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Thiophenes

Springer

39
Topics in Heterocyclic Chemistry

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John A. Joule
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Thiophenes

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Preface

Thiophene was first recognised by the German chemist Viktor Meyer, then at Zurich, as an 'impurity' in the commercial (coal tar) benzene available in the nineteenth century. His isolation of the substance in the 1880s began investigations of this benzene-like aromatic heterocycle, which have continued to the present. Especially important were the extensive investigations by Salo Gronowitz at Lund University, Sweden. Thus, the chemistry of the five-membered aromatic heterocyclc thiophene is well developed, but still remains a very active area of interest in several contexts. In this book we have sought to both summarise the important chemical reactivities of thiophenes and illustrate the role of thiophene chemistry in the development of electroactive materials.

A short, general introductory chapter describes the aromatic structure of thiophene, C_4H_4S, placing it in the same family of heterocycles as pyrrole and furan. We deal with the principal routes for the ring synthesis of thiophenes from precursors which do not contain the nucleus (chapter "De Novo Ring Synthesis of Thiophenes"). This is followed by a discussion of the substitution of thiophenes with electrophilic, nucleophilic and radical reagents (chapter "Thiophene Substitution Chemistry"), and of the metallation of thiophenes, by various means, and the reactivity of the metallated species as nucleophiles and as participants in transition metal-catalysed cross-coupling reactions (chapter "Thiophene Metallation and Cross-Coupling Chemistry"). With this fundamental reactivity background, the book goes on to discuss the application of this knowledge for the synthesis of fused thiophenes (containing two or more thiophene rings) (chapter "Fused Thiophenes and Some Oligomers and Polymers Therefrom") that are of relevance to the construction of organic light emitting diodes, organic field effect transistors, dye sensitized solar cells and electrochromic devices. Chapter "Thiophene in Conducting Polymers: Synthesis of Poly(thiophene)s and Other Conjugated Polymers Containing Thiophenes, for Application in Polymer Solar Cells" shows how thiophenes are incorporated into conducting polymers with applications as light absorbing materials in polymer solar cells. The book is completed with a discussion of *S*-oxidation of thiophenes and the reactions of the resulting thiophene

S-oxides and *S,S*-dioxides, and the reduction of thiophenes, showing how each of these aspects of thiophene chemistry can lead to the construction of other, quite structurally different types of compound (chapter "Thiophene Oxidation and Reduction Chemistry").

I am greatly indebted to my authors for their outstanding contributions to this timely summary of thiophene chemistry. I thank Tanja Jaeger and the Springer staff in Germany who made the administrative aspects of preparing this volume straightforward, especially Elizabeth Hawkins for her calming and constructive advice, and the colleagues in India, especially Arun Manoj Jayaraman. Finally, I particularly wish to record my thanks to Bert Maes for the invitation to act as Editor of this volume in the Springer "Topics in Heterocyclic Chemistry" series.

Manchester, UK John A. Joule
2014

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Thiophenes

John Arthur Joule

Abstract The structure and principal chemical reactivities of thiophenes are briefly introduced.

Keywords Aromaticity · Bromination · Diels–Alder reaction · Electrophilic substitution · Furan · Indophenine · Isatin · Metallation · Palladium(0) catalysis · Pyrrole · S-oxidation · Sulfur lone pair · Thiophene numbering · Viktor Meyer · π-System

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1 Introduction

The simple thiophenes are stable liquids that closely resemble the corresponding benzene compounds in boiling points and even in smell. The discovery of thiophene in coal tar benzene provides one of the classic anecdotes of organic chemistry. In the days when colour reactions were essential for diagnosis, benzene was identified by the production of a blue colour on heating with a mixture of isatin (1*H*-indole-2,3-dione) and concentrated sulfuric acid. In 1882, during a lecture-demonstration

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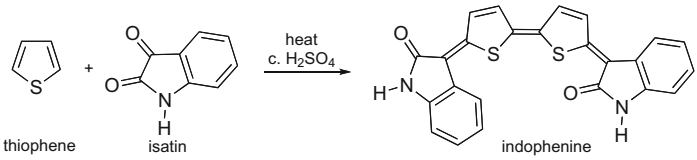


Scheme 1 Indophenine, the blue compound once used to identify benzene, is actually formed from thiophene (in commercial benzene) [3, 4]

by Viktor Meyer before an undergraduate audience, this test failed. An inquiry revealed that Meyer's lecture assistant had run out of commercial (coal tar) benzene and had provided a sample of benzene, which he had prepared by decarboxylation of benzoic acid. It was thus clear that the commercial benzene of that time contained an impurity and that it was this, not benzene, which was responsible for the colour reaction. Meyer went on to isolate the 'impurity' via its sulfonic acid derivative and showed it to have the formula C_4H_4S, and to be the first representative of a new, at that time, ring system, which he named thiophene from *theion*, the Greek word for sulfur, and another Greek word *phaino* which means shining [1, 2]. The structure of the blue compound, known as indophenine, is now known [3, 4] (Scheme 1 shows one geometrical isomer).

2 Thiophene Structure

Thiophene is an aromatic compound: the requisite 6π-electron cyclic system involves one of the two lone pairs on sulfur, as illustrated in Fig. 1 by an orbital representation and by resonance contributors. The sulfur has one lone pair as part of the aromatic sextet, and also a second lone pair that is not involved, and is located in an sp^2 hybrid orbital in the plane of the ring.

As an aromatic compound, thiophene is stabilised by 'resonance energy' – actual values for the stabilisations of five-membered aromatic heterocycles (Fig. 2; kJ mol^{-1}) vary according to the assumptions made, but are always in the same relative order: benzene (150), thiophene (122), pyrrole, (90), and furan (68) – thiophene is the 'most aromatic' of the five-membered heterocyclic trio, i.e. it is the least like a diene. In its reactions, too, thiophene behaves very much like a carbocyclic aromatic compound, exceptions being associated with the presence of the heteroatom.

Figure 2 also shows the numbering system for thiophene and the useful designation of C-2/C-5 as α-positions and C-3/C-4 as β-positions.

Thiophene has a UV absorption maximum at 235 nm. The ^{13}C signals for C-2 and C-3 are, respectively, 126 and 127 ppm and the corresponding ^1H signals are at 7.2 and 7.1 ppm; $J_{2,3}$ is 4.7 Hz and $J_{3,4}$ is 3.4 Hz.

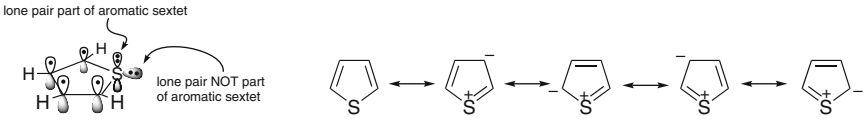


Fig. 1 Thiophene as a 6π-electron aromatic compound

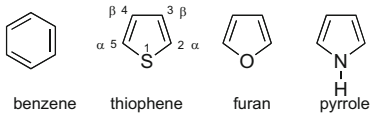
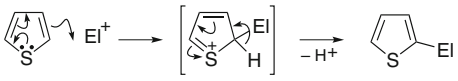
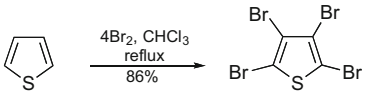


Fig. 2 Five-membered aromatic heterocycles; numbering of thiophene



Scheme 2 Electrophilic substitution of thiophene – preferred at an α-position



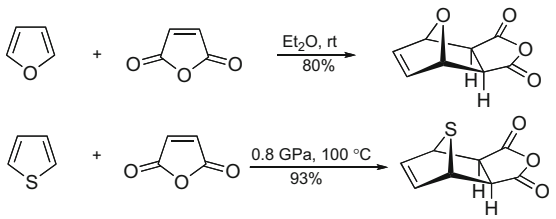
Scheme 3 Electrophilic tetrabromination of thiophene [5]

3 Thiophene Substitution Chemistry

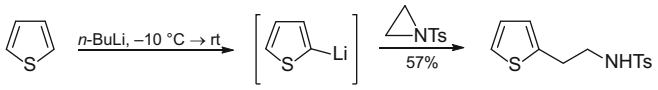
Thiophene, as an aromatic compound like benzene, undergoes electrophilic substitution readily, actually, 10^8 more readily than benzene, at an α-position; substitution at an α-position is about 100-times more favoured than at a β-position, thus even the latter is about 10^6 times more reactive to electrophilic substitution than benzene. Scheme 2 illustrates a generalised substitution (El^+ = electrophile) (electrophilic substitutions are discussed at length in Ryabova and Ignatovich [6]).

A simple illustration of the reactivity of thiophene towards electrophiles is its complete bromination under quite mild conditions [5], even though the introduction of each successive electron-withdrawing bromine reduces the ring nucleophilicity (Scheme 3).

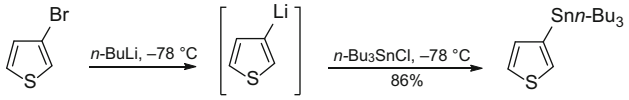
A nice measure of the aromatic, i.e. non-diene-like character of thiophene can be gained from a comparison (Scheme 4) of the conditions necessary to force it to participate as a 1,3-diene in a Diels–Alder cycloaddition with maleic anhydride [7], compared with the classical reaction of furan. Lu et al. [8] shows how S-oxidation of thiophenes (utilisation of the pair of electrons on sulfur that is not involved in the aromatic sextet) reduces the aromaticity and allows cycloadditions to occur easily.



Scheme 4 Extreme conditions to force thiophene to act as a 1,3-diene in a Diels–Alder reaction [7]



Scheme 5 Formation and use of 2-lithiothiophene [9]



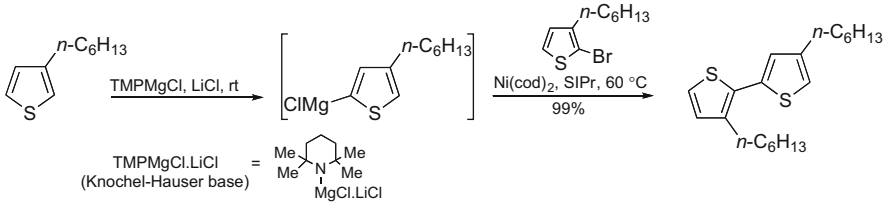
Scheme 6 Formation and use of 3-lithiothiophene [10]

4 Thiophene Metallation

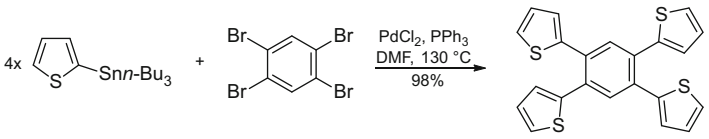
Organometallic chemistry is particularly important in thiophene chemistry. Thiophenes can be directly metallated at an α-position using a strong base at low temperature, and the resulting nucleophile will react with electrophiles to effect 2-substitution; Scheme 5 shows a simple example [9].

Thiophene halides can be converted into Grignard or lithium derivatives; the 3-lithio-thiophenes need to be maintained at a very low temperature to avoid isomerisation to the 2- (more stable) -isomer; Scheme 6 gives a simple example [10] (the organometallic chemistry of thiophenes is discussed in detail in Schatz and Hoffmann [11]).

Extensive use has been made of palladium(0)-catalysed cross-coupling reactions in thiophene chemistry, for the synthesis of both small molecules and polymers (cross-coupling reactions are discussed in detail in Schatz and Hoffmann [11] and polymers in Livi et al. [12]). Schemes 7 and 8 give two examples: in the first, regioselective metallation at the thiophene 5-position (an α-position) preceeds nickel(0)-catalysed cross-coupling [13]; the second (Scheme 8) illustrates a highly efficient Stille cross-coupling [14].



Scheme 7 Regioselective formation and use of a 5-magnesiothiophene for a nickel(0)-catalysed cross-coupling [9]



Scheme 8 Highly efficient Stille cross-coupling 2-tributylstannylthiophene with 1,2,4,5-tetrabromobenzene [10]

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De Novo Ring Synthesis of Thiophenes

John Arthur Joule

Abstract The principal methods for the synthesis of thiophenes from precursors which do not contain a thiophene ring are reviewed. Where possible, recent and/or significant examples of each method are used as illustrations.

Keywords 1,2-Dicarbonyl compound · 1,3-Dicarbonyl compound · 1,3-Diyne · 1,3-Enyne · 1,4-Diketone · 1,4-Dithiin · 3,4-Dihydroxythiophene · Aminothiophenes · Bis(trimethylsilyl)sulfide · Cadiot–Chodkiewicz coupling · Carbon disulfide · Cycloaddition · EDOT · Gewald reaction · Glaser coupling · Hinsberg reaction · Lawesson's reagent · McMurray reaction · PEDOT · Pentaphosphorus decasulfide · Quinquethiophene · Stetter synthesis · Stobbe reaction · Sulfur · Sulfur dichloride · Terthiophene · Thiazolium ylide · Thieno[2,3-*b*]thiophene · Thieno[3,4-*c*]thiophene · Thioamide · Thioglycolate · Thiophene ester · Thiophenophane · Vinamidinium salt · Zirconacycle · α-Haloketone · α-Mercaptoketone · α,α′-Thiobisketone · β-Keto-ester (1,3-keto-ester)

Contents

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1 Introduction

The range of commercially available thiophenes is considerable, and for many purposes, work can start from one of these – for example, isomeric monobromo- and monochlorothiophenes, both of the thiophene aldehydes, thiophene carboxylic acids, and *n*-hexylthiophenes are commercially available. 2,5-Dimethyl-, 2,5-dibromo- and 2,5-dichlorothiophenes and other isomeric dibromo- and dichlorothiophenes, methoxythiophenes, 3,4-dimethoxythiophene and 3,4-ethylenedioxythiophene (EDOT) are commercial compounds. There are in addition many, more heavily substituted examples – the Aldrich catalogue (2012–2013) lists more than 100 altogether. However, for some purposes, a ring synthesis from starting materials which do not contain a thiophene ring and which generates a desired substitution pattern can provide the best starting point for elaboration. This chapter discusses the most useful of these de novo routes. Some of the methods have been known for many years; however where possible, recent and/or otherwise significant examples of the employment of each method are used as illustrations.

2 Ring Synthesis of Thiophenes

2.1 Thiophenes from 1,4-Dicarbonyl Compounds

Perhaps the most obvious strategy for thiophene construction is the interaction of a 1,4-dicarbonyl compound with a reagent able to supply the sulfur. Formally speaking, a thiophene ring is the cyclic, double thioenol ether of a 1,4-dicarbonyl compound, accessible in principle by reaction with hydrogen sulfide with the loss of two equivalents of water. In practice, sulfur sources have been tetraphosphorus decasulfide (for the mechanism of conversion of carbonyl into thiocarbonyl with P_4S_{10} see Scheeren JW, Ooms PHJ, Nivard RJF (1973) Synthesis 149; for the use of P_4S_{10} to prepare thiophenes, and in other roles, see [1]), bis(trimethylsilyl)sulfide, bis(trialkyl/triphenyl)tin sulfides but mainly Lawesson's reagent (LR) (Fig. 1). The use of a fluorous version [2] of LR can facilitate the work-up of reactions where the reagent is used to make a thiophene.

Lawesson's reagent converts carbonyl groups into thiocarbonyl groups (For the mechanism of conversion of carbonyl into thiocarbonyl with LR and reviews of LR

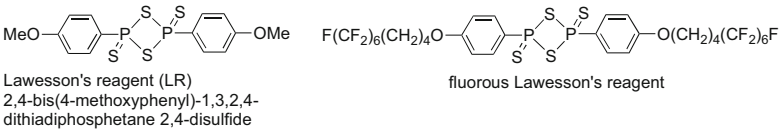
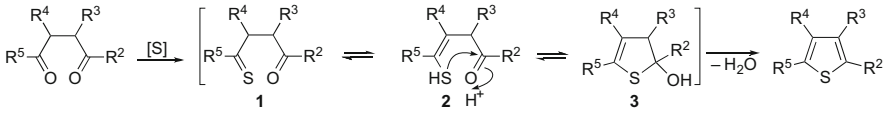
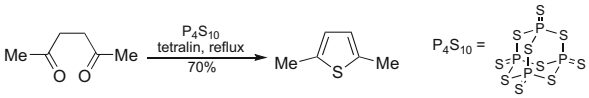


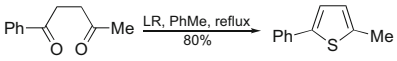
Fig. 1 The structures of Lawesson's reagent (LR) and fluorous analogue



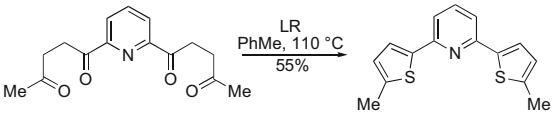
Scheme 1 General sequence for thiophene ring synthesis from a 1,4-dicarbonyl compound



Scheme 2 The synthesis of 2,5-dimethylthiophene using tetraphosphorus decasulfide [6]



Scheme 3 The synthesis of 2-methyl-5-phenylthiophene using Lawesson's reagent [7]

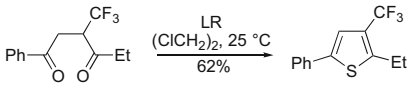


Scheme 4 The synthesis of 2,6-bis(5-methylthien-2-yl)pyridine using Lawesson's reagent [8]

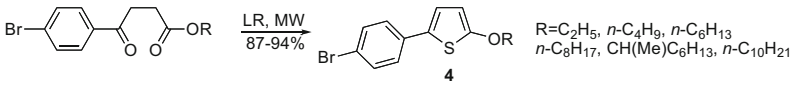
see [3–5]). In the thiophene-forming sequence, it is not known whether both carbonyl groups are converted into C=S before thioenolisation (**1** → **2**), ring closure (arrows on **2**) and aromatisation by loss of water from **3**, so the sequence shown in the generalised Scheme 1 is thus just one reasonable possibility.

The use of either phosphorus sulfides or Lawesson's reagent generally requires heating, as in the typical examples in Schemes 2, 3, and 4 [6–8], but sometimes milder conditions suffice (Scheme 5) [9]. The use of LR with bismuth triflate in [bmim]BF_4 ionic liquid allows a somewhat lower temperature to be used [10].

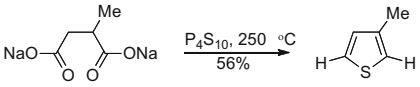
The alkoxy group of 1,4-keto-esters can be retained in the thiophene product using solvent-free LR, with brief microwave heating, giving 2-alkoxythiophenes **4**, as shown in Scheme 6 [11]. However, it has long been known [12] that using succinate salts as starting materials, reductive removal of oxygen leads to 2,5-unsubstituted thiophenes (e.g. Scheme 7), and this was generalised for the



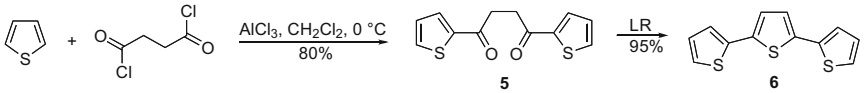
Scheme 5 The synthesis of 2-ethyl-5-phenyl-3-trifluoromethylthiophene using Lawesson's reagent [9]



Scheme 6 The synthesis of 2-alkoxythiophenes from 1,4-keto-esters [11]



Scheme 7 The synthesis of a 2,5-unsubstituted thiophene from a disodium succinate [12]



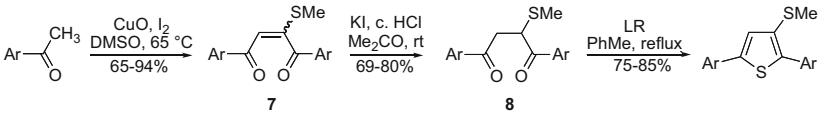
Scheme 8 Double Friedel–Crafts reaction to prepare a 1,4-diketone; the synthesis of 2,2′:5′, 2″-terthiophene [14]

preparation [13] of a series of 3-*n*-alkyl (C_4–C_{18}) thiophenes, using P_4S_{10} in 1,2-dichlorobenzene at 150°C.

