the prodrugs of Fluorouracil discussed above contained the fragment of **1** in their structure; their transformation to **1** included hydrolysis reaction as the key step. On the contrary, 5-fluoro-2-pyrimidinone (5-FP, **38**) which has been studied in Phase I clinical trials [45] is activated through oxidative process. In particular, pyrimidine **38** is transformed to **1** by aldehyde oxidase, which is present in high concentrations in the human livers but not in the gastrointestinal tract [46].

Two prodrugs of **1**, Capecitabine (**6**) and Galocitabine (**39**), are 5-fluorocytidine derivatives. Both the compounds were developed by Hoffman La Roche; whereas Capecitabine was launched in 1998, Galocitabine was terminated at Phase II clinical trials [47]. Both the compounds are close analogues as well as prodrugs of Doxifluridine (**5**), which was used as the lead compound in their design. The main goals of such design were to minimize the mielotoxicity and to increase the tumor selectivity of **5**. In fact, Capecitabine (**6**) indeed demonstrated minimal mielotoxicity in clinical studies. Although the therapeutic indices of **39** were much higher in mice tumor models than in the case of **5**, it was not efficiently metabolised to the active species in humans. The metabolic activation of **6** and **39** includes their hydrolysis by carboxylesterase or acylamidase in liver to give 5′-deoxy-5-fluorocytidine (**47**), which is then transformed to **5** by cytidine deaminase (Scheme 8) [48].



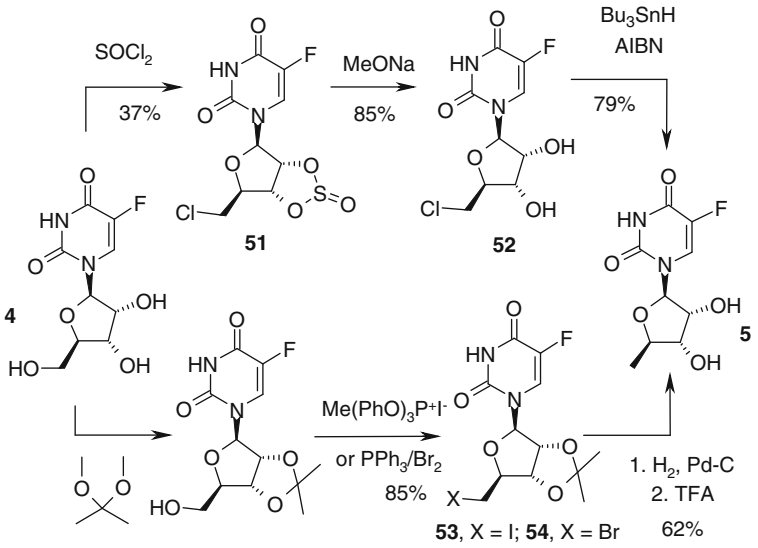
Scheme 8 Metabolic activation of Capecitabine (**6**) and Galocitabine (**39**)

Syntheses of Fluorouracil prodrugs relied on either chemical modification of **1** or direct fluorination of the corresponding pyrimidine derivatives. In particular, Tegafur (**3**) was obtained from **1** by reaction with 2,3-dihydrofuran [49–54], 2-chloro- [55, 56], 2-alkoxy- [57], 2-acetoxytetrahydrofuran [58, 59, 300], and 4-trimethylsilyloxybutyraldehyde dimethyl acetal (**48**) (Scheme 9) [60]. Alternatively, **3** was prepared via fluorination of compound **49** [61] or ester **50** [62].

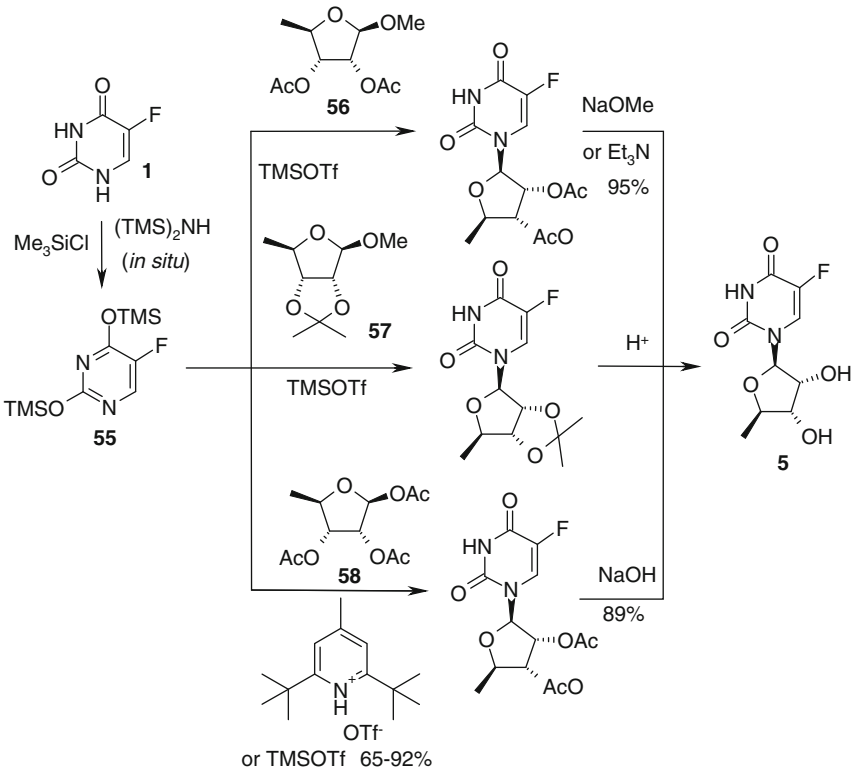


Scheme 9 Syntheses of Tegafur (**3**)

One of the early syntheses of Doxifluridine (**5**) [63, 64] commenced from Floxuridine (**4**) which reacted with thionyl chloride to give cyclic sulphite **51** (Scheme 10). Methanolysis of **51** upon treatment with sodium methylate gave **52**, which was reduced with tributyltin to give **5**. In an analogous approach, the compound **5** was prepared via iodide **53**, in turn obtained from **4** in two steps (Scheme 11) [65]. It should be noted that direct transformation of **4** into the corresponding iodide was done with low yield of the product, hence the protection strategy was necessary to use. Bromide **54** was a key intermediate in one more analogous scheme [66].



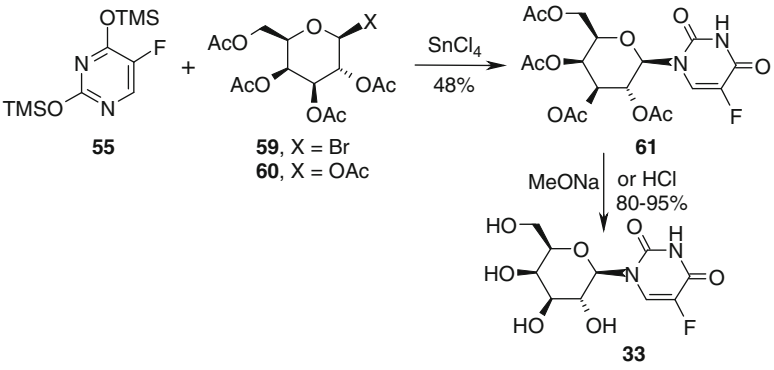
Scheme 10 Syntheses of Doxifluridine (**5**) from Floxuridine (**4**)



Scheme 11 Syntheses of Doxifluridine (**5**) from Fluorouracil (**1**)

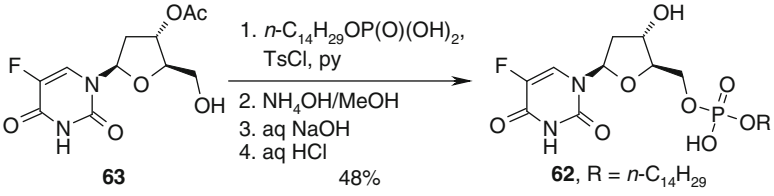
Several syntheses of Doxifluridine relied on glycosylation of Fluorouracil derivative **55**. In particular, 5′-deoxyrybose derivatives **56**, **57**, and **58** were used for that purpose (Scheme 11) [67, 68]. Finally, direct fluorination of 5′-deoxyuridine derivatives with F_2/N_2 [69] or AcOF [70] was also described.

Syntheses of OGT 719 (**33**) relied on glycosylation of the compound **55** (Scheme 12). Reaction of **55** with bromide **59** [71, 72] or acetate **60** [73] gave tetraacetyl derivative **61**, which was transformed to **33** upon deprotection. With **60** as the glycosylating reagent, *in situ* generation of **55** from Fluorouracil was also described [74].



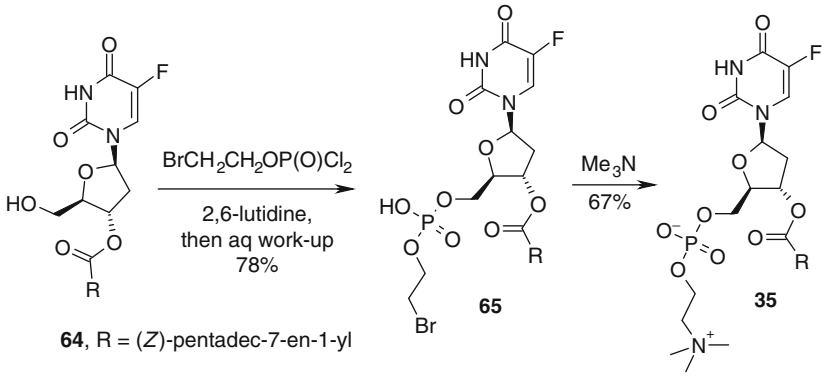
Scheme 12 Synthesis of OGT 719 (**33**)

TT-62 (**34**) was prepared as a free acid (**62**) from **63** which reacted with tosyl-chloride and tetradecylphosphate to give the corresponding phosphodiester, which upon deprotection gave **34** (Scheme 13) [75].



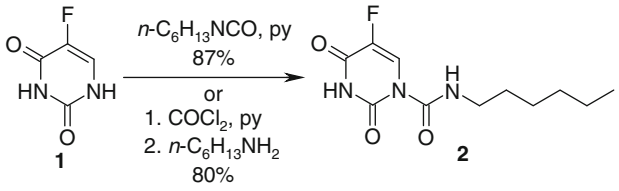
Scheme 13 Synthesis of TT-62 (**34**) as a free acid 62

Synthesis of T-506 (**35**) commenced from Fluorouracil derivative **64** (Scheme 14) [76]. Compound **64** reacted with 2-bromoethyl phosphorodichloridate to give bromide **65**. Compound **65** was transformed to **35** upon reaction with trimethylamine.



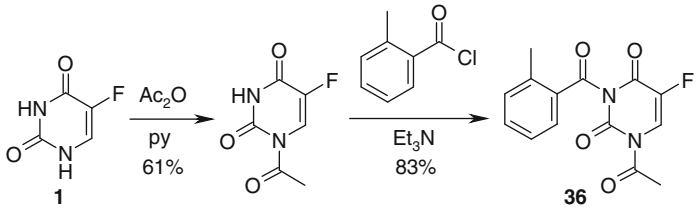
Scheme 14 Synthesis of T-506 (**35**)

Synthesis of Carmofur (**2**) and Atofluding (**36**) was performed in obvious and straightforward manner. Carmofur (**2**) was prepared by reaction of Fluorouracil (**1**) and *n*-hexylisocyanate (Scheme 15) [77, 78]. Alternative approach included reaction of **1** with phosgene and then – with *n*-hexylamine.



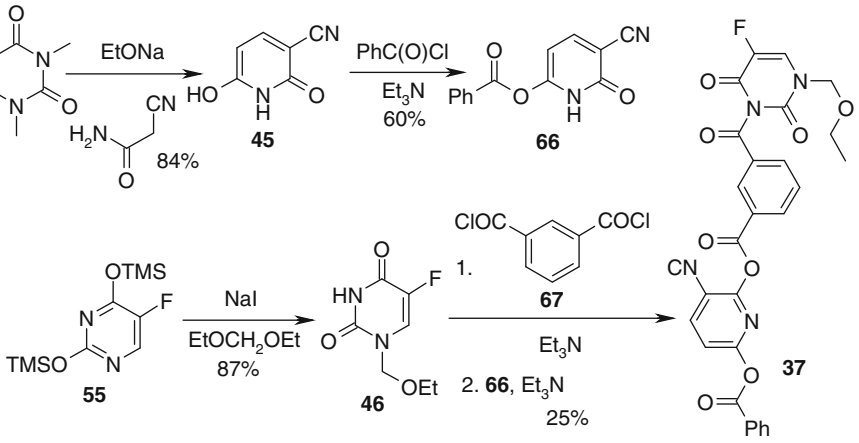
Scheme 15 Synthesis of Carmofur (**2**)

Synthesis of Atofluding (**36**) relied on a stepwise double acylation of Fluorouracil with acetic anhydride and then – with *o*-toluoyl chloride (Scheme 16) [79].



Scheme 16 Synthesis of Atofluding (**36**)

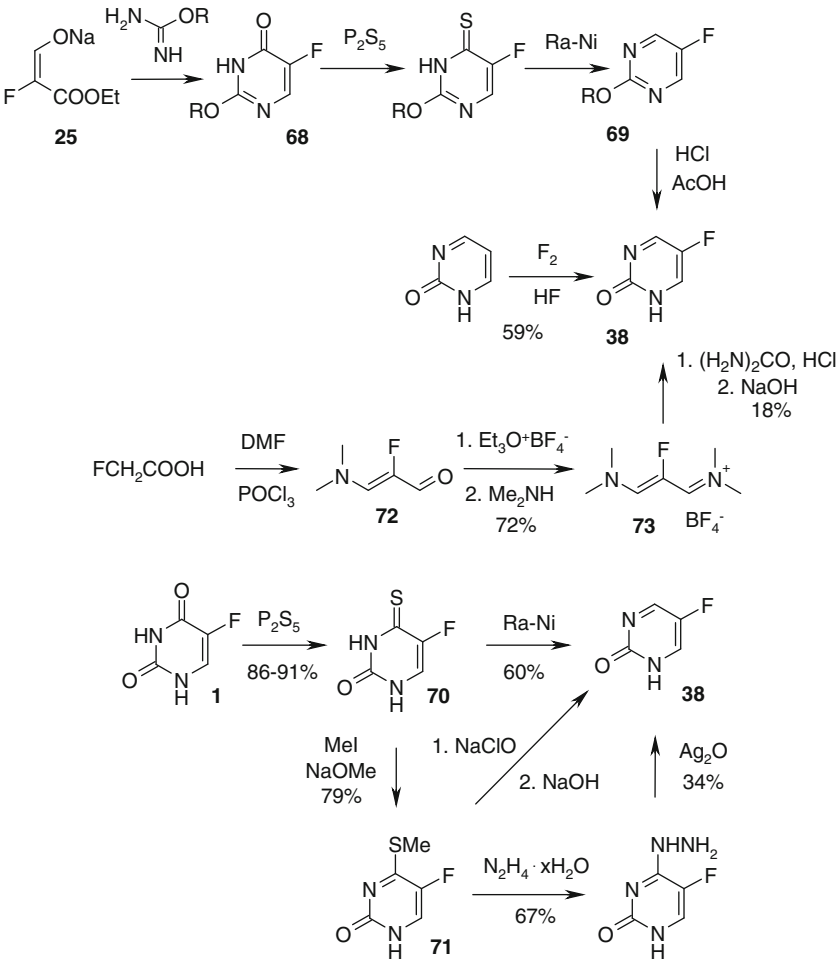
Emitefur (**37**) was obtained by stepwise reaction of building blocks **46**, **67**, and **66** in the presence of triethylamine (Scheme 17) [80–82]. Compound **66** was prepared by benzoylation of 3-cyano-2,6-dihydroxypyridine (**45**), whereas **46** – by ethoxymethylation of the silyl derivative **55**.



Scheme 17 Synthesis of Emitefur (**37**)

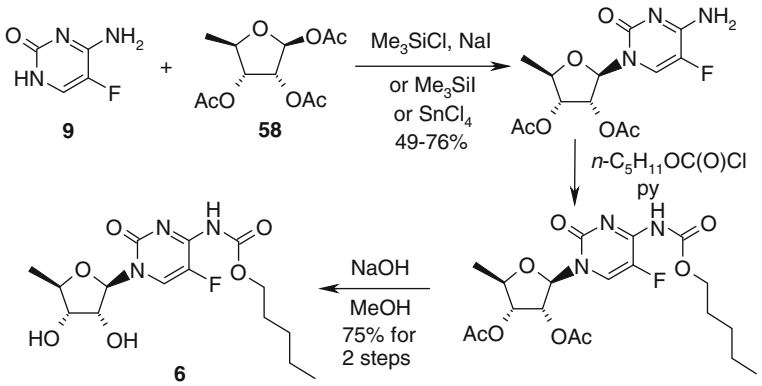
Early syntheses of 5-fluoro-2-pyrimidinone (**38**) relied on desulfurization of Fluorouracil thio-derivatives. In particular, reaction of pyrimidine derivatives **68** with P_2S_5 followed by treatment with Raney nickel and gave alkoxy derivative **69**, which was transformed to **38** upon acidic hydrolysis (Scheme 18) [83]. A more straightforward transformation sequence was also described; including reaction of Fluorouracil (**1**) with P_2S_5 and reduction of thione **70** with Raney nickel [84, 85]. Alternatively, the thione **70** was alkylated to give derivative **71**, which was either oxidated and then hydrolyzed [86] or subjected to reaction with hydrazine and then – silver oxide [301]; in both cases, **38** was obtained. A completely different synthetic scheme commenced from fluoroacetic acid which was subjected to Vilsmeier-type formylation to give 2-fluoro-3-dimethylamino-acrolein (**72**) [87]. Reaction of **72** with triethyloxonium tetrafluoroborate and dimethylamine gave the salt **73**, which led to **38** upon reaction with urea. Finally, **38** was also obtained by direct fluorination of 2-pyrimidinone [88, 89].

Syntheses of Capecitabine (**6**) started from 5-fluorocytosine (**9**) (see further sections for the preparation of **9**, which is used as antifungal drug). In particular, compound **70** reacted with 1,2,3-tri-*O*-acetyl-5-deoxy-β-D-ribofuranose (**58**) to give diacetyl derivative **72**, which was acylated with *n*-pentylchloroformate and then

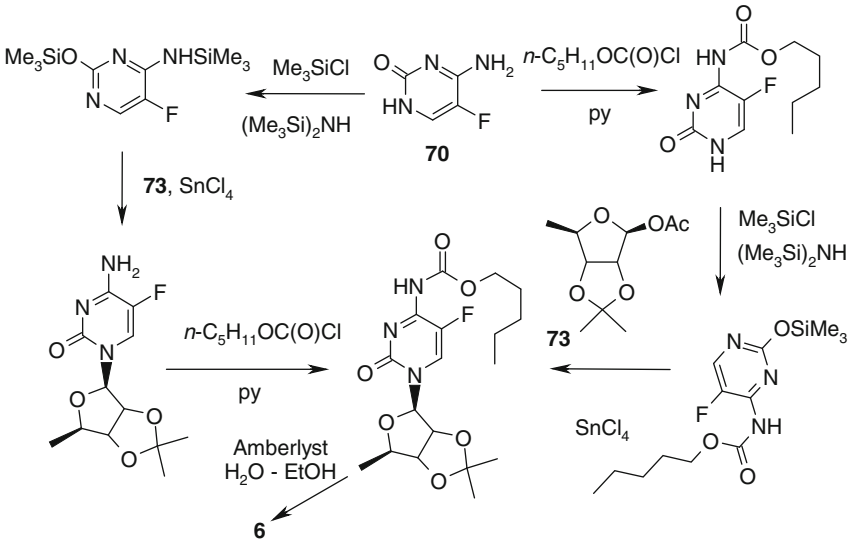


Scheme 18 Syntheses of 5-fluoro-2-pyrimidinone (**38**)

hydrolyzed, resulting in the formation of **6** (Scheme 19) [90–95]. Variations of this method using a silyl derivative of **70** instead of **70** itself [68, 96], as well as 1-*O*-acetyl-2,3-O-isopropylidene-5-deoxy-D-ribofuranose (**73**) (Scheme 20) [96] or 1,2,3-tri-*O*-methoxycarbonyl-5-deoxy-D-ribofuranose [97] as the sugar sources were also reported. Syntheses of Galocitabine (**39**) were performed analogously to that of Capecitabine, 3,4,5-trimethoxybenzoyl chloride being used instead of *n-pentylchloroformate* at the corresponding steps [68, 89, 90, 98].



Scheme 19 Synthesis of Capecitabine (**6**) using 58 as the starting material



Scheme 20 Synthesis of Capecitabine (**6**) using 73 as the starting material

3.3 Other Antimetabolites

Apart from Floxuridine, Fluorouracil and its pro-drugs, there are two additional examples of anti-cancer agents which also act as antimetabolites and have reached clinical development phase, *i.e.* both Trifluridine (**7**) (as a component of TAS-102) and FTC-092 (**74**) (Fig. 4) were developed by Taiho Pharmaceutical. These

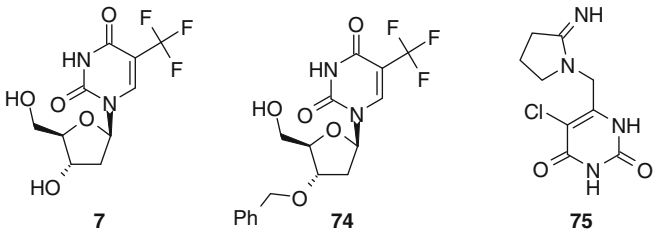
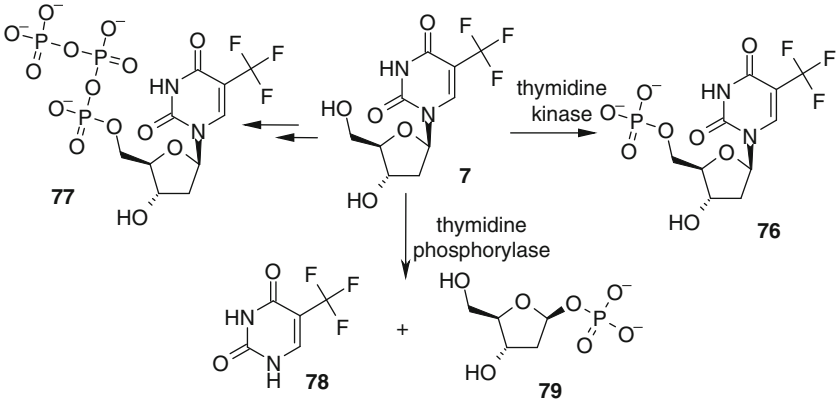


Fig. 4 Drug substances of TAS-102 (**7**, **75**) and FTC-092 (**74**)

compounds are derivatives of α,α,α-trifluorothymine and are thus structurally related to Fluorouracil. Trifluridine was approved by FDA as an ophthalmic drug against herpes virus in 1995 (see also further sections) [5]; it is now being investigated in Phase III clinical trials as a component of anti-cancer drug TAS-102 (which is a combination of **7** and Tipiracil (**75**)) [99] FTC-092 was evaluated for antitumor activity in Phase I clinical trials [3].

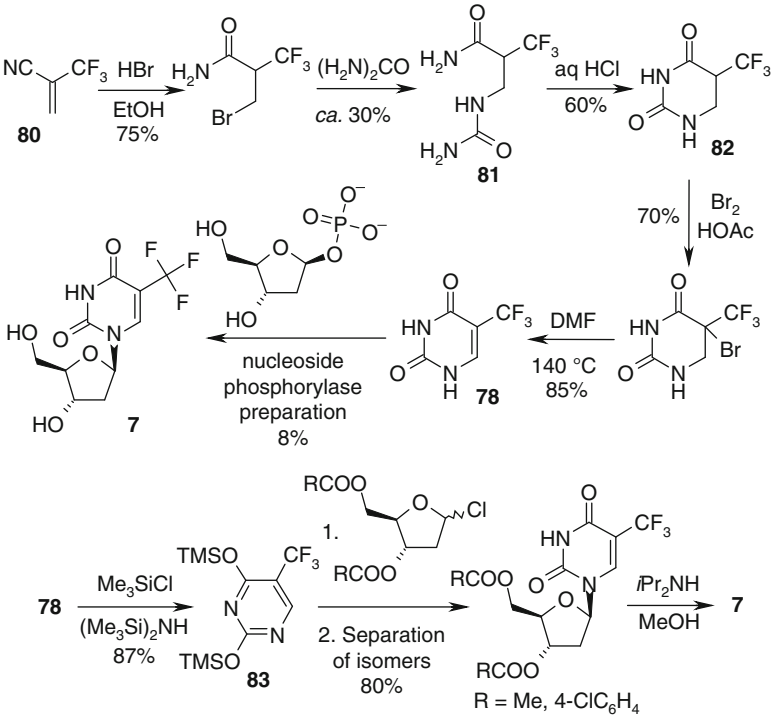
The active principle of both TAS-102 and FTC-092 with anti-cancer effect is Trifluridine (**7**). As in the case of Fluorouracil, one of the mechanisms by which compound **7** exhibits its antitumor activity is inhibition of thymidylate synthase [100]. More precisely, Trifluridine is transformed into α,α,α-trifluorothymidine monophosphate (**76**) by thymidine kinase (Scheme 21); similarly to the Fluorouracil derivatives discussed in the previous sections, compound **76** is true inhibitor of thymidylate synthase. However, compound **7** exhibits an anticancer effect on colorectal cancer cells that have acquired Fluorouracil resistance as a result of the overexpression of thymidylate synthase.



Scheme 21 Metabolic transformations of Trifluridine (**7**)

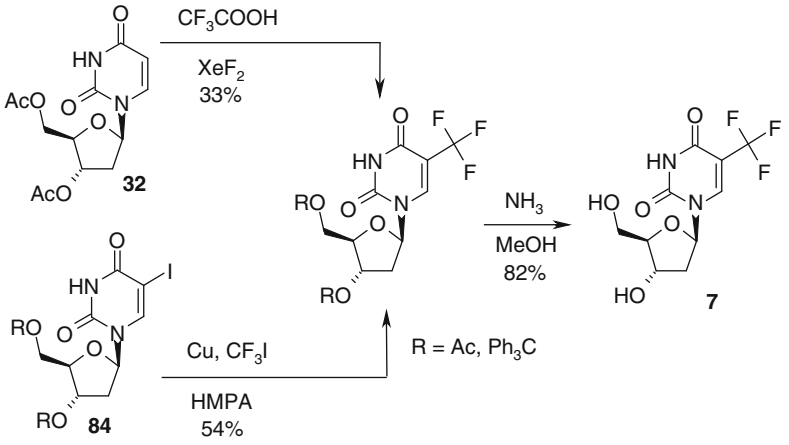
Therefore, an alternative mechanism of action is also in operation, namely, incorporation of α,α,α-trifluorothymidine triphosphate (**77**) into DNA, which results in single-strand breaks, followed by double-strand breaks when the cells progress to a subsequent DNA replication phase [101] The major drawback of Trifluridine (**7**) is its high susceptibility to biodegradation, which is catalysed by thymidine phosphorylase and gives α,α,α-trifluorothymine (**78**) and 2-deoxy-α-D-ribose 1-phosphate (**79**) [102]. In the case of TAS-102, this issue is overcome by co-administration of thymidine phosphorylase inhibitor Tipiracil (**75**) [103], whereas improved biological effect of FTC-092 upon oral administration is achieved by its gradual biotransformation, mainly through the action of liver microsomes, releasing **7** over a long period [104].

The first synthesis of Trifluridine commenced from trifluoromethylacrylonitrile (**80**) which reacted with HBr and then with urea to give amide **81** in moderate yield. Hydrolysis of **81** was accompanied by cyclization and led to dihydropyrimidine **82** (Scheme 22). Two-step aromatization of **81** gave α,α,α-trifluorothymine (**78**). Compound **78** was transformed to **7** in low yield (8 %) by enzymatic glycosylation [105]. The yield of the last step in this sequence was significantly improved when **78** was preliminarily transformed to bis-silyl derivative **83**, and chloride **84** was used for glycosylation [106, 107].



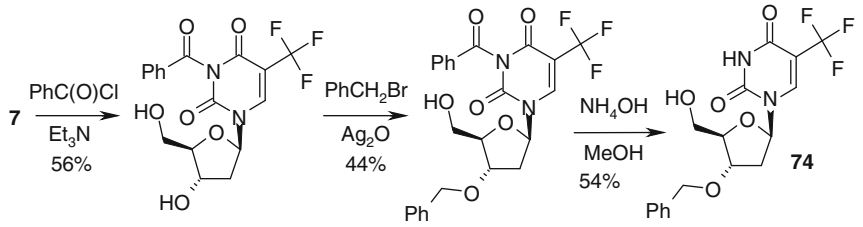
Scheme 22 Syntheses of Trifluridine (**7**) via α,α,α-trifluorothymine (**78**)

An alternative approach to **7** was based on direct trifluoromethylation of the corresponding deoxyuridine derivatives **32** or **84**, using CF_3COOH–XeF_2 [108] and CF_3I–Cu–HMPA [109] as the reagents, respectively (Scheme 23).

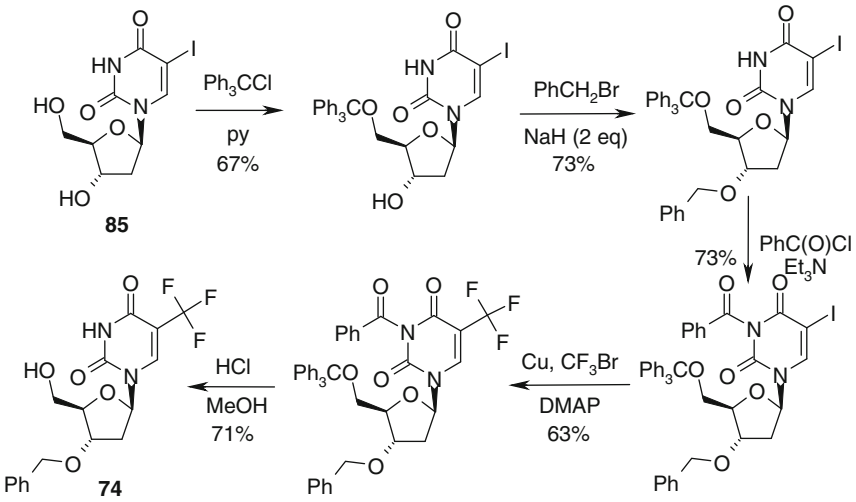


Scheme 23 Syntheses of Trifluridine (**7**) via trifluoromethylation of deoxyuridines

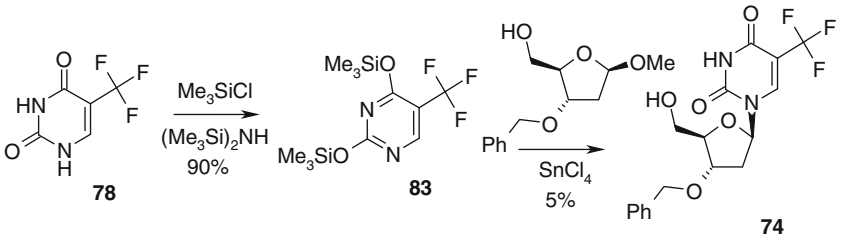
FTC-092 (**74**) was prepared by regioselective benzylation of Trifluridine (**7**) (Scheme 24) [110]. As in the case of **7**, direct trifluoromethylation was also used for synthesis of **74**. The following sequence was established as the most practical: tritylation of 2′-deoxy-5-iodouridine (**85**), 3′-*O*-benzylation, N^3-benzoylation, cross-coupling reaction with CF_3Cu reagent, and acidic deprotection (Scheme 25) [111]. Alternatively, **74** was prepared in low yield by glycosylation of α,α,α-trifluorothymine using the bis-silyl derivative **83** (Scheme 26) [112].



Scheme 24 Synthesis of FTC-092 (**74**) from Trifluridine (**7**)



Scheme 25 Synthesis of FTC-092 (**74**) using direct trifluoromethylation



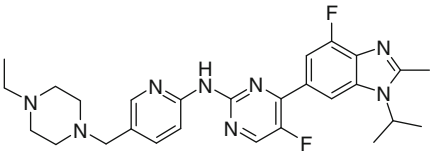
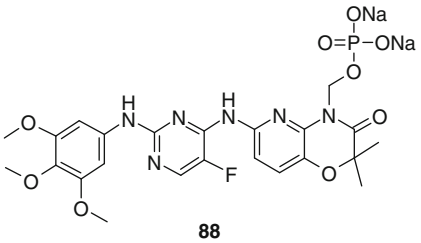
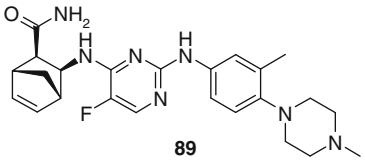
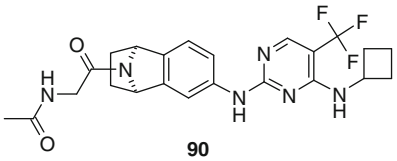
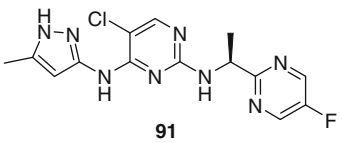
Scheme 26 Synthesis of FTC-092 (**74**) from α,α,α-trifluorothymine derivative 83

3.4 Kinase Inhibitors

An approach to cancer treatment which relies on using fluorinated uracil analogues as antimetabolites is the most recognised in the field of fluorinated diazines relevant to medicinal chemistry. However, other strategies are also gaining momentum; in particular, several compounds which act as kinase inhibitors (*i.e.* **87**–**92**) have reached clinical development phase (Table 2).

Compound LY-2835219 (**87**) is currently being developed by Eli Lilly and Co.; monomesylate salt of **87** has entered Phase I clinical trials in patients with advanced cancer in 2011 [113]. It acts as a potent oral inhibitor of the cyclin-dependent kinases 4 and 6 (CDK4/6), playing a key role in regulating cellular proliferation [114]. In particular, these cyclin D-dependent kinases facilitate progression of gap 1 cell cycle phase (G_1) by phosphorylating retinoblastoma susceptibility protein (Rb), which prevents association of Rb with E2F transcription factor, and thus relieves transcriptional repression by the Rb-E2F complex. In addition, these

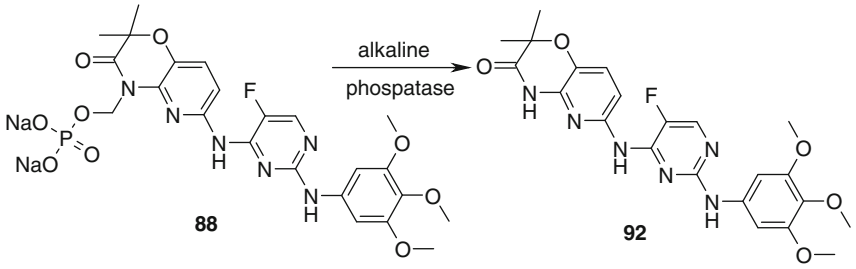
Table 2 Fluorinated diazines as kinase inhibitors in clinical development phase [113]

Structure	INN or ID, development phase, company	Target
 **87**	LY-2835219 Phase I Eli Lilly	CDK4/6
 **88**	Fostamatinib disodium Phase II Rigel, AstraZeneca	Syk
 **89**	R-763, AS-703569 Phase I Rigel, Merck Serono	Aurora kinases
 **90**	PF-03814735 Phase I Pfizer	Aurora kinases
 **91**	AZD-1480 Phase I AstraZeneca	JAK2

kinases also sequester CDK interacting and kinase inhibitory proteins (Cip/Kip) from their complexes with cyclin-dependent kinase 2 (CDK2), facilitating activation of CDK2 with cyclin E [115] Monomesylate salt of **87** inhibits CDK4 and CDK6 with IC50 values of 2 and 10 nM, respectively; moreover, it is able to cross blood-brain barrier and therefore has the potential for the treatment of brain tumors and metastases [114].

Fostamatinib disodium (Tamatinib fosdium, **88**), which is prodrug of Tamatinib (**92**) (Scheme 27), was discovered by Rigel; it is currently studied in Phase II clinical trials by Rigel and Astra Zeneca Plc. for treatment of B-cell lymphoma [113]. Apart from that, compound **88** is also investigated as agent for treatment of autoimmune thrombocytopenia and rheumatoid arthritis. Because of its poor pharmaceutical properties, Tamatinib (**92**) is orally administered as the methylene phosphate

prodrug **88**. Fostamatinib disodium (**88**) is quickly cleaved to **92** by alkaline phosphatases that are present on the apical brush-border membranes of the intestinal enterocytes, after which the more hydrophobic **92** can be readily absorbed [116].



Scheme 27 Metabolic activation of Fostamatinib disodium (**88**)

Tamatinib (**92**) acts as an ATP-competitive inhibitor of Spleen tyrosine kinase (Syk) – a non-receptor tyrosine kinase which is a key component of the B-cell receptor (BCR) signaling pathway [117]. It is shown that BCR-mediated signaling through Syk occurs to a greater degree and for a longer duration in neoplastic cells than in nonmalignant B-cells. Inhibition of the Syk pathway prevents chronic lymphocytic leukemia (CLL) cells from interacting with the microenvironment, and promotes proapoptotic signals.

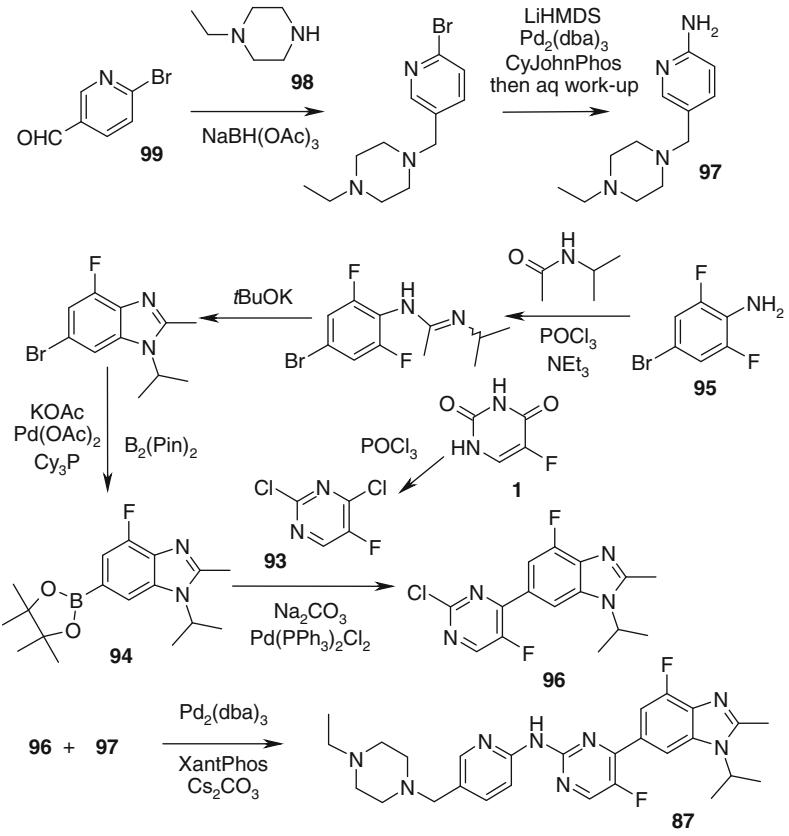
R-763 (**89**), also known as AS-703569, is another kinase inhibitor discovered by Rigel. It was investigated in Phase I clinical trials for several types of tumors by Rigel and Merck Serono; the latest study was terminated in 2012, concerning a review of the available clinical data and low probability of completing the trial based on the observed recruitment rate [113]. Compound **89** inhibits Aurora kinases –serine/threonine kinases which are essential for cell proliferation, mainly due to regulation of gap 2 and mitotic cell cycle phases (G_2/M). Over-expression of Aurora kinases is found in several human cancers and correlated with histological malignancy and clinical outcomes. Although the biological functions of two types of Aurora kinases (A and B) are different, in both cases their inhibition induces apoptosis of the cell, leading to similar phenotypes. Some other kinases are also inhibited by **89**, in particular Fms-like tyrosine kinase 3 (FLT3) [118].

One more Aurora kinase inhibitor – PF-03814735 (**90**) – was developed by Pfizer; it has been investigated in Phase I clinical trials for treatment of solid tumors (the study completed in 2012) [113]. PF-03814735 was generally well tolerated with manageable toxicities, and a recommended phase II dose could be established; however, clinical or metabolic antitumour activity was limited [119]. Similarly to R-763 (**89**), compound **90** inhibits both Aurora A and B kinases; other kinases are affected to a lesser extent [120]. Therefore, PF-03814735 (**90**) produces a block in cytokinesis, resulting in inhibition of cell proliferation and the formation of polyploid multinucleated cells.

AZD-1480 (**91**) was developed by AstraZeneca and studied in Phase I clinical trials for treatment of advanced solid malignancies (the study terminated in 2012) [113]. AZD-1480 is an ATP-competitive inhibitor of Janus kinase 2 (JAK2) – an

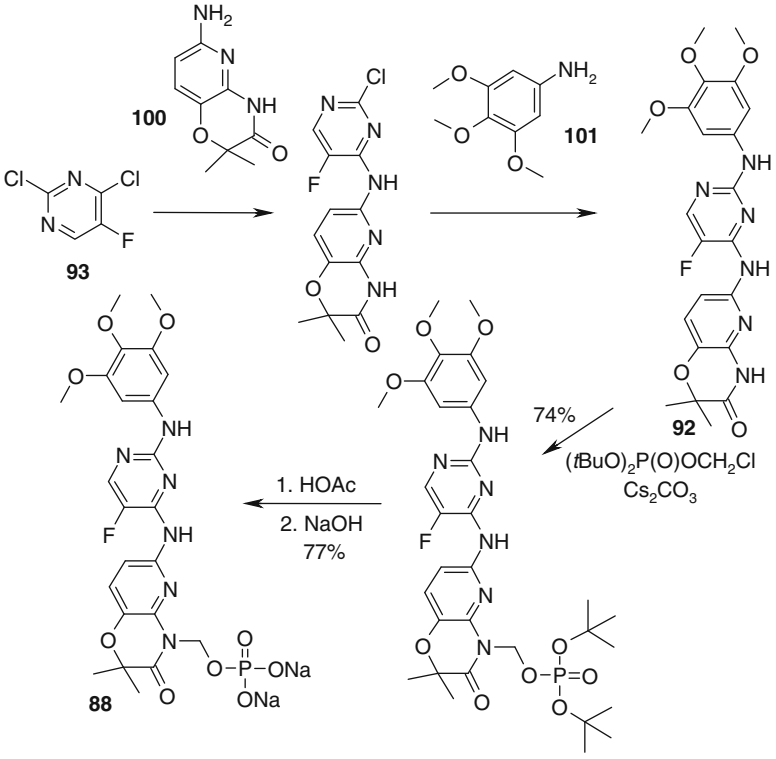
intracellular non-receptor tyrosine kinase that transduce cytokine-mediated signals via the Janus kinase – signal transducer and activator of transcription (JAK–STAT) signaling pathway. In particular, inhibition of JAK2 blocks Stat3 signaling, associated with chronic cytokine stimulation in some tumors [121]. X-Ray diffraction study of complex formed by **91** and JAK2 shows that the donor-acceptor-donor hydrogen-bonding motif provided by aminopyrazole fragment forms three hydrogen bonds with an adenine binding pocket, whereas the fluoropyrimidine ring occupies a nearby hydrophobic pocket [122].

Synthesis of LY-2835219 (**87**) relied on selective functionalization of 2,4-dichloro-5-fluoropyrimidine (**93**), which can be easily obtained from Fluorouracil (**1**) (Scheme 28) [123]. First, boronic ester **94** was prepared from aniline **95** in three steps, including benzimidazole ring construction and palladium-catalyzed coupling with pinacol diborane. Suzuki-type reaction of **93** and **94** resulted in selective functionalization at C-4 of the pyrimidine ring and gave chloride **96**. Buchwald-Hartwig coupling of **96** with amine **97** (prepared in two steps from 1-ethylpiperazine (**98**) and (**99**)) gave the final product **87**.



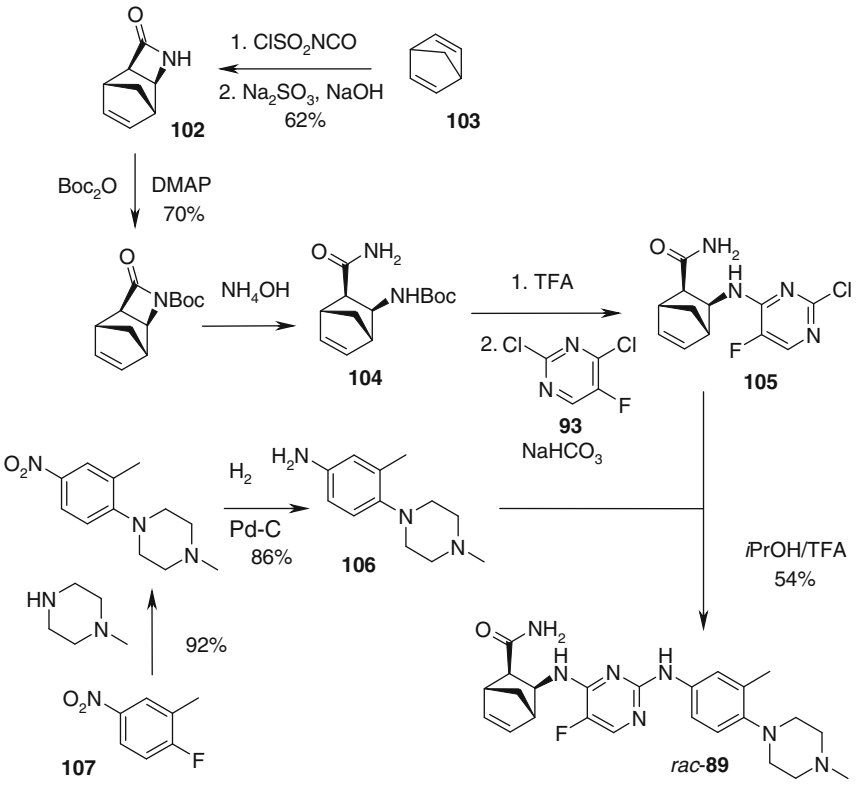
Scheme 28 Synthesis of LY-2835219 (**87**)

Analogously, selective functionalization of **93** was used for the preparation of Fostamatinib disodium (**88**) (Scheme 29). In particular, reaction of **93** with equimolar amount of amine **100** and then – with 3,4,5-trimethoxyaniline (**101**) gave Tamatinib (**92**) [124]. It should be noted that no detailed procedures of performing these transformations were given in the initial patent; moreover, synthesis of the starting compound (amine **100**) is not documented to date. To obtain Fostamatinib disodium (**88**), compound **92** was treated with chloride **102** and Cs_2CO_3; further deprotection subsequent and salt formation gave the target product **88** [125].



Scheme 29 Synthesis of Fostamatinib disodium (**88**)

Similar approach was used for the synthesis of R-763 (**89**) (Scheme 30) [126]. In this case, lactam **102**, which was obtained from norbornadiene (**103**) and Graf isocyanate ($ClSO_2NCO$), was protected with Boc_2O and then subjected to ring-opening with aqueous ammonia to give amide **104**. Deprotection of **104** followed by arylation with **93** gave an intermediate **105**, which was then treated with *N*-arylpiperazine derivative **106** (prepared in two steps from 4-fluoro-3-methylnitrobenzene (**107**)) to give racemic **89**. Optically pure **89** was obtained either by chiral stationary phase HPLC applied at different steps of the synthesis, or *via* enzymatic resolution of Boc-protected lactam **102**.

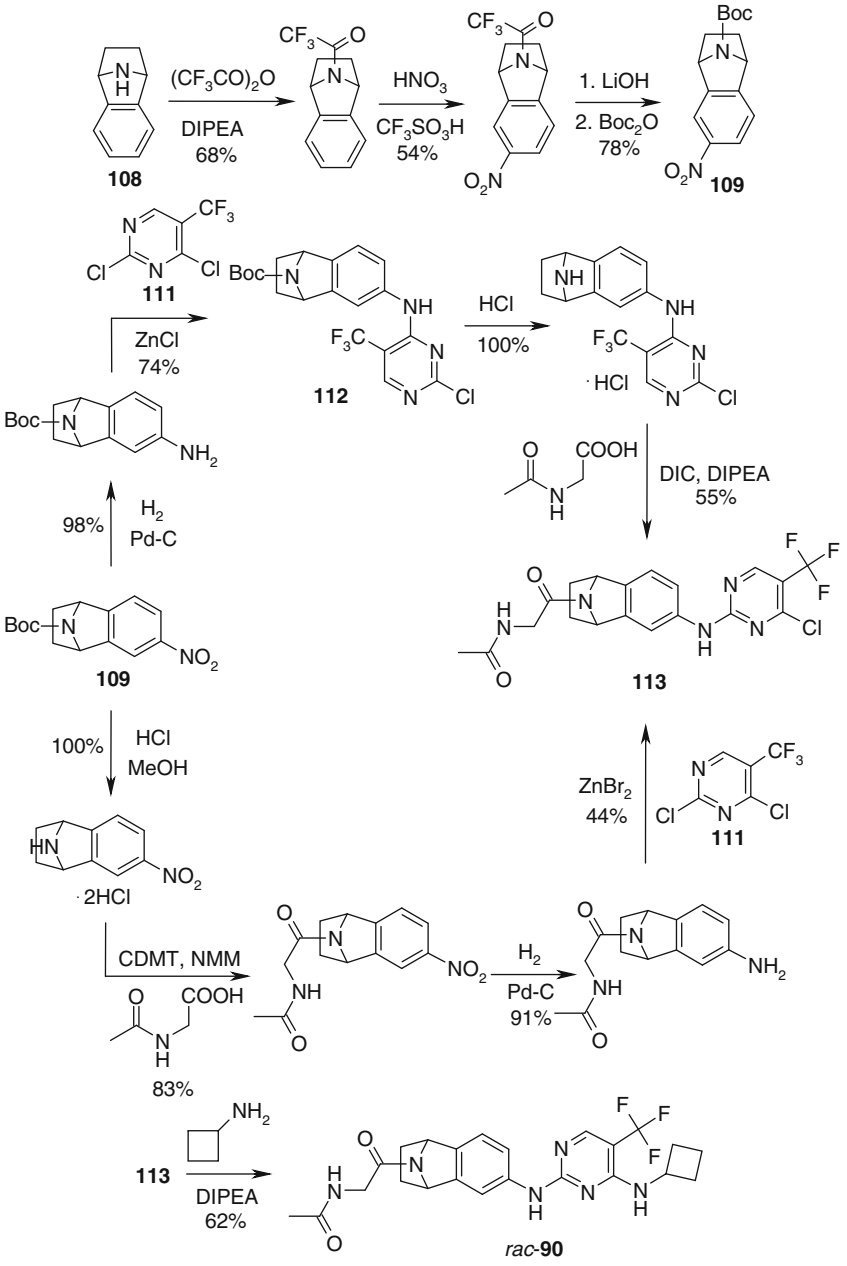


Scheme 30 Synthesis of racemic R-763 (rac-**89**) (Relative configurations are shown)

It is not surprising that synthesis of PF-03814735 (**90**) also followed analogous strategy, 2,4-dichloro-5-trifluoromethylpyrimidine (**111**) being used as a key fluorinated diazine building block instead of **93** (Scheme 31) [302]. The synthetic scheme commenced from amine **108** which was *N*-trifluoroacetylated, then nitrated, and subjected to a change of the protecting group to give Boc derivative **109**. Two alternative pathways were developed for further transformations. In the first one, compound **109** was reduced into fused aniline derivative **110** which reacted with **111** to give compound **112**. Deprotection of **112** followed by coupling with *N*-acetylglycine led to the formation of chloride **113**.