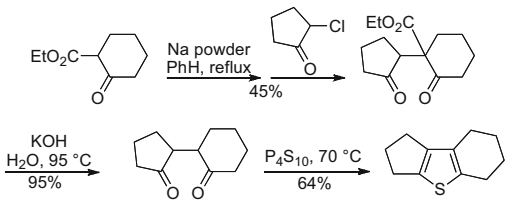
Various methods are available for the preparation of the initial 1,4-dicarbonyl compound, for example, succinyl chloride (ethanedioyl dichloride) reacts in a Friedel–Crafts reaction with two equivalents of thiophene to make 1,4-diketone **5**, which can then be converted into 2,2′:5′,2″-terthiophene **6** (Scheme 8) [14]. Similarly, the reaction of two equivalents of hetaryllithiums with *N*,*N*,*N*′,*N*′-tetramethylsuccinamide gives the corresponding 1,4-di(hetaryl)butane-1,4-diones, converted into the corresponding thiophenes using LR [15].

A quite different route to 1,4-diketones is based on the homo-coupling of aryl methyl ketones to produce 2-methylthio-1,4-di(aryl)but-2-ene-1,4-diones **7** using copper(II) oxide, iodine and dimethyl sulfoxide. The reduction of the C–C double bond in **7** with potassium iodide and concentrated hydrochloric acid then produces 2-methylthio-1,4-di(aryl)butane-1,4-diones **8**, which on treatment with LR leads to 3-methylthio-2,5-diarylthiophenes (Scheme 9) [16].

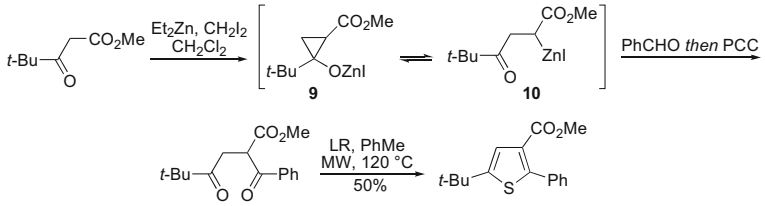
There are two good routes for the synthesis of unsymmetrically substituted 1,4-diketones. The classical route involves the alkylation of a β-keto-ester (1,3-keto-ester) with a 2-haloketone followed by hydrolysis and thence decarboxylation of the resulting β-keto-carboxylate (for some typical modern examples see



Scheme 9 Homo-coupling of aryl methyl ketones to prepare 1,4-di(aryl)-1,4-diketones and the synthesis of 3-(methylthio)thiophenes [16]



Scheme 10 Alkylation of a 1,3-keto-ester with a 2-haloketone then hydrolysis and decarboxylation to form a 1,4-diketone for thiophene ring synthesis [20]. N.B. The original method for enolate formation is shown – an alternative method would be used nowadays

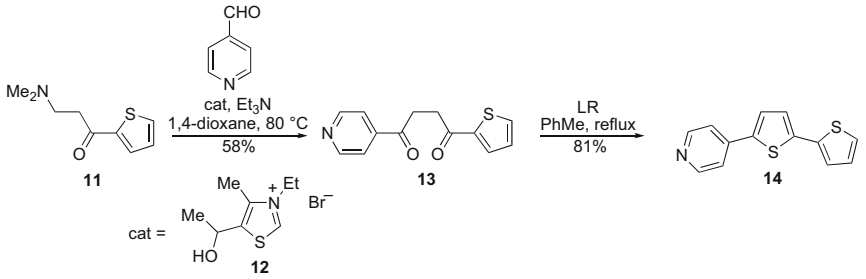


Scheme 11 The conversion of a 1,3-keto-ester into a 2-acylmethyl derivative of a different 1,3-keto-ester; the synthesis of thiophene-3-esters [21]

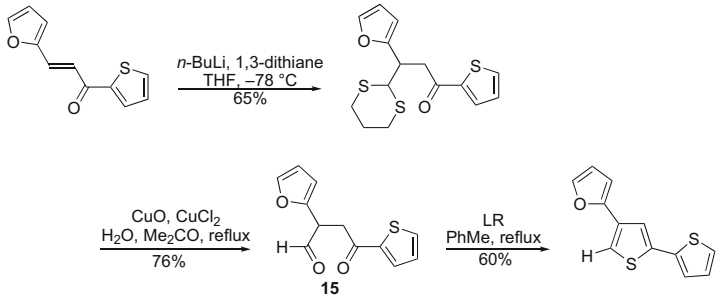
[17–19]); Scheme 10, from work in 1960, illustrates the venerable pedigree of this method [20].

An alternative way in which β-keto-esters can be used to form 1,4-diketones is shown in Scheme 11 [21]. A cyclopropyl intermediate **9** is in equilibrium with organozinc species **10** which can then be trapped, best with an aldehyde followed by oxidation, to give a 1,4-diketone. Note that the thiophene formation (Scheme 11) involves the two ketone carbonyl groups and not the ester carbonyl, although in other cases, it can involve ester carbonyl groups (cf. Scheme 6).

The Stetter procedure [22, 23] is an excellent route to 1,4-diketones. Here, cyanide anion, or more often a thiazolium ylide, catalyses the addition of an aldehyde to an α,β-unsaturated ketone or a precursor thereof, e.g. a Mannich base. For example, the reaction of pyridine-4-carbaldehyde with Mannich base **11**, catalysed by the ylide from 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide **12**, produces the 1,4-diketone **13**, from which the central thiophene ring of **14** can be constructed (Scheme 12) [24]. Comparable thiazolium ylide catalysis



Scheme 12 The use of a thiazolium ylide to prepare an unsymmetrically substituted 1,4-diketone [24]



Scheme 13 The use of 2-lithio-1,3-dithiane to prepare a 1,4-keto-aldehyde and thence a 2-unsubstituted thiophene [27]

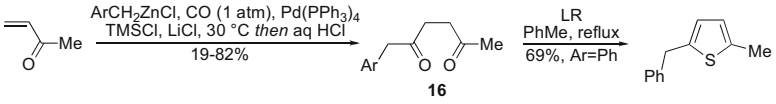
can be used for the addition of aldehydes to chalcones (aryl 2-arylethenyl ketones) whilst attached to a solid support, generating 1,4-diketones; the subsequent LR-induced thiophene-forming step can also be conducted whilst the 1,4-diketone is still attached to the support [25]. Symmetrical 1,4-diketones can be generated from aldehydes, using thiazolium ylide catalysis, by reaction with divinyl sulfone, a vinyl unit providing the central two carbons of the 1,4-diketone unit [26].

The conjugate addition of the anion of 1,3-dithiane to a conjugated ketone, followed by unmasking of the aldehyde, produces a 1,4-keto-aldehyde, e.g. **15**, the thiophene derived from which has a 2,4-disubstitution pattern, as is demonstrated in Scheme 13 [27].

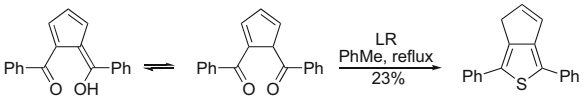
Catalytic carbonylation of methyl vinyl ketone using carbon monoxide and (arylmethyl)zinc chlorides is yet another route to unsymmetrically substituted 1,4-diketones **16** that can then be used for thiophene synthesis (Scheme 14) [28].

Even rather strained thiophenes can be prepared from 1,4-diketones, as Schemes 15 and 16 [29, 30] show, though somewhat less efficiently.

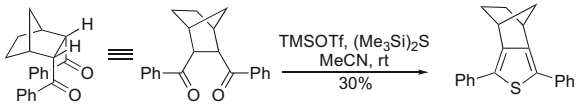
This last example also illustrates the use of bis(trimethylsilyl)sulfide in combination with trimethylsilyl triflate at room temperature for the thionation; however, the use of this reagent combination [31] for thiophene synthesis has not displaced



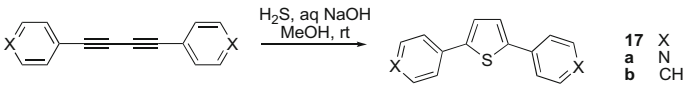
Scheme 14 Catalytic carbonylation to produce 1-aryl-hexane-2,5-diones for thiophene synthesis [28]



Scheme 15 The synthesis of a cyclopentene-fused thiophene [29]



Scheme 16 The use of bis(trimethylsilyl)sulfide in combination with trimethylsilyl triflate to make a strained thiophene [30]

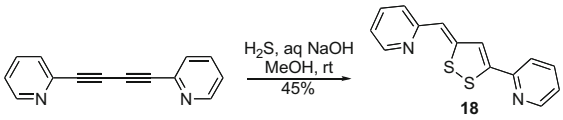


Scheme 17 The synthesis of 2,5-di(pyridin-4-yl)thiophene and 2,5-diphenylthiophene [37]

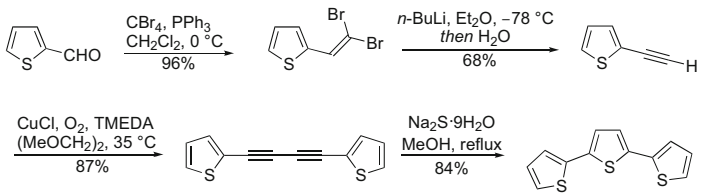
Lawesson's reagent, as the favoured sulfur source. Thiophene formation from 1,4-diketones using bis(tricyclohexyltin) [32] or bis(tripheny1tin) sulfides in refluxing toluene or bis(tributyltin) sulfide at room temperature, in each case in combination with boron trichloride, is also efficient [33], but these combinations have rarely been preferred to LR, no doubt because of associated toxicity problems.

2.2 Thiophenes from 1,3-Diynes

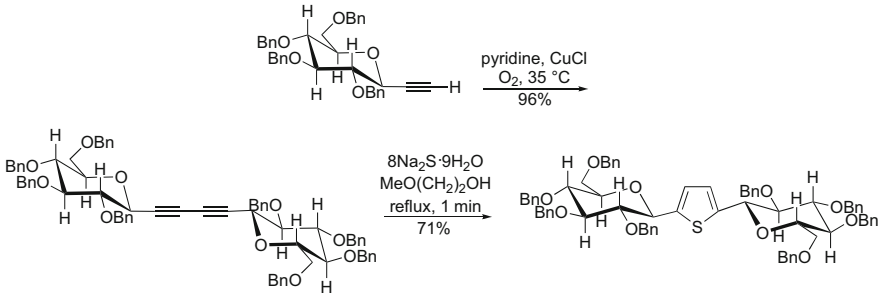
This important route to thiophenes mimics that used by nature in the assembly of thiophene-containing natural products [34, 35]. In essence, the elements of hydrogen sulfide are added to the terminal carbons of 1,3-diyne. This is achieved in the laboratory by reaction with hydrosulfide [36] or sulfide anions and conditions are generally mild. The examples in Schemes 17, 19, 20, 21, 22, 23, 24, 25, 26, and 27 are chosen to illustrate both the mildness of the reaction conditions and the range of substituents that can be tolerated at the 1- and 4-positions of the conjugated diyne. Schemes 25 and 26 show that the process also works with terminal diynes.



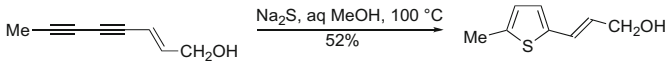
Scheme 18 The synthesis of (*Z*)-2-[[5-(pyridin-2-yl)-*3H*-1,2-dithiol-3-ylidene]methyl]pyridine [37]



Scheme 19 The synthesis of 2-ethynylthiophene, 1,4-di(thien-2-yl)buta-1,3-diene and thence 2,2′:5′,2″-terthiophene [38]

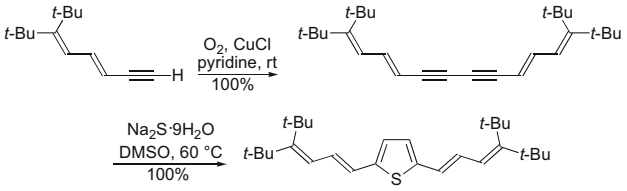


Scheme 20 The synthesis of 1,1′-(buta-1,3-diyne-l,4-diyl)bis[(1*S*)-1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-D-glucitol] and thence 1,1′-(thiophene-2,5-diyl)bis[(1*S*)-1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-D-glucitol] [39]

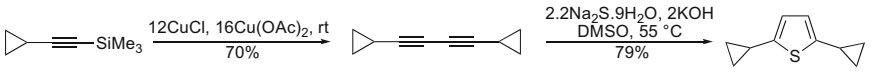


Scheme 21 The synthesis of a thiophene in the presence of a conjugated alkene and an alcohol [40]

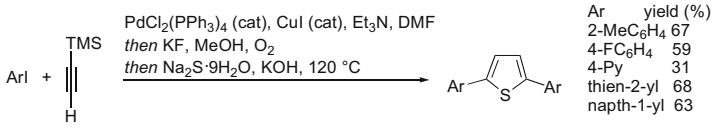
1,4-Di(pyridin-4-yl)buta-1,3-diyne and 1,4-diphenylbuta-1,3-diyne react with hydrogen sulfide and sodium hydroxide to produce thiophenes **17a** and **17b**, respectively (Scheme 17), but it is significant that 1,4-di(pyridin-2-yl)buta-1,3-diyne reacts in a different way, under the same conditions, to give 1,2-dithiole **18** (Scheme 18) [37].



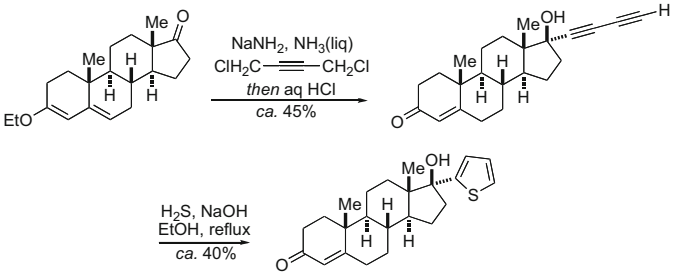
Scheme 22 The synthesis of a thiophene in the presence of other conjugated alkenes [41]



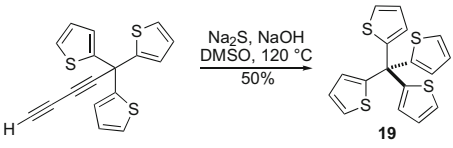
Scheme 23 The synthesis of 1,4-di(cyclopropyl)buta-1,3-diyne and thence 2,5-di(cyclopropyl) thiophene [42]



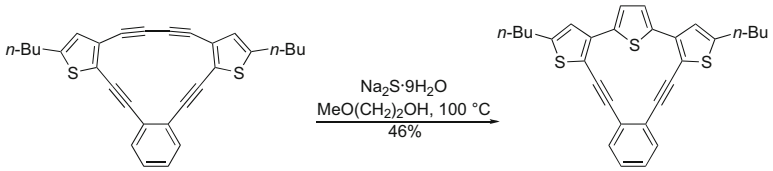
Scheme 24 The synthesis of 2,5-diaryl(hetaryl)thiophenes from an aryl(hetaryl) iodide and TMS-acetylene in one pot [43]



Scheme 25 The synthesis of a 17β-hydroxy-17α-(thien-2-yl) steroid [44]



Scheme 26 The synthesis of tetrakis(thien-2-yl)methane [45]



Scheme 27 The synthesis of a thiophene from a strained diyne [46]

The synthesis of the 1,3-diyne starting material is often achieved via a Glaser coupling (For a review of this and other alkyne-coupling chemistry see [47]) (dimerisation) of a terminal alkyne, though this necessarily produces a 1,4-symmetrically substituted 1,3-diyne. An alternative is Cadiot–Chodkiewicz heterocoupling of a terminal alkyne with a bromo-alkyne, which can produce unsymmetrically substituted 1,3-diynes [47]. Thus, typical routes to 1,3-diynes and thence to thiophenes are presented in Schemes 19, 20, 21, and 22 [38–41]. Scheme 19 also illustrates a widely used route to terminal alkynes, involving the Corey–Fuchs procedure from an aldehyde [38].

Silylalkynes can also be employed for the purpose of making 1,3-diynes (Scheme 23) [42]. In a pseudo five-component reaction, it is possible to take trimethylsilylacetylene, an aryl or hetaryl iodide, a palladium catalyst [$PdCl_2(PPh_3)_2$], copper(I) iodide and triethylamine in DMF; then add potassium fluoride and air and then sodium sulfide; and heat at 120°C and produce thiophenes; the Sonogashira cross coupling, the Glaser coupling and the diyne/sulfide ring synthesis all take place in the same pot [43]. Scheme 24 shows a selection of the 2,5-diaryl(hetaryl)thiophenes produced in this way.

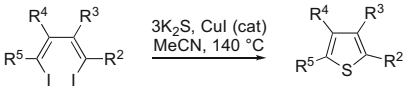
Terminal diynes also react to produce thiophenes with one unsubstituted α-position. A buta-1,3-diynyl unit, with terminal hydrogen, can be introduced by the addition of 1,3-butadiynylsodium, generated in situ, to a ketone. Scheme 25 shows one example of this in operation, from several in the steroid series [44].

Perhaps the most spectacular example of thiophene formation from a terminal 1,3-diyne is the synthesis of compound **19** in which four thien-2-yl units are tetrahedrally disposed round a central carbon (Scheme 26) [45].

In another impressive utilisation of this method, strained systems can be made from strained diynes: Scheme 27 shows one example [46].

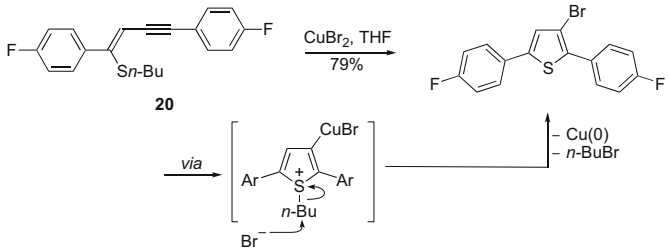
It is appropriate to include in this section the use of 1,4-diodo-1,3-dienes, since these are at the same oxidation level as 1,3-diynes. The reaction of these with potassium sulfide using copper catalysis has been used to produce a range of di-, tri-, and tetraalkyl-substituted thiophenes, a selection of which is specified in Scheme 28 [48].

Also relevant to the use of 1,3-diynes is the ring closure of (*Z*)-1-(*n*-butylthio)-1-en-3-ynes, e.g. **20**, to give 3-halo thiophenes [49]. The starting materials are prepared from 1,3-diynes by hydrothiolation of a 1,3-diyne using *n*-butylthiol and tetrabutylamonium hydroxide in refluxing ethanol [50]. Copper(II) chloride or bromide brings about the ring closure of **20** and the formation of the corresponding 3-halothiophene, as exemplified in Scheme 29.