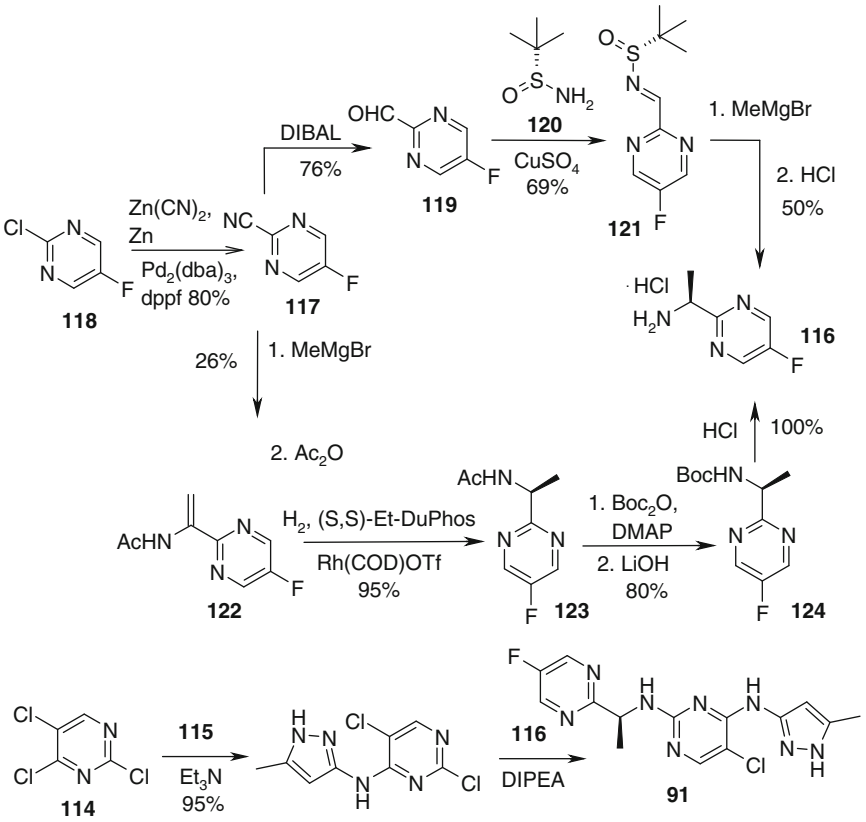
Alternatively, compound **109** was deprotected, coupled with *N*-acetylglycine, reduced catalytically and then arylated with **111** to give **113**. Finally, compound **113** reacted with cyclobutyl amine to give the final product **90** as racemate. Both enantiomers of **90** were also obtained using this scheme if Boc derivative **109** was subjected to chiral stationary phase HPLC prior further transformations.

Although a similar strategy was used for the preparation AZD-1480 (**91**), in this case the fluorinated diazine moiety is not in a central part of the molecule; hence a different approach was used for the construction of the fluorinated



Scheme 31 Synthesis of racemic PF-03814735 (rac-**90**)

pyrimidine fragment. As in the previous syntheses discussed in this section, **91** was obtained by selective functionalization of 5-substited 2,4-dichloropyrimidine derivative (*i.e.* **114**), first by reaction with aminopyrazole **115** and then – with chiral amine **116** (Scheme 32) [122, 127]. For the preparation of enantiopure **116**, two approaches were developed, both starting from nitrile **117**, in turn prepared from 2-chloro-5-fluoropyrimidine (**118**) [127]. In the first method, compound **117** was reduced with DIBAL into aldehyde **119**, which reacted with Ellman's sulfinamide **120** to give imine **121**. Reaction of **121** with MeMgBr and subsequent deprotection led to the formation of **116**. Alternatively, **117** was treated with MeMgBr and then – Ac_2O to give enamine derivative **122**, which was subjected to enantioselective rhodium-catalyzed hydrogenation with (*S*,*S*)-Et-DuPhos as a chiral ligand. The resulting chiral amide **123** was obtained with more than 99 % *ee*. After a change of the protecting group, Boc derivative **124** was deprotected to give the target amine hydrochloride **116**.



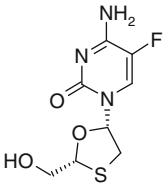
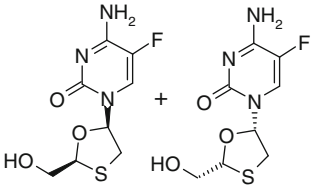
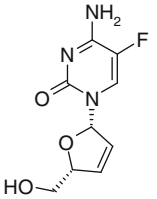
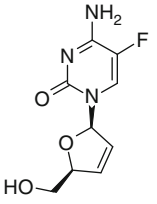
Scheme 32 Synthesis of AZD-1480 (**91**)

4 Antiviral, Antibacterial and Antifungal Agents

4.1 Anti-HIV Agents

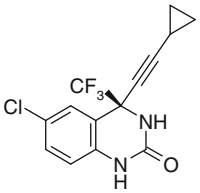
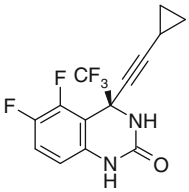
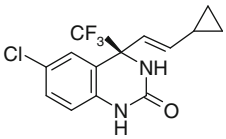
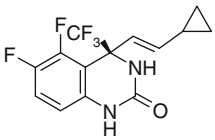
The fight against HIV infection is another important field where fluorinated diazines have remarkable record, including approved drug Emricitabine (**8**) and 7 compounds that have reached clinical development phase (compounds **125**–**131**) (Table 3). All these compounds act as HIV reverse transcriptase inhibitors and fall into two categories: fluorocytidine analogues (**8** and **125–127**) and trifluoromethyl-substituted quinazolone derivatives (**128**–**131**).

Table 3 Anti-HIV drugs – derivatives of fluorinated diazines [5, 113]

Structure	INN or ID, development phase	Company
 **8**	Emtricitabine Launched (2003)	Emory University, Gilead Sciences
 **8** **125**	Racivir Phase II	Pharmasset
 **126**	Elvucitabine Phase II	Yale University, Achillion Pharmaceuticals
 **127**	Dexelvucitabine Phase II	Emory University, Incyte Co.

(continued)

Table 3 (continued)

Structure	INN or ID, development phase	Company
 **128**	DPC-961 Phase I	DuPont Pharmaceuticals
 **129**	DPC-963 Phase I	DuPont Pharmaceuticals
 **130**	BMS-561390, DPC-083 Phase II	DuPont Pharmaceuticals, Bristol-Myers Squibb
 **131**	DPC-082 Phase I	DuPont Pharmaceuticals

Emtricitabine (**8**) was discovered in Emory University (Atlanta, USA); development of the drug was completed by Gilead Sciences, and the compound was approved by FDA under trade name Emtriva® in 2003. It is also marketed in combinations with other anti-HIV agents, *i.e.* Tenofovir (**132**, used as a prodrug) (Truvada®), Efavirenz (**133**) and Tenofovir (Atripla®), Rilpivirine (**134**) and Tenofovir (Complera®), and Elvitegravir (**135**), Cobicistat (**136**), and Tenofovir (Stribild®) [5] Emricitabine is a close analogue of Lamivudine (**137**), which is an example of nucleoside analogs – an important class of reverse transcriptase inhibitors, which has gained much attention since the initial success of the first representative, Zidovudine (**138**) [128] (Fig. 5).

Emtricitabine (**8**) was discovered in Emory University (Atlanta, USA); development of the drug was completed by Gilead Sciences, and the compound was approved by FDA under trade name Emtriva® in 2003. It is also marketed in

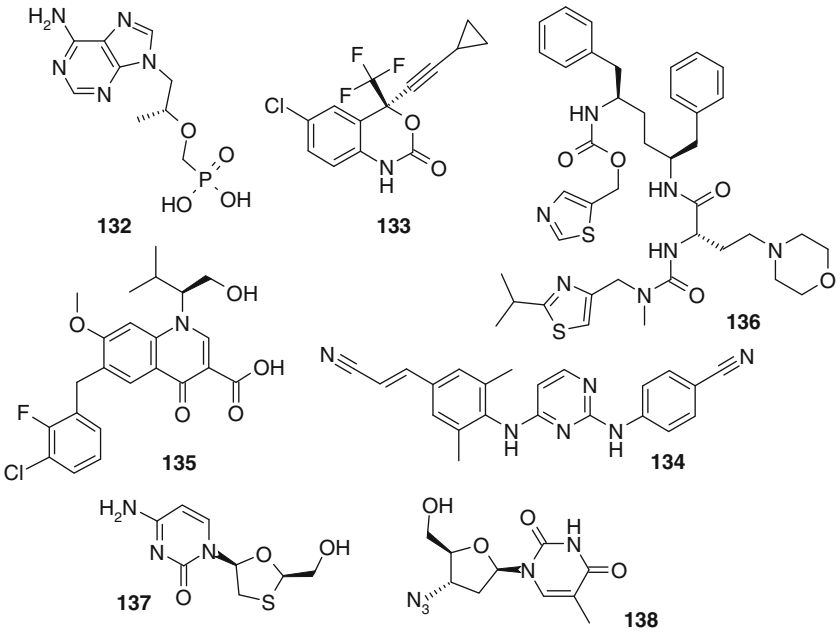
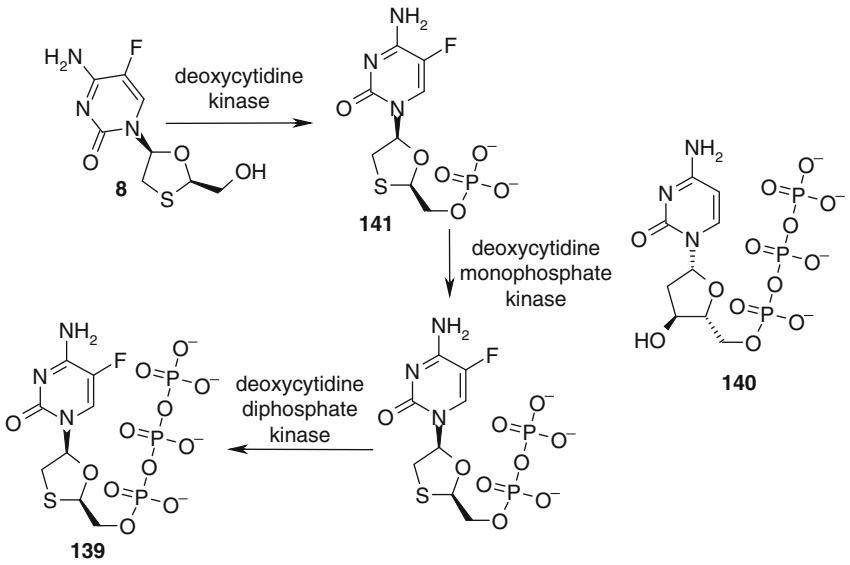


Fig. 5 Some active ingredients of anti-HIV drugs

combinations with other anti-HIV agents, *i.e.* Tenofovir (**132**, used as a prodrug) (Truvada®), Efavirenz (**133**) and Tenofovir (Atripla®), Rilpivirine (**134**) and Tenofovir (Complera®), and Elvitegravir (**135**), Cobicistat (**136**), and Tenofovir (Stribild®) [5] Emricitabine is a close analogue of Lamivudine (**137**), which is an example of nucleoside analogs – an important class of reverse transcriptase inhibitors, which has gained much attention since the initial success of the first representative, Zidovudine (**138**) [128].

Emtricitabine (**8**) is very similar to Lamivudine (**137**) with respect to its activity, convenience, safety and resistance profile; the only remarkable difference is longer intracellular half-life of **8**. Analogously to **137**, the biologically active form of **8** is triphosphate **139**, which is formed by a stepwise phosphorylation of **8** (Scheme 33). Compound **139** can be considered as 2,3-dideoxycytidine trifosphate analogue and acts as a competitive inhibitor and alternate substrate of the normal deoxycytidine triphosphate (**140**). As a competitive inhibitor of the normal substrate, **139** inhibits incorporation of **140** into the growing DNA chain by viral reverse transcriptase; as an alternate substrate, it is incorporated into this chain (as **141**) and acts as a chain terminator (since **141** is missing the 3′-hydroxyl group required for further chain elongation) [128, 129].



Scheme 33 Metabolic activation of Emtricitabine (**8**)

Although Emtricitabine might have the potential for toxicity caused by interaction with human mitochondrial DNA enzymes, both *in vitro* and *in vivo* testing results show that this is not a serious issue. Low toxicity of **8** as compared to other nucleoside reverse transcriptase inhibitors is a remarkable advantage of this drug. As with all representatives of this class, the major drawback of **8** is rapid development of drug resistance by a single point mutation of viral reverse transcriptase [129]. The main route of elimination of **8** is renal excretion, mostly unchanged (86 % of the dose). The metabolic transformations of Emtricitabine include oxidation of the sulphur atom to form the 3′-sulfoxide diastereomers (9 %) and conjugation with glucuronic acid to give 2′-*O*-glucuronide (4 %) [130].

A racemic form of Emtricitabine, Racivir, was also studied in clinics by Pharmasset and has reached Phase II trials [113], designed to measure its efficacy in patients harbouring virus resistant to Lamivudine. It was shown that *D*(+)-enantiomer **125** is less potent and more toxic than Emtricitabine itself. One of the reasons behind lower potency of **125** is that **8** is phosphorylated by deoxycitidine kinase to a greater extent; therefore, the active form (**139**) is formed more readily for (–)-enantiomer [131, 132].

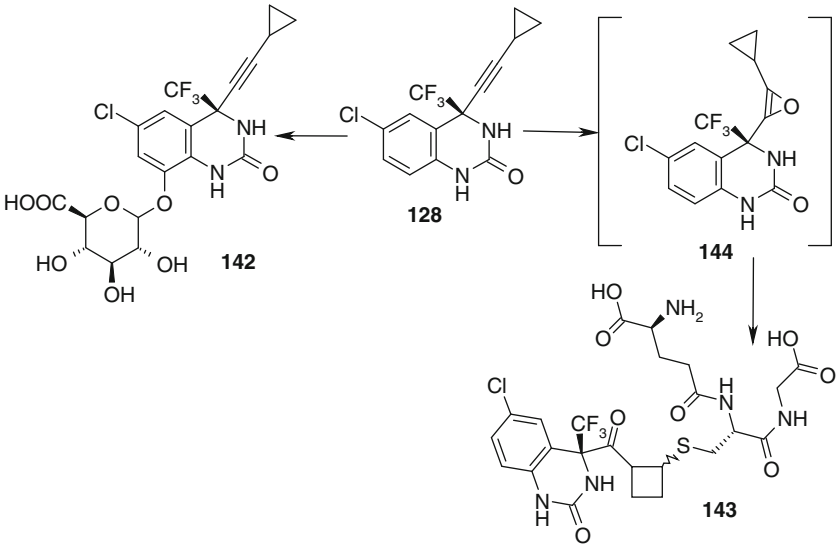
Elvucitabine (**126**) and its enantiomer Dexelvucitabine (**127**) were discovered in Yale University (New Haven, USA) and Emory University (Atlanta, USA), respectively. Both compounds were further developed by commercial companies (Achillion Pharmaceuticals and Incyte Co., respectively), and have reached Phase II clinical trials [113]. Development of **127** was terminated due to inability to pair with other cytidine analogues and higher risk of hyperlipasemia. Phase II studies of **126** were suspended because of bone marrow suppression in several patients [133]. The

mode of action of Elvucitabine is quite similar to that of Emtricitabine; the major advantages of **126** include long plasma half-life (up to ten times greater than that of **8**) and superior potency against common resistance mutations [134].

Four compounds DPC-961 (**128**), DPC-961 (**129**), DPC-083 (**130**), and DPC-082 (**131**) were developed by DuPont Pharmaceuticals as non-nucleoside reverse transcriptase inhibitors. Al the compounds have reached Phase I clinical trials; DPC-083 (**130**) was further progressed into Phase II trials by Bristol-Myers Squibb after the company had acquired DuPont Pharmaceuticals; however, the development was stopped in 2003 due to poor pharmacokinetics [135]. The compounds are close analogues of Efavirenz (**133**) – a non-nucleoside reverse transcriptase inhibitor approved by FDA in 1998 [5]. All the compounds **128**–**131** showed similar to Efavirenz activity towards wild-type virus *in vitro*; however, they were more effective towards single-mutation variants and showed lower plasma serum protein binding [136, 137].

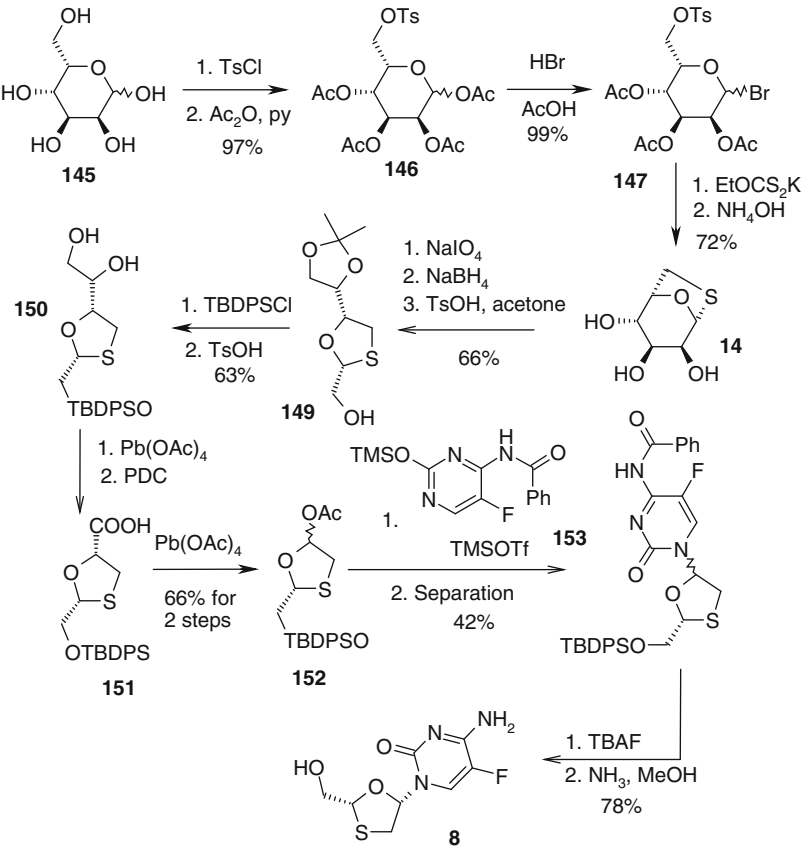
It might be assumed that mechanism of action of **128**–**131** is similar to that of Efavirenz, which is known to bind within the non-nucleoside inhibitor binding pocket of reverse transcriptase [138], both spatially and also functionally associated with the substrate-binding site.

Metabolism of DPC-961 (**128**) was studied in rats. Analogously to Efavirenz, the main metabolite is glucuronide conjugate **142** (more than 90 % of excreted dose in the bile) (Scheme 34). However, a glutatione conjugate **143** was also isolated, which is presumably formed via oxirene intermediate **144**; in this view, metabolism of **128** was different from that of **133** [139].



Scheme 34 Main metabolites of DPC-961 (**128**) in rats

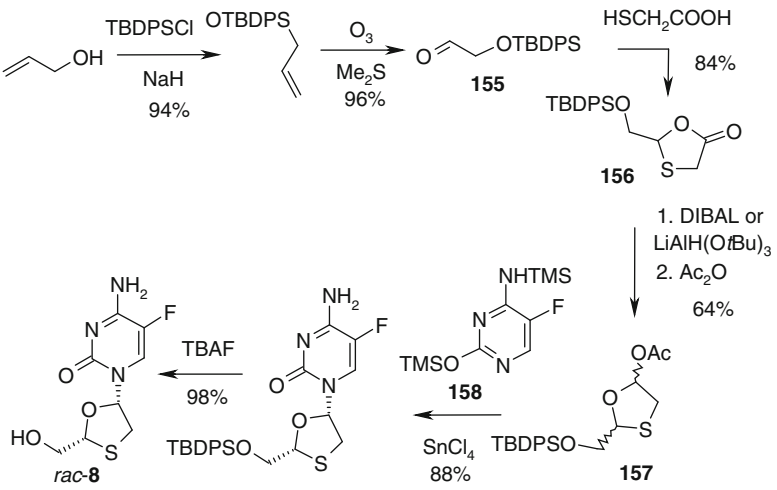
Early synthesis of Emtricitabine (**8**) commenced from L-gulose (**145**) (Scheme 35) [140]. Selective tosylation of **145** followed by acetylation gave **146**. Treatment of **146** with HBr in AcOH yielded the bromo derivative **147**, which was refluxed with *O*-ethylxanthate and then deacetylated using NH_4OH in MeOH to obtain the 1,6-thioanhydro-L-gulopyranose (**148**). Selective oxidative cleavage of vicinal *cis* diol in **148** by $NaIO_4$ and reduction with $NaBH_4$, followed by protection of the resulting diol as the acetonide yielded the 1,3-oxathiolane derivative **149**. Silyl protection of the hydroxyl group followed by deprotection of the isopropylidene moiety afforded derivative **150**. Oxidative cleavage of vicinal diol **150** by $Pb(OAc)_4$ followed by pyridinium dichromate (PDC) oxidation gave the acid **151**. Treatment of **151** with $Pb(OAc)_4$ – pyridine in anhydrous THF afforded acetate **152**. Reaction of **152** with fluorocytosine derivative **153**, separation of anomers and subsequent deprotection gave **8**. The same



Scheme 35 Early synthesis of **8**

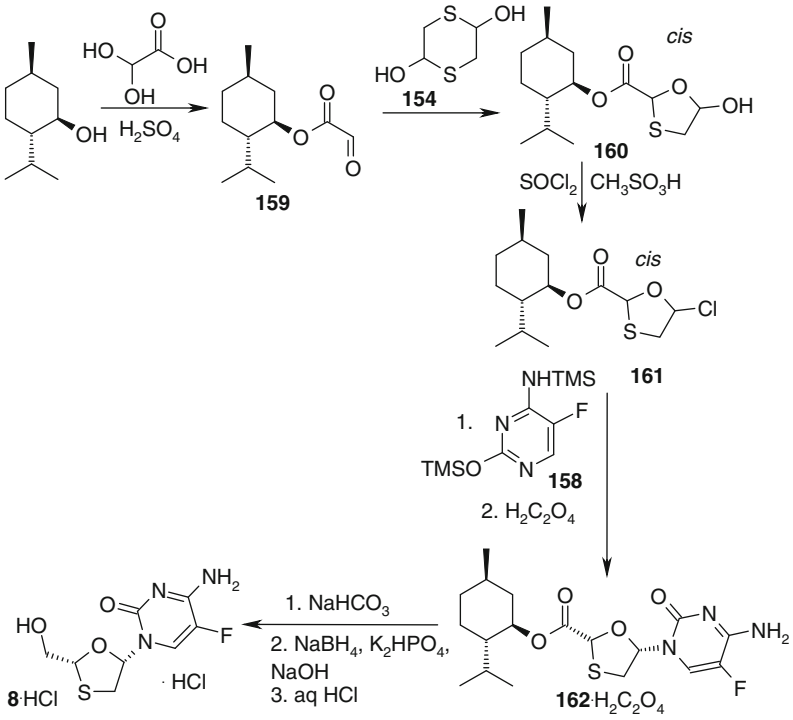
approach starting from D-mannose or D-galactose was used for the preparation of D-enantiomer **125** [141].

Most of the methods describing the preparation of Emtricitabine (and Racivir) rely on the construction of 1,3-oxathiolane ring by reaction of glycolaldehyde or glyoxalic acid derivatives with mercaptoacetic acid or mercaptoacetic aldehyde (which exists as 1,4-ditiane **154**). For example, one of the first of syntheses of this type commenced from allyl alcohol which was silylated and then subjected to ozonolysis to give glycolaldehyde derivative **155** (Scheme 36) [142]. Reaction of **155** with mercaptoacetic acid afforded 1,3-oxathiolane **156**, which was reduced with $LiAlH(OtBu)_3$ or DIBAL and then acetylated to form **157**. Finally, reaction of **157** with silylated fluorocytosine derivative **158** followed by deprotection led to the formation of racemic **8** (Racivir).



Scheme 36 Synthesis of racemic **8** (Racivir) patented by Emory University (Relative configurations are shown)

More than 15 preparations described in patents are variations of the above synthetic scheme. In particular, to obtain optically pure Emtricitabine, lipase-catalyzed enzymatic resolution, as well as chiral stationary phase HPLC was used [143]. However, the most effective procedure included separation of menthyl derivatives. This method evolved significantly since the first publication (which in fact relied on separation of all the 4 possible diastereomers) [144]; one of the recent multigram preparations is shown in the Scheme 37 [145]. The first step of the synthesis included formation of methyl ester **159** from glyoxalic acid and *L*-menthol. Reaction of **159** with 1,4-ditiane **154** gave 1,3-oxathiolane **160** as a mixture of *cis* diastereomers.

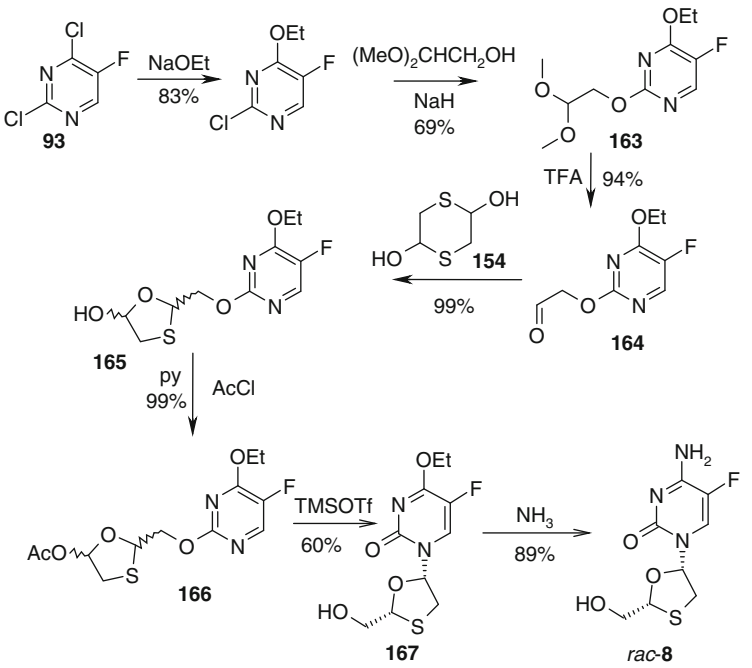


Scheme 37 One of the recent syntheses of Emricitabine (**8**)

Compound **160** was transformed to chloride **161** by treatment with thionyl chloride and methanesulfonic acid. Reaction of **161** and **158** led to the formation of **162**, which was separated as a single diastereomer by transformation to oxalate and subsequent crystallization. Finally, reduction of **162** with $NaBH_4$ gave Emtricitabine (**8**) which was isolated as hydrochloride.

An interesting variation of the method was patented by Glaxo Wellcome Inc [146]. Their synthesis was started from 2,4-dichloro-5-fluoropyrimidine (**93**) (Scheme 38). Reaction of **93** with NaOEt and then – with anion of 2,2-dimethoxyethanol gave pyrimidine derivative **163**, which upon detection formed aldehyde **164**. Reaction of **164** and **154** led to the formation of 1,3-oxathiolane **165**, which was acetylated to give **166**. Treatment of **166** with TMSOTf resulted in rearrangement leading to **167**, which was transformed to racemic **8** (Racivir) by reaction with ammonia.

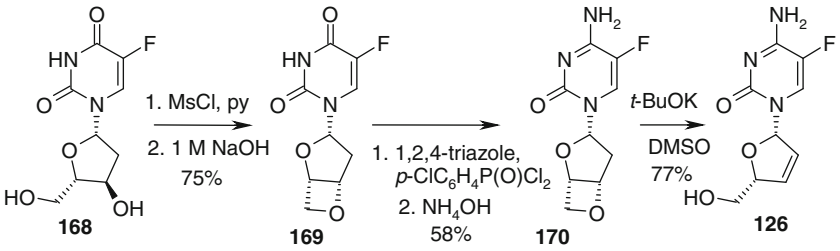
A number of methods for the preparation of Elvucitabine (**126**) were reported in the literature. In the first synthetic scheme developed in Yale University [147], 2′-deoxy-5-fluoro-β-L-uridine (**168**), which is enantiomer of Floxuridine (**4**), was used as the key intermediate (Scheme 39). Compound **168** can be prepared in



Scheme 38 Synthesis of racemic **8** (Racivir) patented by Glaxo Wellcome Inc. (Relative configurations are shown)

several steps from L-arabinose. Mesylation of **168** followed by alkaline cyclization led to the formation of oxetane **169**, which was transformed to cytidine derivative **170**. Compound **170** was rearranged to **126** by treatment with *t*-BuOK in DMSO.

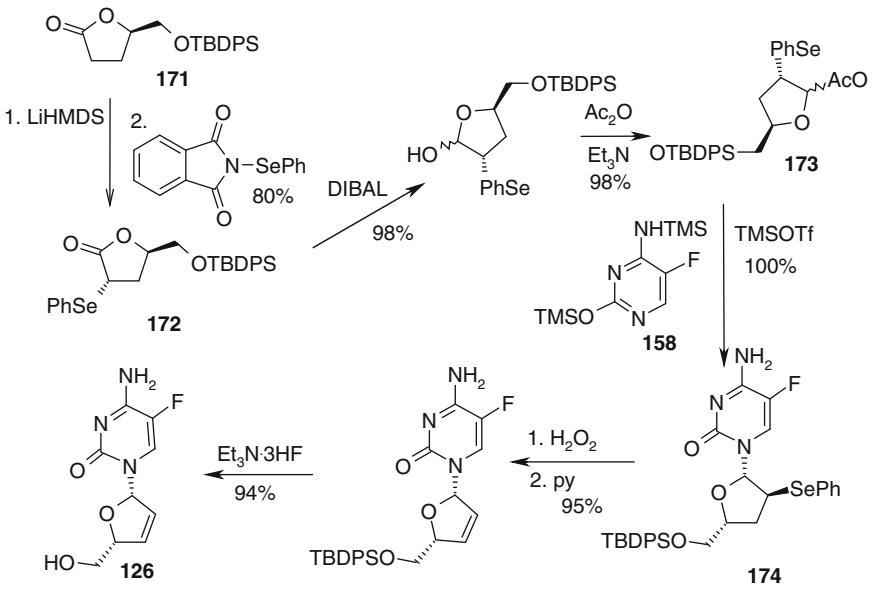
Synthesis of Elvucitabine (**126**) developed by chemists from Vion Pharmaceuticals commenced from lactone **171** (Scheme 40), which can be obtained in 4 steps from



Scheme 39 Synthesis of Elvucitabine (**126**) developed in Yale University

D-glutamic acid [148]. Phenylselenation of enolate generated from **171** proceeded highly diastereoselectively and led to **172**.

Phenylselenide **172** was reduced with DIBAL and then acetylated to give acetate **173** as a mixture of anomers. Reaction of **173** with **158** was also

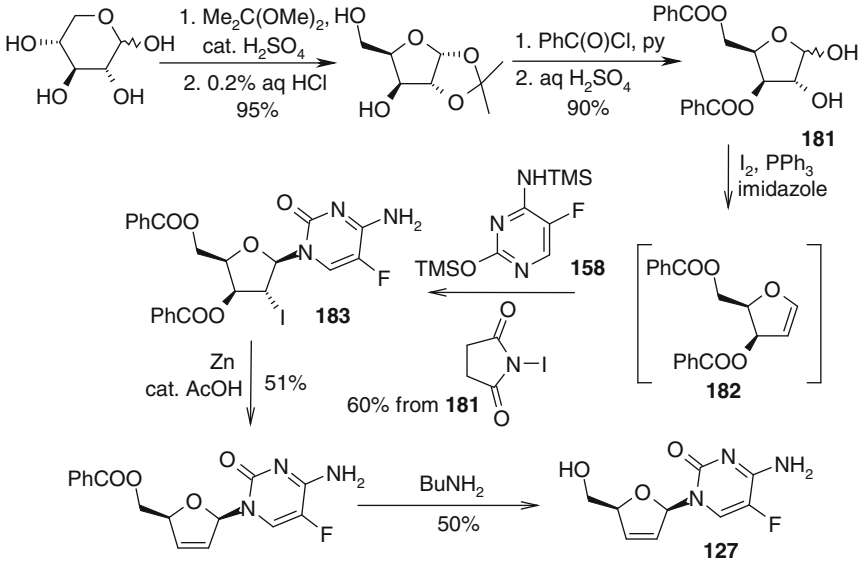


Scheme 40 Synthesis of Elvucitabine (**126**) by Vion Pharmaceuticals

diastereoselective due to the steric effect of bulky phenylselenyl substituent and gave β anomer **174** in almost quantitative yield. Oxidative elimination of the selenide substituent from **174** and subsequent deprotection gave Elvucitabine (**126**) as a single enantiomer. An analogous synthesis was described by chemists from Emory University [149].

Syntheses of Dexelvucitabine (**127**) [150] and later – Elvucitabine (**126**) [151] were described, starting from D- and L-xylose, respectively, both using almost the same methodology. In particular, D-xylose was transformed into the dibenzoyl derivative **181** using standard manipulations (Scheme 41). Under modified Appel conditions (I_2/PPh_3/imidazole), **181** gave unstable glycal **182**, which reacted with fluorocytosine derivative **158** and *N*-iodosuccinimide to yield **183**. Compound **183** was subjected to reductive elimination and deprotection to give **127**.

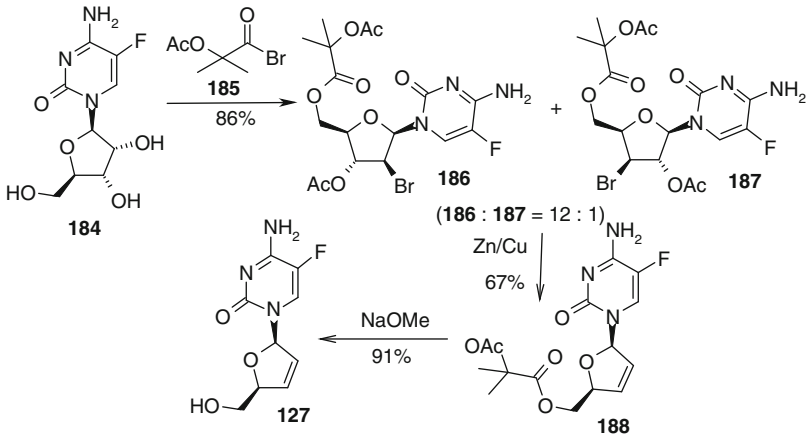
Preparation of Dexelvucitabine (**127**) on a kilogram scale starting from 5-fluorocytidine (**184**) was developed by chemists from Pharmasset (Scheme 42)



Scheme 41 Synthesis of Dexelvucitabine (**127**)

[152]. Compound **184** was subjected to bromoacylation with excess of 2-acetoxy-2-methylpropionyl bromide (**185**) to give a mixture of esters **186** and **187**. This mixture was subjected to reductive elimination to give **188**, which was transformed to **127** upon alcoholysis.

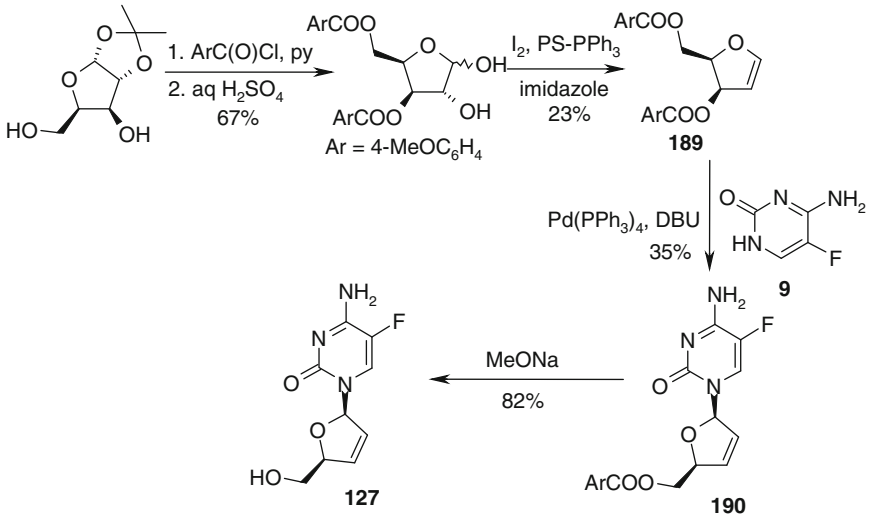
Another synthesis of **127** relied on palladium mediated Ferrier rearrangement-type glycosidation of a furanoid glycal (Scheme 43) [153]. The initial steps of



Scheme 42 Synthesis of Dexelvucitabine (**127**) by Pharmasset

the synthesis were quite similar to those shown in Scheme 41. The major difference was the use of polymer-supported PPh_3 at the glycal generation step, which allowed for isolation of unstable glycal **189** with more than 90 % purity. Palladium-catalyzed reaction of **189** with 5-fluorocytosine (**9**) was accompanied by Ferrier-type rearrangement and led to derivative **190**, which was transformed to **127** upon deprotection.

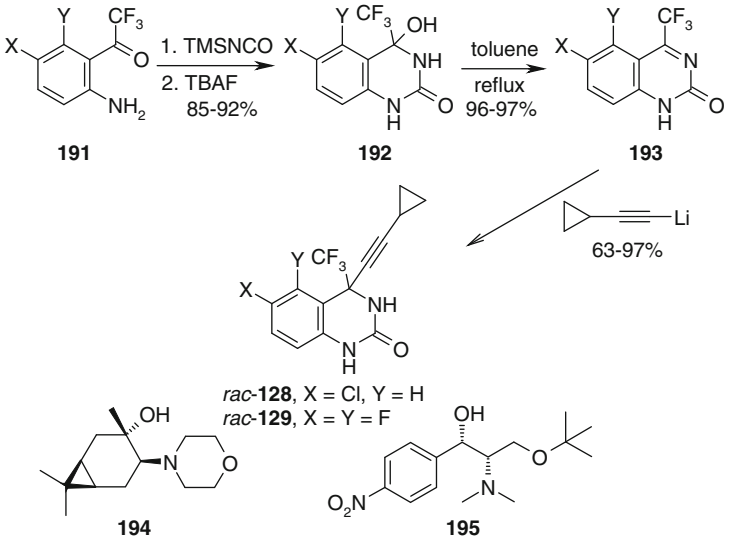
All the reported syntheses of DPC-961 (**128**) and DPC-963 (**129**) commenced from the corresponding *o*-amino-α,α,α-trifluoroacetophenones **191** (Scheme 44).



Scheme 43 Synthesis of Dexelvucitabine (**127**)

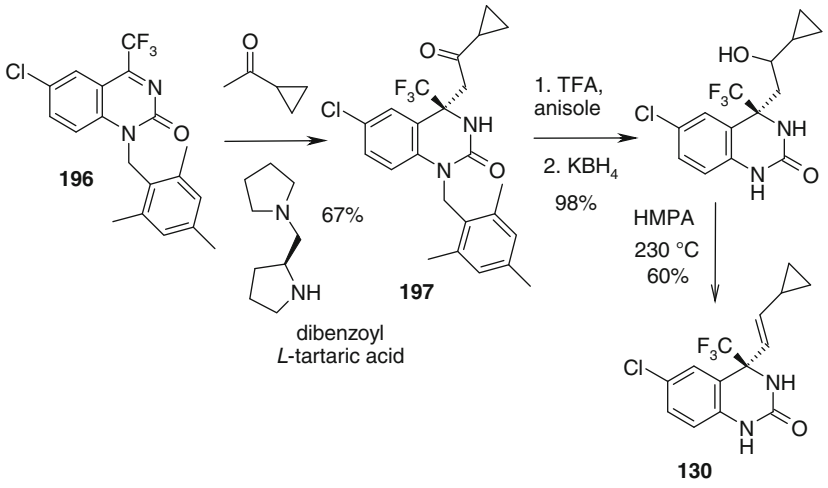
In the first preparations of **128** and **129**, **191** reacted with TMSNCO to give adducts **192**, which were transformed to cyclic imines **193** upon dehydratation. Reaction of **193** with lithium cyclopropylacetylenide gave racemic **128** and **129**, which were subjected to chiral stationary phase HPLC to isolate **128** and **129** as pure enantiomers [136, 137]. Several improvements were reported for this synthetic scheme. In particular, diastereoselective additions of lithium cyclopropyl acetylenide to the derivatives of **193** containing residues of α-phenylethyl amine or campheic acid were developed [154, 155]. Moreover, an enantioselective modification of this method employing amino alcohol **194** as an asymmetric catalyst was discovered [156, 157]. Another enantioselective method involved reaction of the derivatives of **193** and cyclopropyl acetylene itself, catalysed by amino alcohol derivatives (*e.g.* **195**) and $Zn(OTf)_2$ [158].

DPC-083 (**130**) and DPC-082 (**131**) were obtained by reduction of **128** and **129**, respectively, with $LiAlH_4$ [136, 137]. Recently, an alternative approach to the synthesis



Scheme 44 Synthesis of DPC-961 (**128**) and DPC-963 (**129**)

of **130** was reported, which relied on enantioselective organocatalytic Mannich-type reaction of imine derivative **196** and cyclopropyl methyl ketone (Scheme 45) [159]. Although enantioselectivity of the key step was moderate (*ee* 75 %), it could be easily enhanced to >99 % by a single recrystallization of intermediate **197**.

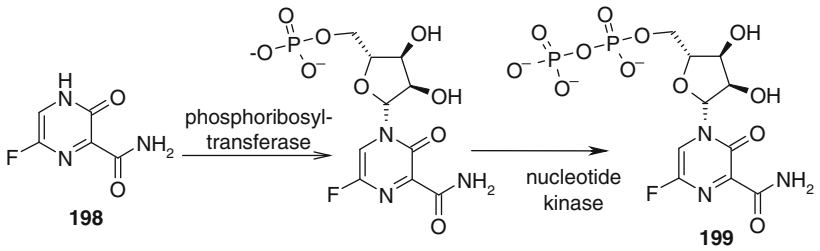


Scheme 45 Synthesis of DPC-083 (**130**) using organocatalytic Mannich-type reaction

4.2 Other Antiviral Agents

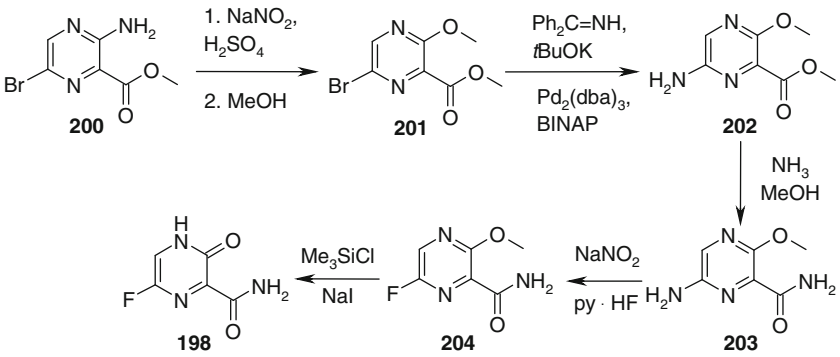
Apart from anti-HIV drugs discussed in the previous section, two additional antiviral agents can be mentioned: Trifluridine (**7**) and Favipiravir (**198**). Trifluridine (**7**) was mentioned above as a component of Phase III investigational drug TAS-102. It is however more known as an ophthalmic anti-herpes agent launched by Glaxo Wellcome (now merged into GlaxoSmithKline) in 1980 [5]. It is effective against herpetic keratitis, and seems to be especially useful in 'difficult' cases [160]. High susceptibility to biodegradation of Trifluridine is advantageous for its use as ophthalmic drug, as its action in other tissues is thus prevented. As in the case of anti-tumor activity, the mechanism of antiviral action of **7** involves the inhibition of viral replication. Trifluridine does this by incorporating into viral DNA during replication, which leads to the formation of defective proteins and an increased mutation rate [161]. Inhibition of thymidylate synthetase also seems to contribute into antiviral effect of **7**. The details of these processes, as well as synthesis of **7** were discussed in the above sections.

Favipiravir (**198**) has been discovered by Toyama Chemicals; it is currently in Phase III (Japan) and Phase II (USA) clinical trials [113, 162]. Favipiravir is under development as an agent against influenza virus, however, it was also tested against other RNA viruses, including arenaviruses, bunyaviruses, West Nile virus (WNV), yellow fever virus (YFV), and foot-and-mouth disease virus (FMDV) [163]. A proposed mechanism of action of **198** includes its biotransformation into ribofuranosyltriphosphate derivative **199** (Scheme 46), which inhibits influenza virus RNA polymerase in the host cells [164].



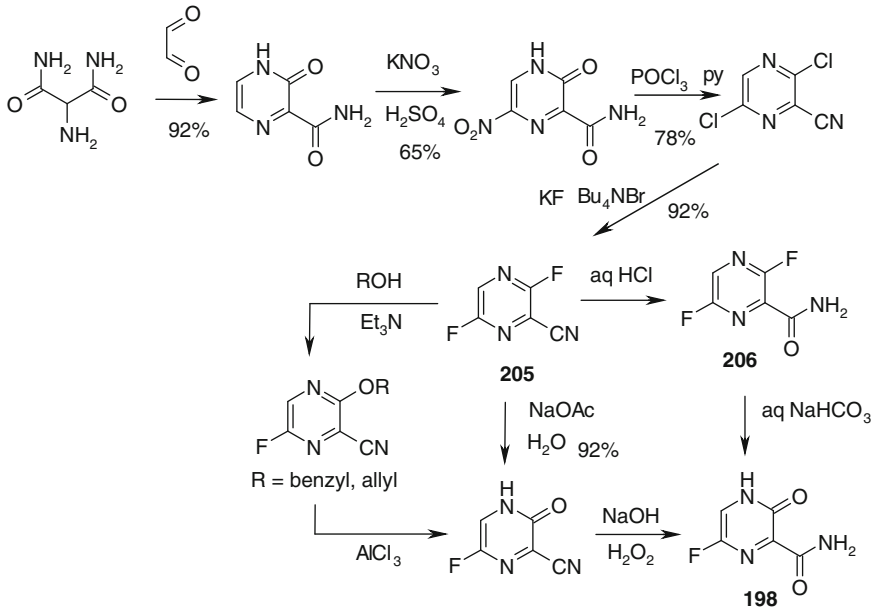
Scheme 46 A proposed pathway of Favipiravir (**198**) bioactivation

One of the syntheses of **198** is based on pyrazine **200** (Scheme 47) [165, 166]. Compound **200** was transformed to methoxy derivative **201** via diazotization step; **201** was then subjected to Buchwald – Hartwig amination to give **202**. Ester **202** was transformed to amide **203**; diazotization of **203** in the presence of pyridine hydrofluoride led to the formation of fluoro derivative **204**. The last step of the synthesis included deprotection of the methyl ether to give **198**.



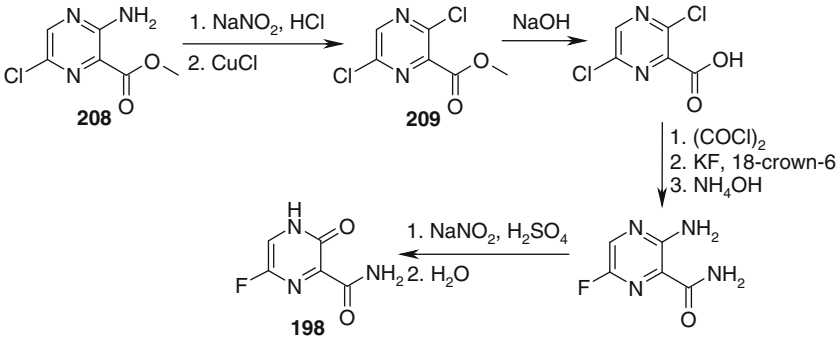
Scheme 47 Synthesis of Favipiravir (**198**) reported in 2002

Several syntheses of **198** involved difluoro derivative **205** as a key intermediate which was prepared in 4 steps from readily available materials (Scheme 48) [166, 167]. Acidic hydrolysis of **205** gave amide **206**, which upon mild alkaline hydrolysis led to **198**. Alternatively, compound **198** was obtained by mild alkaline hydrolysis of **205** followed by reaction with H_2O_2–NaOH, or by reaction of **205** with allyl or benzyl alcohol, removal of the protection, and hydrolysis. Recently, an improved version of this method was patented, which allowed authors to claim its industrial applicability [168].



Scheme 48 Synthesis of Favipiravir (**198**) via the key intermediate **205**

One more method for the preparation of **198** commenced from pyrazine derivative **207**, which was transformed to dichloride **208** using Sandmeyer reaction (Scheme 49) [166]. Hydrolysis of the ester moiety in **208** followed by one-pot chloroanhydride formation, introduction of fluorine atom and amination gave derivative **209**, which was transformed into **198** by diazotization and subsequent hydrolysis.



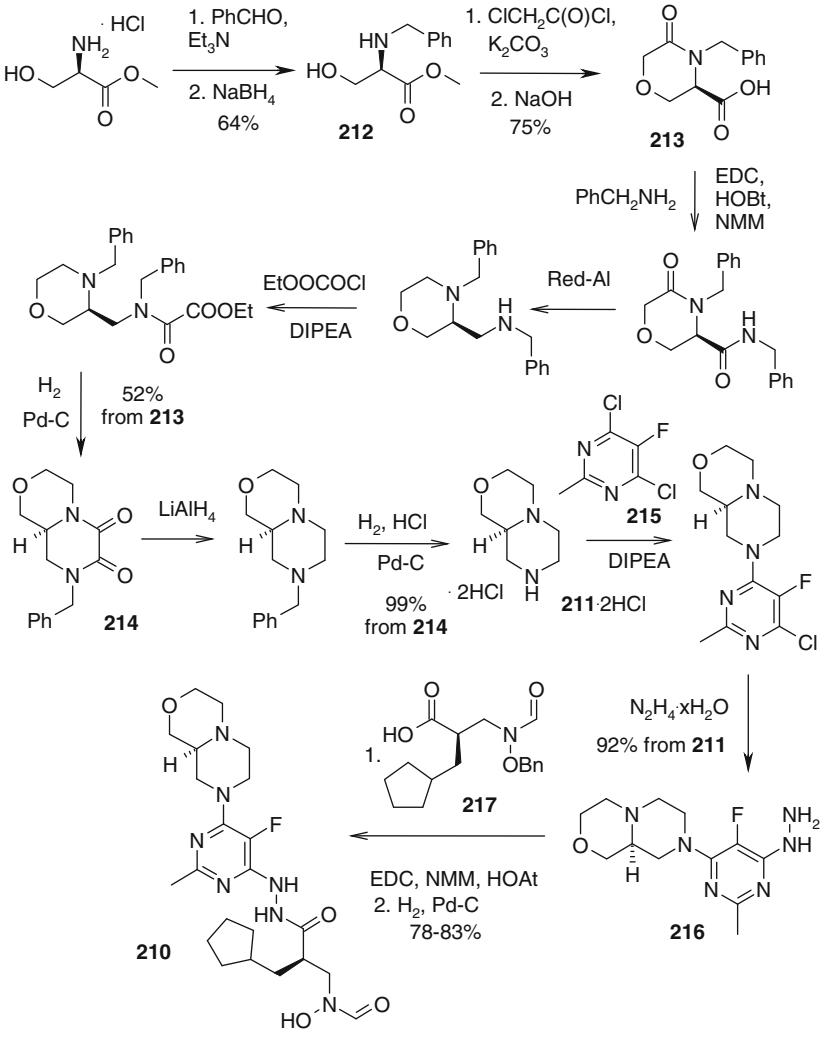
Scheme 49 Synthesis of Favipiravir (**198**) from pyrazine derivative **207**

Several other approaches to the synthesis of Favipiravir were also described, most of them relying on direct fluorination of pyrazine derivatives with molecular fluorine [166] All they were low-yielding and allowed for the preparation of milligram quantities of the final product.