R^2	R^3	R^4	R^5	yield
H	*t*-Bu	*t*-Bu	H	79
H	$(CH_2)_4$		H	72
Ph	Ph	*t*-Bu	H	76
Ph	Me	Ph	Me	83
Ph	Ph	Et	Et	84

Scheme 28 The synthesis of thiophenes from 1,4-diiodo-1,3-dienes [48]



Scheme 29 The synthesis of thiophenes from of (Z)-1-(*n*-butylthio)-1-en-3-ynes [50]

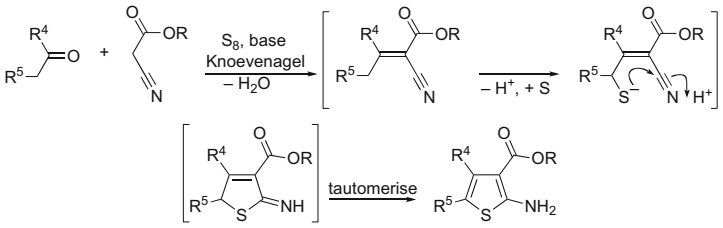
2.3 *Synthesis of 2-Amino-3-Carbonyl-Thiophenes – Gewald Synthesis*

The synthesis of 2-aminothiophenes carrying an ester, amide or nitrile at C-3, can be achieved via the condensation of a ketone or aldehyde, which must have an α-methylene, with a cyanoacetate, a cyanoacetamide or malononitrile, respectively, in the presence of elemental sulfur and a simple organic amine as base (amine-functional polysiloxanes [51] and Mg/La mixed oxide with microwave heating [52] have also been recommended). This route to functionalised thiophenes has been much used. The process involves an initial Knoevenagel condensation, which can also be carried out as a separate first step. The introduction of sulfur at the conjugated γ-position, presumably via an enolate anion, leads to a thiolate that closes onto the nitrile; tautomerisation completes the ring synthesis – Scheme 30 shows this in a general form using a cyanoacetate.

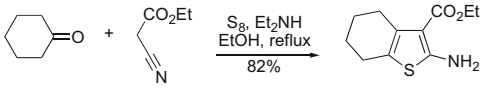
Schemes 31, 32, 33, 34, 35, 37, 38, 39, 40, and 41 show some typical and intriguing examples of the operation of the Gewald synthesis, originally described in 1966 [53]. The examples in Schemes 31 and 32 are taken from Gewald's original paper [53] and illustrate the two alternative protocols – that in Scheme 32 starting from an α,β-unsaturated ester (Knoevenagel condensation product). Either diethylamine or morpholine could be used as the base.

The generation of 2-amino-5-arylthieno[2,3-*b*]thiophenes **23** results from the comparable use of dihydro-3(2*H*)-thiophenones **21**; the sulfur in the reagent mix brings about dehydrogenation of the initial Gewald products **22** (Scheme 33) [54].

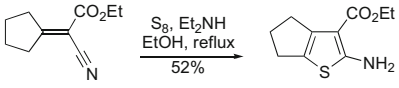
An exception to the otherwise general use of an organic base is the employment of potassium fluoride on alumina with microwave heating [55]. A range of cyclic ketones, β-keto-esters and aldehydes were used successfully – an example is shown in Scheme 34.



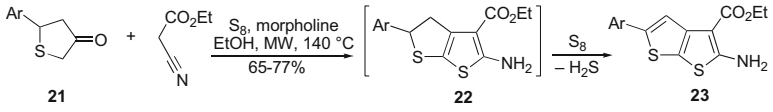
Scheme 30 General scheme for the synthesis of 2-aminothiophene-3-esters – the Gewald synthesis



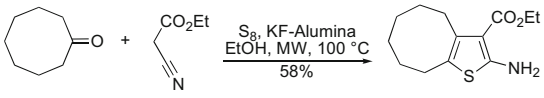
Scheme 31 The synthesis of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate [53]



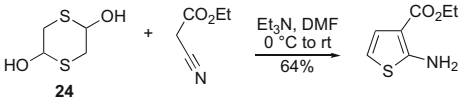
Scheme 32 The synthesis of ethyl 2-amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carboxylate [53]



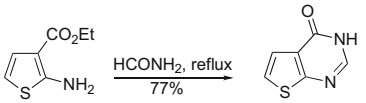
Scheme 33 Gewald syntheses using 5-aryldihydro-3(2*H*)-thiophenones [54]



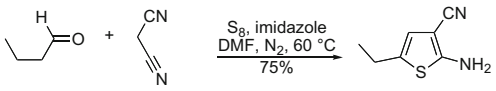
Scheme 34 A Gewald syntheses using KF as base [55]



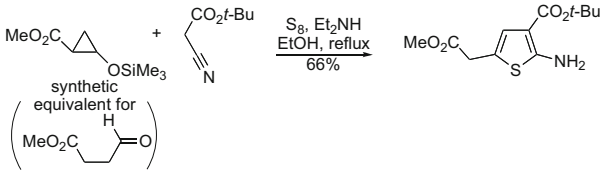
Scheme 35 A Gewald synthesis to produce a 4,5-unsubstituted 2-aminothiophene-3-ester [56, 57]



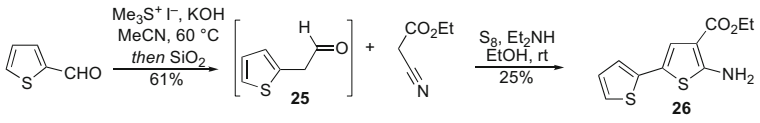
Scheme 36 Using a Gewald product to make a thieno[2,3-*d*]pyrimidine [65, 66]



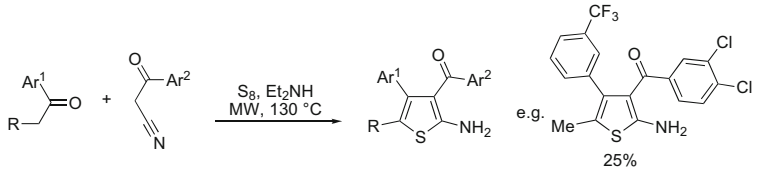
Scheme 37 The use of imidazole as base in Gewald synthesis of 2-amino-3-cyanothiophenes [58]



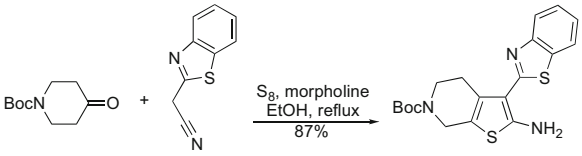
Scheme 38 The use of a 2-trimethylsiloxycyclopropanecarboxylate as a synthetic equivalent for $MeO_2C(CH_2)_2CHO$ in a Gewald synthesis [59]



Scheme 39 The synthesis of ethyl 2-amino-5-(thien-2-yl)thiophene-3-carboxylate using the Gewald route [60]



Scheme 40 The synthesis of 2-aminothien-3-yl ketones using the Gewald route [61]



Scheme 41 The synthesis of a 2-amino-3-(benzothiazol-2-yl)thiophene using Gewald synthesis [62]

In order to obtain thiophenes unsubstituted at C-4 and C-5, ethanal would be required as the aldehyde component, but there are only a few examples of this [63, 64], in one [64] of which zinc oxide was used instead of an organic base. In practice, 1,4-dithiane-2,5-diol **24** is usually used (Scheme 35), and thus no sulfur needs to be introduced into the reaction mixture: the reactant is a dimer of mercaptoacetaldehyde. Reaction is carried out in the presence of a base, which deprotonates an OH group and thus releases the aldehyde carbonyl from its hemithioacetal, ready for Knoevenagel condensation [56, 57].

The substitution pattern produced in the Gewald sequence lends itself to the subsequent fusion of a pyrimidine ring – one of the many examples of this is shown in Scheme 36 [65, 66].

Imidazole works well as the base, for both aldehydes and ketones, in reactions with malononitrile; an aldehyde example is shown in Scheme 37 [58]. Triethylamine was used for malononitrile Gewald reactions with cyclic ketones [67]. 5-Alkoxycarbonylmethyl 2-aminothiophenes are produced by using a 2-trimethylsiloxycyclopropanecarboxylate as a synthetic equivalent for $MeO_2C(CH_2)_2CHO$, as illustrated in Scheme 38 [59].

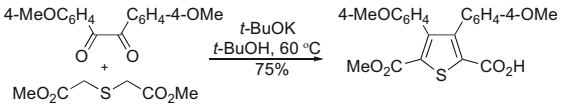
4-Aryl-2-aminothiophene-3-esters can be obtained from acetophenone and its benzene-ring derivatives using morpholine, sulfur, and acetic acid in refluxing ethanol [68]. 5-Aryl-2-aminothiophene-3-esters/amides/nitriles can be obtained efficiently from arylethanals using morpholine and sulfur, in ethanol with microwave heating [69]. A 5-(thien-2-yl)-2-aminothiophene-3-ester **26** was the result of using an in situ generated thien-2-ylethanal **25** (Scheme 39) [60].

2-Aminothien-3-yl ketones [61] can also be accessed via Gewald reactions, i.e. where the activating ester carbonyl group is replaced by a ketone carbonyl; both one-step and two-step [70] sequences have been employed; Scheme 40 illustrates the former.

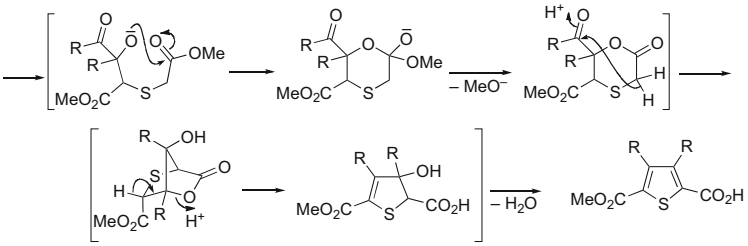
In a final example, the activating carbonyl group in starting cyano-esters (or cyanomethyl ketones) is replaced by a benzothiazole; the ketone component in this example was an *N*-protected piperidin-4-one (Scheme 41) [62].

2.4 Synthesis of Thiophene-2,5-Dicarboxylic Acid Derivatives from Thiodiacetates and 1,2-Dicarbonyl Compounds – Hinsberg Synthesis

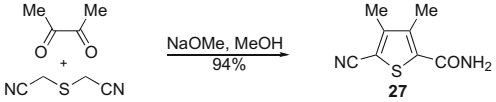
The venerable Hinsberg synthesis (e.g. Scheme 42) [71] involves two consecutive aldol condensations between a 1,2-dicarbonyl compound and diethyl 2,2′-thiobisacetate and produces thiophenes carrying ester and carboxylic acid groups at the 2- and 5-positions, respectively, via a Stobbe-type mechanism [72]. Reactions are often worked up via hydrolysis to afford a diacid as the isolated product. Scheme 43 indicates a reasonable sequence for the condensation and explains the formation of an acid-ester product.



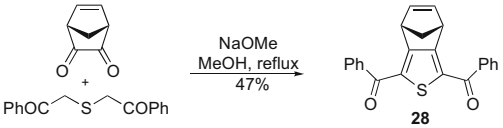
Scheme 42 A typical Hinsberg synthesis [71]



Scheme 43 The mechanism of the Hinsberg reaction



Scheme 44 A Hinsberg reaction using 2,2′-thiobis(acetonitrile) [73]

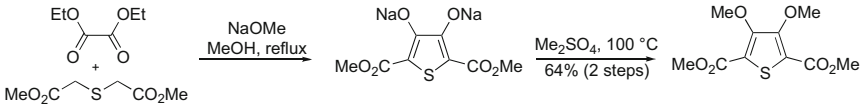


Scheme 45 A Hinsberg reaction with a non-aryl substituted 1,2-diketone [74]

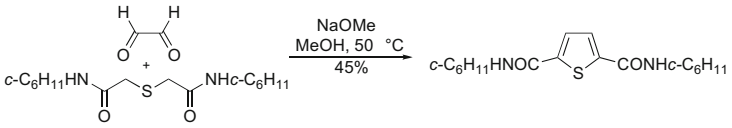
One of the very few examples of the use of non-aryl substituted 1,2-diketones in Hinsberg syntheses involved activation of the sulfur component with nitriles, rather than esters (Scheme 44). Thus, the reaction of butane-2,3-dione with 2,2′-thiobis (acetonitrile) led to mononitrile-monoamide **27** [73].

Scheme 45 shows another, though untypical, 1,2-diketone with saturated substituents, used in the construction of a strained fused 2,5-dibenzoylthiophene **28** [74].

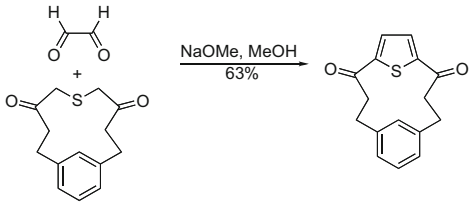
If diethyl oxalate is utilised as the 1,2-dicarbonyl component, with sodium methoxide as base, a 3,4-dihydroxythiophene is generated as its disodium salt, usually trapped by double *O*-alkylation, as indicated in Scheme 46. Note that in this situation, the product of the ring synthesis is the 2,5-diester [75, 76], not an ester-acid.



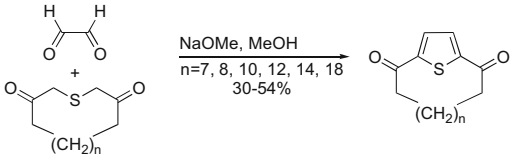
Scheme 46 The Hinsberg reaction using diethyl oxalate: the synthesis of 3,4-dihydroxythiophenes [75, 76]



Scheme 47 The Hinsberg reaction using glyoxal: the synthesis of 3,4-unsubstituted thiophenes [77]



Scheme 48 The Hinsberg reaction using glyoxal for thiophenophane construction [78]

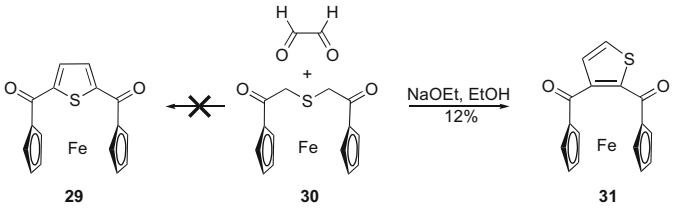


Scheme 49 A Hinsberg reaction using glyoxal for thiophenophane construction [79]

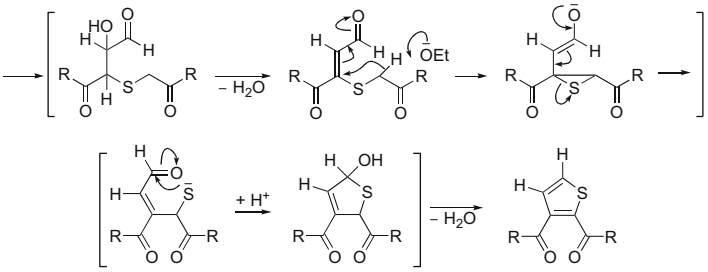
The use of glyoxal as the 1,2-dicarbonyl component produces 3,4-unsubstituted thiophenes, as illustrated in Schemes 47, 48, and 49 [77, 78, 79].

The employment of glyoxal as the 1,2-dicarbonyl component in Hinsberg reactions has been of value in the construction of thiophenophanes: Schemes 48 and 49 [78, 79] are typical.

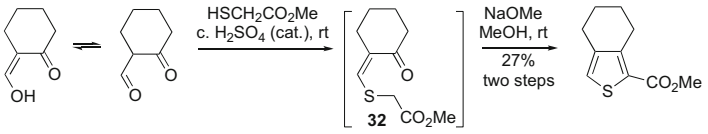
A note of caution must be sounded in this context: in an attempt to form **29** in a Hinsberg reaction, by condensing glyoxal with 3-thia[5](1,1′)ferrocenophane-1,5-dione **30,** the product turned out to have structure **31** [1.1](2,3)thiopheno(1,1′) ferrocenophane-1,7-dione (Scheme 50) [80]. The unexpected product structure can be explained by the sequence shown in Scheme 51, and it should be noted that such a rearrangement could in principle occur during any Hinsberg synthesis.



Scheme 50 A Hinsberg reaction using glyoxal producing a 2,3-disubstituted thiophene [80]



Scheme 51 Mechanism of an abnormal Hinsberg reaction

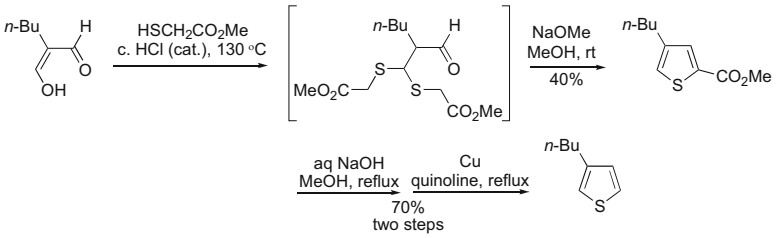


Scheme 52 A typical reaction between a 1,3-keto-aldehyde and methyl thioglycolate giving a 5-unsubstituted thiophene-2-ester [81]

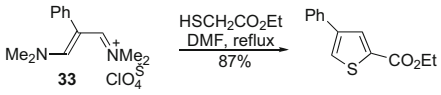
2.5 Synthesis of Thiophene-2-Carboxylates from Thioglycolates (2-Mercaptoacetates) and 1,3-Dicarbonyl Compounds

The combination of a thioglycolate, to provide the sulfur and C-2, and a 1,3-dicarbonyl compound, or a synthetic equivalent, produces thiophene-2-carboxylic esters which, depending on the dicarbonyl component, can have a variety of substituents at the other ring positions. Most examples have involved 1,3-ketoaldehydes, the regiochemistry of combination being governed by the difference between the two carbonyl groups, as in the example in Scheme 52 [81]; thus, thioenol formation involving the aldehyde carbonyl, giving **32**, is followed by a cyclising aldol condensation.

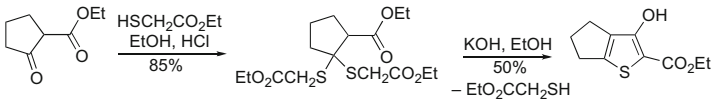
The synthesis of thiophene-2-esters with no substituents at either C-3 or C-5 by this route requires 1,3-dialdehydes. Additionally it should be noted that employing



Scheme 53 A typical reaction between a 1,3-dialdehyde and methyl thioglycolate and then hydrolysis and decarboxylation giving a 3-mono-substituted thiophene [82]



Scheme 54 A reaction between a vinamidinium salt (1,3-dialdehyde equivalent) and ethyl thioglycolate giving a 3,5-unsubstituted thiophene-2-ester [84]



Scheme 55 The conversion of a 1,3-keto-ester into a 3-hydroxythiophene-2-ester [85]

a substituted malondialdehyde and then ester hydrolysis and decarboxylation produces 3-mono-substituted thiophenes, e.g. as in Scheme 53 [82].

Vinamidinium salts [83], e.g. **33**, serve conveniently as 1,3-dialdehyde equivalents, as shown in Scheme 54 [84].

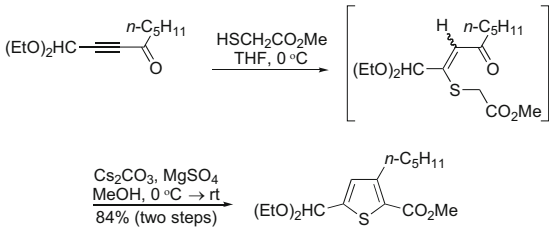
The use of a β-keto-ester leads first to a thioacetal, by interaction of the thiol with the ketone carbonyl; subsequent base-catalysed ring closure produces 3-hydroxythiophene-2-esters, as illustrated in Scheme 55 [85].

Amongst 1,3-dicarbonyl equivalents that have been utilised, conjugated yne-ones react regioselectively – the thiol sulfur interacts with the alkyne, as illustrated in Scheme 56 [86].