4.3 Antibacterial Agents

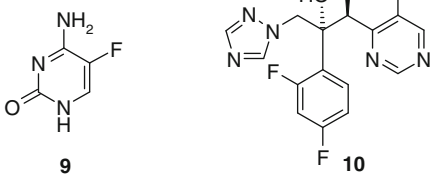
A single compound is discussed in this category, namely GSK-1322322 (**210**), which was developed by GlaxoSmithKline and has reached Phase II clinical trials in bacterial skin infections [113] and Phase III – in community-acquired bacterial pneumonia [169]. Compound **210** acts as an inhibitor of peptide deformylase – an enzyme that removes the formyl group during eubacterial peptide elongation. Bacterial protein synthesis initiates with formyl-methionyl-tRNA and, consequently, all polypeptides newly synthesized in bacteria contain an *N-formyl-methionine* terminus. This residue is further removed in two steps catalyzed by peptide deformylase and methionine aminopeptidase, respectively. Inhibition of peptide deformylase increase production of bacterial *N*-formylated polypeptide, which prevents bacteria growth and possibly triggers an enhanced immune response [170]. Peptide deformylase is a metalloprotease, which mostly utilizes Fe^{2+} in its active site. It was shown for analogs of **210** that *N*-formyl-*N*-hydroxylamine function coordinated to metal ion when the inhibitor was bound to the enzyme [171].

Synthesis of **210** was started from preparation of chiral diamine **211** (Scheme 50) [172]. In particular, *D*-serine methyl ester was converted to *N*-benzyl derivative **212**, which was transformed into carboxylic acid **212** using reaction with chloroacetyl chloride and subsequent hydrolysis. Carboxylic acid **212** was subjected to coupling with benzyl amine, reduction, reaction with ethyl oxalyl chloride and reductive cyclization to give bicyclic compound **213**. Finally, **211** Two-step reduction of **213** led to the formation of diamine **211**, which was isolated as dihydrochloride. Reaction of **211** with dichloro derivative **215** and then – hydrazine hydrate gave the product **216**, which was coupled with carboxylic acid **217** and subjected to catalytic hydrogenation to give **210**.



Scheme 50 Synthesis of GSK-1322322 (**210**)

Fig. 6 Anti-fungal agents

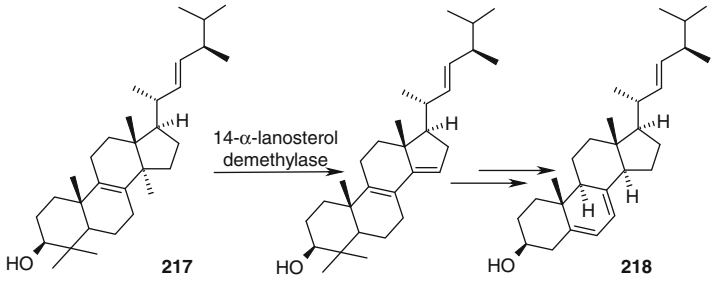


4.4 Antifungal Agents

Two drugs were launched as anti-fungal agents to date: Flucytosine (**9**) (Valeant, 1971) and Voriconazole (**10**) (Pfizer, 2002) (Fig. 6) [5]. Flucytosine itself has no antifungal activity; its activity results from the rapid conversion into Fluorouracil (**1**) within susceptible fungal cells [173]. The mechanism of cytotoxic effect of Fluorouracil has been discussed in the previous sections. Flucytosine is taken up by fungal cells by cytosine permease, which is the transport system for cytosine and adenine. Inside the fungal cells, **9** is deaminated to **1** by cytosine deaminase. The specificity of this step is crucial for the narrow antifungal spectrum of **9**: mammalian cells as well as fungi lacking cytosine deaminase are not sensitive to **9**. On the other hand, Fluorouracil itself cannot be used as an antifungal drug, since it is only poorly taken up by fungal cells and is too toxic to human cells.

The major drawback of Flucytosine is rapid development of resistance in fungi, either by mutations or by increased synthesis of pyrimidines; this limits the use of **9** as a single antifungal agent. Monotherapy with Flucytosine is currently only used in some cases of chromoblastomycosis and in uncomplicated candidosis; in all other cases, **9** is used together with other agents, usually Amphotericin B [173].

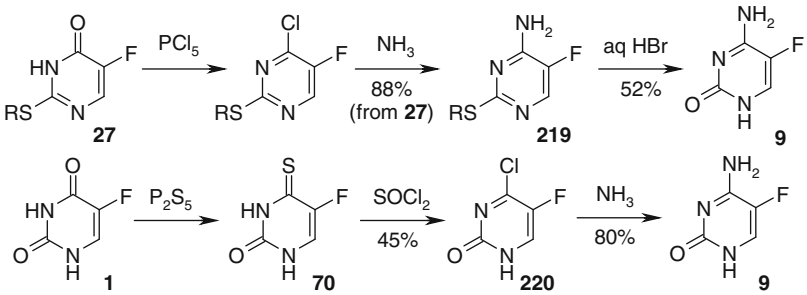
The effect of Voriconazole (**10**) is exerted within the fungal cell membrane. In particular, cytochrome P450-dependent 14-α-lanosterol demethylase is inhibited, which prevents the conversion of lanosterol (**217**) to ergosterol (**218**) – an important component of yeast and fungal cell membranes which does not occur in mammalians (Scheme 51). This mechanism results in the accumulation of toxic methylsterols and inhibition of fungal cell growth and replication [174].



Scheme 51 Conversion of lanosterol (**217**) to ergosterol (**218**)

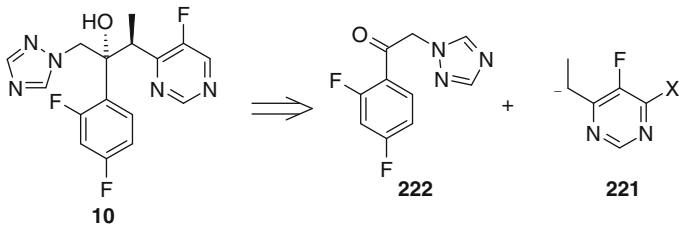
Voriconazole is active against many fungal infections, including invasive aspergillosis, *Pseudallescheria*, *Scedosporium*, *Fusarium* infections [175]. It is also proposed for empirical antifungal therapy [176]. An important advantage of Voriconazole is high oral bioavailability (96 %). The most common side effect, which is unique for Voriconazole among other azole antifungals, is a reversible disturbance of vision (photopsia): it occurs in nearly a third of patients but rarely leads to discontinuation of the drug [174]. Resistance to Voriconazole still remains uncommon, although an increase of resistance and continued surveillance with greater use of the drug has been reported [177].

The first synthesis of Flucytosine (**9**) has been reported in 1957 [13, 14]. The synthetic scheme is quite similar to that for Fluorouracil (**1**); in the case of **9**, compound **27** was subjected to reaction with PCl_5 and then – liquid ammonia to give **219**, which was transformed to **9** upon hydrolysis (Scheme 52). In an alternative method, compound **70** (prepared from Fluorouracil) reacted with $SOCl_2$ to give **220**, which was transformed to **9** upon reaction with ammonia in methanol [84]. Another synthesis commenced from 2,5-difluoro-4-chloropyrimidine, which, however, is not readily accessible [178]. Flucytosine was also obtained by direct fluorination of cytosine using CF_3OF (85 % yield) [179, 180], fluorine [181, 182], and AcOF [20].

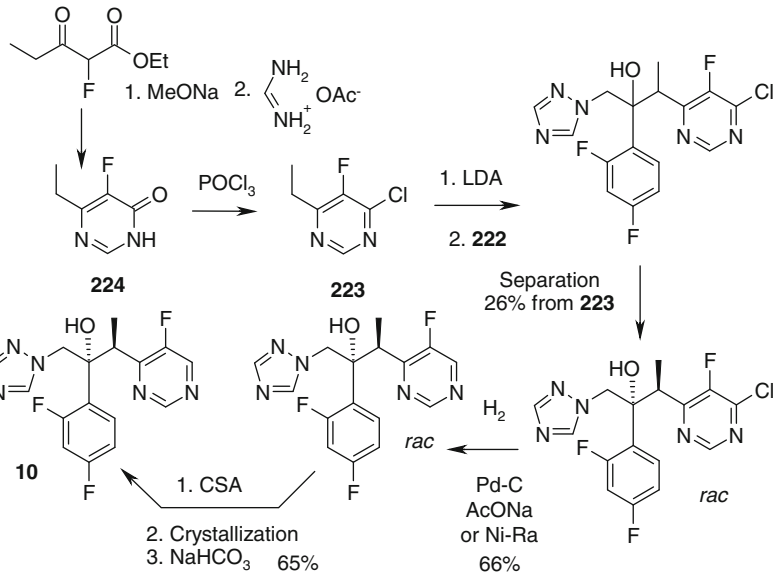


Scheme 52 Syntheses of Flucytosine (**9**)

Despite numerous syntheses of Voriconazole (**10**) were documented, they all followed the same synthetic strategy, namely, addition of anion **221** to ketone **222**, followed by isolation of necessary diastereomeric pair and its resolution with 10-camphorsulphonic acid (Scheme 53). Three different approaches were used for the generation of anion **221** or the corresponding organometallic species. First of them relied on deprotonation of the pyrimidine derivative **222** (prepared from the fluorinated keto ester **223** or dichloro derivative **93**) by strong bases such as LDA (Scheme 54) [183–189].

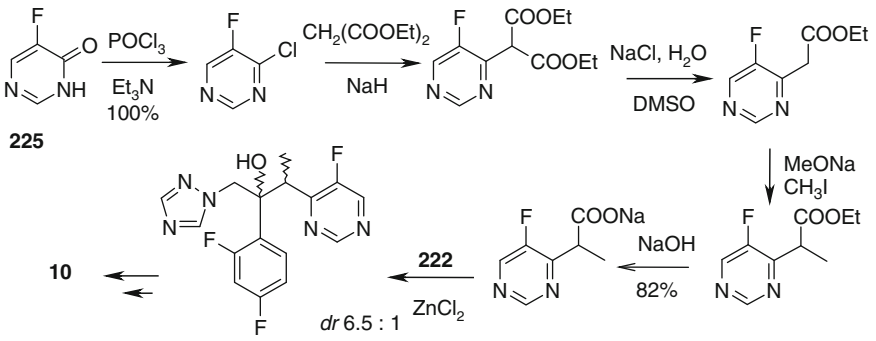


Scheme 53 Retrosynthetic analysis of Voriconazole (**10**)

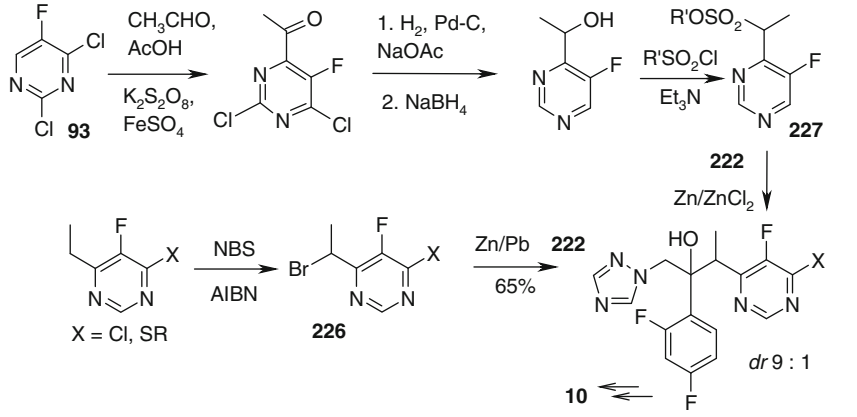


Scheme 54 Synthesis of Voriconazole (**10**) via intermediate **223**

The main drawback of this method was low diastereoselectivity of the key step; therefore tedious separation of diastereomers was necessary. Another approach to generation of **221** relied on $ZnCl_2$-catalyzed decarboxylation of salts **224**, prepared from **225** (Scheme 55) [190]. In this case, the desired diastereomeric pair was obtained with much better selectivity (6.5: 1). The last approach relied on Reformatsky-type reaction involving **222** and bromides **226** (prepared from **223** [191, 192] or its thio analogues [193–195]) or sulfonates **227** (prepared from **93**) (Scheme 56) [196, 197]. In this case, good diastereoselectivities were obtained.



Scheme 55 Synthesis of Voriconazole (**10**) via intermediate **224**

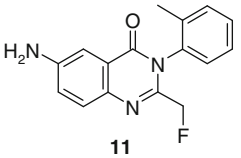
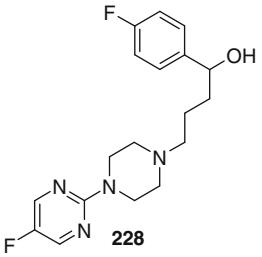
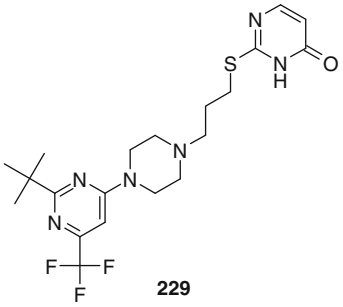
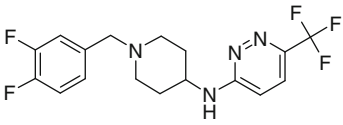
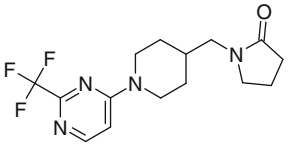
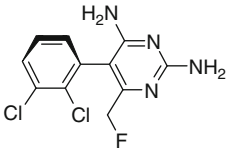
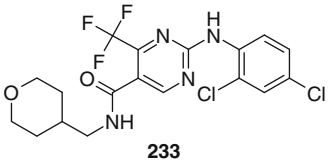


Scheme 56 Synthesis of Voriconazole (**10**) using Reformatsky-type reaction

5 Agents Acting at Nervous System

Seven compounds designed as agents acting at central and/or peripheral nervous system have reached at least Phase II clinical trials, and only one of them was launched (Table 4) [3, 113]. These compounds address different biological targets and act as skeletal muscle relaxants (Afloqualone (**11**)), antipsychotics (BMY-14802 (**228**), A-437203 (**229**), and JNJ-37822681 (**230**)), nootropic agents (BMY-21502 (**231**)) or analgesics (BW-BW-4030W92 (**232**) and GW-842166X (**233**)).

Table 4 Derivatives of fluorinated diazines – nervous system modulators [3, 5, 115]

Structure	INN or ID, development phase, company	Action
 **11**	Afloqualone Launched (1983) Mitsubishi Tanabe Pharma	Skeletal muscle relaxant
 **228**	BMY-14802, BMS-181100 Phase II Bristol-Myers Squibb	Antipsychotic
 **229**	ABT-925, A-437203 Phase II Abbott	Antipsychotic
 **230**	JNJ-37822681 Phase II Johnson & Johnson	Antipsychotic
 **231**	BMY-21502, BMS-181168 Phase II Bristol-Myers Squibb	Nootropic
 **232**	BW-4030W92 Phase II GlaxoSmithKline	Analgesic
 **233**	GW-842166X Phase II GlaxoSmithKline	Analgesic

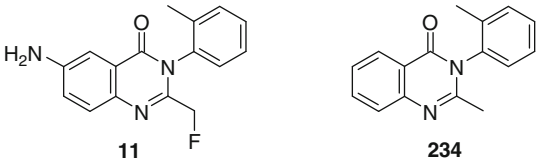


Fig. 7 Afloqualone (**11**) and Methaqualone (**234**)

5.1 Skeletal Muscle Relaxants

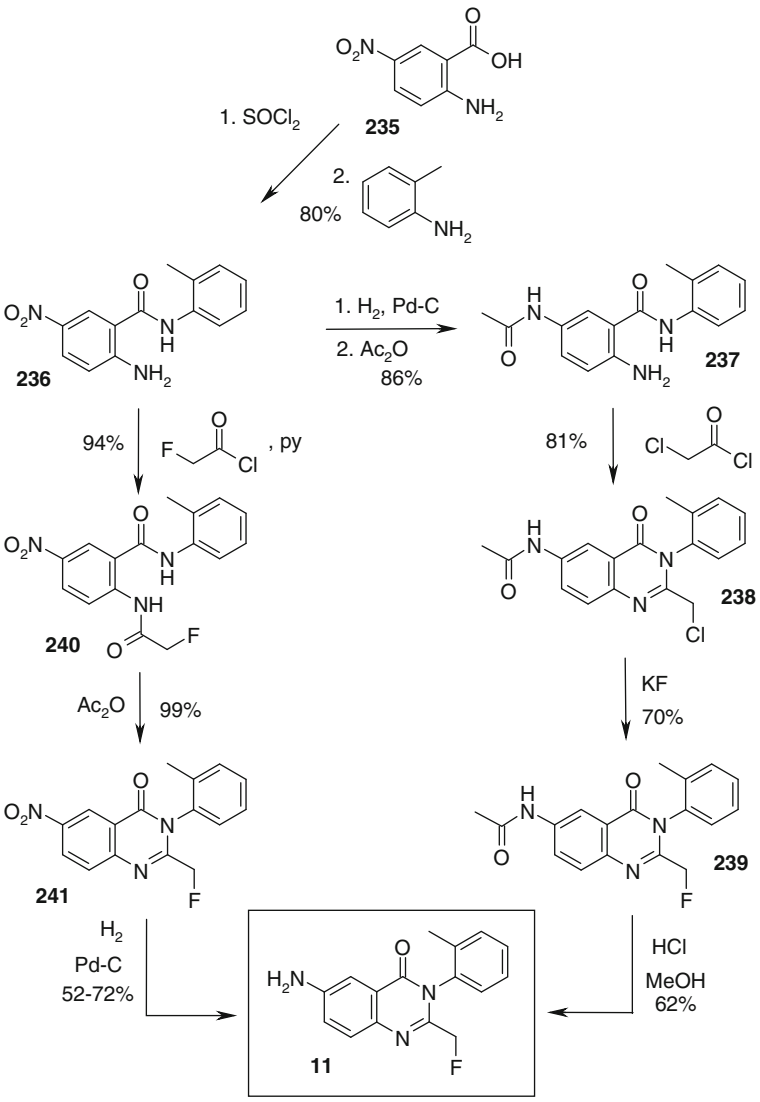
A representative of fluorinated diazines, Afloqualone (**11**), was launched in 1983 in Japan as a central acting muscle relaxant [198]. It is an analogue of Methaqualone (**234**) (Fig. 7) – a drug widely used as a hypnotic, for the treatment of insomnia, and as a sedative and muscle relaxant in 1970s, but reclassified as a Schedule I controlled substance in USA in 1984 [199].

The mechanism of action of Afloqualone is not well studied. It was shown that its site of action is different from that of other central acting muscle relaxants, *i.e.* Mephenesin, Chlormesazone or Diazepam [200]. GABA-enhancing effect was also demonstrated [303]. The main routes of metabolism of **11** in human include *N*-acetylation, followed by hydroxylation at the 2′-methyl and acetyl methyl carbons, as well as glucuronidation of the aromatic amino group. This pattern of metabolism is similar to that observed in monkeys and rats, but drastically different from that in dogs [304].

Synthesis of Afloqualone commenced from 5-nitroanthranilic acid (**235**) which was transformed to amide **236** via the corresponding chloroanhydride (Scheme 57) [201]. Catalytic reduction of **236** followed by acetylation gave **237**, which reacted with chloroacetyl chloride to form quinazoline **238**. Nucleophilic substitution of chlorine atom in **238** with fluorine led to the formation of **239**, which upon deprotection gave Afloqualone (**11**). Alternatively, compound **236** was subjected to acylation with fluoroacetyl chloride or anhydride to give amide **240** [202]. Refluxing of **240** with acetic anhydride gave quinazoline **241**, which was reduced to Afloqualone either by catalytic hydrogenation or using $SnCl_2$.

5.2 Antipsychotics

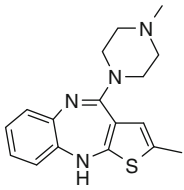
All three compounds discussed in this section (*i.e.* **228**–**230**) have reached Phase II clinical trials as agents for treatment Schizophrenia. Development of BMY-14802 (**228**) was discontinued more than 10 years ago. For ABT-925 (**229**), Phase II trials were terminated in 2011; for JNJ-37822681 (**230**), the latest clinical study was completed in February 2012 [113]. Despite the disease addressed by **228**–**230** is common, the compounds express their effect through interactions with different biological targets. In particular, BMY-14802 (**228**) developed by Bristol-Myers Squibb acts as a dual antagonist of σ_1 and 5-HT_{1A} receptors. However, it should be



Scheme 57 Synthesis of Afloqualone (**11**)

noted that relative role of these two targets in biological effect of **228** was debated in the literature. Whereas in pigeons, the effect was serotonergically mediated primarily through 5-HT_{1A} receptors [203], in other model systems, these interactions did not seem to contribute significantly to the potential antipsychotic action of the compound [204]. Although studies in animal models supported for the suggestion that BMY-14802 (**228**) may possess antipsychotic properties [205], clinical trials showed lack of efficacy in Schizophrenia treatment [206].

Fig. 8 The structure of Olanzapine



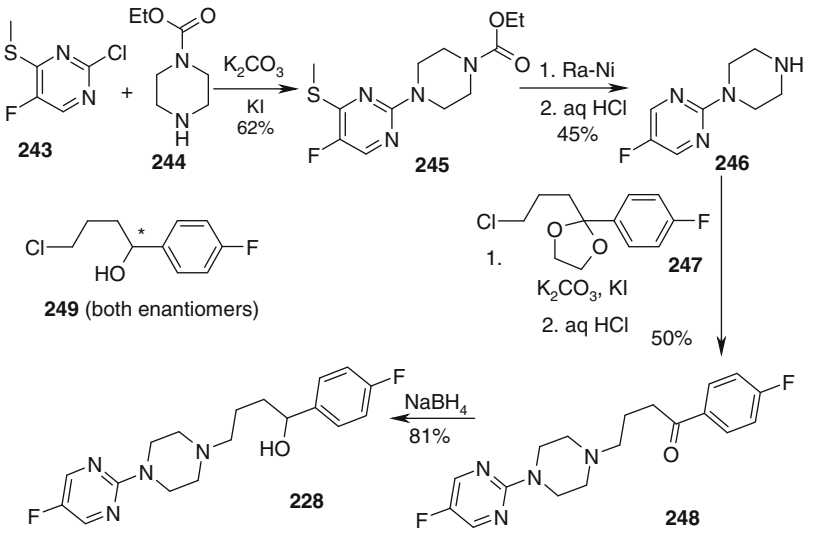
242

Recently, BMY-14802 was proposed as a promising candidate for clinical trials of *L*-DOPA-induced dyskinesia – a common side effect observed during prolonged use of *L*-DOPA in Parkinson disease patients [207]. It was shown that the compound suppresses abnormal involuntary movements related to *L*-DOPA-induced dyskinesia via its 5-HT_{1A} agonistic effect.

ABT-925 (**229**) developed by Abbott is a selective D3 receptor antagonist [208]. It was suggested that selective antagonists of D3 receptor might be promising antipsychotic agents lacking the presumed D2 receptor-mediated side effects, although D3 antagonists may express their effect via mechanisms that cannot be reflected by the commonly used animal models [209]. It was shown that ABT-925 produced cognitive signals but did not achieve sufficient D3 receptor occupancy at the doses used in clinical studies [210]. Nevertheless, these studies allowed for the assumption that the development and clinical testing of newer D3 receptor antagonists with higher potency at D3 receptors, enabling sufficient receptor occupancy, is highly warranted [211].

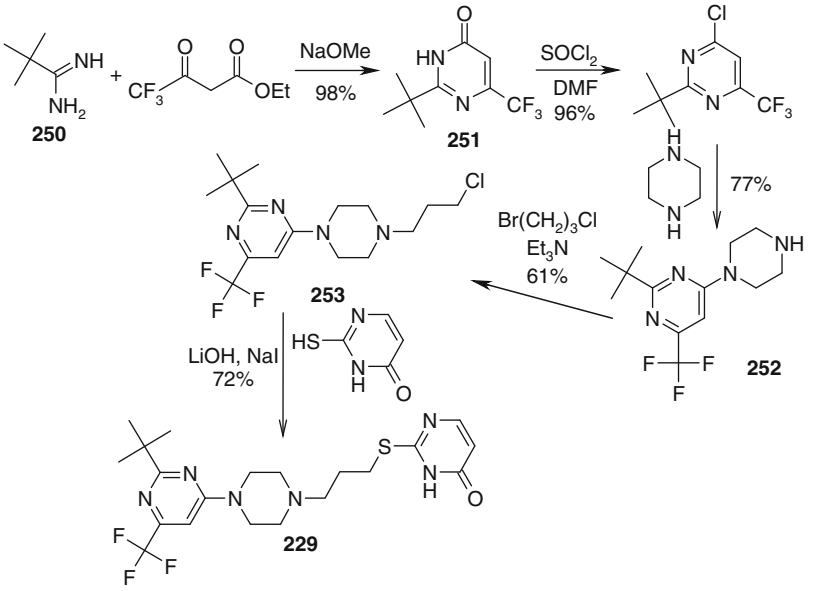
On the contrary, JNJ-37822681 (**230**) is a D2 highly selective receptor antagonist and hence acts in a mode analogous to that of most marketed antipsychotics [212]. JNJ-37822681 is characterized by a rapid dissociation rate from the dopamine D2 receptor, which was hypothesized to confer antipsychotic efficacy and improved tolerability [213]. Clinical studies in patients with an acute exacerbation of schizophrenia showed that JNJ-37822681 had similar biological activity but lesser tendency to induce weight gain compared to a known antipsychotic drug, Olanzapine (**242**) [214] (Fig. 8).

Synthesis of BMY-14802 (**228**) commenced from pyrimidine derivative **243** which reacted with piperazine **244** to give derivative **245** (Scheme 58) [215, 216]. Reduction of the compound **245** followed by deprotection gave amine **246**, which was alkylated with chloride **247** and then subjected to acidic hydrolysis to form ketone **248**. Reduction of **248** allowed BMY-14802 (**228**) to be obtained. Pure enantiomers of **228** were also obtained. To achieve this, the following methods were used: resolution of **228** with using reaction with α-phenylethyl isocyanate [217] or lipase-catalyzed acetylation or hydrolysis [218], alkylation of **245** with enantiopure alcohols **249** [219]; and microbial reduction [305] or Ru-catalyzed enantioselective hydrogenation [220] of **248**.



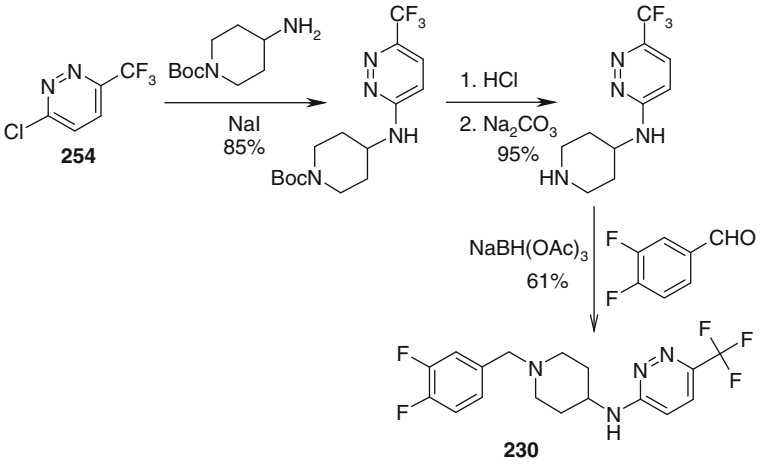
Scheme 58 Synthesis of racemic BMY-14802 (**228**)

ABT-925 (**229**) was obtained starting from amidine **250** and ethyl trifluoroacetoacetate to give pyrimidine **251** (Scheme 59) [221]. Reaction of **251** with $SOCl_2$ and then – piperazine led to the formation of amine **252**. Selective alkylation of **252** with 1-bromo-3-chloropropane gave chloride **253**, which reacted with thiouracil anion to form ABT-925 (**229**).



Scheme 59 Synthesis of ABT-925 (**229**)

Synthesis of JNJ-37822681 (**230**) was quite trivial and relied on selective functionalization of 4-aminopiperidine core, first with 3-chloro-6-trifluoromethylpyridazine (**254**) and then – with 3,4-difluorobenzaldehyde (Scheme 60) [222].

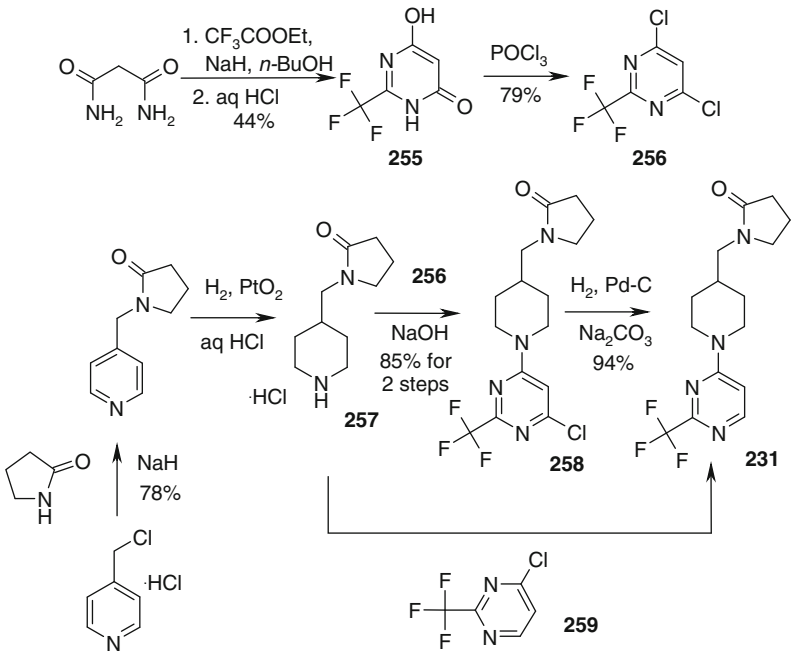


Scheme 60 Synthesis of JNJ-37822681 (**230**)

5.3 *Nootropic Agents*

BMY-21502 (**231**) was developed by Bristol-Myers Squibb as nootropic agent (*i.e.* for cognition disorders) and has reached Phase II clinical studies. The compound was effective in vitro [223] as well as in animal models [223–227, 306] that may predict cognitive enhancement. The mode of action of BMY-21502 is poorly understood. It was shown that the compound has an anti-anoxic action, and activation of the CNS cholinergic system is involved as one of the causative mechanisms for this effect [228]. Clinical trials showed that BMY-21502 was not significantly superior to placebo in Alzheimer's disease; moreover, although generally well tolerated, **231** also had a higher rate of discontinuations [229, 230].

Synthesis of BMY-21502 (**231**) optimized for large scale preparations commenced from malonodiamide and ethyl trifluoroacetate, which reacted to give pyrimidine **255** (Scheme 61) [231]. Compound **255** was transformed into dichloro derivative **256** upon treatment with $POCl_3$. Reaction of **256** with piperidine **257** (prepared from 4-pyridinylmethyl chloride in two steps) gave **258**, which was reduced catalytically to form BMY-21502 (**231**). Alternatively, BMY-21502 was obtained by arylation of **257** with 4-chloro-2-trifluoromethylpyrimidine (**259**) [232].



Scheme 61 Synthesis of BMY-21502 (**231**)

5.4 Analgesics

Both the compounds discussed in this section, *i.e.* BW-4030W92 (**232**) and GW 842166X (**233**), were developed by GlaxoSmithKline. Development of BW-4030W92 was discontinued in 2002; the latest Phase II clinical studies of GW-842166X were completed in 2009 [113]. BW-4030W92 (**232**) was developed as a CNS-acting antihyperalgesic agent (*i.e.* for treatment of increased sensitivity to pain). It is an analogue of anticonvulsant drug Lamotrigine (**260**) (Fig. 9), used n the treatment of epilepsy and bipolar disorder [233]. Like Lamotrigine, BW-4030W92 binds to the transmembrane segment S6 in domain IV of α subunit of voltage-gated sodium channels (Na_v), thus acting as a pore blocker [234]. It is assumed that neuropathic pain is partially mediated by an increase in the density of Na_V channels in injured axons and their dorsal root ganglions. Clinical studies in patients with chronic neuropathic pain showed that although BW-4030W92 significantly lowered allodynia severity at the first day, the effect did not maintain in further treatment [235].

GW-842166X (**233**) is a selective CB2 receptor full antagonist which has potent analgesic, anti-inflammatory and anti-hyperalgesic actions. It was selected as a clinical candidate after lead optimization of a pyrimidine ester **261** (GK02076, Fig. 9), identified in a focused screen as a partial agonist at the CB2 receptor with

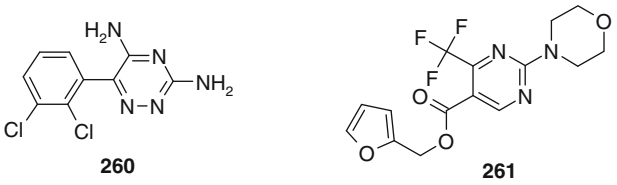
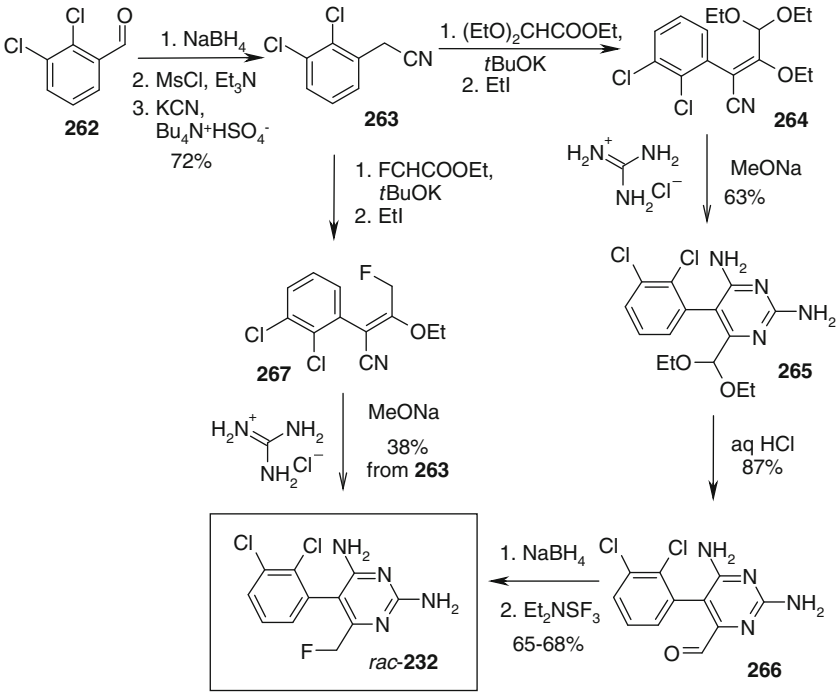


Fig. 9 The structures of Lamotrigine (**260**) and GK02076 (**261**)

micromolar potency [236]. The compound was evaluated as an analgesic for treatment of inflammatory pain (Phase I trials) and dental pain (Phase II trials) [113]. In the latter study, single doses of GW842166 failed to demonstrate clinically meaningful analgesia in the setting of acute dental pain [237].

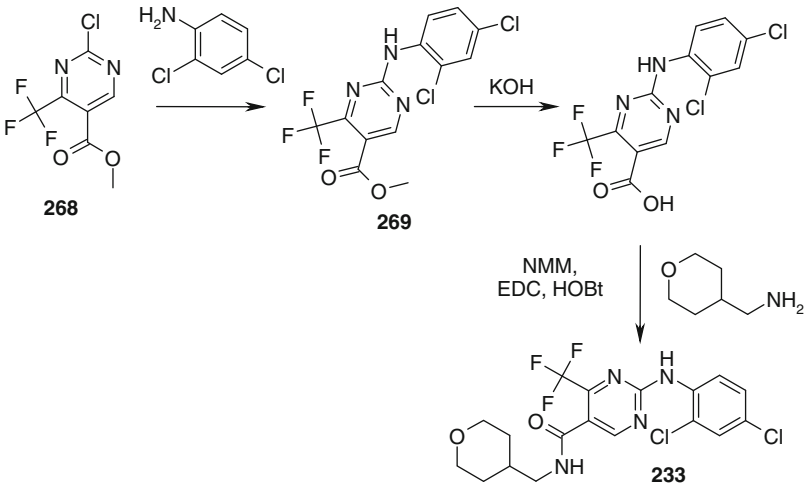
Synthesis of BW-4030W92 (**232**) started from 2,3-dichlorobenzaldehyde (**262**) which was transformed into nitrile **263** (Scheme 62) [238]. Compound **263** which reacted with ethyl diethoxyacetate – *t*-BuOK and then – ethyl iodide to give enol ether **264**. Reaction of **264** with guanidine afforded pyrimidine derivative **265**, which upon deprotection gave aldehyde **266**. Compound **266** was reduced with sodium borohydride and then subjected to reaction with diethylaminosulphur



Scheme 62 Synthesis of racemic BW-4030W92 (rac-**232**)

trifluoride (DAST) to give racemic **232**. Alternatively, nitrile **263** reacted with ethyl fluoroacetate – *t*-BuOK and then – ethyl iodide to give enol ether **267**, which was transformed to racemic **232** by reaction with guanidine. Resolution of enantiomers of **232** was achieved by crystallization of dibenzoyl-*L*-tartaric acid salt; the more active *R*-enantiomer was isolated.

In the synthesis of GW-842166X (**233**), commercially available pyrimidine **268** reacted with 2,4-dichloroaniline to give ester **269**, which was subjected to hydrolysis followed by amide coupling with 4-aminomethyltetrahydropyran (**270**) to afford **233** (Scheme 63) [236, 239, 240].



Scheme 63 Synthesis of GW-842166X (**233**)

6 Other Classes

In the previous sections, compounds targeting cancer cells or nervous system, as well as those fighting foreign organisms were discussed.

Three compounds do not fall into any of these categories. Fostamatinib disodium (**88**) was mentioned above as an anti-cancer investigational drug, but it was also studied as agent for autoimmune diseases, *i.e.* rheumatoid arthritis (currently in Phase III) and autoimmune thrombocytopenia (in Phase II). Gemigliptin (**12**) was approved as an anti-diabetic drug in South Korea in 2012. PF-04634817 (**271**) was discontinued after Phase I studies as an agent for liver fibrosis; nevertheless, it is currently investigated in diabetic nephropathy (Fig. 10) (Phase II, October 2012) [113].

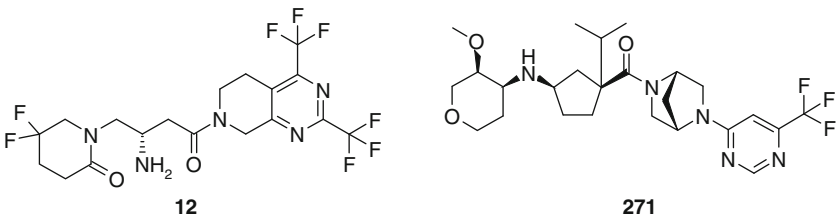


Fig. 10 The structure of Gemigliptin (**12**) and PF-04634817 (**271**)

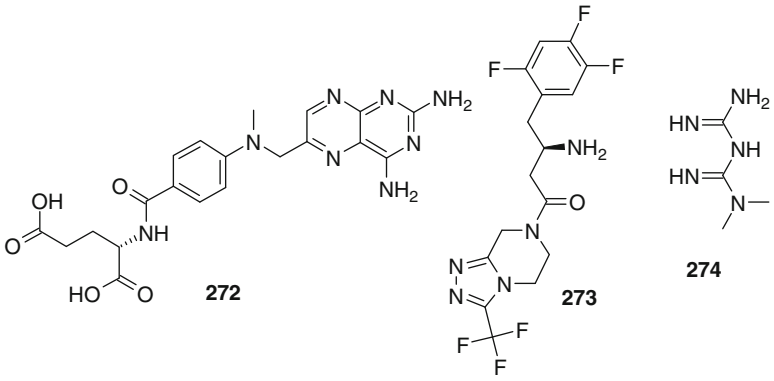


Fig. 11 The structures of Methotrexate (**272**), Sitagliptin (**273**) and Metformin (**274**)

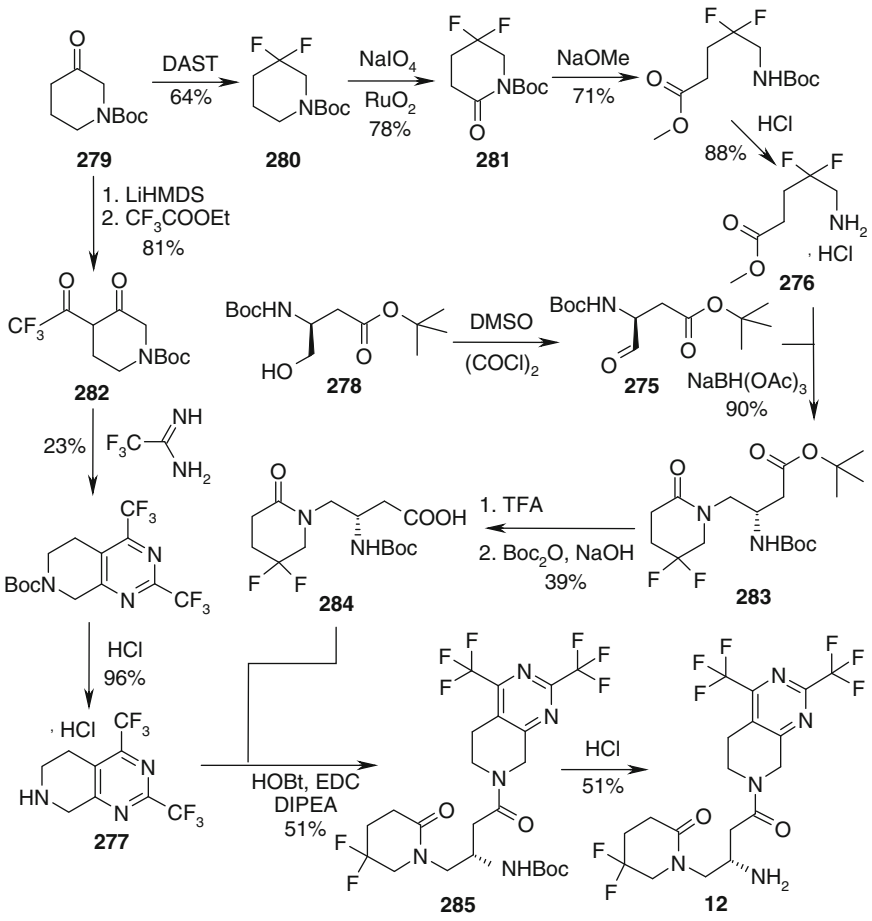
As it was mentioned in the previous sections, the active principle of Fostamatinib disodium (**88**) is Tamatinib (**92**), which is formed by enzymatic hydrolysis of **88** in the intestine. As in the case of lymphoma, the effect of **88** in autoimmune diseases is related to inhibition of Spleen tyrosine kinase (Syk) by **92** [241, 242]. As Syk has the central role in transmission of activating signals within B cells, inhibition of this enzyme lowers expression of a number of pro-inflammatory cytokines and hence leads to immunosuppression [243]. Fostamatinib has shown significant efficacy in the treatment of patients with rheumatoid arthritis not responding to Methotrexate (**272**) (a drug which is used conventionally in therapy), although a number of adverse events were observed [244]. If these results are confirmed once Phase III studies are completed, it may find a place in the treatment of patients with rheumatoid arthritis with poor response to conventional therapy (Fig. 11).

Gemigliptin (**12**) was developed by LG Life Sciences as an inhibitor of dipeptidyl peptidase 4 (DPP-4) – a target of oral drugs used to treat used to treat type 2 diabetes (characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency) [245]. The first representative of this class, Sitagliptin (**273**) was launched in 2006. In human body, Gemigliptin is metabolized to LC15-0636, which is a major active metabolite, by cytochrome P450 3A4 isozyme [246]. Inhibition of DPP-4 results in increase of incretin levels (which is normally inactivated by DPP-4), in particular glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) [247]. Incretins inhibit glucagons release and stimulate insulin secretion, which leads to decrease in glucose blood levels. Clinical trials showed efficacy and safety of Gemigliptin administered once daily as a monotherapy, [248] as well as in addition to Metformin (**274**) [249] for type 2 diabetes patients.

PF-04634817 (**271**) is a Phizer's investigational drug, initially developed as agent for liver fibrosis – formation of excess fibrous connective tissue in liver [250]. The development of the compound was discontinued since February 2012 after Phase I trials. Recently, a Phase II study of PF-04634817 in diabetic nephropathy – a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli [251] – was registered [113]. PF-04634817 is an antagonist of chemokine receptors (*i.e.* CCR2 and CCR5) [252]. These chemokine receptors are important players in the trafficking of monocytes/macrophages and in the functions of other cell types relevant to pathogenesis of many diseases [253], including liver fibrosis [307] and diabetic nephropathy [254].

Gemigliptin (**12**) was prepared by a convergent synthesis involving key intermediates **275**, **276** and **277** (Scheme 64) [255]. Compound **275** was obtained by Swern oxidation of β-amino acid derivative **278**. Both **276** and **277** were prepared starting from *N*-Boc-3-piperidone **279**. In particular, **279** reacted with diethylaminosulfur trifluoride (DAST) to give difluoro derivative **280**. Ru-catalyzed oxidation of **280** led to the formation of amide **281**, which was subjected to ring-opening with NaOMe and then acidic deprotection to give hydrochloride **276**. To obtain **277**, *N*-Boc-3-piperidone was deprotonated and then acylated with ethyl trifluoroacetate to give β-diketone **282**. Reaction of **282** with trifluoroacetamidine followed by deprotection afforded **277**. Further step of the synthesis included reductive amination of aldehyde **275** with amine **276**, which was accompanied with piperidone ring formation to give **283**. Full deprotection of **283** followed by selective protection of the amino group gave carboxylic acid **284**, which was coupled with amine **277** to afford Boc derivative **285**. Finally, deprotection of **285** led to the formation of Gemigliptin (**12**).

Synthesis of optically active PF-04634817 (**271**) based on commercially available (-)-Vince Lactam as chirality source. Starting from (-)-Vince Lactam the chiral key 4-amino-2-cyclopentene-1-carboxylic acid derivative **286** was synthesized. The compound **286** is dimethyl pyrrole protected form of corresponding aminoacid, which was subjected to amide coupling with Boc-protected diamine **287** to give

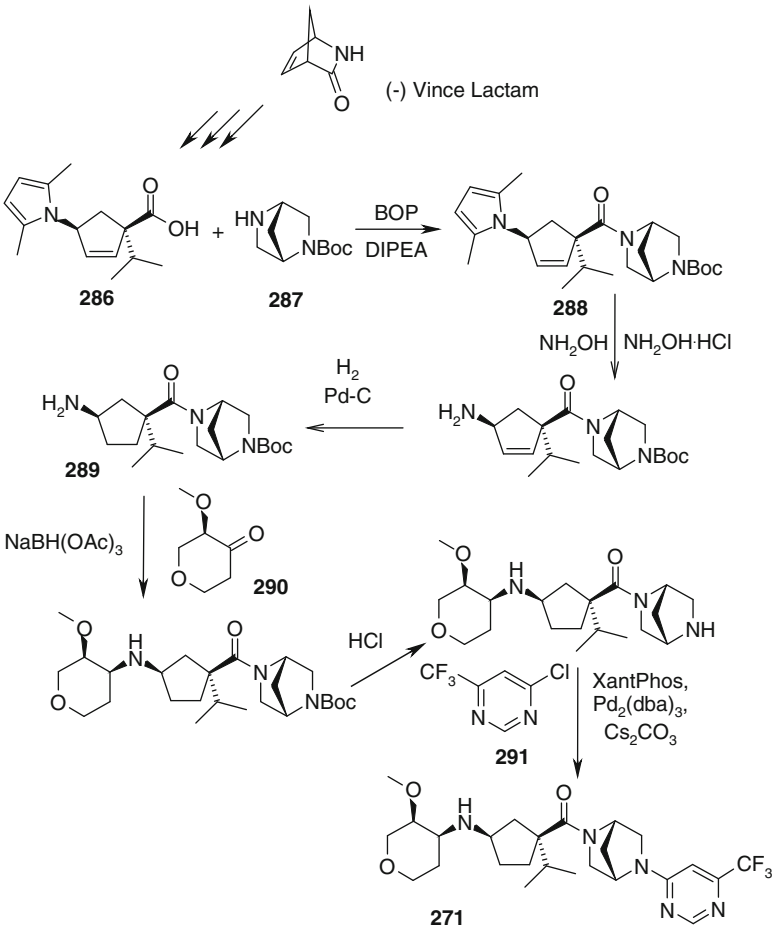


Scheme 64 Synthesis of Gemigliptin (**12**)

amine **288** (Scheme 65) [252]. Removing of the pyrrole function followed by catalytic hydrogenation gave amine **289**, which was subjected to reductive amination of ketone **290**, separation of diastereomers, deprotection and then – arylation with pyrimidine derivative **291** to afford the final product, **271**.

7 Fluorine-Containing Diazines in Agrochemistry

Agrochemistry is one of more important field of application of the fluorinated compounds which is widely recognized [256, 257]. Eleven derivatives of fluorine-containing diazines are agrochemicals: 8 compounds (**292**–**299**) are herbicides;



Scheme 65 Synthesis of PF-04634817 (**271**)

Fluoxastrobin (**300**) is a fungicide, Fluacrypyrim (**301**) – an acaricide, and Flufenerim (**302**) is currently under development as an insecticide (Fig. 12).

8 Herbicides

8.1 Protoporphyrinogen Oxidase Inhibitors

Uracil derivatives Butafenacil (**292,** Inspire®, Rebin®) and Benzfendizone (**293**) were introduced as herbicides in 1998, whereas their pyridazine-derived analogue Flufenpyr-ethyl (**295**) – in 2000 [258]. Butafenacil (developed by Syngenta

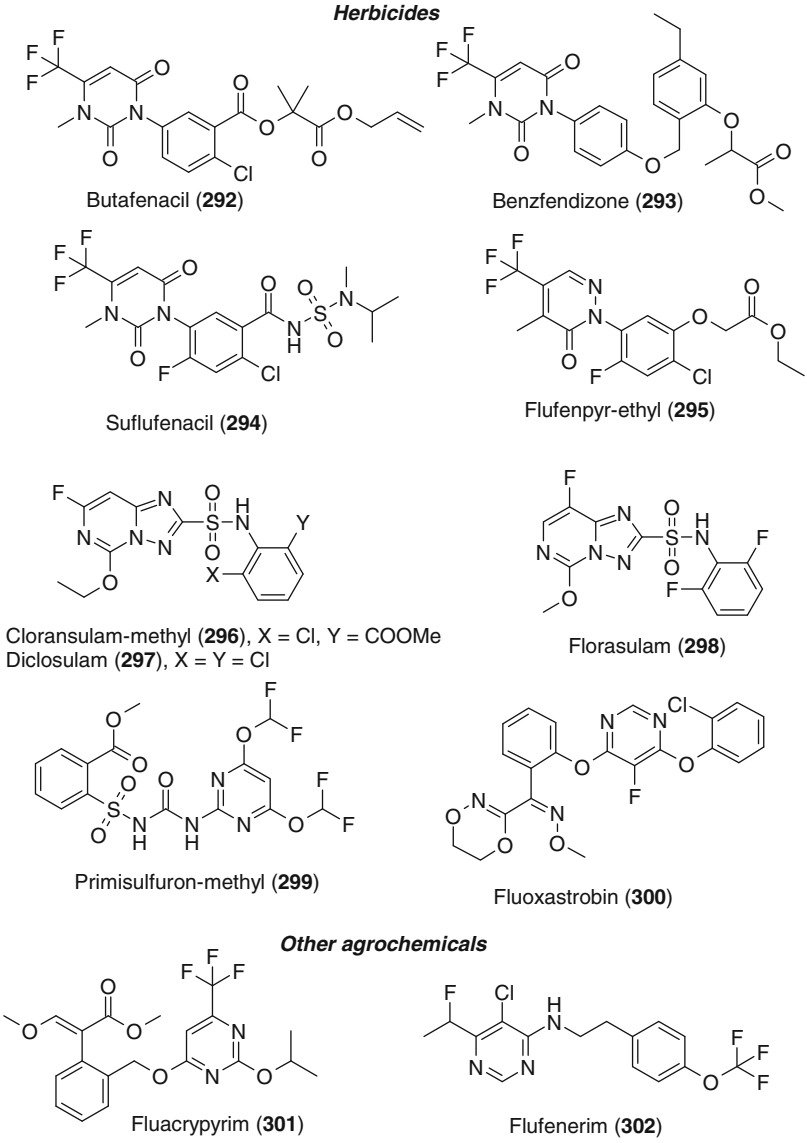
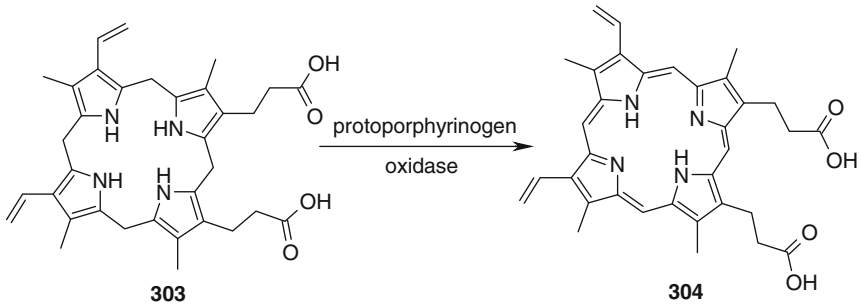


Fig. 12 Agrochemicals derived from fluorine-containing diazines

AG) is used for weed control in grapes, nut crops, pome and stone fruits and also as a cotton defoliant [259]. It was registered in Australia and approved by U. S. environmental protection agency. Benzfendizone (developed by FMC Corporation) is a post-emergence herbicide that provides good control of grass and broadleaf weeds in tree fruits and vines, as a cotton defoliant, and in total vegetation control [256]. Flufenpyr-ethyl (developed by Sumitomo Chemical

Company) was registered in USA for use on corn, soybeans and sugarcane [259]. The most recent example is Saflufenacil (**294**, Kixor®), introduced by BASF in 2009 for preplant burndown and selective PRE dicot weed control in multiple crops, including corn. [260].

Compounds **292–295** act as inhibitors of protoporphyrinogen oxidase (Protox) – an enzyme in the chloroplasts of the plant cells that oxidizes protoporphyrinogen IX (**303**) to produce protoporphyrin IX (**304**) (Scheme 66) [261]. In turn, **304** is a precursor molecule for both chlorophyll and heme. When protoporphyrinogen oxidase is inhibited, protoporphyrinogen IX is accumulated and transferred from chloroplasts into the cytoplasm, where non-enzymatic conversion of **303** to **304** occurs. When present in cytoplasm, **304** is cytotoxic due to interaction with oxygen upon action of light, which results in formation of singlet O_2 molecules. $^1O_2$ causes lipid peroxidation, membrane disruption and plant cell death.

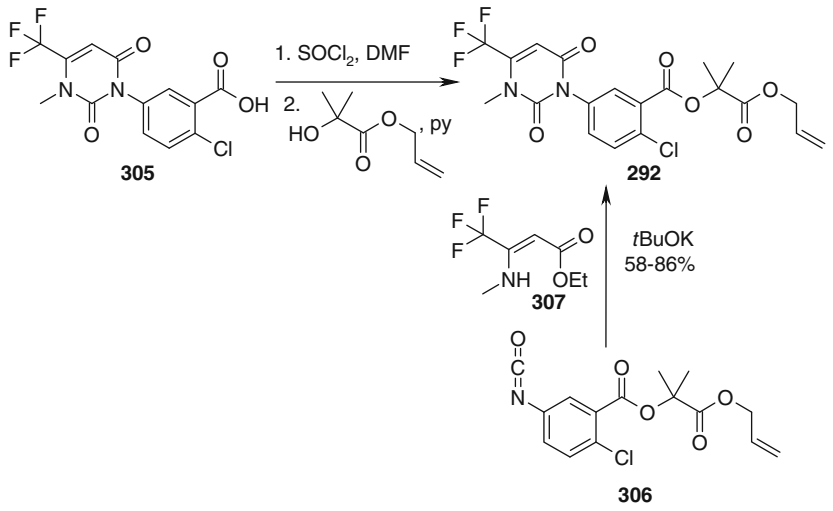


Scheme 66 Biological role of protoporphyrinogen oxidase

Butafenacil is known to be eye, skin and respiratory tract irritant in humans [262]. It also demonstrated very high toxic effect to algae, and moderate toxicity to fish, aquatic invertebrates and honeybees. For Benzfendizone and Flufenpyr-ethyl, no reports on toxic effects are available. Acute mammalian toxicology studies of Saflufenacil indicate that herbicide has low toxicity for mammals after ingestion, dermal exposure or inhalation. It is not an irritant for eyes and skin and does not act as a sensitizer.

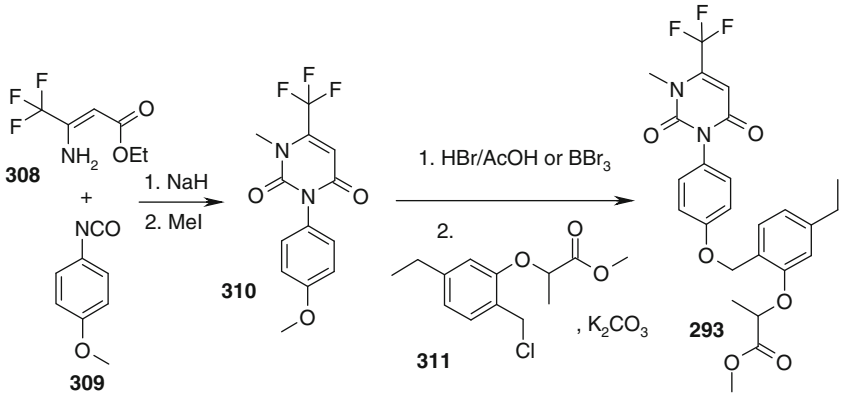
Studies of the structure–activity relationship (SAR) of uracile derivatives as protox inhibitor showed that presence of a polyfluorinated alkyl group at position 6 of the uracil ring critical. Alkyl groups such as methyl at position 6 of the uracil ring resulted in compounds with low or no biological activity [263].

Limited data are available on the synthesis of Butafenacil (**292**). In particular, it was prepared by esterification of carboxylic acid **305**, [264] as well as by reaction of isocyanate **306** with ester **307** (Scheme 67) [265]. Preparation of neither **305** nor **306** was disclosed in the corresponding patents, although synthesis of carboxylic acid **305** was partially described elsewhere [266].



Scheme 67 Syntheses of Butafenacil (**292**)

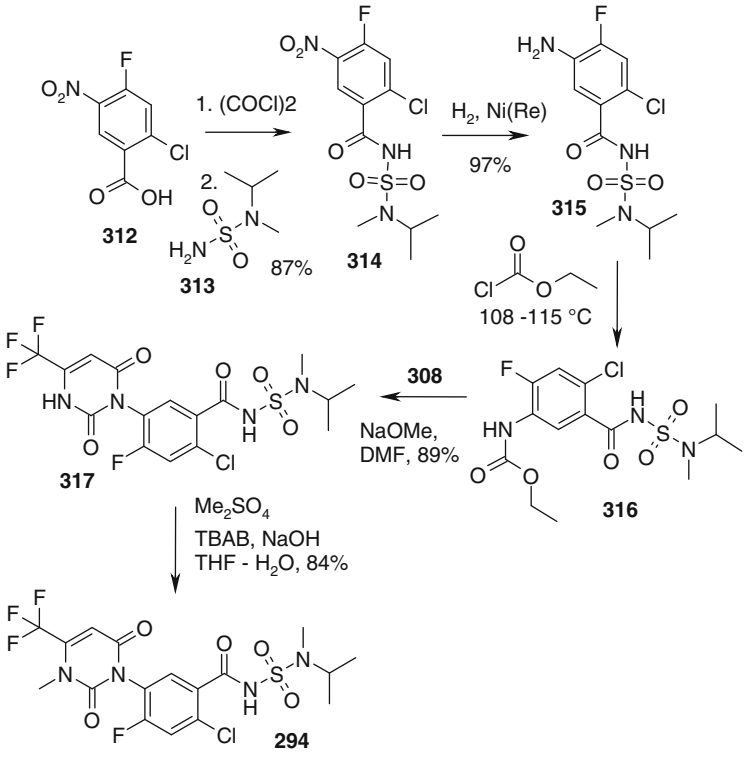
Benzfendizone (**293**) was obtained from ethyl trifluoromethylaminocrotonate (**308**) which reacted with isocyanate **309** in the presence of NaH and then directly methylated to give **310** (Scheme 68) [267]. Demethylation of phenol moiety in **310** followed by alkylation with benzyl chloride **311** gave Benzfendizone.



Scheme 68 Synthesis of Benzfendizone (**293**)

The synthesis of Saflufenacil (**294**) is similar to Benzfendizone synthesis, but on the key step of uracile formation instead of isocyanate corresponding urethane **316** was used in basic conditions. Starting amine **315** was obtained in 3 steps from acid

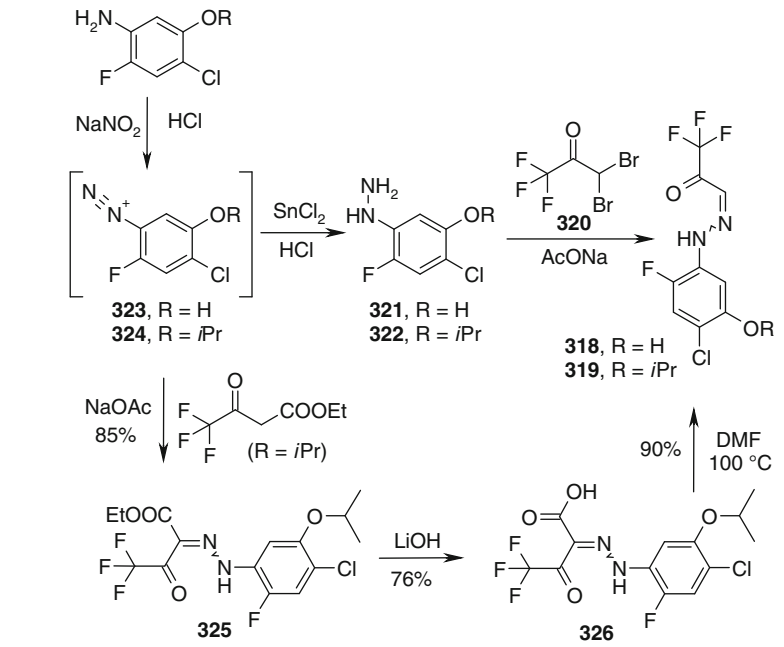
312. The final step of Saflufenacil formation is alkylation by Me_2SO_4 in phase transfer conditions (Scheme 69) [268].



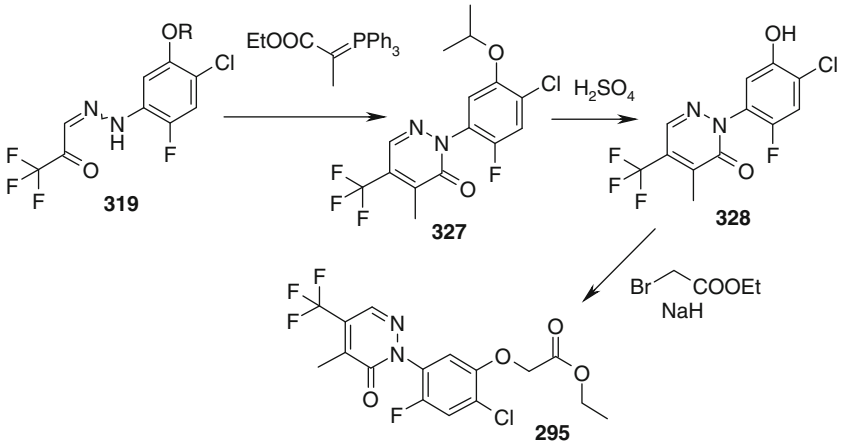
Scheme 69 Synthesis of Saflufenacil (**294**)

In the preparation of Flufenpyr-ethyl (**295**), hydrazones **318** or **319** were the key synthetic intermediates (Scheme 70) [269–271]. Both compounds **318** and **319** were prepared by reaction of dibromoketone **320** and the corresponding hydrazines **321** and **322**, in turn obtained by reduction of diazonium salts **323** and **324**. Alternatively, hydrazone **319** was prepared by reaction of **324** and ethyl trifluoroacetoacetate, followed by hydrolysis and decarboxylation.

Further transformations of **319** included reaction with (carbethoxylidene)triphenylphosphorane resulting in the formation of pyridazine derivative **327**. Acidic hydrolysis of **327** led to **328**, which was alkylated with ethyl bromoacetate to give **295** (Scheme 71).

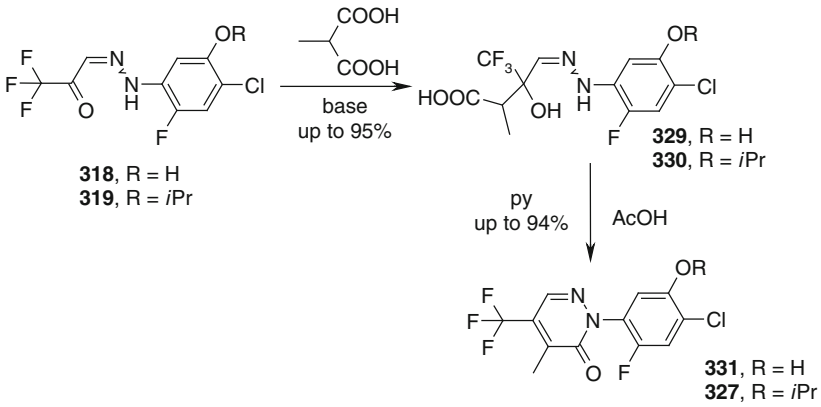


Scheme 70 Syntheses of key intermediates for Flufenpyr-ethyl (**295**)



Scheme 71 Synthesis of Saflufenacil *via* Wittig approach (**295**)

Alternatively, either **318** or **319** reacted with methylmalonic acid to give adducts **329** or **330**, which underwent cyclization upon heating with carboxylic acid and a base to give **331** and **327**, respectively. Both **331** and **327** were transformed to Flufenpyr-ethyl (**295**) as described above (Scheme 72).

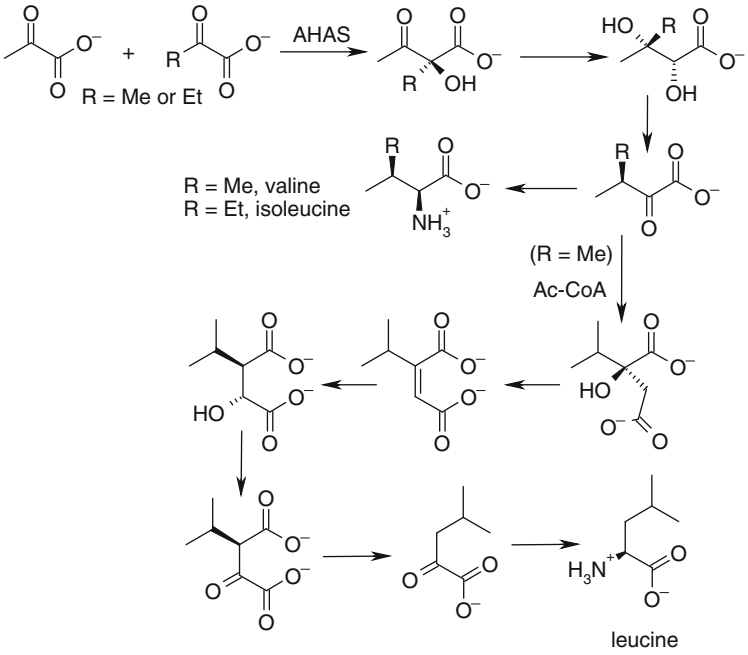


Scheme 72 Synthesis of Saflufenacil *via* malonate addition (**295**)

8.2 Acetohydroxy Acid Synthase Inhibitors

Compounds discussed in this section are derivatives or analogues of sulfonylurea herbicides – agrochemicals which began the present low-dose era of herbicide chemistry in 1970s [257]. Primisulfuron-methyl (**299**) (from Ciba-Geigy Corporation and Syngenta AG) is a sulfonylurea derivative introduced in 1990 [262]. It is used for post-emergence control of actively growing weeds in corn and in non-cropland areas [272]. Cloransulam-methyl (**296**), Florasulam (**298**), and Diclosulam (**297**), all developed by Dow AgroSciences, are examples of the triazolopyrimidine sulfonanilide herbicides; they were introduced in 1998, 1999, and 2000, respectively. Cloransulam-methyl is used for soil-applied and post-emergence control of broadleaf weeds in soybeans [273]. Florasulam is a highly-selective broadleaf herbicide which is registered for use in cereals in many countries around the world. Diclosulam-based products are registered for use to control annual and certain perennial broadleaf weeds; they can be can be applied as soil, foliar, or burndown treatments in crops such as sugar cane, peanuts and soybeans and in forestry applications.

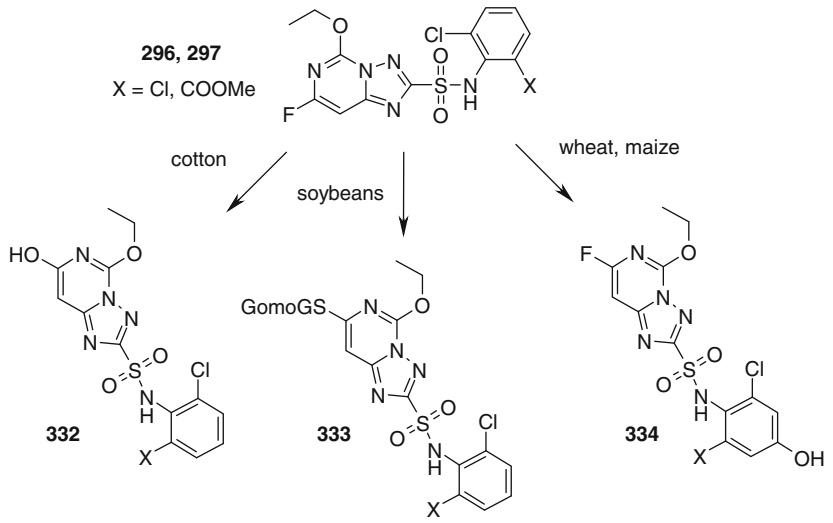
Compounds **296**–**299** inhibit acetohydroxy acid synthase (AHAS), formerly known as acetolactate synthase. Its activity is not present in animals, but it has been found in all plants where measurements have been attempted. Acetohydroxy acid synthase catalyses the first step in production of branched amino acids (leucine, valine and isoleucine) (Scheme 73), which are obviously needed for the protein synthesis and cell growth. The compounds **296**–**299** seem to bind within the substrate-access channel of the enzyme, thus blocking α-ketocarboxylate access to the active site. While these herbicides are undoubtedly highly successful, resistance developed due to mutations within AHAS is becoming a serious problem [274, 275].



Scheme 73 Biological role of acetohydroxy acid synthase (AHAS)

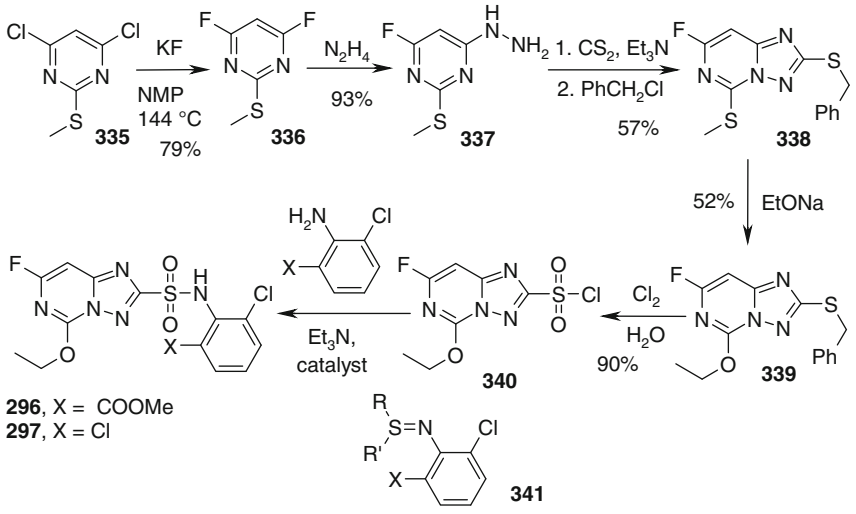
Primisulfuron-methyl is a slightly toxic for skin, inhalation and eye exposure, with little metabolic activity in mammalian. It is slightly toxic to freshwater fish, aquatic organisms and to marine shrimp and has no toxic effect on birds and honeybees [276]. Cloransulam-methyl can be highly toxic to certain aquatic plants and algae on an acute basis; it is practically nontoxic to other non-plant organisms. Florasulam is highly toxic to aquatic organisms and slightly toxic to birds, and Diclosulam is very highly toxic to aquatic organisms [272].

In contrast to uracile herbecides in which CF_3-group is critical for activity in fluorinated triazolopyrimidine series fluorine atom responsible for the methabolitic transformation of the herbecides. The different metabolic pathway of the triazolopyrimidine herbicide diclosulam and Cloransulam-methyl are guided by the fluorine atom at the 7-position on the triazolopyrimidine ring system (Scheme 74). The predominance of one pathway is very crop specific. In cotton, **296** and **297** are metabolized by the displacement of the 7-flouro substituent on the triazolopyrimidine ring by a hydroxy group, forming **332**. Its soybean selectivity is attributed to facile conjugation with homo-glutathion (homoGSH), which displaces the 7-fluoro substituent (**333**). This mechanism was found to only occur in soybeans for these herbecides. In maize and wheat, **296** and **297** are detoxified by hydroxylation at the 4-th position on the aniline moiety (**334**) followed by subsequent glycosidation [277].



Scheme 74 Metabolism of Cloransulam-methyl (**296**) and Diclosulam (**297**) in crops

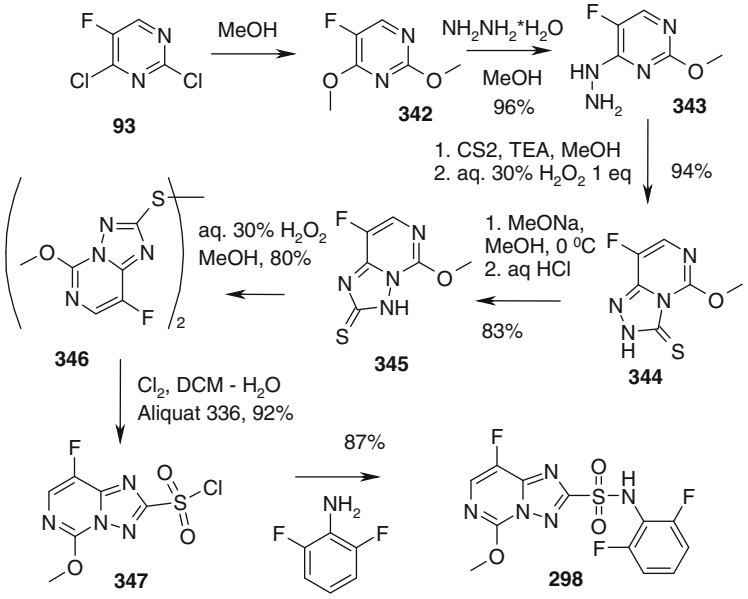
Cloransulam-methyl (**296**) and Diclosulam (**297**) were obtained by reaction of sulfonyl chloride **340** with the corresponding aniline derivatives (Scheme 75). Synthesis of **340** commenced from dichloropyrimidine **335** [278], which reacted with KF and then – hydrazine hydrate to give **337**. Reaction of **337** with CS_2/Et_3N and then – benzyl chloride was accompanied by Dimroth rearrangement and gave



Scheme 75 Synthesis of Cloransulam-methyl (**296**) and Diclosulam (**297**)

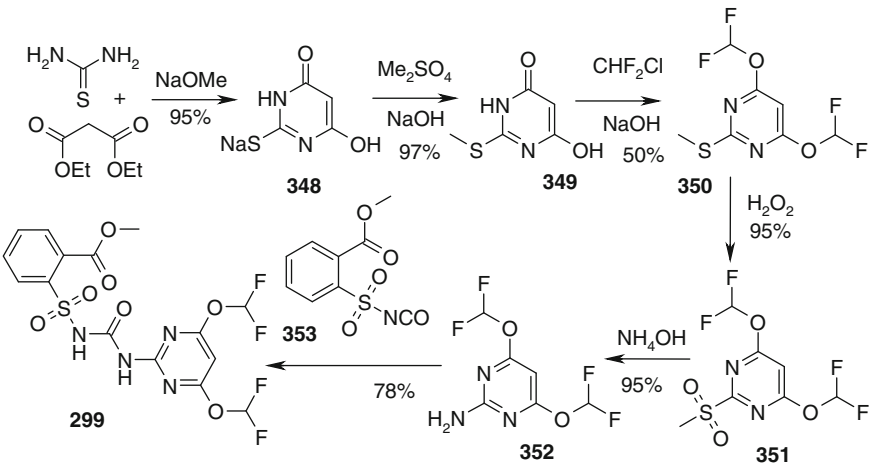
[1,2,4]triazolo[1,5-*c*]pyrimidine derivative **338**, which was transformed to **339** by treatment with EtONa. Finally, chlorination of **339** in H_2O–$CHCl_3$ led to the formation of **340**. Reaction of **340** with the corresponding aniline derivatives was performed in the presence of Me_3SiCl–NaI [278], as well as of *N*-arylsulfilimine compounds **341** [279] or 1,2-diols (*e.g.* 1,2-propanediol) [280].

Florasulam (**298**) was synthesised starting from dichloropyrimidine **93**, which was converted to dimethoxy derivative **342**. The reaction of **342** with hydrazine hydrate in MeOH regioselectively leads to hydrazine **343**, which was cyclized with CS_2 into [1,2,4]triazolo[4,3-c]pyrimidine-3-thion **344**. The based catalysed Dimroth rearrangement of **344** gave [1,2,4]triazolo[1,5-c]pyrimidine-2-thione **345**. Oxidation of **345** followed by chlorination and sulfamide coupling afforded target Florasulam (**298**) in high preparative yield (Scheme 76) [281–283].



Scheme 76 Synthesis of Florasulam (**298**)

The synthesis of Primisulfuron-methyl (**299**) started from reaction of diethyl malonate and thiourea (Scheme 77) [284]. The resulting pyrimidine derivative **348** was methylated, difluoromethylated and then oxidized to give sulfone **351**. Reaction of **351** with aqueous ammonia gave heteroaromatic amine **352**, which was transformed to Primisulfuron-methyl (**299**) upon treatment with isocyanate **353**.



Scheme 77 Synthesis of Primisulfuron-methyl (**299**)

9 Mitochondrial Respiratory Chain Inhibitors

Fluoxastrobin (**300**) is a pesticide from Bayer CropScience for the control of fungal diseases, which was registered by U. S. environmental protection agency (EPA) in 2005 [276]. Fluoxastrobin is used on peanuts, tuberous and corm vegetables, leaf petiole vegetables, fruiting vegetables and turf. Fluacrypyrim (**301**) was discovered by BASF AG and introduced in 2002 by Nippon Soda Co., shows acaricidal effect against all stages of tetranychid [285]. Both **299** and **300** are representative of strobilurin family with parent compound Strobilurin A (**354**) (Fig. 13), discovered in late 1970s [286]. Interestingly, Fluacrypyrim (**301**) is the first representative of strobilurin family which is not used as a fungicide.

Strobilurins are the part of the larger group of the so-called quinone outside inhibitors (QoI) –compounds which act at the quinol outer binding site of the cytochrome bc_1 complex. This enzyme, also referred to as ubiquinol: ferricytochrome *c* reductase, or complex III, is the third complex in the electron transport chain – a cascade of enzymes which couples electron transfer between NADH and O_2 with the transfer of H^+ ions across a membrane to generate chemical energy in the form of adenosine triphosphate (ATP) [287]. The overall result of the reaction catalyzed by cytochrome bc_1 complex is reduction of ferricytochrome *c* by oxidation of ubiquinol (**355**) and the concomitant pumping of 4 protons from the mitochondrial matrix to the intermembrane space. The mechanism of this process is too sophisticated to be discussed herein. It is important that the enzyme has two binding sites for the substrate **355** or its oxidized form **356** (Fig. 14), *i.e.* outer (Q_0) and inner (Q_1), and the quinone outside inhibitors bind to the outer site. This leads to inhibition of mitochondrial respiration – a process which is essential to all living organisms. The selective biological effect of quinone outside inhibitors on certain organisms (*i.e.* fungi or mites) is achieved by differential penetration and

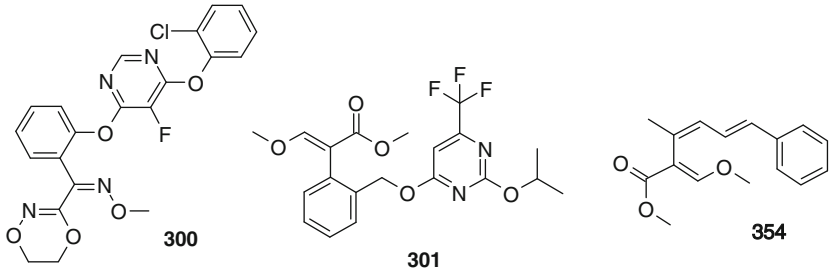
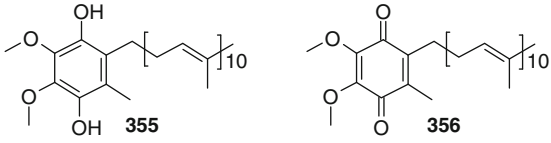


Fig. 13 Representatives of strobilurin family

Fig. 14 The structures of ubiquinol (**355**) and ubiquinone (**356**)



degradation between various species, leading to a combination of high fungicidal (or acaricidal, in the case of **301**) potency and good crop safety [288]. Unfortunately, resistance has already evolved to this class of pesticides in some plant pathogens in certain geographical areas [289].

Although the *in vitro* fungicidal activity of the natural strobilurin **A** was discovered soon, its agrobiological testing *in vivo* was difficult because of its volatility and the inherent lability of the (*E,Z,E*)-triene system, which resulted in rapid photolytic or metabolic degradation. The unusual structural simplicity of this natural product soon made it a target for chemical derivatization. Below a set of isosterical replacement in a course of lead optimization of natural strobirulin **A** leading to commercial synthetic products shown on the Fig. 15.

The first sequence leads to first commercialized strobilurin azoxystrobin (1996, Amistar®, Syngenta) and than to fluoxastrobin (**300**), which structure combines a methoximino 5,6-dihydro-1,4,2-dioxazin-2-yl toxophore (Bayer toxofore) with an optimally adjusted side-chain bearing a 6-(2-chlorophenoxy)-5-fluoro-pyrimidin-4-yl-oxy moiety as an essential element. Fluoxastrobin (**300**) has an advantage as no reorientation of the toxophore is necessary for binding to the target. The SARs studies indicate that the fluorine atom has a beneficial effect on the phytotoxicity and leaf systemicity. Another sequence leads to Picoxystrobin (2002, Acanto®, Syngenta), which has a 6-CF_3-pyridin-2-yl moiety in its arylalkyl ether side-chain. An indication switch from the fungicidally to acaricidally active strobilurin type with β-methoxyacrylate pharmacophore is achieved by exchange of the 6-CF_3-pyridin-2-yl moiety in the arylalkyl ether side-chain of Picoxystrobin with a 2-iPrO-6-CF_3-pyrimidin-4-yl moiety to give fluacrypyrim (**301**).

Fluoxastrobin (**300**) was obtained by reaction of compounds **359** and **360** in the presence of K_2CO_3 (Scheme 78) [290]. Compound **359** was prepared by reaction of 4,5,6-trifluoropyrimidine (**358**) with potassium *o*-chlorophenolate. In turn, **358** was obtained from 5-chloro-4,6-difluoropyrimidine (**357**) by reaction with KF.

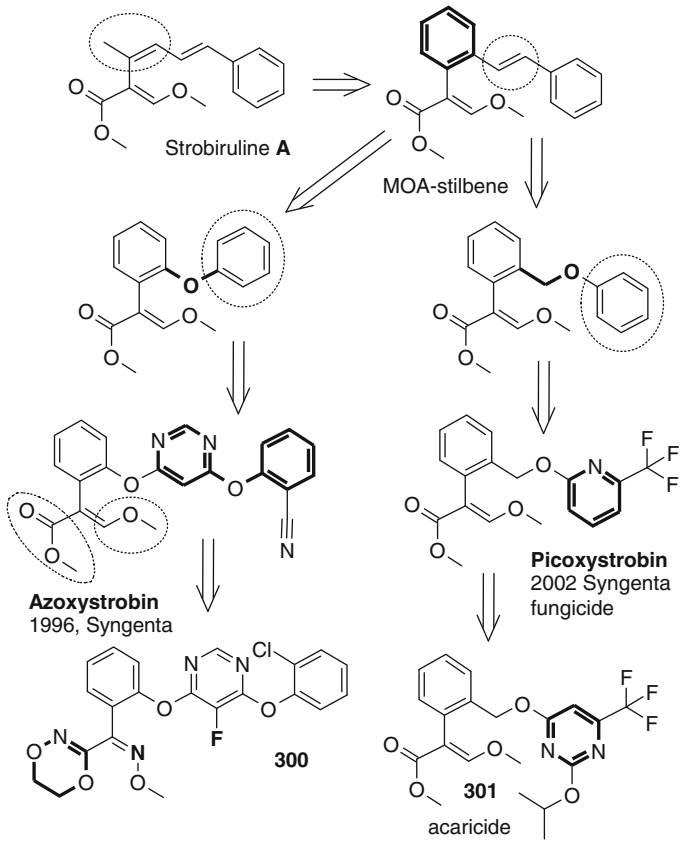
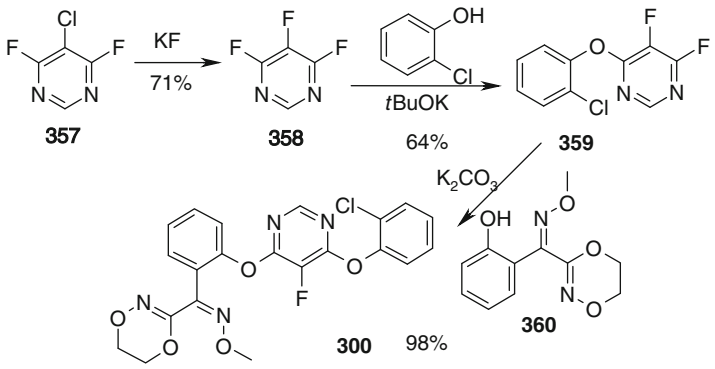


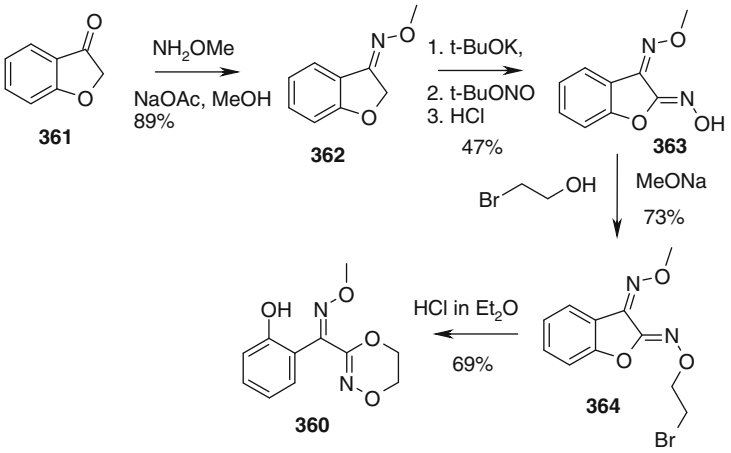
Fig. 15 Map of isosterical replacement for lead optimization of natural strobirulin A



Scheme 78 Synthesis of Fluoxastrobin (**300**)

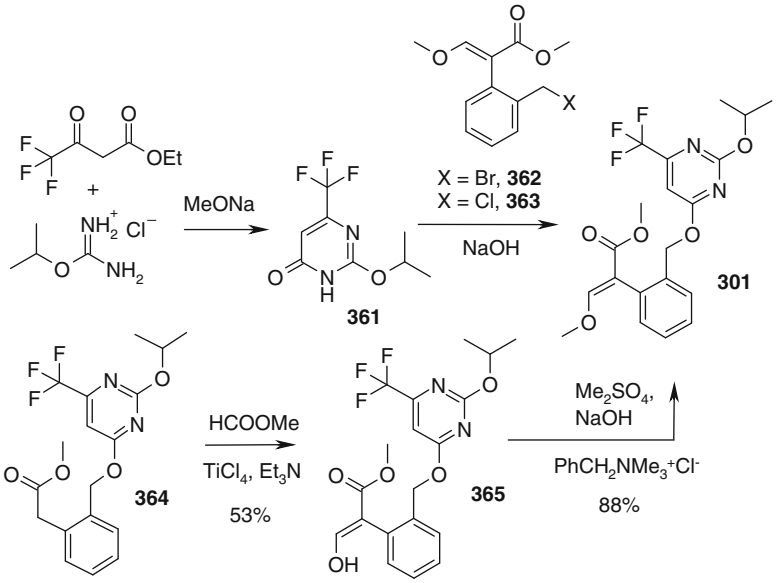
The synthesis of key intermediate **360** bearing unusual fragment of 5,6-dihydro-1,4,2-dioxazin was developed by Bayer in 2002. Synthesis started from

benzofuran-3-one which was converted to oxime **362**. Nitrozation of **363** with followed alkylation with bromoethanole leads to bisoxime **364**, with under acidic treatment gave target dioxazin **360** (Scheme 79) [291].



Scheme 79 Synthesis of key intermediate **360**

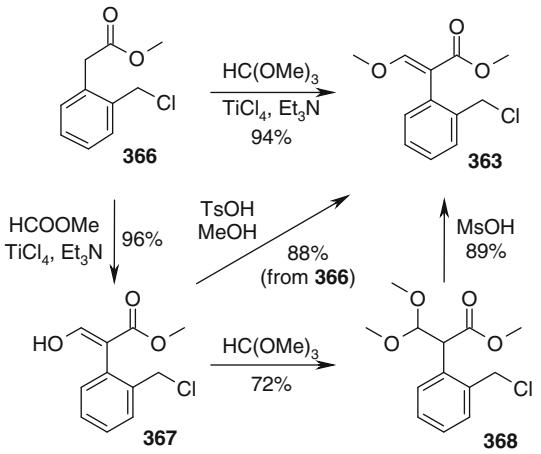
Preparation of Fluacrypyrim (**301**) started with reaction of *O*-isopropylisourea hydrochloride and ethyl trifluoroacetoacetate to give pyrimidine **361** (Scheme 80) [292]. Alkylation of **361** with bromide **362** (or the corresponding chloride **363** [293,



Scheme 80 Syntheses of Fluacrypyrim (**301**)

294]) in the presence of alkali or K_2CO_3 gave Fluacrypyrim. Cu_2O-catalyzed alkylation of **361** was also developed for the synthesis of **300** [295]. Compounds **362** and **363** were obtained using several closely related methods. In particular, $TiCl_4$-mediated reaction of chloride **366** and methyl orthoformate was used to obtain **363** (Scheme 81) [293, 294]. Alternatively, **366** reacted with methyl formate in the presence of $TiCl_4$–Et_3N to give **367**, which was treated with *p*-toluenesulfonic acid in methanol to give **363**. Yet another method included reaction of **367** with methyl orthoformate to give **368**, which was transformed to **363** upon treatment with methanesulfonic acid.

Another approach to Fluacrypyrim (**301**) commenced from pyrimidine derivative **364**, which reacted with methyl formate in the presence of $TiCl_4$–Et_3N to give **365**



Scheme 81 Synthesis of key intermediate **363**

(Scheme 80) [293, 294]. Methylation of **365** using methyl orthoformate or dimethyl sulphate and alkali led to the formation of **301**.

The last pesticide from this section is Flufenerim (Flumfen® **302**), which is under development by Ube Industries as an insecticide. It is reported to control aphids, whiteflies, and cotton leafworm, but has no activity against thrips [296]. Since Flufenerim is chemically related to Pyrimidifen (Miteclean® **369**) (Fig. 16), it was initially believed to have similar mechanism of action, *i.e.* inhibition of the mitochondrial electron transport of NADH dehydrogenase (NADH: ubiquinone oxidoreductase, complex I) – an enzyme which transfers electrons from NADH to ubiquinone and hence opens the electron transport chain cascade. Nevertheless, it was shown that **302** reduced activity of acetylcholinesterase – an effect which possibly can be addressed to interaction with other systems [297].

Flufenerim (**302**) was prepared from 4,5-dichloro-6-ethylpyrimidine (**347**) (Scheme 82) [298]. Compound **370** was chlorinated with chlorine gas; the product **371** thus obtained was subjected to nucleophilic substitution with AcOK to give acetate **372**, which upon hydrolysis and subsequent reaction with diethylaminosulphur trifluoride (DAST) gave fluoride **374**. Finally, reaction of **374** with amine **375** led to the formation of Flufenerim (**302**).

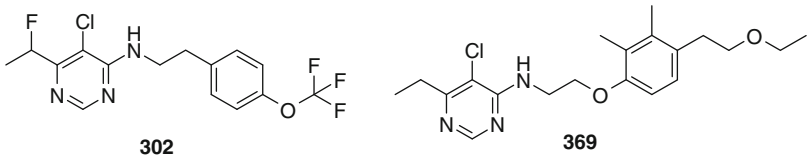
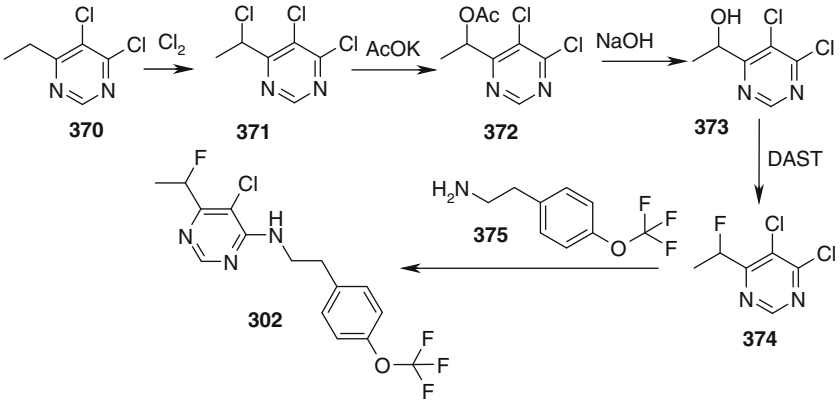


Fig. 16 Flufenerim (**302**) and Pyrimidifen (**369**)



Scheme 82 Synthesis of Flufenerim (**301**)

10 Conclusions and Outlook

Since discovery of the first fluorinated diazine – antineoplastic agent 5-fluorouracil more than 20 compounds from the class were introduced into the market. Undoubtedly the success was achieved due to joint progress of medicinal chemistry, agrochemistry as well as synthetic methods of heterocyclic and fluoroorganic chemistry. The continued progresses in these fields of science allow us to predict that the number of fluorine containing diazines as drugs or agrochemicals on the market will be increased. Recent trends in using of perfluorinated diazines as core scaffold for the synthesis of a diverse array of polysubstituted fluorinated diazines for HTS increases probability of these compounds as potential hits and leads. Also the new methodologies of direct introduction of fluorinated substituent, like Baran approach, continue to appear facilitating further investigation. Moreover in the chemical space covered by fluorinated diazines remains "white spots". Thus diazine scaffold decorated by important in med and agrochem fluorinated fragments such as $-CHF_2$, $-CH_2CF_3$, $-OCF_3$, $-SCF_3$, $-SF_5$ not investigated because the synthetic chemistry of these compounds on development phase or not developed at all. Therefore the comprehensive investigations in the field of fluorinated diazines still are interesting both for academic and industrial scientists.

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Fluorinated Triazines

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V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 2: 6-Membered Heterocycles*, 673
DOI 10.1007/978-3-319-04435-4_8, © Springer International Publishing Switzerland 2014

Abstract In this chapter data on structure, synthetic routes, reactivity of derivatives of 1,2,3-triazines, 1,2,4-triazines and 1,3,5-triazines – bearing one or several fluorine atoms in heterocyclic ring as well as trifluoromethyl substituted triazines are considered and analyzed, and also their certain representatives are discussed. The bibliography – 119 references.

Keywords Fluorine • Trifluoromethyl group • Triazine • NMR spectroscopy • Antiviral activity • Dyes

1 Introduction

A growing interest to fluorinated derivatives of triazines which is observed for the recent two decades has undoubtedly stimulated the development of new synthetic methods, as well as studying of their reactivity and elucidation of areas of their plausible applications.

2 Structure

In this section the data of theoretical studies reflecting the effects of fluorine atom(s) on geometrical characteristics of fluorine-containing triazines will be discussed. Selected examples of the X-ray crystallography analysis of 1,3,5-triazines, 1,2,4-triazines and 1,2,3-triazines as well as the data of ^{19}F NMR spectroscopy elucidations will be considered.

2.1 Quantum-Chemical Calculations

The effects of incorporating of a fluorine atom in the position 2 of 1,3,5-triazine ring have been estimated by *ab initio gradient* method [1]. According to the data of quantum chemical calculations (Table 1), the angle of $N^1C^2N^3$ increases of 1.6°, the bonds C^2-N^1 and C^2-N^3 become shorter of 0.0017 nm. It should be noted that the C-F bond in 2-fluoro-1,3,5-triazine is shortest one relative to 2-fluoropyridine (the

Table 1 Characteristics of 1,3,5-triazine and 2-monofluoro analogue

Parameter		
Bond length, nm		
N^1–C^2, N^3–C^2	0.1332	0.1315
N^3–C^4	0.1332	0.1332
C^4–N^5	0.1332	0.1332
C^2–X^2	0.1067	0.1332
C^4–H^4	0.1067	0.1066
C^6–H^6	0.1067	0.1066
Valency angles		
$C^6N^1C^2$	116.1	115.5
$N^1C^2N^3$	***123.9***	***125.5***
$N^3C^4N^5$	123.9	123.7
$C^4N^5C^6$	116.1	116.0
$N^1C^2X^2$	118.1	119.0
$N^3C^4H^4$	118.1	117.8
Dipolar moment	0	2.28

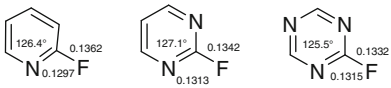


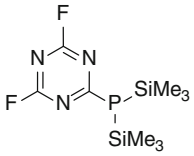
Fig. 1 Bond lengths (nm) and angles for 2-fluoropyridine, 2-fluoropyrimidine and 2-fluoro-1,3,5-triazine

difference is −0.003 nm) and 2-fluoropyrimidine (−0.001 nm) (Fig. 1). Calculations using HF//6-31G*//6-31G* gave following values of the N-F bond distances in 1-fluoro-2,4,6-trichloro-*s*-triazinium hexafluoroarsenate and 1-fluoro-*s*-triazinium hexafluoroarsenate: 0.1314 nm and 0.1317 nm respectively [2].

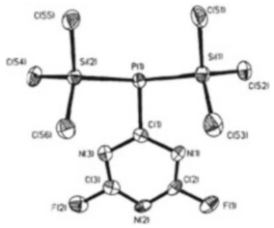
2.2 X-ray Crystallography Analysis Data

Research of fluorinated derivatives of triazine by the X-ray method has fragmentary character. Fluorinated 1,3,5-triazines are most in detail considered. The X-ray data for 2,4-difluoro-6-bis(trimethylsilylphosphino)-1,3,5-triazine (Fig. 2) have been obtained [3]. The $P(CN)_3$ fragment of the molecule is practically planar, however the angles in the 1,3,5-triazine ring proved to differ considerably from those of the correct hexagon figure. The C^1–N^1–C^2 angle is 112.3°, while the opposite angle N^2–C^3–N^3 has a much higher value of 132.0°. The C-N bond lengths have value which are typical for the corresponding double bond (0.131–0.135 nm), whereas C-P bond is significantly longer (0.181 nm), but keeps within an interval of typically C-P bond.

Also fluorinated anionic triazine systems with TAS^+ $[(Me_2N)_3S^+]$ cation have been studied by the X-ray crystallography (Figs. 3, 4, 5 and 6) [4]. It has been shown that values of the C^1–N^1 and C^1–N^3 bonds in the anion $C_3N_3F_4^-$ correspond to those

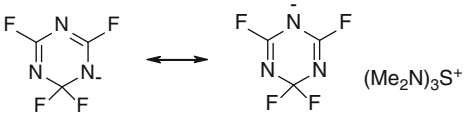


Bond lengths (nm):
C^1-N^1 0.131(2), C^1-N^3 0.136(2), C^1-P^1 0.181(1), C^2-N^1 0.130(2), C^2-N^2 0.132(2), C^2-F^1 0.133(1), C^3-N^2 0.131(1), C^3-N^3 0.130(2), C^3-F^2 0.134(2), P^1-Si^1 0.2256(5), P^1-Si^2 0.272(5), Si^1-C^{51} 0.186(2), Si^1-C^{52} 0.186(2), Si^1-C^{53} 0.186(1), Si^2-C^{54} 0.186(2), Si^2-C^{55} 0.186(2), Si^2-C^{56} 0.186(2).



Valency angles:
N^1-C^1-N^3 123.4(8), N^1-C^1-P^1 118.4(8), N^3-C^1-P^1 117.1(6), N^1-C^2-N^2 130.7(8), N^2-C^3-N^3 130.5(8), C^1-N^1-C^2 113.1(7), S-^{1}-P^1-Si^2 112.6(3), C^1-P^1-Si^2 101.1(4), C^1-P^1-Si^1 101.9(4), C^1-N^3-C^3 112.6(7), C^2-N^2-C^3 109.4(8).

Fig. 2 X-ray data for 2,4-difluoro-6-bis(trimethylsilylphosphino)-1,3,5-triazine (Reproduced with permission of ACS [3])



Bond lengths (nm):
C^1-F^1 0.1400(4), C^1-F^2 0.1383(4), C^1-N^1 0.1403(4), C^1-N^3 0.1400(4), N^1-C^2 0.1277(4), N^3-C^3 0.1279(4), C^2-N^2 0.1329(4), N^2-C^3 0.1319(4), C^2-F 0.1345(3), C^3-F 0.1348(3).
Valency angles: N^1-C^1-N^3 120.4(3), N^1-C^2-N^2 132.0(3), F^1-C^1-F^2 101.1(2)

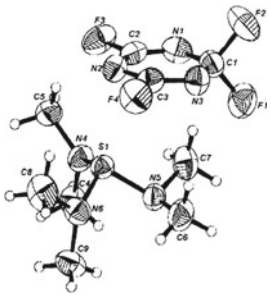
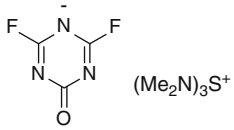


Fig. 3 X-ray data for TAS^+ $C_3N_3F_4^-$ (Reproduced with permission of RCS [4])



Bond lengths (nm):
C^1-O 0.1225(4), C^1-N^1 0.1390(4), C^1-N^3 0.1391(5), N^1-C^2 0.1288(5), N^3-C^3 0.1281(5), C^2-N^2 0.1310(6), N^2-C^3 0.1322(6), C^2-F 0.1350(5), C^3-F 0.1342(5).
Valency angles: N^1-C^1-N^3 119.4(3), N^1-C^2-N^2 132.1(4).