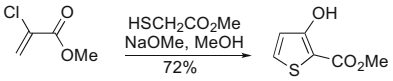
3-Hydroxythiophene-2-esters, i.e. unsubstituted at C-4 or C-5, can be obtained very simply via the reaction of a 2-chloroacrylate with a thioglycolate (Scheme 57) [87].

Similarly, 4,5-unsubstituted 3-aminothiophene-2-carboxylates are obtained from 2-chloroacrylonitrile reacting with a thioglycolate (Scheme 58) and 4,5-disubstituted 3-aminothiophene-2-carboxylates in general from 1-chloro-2-cyanoalkenes [$R^1C(Cl)=C(R^2)CN$] [87, 88].

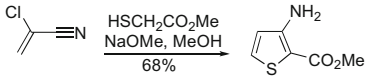
Conjugated ynones are easily accessible via palladium-catalysed condensation of terminal alkynes with acid chlorides and this was used to generate several 1,5-bis



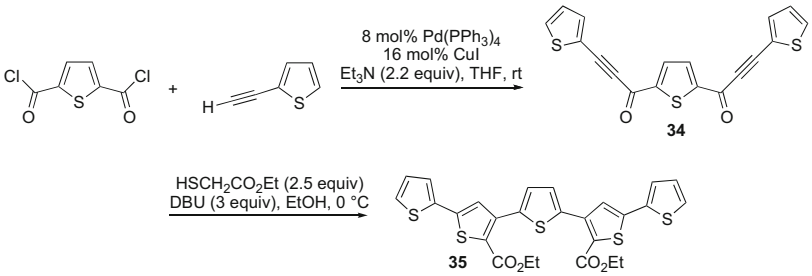
Scheme 56 A regioselective reaction between a conjugated ynone and methyl thioglycolate giving a thiophene-2-ester [86]



Scheme 57 The synthesis of methyl 3-hydroxythiophene-2-carboxylate [87]



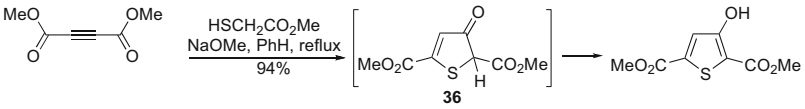
Scheme 58 The synthesis of methyl 3-aminothiophene-2-carboxylate [87, 88]



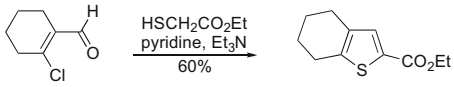
Scheme 59 Palladium-catalysed synthesis of a conjugated ynone and its reaction with methyl thioglycolate giving diethyl [2,2′:4′,2″:5″,4‴:2‴,2⁗-quinquethiophene]-5′,5‴-dicarboxylate [89]

(aryl[hetaryl]alkynylcarbonyl)thiophenes, e.g. **34**, then taken on, to the quinquethiophene **35**, in this case (Scheme 59) [89].

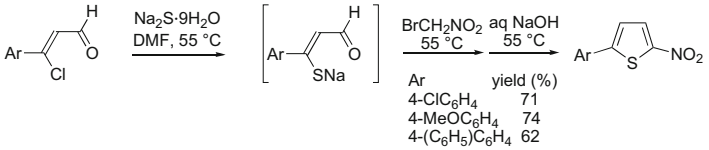
In the earliest examples of this approach, Fiesselmann studied acetylenic esters, including acetylenedicarboxylic acid esters, the former producing 5-substituted 3-hydroxythiophene-2-esters whilst the latter giving rise to 3-hydroxythiophene-2,5-dicarboxylic esters (Scheme 60) [90–92] (Later work used milder conditions for this synthesis: [93]). The final ring closing condensation to produce the 3-hydroxythiophene-2-esters is of the Claisen type and one can envisage the first cyclic intermediate as **36** which tautomerises.



Scheme 60 Reaction between dimethyl acetylenedicarboxylate and methyl thioglycolate giving a 3-hydroxythiophene-2,5-bis(ester) [90]



Scheme 61 The use of a 3-chloro-enal as a synthetic equivalent of a 1,3-keto-aldehyde [95]



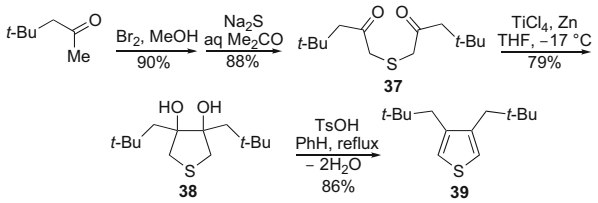
Scheme 62 The use of a 3-chloro-enal to make a 2-nitro-5-arylthiophene [96]

Amongst other 1,3-dicarbonyl equivalents which will serve for interaction with thioglycolates are 3-chloro-enones [94] and 3-chloro-enals [95, 96] (illustrated in Schemes 61 and 62 – the latter also showing the use of a nitro group in lieu of an ester, leading to a 2-nitrothiophene), 3-amino-enones [94], 3-methoxy-acrylates [97] 3,3-bis(methylthio)-enones (producing 5-methylthio-products) [98] and 3-phenylthio-enones [99].

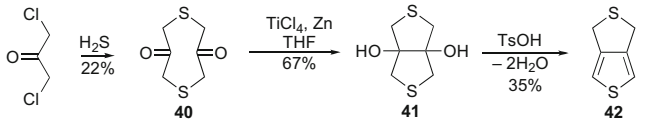
2.6 *Synthesis of 3,4-Disubstituted Thiophenes from α,α′-Thiobisketones*

Sodium sulfide reacts with two equivalents of a 2-halo-ketone to generate an α,α′-thiobisketone, e.g. **37**, and these can be cyclised to give aromatic thiophenes [100] via an intramolecular pinacol reaction promoted by low valent titanium, generated in situ, followed by the elimination of two equivalents of water, for example, from **37** to **39** via **38** (Scheme 63) [101].

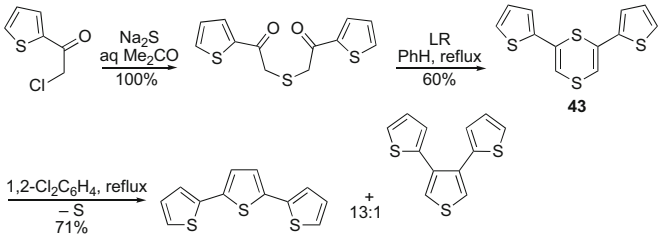
This route can be used to prepare thiophenes with adjacent bulky groups: 3,4-di-*tert*-butylthiophene [102] and 3,4-di(adamant-1-yl)thiophene [103] can be accessed. Another nice example (Scheme 64) is the reaction of 1,3-dichloropropanone with hydrogen sulfide, which produces diketone **40**. The application of the pinacol-forming conditions gives rise to the diol **41** and double dehydration produces the bicyclic 1*H*,3*H*-thieno[3,4-*c*]thiophene **42** [104].



Scheme 63 The use of a 2-halo-ketone to make an α,α′-thiobisketone, ring closure using a pinacol reaction and then double dehydration [101]



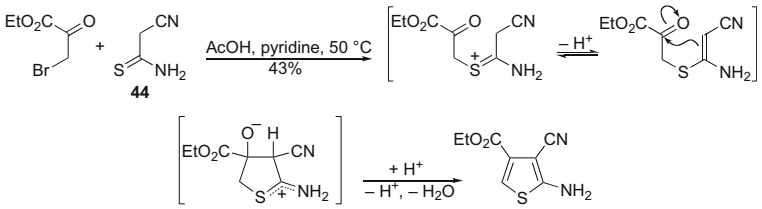
Scheme 64 Ring closure of a double α,α′-thiobisketone [104]



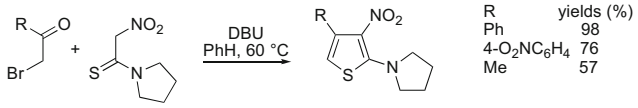
Scheme 65 The use of an α,α′-thiobisketone to make a 1,4-dithiin which is then converted into a thiophene via sulfur extrusion [108]

Alternatively, McMurray coupling of α,α′-thiobis(aryl)ketones leads to 2,5-dihydrothiophenes, using comparable conditions, but at a higher temperature [105, 106]. The 2,5-dihydrothiophenes can easily be dehydrogenated to the 3,4-diarylthiophenes, with DDQ [105] or copper(II) bromide [107].

A variant involves the use of the α,α′-thiobisketones in reaction with Lawesson's reagent which produces 1,4-dithiins, e.g. **43**, from which, by expulsion of sulfur, aromatic thiophenes result, as in the example in Scheme 65 [108]. However, expulsion of either dithiin sulfur is possible, so a mixture of isomers results, but usually with one isomer predominating.



Scheme 66 The synthesis of a 2-aminothiophene using a thioamide [109]



Scheme 67 The synthesis of a 2-(pyrrolidin-1-yl)thiophenes using thioamides [110]

2.7 *Synthesis of 2-Aminothiophenes from Thioamides*

Thioamides can be used in various ways to make 2-aminothiophenes. These methods should be compared with the Gewald synthesis (Sect. 2.3), which also produces 2-aminothiophenes.

Thioamides are nucleophilic at sulfur. S-alkylation of a thioamide which has an α-electron-withdrawing group, for example in **44** the electron-withdrawing group is a nitrile [109], with, for example, ethyl bromopyruvate, leads to ring closure, forming the 3,4-bond as shown in Scheme 66, producing in this case a 2-aminothiophene-4-ester with the electron-withdrawing group at C-3.

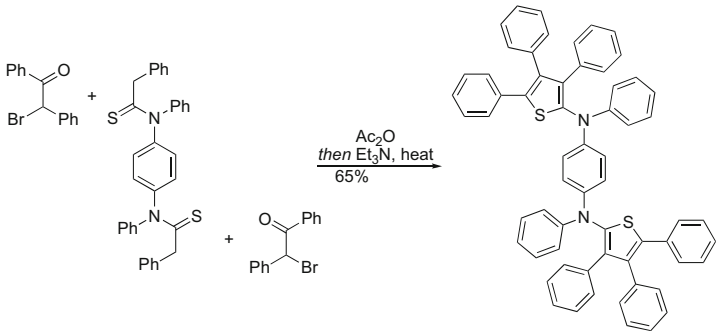
In another example, the α-electron-withdrawing group was nitro [110]; Scheme 67 shows how various 2-(pyrrolidin-1-yl)thiophenes were thus generated.

An aromatic ring, as a 2-substitutent of a thioamide, also has a sufficient acidifying effect on the adjacent methylene to allow thiophene formation. Indeed, some rather exotic structures have been prepared in this way, as shown in Scheme 68 [111].

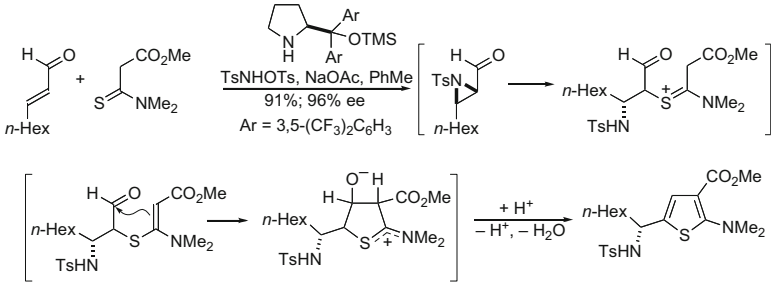
An alternative to the 2-halo-carbonyl component is an epoxide or *N*-tosylaziridine. A cascade sequence was used to bring about formation of the three-membered ring and also reaction with a suitable thioamide in one pot. Whether it is the S-alkylation or the C-3–C-4 bond forming step that occurs first is not known. By producing optically active epoxides/*N*-tosylaziridines in situ, the final thiophenes were also optically active (Scheme 69 [112] shows an aziridine sequence).

In an alternative use of thioamides, the ring-closing step involves the formation of the 4,5-bond of thiophene product (Scheme 70) [113].

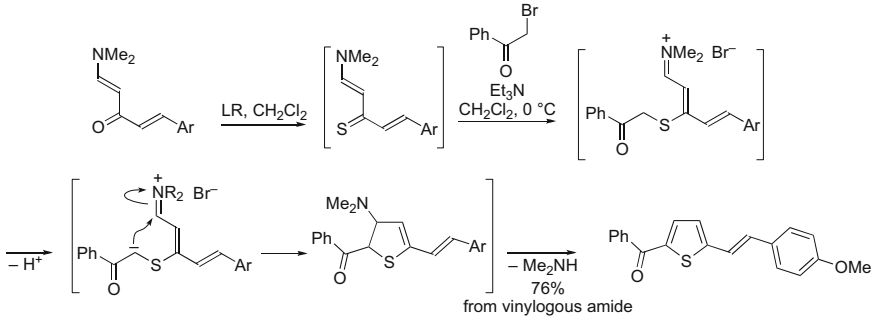
Extrapolating the vinylogous amide theme, 2-amino-5-acylthiophenes can be prepared from 3-amino-thioacrylamides, with the formation of the 4,5-bond in the ring closing step [114–117]. Thus, 3-amino-thioacrylamides **45** are S-alkylated



Scheme 68 The synthesis of hole transport materials from thioamides and 2-bromoketones [111]



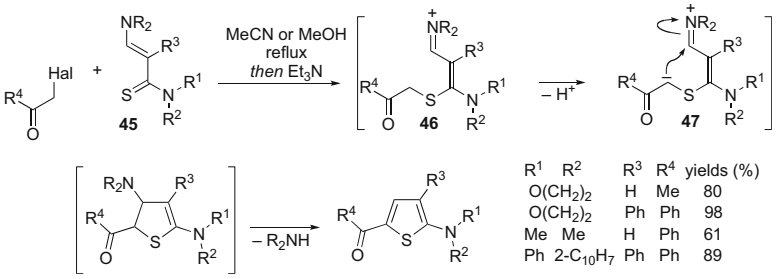
Scheme 69 The synthesis of 2-aminothiophenes from thioamides and an *N*-tosylaziridin-2-yl-aldehyde [112]



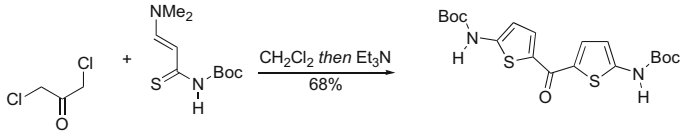
Scheme 70 The synthesis of 2-acylthiophenes from vinylogous thioamides [113]

with a 2-halo-ketone producing a salt, and **46** deprotonation (→ **47**) and then ring closure and aromatisation follow. Scheme 71 details some typical examples.

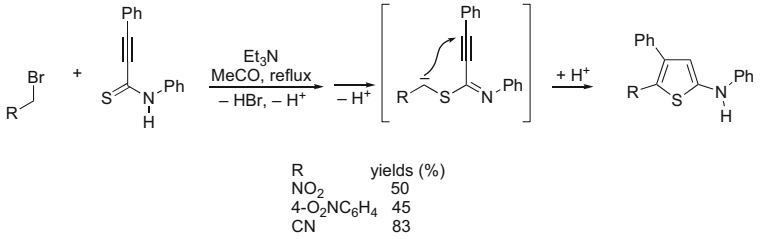
In a related work, it was found preferable to protect (Ac or Boc) the nitrogen of the 3-amino-thioacrylamide before reaction with the 2-halo-carbonyl component:



Scheme 71 The synthesis of a 2-amino-5-acylthiophenes from 3-amino-thioacrylamides [116]



Scheme 72 The synthesis of a 2-amino-5-acylthiophenes using 1,3-dichloroacetone [118]

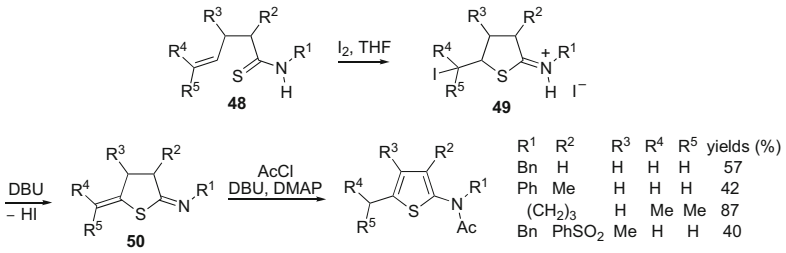


Scheme 73 The synthesis of 2-phenylaminothiophenes from thiopropargylanilides [119]

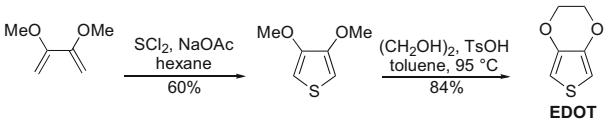
Scheme 72 shows a nice example of this modification using 1,3-dichloroacetone, thus producing two 2-amino-thiophene units [118].

There are a few examples of the conversion of thiopropargylamides into thiophenes. Scheme 73 shows the reaction of bromomethanes with an acidifying substituent converting thiopropargylanilides into 2-phenylamino-thiophenes [119].

Finally, γ,δ-unsaturated secondary thioamides **48** ring close to hydriodide salts **49** on reaction with iodine. The salts lose hydrogen iodide when exposed to base-forming imino-thiolactones **50** which react with acetyl chloride in the presence of a base to finally form 2-acetylamino-5-alkylthiophenes (Scheme 74) [120].



Scheme 74 The synthesis of a 2-amino-5-akyllthiophenes from γ,δ-unsaturated secondary thioamides [120]



Scheme 75 The reaction of 2,3-dimethoxy-1,3-butadiene with sulfur dichloride [122]

2.8 Miscellaneous Methods for the Synthesis of Thiophenes

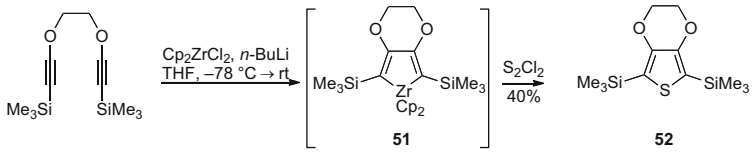
Here we review several useful methods that have been used rarely or are specific for certain products.

2.8.1 Using Sulfur Dichloride

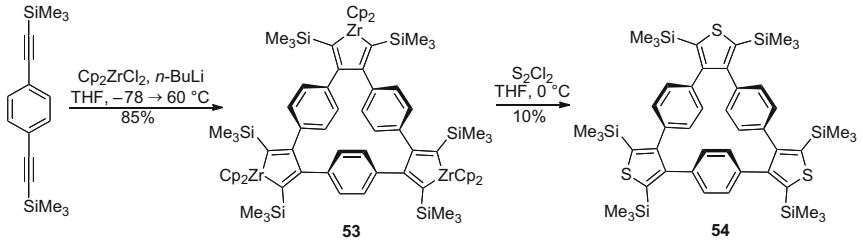
3,4-Dimethoxythiophene, which can be easily transformed into 3,4-ethylenedioxythiophene (EDOT) [121], the monomer for the production of poly(3,4-ethylenedioxythiophene) (PEDOT), can be neatly obtained by the reaction of 2,3-dimethoxy-1,3-butadiene with sulfur dichloride (Scheme 75) [122]. Note the contrast with the use of 1,3-diynes (Sect. 2.2) where the sulfur is introduced as a nucleophile – here the sulfur is provided as an electrophile.

Sulfur dichloride was also used in the synthesis of 2,5-bis(trimethylsilyl)-EDOT **52**, from which EDOT could be obtained by reaction with fluoride [123]. The basis of the route is a zirconocene coupling generating zirconacyclopentadiene **51** from the reaction of two alkynes, linked with a $O(CH_2)_2O$ tether, with zirconocene dichloride (bis(cyclopentadienyl)zirconium(IV) dichloride). The zirconacycle reacted with sulfur dichloride generating the thiophene ring of **52** (Scheme 76).