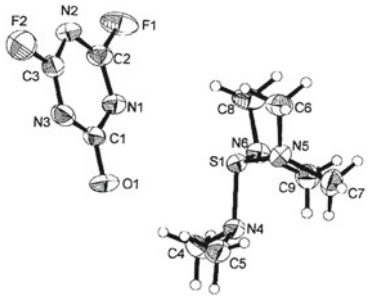
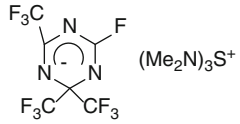


Fig. 4 X-ray data for PCA TAS^+ $C_3N_3F_2O^-$ (With permission of RCS [4])



Bond lengths (nm):
C^1-N^1 0.1444(6), N^1-C^3 0.1263(7)
N^2-C^3 0.1332(8), C^1-C^2 0.1536(5),
C^4-C^5 0.1458(8).
Angle N^1-C^3-N^3 118.3(4),
sum of angles 720.3.

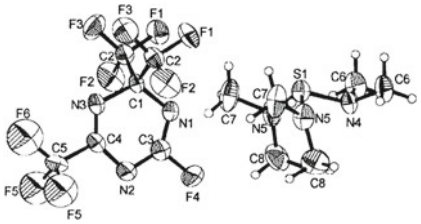
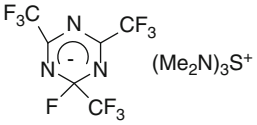


Fig. 5 X-ray data for TAS^+ $C_3N_3F(CF_3)_3^-$ (Reproduced with permission of RCS [4])



Bond lengths (nm):

C^1-N^1 0.1456(4), N^1-C^3 0.1302(4),
N^2-C^3 0.1334(4), C^1-C^2 0.1526(4),
C^5-C^6 0.1514(4).
Angle N^1-C^3-N^3 117.0(2),
sum of angles 716.7°.

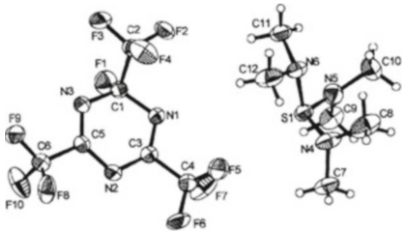
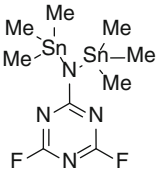


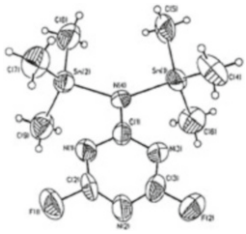
Fig. 6 X-ray data for TAS^+ $C_3N_3F(CF_3)_3^-$ (Reproduced with permission of RCS [4])

of the ordinary bond, the N^1–C^2 and C^3–N^3 bonds are double, while the C^2–N^2 and N^2–C^3 bonds proved to have intermediate values between ordinary and double bonds. The ring C_3N_3 fragment of compound TAS^+ $C_3N_3F_4^-$ is a planar one with the C^1 carbon atom to be in a tetrahedral configuration.

X-ray data for 2-tris(trimethylstannyl)amino-4,6-difluoro-1,3,5-triazine (Fig. 7) show that the triazine ring is a little distorted, the molecule is nearly planar with the exception of methyl groups. The maximum deviation from the plane is exhibited by tin atoms (0.009 nm). The enlarged angle N^2–C^3–N^3 (130.0°) is resisted by the angle C^2–N^1–C^1 (114.7°). The C-N bond attached to the triazine ring is unusually small and its length is very close to values of three other C-N bonds of the ring, thus indicating at a considerable π-linkage of the ring with the exocyclic nitrogen atom [5].

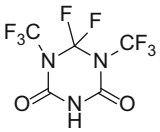
The N-F bond length (0.11 nm) in 1-fluoro-2,4,6-trichloro-*s*-triazine hexafluoroarsenate is shorter than its calculated value of 0.0214 nm [2]. Also perfluorinated hexahydro-1,3,5-triazin-2,6-dione has been studied by X-ray crystallography method (Fig. 8) [6].

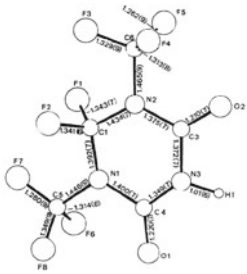




Bond lengths (nm):
N^4-C^1 0.1333(16), C^1-N^1 0.1366(16),
N^1-C^2 0.1297(18), C^2-N^2 0.1277(20),
N^2-C^3 0.1318(20), C^3-N^3 0.1311(19),
N^3-C^1 0.1356(16).
Valency angles: N^3-C^1-N^4 120.9(11),
N^4-C^1-N^1 118.8(11), C^1-N^1-C^2 114.7(11),
N^1-C^2-N^2 131.2(12), C^2-N^2-C^3 109.2(11),
N^2-C^3-N^3 130.0(12), C^3-N^3-C^1 144.3(11).

Fig. 7 X-ray data for 2-*tris*(trimethylstannyl)amino-4,6-difluoro-1,3,5-triazine (Reproduced with permission of ACS [5])





Valency angles: N^1-C^1-N^2 113.0(5),
C^1-N^2-C^3 124.3(5), N^2-C^3-N^3 115.4(5),
C^3-N^3-C^4 125.7(5), N^3-C^4-N^1 115.3(5),
C^4-N^1-C^1 125.1(5), F^1-C^1-F^2 104.9(4),
F^8-C^5-F^6 107.6(6), C^8-C^5-F^7 110.2(6),
F^6-C^5-F^8 106.3(6), F^5-F^6-F^4 108.7(6),
F^5-C^6-F^3 107.6(6), F^4-C^6-F^3 108.2(6).

Fig. 8 X-ray data for perfluorinated hexahydrotriazindione (Reproduced with permission of Elsevier [6])

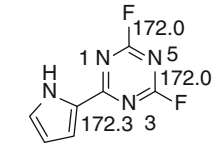
2.3 NMR Spectroscopy

Existence of three nitrogen atoms in a ring and such substituents as fluorine atoms in molecules of considered group of compounds does the most informative for the analysis of structure and properties NMR ^{13}C and ^{19}F spectroscopy.

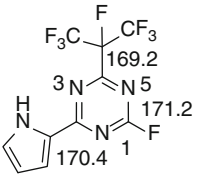
2.3.1 NMR ^{13}C Spectroscopy

The data on NMR ^{13}C spectroscopy of 6-substituted fluorinated 1,3,5-triazines have been analyzed [3, 5, 7, 8]. Replacement of fluorine atom by $CF(CF_3)_2$ group leads to upfield shift of signals of triazine carbons in NMR ^{13}C spectra.

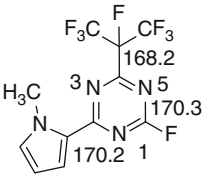
NMR ^{13}C spectra of perfluorinated hexahydrotriazinedione have been also studied (Scheme 1) [6].



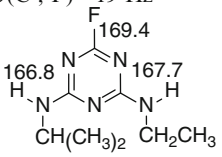
$^3J(C^2, F)= 14$,
$^1J(C^4, F)= 226$,
$^3J(C^4, F)= 19$ Hz



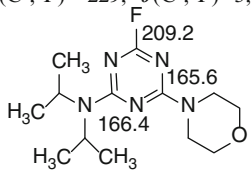
$^3J(C^2, F)= 13$, $^4J(C^2, F)=3$,
$^2J(C^4, F)= 22$, $^3J(C^4, F)= 12$,
$^1J(C^6, F)= 229$, $^4J(C^6, F)=3$,



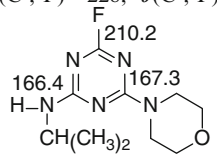
$^3J(C^2, F)= 13$, $^4J(C^2, F)=3$,
$^2J(C^4, F)= 21$, $^3J(C^4, F)= 12$,
$^1J(C^6, F)= 228$, $^4J(C^6, F)=3$,



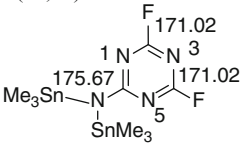
$^1J(C^2, F)=211.5$ Hz



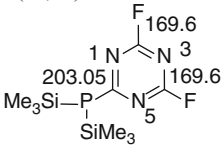
$^1J(C^2, F)= 209.2$ Hz



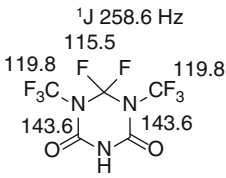
$^1J(C^2, F)= 210.5$ Hz



$^1J(C^2, F)= 222.28$,
$^3J(C^2, F^4)= 22.9$,
$^3J(C^6, F^4)= 16.0$



$^1J(C^2, F)= 230$, $^3J(C^2, F^4)= 70$,
$^3J(C^2, F)= 27$, $^1J(C^6, P)= 38.8$,
$^3J(C^6, F^4)= 42$



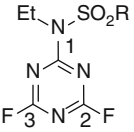
Scheme 1 NMR ^{13}C spectra data of fluorinated triazines

Cyclic carbons with fluorine atom in NMR ^{13}C spectra of boronfluoride salt of 2,4-difluoro-6-(1,3-diisopropyl-4,5-dimethylimidazolyl-2)-1,3,5-triazine are fixed in the form of a multiplet at 170.6–172.9 ppm [9]. NMR ^{13}C spectra of difluoro-sulphonamido-1,3,5-triazines in THF-d_8 at different temperatures (Table 2) reveal that at the room temperature C^2 and C^3 atoms are equivalent, and at low temperatures rotation of the substituent round exocyclic C-N bond slows down so that C^2 and C^3 atoms become magnetically nonequivalent [10].

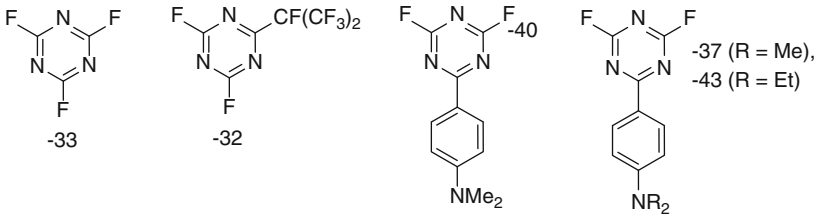
2.3.2 ^{19}F NMR Spectroscopy

The ^{19}F NMR spectra of a number of fluorinated 1,3,5-triazines have been reported (solvent $CDCl_3$), the chemical shifts of fluorine are observed at -32-(-42) ppm [8]. As the information about spectra of fluorine-containing diazines in the same solvent is absent, it is difficult to compare ^{19}F NMR spectra of fluorotriazines and fluorodiazines (Scheme 2).

Table 2 NMR ^{13}C data of difluorosulphonamido-1,3,5-triazines in THF-d_8 at different temperatures

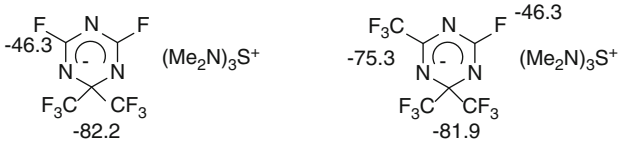


R	T, °C	Chemical shift of C^1	Chemical shift of C^2 and C^3
C_8F_{17}	2	170.6 t	172.4 dd
	–60	170.5 t	172.2 dd
C_8H_{17}	20	170.3 t	172.0 dd
	–50	170.0 t	173 br, 170 br
	–90	170.0 t	171.2 dd, 172.1 dd
$C_6H_4CH_3$	24	169.3 t	171.8 dd
	–60	168.9 t	173 br, 170 br
	–90	168.8 t	171.0 dd, 171.9 dd



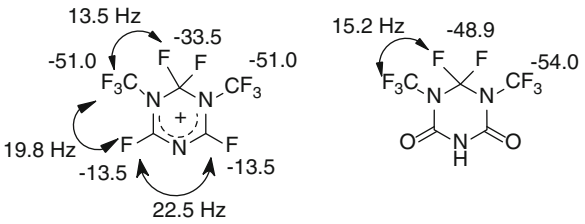
Scheme 2 Chemical shifts in ^{19}F NMR spectra of fluorinated 1,3,5-triazines

The NMR ^{19}F spectra of the salts consisting of the anionic fluorine-containing triazine systems and TAS$^+$ [$(Me_2N)_3S^+$] as the cation have been elucidated, the chemical shifts of aromatic fluorine are equal –46.3 ppm (Scheme 3) [4]:



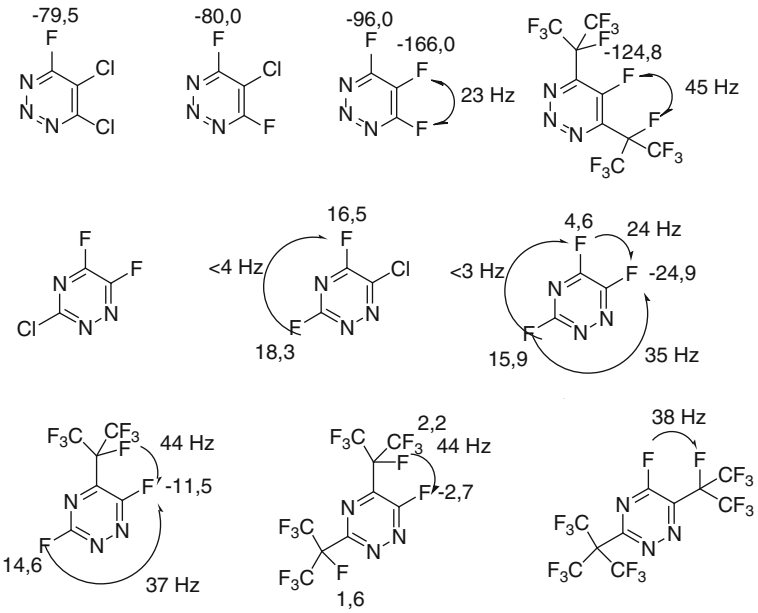
Scheme 3 The NMR ^{19}F spectra data of the anionic fluorine-containing triazine systems and TAS$^+$

The NMR ^{19}F spectra data for the delocalized 1,3,5-triazinium cation which is formed on treatment of 3,5-trifluoromethyl-2,4,4,6,6-pentafluoro-3,4,5,6-tetrahydro-1,3,5-triazine with SbF_5 have been presented, the chemical shifts of aromatic fluorine are –13.5 ppm (Scheme 4) [6].



Scheme 4 The NMR ^{19}F spectra data for the delocalized 1,3,5-triazinium cation

The data of ^{19}F NMR spectroscopy show that chemical shifts of fluorine atoms attached to the ring in 1,2,3-triazines are varied greatly and lay in range from −79.5 to −166.0 ppm [11]. The data on ^{19}F NMR spectra of fluorinated 1,2,4-triazines have recently been presented and discussed [12]. Coupling constants $^{5}J_{F(3),F(6)}$ lay in range from 35 to 37 Hz, constant $^{3}J_{F(5),F(6)}$ proved to be 24 Hz, whereas the $^{4}J_{F(3),F(5)}$ has smallest value (<4 Hz) (Scheme 5).



Scheme 5 Chemical shifts and coupling constants in ^{19}F NMR spectra of fluorotriazines

3 Synthetic Methods

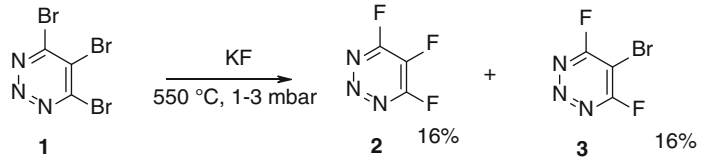
One of the most common synthetic approach to 1,2,3-, 1,2,4- and 1,3,5-triazines, bearing fluorine atoms as substituents in the ring, consists of the nucleophilic displacement of chlorine or bromine atoms with the fluoride anion in the

corresponding haloderivatives, a direct fluorination, the Shimman reaction in addition to another synthetic strategies based on condensations and ring transformations.

3.1 Synthesis of Fluorine-Containing 1,2,3-Triazines

3.1.1 Nucleophilic Displacement of Bromine or Chlorine Atoms with the Fluoride Anion

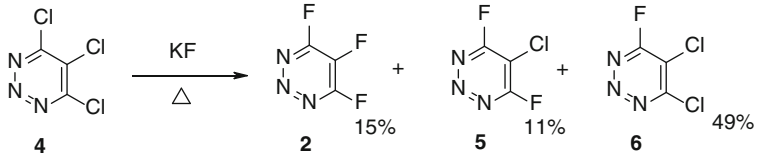
The displacement of bromine or chlorine atoms in heteroaromatic compounds is certainly one of the most effective synthetic methods leading to fluorinated heterocyclic compounds [13]. For instance, heating 4,5,6-tribromo-1,2,3-triazine **1** with dry potassium fluoride at 550 °C in vacuum results in the formation of a mixture of 4,5,6-trifluoro-1,2,3-triazine **2** and 5-bromo-4,6-difluoro-1,2,3-triazine **3** in the ratio 1:1 (Scheme 6) [14].



Scheme 6 Nucleophilic displacement of bromine atoms with the fluoride anion

The reaction of 4,5,6-trichloro-1,2,3-triazine **4** with potassium fluoride at an elevated temperatures provides fully substituted 4,5,6-trifluoro-1,2,3-triazine **2** in addition to compounds **5** and **6** with partial displacement of chlorine atoms (Scheme 7) [11]. It is clear that yields of fluorinated products depend on the reaction conditions (Table 3) [11]. At temperatures of 150–200 °C replacement of one or two chlorine atoms take place. The polyfluorinated 1,2,3-triazines **2, 5** were obtained when using two-step process in 55–69 % yields.

Interaction of 4,5,6-trichloro-1,2,3-triazine **4** with hexafluoropropene in the presence of potassium and cesium fluorides leads to the formation of

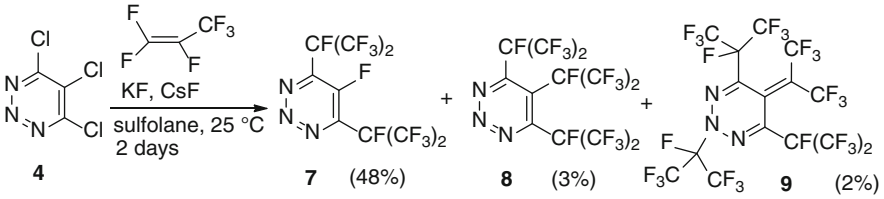


Scheme 7 The reaction of 4,5,6-trichloro-1,2,3-triazine **4** with KF

Table 3 Fluorination of 4,5,6-trichloro-1,2,3-triazine [11]

Reaction conditions		Yields, %		
	Temperature	**2**	**5**	**6**
KF, sealed tube	150 °C	–	11	49
10^{-2} mm, 18 h	180 °C	–	58	9
	200 °C	–	37	0
KF, vacuum	500 °C (1 cycle)	3	40	47
Transfer 10^{-2} mm	500 °C (4 cycles)	18	65	–
	(a) 500 °C (b) 600 °C	69	15	–
	(a) 450 °C (b) 700 °C	55	4	–
	(a) 450 °C (b) 600 °C	65	18	–

4,6-di-(perfluoroisopropyl)-5-fluoro-1,2,3-triazine **7** in addition to small quantities of polyfluorinated alkyl-1,2,3-triazines **8** and **9** (Scheme 8) [11, 15]. Trifluoromethyl substituted 1,2,3-triazines are still unknown compounds.



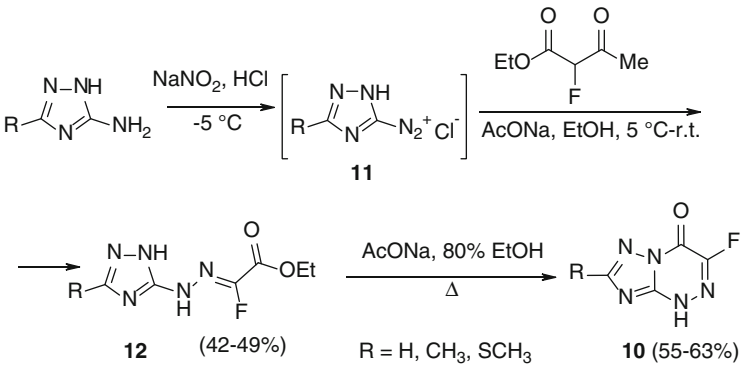
Scheme 8 Interaction of **4** with hexafluoropropene in the presence of KF and CsF

3.2 Synthesis of Fluorine-Containing 1,2,4-Triazines

Fluorinated 1,2,4-triazines can be obtained by means of several synthetic approaches: the formation of 1,2,4-triazine ring through cyclocondensations of fluorine-containing synthones, a direct fluorination of the ring, replacement of chlorine atoms in chlorotriazines with the fluoride anion and other methods.

3.2.1 Cyclocondensation Reactions

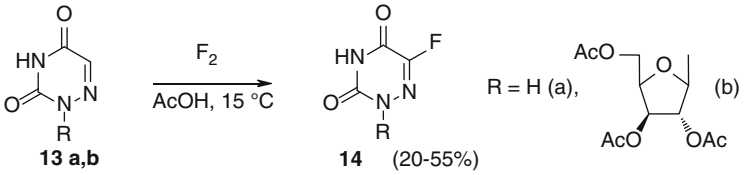
The synthesis of azoloannelated fluoro-1,2,4-triazines – 2-R-6-fluoro-1,2,4-triazolo[5,1-*c*][1,2,4]triazin-7(4H)-ones **10** has been recently described [16]. The coupling of 1,2,4-triazolyl-5-diazonium salts **11** with ethyl 2-fluoroacetate and the accompanied deacetylation leads to the formation of hydrazones **12** followed by cyclization on heating in aqueous alcohol in the presence of sodium acetate into the target fluoro compounds **10** (Scheme 9).



Scheme 9 Synthesis of triazolotriazin-7(4H)-ones **10**

3.2.2 Direct Fluorination Reactions

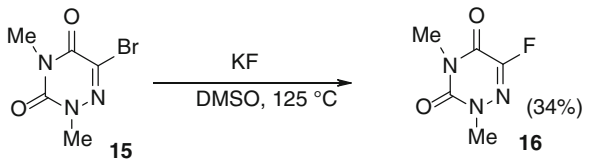
A rare example of the incorporation of a fluorine atom into azaaromatic compounds is the direct fluorination reaction of 6-azauracyl **13a** and 2-(2,3,5-tri-O-acetyl-β-D-ribofuranozyl-1,2,4-triazin)-3,5(2H,4H)-dione **13b** which takes place on passing of fluorine through a solution of azauracils **13a,b** in acetic acid, thus giving 6-fluoro-1,2,4-triazin-3,5(2H,4H)-diones **14** in 20–55 % yields (Scheme 10) [17, 18].



Scheme 10 Direct fluorination reactions

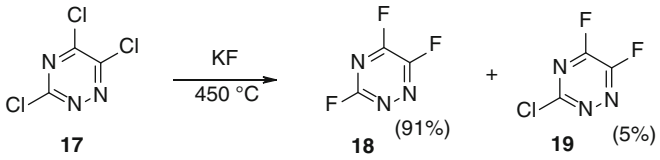
3.2.3 Nucleophilic Displacement of Bromine or Chlorine Atoms with the Fluoride Ion

The reaction of bromo or chloro derivatives of triazines with the fluoride ion is one of the main methods for the synthesis of fluorinated 1,2,4-triazines [13]. For instance, 1,3-dimetyl-5-fluoro-6-azauracyl **16** was obtained by reacting dry potassium fluoride with the corresponding bromo precursor **15** (Scheme 11) [19].



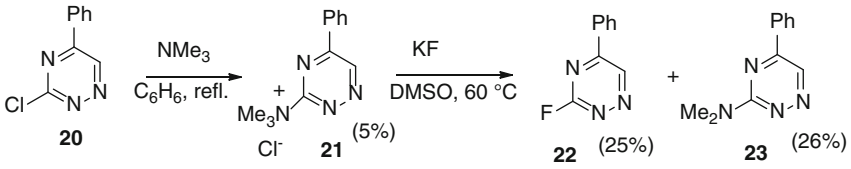
Scheme 11 Synthesis of 1,3-dimetyl-5-fluoro-6-azauracyl **16**

Another example illustrating utility of this approach is displacement of chlorine atoms in 3,5,6-trichloro-1,2,4-triazine which does occur in a melt of compound **17** with dry KF (Scheme 12) [20]. The conversion degree depends on the reaction conditions: at 450 °C the dominant product of the reaction proved to be 3,5,6-trifluoro-1,2,4-triazine **18**, while 3-chloro-5,6-difluoro-1,2,4-triazine **19** was isolated as a minor product.



Scheme 12 Displacement of chlorine atoms in 3,5,6-trichloro-1,2,4-triazine

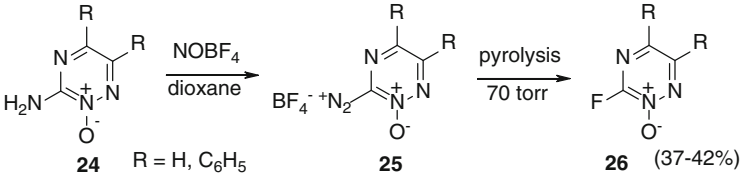
In order to obtain 3-fluoro-5-phenyl-1,2,4-triazine **22** from the corresponding 3-chloro derivative **20** the chlorine atom has to be displaced first with the trimethylammonium fragment (compound **21**), which undergoes easily the fluorination reaction by action of potassium fluoride to give 3-fluoro-1,2,4-triazine **22** in addition to 3-dimethylamino-5-phenyl-1,2,4-triazine **23** [21] (Scheme 13).



Scheme 13 Reaction of compound **21** with KF

3.2.4 The Baltz-Schiemann Reaction

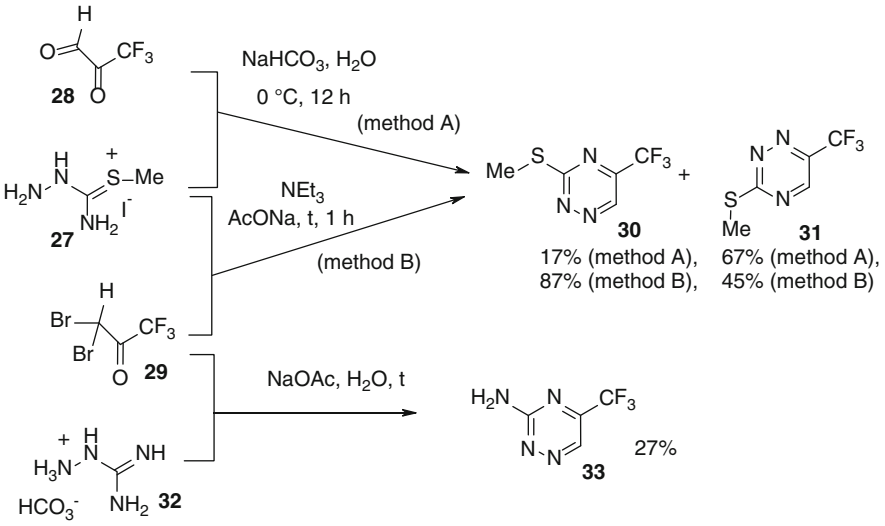
3-Fluoro-1,2,4-triazin-2-oxides **26** were obtained through diazotization of the corresponding amino derivatives **24** followed by thermolysis of the resulting diazonium tetrafluoroborates **25** (Scheme 14). It should be noted the salts **25** have been isolated first as rather stable heterocyclic diazonium species [22].



Scheme 14 The Baltz-Schiemann reaction

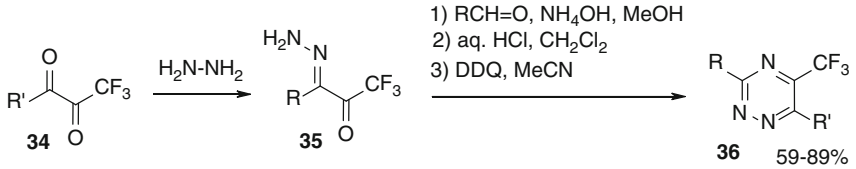
Two main synthetic approaches to trifluoromethyl substituted 1,2,4-triazines are known. They are cyclocondensation process based on (trifluoromethyl)carbonyl derivatives and transformation of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine ring.

A synthesis of 3-methylthio-5-trifluoromethyl-1,2,4-triazine **30** was described using dibromotrifluoroaceton **3** and S-methylthiosemicarbazide **27** as starting materials (Scheme 15) [23]. The synthesis of 3-methylthio-6-trifluoromethyl-1,2,4-triazine **31** was achieved by using trifluoropyruvaldehyde **28** and S-methylthiosemicarbazide **27** as starting materials (Scheme 15) [24]. 3-Aminotriazine **33** was prepared by the condensation of aminoguanidine **32** with dibromoketone **29**, this condensation was non-selective, and 6-trifluoromethyl-isomer as by-product was formed (Scheme 15) [25].



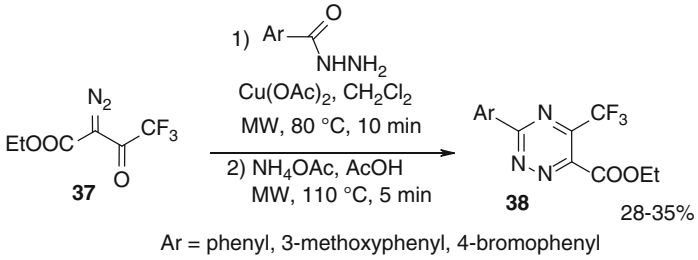
Scheme 15 Synthetic approaches to trifluoromethyl substituted 1,2,4-triazines

3-Hydrazono-1,1,1-trifluoroalkan-2-ones **35** prepared from 1,1,1-trifiuoroalkane-2,3-diones **34** reacted with several aldehydes in the presence of aqueous NH_4OH to afford 5-trifluoromethyl-2,3-dihydro-1,2,4-triazines, of which oxidation gave 5-trifluoromethyl-1,2,4-triazines **36** (Scheme 16) [26].



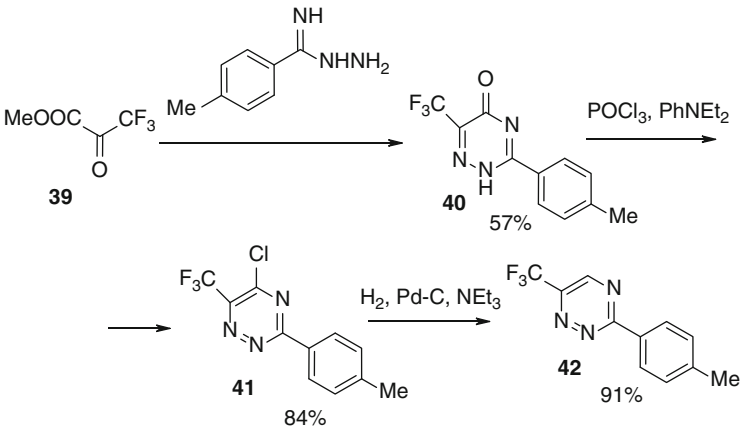
Scheme 16 Synthesis of 5-trifluoromethyl-1,2,4-triazines **36**

Microwave assisted reaction of 2-diazo-4,4,4-trifluoro-3-oxobutanoate **37** with aryl hydrazides in the presence of copper(II)acetate, followed by reaction with ammonium acetate in acetic acid gave the 1,2,4-triazines **38** in modest yield (Scheme 17) [27].



Scheme 17 Synthesis of 1,2,4-triazines **38**

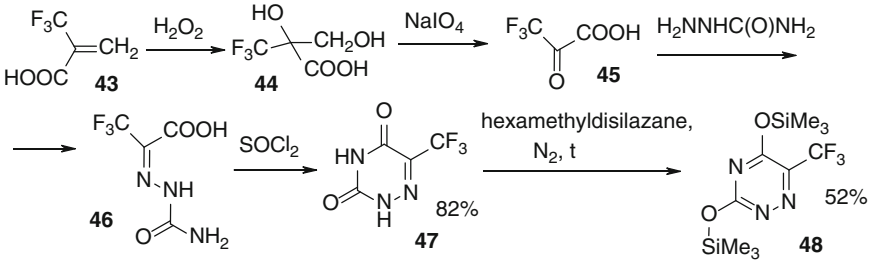
The reaction of trifluoropyruvate **39** with 4-methylbenzoic acid amidrazone was carried out in refluxing ethanol to give 3-(p-tolyl)-6-trifluoromethyl-1,2,4-triazin-5(2H)-one **40** in 57 % yield. A 6-trfluoromethyl-1,2,4-triazine derivative **42** was synthesized in almost quantitative yield from **40** by chlorination followed by catalytic hydrogenation to remove chlorine substituent (Scheme 18) [28].



Scheme 18 Synthesis of triazine **42**

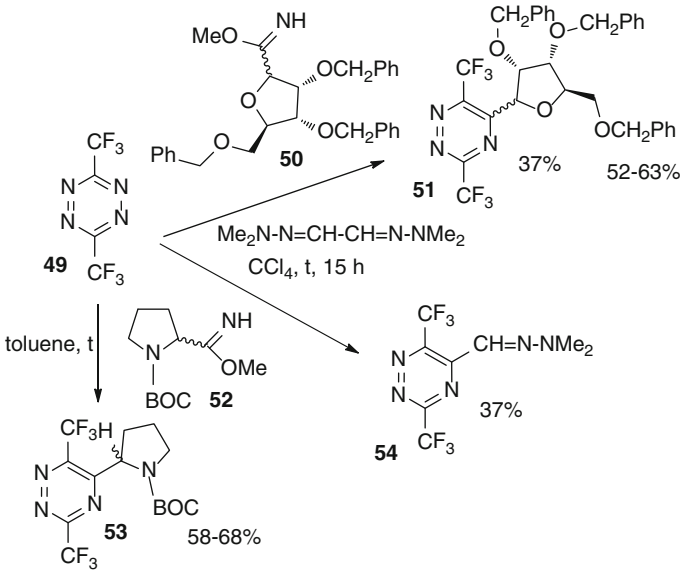
Bis(trimethylsilyl) ether of 5-trifluoromethyl-6-azauracil **48** was obtained for the synthesis of the corresponding β-D-deoxyribonucleoside and nucleotide. α-Trifluoromethacrylic acid **43** has been converted with hydrogen peroxide to α,β-dihydroxy-α-trifluoromethylpropionic acid **44**, which gave the hydrate of perfluoropyruvic acid **45** on treatment with sodium periodate. The semicarbazone **46**

was cyclized using thionyl chloride to 5-trifluoromethyl-6-azauracil **47**, compound **47** was heated under reflux in hexamethyldisilazane under nitrogen atmosphere thus resulting in the formation of 6-trifluoromethyl-1,2,4-triazine **48** (Scheme 19) [29].



Scheme 19 Synthesis of 6-trifluoromethyl-1,2,4-triazine **48**

Examples of synthesis of trifluoromethyl-substituted 1,2,4-triazines by transformation of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **49** ring are presented at Scheme 20. The anomeric *C*-glycosyl precursors **50**, functionalized by an imidate group and appropriate for *C*-nucleoside synthesis were utilized as heterodienophiles in a *Diels-Alder* reaction with inverse electron demand to yield the *O*-benzyl protected 5-(β-D-ribofuranozyl)- and 5-(α-D-ribofuranosyl)-1,2,4-triazines **51** (Scheme 20) [30].



Scheme 20 Transformation of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **49** ring

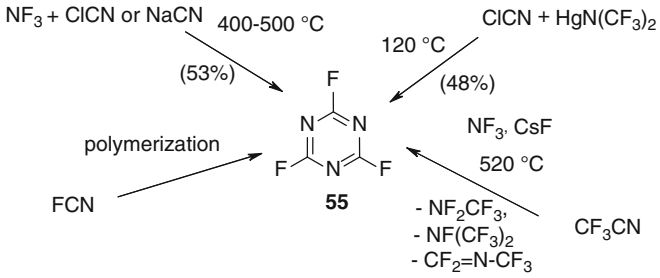
Analogues synthesis of 3,6-bis(trifluoromethyl)-1,2,4-triasines bearing (2′,3′-dideoxy-β-D-ribofuranosyl)- or (2′-deoxy-β-D-ribofuranosyl)-residue at position 5 was reported [31, 32]. A new strategy for a straightforward synthesis of chiral 5-(2′-pyrrolidinyl)-1,2,4-triazines **53** starting from (*S*)- and (*R*)-proline iminoester **52** utilizing as the key steps the inverse electron demand Diels–Alder reaction of tetrazine **49** was achieved (Scheme 20) [33]. Electron-rich C=N bond of the hydrazone Me_2N-N=CH-CH=N-NH_2 proved to be effective dienophiles towards the electron-deficient tetrazine **49**. The substituted 1,2,4-triazine **54** was formed by way of [4+2]cycloaddition and elimination of nitrogen [34].

3.3 Synthesis of Fluorine-Containing 1,3,5-Triazines

The most studied and widespread type of fluorinated triazines are 1,3,5-triazines. As well as their isomer compounds, fluorinated 1,3,5-triazines can be synthesized by several ways: (i) the formation of heterocyclic ring by means of cyclization reactions from fluorine-containing precursors; (ii) direct fluorination of triazines; (iii) nucleophilic displacement reactions of chlorinated triazines with the fluorine ion, and other synthetic procedures.

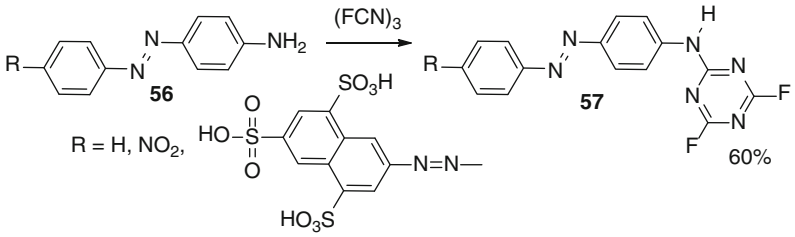
3.3.1 Cyclocondensation Reactions

Heating of a mixture of NaCN and NF_3 (or ClCN and NF_3) at 400–500 °C affords 2,4,6-trifluoro-1,2,3-triazine (cyanuric fluoride) **55** in a high yield (Scheme 21) [35]. The formation of triazine **55** is also observed on heating of chlorocyane with copper chloride at 300 °C [or on heating of chlorocyane with $HgN(CF_3)_2$ at 120 °C] [36], or by the reaction of trifluoroacetonitrile with cesium fluoride and NF_3 (Scheme 21) [37]. At room temperature, liquid cyanogen fluoride FCN is converted rapidly to polymeric materials, including cyanuric fluoride and a high-melting, water-sensitive solid polymer, but in the gas phase at atmospheric pressure it has been recovered partially after several weeks or under the conditions of polymerization [38].



Scheme 21 Synthesis of 2,4,6-trifluoro-1,2,3-triazine (cyanuric fluoride) **55**

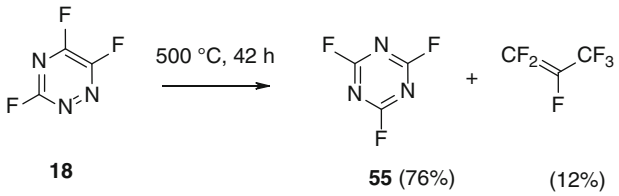
N-(4,6-Difluoro-1,3,5-triazin-2-yl)-N-ethyloctane-1-sulphonamide has been obtained from N-ethyloctane-1-sulphonamide and cyanuric fluoride [9]. The formation of 2,4-difluoro-1,3,5-triazine fragment has been exploited in the synthesis of dyes. The synthesis of triazine dyes has also been reported in a number of publications [39, 40] (Scheme 22). 2,4-Difluoro-6-arylamino-1,3,5-triazines **57** were obtained by the reaction of arylazoanilines **56** with cyanuric fluoride.



Scheme 22 Synthesis of 2,4-Difluoro-6-arylamino-1,3,5-triazines **57**

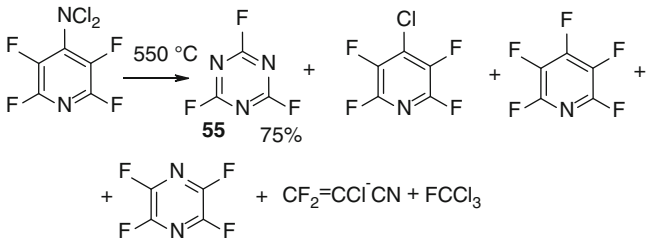
3.3.2 Ring Transformations

Heating of 3,5,6-trifluoro-1,2,4-triazine **18** at a high temperature (approximately 500 °C) for many hours gave 2,4,6-trifluoro-1,3,5-triazine **55**, as the ring transformation product, and perfluoropropylene (Scheme 23) [12].



Scheme 23 Transformation of 3,5,6-trifluoro-1,2,4-triazine **18** under heating

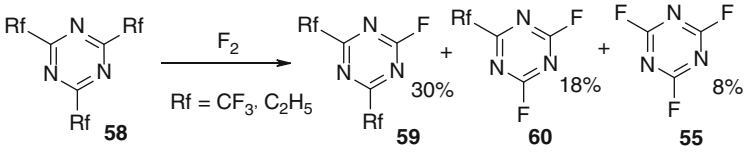
A rather complicated mixture of fluorinated compounds, including triazine **55**, is formed on heating of 4-dichloroamino-2,3,5,6-tetrafluoropyridine at 550 °C [41]. Such transformations are supposed to occur due to decomposition of one fluorinated heterocycle into fluorocyane followed by the construction of a new fluorinated triazine system (Scheme 24).



Scheme 24 Transformation of 4-dichloroamino-2,3,5,6-tetrafluoropyridine

3.3.3 Direct Fluorination

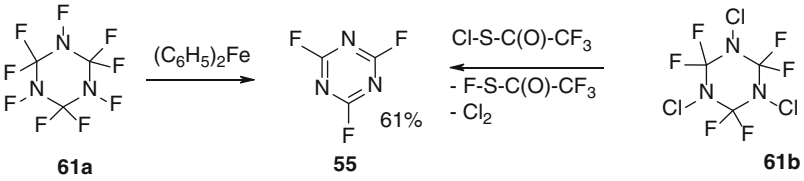
Fluorination of the ring has been shown to take place on treatment of perfluoroalkyl-1,3,5-triazines **58** with fluorine, thus resulting in the formation of a mixture of cyanuric fluoride **55** in addition to mono- and difluoro-1,3,5-triazines **59** and **60** (Scheme 25) [42].



Scheme 25 Fluorination of perfluoroalkyl-1,3,5-triazines **58**

3.3.4 Dehalogenation of Cyclic Halogenoamidines

Fluoroanhydride of cyanuric acid **55** was formed in a high yield by the defluorination reaction of perfluoro-1,3,5-triazacyclohexane **61a** by action of ferrocene (Scheme 26) [43]. Dehalogenation of $(NClCF_2)_3$ **61b** under the action of ClSC(O)CF_3 was reported (Scheme 26) [44].



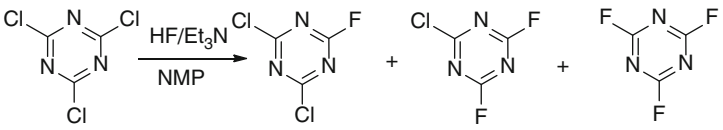
Scheme 26 Dehalogenation of cyclic halogenoamidines

Table 4 Fluorination of cyanuric chloride

Reaction conditions	Yield, %			Literature
	63	**64**	**55**	
SbF_3, $SbCl_3$, Cl_2, 160–180 °C	–	–	91	[47]
SF_4, 150–250 °C, autoclave, 12 h	–	–	40	[48]
SF_4, 150–250 °C, autoclave, 6 h	29	39	–	[48]
HF, 1-methyl-pyrrolidinone, $N(C_2H_5)_3$, 20–25 °C	–	–	90	[51]
CsF, 1-*n*-butyl-3-methylimidazolium hexafluorophosphate, 80 °C	11	3	10	[51, 53]
KSO_2F, 120–150 °C	3	11	31	[46]
KF, $C_3Cl_3N_3$/KF, 300 °C	–	–	48	[52]
AgF, 100 °C, 1 h	–	–	78	[53]
F_2, 125 °C	–			[50]

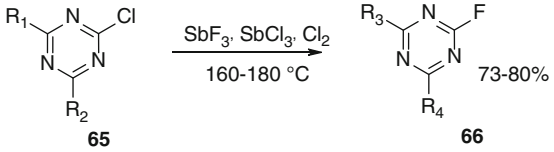
3.3.5 Replacement of Chlorine Atoms with Fluoride Ion

Replacement of chlorine atoms with fluoride ion is one of the main synthetic procedure to obtain fluorinated 1,3,5-triazines. Being depending on the reaction conditions and the nature of reagents, the reactions of cyanuric chloride with various fluorinating reagents lead to mono-, di- and trifluoro-1,3,5-triazines (Scheme 27, Table 4) [45–56]. A mixture of SbF_3, $SbCl_3$ and Cl_2 is an appropriate agent for total fluorination of cyanuric chloride **62.** Formation of trifluoroderivative **55** proceeds selectively in high yield under reaction of **62** with HF and $N(C_2H_5)_3$ in 1-methyl-pyrrolidinone at room temperature.



Scheme 27 Fluorination of cyanuric chloride **62**

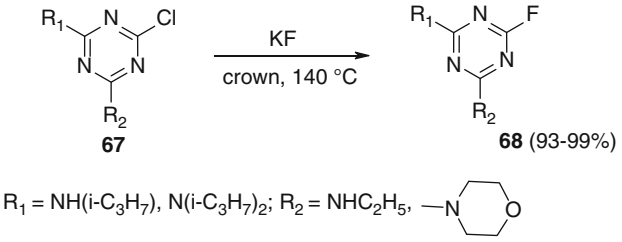
It is worth to note that chlorine atoms both in the ring and in CCl_3 groups of compound **65** are subjected to the replacement reaction (Scheme 28) [47].



R^1	R^2	R^3	R^4	Yield, %
CCl_3	Cl	CF_3	F	73
CCl_3	CCl_3	CF_3	CF_3	79
C_6H_5	Cl	C_6H_5	F	73
C_6H_5	C_6H_5	C_6H_5	C_6H_5	80

Scheme 28 Synthesis of fluorinated 1,3,5-triazines **66**

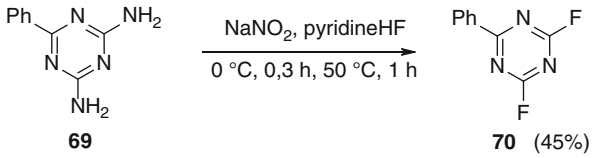
Fluorination of 2,3-diamino-6-chloro-1,3,5-triazines **67** with anhydrous KF has been shown to proceed smoothly in the presence of catalytical amounts of dicyclohexano-18-crown-6 (Scheme 29). Fluoro-1,2,4-triazines **68** were obtained in 93–99 % yields [7]. 2-Isopropylamino-4-ethylamino-6-fluoro-1,2,4-triazine **68** (R^1=NH(*i*-C_3H_7), R^2=C_2H_5) was isolated in 66 % yield under similar reaction conditions with triethylpentadecylammonium bromide as the phase transfer catalyst [7].



Scheme 29 Synthesis of fluorinated 1,3,5-triazines **68**

3.3.6 The Baltz-Schiemann Reaction

2,4-Difluoro-1,3,5-triazine **70** was obtained by diazotization of the corresponding diamino compound **69** followed by thermolysis of the resulting diazonium tetrafluoroborate (Scheme 30) [57].

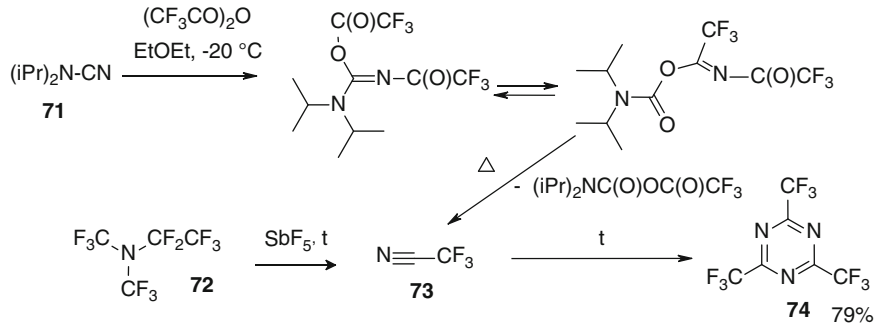


Scheme 30 Synthesis of fluorinated 1,3,5-triazines **70**

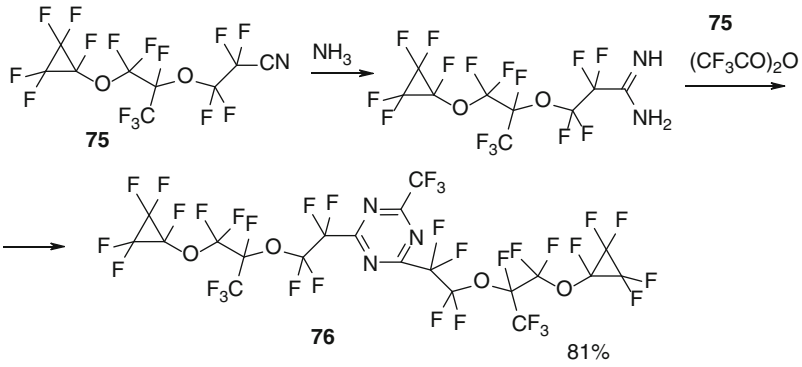
The main synthetic approaches to trifluoromethyl substituted 1,3,5-triazines are trimerization of CF_3CN [58], cyclocondensation process based on imidoylamidines [59], cyanoguanidines [60] or biguanides [61] and also fluorination of trichloromethyl-1,3,5-triazines [47, 62].

For example, trifluoroacetonitrile **73** trimerizes to give 2,4,6-tris(trifluoromethyl)-1,3,5-triazine **74** [63]. Monomeric CF_3CN was generated by reaction of diisopropylcyanamide **71** and trifluoroacetic anhydride [58] or from perfluoroethyldimethylamine **72** [6] (Scheme 31).

Di(pentafluorocyclopropanyl)-substituted triazine **76** was prepared from nitrile **75** by reaction with ammonia followed by acylation-cyclization with trifluoroacetic anhydride (Scheme 32) [64].

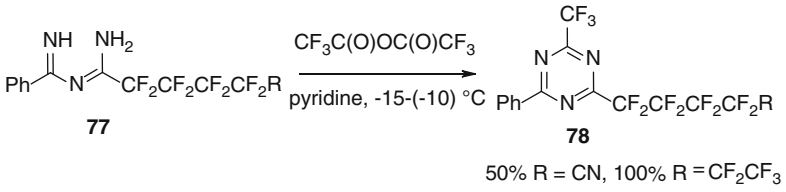


Scheme 31 Synthesis of 2,4,6-tris(trifluoromethyl)-1,3,5-triazine **74**



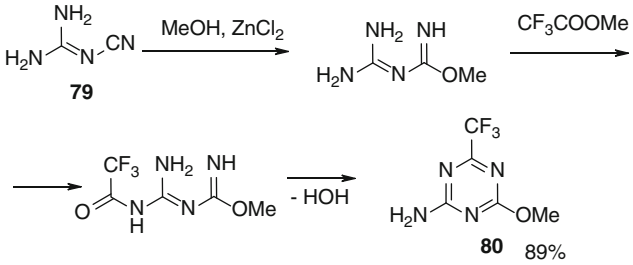
Scheme 32 Synthesis of fluorinated 1,3,5-triazine **76**

By the method of acylation-cyclodehydration of imidoylamidines **77** 1,3,5-triazines **78** have been prepared (Scheme 33) [59]. Synthesis of 2-trifluoromethyl-4,6-bis(2,3-dichloro-1,1,2,3,3-pentafluoro)-1,3,5-triazine from 3,4-dichloro-2,2,3,4,4-pentafluorobutyronitril, NH_3 and trifluoroacetic anhydride was reported [65].