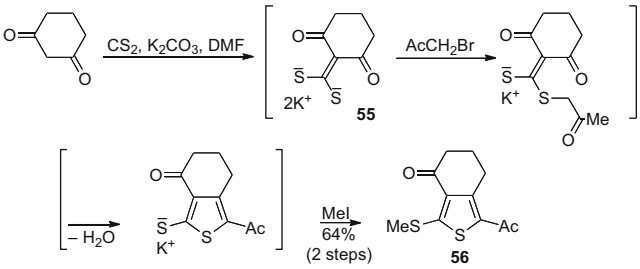
A particularly spectacular example (Scheme 77) of the zirconocene/S_2Cl_2 protocol (and of zirconocene coupling) is provided by the synthesis of trithiophene macrocycle **54** [124] from **53** [125].



Scheme 76 The synthesis of a thiophene via the reaction of a zirconacycle with sulfur dichloride [123]



Scheme 77 The synthesis of a trithiophene macrocycle via a tris(zirconacyclopentadiene) [124]

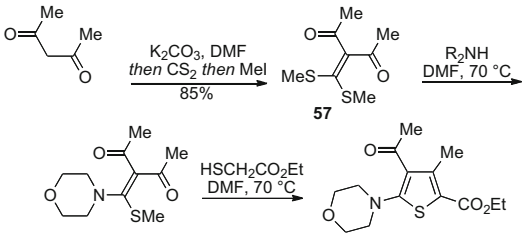


Scheme 78 The reaction of a 1,3-diketone enolate with carbon disulfide leading to a 2-methylthio-3-acyl thiophene [126]

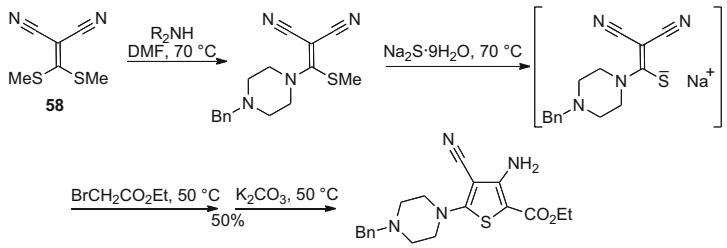
2.8.2 Using Carbon Disulfide

The addition of the enolate of a 1,3-diketone to carbon disulfide generates a dianion, e.g. **55**, which, following two successive S-alkylations, can produce 2-methylthio-3-acyl thiophenes **56**. The first alkylation requires a 2-halo-carbonyl compound (a 2-halo-ketone in the example in Scheme 78) to allow the ring closure via an intramolecular aldol condensation and then a second with iodomethane to complete the sequence [126].

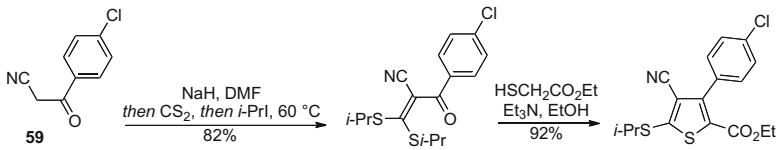
2-Aminothiophenes can also be obtained from carbon disulfide-derived intermediates. For example, one of the methylthio groups of ketene dithioacetal **57**, obtained from pentane-2,4-dione as shown, can be displaced with a secondary amine and the thiophene ring constructed by reaction with, for example, ethyl thioglycolate for final ring closure (Scheme 79) [127].



Scheme 79 The synthesis of a 3-acyl-2-aminothiophene starting from carbon disulfide [127]



Scheme 80 The synthesis of a 3-aminothiophene-4-nitrile [127]

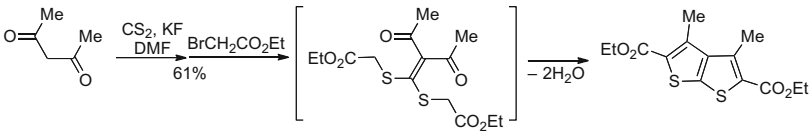


Scheme 81 The reaction of a 2-cyanoketone enolate with carbon disulfide giving a 3-cyano thiophene [128]

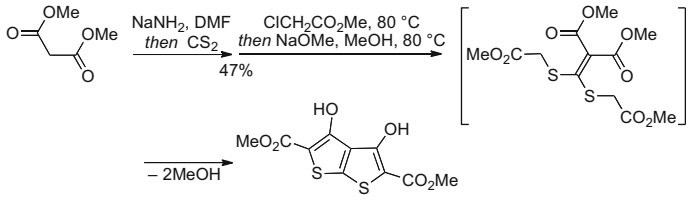
A comparable ketene dithioacetal **58** derived from malononitrile in the same way can also be converted into thiophenes, in these cases with an additional primary amino group at C-3, derived from one of the nitrile substituents (Scheme 80) [127].

Similar use of the enolate from a 2-cyanoketone, e.g. **59**, results in the formation of a 3-cyanothiophene (Scheme 81) [128].

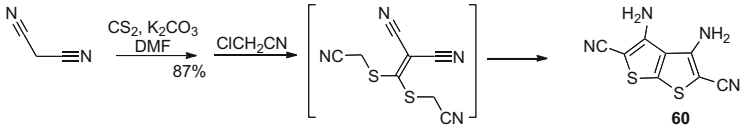
If two equivalents of the 2-halo-carbonyl compound (or 2-halo-nitrile) are utilised to react with an enolate/carbon disulfide adduct, double S-alkylation and then double ring closure produce thieno[2,3-*b*]thiophenes [129]; Scheme 82 shows how this works. Taking this idea further, if a malonate is used as the 1,3-dicarbonyl component, 3,4-dihydroxythieno[2,3-*b*]thiophenes are the final result (Scheme 83) [130], the ring closure steps then having the character of Claisen condensations. If malononitrile is used instead of a 1,3-dicarbonyl compound, the product is a 3,4-diaminothieno[2,3-*b*]thiophene – product **60** in Scheme 84 is the result of using chloroacetonitrile in the alkylation step [131].



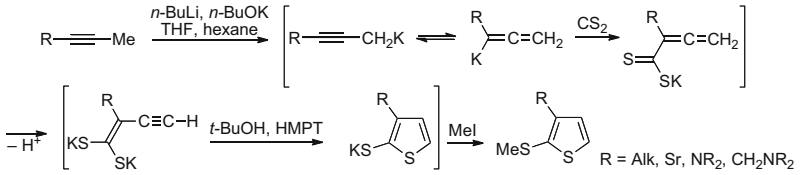
Scheme 82 The reaction of a 1,3-diketone enolate with carbon disulfide leading to a thieno[2,3-*b*] thiophene [129]



Scheme 83 The reaction of dimethyl malonate anion with carbon disulfide leading to a 3,4-dihydroxythieno[2,3-*b*]thiophene [130]

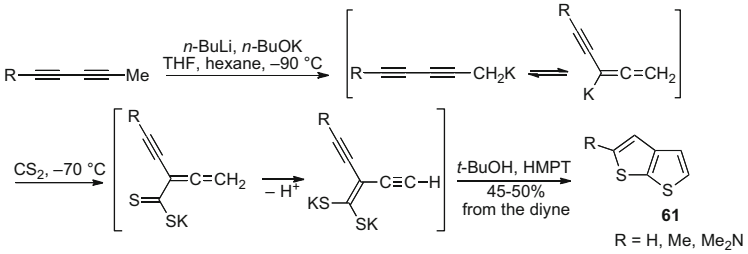


Scheme 84 The reaction of malononitrile with carbon disulfide leading to a 3,4-diaminothieno [2,3-*b*]thiophene [131]

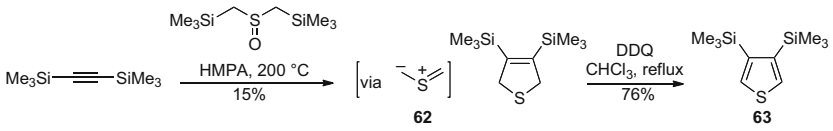


Scheme 85 The synthesis of 2-methylthiothiophenes starting from an alkyne and carbon disulfide [132]

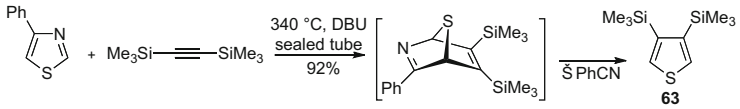
Finally, anions produced by deprotonation of an alkyne α to the triple bond can also be added to carbon disulfide. This can produce 2-(methylthio)thiophenes via the sequence shown in Scheme 85 or can be extrapolated (Scheme 86) [132] to penta-1,3-diynes and lead to thieno[2,3-*b*]thiophenes **61**.



Scheme 86 The synthesis of thieno[2,3-*b*]thiophenes from penta-1,3-diynes [132]



Scheme 87 Cycloaddition of a thiocarbonyl ylide to an alkyne followed by dehydrogenation [133]



Scheme 88 Intermolecular cycloaddition of a thiazole to an alkyne followed by cycloreversion [133]

2.8.3 Using Cycloadditions

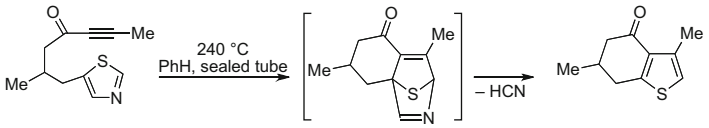
Cycloaddition sequences can be used to access thiophenes. For example, the reaction of the thiocarbonyl ylide, thioformaldehyde *S*-methylide **62**, with an alkyne produces a 2,5-dihydrothiophene, e.g. **63**, which can be dehydrogenated to the aromatic level (Scheme 87) [133].

A cycloaddition–cycloreversion sequence between 4-phenylthiazole and an alkyne, though requiring high temperatures, can efficiently generate thiophenes, as shown in Scheme 88 [133]. 3,4-Bis(trimethylsilyl)thiophene **63** can be utilised in a number of ways for manipulation to other 3-/4-substituted thiophenes.

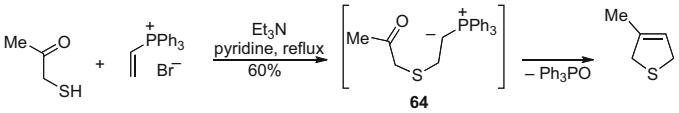
Thiophene ring formation via cycloaddition to a thiazole can also be achieved in an intramolecular sense as shown in Scheme 89 [134].

2.8.4 Using α-Mercapto-Ketones

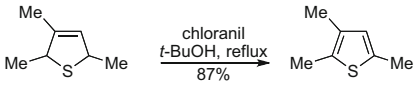
The sulfur of an α-mercapto-ketone (or α-mercapto-aldehyde [135]) will add to a vinyltriphenylphosphonium salt generating an intermediate ylide, e.g. **64**, that undergoes an intramolecular Wittig reaction to produce a 2,5-dihydrothiophene



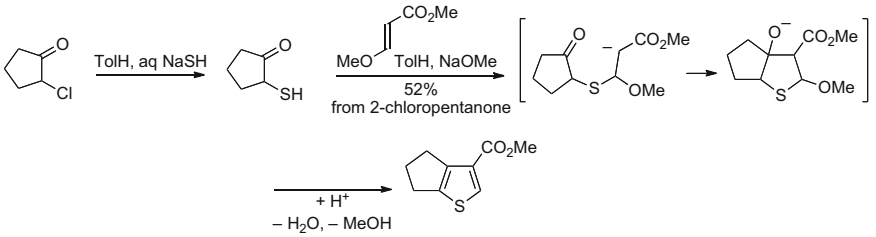
Scheme 89 Intramolecular cycloaddition of a thiazole to an alkyne followed by cycloreversion [134]



Scheme 90 The addition of an α-mercapto-ketone to vinyltriphenylphosphonium bromide [136]



Scheme 91 Dehydrogenation of a 2,5-dihydrothiophene [137]



Scheme 92 Condensation of an α-mercapto-ketone and 3-methoxyacrylate [138]

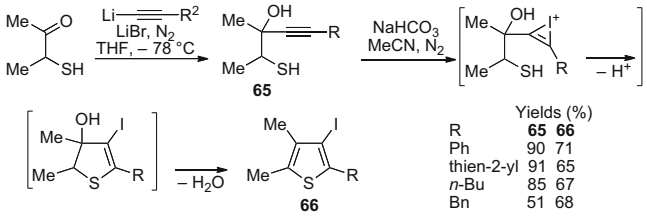
(Scheme 90) [136]. The conversion of 2,5-dihydrothiophenes to the aromatic species can be achieved efficiently with chloranil in hot *t*-butanol or hot pyridine, as exemplified in Scheme 91 [137].

No dehydrogenation step is required in the related reaction of an α-mercapto-ketone with a 3-methoxyacrylate, forming thiophene-3-esters (Scheme 92) [138].

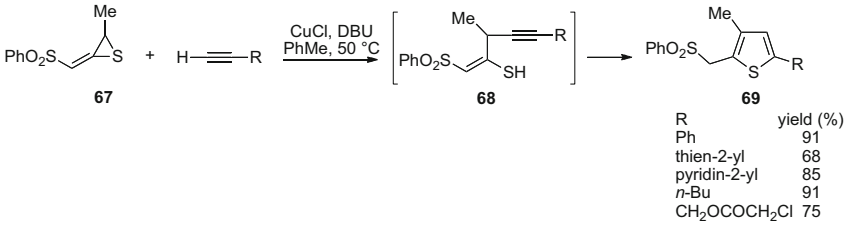
α-Mercapto-ketones are also the starting point for iodine-promoted ring closures that give rise to 3-iodothiophenes [139]. The addition of an alkyne anion to the carbonyl group of the α-mercapto-ketone produces a 1-mercapto-3-yn-2-ol **65** and now, iodine treatment promotes ring closure giving **66** (Scheme 93).

Double addition of an alkyne anion to an ester and then ring closure as above produce 3-iodo-4-alkynyl thiophenes [139].

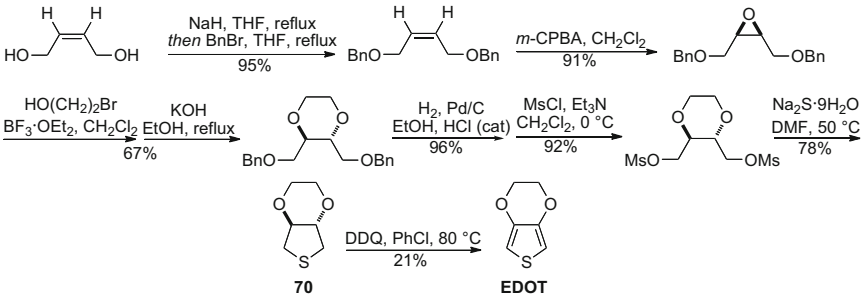
The intervention of a 1-mercapto-3-yne is also involved in the conversion of 1-phenylsulfonylalkylidenethiiranes **67** into 2-(α-phenylsulfonylalkyl)-thiophenes



Scheme 93 Iodine-promoted closure of a 1-mercapto-3-yn-2-ol to a 3-iodothiophene [139]



Scheme 94 Copper-promoted closure of a 1-mercapto-3-yne intermediate [140]



Scheme 95 Transformation of (*Z*)-but-2-ene-1,4-diol into EDOT [141]

69. Thus, reaction with terminal alkynes under copper catalysis generates the thiol intermediate **68** (Scheme 94) [140].

2.8.5 From (Z)-But-2-Ene-1,4-Diol

In a single example of the use of this starting material, EDOT was produced and *en route* various chiral intermediates [141]. The commercially available diol was first *O*-protected and then epoxidised and the epoxide taken through some standard transformations ending with tetrahydro-EDOT, **70**, which was aromatised using DDQ (Scheme 95).

3 Summary, Conclusions, and Outlook

The methods for de novo thiophene ring synthesis described in this chapter, many of which have been known for some time, continue to dominate the field. No doubt there will be future innovations, but the range of substituted thiophenes which can already be readily produced by these known methods, taken with the well-developed substitution chemistry of thiophenes (Chapter 3, Thiophene Substitution Chemistry), makes accessing any desired thiophene-containing compound a relatively well-developed art.

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Top Heterocycl Chem (2015) 39: 43–108
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Thiophene Substitution Chemistry

Victoria Ryabova and Luba Ignatovich

Abstract The nucleophilic, electrophilic and radical reactions leading to substitution on a thiophene ring are reviewed. Short historical views are presented where suitable. Recent examples, which in several cases demonstrate the modern application of the method, are presented where possible.

Keywords Acylation · Alkylation · Amino acid · Aminoalkylation · Base-catalysed halogen dance · Bromination · Chlorination · Chloromethylation · Electrophilic substitution · Formylation · Friedel–Crafts reaction · Glyoxylate imine · Halogenation · Iodination · Ionic liquid · Lewis acid · Mannich reaction · McMurry reaction · Meisenheimer complex · Nitration · Nucleophilic substitution · Oxidative nucleophilic substitution of hydrogen · Photochromic 1,2-di(thien-3-yl)ethenes · Protonation · Radical substitution · Sulfonation · Thiophenium ions · Triarylmethane · Vicarious nucleophilic substitution of hydrogen · Vilsmeier reaction

Contents

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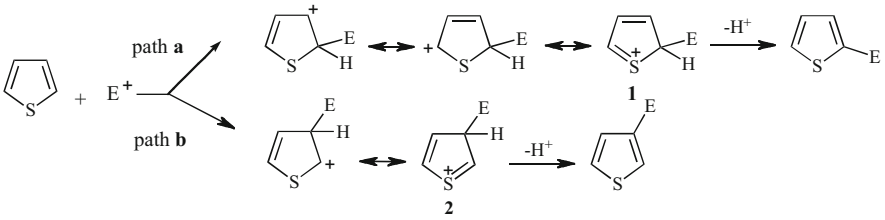
1 Introduction

Functionalisations of thiophenes by electrophilic, nucleophilic or radical reactions are well-investigated methods. Suitable reagents and catalysts are well known, and regioselectivity of substitution reactions can be predicted. Nevertheless, the demand on new materials and new medicines encourages searches for new methods as well as to improve the existing ones, for example, cheaper and environmentally friendly but still effective and selective reaction procedures are required. Electrophilic, nucleophilic and radical substitutions are very different, not only in the reagents and reaction conditions required, but also in the history of their development. Electrophilic reactions of thiophene have been known for as long as thiophene itself, while nucleophilic and radical reactions of thiophene were developed later. The descriptions of these methods as well as their applications in the modern chemistry of thiophene are presented together with historical examples where relevant.

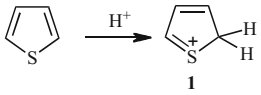
2 Electrophilic Substitution

Thiophene is a heterocycle that incorporates a sulfur atom that contributes two π electrons to the aromatic sextet, and thus, thiophene belongs to the group of π-excessive heteroaromatics [1]. For this reason, thiophene easily reacts with electrophiles (Scheme 1).

Positional selectivity for electrophilic substitution in thiophene is influenced both by the heteroatom and by substituents on the ring. Simple thiophenes give mostly 2-substituted derivatives, because of more favourable conjugation in cationic intermediate **1** than in intermediate **2**. In structure **1**, the C=C bond can delocalise the positive charge more effectively than in **2** [1–3]. Release of a proton from the intermediate cation returns the aromaticity to the thiophene ring and gives the product of aromatic electrophilic substitution.



Scheme 1 The possible ways (*a* or *b*) for electrophilic substitution of thiophene [2]



Scheme 2 Formation of 2*H*-thiophenium ion

Table 1 Selected values of bond lengths for neutral thiophene and 2*H*- and 3*H*-thiophenium ions calculated by the RHF/6-31G method [9]

Molecule	S–C-2	S–C-5	C-2–C-3	C-3–C-4	C-4–C-5
thiophene	1.73	1.73	1.35	1.44	1.35
2*H*-thiophenium	1.81	1.66	1.48	1.35	1.42
3*H*-thiophenium	1.62	1.77	1.48	1.50	1.32

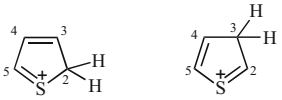
2.1 Thiophene Protonation

In the presence of Brønsted acids, thiophene is prone to protonation with the formation of thiophenium ions – C-protonated thiophenes (Scheme 1, E=H). Thiophenium ions were generated in pioneering investigations by treatment of thiophene with the excess of HF, HF-BF_3 or HF-SbF_5 and later also with H_2SO_4, HSO_3F and its mixtures with Lewis acids [4–7]. C-2-protonated thiophenes are stable in solution, even at room temperature, and were investigated by NMR spectroscopy (Scheme 2) [8].

The values of bond lengths for neutral thiophene, 2*H*-thiophenium ion and 3*H*-thiophenium ion were calculated by the RHF/6-31G method and selected values are given in Table 1 [9].

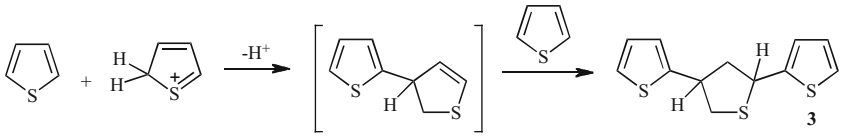
It can be seen that in the 2*H*-thiophenium ion, the bonds S–C-2, C-2–C-3 and C-4–C-5 are longer than in thiophene, and the bonds S–C-5 and C-3–C-4 are shorter than in thiophene. In the 3*H*-thiophenium ion, S–C-2 and C-4–C-5 are shorter than in thiophene, and the bonds S–C-5, C-2–C-3 and C-3–C-4 are longer than in thiophene, and thus the calculations are consistent with the structures shown in Fig. 1.

Protonated thiophene reacts as an electrophile with starting thiophene according to Scheme 3, thus rationalising the formation of oligo- and polythiophenes in acidic media, for example, the trimer **3** [10, 11].



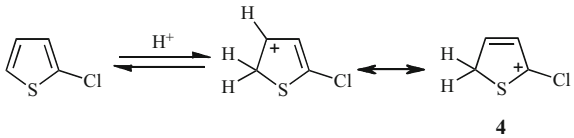
1 **2**

Fig. 1 The structures of 2*H*- and 3*H*-thiophenium ions



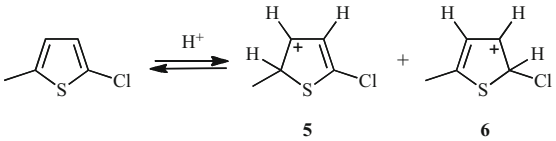
3

Scheme 3 Formation of a trimer **3** of thiophene [10]



4

Scheme 4 Protonation of 2-chlorothiophene [12]



5 **6**

Scheme 5 Protonation of 2-chloro-5-methylthiophene [12]

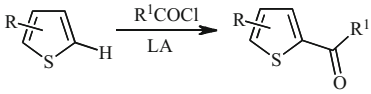
The targeted protonation of several substituted thiophenes was achieved by their treatment with HSO_3F or $AlCl_3$–HCl–CH_2Cl_2 [12]. The thiophenium ions were investigated by means of low-temperature NMR spectroscopy, and it was shown that even substituted thiophenes are protonated exclusively at an α-position; thus, 2-chlorothiophene gives a C-5-protonated species **4** (Scheme 4) [12].

2,5-Disubstituted thiophenes – 2,5-dichlorothiophene and 2-chloro-5-methylthiophene – were also protonated by HSO_3F and $AlCl_3$–HCl–CH_2Cl_2, again at an α-carbon. For 2-chloro-5-methylthiophene, the protonation by HSO_3F at −70°C gave a mixture of 2- and 5-protonated thiophenes, i.e. **5** and **6**, in a 3:1 ratio (Scheme 5) [12]; however, in the $AlCl_3$–HCl–CH_2Cl_2 system, **5** was formed selectively [12].

2.2 *Friedel–Crafts-Type Reactions*

At the end of nineteenth century, several reports appeared in the most important chemical journals of that time, *Justus Liebigs Annalen der Chemie* and *Chemische*

Scheme 6 Friedel–Crafts acylations of thiophene



Berichte, showing how the chemical behaviour of thiophene is similar to that of benzene. Preparing this chapter, we ourselves were amazed by the fact that eleven out of 51 reports published in the March 1884 issue of *Chemische Berichte* were devoted to thiophene and its derivatives.

Thus Friedel–Crafts (FC) acylation of thiophene was described in 1884 in reports of the synthesis of 2-benzoylthiophene [13, 14] and 2-acetylthiophene [15, 16] using benzoyl or acetyl chloride in benzene at room temperature [14, 15] or, with slight heating [13, 16], in the presence of $AlCl_3$ as Lewis acid (LA). Later, it was shown that the application of $AlCl_3$ caused polymerisation as a side reaction and $AlCl_3$ was successfully substituted by a milder Lewis acid, $SnCl_4$ (Scheme 6) [17, 18].

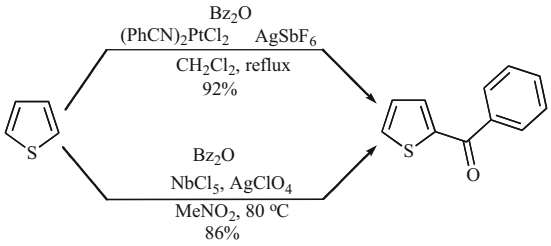
Known for 140 years, the functionalisation of thiophene under Friedel–Crafts conditions still remains very popular. Friedel–Crafts-type reactions allow for convenient, direct and thus atom-economic formation of a new C–C bond to the thiophene ring. In some cases, it is still performed under classical conditions using $AlCl_3$ in an equimolar amount as Lewis acid together with the acyl chloride; however, this produces strongly acidic waste. The Friedel–Crafts-type reaction applied to thiophene has been reviewed several times [19–22].

A very important question is the regioselectivity of substitution reactions of thiophenes. A comprehensive review on electrophilic substitution on thiophenes [21] described in detail the directing effects of substituents, their position and the way the electronic properties of different functional groups activate or deactivate various positions in thiophene. Many publications (e.g. [23, 24]) and reviews [3, 9, 25] discuss the mechanisms of electrophilic substitution on thiophene, proceeding through the formation of thiophenium ions.

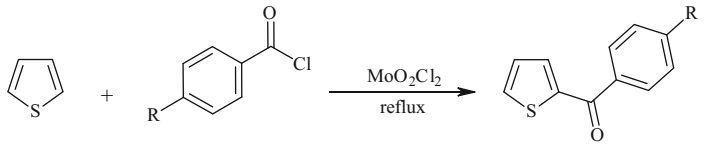
In the next section, the progress of Friedel–Crafts acylation of thiophene, including different acylating agents, different Lewis acids as well as catalytic and enantioselective variants, is shown.

2.2.1 Friedel–Crafts Acylations of Thiophene

To overcome the recognised problem of strong coordination between Lewis acids and reaction products, thienyl ketones, metal salts that are less oxophilic have been employed. The ‘hard/soft mismatch’ concept was suggested and explored. It was supposed that the ‘softer’, in comparison to traditional FC salts, late transition metal centres would not form a kinetically inert complex with ‘hard’ carbonyl oxygen atoms, and thus catalytic turnover would be improved. Indeed, the application of a Pt(II)-based catalyst – $(PhCN)_2PtCl_2$ – at only 2.5 mol% accompanied by 5 mol% of $AgSbF_6$ in boiling dichloromethane allowed the successful acylation of several

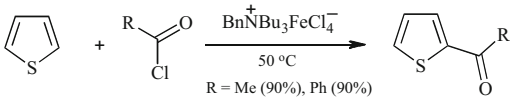


Scheme 7 Use of the combinations $(PhCN)_2PtCl_2$ and $AgSbF_6$ [26] or $NbCl_5$ and $AgClO_4$ for FC acylation of thiophene [27]



R = Cl (61%), CH_3 (66%), OCH_3 (66%)

Scheme 8 Use of MoO_2Cl_2 for FC acylation of thiophene [28]



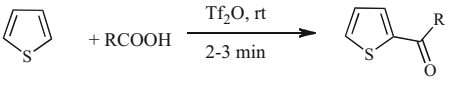
Scheme 9 Use of $FeCl_3$-based ionic liquid for FC acylation of thiophene [29]

aromatic compounds by carboxylic acid anhydrides. Benzoyl thiophene was obtained under these conditions in 92% yield (Scheme 7) [26].

Both $NbCl_5$ and $AgClO_4$ can catalyse FC acylation reactions, but the yields are rather low. The combination of these salts is much more effective, and 2-benzoyl thiophene was obtained with 86% yield using only 1 mol% of $NbCl_5$ and 3 mol% of $AgClO_4$ (Scheme 7) [27].

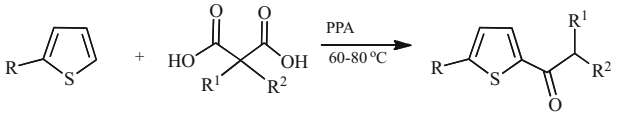
The high valent dioxomolybdenum(VI) complex MoO_2Cl_2 can also catalyse FC reactions; thus, thiophene was acylated by several 4-substituted benzoyl chlorides in the presence of 20 mol% of MoO_2Cl_2, without a solvent, to give 2-thienyl ketones in 61–66% yields (Scheme 8) [28].

The application of the $FeCl_3$-based ionic liquid, benzyltributylammonium tetrachloroferrate ([BTBA]Cl-$FeCl_3$), to promote the Friedel–Crafts acylation was also used to improve the method. Advantages are: excellent yields, short reaction times, mild reaction conditions, a simple work-up procedure, low cost and easy preparation and handling of the catalyst. This enviromentally friendly method gave both 2-acetylthiophene and 2-benzoylthiophene in only two to three minutes in 90% yields (Scheme 9) [29].



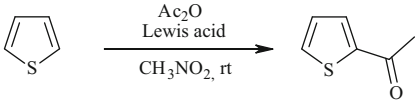
R = Me (solvent free), 98%
R = Ph (solvent = $MeNO_2$), 93%

Scheme 10 Application of carboxylic acids for thiophene acylation [30]



Yields: R, R^1, R^2= H (86%); R, R^1 = H, R^2 = Ph (90%); R = H, R^1, R^2= Et (89%); R = Br, R^1, R^2= H (93%); R = Br, R^1=H, R^2= Ph (93%); R = Br, R^1, R^2 = Et (88%); R = COOH, R^1, R^2 = H (10%).

Scheme 11 Acylation of thiophene by malonic acids in the presence of PPA [31]



Lewis acid = $Sc(OTf)_3$ (87%), $Sn(OTf)_2$ (95%)

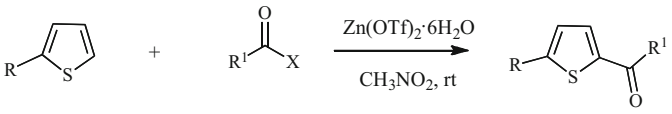
Scheme 12 Use of Sc(III) or Sn(II) triflates as effective catalysts for thiophene acetylation [32]

Carboxylic acids are more convenient as acylating reagents in comparison to acid chlorides or anhydrides [30]. The formation of ketones in the reaction of thiophene with acetic or benzoic acid in the presence of triflic anhydride, without involving a metallic catalyst, was complete at room temperature in only minutes with high yields. Acetylation with acetic acid proceeded in solvent-free conditions, but benzoic acid needed nitromethane as the solvent. The reaction mechanism is believed to involve the formation of a mixed anhydride between the carboxylic acid and triflic anhydride which then reacts with thiophene. Triflic acid is formed as a side product (Scheme 10) [30].

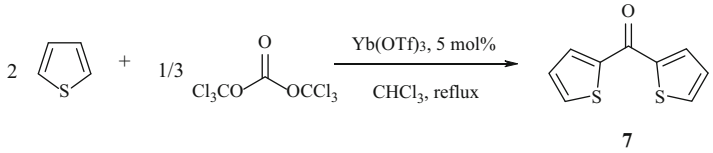
Several malonic acids have been used as acylating reagents in the presence of polyphosphoric acid (PPA) as both catalyst and solvent [31]. Probably the reactive intermediates are malonic anhydrides. Decarboxylation following the acylation gives the desired products (Scheme 11) [31].

Several metal triflates were demonstrated to be effective catalysts for FC reactions. Thus, both $Sc(OTf)_3$ and $Sn(OTf)_2$ applied at 5 mol% gave good yields of 2-acetylthiophene using acetic anhydride (Scheme 12) [32].

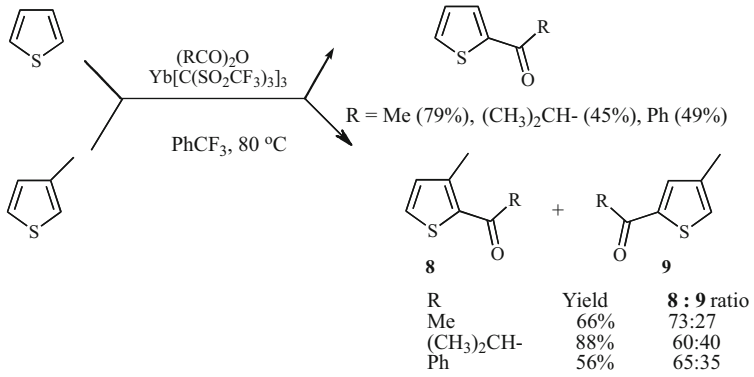
It was shown that hexaaqua zinc triflate [$Zn(OTf)_2 \cdot 6H_2O$] is a nice alternative choice for a catalytic variant of the Friedel–Crafts acylation reaction. Thus, 2-acetylthiophene, 2-propionylthiophene, 2-*p*-methylbenzoylthiophene, 5-chloro-2-acetylthiophene and 5-bromo-2-acetylthiophene were obtained by reaction with



Scheme 13 Use of hexaaqua zinc triflate for FC acylations of thiophene [33]



Scheme 14 Use of $Yb(OTf)_3$ as catalyst for thiophene acylation [34]



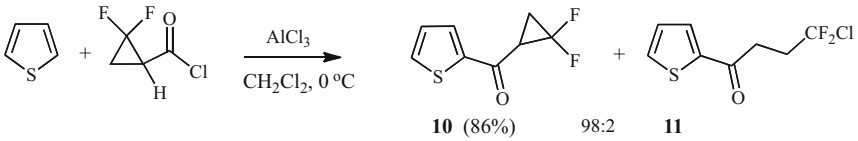
Scheme 15 Use of $Yb[C(SO_2CF_3)_3]$ for acylation of thiophenes with anhydrides [35]

acylating reagents in 84–89% yields in the presence of only 10 mol% of hexaaqua zinc triflate (Scheme 13) [33].

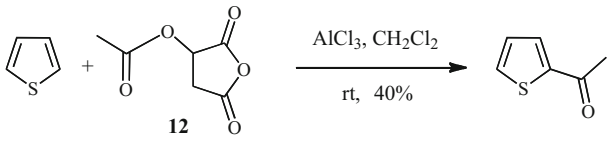
Two equivalents of thiophene react with bis(trichloromethyl) carbonate (triphosgene) catalysed by $Yb(OTf)_3$ giving di(thien-2-yl)methanone (**7**) in 77% yield after 5 h reflux in chloroform (Scheme 14) [34].

Ytterbium(III) tris(trifluoromethanesulfonyl)methide (ytterbium(III) triflide) was applied in a catalytic amount to catalyse FC processes. Only 1 mol% of ytterbium (III) triflide at 80°C allowed acylation of thiophene and 3-methylthiophene with acid anhydrides [35]. Acylation of thiophene led exclusively to 2-substitution; 3-methylthiophene gave a mixture of 2-acylated (**8**) and 5-acylated (**9**) products (Scheme 15) [35].

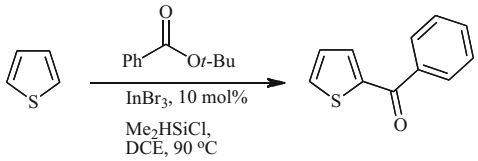
Catalyst poisoning in the course of FC reactions is due to the formation of an inert complex between catalyst and ketone, the reaction product. Increasing the reaction temperature suppresses the formation of such complexes, and as a result,



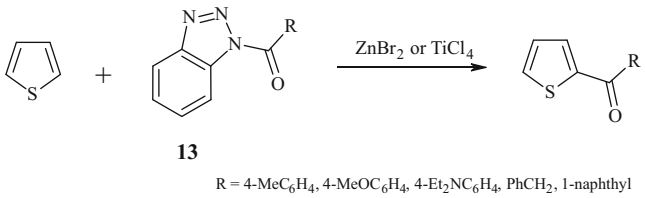
Scheme 16 Reaction of thiophene with 2,2-difluorocyclopropanecarbonyl chloride [36]



Scheme 17 Application of an ester for FC acylation of thiophene [37]



Scheme 18 Use of $InBr_3$ in the presence of Me_2HSiCl for acylation of thiophene with an ester [38]



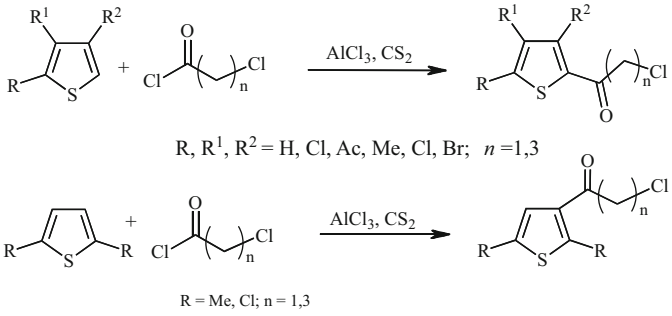
Scheme 19 Use of 1-acylbenzotriazoles for thiophene acylation [39]

at elevated temperatures, a reduced catalyst load is sufficient to effectively catalyse the FC acylation reaction.

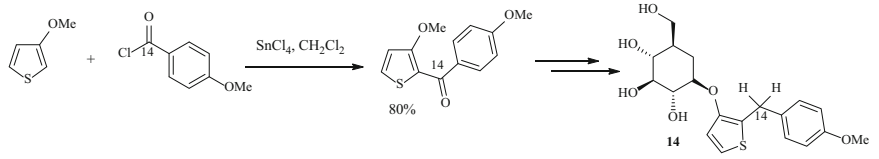
Reaction of thiophene with 2,2-difluorocyclopropanecarbonyl chloride under Friedel–Crafts conditions gave the expected acylation product **10** along with a small amount of ring-opened product **11** in an overall 86% yield (Scheme 16) [36]. This case demonstrates the high reactivity of thiophene in electrophilic substitution reactions since less reactive benzene and alkylated benzenes gave mostly the ring-opened products [36].

Esters can also be used for FC acylation, for example, 2,5-dioxotetrahydrofuran-3-yl acetate (**12**) produced 2-acetylthiophene in 40% yield under classical conditions (Scheme 17) [37].