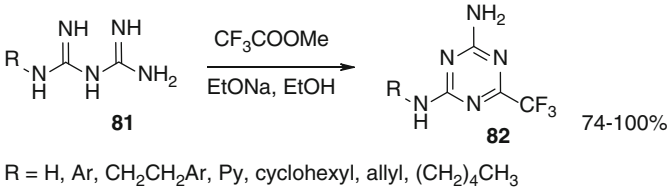
Scheme 33 Synthesis of fluorinated 1,3,5-triazine **78**

2-Amino-4-trifluoromethyl-6-methoxy-1,3,5-triazine **80** can be easily prepared starting from cyanoguanidine **79** by a zinc chloride-catalysed process (Scheme 34) [60].



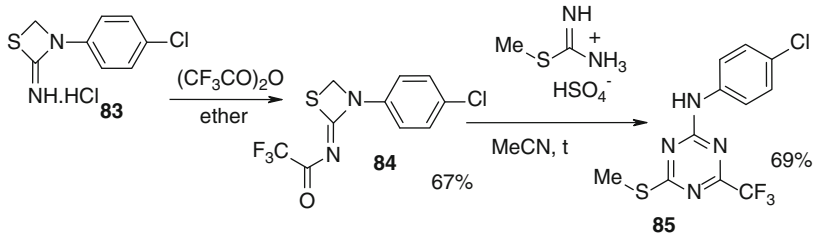
Scheme 34 Synthesis of fluorinated 1,3,5-triazine **80**

Cyclocondensation of substituted biguanides **81** with methyl trifluoroacetate in the presence of catalytic amounts of sodium ethylate gave 2-amino-4-(substituted amino)-6-trifluoromethyl *sym*-triazines **82** (Scheme 35) [66–72]. A rapid and efficient synthesis under microwave irradiation has been developed for various substituted 1,3,5-triazines that can serve as versatile building blocks for both supramolecular and medicinal chemistry [61, 73].



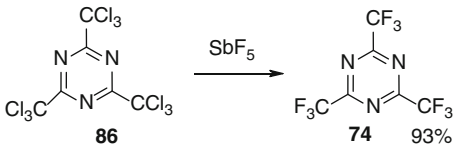
Scheme 35 Synthesis of fluorinated 1,3,5-triazines **82**

2-Imino-1,3-thiazetidine **83** was used as precursor in the synthesis of triazine **85** (Scheme 36) [74]. Reaction of **83** with trifluoroacetic anhydride leads to 2-trifluoromethylimino-3-(4-chlorophenyl)-1,3-thiazetidine **84**, the treatment of **84** with S-methylisothiourea sulfate results in trifluoromethyl substituted triazine **85**.



Scheme 36 Synthesis of fluorinated 1,3,5-triazine **85**

2,4,6-Tris(trichloromethyl)-1,3,5-triazine **86** was transformed to trifluoromethylderivative **74** under the action of SbF_5 (Scheme 37) [62].



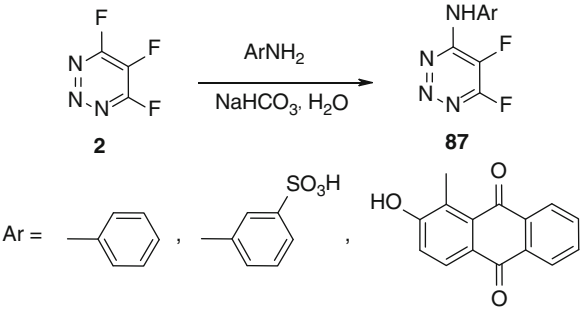
Scheme 37 Synthesis of 2,4,6-tris(trifluoromethy1)-1,3,5-triazine **74**

4 Chemical Properties

The main reactions of fluorine-containing triazines are connected with attack on the carbon atom bearing fluorine, which results to replacement of the fluorine atom or cycle transformation.

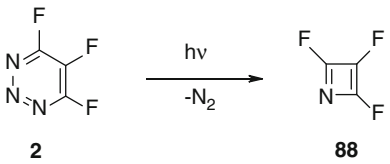
4.1 Chemical Properties of 1,2,3-Triazines

Aromatic amines are capable to displace fluorine atoms in trifluroro-1,2,3-triazine **2** to give 4-substituted products **87** (Scheme 38) [75–77].



Scheme 38 Amino-defluorination process in trifluroro-1,2,3-triazine **2**

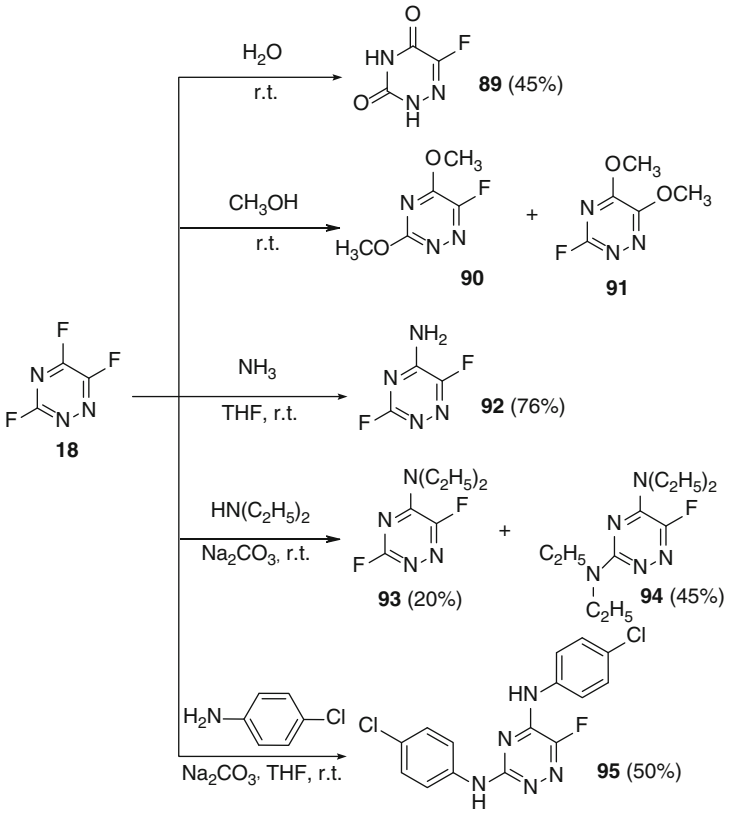
Being UV-irradiated 4,5,6-trifluoro-1,2,3-triazine **2** is transformed into trifluoroazet **88** (Scheme 39) [78].



Scheme 39 Transformation of 4,5,6-trifluoro-1,2,3-triazine **2** under UV-irradiation

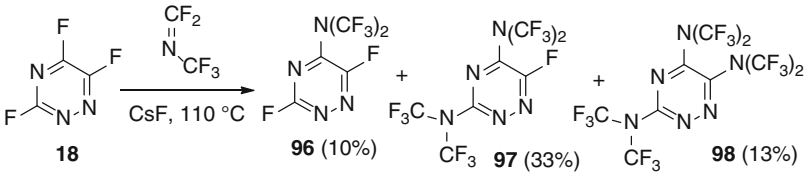
4.2 Chemical Properties of 1,2,4-Triazines

A number of transformations involving the displacement of fluorine atoms in fluorinated 1,2,4-triazines have been described. In case of 3,5,6-trifluoro-1,2,4-triazine **18** the leaving mobility of fluorine atoms in these displacement reactions is decreasing as follows $F^5 > F^3 > F^6$. In accordance with this sequence the hydrolysis of 1,2,4-triazine **18** results in the formation of 6-fluoro-1,2,4-triazine-3,5-(2H,4H)-dione **89** (Scheme 40) [20]. The reaction of compound **18** with methanol in a sealed tube afforded 3,5-dimethoxy-6-fluoro- and 5,6-dimethoxy-3-fluoro-1,2,4-triazines **90** and **91** in the ratio 1:2 in total yield of 46 % [20]. Reactivity of 3,5,6-trifluoro-1,2,4-triazine **18** towards N-nucleophiles can be illustrated by the reactions with ammonia (leading to 5-amino-3,6-difluoro-1,2,4-triazine **92**), diethylamine and 4-chloroaniline. The reaction of **18** with diethylamine affords two products, 5-diethylamino-3,6-difluoro-1,2,4-triazine **93** and 3,5-bis(diethylamino)-6-fluoro-1,2,4-triazine **94** (Scheme 40) [20], while the only compound **95** was obtained from the reaction of **18** with 4-chloroaniline.



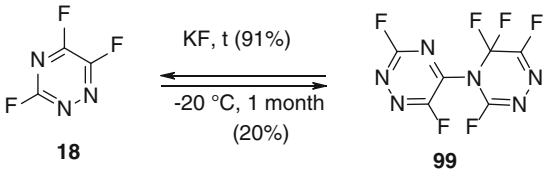
Scheme 40 Displacement of fluorine atoms in fluorinated 1,2,4-triazines

It is worth to note that the replacement of fluorine atoms in 3,5,6-trifluoro-1,2,4-triazine **18** by action of bis(trifluoromethyl)amino anion (the latter can be obtained from perfluoro-2-azapropene and cesium fluoride) provides a mixture of mono-, di- and trisubstituted perfluorodimethylamino-1,2,4-triazines **96–98** (Scheme 41) [12].



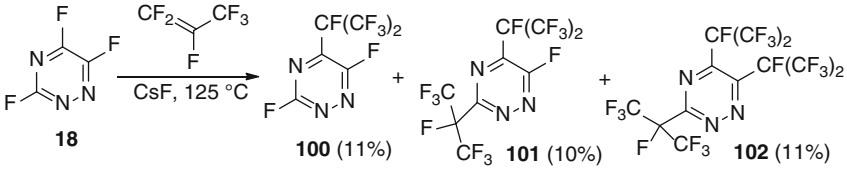
Scheme 41 Interaction of **18** with bis(trifluoromethyl)amino anion

When 3,5,6-trifluoro-1,2,4-triazine **18** was kept in vacuo at -20 °C for 1 month in a Pyrex ampoule the dimeriration product, 3,6-difluoro-5-(3,5,5,6-tetrafluoro-4,5-dihydro-1,2,4-triazine-4-yl)-1,2,4-triazine **99,** was shown to be formed (Scheme 42) [20]. The dimer **99** was passed over potassium fluoride at 250 °C to form triazine **18**.



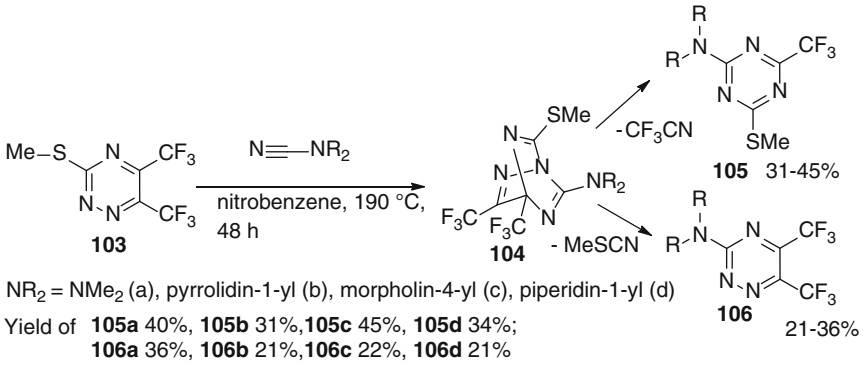
Scheme 42 Dimeriration of 3,5,6-trifluoro-1,2,4-triazine **18**

Incorporation of perfluoroisopropyl groups into trifluoro-1,2,4-triazine takes place smoothly in the reaction of **18** with hexafluoropropene and cesium fluoride without of any solvent [12]. When the reaction is carried out at 125 °C for 25 min a mixture of 5-perfluoroisopropyl-derivative **100** and 3,5-di- and 3,5,6-tri (perfluoroisopropyl)-1,2,4-triazines **101, 102** are formed (Scheme 43), while the formation of trisubstituted derivative **102** (yield 52 %) takes place on heating at 110 °C for 2 h.



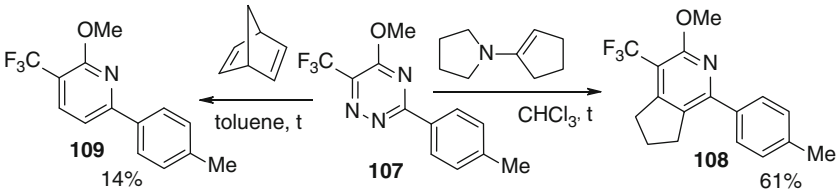
Scheme 43 Reaction of **18** with hexafluoropropene

A number of ring transformations and reactions involving the displacement of substituents such as SMe-group in trifluoromethyl containing 1,2,4-triazines have been described. *N*-substituted cyanamides participate in cycloaddition exclusively across C-5/N-2 of the 1,2,4-triazine nucleus **103** yielding the bicycle **104** as nonisolable intermediate. Elimination of trifluoroacetonitrile leads to the 1,3,5-triazines **105** as the main reaction products. Besides, the 1,2,4-triazines **106** are formed by loss of methyl thiocyanate (Scheme 44) [28].



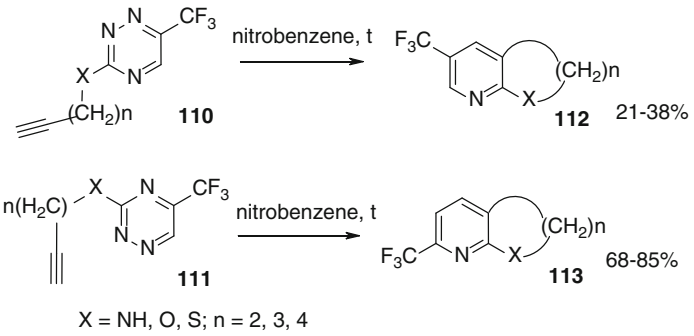
Scheme 44 Transformations and displacement of SMe-group in trifluoromethyl containing 1,2,4-triazines

When the 5-methoxy derivative **107** was reacted with enamine in refluxing chloroform, pyridine **108** was obtained (Scheme 45) [28]. Diels-Alder reaction of triazine 5 with norbornadiene leads to formation of pyridine **109** (Scheme 45). Low yield of **109** clearly shows that this Diels-Alder reaction proceeds in an inverse electron demand manner [28].



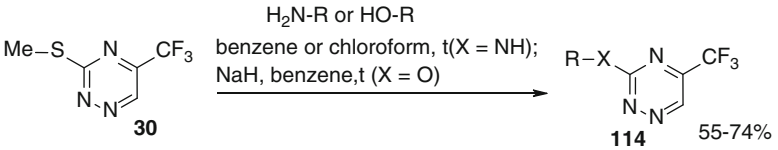
Scheme 45 Diels-Alder reactions of triazine **107**

Annulated pyridines **112** or **113** were formed on heating of triazines **110** or **111** bearing at position 3 NH-$(CH_2)_n$-C≡CH, O-$(CH_2)_n$-C≡CH or S-$(CH_2)_n$-C≡CH groups in chlorobenzene or diphenylether (Scheme 46) [23, 24]. This transformation is an example of intramolecular Diels-Alder reaction of 1,2,4 triazines accomplished with nitrogen elimination.



Scheme 46 Transformations of triazines **110** or **111**

Nucleophilic displacement of the thiomethyl group in triazines **30** is described (Scheme 47) [23, 24, 80]. This reaction is valuable approach to broad variety of trifluoromethylated triazines.



Scheme 47 Nucleophilic displacement of the thiomethyl group in triazines **30**

4.3 Chemical Properties of 1,3,5-Triazines

The chemistry of fluorinated 1,3,5-triazines is not as well studied as the chemistry of their chloro derivatives. In case of fluorotriazines the reactions directed on the ring nitrogen atoms, displacement of fluorine atoms and reactions on carbon atoms on the ring with retention of the fluorine atoms appear to be the most characteristic ones. In this section the N-alkylation and N-acylation reactions, as well as replacement of fluorine atoms by a variety of nucleophiles will be considered. Metallation of fluorotriazines and synthesis on the basis of organometallic compounds, as well as the cross-coupling reactions were described. Also several examples of photochemical reactions and transformations are presented.

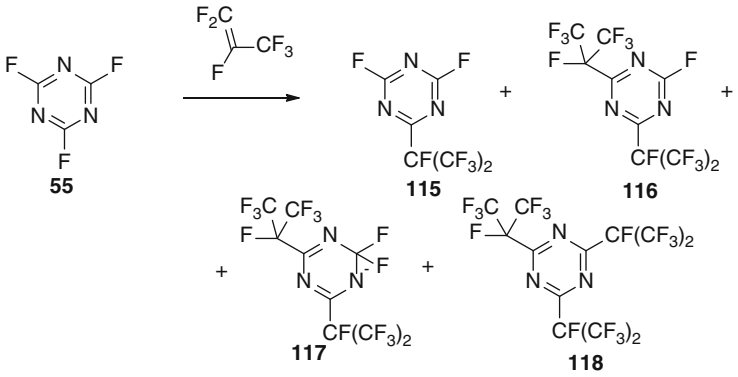
4.3.1 Replacement of Fluorine Atoms

Nucleophilic replacement of fluorine atoms in azaaromatic compounds can be performed under rather mild reaction conditions, and this method is certainly one of the most effective approaches to their functionalization. Incorporation of perfluoroisopropyl groups into 2,4,6-trifluoro-1,3,5-triazine **55** proceeds smoothly

Table 5 The reaction of cyanuric fluoride **55** with hexafluoropropene

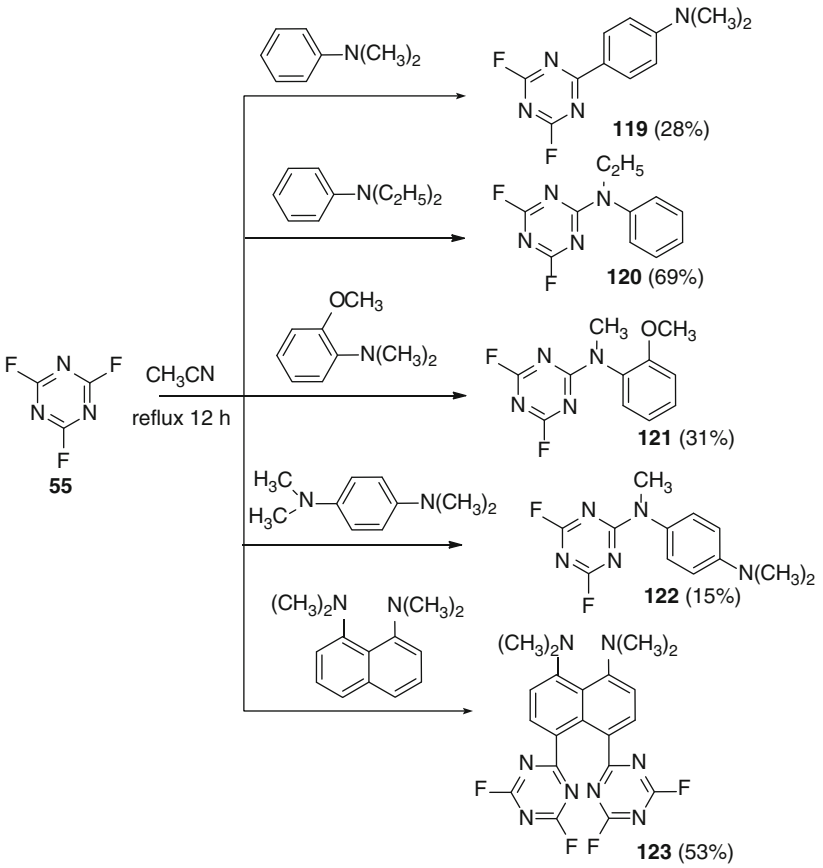
Reaction conditions	Yield, %				Ref
	115	**116**	**117**	**118**	
CsF, 125 °C	11	10	–	11	[11]
CsF, 110 °C, 2 h				52	[11]
KF, 70 °C, 19 h, sulfolane	36	15	–	8	[83]
PSHF, 72 h, sulfolane	35	8	–	–	[47]
$N(C_2H_5)_3$, 60 °C, 48 h, CH_3CN	11	29	40	16	[82]
NCH_3, 60 °C, 48 h, CH_3CN	11	16	40	–	[82]
NCH_3, r.t., 10–12 h	20	37	–	36	[83]
NCH_3, 60 °C, no solvent, 48 h	–	–	–	95	[82]

by action of hexafluoropropene and cesium fluoride without of any solvent (Scheme 48, Table 5) [11, 81–83]. Trisubstituted derivatives **118** were formed in 52 % yield at 110 °C during 2 h. If reaction was carried out at 125 °C within 25 min the mixture of trisubstituted derivative **118** and 5-perfluoroisopropyl-1,2,4-triazine **115** and 3,5-di-(perfluoroisopropyl)-1,2,4-triazine **116** (Scheme 48) was isolated.



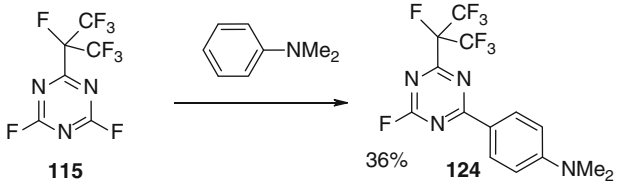
Scheme 48 Incorporation of perfluoroisopropyl groups into 1,3,5-triazine **55**

It is worth noting that 2,4,6-trifluoro-1,3,5-triazine **55** is less active than cyanuric chloride in the reaction of with aniline (Scheme 49) [84]. N,N-Dimethylaniline and 1,8-bis(dimethylamino)naphthalene react with cyanuric fluoride **55** as C-nucleophiles to give 2,4-difluoro-6-(4-dimethylaminophenyl)-1,3,5-triazine **119** and 1,8-bis(dimethylamino)-4,5-(2,4-difluoro-1,3,5-triazinyl-6)naphthalene **123** (Scheme 49) [8]. Contrary to it, N,N-diethylaniline, and *ortho*- or *para*-substituted N,N-dimethylanilines react with trifluoro-1,3,5-triazine **55** as N-nucleophiles. These reactions are accompanied by elimination of N-alkyl group and the formation of 2,4-difluoro-6-arylamino-1,3,5-triazines **120–122** (Scheme 49).



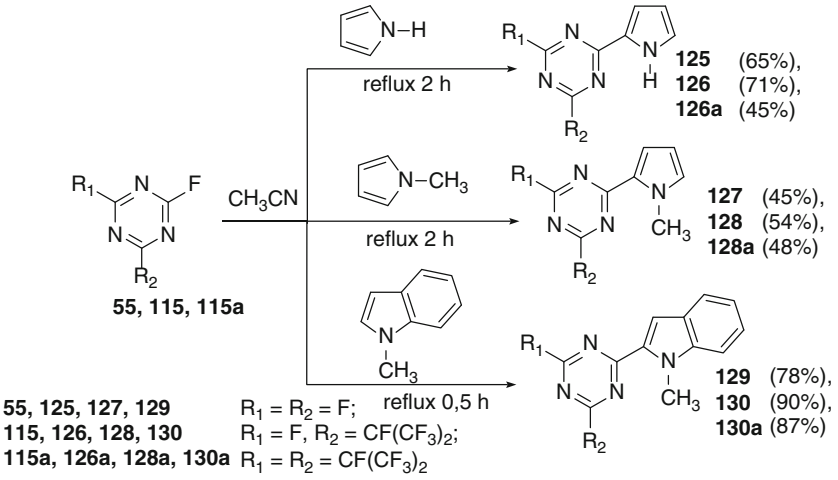
Scheme 49 Reactions of cyanuric fluoride **55**

In a similar way, on treatment of perfluoro-1,3,5-triazine **115** with dimethylaniline 2-fluoro-4-heptafluoroisopropyl-6-(4-dimethylaminophenyl)-1,3,5-triazine **124** was obtained in 36 % yield (Scheme 50) [8].



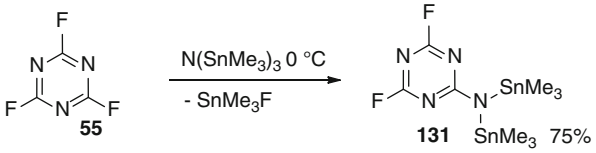
Scheme 50 Formation of triazine **124**

Replacement of fluorine atoms in triazines **55, 115** and **115a** take place also by action of pyrrole, N-methylpyrrole and N-methylindole resulting in the formation of the corresponding 1,3,5-triazines **125–130** (Scheme 51) [8].



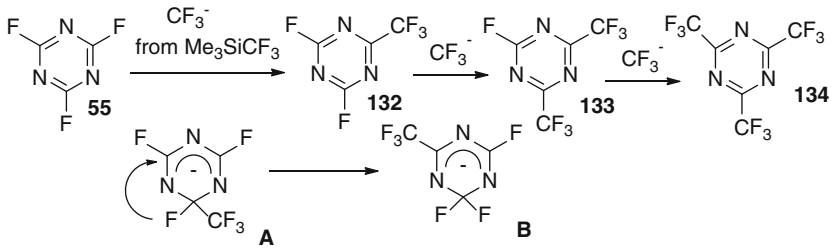
Scheme 51 Replacement of fluorine atoms in triazines **55, 115** and **115a**

In a similar manner, the reaction of cyanuric fluoride **55** with tris(trimethylstannyl) amine in dry ether at 0 °C leads to the formation of 2,4-difluoro-6-[di(trimethylstannyl)]-amino-1,3,5-triazine **131** (Scheme 52) [5].



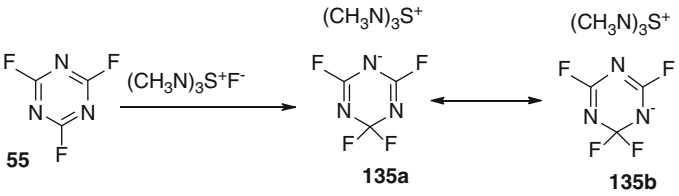
Scheme 52 Reaction of cyanuric fluoride **55** with tris(trimethylstannyl)amine

Reaction pathway for substitution of fluorine atom in 2,4,6-trifluoro-1,3,5-triazine **55** under the action of trifluoromethyl anion has been studied [4] (Scheme 53). Since $\mathbf{C_3N_3F_4^-}$ can act as a potential fluoride donor, initial reaction takes place between $\mathbf{C_3N_3F_4^-}$ **(A)** and Me_3SiCF_3 forming a reactive silane, a source of the elusive CF_3 anion, which can then attack the neutral triazine (Scheme 53). Through **A** → **B** rearrangement, elimination, and further addition reactions the observed. As a result products **132**, **133** and **134** are formed (Scheme 53).



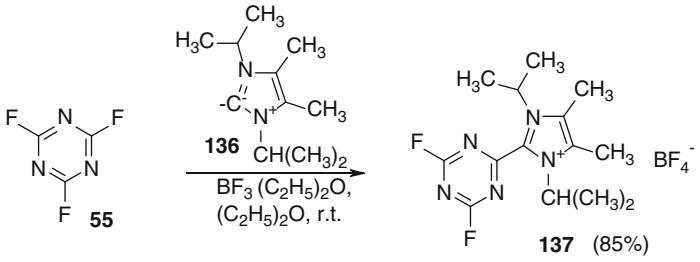
Scheme 53 Substitution of fluorine atoms in 2,4,6-trifluoro-1,3,5-triazine **55**

The anion $C_3N_3F_4$ (**135**) was prepared using TASF as the fluoride source via a simple fluoride addition to a carbon centre of $C_3N_3F_3$. After removal of the solvent and all volatile products in vacuo, a colourless solid was isolated in quantitative yield (Scheme 54). The compound shows two signals in the ^{19}F NMR spectrum, due the presence of two magnetically nonequivalent fluorine groups. This indicates the absence of fast intramolecular fluorine exchange, which was found e.g. in cyclic fluorophosphazenates [4, 85].



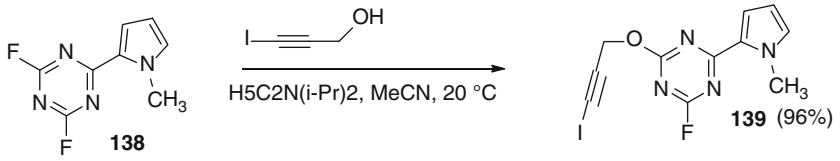
Scheme 54 Fluoride addition to a carbon centre of $C_3N_3F_3$

2,4,6-Trifluoro-1,3,5-triazine **55** reacts with 2,3-dihydro-1,3-isopropyl-4,5-dimethylimidazol-2-ylidene tetrafluoroborate **136** resulting in replacement of one fluorine atom to yield difluoro-1,3,5-triazine **137** (Scheme 55) [8].



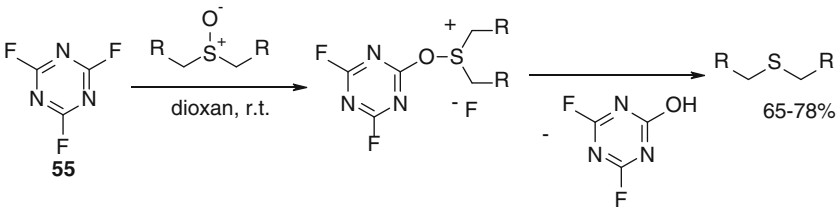
Scheme 55 Interaction of **55** with 2,3-dihydro-1,3-isopropyl-4,5-dimethylimidazol-2-ylidene tetrafluoroborate **136**

The reaction of 2,4-difluoro-6-(1-methylpyrrolyl-2)-1,3,5-triazine **138** with iodpropargyl alcohol affords the product **139** due to replacement of one fluorine atom (Scheme 56) [86].



Scheme 56 Formation of fluorotriazine **139**

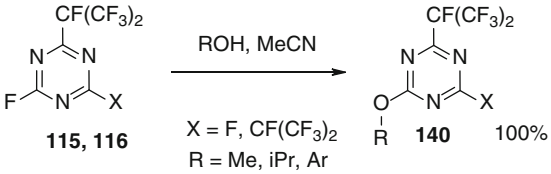
Deoxygenative ability of cyanuric fluoride **55** for sulfoxides has been shown (Scheme 57) [87]. In contrast to cyanuric chloride no concomitant formation of undesired halogenated sulfides forms due to relatively low nucleophilicity of the fluoride ion.



55

Scheme 57 Deoxygenative ability of cyanuric fluoride **55**

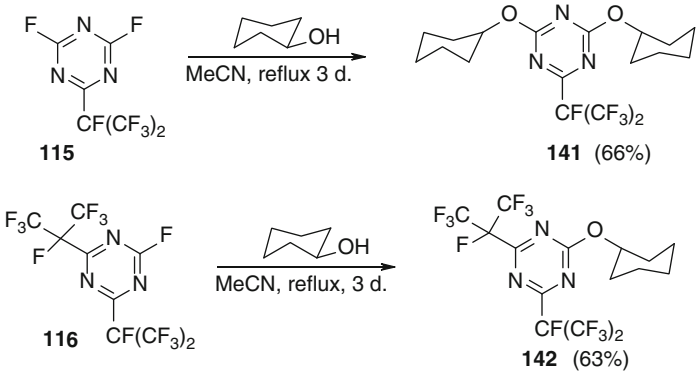
Replacement of fluorine atoms in 2,4-difluoro-6-heptafluoro-*iso*-propyl- and 2-fluoro-4,6-bis(heptafluoro-*iso*-propyl)-1,3,5-triazines **115** and **116** takes place quantitatively on reflux of **115** or **116** with methanol, isopropanol or phenols in acetonitrile (Scheme 58) [83].



115, 116 **140**

Scheme 58 Replacement of fluorine atoms in compounds **115** and **116**

Heating of compound **115** with cyclohexanol has been established to afford 2,4-dicyclohexyloxy-6-heptafluoro-*iso*-propyl-1,3,5-triazine **141**, while 2-cyclohexyloxy-4,6-bis(heptafluoro-*iso*-propyl)-1,3,5-triazine **142** was formed from compound **116** (Scheme 59) [83].

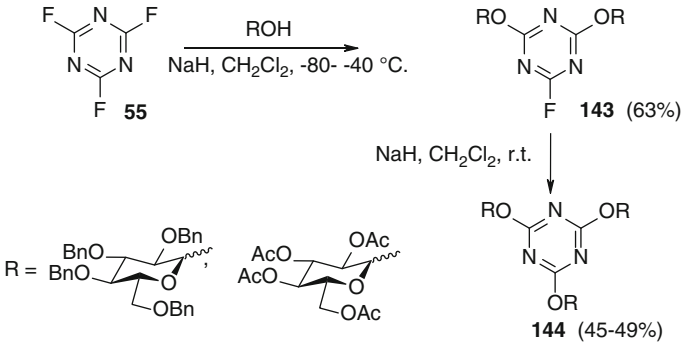


115 **141** (66%)

116 **142** (63%)

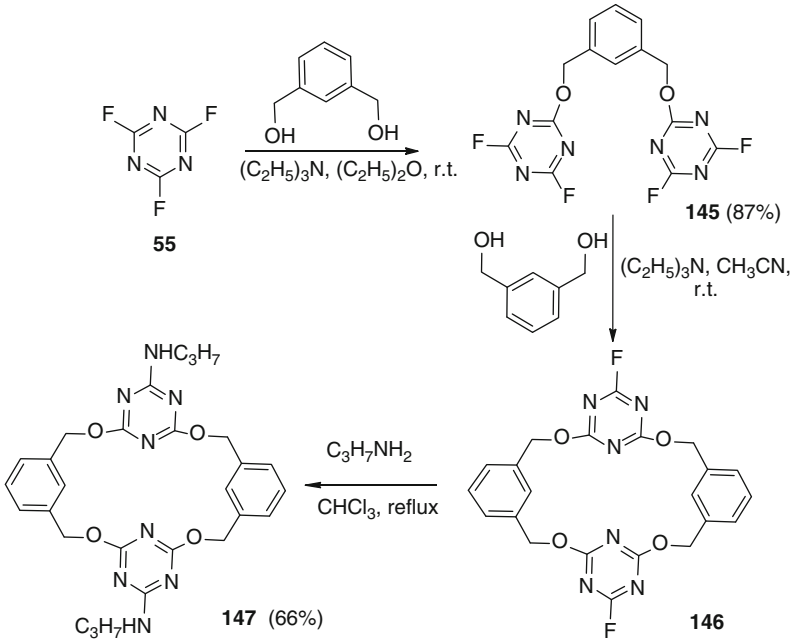
Scheme 59 Synthesis of cyclohexyloxy-derivatives of fluorinated triazines

It is known [88] that replacement of fluorine atoms in cyanuric fluoride **55** with tetra-O-benzyl- or tetra-O-acetylglucose takes place consequently with the formation of di- and trisubstituted 1,3,5-triazines **143** and **144** (Scheme 60).



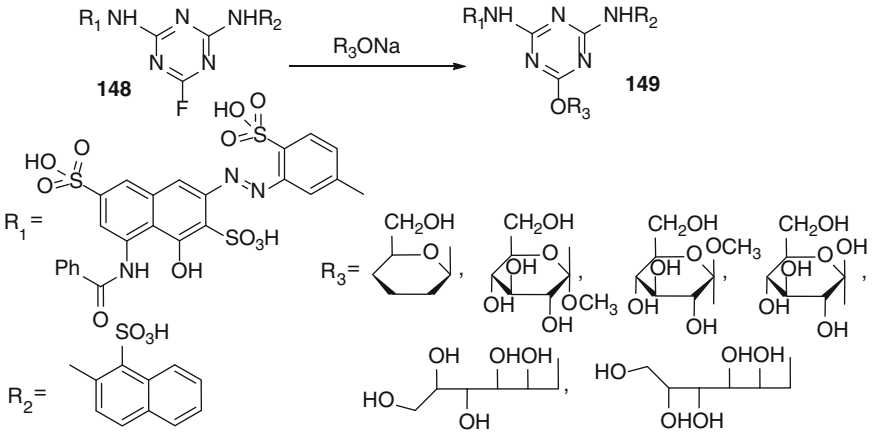
Scheme 60 Replacement of fluorine atoms in **55** with tetra-O-benzyl- or tetra-O-acetylglucose

The ability of fluorine atoms in cyanuric fluoride **55** to be replaced by action of O-nucleophiles can be exploited for the synthesis of calix[2]arene-[2]triazines **146** and **147** [89]. The reaction of **55** with 1,3-phenylenedimethanol leads to the formation of fluoro compound **145**, and then to calix **146**. Remaining fluorine atoms in the triazine fragments of calix **146** can be replaced easily by action of amines (Scheme 61).



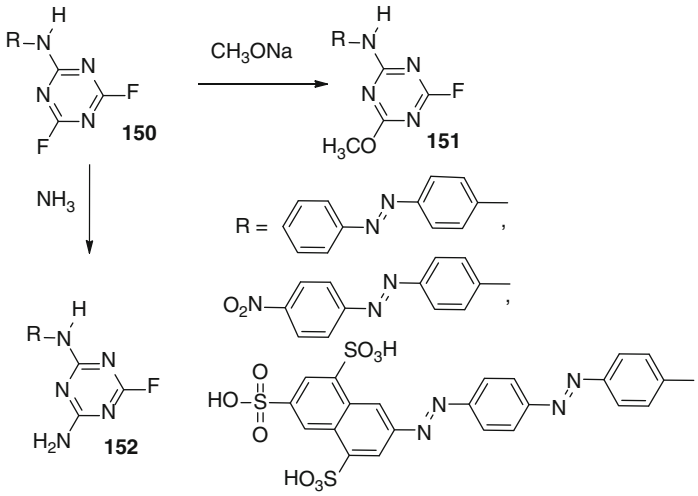
Scheme 61 Synthesis of calix[2]arene-[2]triazines **146** and **147**

Reaction of 2,4,6-trifluoro-1,3,5-triazine **55** with 1-amino-8-naphthol-3,6-disulfonic acid provides 1-(4′,6′-difluoro-1′,3′,5′-triazyn-2′-yl)amino-8-naphthol-3,6-disulfonic acid in 95 % yield [90]. Substitution of fluorine atoms in fluorotriazine dye **148** with the alkoxides, generated from tetrahydropyran-2-methanol, α- and β-methylglucopyranoside, D-sorbitol, D-mannitol and D-glucose, has been found to lead to the corresponding conjugates **149** (Scheme 62) [91].



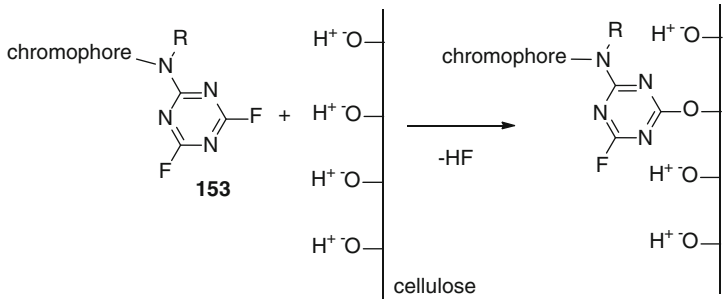
Scheme 62 Synthesis of derivatives **149**

Replacement of one of fluorine atoms in 2,4-difluoro-6-(4-arylazophenyl)-amino-1,2,4-triazines **150** with methoxy or amino group is used for the synthesis of fluorotriazine dyes **151** and **152**, which are effective for cotton coloring (Scheme 63) [39, 40].



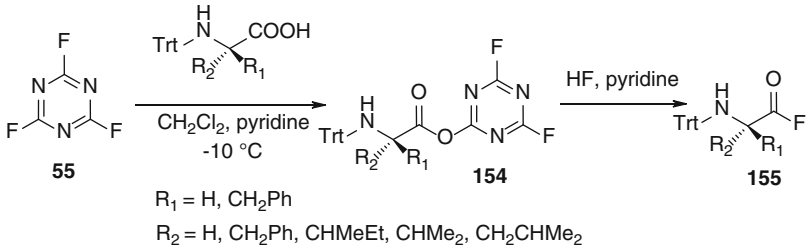
Scheme 63 Synthesis of fluorotriazine dyes **151** and **152**

The chemical process of replacement of fluorine atoms has found its practical application for fixing of yellow and dark blue fluorotriazine dyes **153** on cellulose (Scheme 64) [92–94].



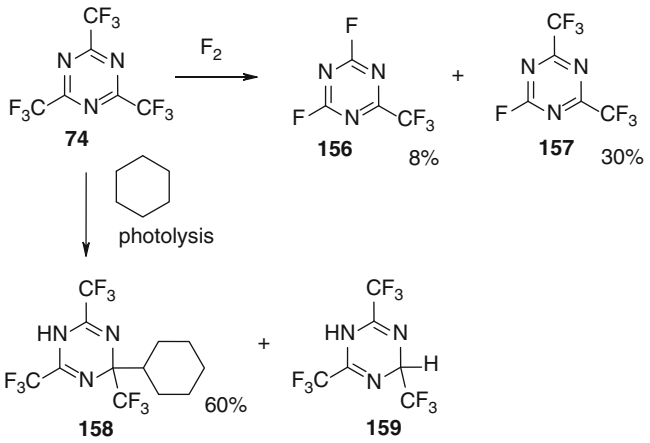
Scheme 64 Fixing of yellow and dark blue fluorotriazine dyes **153** on cellulose

Replacement of three fluorine atoms in cyanuric fluoride **55** was applied for construction biologically active molecules of deazapurine type [95]. Cyanuric fluoride mediated reaction of chiral Nα-tritylamino acids leads to the corresponding acyl fluorides **155** which are powerful acylating agents for peptide synthesis (Scheme 65) [96].



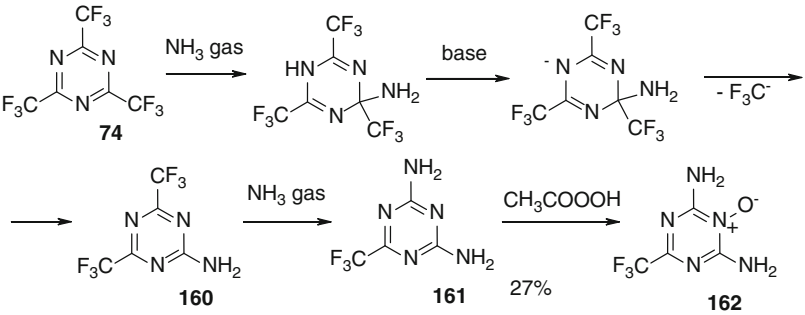
Scheme 65 Acyl fluorides **155**, powerful acylating agents for peptide synthesis

Reactions of replacement of SMe [79], trichloromethyl [97] or trifluoromethyl groups represent effective approaches for modifications of trifluoromethyl containing 1,3,5-triazines. Direct vapor-phase fluorination of tris-(trifluoromethy1)-s-triazine **74** has been studied and was found that the perfluoroalkyl groups of **74** were progressively replaced by fluorine to give mixture of 2,4-difluoro-6-trifluoromethyl-s-triazine **156** and 2,4-bis-(trifluoromethyl)-6-fluoro-s-triazine **157** (Scheme 66) [98]. Photoirradiation of tris-(trifluoromethy1)-*s*-triazine in cyclohexane leads to a mixture of adduct **158** and dihydrocompound **159** (Scheme 66) [99].



Scheme 66 Transformations of tris-(trifluoromethy1)-*s*-triazine

Diamine compound **161** was obtained in the reaction of tris(trifluoromethyl)-s-triazine **74** with ammonia. The reaction was presumed to proceed through addition-elimination mechanism as shown at Scheme 67 from the fact that 1,4-adduct was obtained, when ammonia gas was bubbled into the ether solution of the s-triazine [100].

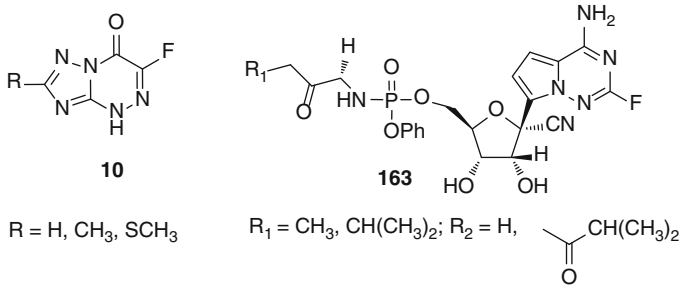


Scheme 67 Reaction of tris(trifluoromethyl)-s-triazine **74** with ammonia

Transformation of diamino-derivative **161** to N-oxide **162** was reported via oxidation with peracetic acid [101]. 2,4,6-Tris-(trifluoromethyl)-1,3,5-triazine **74** reacts with ethanol an the presence of hydrochloric acid to form ethyl trifluoroacetate [62].

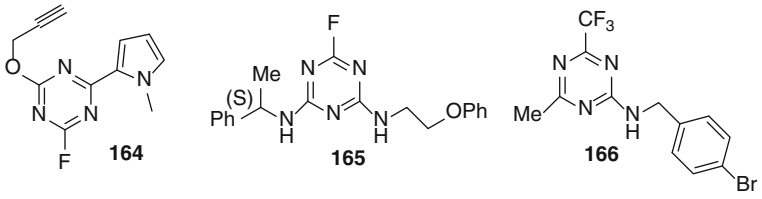
5 Application of Fluorinated Triazines

2-R-6-Fluoro-1,2,4-triazolo[5,1-*c*][1,2,4]triazin-7(4*H*)-ones **10** were shown to be active against flu A virus [16], while 1′-substituted carbonucleosides **163** bearing the fragment of pyrrolo[5,1-*f*][1,2,4]triazine were reported to possess antiviral activity (Scheme 68) [102].



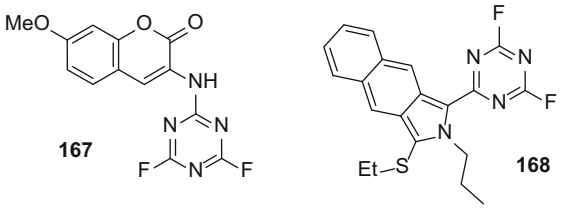
Scheme 68 Annelated fluorotriazines possessing antiviral activity

2,4,6-Trifluoro-1,3,5-triazines are widely used as starting materials for the synthesis of dyes, sensors, and biologically active compounds. A series of synthetic dyes containing one or two fluorine atoms, for example **148** [91], **151, 152** [39, 45], **54** [86, 92, 94] have been described. Also patents [103–112] are dedicated to fluorotriazine dyes. The reaction of cyanuric fluoride with amines has been used for the synthesis of analogs of the anticancer drug trimelamol which is 2,4,6-tris-[(hydroxymethyl)methylamino]-1,3,5-triazine. That is why cytotoxic properties of its analogs, such as 2-fluoro-4,6-bis[(2,2,2-trifluoroethyl)amino]-1,3,5-triazine and 2-fluoro-4,6-*bis*(propargylamino)-1,3,5-triazine, towards a variety of tumor cell lines in vitro have been studied. They revealed that 2,4,6-trisubstituted derivatives proved to be more active than 2-fluoro-4,6-disubstituted analogs [113]. Compound **164** was shown to inhibit enzyme Akt1-kinase [114], while aminotriazine **165** was found to act as 5-HT_7 receptor antagonist (binding affinity $K_i = 10$ nM) [115]. 6-(4-Bromobenzylamino)-2-methyl-4-trifluoromethyl-1,3,5-triazine **166** was found to possess strong pre- and post-emergence herbicidal activities (Scheme 69) [97].



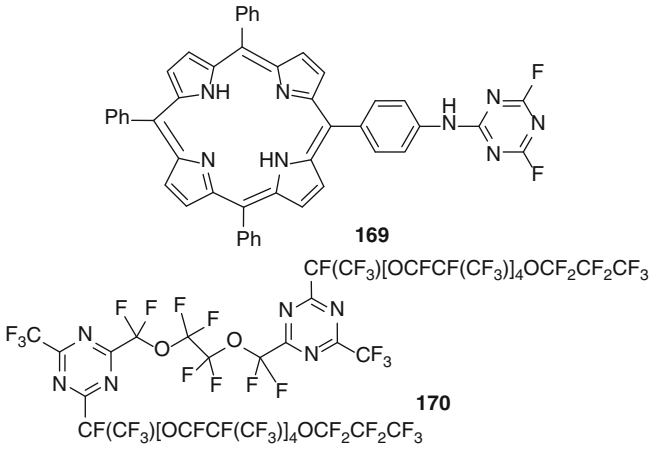
Scheme 69 Structure of fluorotriazines **164**–**166**

3-(4,6-Difluorotriazinyl)amino-7-methoxycoumarin (FAMC, **167**) is useful for determination of antiviral drug amantadine by high-performance liquid chromatography. Amantadine was derivatized quantitatively into fluorescent compound through the amino group treatment with FAMC, this method gave satisfactory results with respect to recovery and precision to quantify amantadine spiked in urine [116]. 3-(Difluoro-1,3,5-triazinyl)-1-(ethylthio)-2-n-propylbenz[f]isoindole (**168**), which reacts with phenolic hydroxyl groups, can use as a fluorescence derivatization reagent for estrogens in high-performance liquid chromatography (Scheme 70) [117].



Scheme 70 Structure of fluorotriazines **167**, **168**

Receptor for naphthalene diimide guest with efficient quenching of prophyrin fluorescence was obtained by replacement of two fluorine atoms in compound **169** by n-pentylamine [118]. Perfluoroalkyl-s-triazines **170** can be used as high-temperature fluids (Scheme 71) [119].



Scheme 71 Structure of fluorotriazines **169**, **170**

6 Conclusion

It is worth to mention that triazines and their fluorinated derivatives continue to be important for applications in medicine as well as intermediates for dyes and sensors.

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Chemistry of Fluorinated Purines

Alan M. Jones, Paul C.M. Winship, John J. Caldwell, and Ian Collins

Contents

Abstract Fluorinated purines and related nucleosides exhibit a diverse range of biological activities. The presence of a single fluoro or trifluoromethyl group at the 2-, 6-, or 8-position of a purine or purine nucleoside, or combinations of multiple substitutions at these positions, can confer advantageous changes to physicochemical, metabolic and biological properties. The incorporation of an ^{18}F label into purine nucleosides provides tools for *in vivo* imaging by positron emission tomography (PET). In this chapter we outline the many synthetic routes, both well established and more unusual, that are available for the selective preparation of 2-, 6-, or 8-substituted fluorinated purines, and the extension of these methods to make

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V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 2: 6-Membered Heterocycles*,
DOI 10.1007/978-3-319-04435-4_9,

derivatives fluorinated at specific combinations of these positions. Applications of fluorinated purines in biomedical research are highlighted. The reactions of fluorinated purines are also summarised, in particular the range of nucleophilic displacements that make the molecules useful as synthetic intermediates for medicinal chemistry and reagents for chemical biology studies.

Keywords Purines • Nucleosides • Fluorination • Trifluoromethylation • Diazotization • Fluorodediazonation • Positron emission tomography

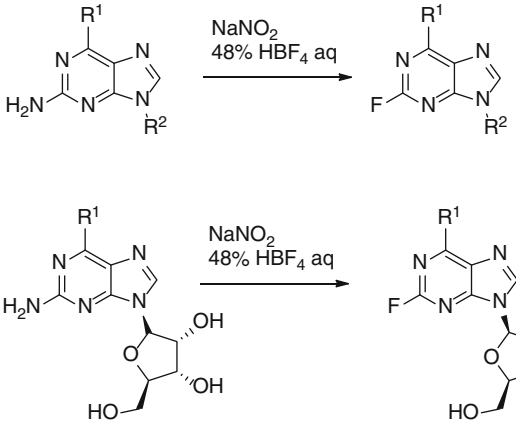
1 Introduction

This chapter reviews the synthetic chemistry to prepare fluorinated purines, and their subsequent reactions, concentrating in particular on simple fluoro and trifluoromethyl substitution. The major applications of fluorinated purines in biomedical research are surveyed. The chemistry of fluorinated purines has evolved substantially since its origins some 60 years ago, and while efforts have been made to show this general development in the choice of examples discussed, this short chapter is not intended as a comprehensive historical survey. In organising the material, the uses of fluorinated purines as synthetic intermediates are discussed in the synthetic chemistry sections, while the applications of stable fluorinated compounds are treated separately.

2 2-Fluoro- and 2-(Trifluoromethyl)Purines

2.1 Synthetic Chemistry

A range of simple 2-fluoropurine derivatives **1**–**11** and nucleosides were first prepared through the Balz-Schiemann reaction of the corresponding 2-aminopurine starting materials by diazotization-fluorodediazoniation in aqueous fluoroboric acid [1, 2] (Scheme 1). Yields were generally low but could be improved when the purine *N*-9 was protected, as purification was simplified. 2,6-Diaminopurine reacted selectively at the 2-amino group, and this selectivity has been generally observed with other substrates, although conversion of certain derivatives of 2,6-diaminopurine to the 2,6-difluoropurines under these conditions has also been reported [3]. The increased reactivity of the 2-fluoro substituents to hydrolysis compared with analogous 2-chloropurines was demonstrated in these compounds. Addition of the electron-withdrawing 2-fluoro substitution resulted in the thiopurines **5** and **11** adopting the thiol tautomers in acidic and neutral solutions, rather than the thione forms observed for the 2-unsubstituted parent molecules. A significant improvement in the yield and ease of synthesis of 2-fluoroadenine **2** directly from 2,6-diaminopurine was achieved by using anhydrous conditions ($NaNO_2$, anhydrous HF; 22 % yield) [4].

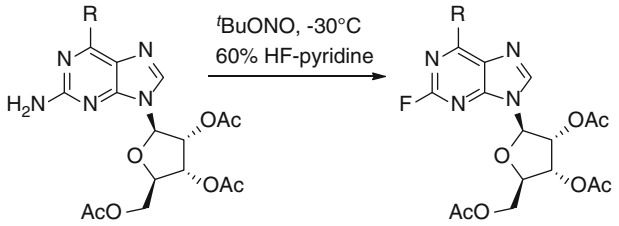


	R^1	R^2	Yield (%)
1	H	H	40
2	NH_2	H	0.7
3	NH_2	Bn	16
4	OH	H	2
5	SH	H	12
6	SMe	H	23
7	NMe_2	H	23
8	Me	H	26
9	Cl	H	13

	R^1	Yield (%)
10	NH_2	16
11	SH	7

Scheme 1 Preparation of 2-fluoropurines and nucleoside derivatives by the Balz-Schiemann reaction

Variations on the Balz-Schiemann reaction conditions have remained the most frequent method for the synthesis of 2-fluoropurines since these early publications. A major development was the introduction of HF-pyridine as the fluoride source, which gives improved yields in some cases (e.g. 80 % yield of **10** from 2-aminoadenosine using KNO_2/HF-pyridine) [5, 6]. The application of *tert*-butyl nitrite as the diazotization reagent in anhydrous 45–60 % HF-pyridine proved an especially versatile method, proceeding rapidly at low temperatures (−30 to −20 °C) in high yield [7] (Scheme 2). The anhydrous methods are tolerant of N-, O- and S-substitution at C-6, and of alkyl, acetal or no substitution at N-9. In a study of the fluorination of 2-aminoinosine derivatives containing *O*-silyl protecting groups, a combination of *tert*-butyl nitrite and the milder fluoride sources, antimony trifluoride or polyvinylpyridinium polyhydrogenfluoride (PVPHF) offered improved yields compared to HF-pyridine [8]. *In situ* diazotization using *tert*-butylthionitrate in the presence of sodium tetrafluoroborate has also been reported as a mild method for the 2-fluorination of guanosine derivatives [9]. The aqueous or anhydrous

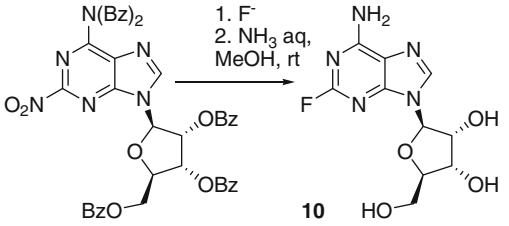


	R	Yield (%)
12	NH_2	48
13	Cl	85
14	F	66

Scheme 2 A variation of the Balz-Schiemann reaction to prepare protected 2-fluoropurine nucleosides

diazotization-fluorodediazoniation of 2-aminopurines is now the routine approach to 2-fluoropurines and 2-fluoropurine nucleosides for biomedical research [10–13 and citations in Sect. 2.2].

2-Fluoropurines have also been prepared by S_NAr displacement of 2-nitropurine derivatives, using tetra-*N*-butyl ammonium fluoride (TBAF) as the fluoride source [14]. A variation on this method proved particularly useful for the introduction of an ^{18}F radiolabel into 2-fluoroadenosine **10**, since the Balz-Schiemann reaction is poorly applicable to radiochemistry and the displacement of 2-iodo- or 2-fluoropurines with radioactive fluoride ion is inefficient [15] (Scheme 3).

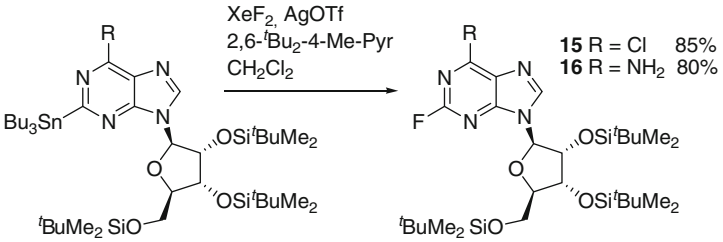


Conditions	Yield (%)
TBAF, THF, DMF, rt, 1 h	67
[18F]KF, K_2CO_3, K_{222}, MeCN, 60°C, 8 min	28

K_{222} = 4,7,13,16,21,24-tetraoxa-1,10-diazabicyclo[8.8.8]hexacosane

Scheme 3 The preparation of a 2-fluoroadenosine derivative by S_NAr reactions

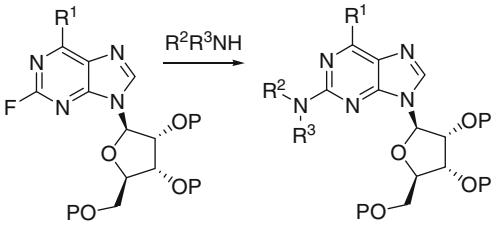
The introduction of a 2-fluoro substituent through reaction with an electrophilic fluorine source was achieved following the synthesis of 2-tributylstannyl derivatives of purine nucleosides [16] (Scheme 4). Xenon difluoride was used as the fluorinating reagent, and the method was compatible with the presence of alkenes in the substrate, as well as *O*-silyl and acetonide protecting groups, and with amine substitution of the purine [16–18].



Scheme 4 The use of XeF_2 to prepare 2-fluoropurine nucleosides from the 2-(tributylstannyl) derivatives

The most frequently reported reactivity of 2-fluoropurines involves aromatic nucleophilic substitution (S_NAr) with amine nucleophiles under basic conditions, and has been amply demonstrated with simple 2-fluoropurines and 2-fluoropurine nucleosides as substrates. The reaction of 2-fluoropurine nucleosides with amines is successful with a wide range of functionality present at the purine 6-position, including hydrogen

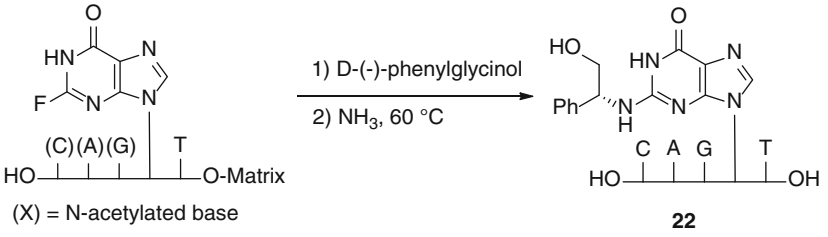
[19, 20], alkoxy, hydroxy, alkylthio [21–23], and thiol [22] substituents (**17**–**21**) (Scheme 5). The use of a 2-(*p*-nitrophenyl)ethyl protecting group at the O-6 position of 2-fluoroguanosine derivatives allowed simultaneous O-deprotection during amine substitution at C-2 [24]. The S_NAr reaction extends to alkoxy and thiol nucleophiles, as demonstrated on 2-fluoro-2′,3′-dideoxyadenosine [25].



	P	R^1	R^2	R^3	Yield (%)
17	Ac	H	n-Pr	H	78
18	H	OBn	Me	H	72
19	H	SBn	Me	H	82
20	H	OH	Me	Me	55
21	H	SH	Me	Me	70

Scheme 5 The reactivity of 2-fluoropurine nucleosides toward a selection of primary and secondary amines

The introduction of 2-amino substituents by S_NAr displacement of 2-fluoropurine nucleosides has been extensively used to prepare functionalised nucleoside intermediates for subsequent incorporation into DNA or RNA [19, 20, 26–29]. Importantly, the reaction can also be carried out on 2-fluoropurines after incorporation into deoxyribonucleotide oligomers. Thus in an early example, 2-fluorodeoxyinosine was introduced into a DNA pentamer and subsequently converted to the *N*-phenylglycinol derivative **22** to provide a mimic of the carcinogenic and mutagenic adduct formed between metabolically activated styrene and guanine bases in DNA [30] (Scheme 6). The reaction of DNA-incorporated 2-fluoropurines with amine nucleophiles has been used to prepare models of adducts of other reactive molecules with DNA, e.g. methylglyoxal [31] and mitomycin C [32], and to cross-link the strands in a DNA duplex [33].

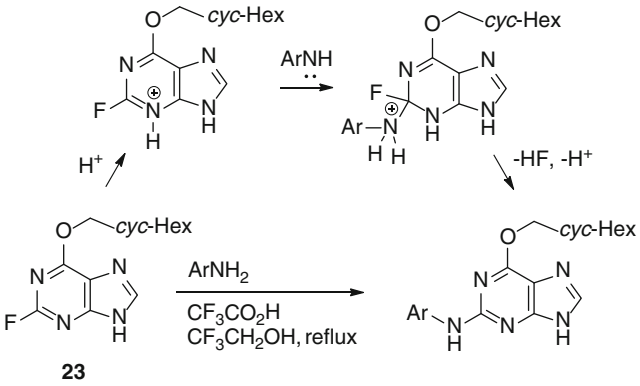


Scheme 6 The nucleophilic substitution of 2-fluorodeoxyinosine incorporated into a DNA oligomer

The introduction of exocyclic ^{15}N-containing substituents into purine nucleosides has been achieved, starting with the 2-fluoropurine derivatives, to provide labelled materials for NMR studies, using ^{15}N-ammonia [34, 35], ^{15}N-benzylamine

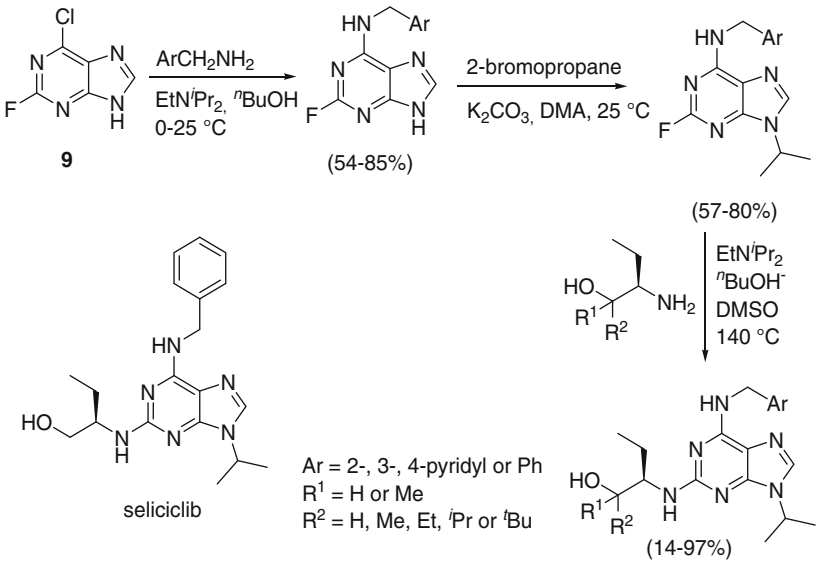
or ^{15}N-phthalimide [36]. Similarly, ^{13}C-labelled dimethylamine was used to introduce a spin label into dinucleotide analogues of mRNA caps [37].

Nucleophilic substitution reactions of non-nucleoside 2-fluoropurines by amines have found extensive use in medicinal chemistry. For example, a large number of 2-substituted-*O*6-cyclohexylmethylguanines were efficiently prepared for assessment as cyclin dependent kinase (CDK) inhibitors through the displacement of 2-fluoro-*O*6-cyclohexylmethylguanine **23** by primary and secondary alkylamines under basic conditions [38, 39]. The use of anilines as the nucleophilic component required the addition of trifluoroacetic acid, where protonation was postulated to activate the purine to attack by the (unprotonated) weakly nucleophilic anilines in the addition-elimination sequence [40] (Scheme 7). Yields were improved by conducting the reactions in 2,2,2-trifluoroethanol, chosen to favour formation of the charged intermediates. An advantage of this acid-mediated procedure was its compatibility with the nucleophile-sensitive 2,2,2-trifluoroethoxysulfonate functionality, which allowed a new electrophilic centre for subsequent reactions to be incorporated into the purines [41]. Microwave irradiation has been applied to enhance the efficiency of the base-mediated S_NAr reaction of amines with 2-fluoropurines to generate 2,6-diaminopurines [42], where sodium iodide was also observed to catalyze the reaction.



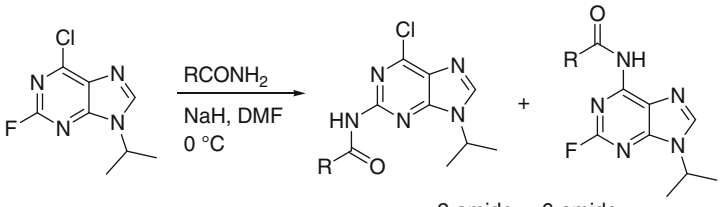
Scheme 7 Nucleophilic substitution of a 2-fluoro-6-alkoxypurine is mediated through protonation at N3

An early report on a 2-fluoro-6-chloropurine nucleoside suggested that displacement of the 2-fluoro substituent was the major product from the reaction with ammonia [22]. However, despite the increased reactivity of directly comparable fluoro *vs* chloro substituents towards S_NAr, in simple 2-fluoro-6-chloropurines the 6-chloro substituent is more usually selectively displaced by amines and this has led to the development of several powerful combinatorial approaches to polysubstituted purines. A recent example of a typical synthetic route using this process started from 2-fluoro-6-chloropurine **9** for the preparation of CDK inhibitors related to the clinical candidate seliciclib [43] (Scheme 8).



Scheme 8 2-Fluoro-6-chloropurine undergoes selective, sequential S_NAr reactions

Similar strategies have been used to prepare 2-alkylamino-6-anilinopurine CDK inhibitors [44], Src tyrosine kinase inhibitors [45] and protein A mimetics from **9** [46], as well as 2,6-dialkylamino- and 2-anilino-6-alkylaminopurine adenosine A_3 receptor antagonists [47]. Interestingly, in contrast to the above reactions the treatment of *N*9-isopropyl 2-fluoro-6-chloropurine **24** with deprotonated amides under strongly basic conditions gave predominantly displacement of the 2-fluoro group [48] (Scheme 9). Highly selective reaction of the 6-chloro substituent of **24** with alkyl and aryl amides was achieved using Buchwald palladium-catalysed conditions ($RCONH_2$, Pd_2dba_2, xantphos, Cs_2CO_3, 100 °C, 69–85 %), which could be followed by amine displacement of the 2-fluoro group. Substitution reactions of non-nucleoside

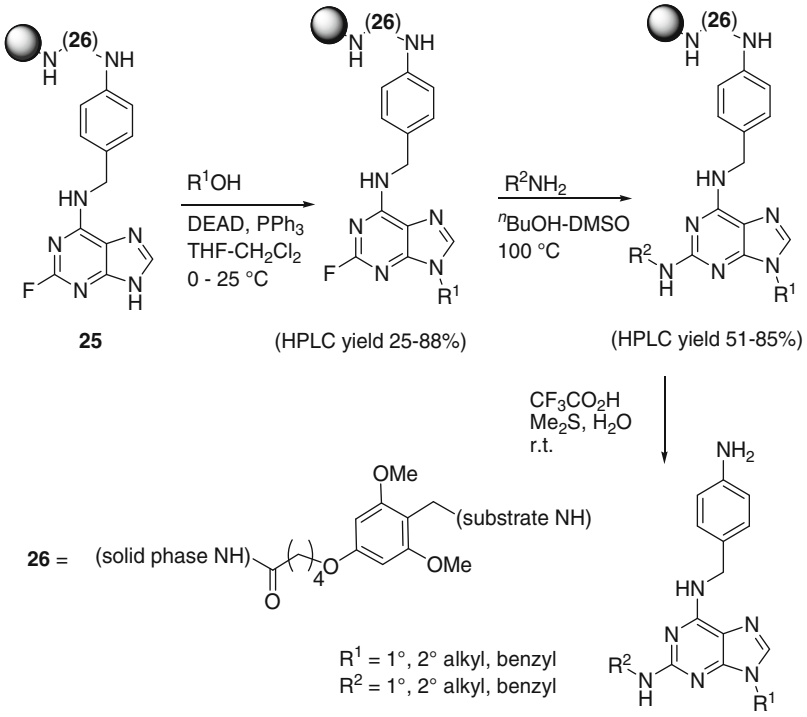


R	2-amide yield (%)	6-amide yield (%)
Ph	58	15
4-Cl-Ph	58	11
iBu	30	-

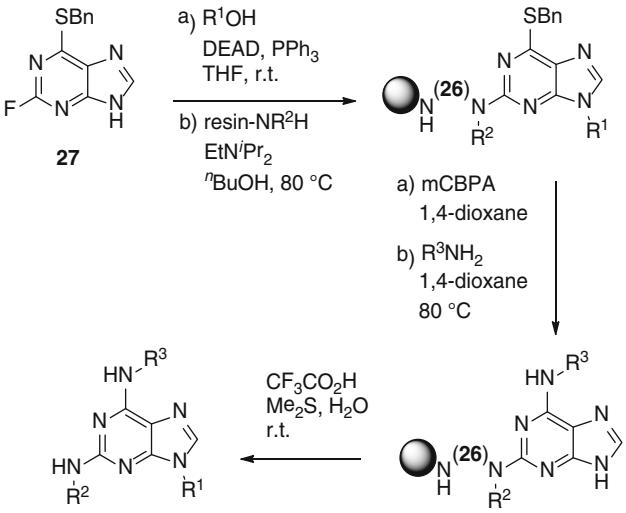
Scheme 9 An N9-alkyl 2-fluoro-6-chloropurine reacts preferentially with amide nucleophiles at the 2-position

2-fluoropurines with nucleophiles other than amines are uncommon, but examples have been reported with phenols [38, 47], thiophenol [47] and hydroxide [42].

The selective S_NAr reactivity of 2-fluoro-6-chloropurine **9** has formed the basis of several solid-phase strategies for the synthesis of purine compound libraries**.** Shultz, Gray and colleagues developed a sequence to 2,9-substituted purines involving attachment of **9** to an amine-functionalised resin through a 6-benzylamino linker to give **25** [49] (Scheme 10). Mitsunobu alkylation at N-9 was followed by S_NAr amination at C-2 before acid-mediated cleavage from the resin [49]. A similar strategy to give 2,6,9-trisubstituted products used an indole-3-carboxaldehyde derived linker that allowed for the introduction of varied potential N-6 substituents, through reductive amination of the resin before the loading of **9** [50]. A traceless linker strategy to 2,6,9-trisubstituted products from Shultz, Gray and co-workers involved resin-capture, using a pre-functionalised amine resin to react with and purify the crude Mitsunobu products from the reactions of 2-fluoro-6-thiobenzylpurine **27** [51, 52] (Scheme 11). Oxidation of the 6-thiobenzyl substituent to the sulfoxide activated the substrate for a final S_NAr amination at C-6 prior to release from the resin. Microwave irradiation was found to accelerate the S_NAr reaction of resin-bound 2-fluoro-6-(substituted amino)purines [53].

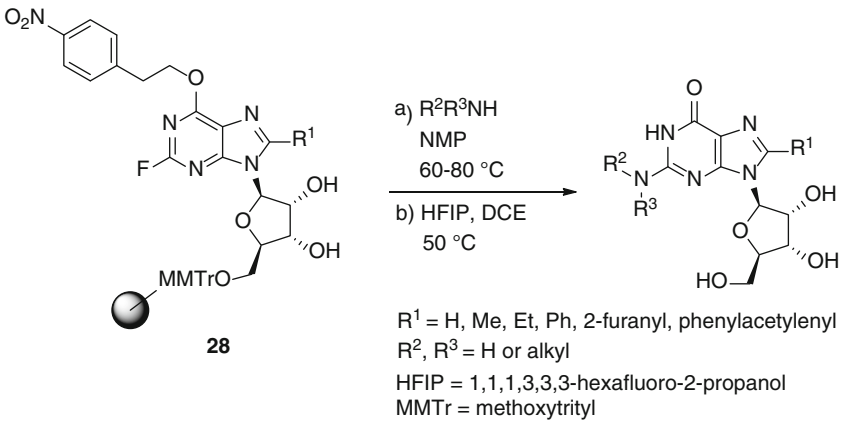


Scheme 10 A solid supported synthesis of 2,6,9-trisubstituted purines from 2-fluoroadenine



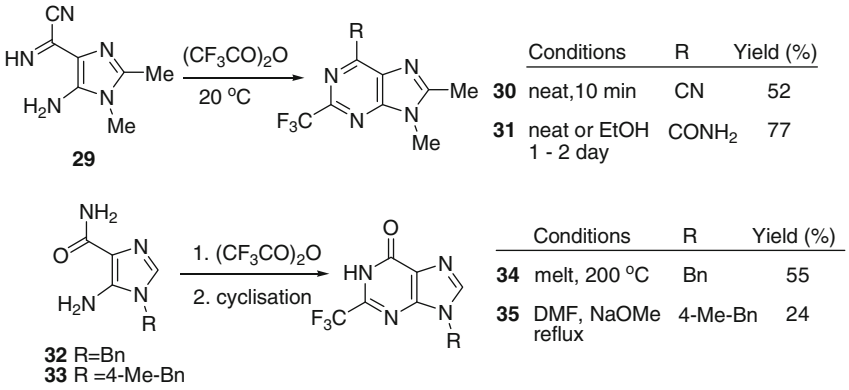
Scheme 11 A traceless linker solid phase synthesis of 2,6,9-trisubstituted purines from 2-fluoro-6-thiobenzylpurine

Solid phase combinatorial synthesis is also applicable to purine nucleosides, as exemplified by the preparation of a library of more than five hundred 2,8-disubstituted guanosine analogues using S_NAr displacement of the 2-fluoro group in the protected nucleoside **28**, linked to the polystyrene resin with a methoxytrityl group through the ribose C-5′ hydroxyl [54] (Scheme 12). The S_NAr reactions were successful with primary or secondary alkylamines, but not with anilines or other arylamines.



Scheme 12 A solid phase synthesis of guanosines by amine substitution of 2-fluoro-6-alkoxypurine derivatives

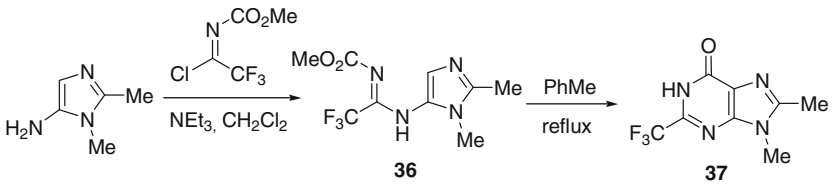
2-Trifluoromethylpurines have been prepared mainly through formation of the pyrimidine ring starting from highly functionalised imidazoles. 5-Amino-4-(cyanoformimidoyl)imidazole **29** reacted rapidly with neat trifluoroacetic anhydride to give the 6-cyano-2-trifluoromethylpurine **30** (20 °C, 10 min, 52 %) [55] (Scheme 13). However, hydrolysis to the 6-carboxamidopurine **31** was observed when the reaction was carried out over several days [55, 56]. This latter transformation has been applied to prepare 9-(3-hydroxy-propyl)-2-trifluoromethyl-9*H*-purine-6-carboxamide [57].



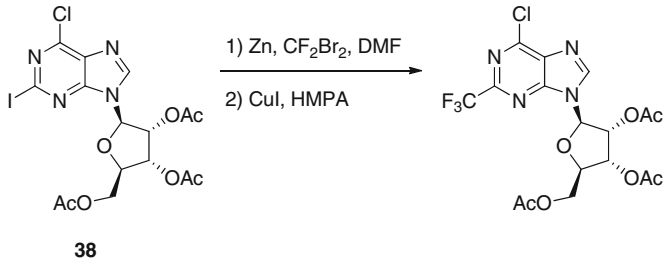
Scheme 13 The preparation of 2-trifluoromethylpurines through synthesis of the fused pyrimidine ring

5-Amino-1*H*-imidazole-4-carboxylic acid amides **32** and **33** have also served as the substrates for forming 2-trifluoromethylpurines (Scheme 13). Acylation of **32** with trifluoroacetic anhydride generated an amide intermediate that was resistant to cyclization using dehydrating agents, but which gave the purinone **34** in high yield (77 %) on melting of the solid followed by cooling and recrystallization [58]. Alternative but lower yielding conditions for the similar cyclization of **33** to give **35** have been reported [59].

The reaction of 5-amino-imidazole-4-carboxamidine with refluxing trifluoroacetamide gave 2-trifluoromethyladenine (86 %) [60], and this reaction was found to be applicable to nucleosides in the preparation of 2-trifluoromethyladenosine cyclic 3′,5′-phosphate (CF_3CONH_2, DBU, *N,N,N′,N′*-tetramethylurea, 135 °C, 47 %) [61]. Pyrimidine ring formation has also been achieved by low yielding (36 %) acylation of 1,2,-dimethyl-5-aminoimidazole with methyl 1-chloro-2,2,2-trifluoroethylidenecarbamate, to give an intermediate amidine **36** which underwent efficient thermal *6-exo-trig* intramolecular acylation to generate 2-trifluoromethylpurine **37** (toluene, reflux, 88 %) [62] (Scheme 14). The organometallic reagent formed *in situ* from CF_3ZnBr and CuI has been used to effect selective 2-trifluoromethylation of 6-chloro-2-iodopurine (triacetoxy)riboside **38** (HMPA, DMF, 50 °C, 77 %) [63] (Scheme 15).

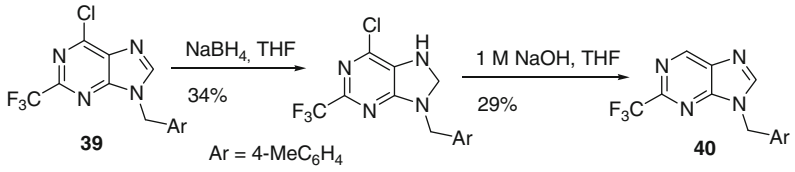


Scheme 14 A thermal intramolecular cyclisation to prepare a 2-trifluoromethylpurine



Scheme 15 The reaction of a 2-iodopurine nucleoside with a trifluoromethyl organometallic reagent prepared *in situ*

2-Trifluoromethyl-purinones such as **34** and **35** have been further functionalised through conversion of the 6-oxo substituent to 6-chloro with $POCl_3$, followed by displacement with amines [58, 59, 63, 64]. 6-Chloro-2-trifluoromethyl-9-(4-methylbenzyl)purine **39** underwent partial reduction of the imidazole ring upon treatment with sodium borohydride [65] (Scheme 16). An unusual base-mediated dehydrochlorination was then observed in the presence of sodium hydroxide, to give access to the simple 6-unsubsituted 2-trifluoromethyl purine **40**.



Scheme 16 An unusual base-mediated dehydrochlorination reaction of 2-trifluoromethyl-6-chloropurines

2.2 Applications

Due to the many enzymes and receptors using adenosine or adenosine derivatives as co-factors or ligands, 2-fluoroadenine nucleosides and nucleoside-mimics have been extensively investigated for antiparasitic [66, 67], antiviral [10, 12, 68–72], and anticancer activity [1, 2, 10, 12, 18, 72, 73]. The presence of the 2-fluoro

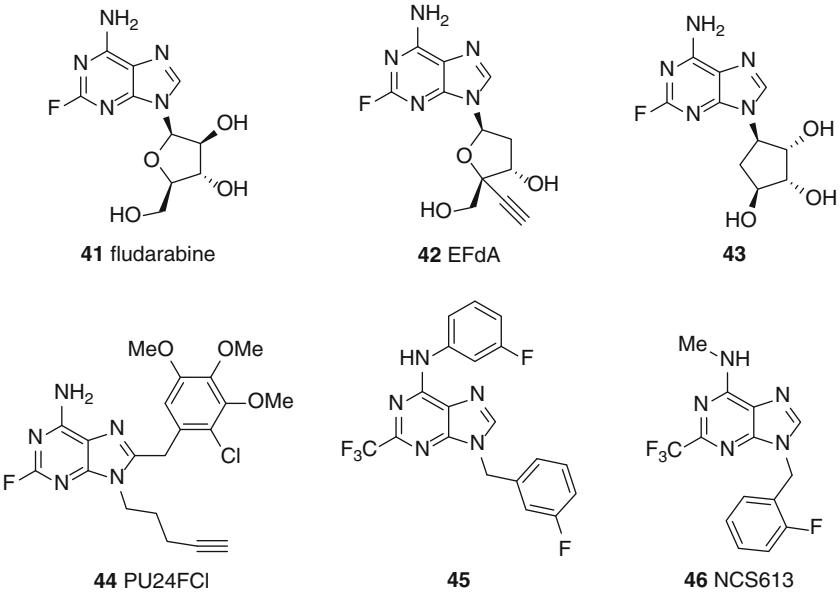


Fig. 1 Examples of 2-fluoropurine derivatives with diverse biological activities discussed in the text

substituent often confers resistance to metabolism of the purine ring, particularly by attenuating susceptibility to adenosine deaminase [74]. In several cases highlighted below, the fluorine substituent favourably modified the potency or selectivity over the unfluorinated analogues. For example, biological activity was significantly increased by the incorporation of 2-fluoroadenine in place of adenine in adenosine A_1 and A_{2A} receptor agonists [17, 75] and inhibitors of adenylyl cyclase [76]. 2-Fluoro-4-nitrobenzyl mercaptopurine riboside was identified as the most potent analogue in a series of inhibitors of the hENT1 nucleoside transporter [23].

The 2-fluoropurine nucleoside fludarabine (**41**) (Fig. 1), administered intravenously as the monophosphate derivative and more recently formulated for oral dosing [78], is a fluorinated analogue of the antiviral agent vidarabine (adenosine arabinoside). It is approved for the treatment of chronic lymphocytic leukaemia, and is also used in combinations for the treatment of Hodgkins lymphoma and acute myeloid leukaemia [77–79]. Fludarabine phosphate is rapidly dephosphorylated in cells and then transformed to the pharmacologically active triphosphate derivative (2-fluoro-ara-ATP) by deoxycytidine kinase [80]. The metabolite appears to act by inhibiting DNA polymerase α, ribonucleotide reductase and DNA primase, resulting in inhibition of DNA synthesis [81]. Fludarabine was originated by Montgomery and Hewson [82] as a more metabolically stable analogue to 9-β-D-arabinofuranyosyladenine [83]. The nucleoside 2′-deoxy-2-fluoroadenosine has been investigated as the prodrug component in a gene therapy approach for selective introduction of cytotoxic 2-fluoroadenine to tumours [73], while 2-[^{18}F]fluoroadenosine itself has been proposed as a tool for PET imaging [15].

4′-Ethynyl-2-fluoro-2′-deoxyadenosine (EFdA, **42**, Fig. 1) is an exceptionally potent reverse transcriptase (RT) inhibitor under development for the treatment of HIV infection [68, 70, 71]. Unusually for this class of inhibitors, **42** retains the 3′-OH group of the ribose, which renders the monophosphate derivative a better substrate for RT than adenosine monophosphate, and contributes to the high potency [69].

2-Fluoronoraristeromycin (**43**, Fig. 1) was investigated as an inhibitor of *S*-adenosyl-L-homocysteine (SAH) hydrolase in *Plasmodium falciparum*, and showed 100-fold enhanced selectivity for toxicity to the parasite versus mammalian cells when compared to the unfluorinated noraristeromycin [67]. Analogues of SAH inhibit human DNA methyltransferases, which use *S*-adenosyl-L-methionine as the cofactor to transfer methyl groups to DNA [18]. The addition of a 2-fluoro substituent to SAH was found to confer selectivity for inhibition of the DNMT1 isoform of enzyme over the DNMT3b2 subtype, while unfluorinated SAH was a better inhibitor of the DNMT3b2 enzyme.

2-Fluorination of the purine substrates of enzymes has been successfully used to elucidate biochemical mechanisms. Thus, nicotinamide 2-fluoroadenine dinucleotide (2-F-NAD^+) was prepared as a sterically equivalent analogue of the natural co-factor NAD^+ to probe the mechanism of ADP-ribosyl cyclases. 2-Fluorination reduced the electron density of the purine N-1 atom, retarding the enzymic cyclization and revealing a previously kinetically cryptic NAD^+ glycohydrolase activity of the ADP-ribosyl cyclase from the invertebrate *A. californica* [84]. Fluorination of purines was used to control the pKa of adenosine monomers incorporated into functional RNAs [85]. NMR studies showed the most basic site of 2-fluoroadenosine to be N-7, with negligible basicity at N-1. 2-Fluoroadenosine was used with other fluorinated analogues to demonstrate that the ligating function of the VS ribozyme required N-1 protonation at a specific residue in the oligonucleic acid.

Non-nucleoside 2-fluoropurine derivatives have shown important biological activity. PU24FCl (**44**, Fig. 1) is a purine inhibitor of heat shock protein 90 (HSP90), a molecular chaperone essential for the folding of many oncogenic proteins, and thus an attractive target for anticancer therapy [86, 87]. PU24FCl was discovered through structure-based design combined with the synthesis and screening of libraries of elaborated purine derivatives. The incorporation of the 2-fluoro substituent was found to increase the aqueous solubility and inhibitory potency of compounds in this series [6, 11, 86, 88], which is speculated to be due to increased hydrogen-bond donor capability of the N-6 amino group.

2-Trifluoromethyl-9-benzyl purines have been extensively investigated for antiviral activity [59, 64, 89–91], where the lipophilic electron withdrawing properties of the 2-CF_3 group were found to be optimal for activity against rhinovirus. 6-(3-Fluoroanilino)-9-(3-fluorobenzyl)-2-trifluoromethyl-9*H*-purine (**45**, Fig. 1) was found to have broad spectrum activity, with IC_{50} between 0.4 and 13 μM against 80 % of 43 rhinovirus serotypes, but further development was precluded by low oral bioavailability [91].

The 2-trifluoromethyl adenine derivative NCS613 (**46**, Fig. 1) was found to be a potent and highly selective inhibitor of cAMP phosphodiesterase type-4 (PDE4) [92, 93]. Introduction of the 2-CF_3 group into a series of 9-benzyladenines was found to confer increased potency (**46**, PDE4 IC_{50} 40 nM), and to give more than

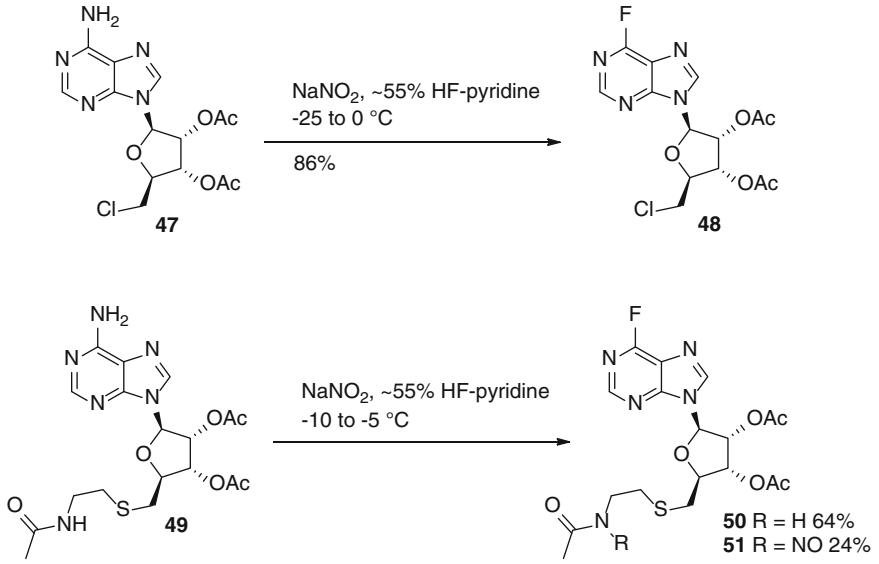
100-fold selectivity for inhibition of the PDE4 subtype over PDE1, 2 and 3. Replacement of the 2-fluorobenzyl substituent by 2-methoxybenzyl further increased potency and selectivity (PDE4 IC_{50} 1.4 nM; >50,000-fold selectivity). NCS613 (**46**) was recently shown to be effective for slowing disease progression in a genetically-engineered mouse model of the autoimmune disease, lupus, and in reducing tumour necrosis factor alpha (TNFα) secretion by peripheral blood lymphocytes from lupus patients [94].

3 6-Fluoro- and 6-(Trifluoromethyl)Purines

3.1 Synthetic Chemistry

Methods to synthesise 6-fluoro substituted purines have included reactions involving tertiary amine displacement of a 6-halo substituent and subsequent fluoride displacement of the intermediate, diazotization-fluorodediazonation strategies, direct HALEX (HALogen EXchange) reactions, ring closure of an appropriately substituted precursor and S_NAr chemistry on a 6-nitropurine.

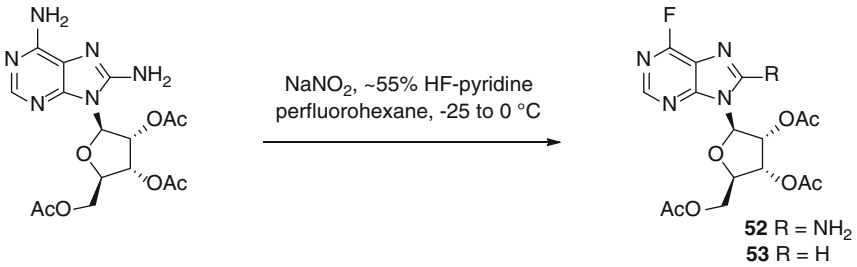
Unlike the 2-fluoro purines discussed in **2.1**, diazotization-fluorodediazonation reactions are not as well represented. Treatment of **47** with $NaNO_2$ in ~55 % HF-pyridine at −25 °C yielded the 6-fluoropurine **48** in high yield [95] (Scheme 17). This transformation depended strongly on the HF-pyridine concentration and



Scheme 17 Diazotization-fluorodediazonation reactions to prepare 6-fluoropurine nucleosides

temperature, which required optimisation for each substrate. Diazotization-fluorodediazonation of *N*-acetyl protected **49** resulted in a significant amount of an *N*-nitrosoamide by-product (**51**), as well as the desired 6-fluorinated purine (**50**).

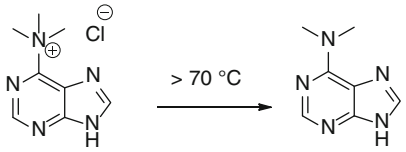
An earlier report found that if a 6,8-diamino substituted purine was used; the desired 6-fluoro-8-amino purine **52** could be isolated (Scheme 18). However, the 8-position was susceptible to hydrodeamination, which afforded **53** [96]. Interestingly, 8-amino-6-fluoro-9-*β*-D-ribofuranosyl-9*H*-purine was stable in the presence of ammonia, unlike a variety of 6-fluoropurines discussed below.



Scheme 18 An example of the susceptibility of 8-aminopurines to hydrodeamination during diazotization-fluorodediazonation

The introduction of *tert*-butyl nitrite as the diazotization reagent coupled with the use of HF-pyridine has proved a versatile alternative reagent combination [97]. Other methods involving a diazo intermediate have used $^{t}BuSNO_n$ (n = 1 or 2) with $NaBF_4$ [9] and $NaNO_2$ with fluoroboric acid, although the latter method was heavily substrate dependent and generally lower yielding than the more recent improvements [3, 98].

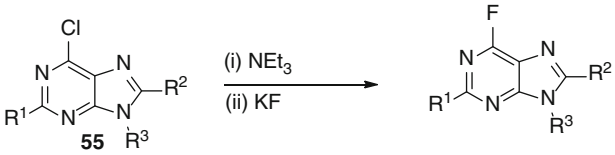
The most commonly used route to 6-fluoropurines involves tertiary amine displacement of a 6-chloro substituent and subsequent fluoride displacement of the intermediate. In general, a 6-chloropurine is reacted with trimethylamine to form a trimethylammonium intermediate which is then displaced with KF in DMF [99, 100]. Alternative procedures have used potassium hydrogen fluoride in ethanol/water or potassium fluoride in *n*-butanol to afford the 6-fluoro product but in lower yields. Various attempts to improve the overall yield from the trimethyl(purin-6-yl) ammonium chloride by performing the fluorination at a higher temperature (above 70 °C) resulted in a Martius-Hofmann rearrangement of the quaternary ammonium-substituted purine to afford a 6-dimethylaminopurine **54** (Scheme 19).

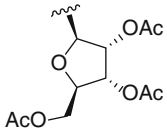
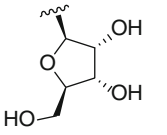


Scheme 19 A common side reaction in the preparation of 6-fluoropurines from trimethyl(purin-6-yl)ammonium chlorides by nucleophilic substitution

The stability of 6-fluoropurine was probed by exposure to 1 M sodium hydroxide at 25 °C with no formation of hypoxanthine, but increasing the temperature resulted in complete conversion. Exposure to hydrochloric acid resulted in the formation of hypoxanthine after 30 min at 25 °C [99, 100].

The chloro-amino-fluoro displacement sequence is a general and very useful method for the synthesis of 6-fluoropurines (e.g. **56**–**62**) (Scheme 20). The preparation of **60** demonstrates the selectivity for the displacement sequence at the 6-chloro position over the 2-chloro position, while formation of **61** demonstrates the selectivity of the reaction for the 6-position over the 8-position [101].

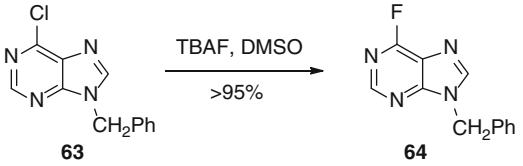


	R^1	R^2	R^3	Yield (%)
56	H	H	H	35
57	H	H	Me	58
58	NH_2	H	Me	46
59	NH_2	H	$CH_2O(CH_2)_2OH$	78
60	Cl	H	(*N7*)-Me	88
61	NH_2	Cl		89
62	NH_2	H		47

Scheme 20 Examples of the 6-chloro-amino-fluoro displacement sequence on purines and purine nucleosides

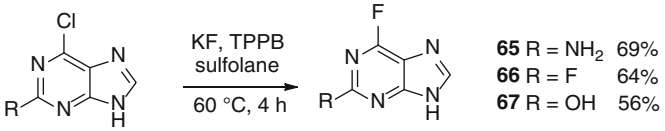
Variations of these reaction conditions have remained the most frequent method for the synthesis of 6-fluoropurines since these early publications [12, 25, 102–108]. A development of the conditions was the use of *N*-methyl pyrrolidine instead of condensing gaseous trimethylamine which led to a simplification of the reaction procedure [35]. Alternatively, a silver fluoride mediated reaction was used to great effect to convert a *N*-norbornyl-6-chloropurine to the corresponding *N*-norbornyl-6-fluoropurine in good yield (71 %) [109].

An improvement to an industrially important selective HALEX reaction was reported by the Di Magno group [110] (Scheme 21). Traditionally this reaction requires prolonged and harsh conditions in a high boiling point, polar aprotic solvent with spray-dried KF and a phase transfer catalyst to solubilise the fluoride ion. *N*-Benzyl-6-chloropurine **63** was treated with a soluble, highly nucleophilic fluoride ion source derived from anhydrous tetrabutylammonium fluoride ($TBAF_{anh}$) for 30 min in DMSO to give the desired 6-fluoropurine **64** in quantitative yield [110]. However, if the *N*9-position was not protected the reaction required 14 days and an excess of $TBAF_{anh}$ to afford a 65 % yield of the desired compound. This disparity in reactivity was suggested to result from deprotonation of the unprotected 6-chloropurine.



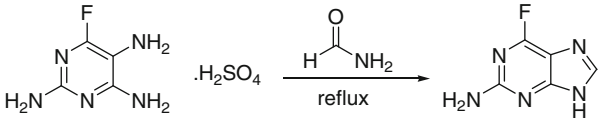
Scheme 21 An example of a TBAF-mediated HALEX reaction to prepare 6-fluoro-9-benzylpurine

A report by Scammells demonstrated the susceptibility of the 6-chloropurine position to TBAF-mediated displacement to yield an inseparable mixture of the 6-chloro and 6-fluoro purines [111]. Alternatively, a selection of 2-substituted (NH_2, F or OH) 6-chloropurines were converted to the 6-fluoropurines (**65**–**67**) in moderate yield (56–69 %) using the HALEX conditions of KF in sulfolane with the phase transfer catalyst tetraphenyl phosphonium bromide (TPPB) [112] (Scheme 22).



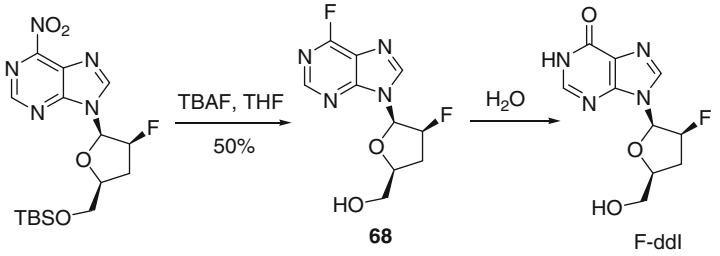
Scheme 22 A mild variant of the HALEX reaction using a phase transfer catalyst

Less common methods to prepare 6-fluoropurines include a thermally assisted ring closure of a triamino pyrimidine (containing a fluoro group) with formamide [113] (Scheme 23) and S_NAr reaction of a 6-nitropurine [114] (Scheme 24).



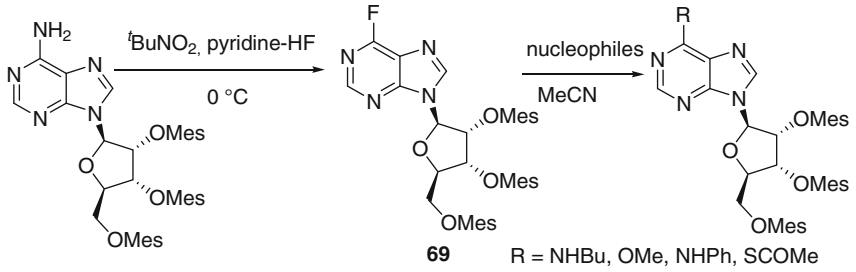
Scheme 23 A thermally assisted ring closure to prepare a 6-fluoropurine

However, the product **68** was shown to be difficult to characterise due to its hydrolytic instability, which resulted in 9-(2,3-dideoxy-2-fluoro-β-$_D$-*threo*-pentafuranosyl)hypoxanthine (F-ddI) [114]. This is a useful property for potential prodrugs and is discussed further in Sect. 3.2.



Scheme 24 S_NAr reaction of a 6-nitropurine to generated a rapidly hydrolysable 6-fluoropurine nucleoside

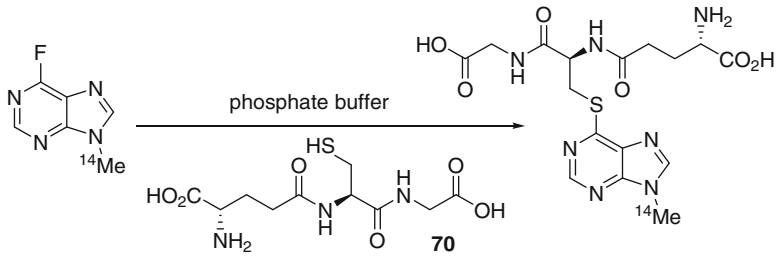
A major study addressing the synthesis, kinetics and mechanism of S_NAr displacement of 6-halopurine nucleosides with nitrogen, oxygen and sulphur nucleophiles was reported by Liu and Robins [97] (Scheme 25). The 6-fluoro group of **69** was displaced with butylamine, aniline, methanol and KSCOMe. The well understood order of reactivity at the 6-position was switched when a weakly basic aniline was used, to be I > Br > Cl >> F. An autocatalytic induction period was identified and the addition of trifluoroacetic acid eliminated this lag time and returned the reactivity order to F > other halogens.



Scheme 25 A 6-fluoropurine nucleoside undergoes reaction with O–, N-, and S-nucleophiles

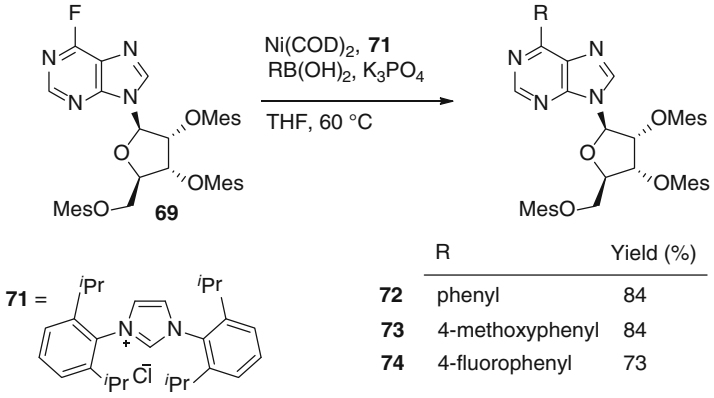
Robins and Cass also employed a range of electron-rich and electron-poor benzylamines to react with 6-fluoropurine thionucleoside in high yield [95]. Sterically congested aminotriols of relevance to the study of poly aromatic hydrocarbons (PAHs) have also been incorporated in modest to excellent yields (50–93 %, dependent on the bulk of the amine) [105, 115]. Similarly, aminoesters [116] and amino alcohols [117] have been incorporated *via* a S_NAr reaction with 6-(fluoro)-2′-deoxyadenosine analogs in modest yield. Glutathione (**70**) has also been shown to

undergo reaction at the 6-fluoro position of the purine ring, both enzymatically and nonenzymatically [118] (Scheme 26).



Scheme 26 Glutathione reacts both enzymatically and non-enzymatically with 6-fluoropurines

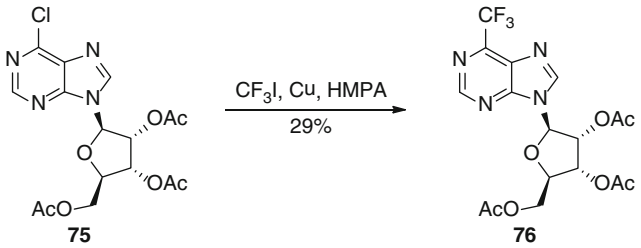
The only example of 6-fluoropurine analogues undergoing metal-catalysed cross-coupling reactions was reported by Liu and Robins [119]. A combination of an imidazolium-carbene and nickel (0) bis(cyclooctadiene) was used to form a catalyst capable of insertion into the C–F bond of 6-fluoropurine nucleosides such as **69** [119] (Scheme 27). A variety of boronic acids bearing electron donating and withdrawing groups were successfully incorporated (**72**–**74**).