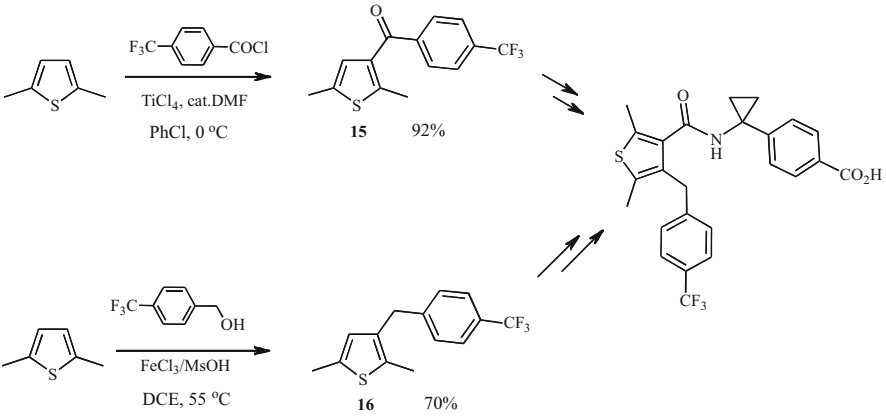
However, despite the advantages of esters as being more stable, less expensive and easier to handle in comparison to conventional acylating reagents such as acid



Scheme 20 Synthesis of potential GSK-3β inhibitors [40, 41]



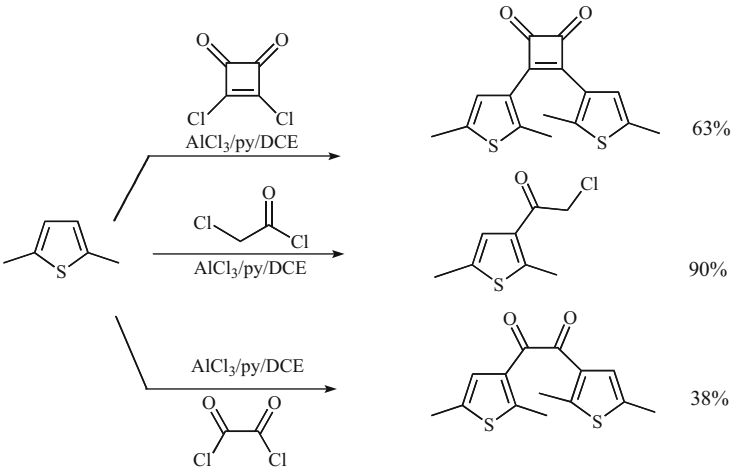
Scheme 21 Friedel–Crafts benzoylation of 3-methoxythiophene with [^{14}CO]4-methoxybenzoyl chloride [42]



Scheme 22 Synthesis of intermediates for prostaglandin EP4 antagonists by FC reactions of 2,5-dimethylthiophene [43]

chlorides and anhydrides, they have a much lower reactivity in FC reactions [38]. This drawback can be overcome by applying $InBr_3$ as catalyst together with a silane – Me_2HSiCl – which forms an active complex with the ester and catalyst thus allowing effective acylation of arenes by esters. The *tert*-butyl esters were found to be the most useful reagents for this regime (Scheme 18) [38].

Both thiophene acylation (Scheme 19) and alkylation (see Sect. 2.2.3) [39] were achieved by application of benzotriazole derivatives as active reagents. Thus,



Scheme 23 C-3 acylations of 2,5-dimethylthiophene [44]

thiophene was acylated by various 1-acylbenzotriazoles **13** in the presence of $ZnBr_2$ or $TiCl_4$ under mild conditions with good yields (58–97%) (Scheme 19) [39].

For the synthesis of potential glycogen synthase kinase 3β (GSK-3β) inhibitors, C-5 acylated 2,3,4-trisubstituted thiophenes were obtained by chloroacetylation in the presence of $AlCl_3$ in CS_2. The same conditions were applied to acylate C-3 of 2,5-disubstituted thiophenes (Scheme 20) [40, 41].

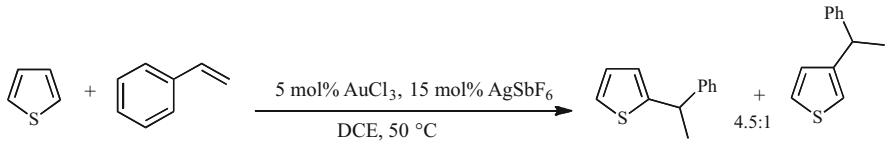
To keep track of drug molecules through the body, the synthesis of isotopically labelled novel inhibitors of sodium glucose cotransporters (SGLT-2) **14** for the treatment of type II diabetes mellitus was undertaken [42]. These thiophene-based molecules were synthesised by different approaches including Friedel–Crafts benzoylation of 3-methoxythiophene with [^{14}CO]4-methoxybenzoyl chloride as the first step (Scheme 21) [42].

As intermediates for the synthesis of prostaglandin EP4 antagonists, **15** and **16** were obtained by Friedel–Crafts acylation and alkylation reactions [43]. The use of $TiCl_4$ in chlorobenzene in the presence of catalytic DMF gave **15** in 92% yield. Since reduction of **15** to **16** would be one of the following steps, a shorter route to the product was desired. It was shown that 2,5-dimethylthiophene can be alkylated by *para*-trifluoromethylbenzyl alcohol under Friedel–Crafts conditions, best with $FeCl_3$ in the presence of MsOH (Scheme 22) [43].

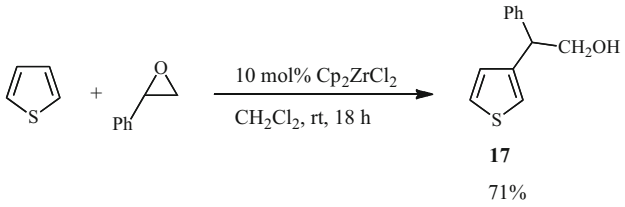
The acylation of 2,5-dimethylthiophene by various acylating agents in the presence of $AlCl_3$ and pyridine in dichloroethane gave 3-acylated 2,5-dimethylthiophenes in 38–90% yields (Scheme 23)[44].

2.2.2 Friedel–Crafts-Type Alkylation of Thiophene

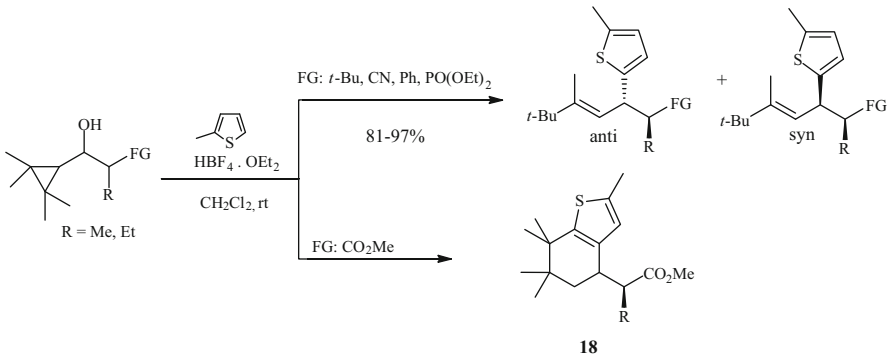
Thiophene alkylation by styrene, catalysed by combination of 5 mol% gold(III) chloride with 15 mol% of silver hexafluoroantimonate in 1,2-dichloroethane at



Scheme 24 Thiophene alkylation by styrene [45]



Scheme 25 Reaction of styrene epoxide with thiophene [46]



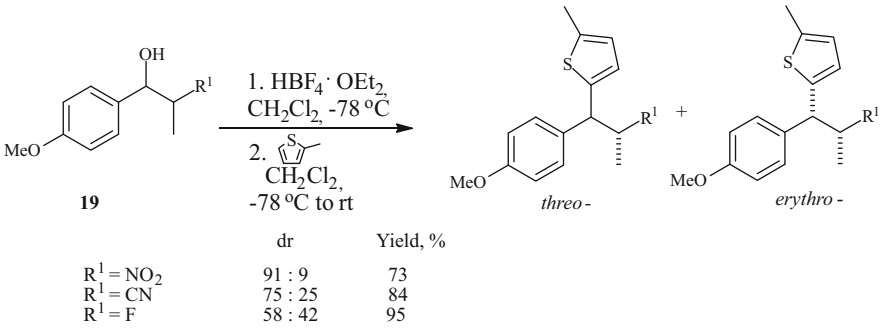
Scheme 26 Diastereoselective FC alkylation reactions of 2-methylthiophene with 1-(2′,2′,3′,3′-tetramethylcyclopropyl)-alkan-1-ols [47]

50°C gave 2- and 3-alkylated thiophenes in the ratio 4.5:1 with an overall yield of 87% (Scheme 24) [45].

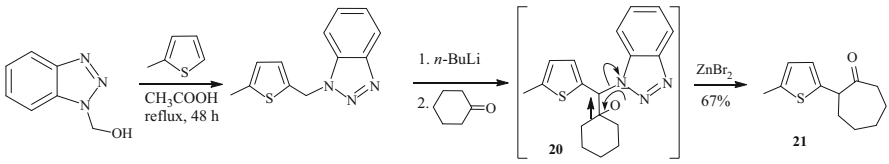
Epoxide ring opening by thiophene was catalysed by 10 mol% of bis(cyclopentadienyl)zirconium dichloride complex. The reaction was performed in acetonitrile and, rather surprisingly, the 3-alkylated thiophene **17** was isolated in 71% yield (Scheme 25) [46].

2-Methylthiophene undergoes diastereoselective Friedel–Crafts-type alkylation with 1-(2′,2′,3′,3′-tetramethylcyclopropyl)-alkan-1-ols under Brønsted acid catalysis [47]. Tetramethylcyclopropyl-substituted carbocations formed under the reaction conditions underwent a fast ring opening which led to the formation of allylic cations, which by reaction with thiophene gave the products (Scheme 26) [47].

In the case when R=CO_2Me or CO_2Et, the reaction pathway was different: here the Friedel–Crafts reaction is faster than the formation of dehydrated cation, and it



Scheme 27 Diastereoselective Friedel–Crafts alkylation of 2-methylthiophene [48]



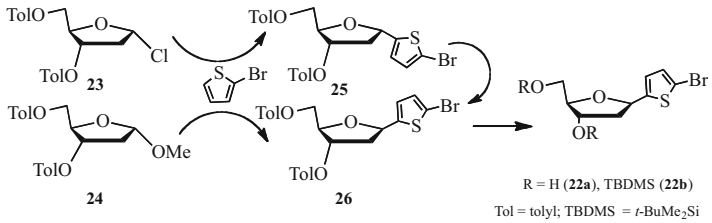
Scheme 28 Synthesis of 2-(5-methylthien-2-yl)cycloheptanone [39]

is followed by an intramolecular Friedel–Crafts reaction, giving a cyclised product **18** (Scheme 26) [47].

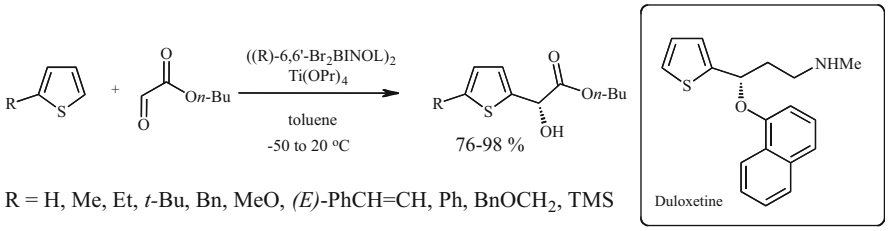
Reaction of 2-methylthiophene with precursors to benzylic cations **19** (R^1=NO_2, CN) in the presence of Brønsted acid $HBF_4{\cdot}OEt_2$ at −78°C resulted in the formation of 1,1-diarylpropanes; *threo*-isomers were the major diastereomers. When R^1=F, almost no selectivity was observed (Scheme 27) [48].

C-5-Alkylation of 2-methylthiophene with benzotriazol-1-ylmethanol was performed by prolonged heating in glacial acetic acid. The product could be metallated by *n*-BuLi at the methylene group, and addition of this anion to the carbonyl group of cyclohexanone led to the alkoxide anion **20**, in situ treatment of which with $ZnBr_2$ promoted rearrangement with elimination of the benzotriazolide anion and ring expansion to a cycloheptanone **21** (Scheme **28**) [39].

The key intermediates **22a–b** of 5-substituted thien-2-yl *C*-2′-deoxyribonucleosides were synthesised through Friedel–Crafts-type C-glycosidation of 2-bromothiophene by either halogenose **23** or methyl glycoside **24**, both tolyl protected [49]. The reaction of a chloro-sugar with 2-bromothiophene in the presence of $BF_3{\cdot}Et_2O$ led to the mixture of α- (**25**) and β-anomers (**26**) in 1:1 ratio with 22% yield of each anomer. The yield of desired β-anomer – β-(5-bromothien-2-yl) *C*-nucleoside (**26**) – was improved after changing Lewis acid to $AgBF_4$ (54% of β-anomer and only 14% of α-anomer). The Friedel–Crafts reaction of a more stable and easily available methyl glycoside **24** with 2-bromothiophene in the presence of $SnCl_4$ and $AgOCOCF_3$ gave the desired protected β-C-nucleoside **26** in 60% yield along with 25% of α-anomer **25**



Scheme 29 C-Glucosidation of 2-bromothiophene [49]



R = H, Me, Et, *t*-Bu, Bn, MeO, *(E)*-PhCH=CH, Ph, $BnOCH_2$, TMS

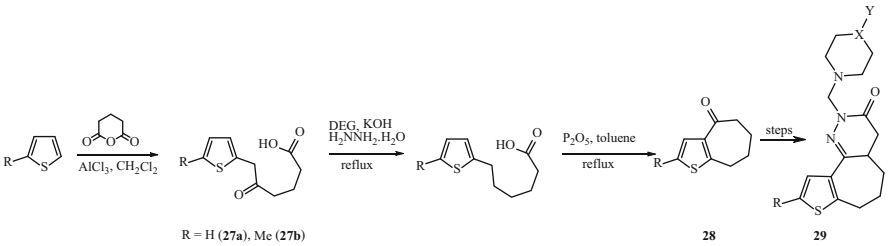
Scheme 30 The synthesis of 2-hydroxy-2-(thien-2-yl)acetates [50]

(Scheme 29) [49]. Deprotection of toluoylated nucleosides with NaOMe in methanol led to the desired thiophene-substituted nucleoside **22a** in 93% yield. Following reaction with TBDMSCl and imidazole gave persilylated intermediate **22b** in 94% yield and allowed further transition metal-catalysed reactions at the thiophene ring.

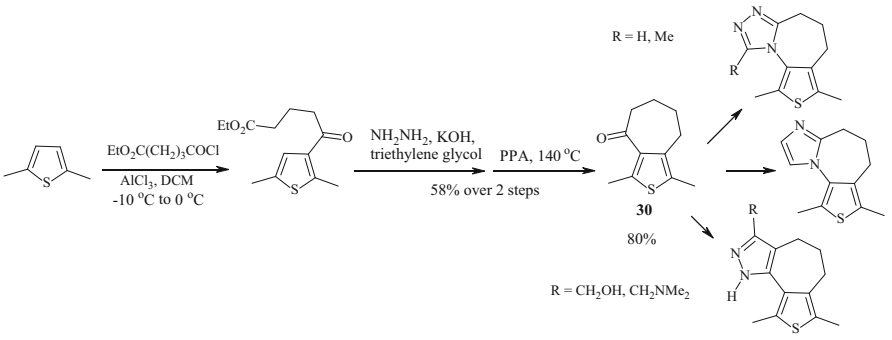
Friedel–Crafts hydroxyalkylation offers a very attractive, direct approach to the synthesis of 2-hydroxy-2-(thien-2-yl)acetates. Highly enantioselective reactions of glyoxylates with various thiophenes were achieved by applying $(6,6'\text{-}Br_2\text{-}BINOL)_2/Ti(IV)$ as the chiral Lewis acid catalyst [50]. 2-Substituted thiophenes gave the desired 5-substituted thien-2-yl α-hydroxy esters in good yields (65–97%) and with high optical purity (92–98% *ee*). Very high enantioselectivity and yield were also obtained using 2,3-dimethylthiophene. Thiophene itself gave a product in only 40% yield but with the same high enantioselectivity. In the case of 2,5-dimethylthiophene, substitution at C-3 took place, but with low enantioselectivity (35% *ee*) [50]. With the aid of this method, duloxetine – a serotonin–norepinephrine reuptake inhibitor of wide pharmacology utility – was synthesised starting from thiophene itself and glyoxylate (Scheme 30) [50].

2.2.3 Friedel–Crafts-Type Acylations with Ring Closure

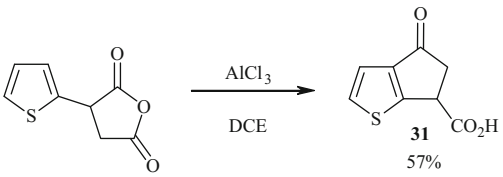
Reactions leading to a ring closure are always of interest. Two 5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophen-4-ones were synthesised as intermediates for new cytotoxic agents [51] using two successive Friedel–Crafts reactions, the last intramolecular. Friedel–Crafts acylation of thiophene or 2-methylthiophene with glutaric anhydride in the presence of $AlCl_3$ gave 5-(thien-2-yl)-5-oxopentanoic acid **27a** (R=H) and 5-(5-methylthien-2-yl)-5-oxopentanoic acid **27b** (R=Me),



Scheme 31 Synthesis of thienocyclohepta[1,2-*c*]pyridazinones **29** [51]



Scheme 32 Synthesis of cyclohepta[*c*]thiophen-3-ones using FC reactions [52]

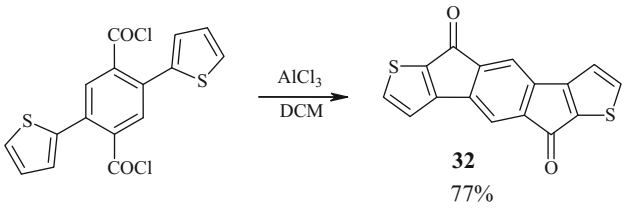


Scheme 33 Synthesis of precursors of heterocarbocyclic nucleoside analogues [53]

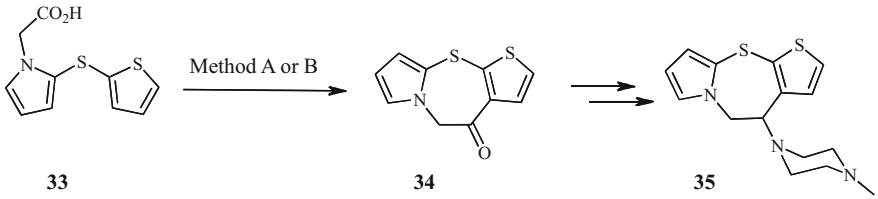
both in 60% yield. Their reduction with hydrazine hydrate and KOH in diethyleneglycol (DEG) was followed by intramolecular Friedel–Crafts acylation in toluene in the presence of P_2O_5 giving cyclic ketones **28** [51]. After several further steps, polycondensed heterocycles **29** containing a pyridazinone moiety were obtained (Scheme 31) [51].

A comparable sequence starting from 2,5-dimethylthiophene (Scheme 32) [52] utilised ethyl glutaryl chloride, hydrolysis of the first product giving 5-(2,5-dimethylthien-3-yl)valeric acid which in turn was converted into cyclohepta[*c*]thiophene **30** by cyclisation using polyphosphoric acid. The bicyclic ketone was used to make a series of 1*H*-pyrazolo[3,4-*c*]cyclophepta[1,2-*c*]thiophenes, being a unique structural class of dopamine D4-selective ligands (Scheme 32) [52].