	R	Yield (%)
72	phenyl	84
73	4-methoxyphenyl	84
74	4-fluorophenyl	73

Scheme 27 Metal-catalysed cross-coupling reactions of a 6-fluoropurine nucleoside derivative

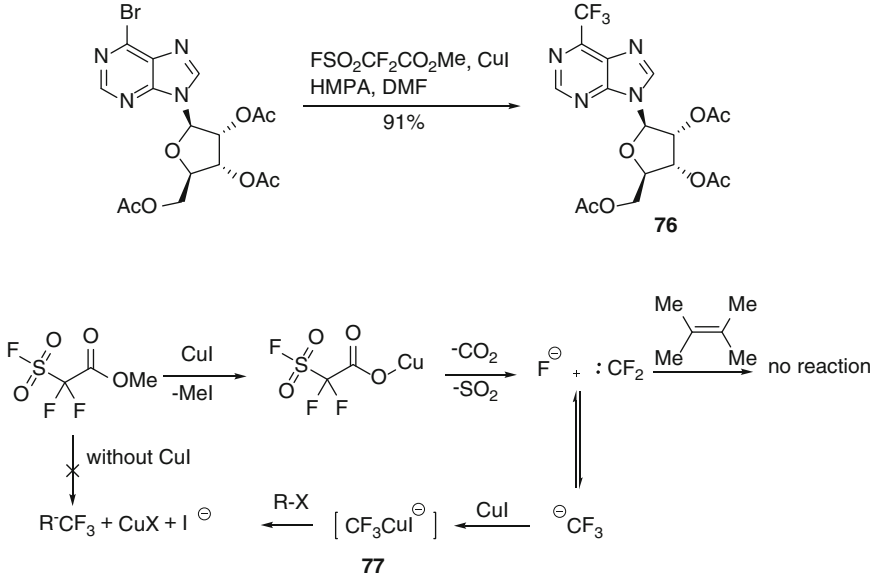
Installation of the 6-(trifluoromethyl) group onto a purine is most widely reported to occur *via* copper mediated cross-coupling of a trifluoromethyl containing reagent and a 6-halopurine [120]. For example, treatment of **75** with a CF_3-Cu solution (obtained by filtration under inert conditions of a vigorously shaken and heated mixture of CF_3I, Cu and HMPA) afforded **76** in a modest yield [120] (29 %) (Scheme 28). The introduction of the filtration step eliminated a problematic reductive dehalogenation. This procedure has been used successfully elsewhere [121].



Scheme 28 The preparation of a 6-trifluoromethylpurine nucleoside using CF_3Cu reagent prepared *in situ*

Modifications to this route have generally involved an alternative trifluoromethylation reagent; examples employed in purine chemistry include CF_3TMS [109, 122], $FSO_2CF_2CO_2Me$ (MFSDA) [123], and CF_3CO_2Na [112]. The use of CF_3TMS in conjunction with CuI, KF, DMF and NMP was used to install a trifluoromethyl group onto an *N*-norbornyl-6-chloropurine in good yield (81 %) [109]. The sodium salt of trifluoromethylacetic acid with CuI in DMF was used to functionalise a range of 6-chloro purines in modest to good yields (53–84 %) [112].

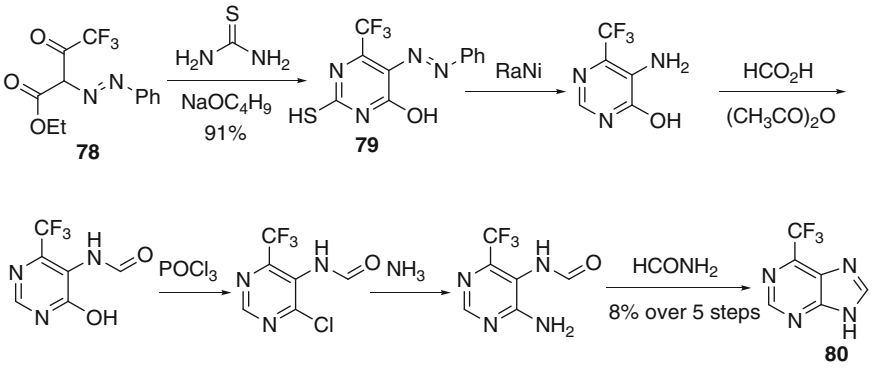
An elegant use of both the CF_3I-Zn-CuI and MFSDA-CuI-HMPA routes was employed by Veliz et al. [123]. Both reagents afforded the desired 6-(trifluoromethyl) purine riboside **76** in excellent yield (96 % and 91 %, respectively). However, the use of liquid MFSDA over gaseous CF_3I conferred a practical advantage. A mechanism for this reagent was reported by Chen and Wu [124]. The proposed mechanism implies a transient difluorocarbene species, however the equilibrium would lie mainly with the CF_3^- species in the presence of CuI to give **77** (Scheme 29). The suggestion of a



Scheme 29 Trifluoromethylation of a 6-bromopurine nucleoside using MFSDA and the postulated mechanism

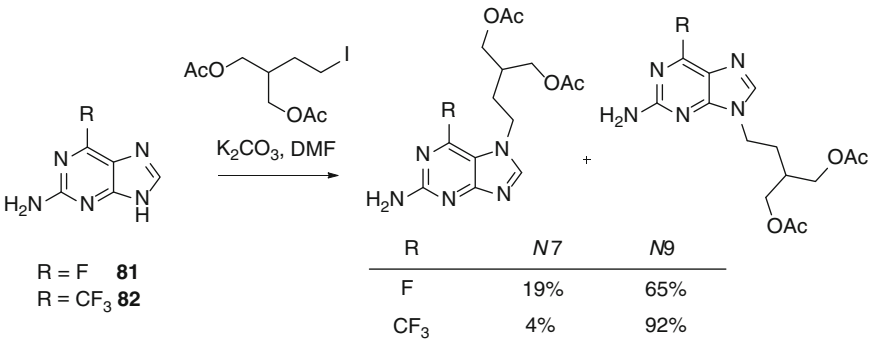
carbene or a radical mechanism was ruled out by unsuccessful trapping experiments using 2,3-dimethylbut-2-ene (carbene scavenger) and *p*-dinitrobenzene (a single electron scavenger), respectively, which has supported the involvement of a [CF_3CuI^-] intermediate **77**. Furthermore, no reaction occurred in the absence of copper (I) iodide.

Of historical importance was a seven-step synthesis of 6-(trifluoromethyl)purine, which was accomplished by the Bendich group in 1958 [60] (Scheme 30). The key step was the installation of the trifluoromethyl group into a pyrimidine (**79**) by condensation of the phenyldiazo ester **78** with thiourea in the presence of sodium butoxide. Subsequent conversion of the hydroxyl to an amine and formamide-mediated ring closure gave **80**. Similarly, the research group of Geen prepared 6-(trifluoromethyl)purines from a trifluoromethyl containing triamino pyrimidine with a thermally assisted formamide-mediated ring closure [113].



Scheme 30 The synthesis of 6-trifluoromethylpurine by Bendich and colleagues

N-alkylation is a common reaction of both 6-fluoro and 6-trifluoromethyl substituted purines. However, there are two possible outcomes; *N*9- or *N*7-alkylation. A study detailing the effect of the 6-substituent was reported by Geen [113] (Scheme 31). In their particular example, a 6-fluoro group (**81**) exerted a small influence on the *N*9:*N*7

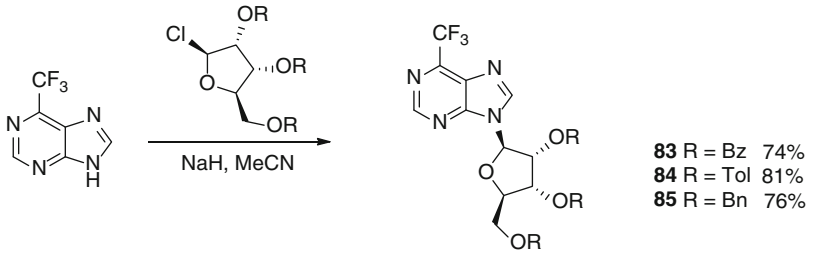


R	*N*7	*N*9
F	19%	65%
CF_3	4%	92%

Scheme 31 N7 versus N9 alkylation of purines controlled by the presence of a 6-fluoro or 6-trifluoromethyl group

ratio (3.4:1) and a 6-(trifluoromethyl)group (**82**) exerted a substantially larger influence on the reaction outcome (21:1), presumably due to a larger steric influence over the reacting centres. The 6-fluoro group will also better stabilise the charged transition state at the 7-position, leading to a less dramatic effect compared to the parent substrate.

Of importance for purine riboside chemistry, the reaction of 2′-chloro-3′,4′,5-(Tol, Bn or Bz) protected ribose with 6-(trifluoromethyl)purine gave the desired *N*9-isomer in high yields (**83–85**, 74–81 %) (Scheme 32). All the glycosylation reactions reported were regio- (and stereo-) selective to afford the β-nucleoside [121].



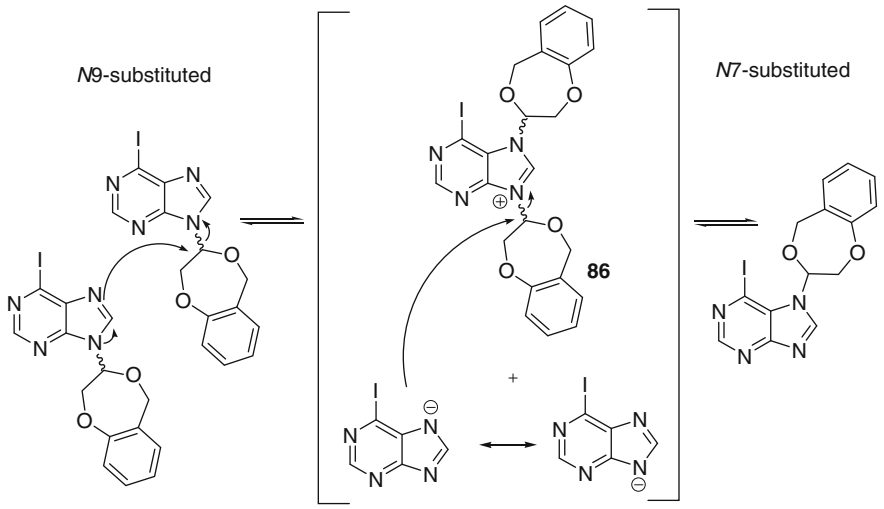
Scheme 32 Stereo- and regioselective preparation of N9-ribosylated products from 6-trifluoromethylpurine

Further evidence of the *N*9:*N*7 effect was witnessed when 6-fluoropurine was reacted with ^{14}MeI to give methylated purines in high radiochemical purities (>95 %) with 36 % isolated yield for *N*9-^{14}Me and 13 % isolated yielded for the *N*7 isomer [118].

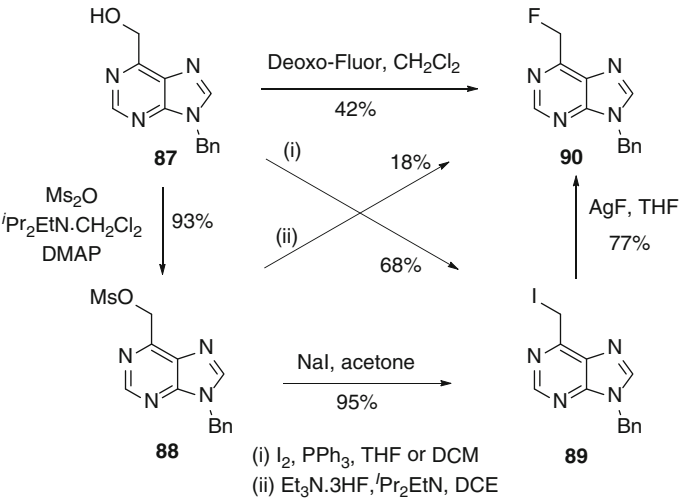
Campos et al. have reported that aminal functionality at the N-9 position of a purine can migrate to an extent to the N-7 position during trifluoromethylation of a 6-iodopurine analogue using CF_3TMS-CuI-KF at 60 °C. A rationale for this unusual migration was proposed to explain the reversibility of the process at elevated temperatures. An important experiment revealed that the migration occurred simply by heating the starting material for a short time, *via* intermediate **86** [122] (Scheme 33). The transformation is reversible and the outcome is thermodynamically controlled with the *N*9-isomer being ~5 kcal/mol more stable than the *N*7-isomer.

The incorporation of a 6-(fluoromethyl) group into purines has been achieved *via* two main routes; metalation of a 6-methyl substituent and trapping of the anion with NFSI [125, 126] and fluorination of a 6-(hydroxymethyl)purine riboside [127]. The metalation and NFSI trapping procedure gave the desired 6-fluoromethyl purine in a modest yield (48–57 %) with only a trace of the 6-difluoromethyl purine analogue observed. Importantly, the use of *n*-BuLi and LiHMDS resulted in unselective metalation at both the 6–CH_3 and 8-CH positions. Switching to NaHDMS or KHMDS resulted in a regioselective metalation at the 6-methyl position [125, 126].

Silhar et al. [127] investigated three alternative fluorination reagents (DAST, $C_4F_9SO_2F$ and Deoxo-Fluor) for the conversion of hydroxymethyl purine **87** into **90** using different bases and also pre-conversion of the hydroxyl group to a mesylate (**88**) or iodide (**89**) and treatment with AgF (Scheme 34). Ultimately, it was found that the silver fluoride displacement of the iodide was the most general route affording *N*-benzyl-6-(fluoromethyl)purine **90** in isolated yields of between 72 and 84 %.



Scheme 33 A reversible N9 to N7 migration observed during the reaction of a 6-iodopurine with CF_3TMS-CuI-KF



Scheme 34 Direct and indirect routes to 6-(fluoromethyl)purines

3.2 Applications

The major use of 6-fluoropurine analogues has been as prodrugs, as although the 6-fluoro position is more chemically stable than the 2- and 8-fluoro purines, it is readily enzymatically hydrolysed to the carbonyl-containing inosine analogue. A body of work has been published by the research group of Kim with the intention of designing

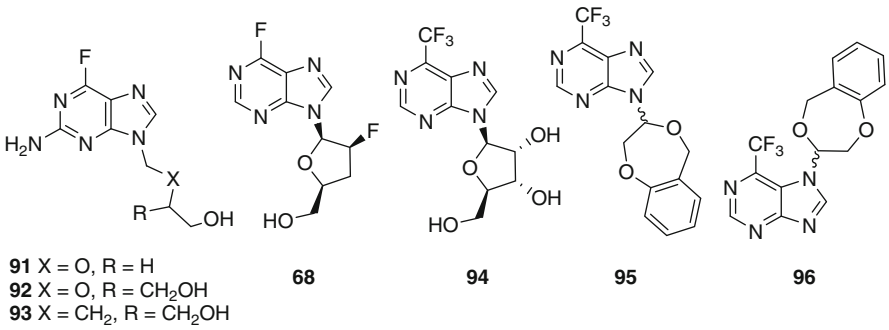


Fig. 2 Examples of 6-fluoro- and 6-trifluoromethyl purines and purine nucleosides discussed in the text

and preparing 6-fluoropurine analogues of the potent and selective antiherpetic drugs: Acyclovir, Ganciclovir and Penciclovir as prodrugs [102, 106–108]. Examples of compounds prepared include; **91** (prodrug of Acyclovir, Fig. 2), **92** (prodrug of Ganciclovir, Fig. 2), and **93** (prodrug of Penciclovir, Fig. 2). All of these prodrugs contain a substitution of the parent 6-oxo group with a fluorine atom. The major advantage conferred by the substitution of the 6-position of the purine with a fluoro group is the increase in the efficiency of the metabolism of the prodrug to the active form by adenosine deaminase, compared to the previously prepared 6-amino purine analogues [108]. The dehalogenation of a 6-fluoropurine substituent using adenosine deaminase and/or adenosine kinase has been widely published [96, 128]. An important property of these 6-fluoropurine analogues was the increase in water solubility compared to the 6-oxo drugs which is of relevance for oral administration.

The introduction of a 6-fluoropurine group has also been applied to anti-HIV prodrugs for delivery to the central nervous system [12, 104, 114]. The 6-fluoro purine prodrug **68** (Fig. 2) of F-ddI was converted by adenosine deaminase to the active inosine compound. The fluoro analog had the greatest conversion rate to the active species when exposed to adenosine deaminase, compared to ten other structurally similar non-fluoro analogs. Crucially, the 6-fluoro analog was one of the most potent analogs tested with an $EC_{50} < 5$ μM [104, 114]. A further advantage of the 6-fluoro group is the increase in lipophilicity and improved blood-brain-barrier penetration. However, in another study introduction of a 6-fluoro group onto a different series of purines was shown to be of no benefit in an *in vitro* anti-HIV assay [12].

The anti-cancer properties of 6-fluoro- and 6-(trifluoromethyl)purines have been published widely [12, 96, 121, 125–127]. A 6-(trifluoromethyl)purine ribofuranosyl derivative **94** (Fig. 2) was shown to possess cytotoxicity against HeLaS3 and CCRF-CEM cell lines, with GI_{50} of 2 μM and 450 nM respectively, whilst being inactive against L929 and L1210 cultures. A range of other 6-(trifluromethyl)purine analogs were tested and shown to be inactive [121]. Data presented for antiproliferative activity against the MCF-7 human breast cancer cell line showed IC_{50}s of 3 μM for the *N*9-substituted compound **95** (Fig. 2) and 25 μM for its *N*7-substituted isomer

96 (Fig. 2) [122, 129]. In all other examples in these reports the *N*7-substituted isomers were similarly more potent, and the presence of a trifluoromethyl group or a halogen in the 6-position conferred increased antiproliferative activity.

Of interest for suicide gene therapy, a 6-(fluoromethyl)purine nucleoside was a non-toxic prodrug, shown to be a good substrate for *E. coli* purine nucleoside phosphorylase (*E. coli* PNP) and converted to a highly toxic purine analogue (equipotent with the methyl analogue). These results demonstrated that the fluorine atom incorporation did not affect the *E. coli* PNP enzyme activity [126].

6-Fluoro and 6-(trifluoromethyl) containing purines have also been screened for activity against fungi including *Bacillus subtillis, Aspergillus niger* and *Candida tropicalis* and were all shown to have an effect on the diameter of the inhibition zone [112]. An example of a 6-fluoropurine analogue was shown to have no significant effect on three protozoan parasites, *T. b. brucei*, *T. cruzi* and *L. donvani* [130].

6-Fluoro and 6-(trifluoromethyl)purines bearing an *N*9-norbornyl group have been investigated as inhibitors of Coxsackievirus B3 (CVB3) which is of the enteroviruses family and an important human pathogen. The 6-fluoro derivative was inactive against CVB3 in contrast to the 6-(trifluoromethyl)derivative which had an EC_{50} of 16 μM ± 10 μM [109].

A 6-(trifluoromethyl)purine ribonucleoside containing a phosphoramidite group was used to perform a site-specific attachment onto RNA to study the RNA structure and the binding of RNA-modifying enzymes [123]. Furthermore, 6-fluoropurines have been used as part of a post-oligomerization strategy. The incorporation of the fluorine-containing purine bearing a phosphoramidite group into an oligonucleotide was used to study the interaction of polyaromatic hydrocarbons (PAHs), *via* reaction at the 6-fluoropurine position, on the *ras* codon 61 [105].

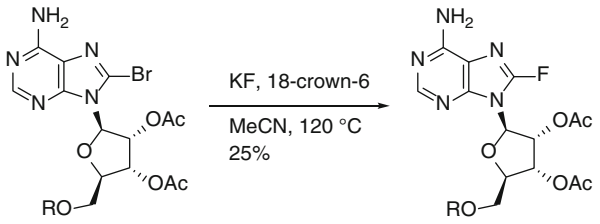
Unlike the 2- and 8-positions of purines (see Sects. 2.2 and 4.2, respectively), the 6-position has not been used to the same extent for ^{18}F labelling experiments. The 6-^{18}F group was incorporated in high radiochemical yield using a $Ag^{18}F$ mediated reaction on a selection of purines where *N*9 was substituted with benzyl or ribosyl groups [131–133]. 6-^{18}Fluoro-9-benzylpurine was demonstrated to be unstable in acid but showed promise as a brain imaging PET agent due to its biodistribution in a mouse model with high uptake in the brain [133].

4 8-Fluoro- and 8-(Trifluoromethyl)Purines

4.1 Synthetic Chemistry

Compared to the analogous 2- and 6-fluoropurines (see Sects. 2.1 and 3.1), relatively few examples exist of the syntheses of 8-fluoropurines. The first synthesis of an 8-fluoropurine was reported in 1963, whereby treatment of 8-chloro-9-methylpurine with silver fluoride in refluxing toluene resulted in the formation of 8-fluoro-9-methylpurine *via* an S_NAr mechanism [134]. This original method was modified

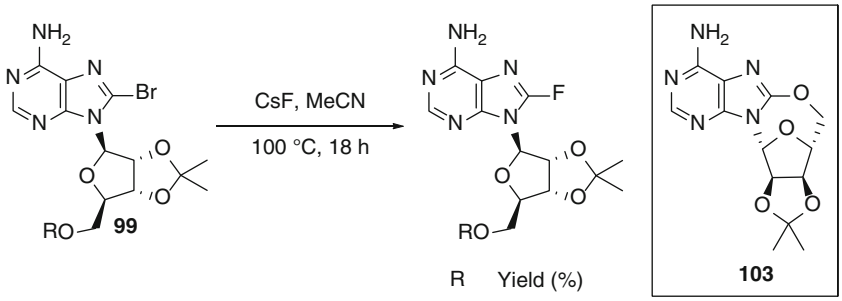
and improved some years later, by starting from analogous 8-bromopurines. In this case, 2′,3′,5′-tris-*O*-acetyl-8-bromoadenosine **97** was treated with dry KF and 18-crown-6 in MeCN, giving the corresponding 8-substituted fluoropurine **98** in 25 % yield [135] (Scheme 35). In both instances, the low yields of the 8-fluoropurine were attributed to the lability of the resulting C-F bond.



97 **98**

Scheme 35 The preparation of an 8-fluoropurine nucleoside

A further elaboration of this strategy was used to prepare various protected 8-fluoropurine nucleosides (**100–102**), using CsF as the fluorinating agent [136] (Scheme 36). In this case, initial attempts were made to fluorinate 8-bromo-2′,3′-*O*-(1-methylethylidene)adenosine **99**, however, despite consumption of the starting material, no fluorinated product was observed. Further investigation revealed that the corresponding 5′,8-anhydro-adenosine derivative **103** was being formed, presumably by intramolecular nucleophilic attack of the 5′-hydroxyl group of the ribose on the intermediate 8-fluoro compound. Upon protecting the 5′-hydroxyl group with either an acetate or a tetrahydropyran group, the desired 8-fluoroadenosine compounds were produced in moderate yields. Analysis of these crude reaction mixtures also revealed the presence of a dimer, which was attributed in an intermolecular attack of the 6-NH_2 group of another adenosine molecule, demonstrating the highly labile nature of the 8-fluoro substituent.



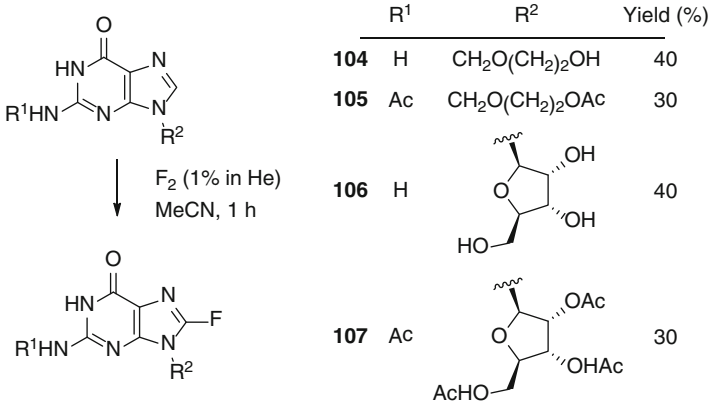
	R	Yield (%)
100	H	0
101	Ac	24
102	THP	28

103

Scheme 36 5′-Hydroxyl protection is required to prevent intramolecular reaction of an 8-fluoropurine nucleoside

In contrast to 2- and 6-fluoropurines, the Balz-Schiemann reaction rarely features in the synthesis of 8-fluoropurines. In fact, the only example to date was reported, whereby 2′,3′,5′-tris-*O*-acetyl-8-aminoadenosine was treated with fluoroboric acid and sodium nitrite, to afford triacetylated-8-fluoroadenosine [137]. However, subsequent attempts by other research groups to repeat this reaction were unsuccessful, believed to be as a consequence of the lability of the C-F bond [135].

An alternative strategy to access 8-fluoropurines is through the electrochemical oxidation of 2,6-disubstituted purines. Subjecting either caffeine or guanosine tetraacetate to anodic oxidation in the presence of Et_3N-3HF, resulted in 8-fluorocaffeine (40 %) and 8-fluoroguanosine tetraacetate (6 %), respectively [138]. Despite the low yields, this method enables access to 8-fluoropurines directly from the corresponding unsubstituted purine. Another way in which 8-fluoropurines can be prepared directly is *via* an electrophilic aromatic substitution with fluorine gas. A range of purines have been shown to react cleanly with F_2 (1 % in He) in polar solvents, such as MeCN, affording the corresponding 8-fluoropurine analogues (**104**–**107**) in 30–40 % yield, along with recovered starting material [139] (Scheme 37). Attempts to force the reaction to completion, or exchange fluorine gas for a more conventional fluorinating agent, (such as XeF_2, or Selectfluor®) were unsuccessful.

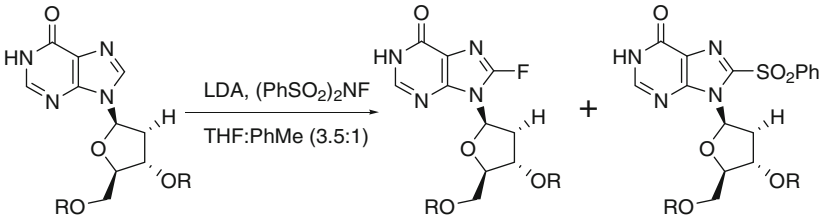


	R^1	R^2	Yield (%)
104	H	$CH_2O(CH_2)_2OH$	40
105	Ac	$CH_2O(CH_2)_2OAc$	30
106	H		40
107	Ac		30

Scheme 37 The preparation of 8-fluoropurines using fluorine gas

Approaching the 8-fluorination of purines by deprotonation of the C8-H, followed by reaction of the corresponding anion with an electrophilic fluorinating agent has proved successful. After screening a range of strong bases, it was discovered that the use of LDA in a mixture of toluene and THF, in combination with *N*-fluorobenzenesulfonamide (NFSI) as a fluorine source, resulted in the formation of a range of 8-fluoro substituted nucleosides [140] (Scheme 38). It was noted that the product distribution of the reaction was very sensitive to the solvent system used. The isolation of phenylsulfonyl-derivative **108** as a side product also suggested that a competing single electron-transfer (SET) mechanism was in operation.

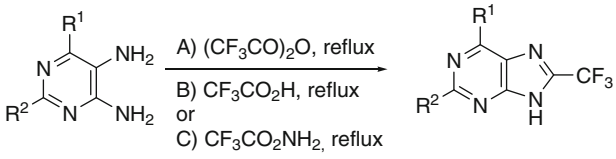
In fact, under homogenous reaction conditions it was found that the SET mechanism prevailed, affording phenylsulfonyl-derivative **108** as the major product. Similar reactivity patterns were observed in guanidine analogues, with sulfonylation of the 2-NH_2 group occurring as the most common side product.



Scheme 38 8-Fluoropurine nucleosides formed by direct deprotonation of the C8 position and quenching with an electrophilic fluorine source

Further elaboration of this methodology revealed that 6-methyl substituted purines, when treated under similar conditions, were deprotonated unselectively at both the 8- and 6-methyl positions with LDA [126]. On optimising the reaction, it was found that by using NaHMDS as the base, regioselective deprotonation at the 6-methyl position could be achieved. Subsequently, fluorination of the anion with NFSI afforded 6-fluoromethyl purine in 57 %, with none of the corresponding 8-fluoropurine isolated (see Sect. 3.1).

As with the 8-fluoropurines, the 8-trifluoromethylpurines are less common than the corresponding 2- and 6-substituted purines. The most frequent method for accessing 8-trifluoromethylpurines is from the corresponding 4,5-diaminopyrimidines. For example, treatment of a range of 4,5-diaminopyrimidines, in either refluxing trifluoroacetic anhydride, trfluoroacetic acid, or trifluoroacetamide resulted in the formation of the corresponding 8-trifluoromethylpurines (**109**–**112**) in high yields (47–82 %) [60] (Scheme 39). This methodology has been used by several groups for

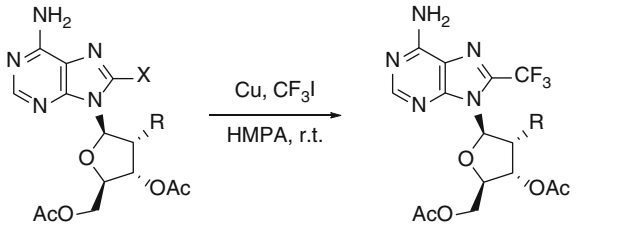


	R^1	R^2	Method	Yield (%)
109	H	H	A	82
110	NH_2	NH_2	B	47
111	Cl	H	A	78
112	NH_2	H	C	80

Scheme 39 The preparation of 8-trifluoromethylpurines from 4,5-diaminopyrimidine precursors

the synthesis of 8-CF_3 substituted purines [141, 142]. In one case, subjecting 4,5-diaminopyrimidines to an excess of trifluoroacetic anhydride and heating in an autoclave resulted in the isolation of a range of 8-CF_3 substituted purines in 60–90 % yields, which were then shown to undergo partial reduction under hydrogenation conditions at the N-7 = C-8-CF_3 alkene. This reduction was not seen in the corresponding unsubstituted purines.

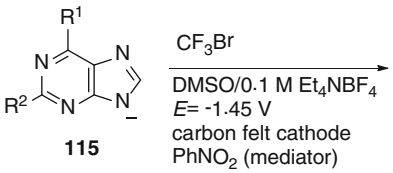
While achieving 8-CF_3 substitution from the corresponding 4,5-diaminopyrimidines proved to be an efficient and high yielding transformation, it is important to be able to access 8-CF_3 substituted purines directly from the corresponding purines in order to prepare fluorinated purine nucleosides. Similar to the synthesis of 8-fluoropurines, it is possible to make 8-trifluoromethylpurines from the 8-bromo substituted analogues. It has been reported that subjecting 8-Br and 8-I analogues of adenosine to a CF_3-Cu complex in HMPA resulted in the formation of the corresponding 8-trifluoromethyl adenosine compounds (**113**, **114**) in moderate yields [120] (Scheme 40). The active copper complex was formed *in situ* by shaking trifluoromethyl iodide and copper powder in HMPA.



113 (46%), R = OAc, X = I
114 (64%), R = H, X = Br

Scheme 40 The synthesis of 8-trifluoroadenosines using a trifluoromethyl-copper complex prepared *in situ*

Finally, 8-CF_3 substituted purines can also be synthesised by an electrochemical approach. In this case, reduction of CF_3Br in the presence of an adenine anion **115** was performed under redox catalysis [143] (Scheme 41). It was postulated that this reaction occurs *via* an $S_{RN}1$ mechanism to afford the corresponding 8-CF_3 substituted purines (**116**–**119**); however, no yields have been reported for these transformations.



	R^1	R^2
116	NH_2	H
117	OH	H
118	OH	OH
119	Cl	H

Scheme 41 An electrochemical synthesis of 8-trifluoromethylpurines

4.2 Applications

Due to the difficulties in synthesising 8-fluoropurines, scope remains for the exploration of their biological applications. It has been postulated that the electronegative effects of the C-8 fluorine may be significant on the substrate activity of 8-fluoropurine ribosides with enzymes such as N-ribosylhydrolases and transferases [144]. The kinetics of 8-fluoroadenosine deamination with calf spleen adenosine deaminase have been measured and compared to adenosine. Since the mechanism of deamination is proposed to proceed *via* protonation of N-1, it was correctly postulated that the variation in pKa between the N-1 of adenosine (3.59) and 8-fluoroadenosine (2.95) would result in the latter undergoing deamination at a slower rate.

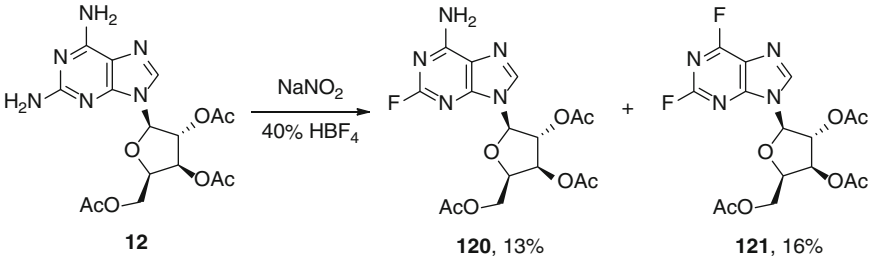
Direct fluorination of purines using F_2 gas has been used to good effect in the ^{18}F- radiolabelling of substrates for biological studies. 8-[^{18}F]Fluoroganciclovir (FGCV) was synthesised using this technique and was demonstrated to be a substrate for herpes simplex virus 1 thymidine kinase (HSV1-TK) [145]. The binding of FGCV to HSV1-TK was observed by positron emission tomography (PET) imaging during non-intrusive *in vivo* studies. This work has led to an increased understanding of how the drug is distributed *in vivo*, and where the drug accumulates in cells that express the HSV1-tk gene.

Pharmacological applications of 8-trifluoromethylpurines are less widespread. 8-Trifluoromethyladenosine and its 2-deoxy analogue have been screened against leukaemia L1210 cells, but showed no significant activity [120]. More recently, *O6*-benzyl-8-(trifluoromethyl)guanine has been shown to inactivate the angiotensin (AGT) protein in HT29 human colon tumor cells, however, the compound was found to be less active than the corresponding unfluorinated *O*6-benzylguanine [146].

5 2,6- 2,8- and 6,8-Disubstituted Analogues

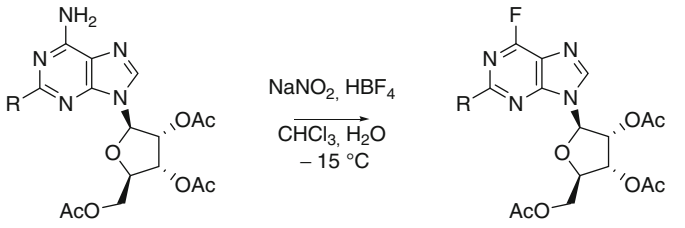
5.1 Synthesis and Applications

Purines or purine nucleosides that have been fluorinated at multiple positions are of great interest in medicinal chemistry. Most techniques currently available for the synthesis of difluorinated purines rely on combining several fluorination techniques. The first examples of difluorinating purines came from subjecting 2-amino-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine derivative **12** to a modified Schiemann reaction (Scheme 42). In this case, treatment with $NaNO_2$ and 48 % fluoroboric acid afforded a mixture of the 2-fluoroadenine **120** and the 2,6-difluoroadenine derivative **121**, which were isolated in 13 % and 16 %, respectively [3]. The fact that no 6-fluoroadenine derivative was isolated led to the hypothesis that under the reaction conditions, diazotization-fluorodediazonation at the 2-position occurred before fluorination at the 6-position could take place.



Scheme 42 The preparation of 2-fluoro- and 2,6-difluoropurine nucleosides by double Balz-Schiemann reaction

It was rationalised that fluorination at the 2-position decreased the basicity of the 6-NH_2, leading to less protonation at this position and enhancing subsequent reaction of the 6-NH_2 with the diazotizing species. This hypothesis is supported by results obtained upon fluorinating various adenosine derivatives, with varying substituents at C-2 [3] (Scheme 43). It was discovered that when X=H (**52**), no fluorination was observed at C-6. However, when an electron withdrawing group such as F or CF_3 resided at C-2, diazotization of the less basic 6-NH_2, followed by fluorination occurred readily, to afford disubstituted nucleosides **122** and **123** in moderate yields.

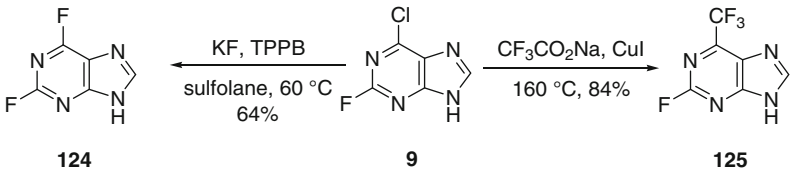


	R	Yield (%)	RSM (%)
52	H	0	0
122	F	25	65
123	CF_3	25	0

RSM = recovered starting material

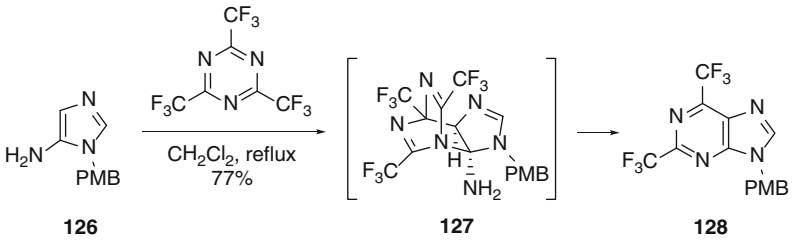
Scheme 43 2-Fluoro- and 2-trifluoromethyl substitution alter the reactivity of 6-aminopurines

This general strategy has been optimised by taking 2-fluoro-6-chloropurine **9**, and subsequently treating it either with KF and tetraphenyl TPPB as a phase transfer catalyst to form 2,6-difluoropurine **124** (64 % yield), or with sodium trifluoroacetate incorporated with a copper catalyst to afford 2-fluoro-6-trifluoromethylpurine **125** (84 % yield) [112] (Scheme 44). Both of these compounds were found to have high antifungal activity against *Bacillus subtillis*, *Aspergillus niger* and *Candida tropicalis*.



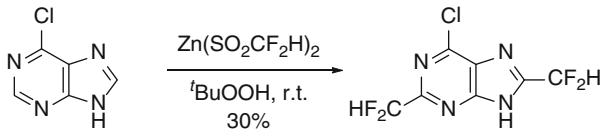
Scheme 44 The syntheses of 2,6-difluoropurine and 2-fluoro-6-trifluoromethylpurine from 2-fluoro-6-chloropurine

In order to access 2,6-ditrifluoromethylpurines, a novel approach consisting of an inverse electron-demand Diels-Alder reaction has been developed. The reaction of 1-substituted-1*H*-imidazol-5-amines (e.g. **126**) with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine in dichloromethane led to a successful Diels-Alder – retro Diels-Alder reaction *via* intermediate **127**, to afford the corresponding N-9 substituted 2,6-ditrifluoromethylpurines (e.g. **128**) in good yields (48–93 %) [147] (Scheme 45). These compounds are of particular interest as potential adenosine deaminase (ADA) inhibitors. It is considered that the CF_3-group is isosterically close to an -NH_2 group, and *in vivo*, that hydration can occur at the 6-position of the purine, affording an adenosine-like nucleoside, which mimics the transition state in the ADA deamination process. Inhibition of the ADA enzyme could have potential therapeutic applications to Parkinson's disease, auto immune and a range of other diseases.



Scheme 45 An inverse-electron demand Diels-Alder reaction for the synthesis of 2,6-di(trifluoromethyl)purines

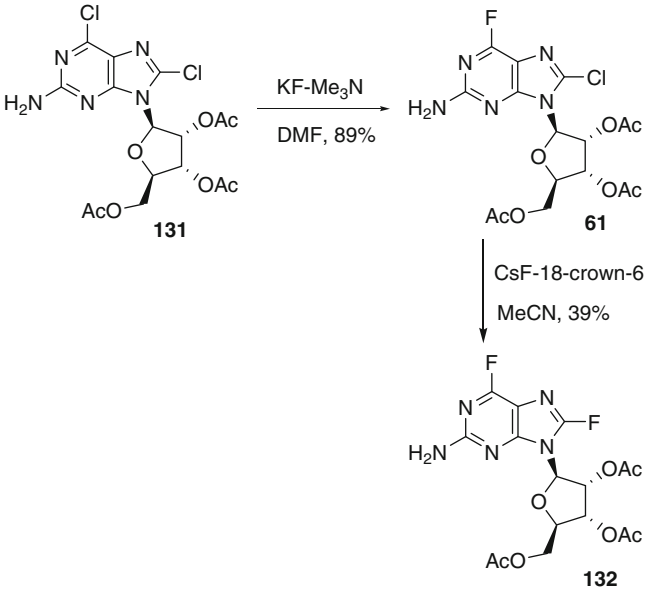
In contrast to the 2,6-difluoropurines, very few methods exist for the direct synthesis of 2,8-difluorinated purine species. However, it is assumed that using a combination of monofluorination methods would enable the formation of 2,8-difluoropurines. In one interesting case, it has been shown that it is possible to substitute at the 2- and 8- positions of purines with difluoromethyl groups. By using a novel reagent, zinc difluoromethylsulfinate, in combination with *tert*-butylhydroperoxide, it has been demonstrated that 6-chloropurine **129** will readily undergo a radical reaction to install two CF_2H groups at the 2- and 6-position, to give **130** in 30 % yield [148] (Scheme 46). Substitution with CF_2H offers an alternative isostere to more traditional hydrogen bond donors and has the added benefit to potential therapeutics of improving membrane permeability, though increasing lipophilicity.



129 **130**

Scheme 46 Radical reaction of 6-chloropurine with zinc difluoromethylsulfinate generates 2,8-di(difluoromethyl)-6-chloropurine

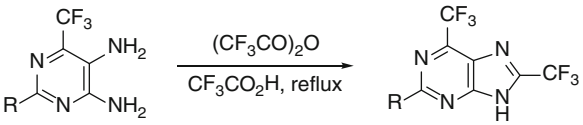
6,8-Difluoropurines are also relatively sparsely described. To date, the only reported method for accessing 6,8-difluorinated purines is by an S_NAr strategy. Subjecting a 6,8-dichloropurine nucleoside **131** to a two step fluorination procedure afforded the corresponding 6,8-difluoropurine nucleoside **132** in 35 % over two steps [101] (Scheme 47). It was found that using potassium fluoride with trimethylamine in DMF resulted in substitution primarily at the 6-position (see Sect. 3.1). Although small quantities of difluorinated **132** were also isolated, it was necessary to subject mono-fluorinated **61** to more forcing conditions, with cesium fluoride and 18-crown-6 in acetonitrile, to give the desired disubstituted purine. Attempts to create a one-pot reaction by treating dichloropurine **131** with the more nucleophilic CsF conditions resulted in the formation of difluorinated **132**, albeit in significantly lower yields. This case highlights the fundamental reactivity differences between the 6-position and 8-position of the halogenated purines, with the 6-chloropurines undergoing a higher yielding reaction under less forcing conditions than the corresponding 8-chloropurines.



131 **61** **132**

Scheme 47 The preparation of a 6,8-difluoropurine nucleoside

To date, no methods for directly accessing 6,8-ditrifluoromethylpurines from purine starting materials exist. It is, however, possible to prepare these compounds from the corresponding 4,5-diaminopyrimidines. Subjecting either 4,5-diamino-2-chloro-6-trifluoromethylpyrimidine or 2,4,5-triamino-6-trifluoromethylpyrimidine to a mixture of trifluoroacetic acid and trifluoroacetic anhydride at reflux, gave the corresponding 2-substituted-6,8-ditrifluoromethylpurine in 28 % (**133**) and 22 % (**134**), respectively [60, 149] (Scheme 48).



133, R = Cl, 28%
134, R = NH_2, 22%

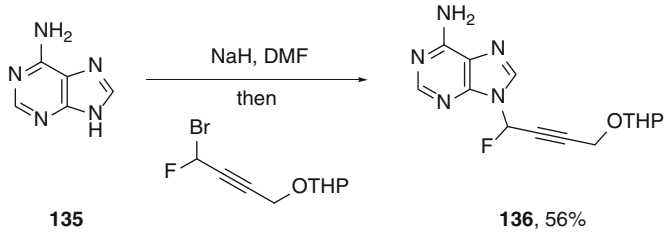
Scheme 48 The preparation of 6,8-di(trifluoromethyl)purines

6 *N*9-(Fluoroalkyl)- and *N*9-(Fluoroalkenyl)Purines

6.1 Synthesis and Reactivity

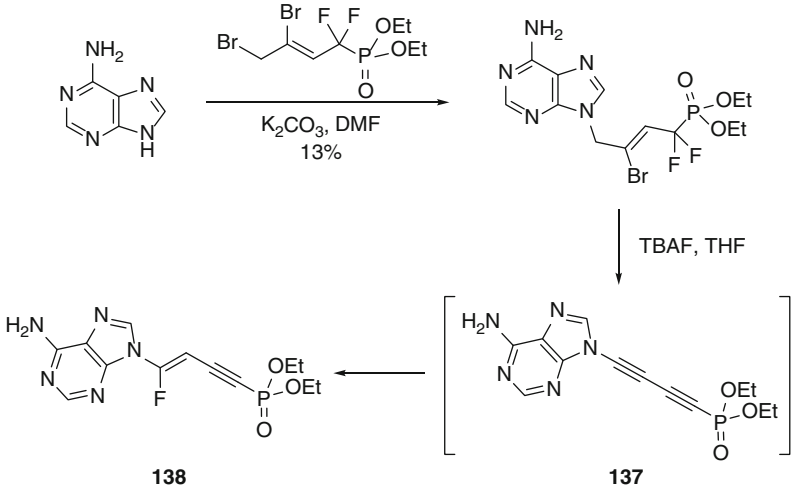
Currently, few techniques exist for the *N*-fluoroalkylation or *N*-fluoroalkenylation of purines. Of those that have been described, *N*-alkylation and *N*-alkenylation reactions of purines proceed with a preference for the N-9 position over N-7. The most common method for alkylation of N-9 consists of treating the purine with a base, followed by the addition of an alkyl halide. These conditions were first used to install a CF_3 group at the N-9 position of 2-chloro-6-(4-chlorobenzylamino)purine, using sodium hydride as the base in combination with an unspecified trifluoromethyl halide [150]. The resulting compound was screened for CDK2 kinase inhibition along with a range of non-fluorinated purines and exhibited an IC_{50} of 1 μM, one of the most potent inhibitors in the screen.

This general approach to alkylation was also used to install a more complex fluoro-alkyl group regioselectively at N-9 in the synthesis of the adenine-fluorobutynol derivative **136** [151] (Scheme 49). The transformation of **135**–**136** was also achieved with potassium carbonate in DMSO, however, the yield in this instance was lowered to 25 %. Subsequent removal of the THP group afforded 4-(adenin-9-yl)-4-fluorobut-2-yn-1-ol, which was found to be stable under mildly basic conditions. However, upon subjection to stronger base, such as potassium *tert*-butoxide in DMF, hydrolysis of the fluorobutynol group took place. This presumably occurred *via* deprotonation of the 6-NH_2, which in turn promoted an increase in the reactivity of the N-9 nitrogen lone pair. As a result of this, displacement of the fluoride could occur, to form the corresponding enamine, which was subsequently hydrolysed. It was also observed that subjecting 4-(adenin-9-yl)-4-fluorobut-2-yn-1-ol to phosphate buffer at pH 7 led to a similar decomposition pathway, which could adversely affect biological assays of this compound.



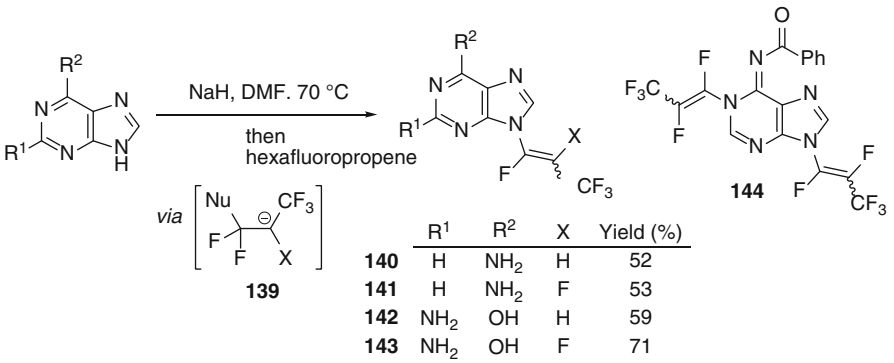
Scheme 49 The preparation of an N9 4-fluorobut-2-yn-1-ol derivative of adenine

*N*9-(Fluoroalkenyl)adenine derivatives containing a pendant alkynyl-phosphonate group have been synthesised by similar methods. Upon subjecting adenine to an initial alkylation with diethyl (3,4-dibromo-1,1-difluorobut-2-en-1-yl)phosphonate, a series of eliminations took place in the presence of TBAF to afford an intermediate 1′,3′-diyne-phosphonate **137** [152] (Scheme 50). Further reaction with TBAF was found to facilitate fluoride attack alpha to N-9 to afford the corresponding *N*9-(fluoroalkenyl)purine **138**.



Scheme 50 The preparation of an N9-(fluoroalkenyl)adenine bearing a pendant phosphonate

Other techniques have been reported to enable the synthesis of *N*9-(fluoroalkenyl) purines. Using either adenine or guanine in combination with sodium hydride and hexafluoropropene (HFP), afforded a range of N9-(fluoroalkenyl)purines **140**–**143** [153] (Scheme 51). Despite being formed as *E*/*Z* mixtures (60:40), the olefination took place exclusively at the CF_2=terminus, as the intermediate anion **139** is strongly stabilised by the CF_3 group. Interestingly, it was also found that subjecting *N*6-benzoyladenine derivatives to a fourfold excess of sodium hydride and hexafluoropropene resulted not only in olefination at N-9, but also olefination at N-1 (compound **144**). This compound was formed in a 3:1 ratio of di- to mono- olefinated product. Subsequent NMR studies were conducted on all of these compounds in order to investigate the structural differences in the *E* and *Z* stereoisomers [154].



	R^1	R^2	X	Yield (%)
140	H	NH_2	H	52
141	H	NH_2	F	53
142	NH_2	OH	H	59
143	NH_2	OH	F	71

Scheme 51 The reaction of purine derivatives with hexafluoropropene

7 Conclusion

Fluorinated purines have an established and continuing role in biomedical research, in large part reflecting the widespread importance within biology of purine nucleosides and nucleotides. The presence of fluoro or trifluoromethyl substitution often substantially and favourably modifies the biological activities, physicochemical properties and metabolic stability of nucleosides and simpler purine derivatives. Fluorine incorporation provides an opportunity for developing useful ^{18}F-radiolabelled derivatives for *in vivo* imaging by positron emission tomography. The synthetic modification of fluorinated purines, primarily through nucleophilic displacement reactions, is widely used in the generation of new compounds for medicinal chemistry and these reactions can also be applied within biological macromolecules. Despite these important uses, there are only a few general methods available for the synthesis of fluorinated purines. Diazotization-fluorodediazoniation or displacements of other halopurines by fluoride dominate, while electrophilic fluorination is currently less exemplified. For the introduction of fluoroalkyl substituents, *de novo* syntheses of the heteroaromatic rings are often employed, although the introductions of trifluoromethyl organometallic species and radical chemistry for direct fluoroalkylation promise increased flexibility for the synthesis of these derivatives in the future.

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ERRATUM

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6-Membered Heterocycles

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V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 2: 6-Membered Heterocycles*, DOI 10.1007/978-3-319-04435-4, © Springer International Publishing Switzerland 2014

DOI 10.1007/978-3-319-04435-4_10

Acknowledgment

This work was supported by the Russian Science Foundation (Grants 14-13-00083 and 14-13-00388).