3-(Thien-2-yl)succinic anhydride was converted into 4-oxo-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-6-carboxylic acid **31** under Friedel–Crafts conditions (Scheme 33) [53].



Scheme 34 Synthesis of a polycondensed indacenodithiophene dione **32** [54]



Method A: P_2O_5, toluene (yield 10%)
Method B: 1) PCl_5, benzene, 2) $SnCl_4$ (yield: 7%)

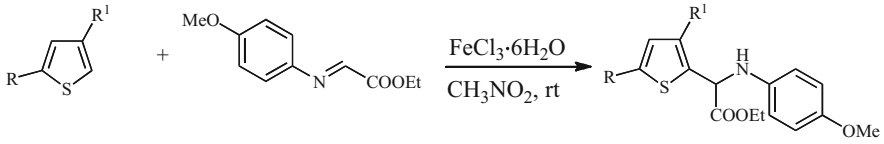
Scheme 35 Synthesis of a pyrrolo[2,1-*b*]thieno[3,2-*f*][1, 3]thiazepine via an intramolecular FC reaction [55]

Polycondensed **32** was the intermediate for the synthesis of indacenodithiophene semiconducting polymers, and it was obtained by double Friedel–Crafts intramolecular cyclisation of 2,5-di(thien-2-yl)terephthalic acid dichloride (Scheme 34) [54].

4,5-Dihydropyrrolo[2,1-*b*]thieno[3,2-*f*][1,3]thiazepin-4-one **34** as an intermediate for the synthesis of 4-(4-methylpiperazino)pyrrolo[2,1-*b*]thieno[3,2-*f*][1, 3]thiazepine **35** – a potential antipsychotic agent – was obtained from 2-[2-(thien-2-ylsulfanyl)-1*H*-1-pyrrolyl]acetic acid **33** by cyclisation onto the β-position of the thiophene ring using either exposure of the acid to phosphorus pentoxide (method A) or (method B) conversion to acid chloride followed by the addition of tin (IV) chloride (Scheme 35) [55].

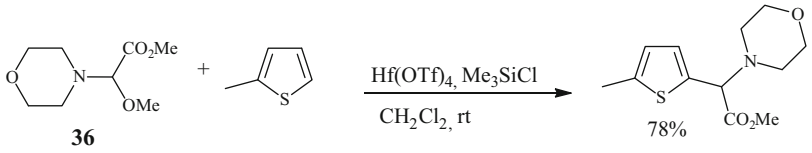
2.2.4 Synthesis of Precursors of Thiophene-Containing Amino Acids (See Also Sect. 2.7 the Mannich Reaction)

α-Arylglycine derivatives can serve as the building blocks for the synthesis of biologically active compounds. Their synthesis by Friedel–Crafts-type reactions of electron-rich aromatics with glycine cation equivalents is well established, presenting a simple access to α-aromatic amino acid derivatives. Several examples of the synthesis of thien-2-yl glycines are summarised in Scheme 36 [56].

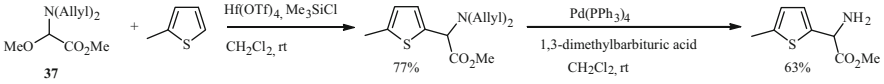


R, R^1 = H; R = H, R^1 = Me, Et, Ph, benzyl, 2,4-dichlorobenzyl, 4-methoxybenzyl, 4-(2-phenyl)propyl; R = H, R^1 = Me, $C_{10}H_{21}$, OMe, OEt

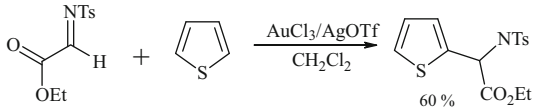
Scheme 36 FC alkylation of substituted thiophenes with a glyoxylate imine [56]



Scheme 37 Aminomethylation of 2-methylthiophene with an *N,O*-acetal [57]



Scheme 38 Reaction of thiophene with an *N,N*-diallylamino-*N,O*-acetal [57]

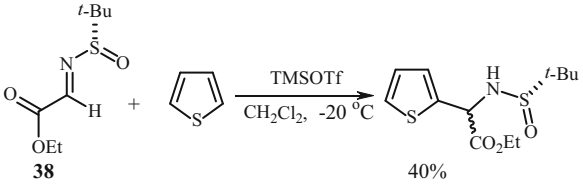


Scheme 39 Reaction of thiophene with ethyl glyoxylate *N*-tosylimine [58]

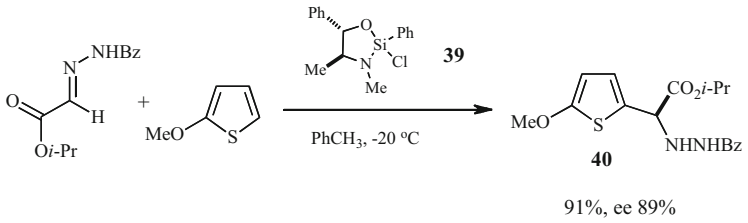
Various α-amino acids were obtained by the FC alkylation of glyoxylate imines with substituted thiophenes in the presence of $FeCl_3 \cdot 6H_2O$ in a very simple manner [56]. Yields and reaction time depend on the substituents on the thiophene ring (10–95%). Thiophene itself reacts with difficulty (120 h) and the yield did not exceed 10%. 3-Bromothiophene did not react even after 144 hours (Scheme 36) [56].

The aminomethylation of 2-methylthiophene with methyl 2-methoxy-2-morpholinoacetate (**36**) as glycine cation equivalent, with $Hf(OTf)_4/Me_3SiCl$ as catalyst, is presented in Scheme 37 [57].

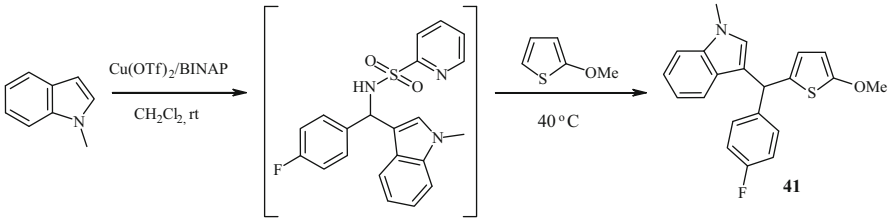
Another acetal – methyl 2-(diallylamino)-2-methoxyacetate **37** – gave a comparable yield in aminomethylation of 2-methylthiophene (Scheme 38) [57]. The advantage of the allyl-protecting groups is that the amino group of the final product could be easily deprotected by applying 5% $Pd(PPh_3)_4$ and six equivalents of 1,3-dimethylbarbituric acid in CH_2Cl_2 at room temperature.



Scheme 40 Reaction of thiophene with an optically active *N*-sulfinylimino glyoxylate ester [59]



Scheme 41 Reaction of 2-methoxythiophene with benzoylhydrazone of *i*-propyl glyoxylate in the presence of chiral cyclic silane [60]



Scheme 42 The synthesis of unsymmetrical triarylmethanes, containing a thiophene ring [61]

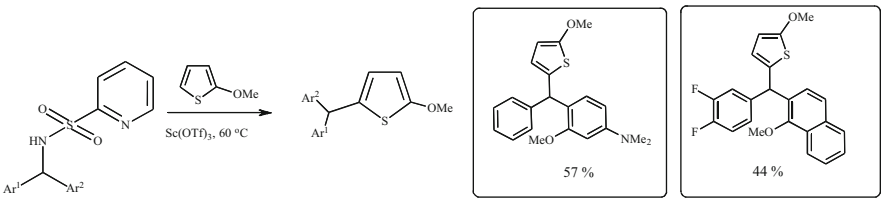
Yet another imino Friedel–Crafts reaction was catalysed by a gold/silver system using ethyl glyoxylate *N*-tosylimine, and this was successful with thiophene itself (Scheme 39) [58].

An asymmetric variant utilised optically active *N*-sulfinylimino ester (**38**) and gave a mixture of two epimers in a ratio of 1:1.5 in the presence of TMSOTf as Lewis acid in an overall yield of 40% (Scheme 40) [59].

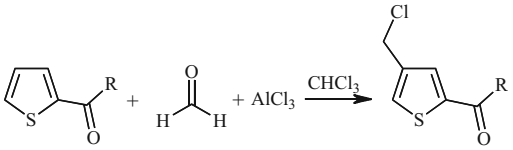
Application of a chiral Lewis acid, cyclic silane **39**, was more successful: the benzoylhydrazone of *i*-propyl glyoxylate, in reaction with 2-methoxythiophene, gave desired product **40** in 91% yield and 89% *ee* (Scheme 41) [60].

2.2.5 Synthesis of Triarylmethanes

The synthesis of unsymmetrical triarylmethanes is not trivial. The application of the aza Friedel–Crafts reaction to their synthesis was elaborated [61]. Thus,



Scheme 43 Synthesis of two unsymmetrical triarylmethanes containing a thiophene ring [61]



R = H (62.5%); R = Me (62%); R = Et (39%)

Scheme 44 Synthesis of 4-chloromethyl derivatives of 2-acyl thiophenes [62]

triarylmethanes containing a thiophene ring, e.g. **41**, were obtained by two consecutive Friedel–Crafts reactions in the presence of $Cu(OTf)_2$-BINAP as catalyst. In the first step, Friedel–Crafts addition of the aryl nucleophile to the sulfonyl imine occurs, followed by Friedel–Crafts substitution (Scheme 42) [61].

When the starting arene was other than *N*-methylindole, isolation of the addition product was necessary for a subsequent successful substitution reaction using Sc $(OTf)_3$ (Scheme 43) [61].

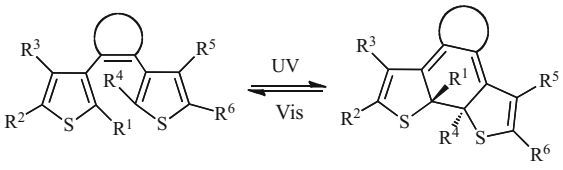
2.2.6 Thiophene Chloromethylation

2-Acetylthiophene and 2-formylthiophene underwent chloromethylation at C-4 in reaction with paraformaldehyde in the presence of $AlCl_3$ (Scheme 44) [62]; the $AlCl_3$ forms a complex with the carbonyl compound, catalyses the process and serves as the source of chlorine. This transformation is applicable only to compounds that contain an electron-withdrawing group and are stable to $AlCl_3$ (Scheme 44).

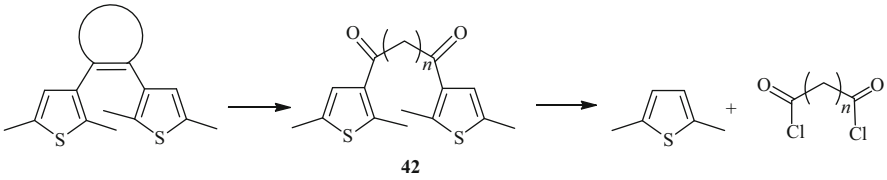
2.2.7 Synthesis of Photochromic 1,2-di(thien-3-yl)ethenes (DTEs)

1,2-Di(thien-3-yl)ethenes are promising compounds for optical switching processes. They undergo ring closure on irradiation with ultraviolet or visible light. The alkyl groups R^1 and R^4 are essential for this property (Scheme 45) [63].

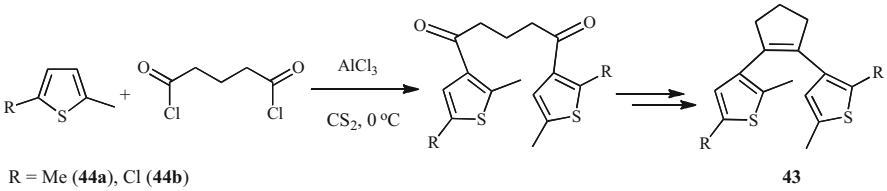
Many compounds with photo-switchable properties have been synthesised and their physical properties investigated (see, e.g. [64, 65]). We discuss here only those aspects of the synthetic procedures involving thiophene substitution reactions.



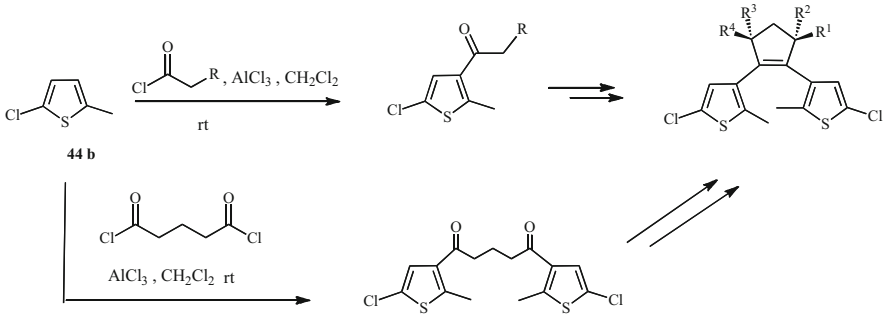
Scheme 45 Reversible ring closure of 1,2-di(thien-3-yl)ethenes [63]



Scheme 46 Retrosynthetic analysis for synthesis of 1,2-di(thien-3-yl)ethenes [63]



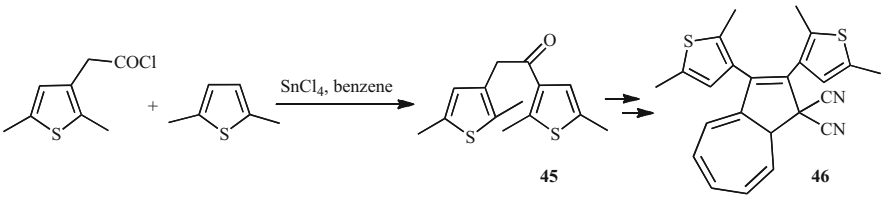
Scheme 47 The synthesis of 1,2-di(thien-3-yl)cyclopentene **43** [63]



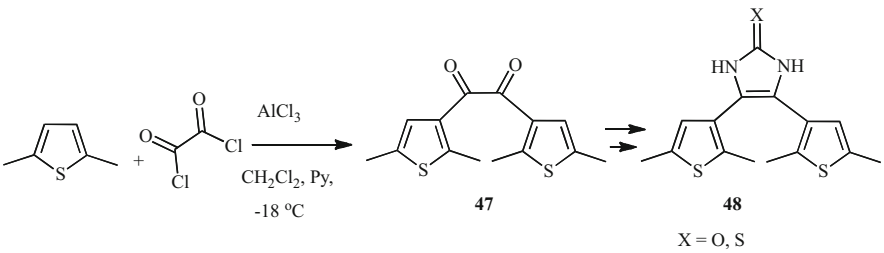
Scheme 48 The synthesis of variously substituted 1,2-di(thien-3-yl)ethenes [66]

Dithien-3-yl diketones **42** (Scheme 46) are the key intermediates for the synthesis of 1,2-di(thien-3-yl)ethenes through McMurry reactions. Friedel–Crafts acylation of thiophenes with a dicarboxylic dichloride is a simple and direct route to the di(thien-3-yl) diketones **42** [63].

For the synthesis of 1,2-di(thien-3-yl)cyclopentene **43** (Scheme 47), acylation of 2,5-dimethylthiophene (**44a**) by glutaryl dichloride was accomplished in CS_2 using $AlCl_3$ as Lewis acid catalyst giving the diketone in 40% yield (Scheme 47) [63].



Scheme 49 Synthesis of 2,3-bis(2,5-dimethylthien-3-yl)azulene-1,1(8a*H*)-dicarbonitrile **46** [67]



Scheme 50 Synthesis of dithienylimidazolones/thiones **48** [64, 68]

Aiming at better 1,2-di(thien-3-yl)ethenes, compounds with different substituents on the cyclopentene ring were targeted. Thus, the idea of acylating 2-bromo-5-methylthiophene (**44**, R=Br) emerged. Unfortunately, the desired product was not obtained, and instead, the bromine substituent migrated to C-3, and acylation took place at C-2. However, 2-chloro-5-methylthiophene (**44**, R=Cl) was smoothly converted into the desired diketone giving a 98% yield under Friedel–Crafts conditions (Scheme 48) [63, 66].

Friedel–Crafts acylation of 2,5-dimethylthiophene with 2,5-dimethylthiophene-3-carboxylic acid chloride in the presence of $SnCl_4$ gave ketone **45** in 85% yield, which was then progressed to **46** (Scheme 49) [67].

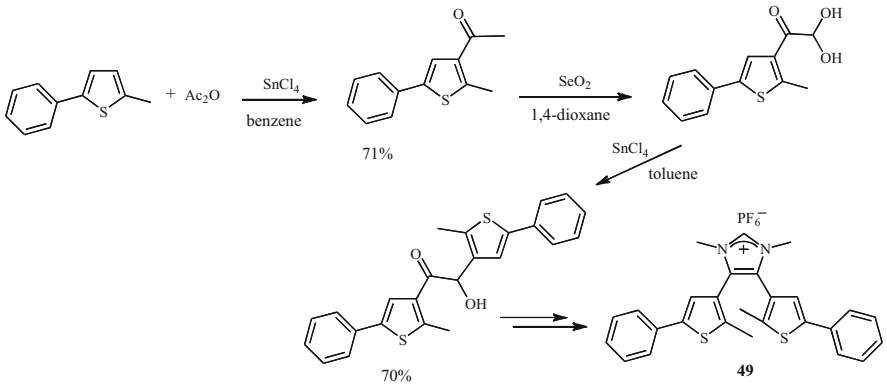
On the way to 1,2-di(thien-3-yl)imidazolones **48,** 2,5-dimethylthiophene was acylated with oxalyl chloride, giving diketone **47** in 35% yield (Scheme 50) [64, 68].

The *N*-heterocyclic carbene precursor **49** is a photo-switchable catalyst for amidation reactions. The synthesis of this catalyst begins with two Friedel–Crafts reactions: firstly, 2-methyl-5-phenylthiophene was 3-acetylated with acetic anhydride using $SnCl_4$, then product ketone oxidised to a glyoxal by SeO_2. The glyoxal itself was used as acylating agent to react with 2-methyl-5-phenylthiophene with the assistance of $SnCl_4$. After several further steps, the salt **49** was obtained (Scheme 51) [69].

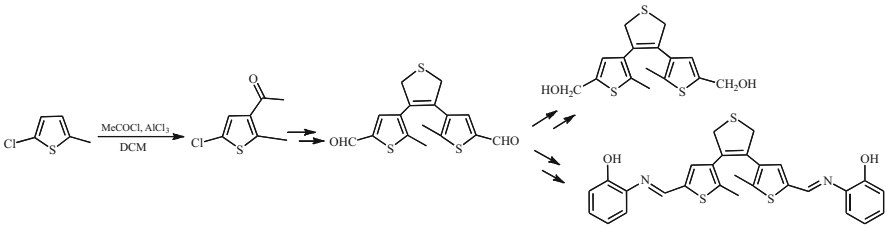
2,5-Dihydrothiophene as a bridging unit was also investigated instead of cyclopentene [70]. In this case, acetylation of 2-chloro-5-methylthiophene in the presence of $AlCl_3$ gave C-4-acylated product in 78% yield (Scheme 52) [70].

A di(thien-3-yl)ethene with a 2,5-dihydropyrrole as bridging unit (Fig. 2) was assembled in the same way [71].

A similar behaviour was demonstrated by 5-(coumarin-3-yl)-4-(thien-3-yl)thiazoles [72] obtained via Friedel–Crafts acylation of 2,5-dimethylthiophene with a



Scheme 51 Synthesis of a *N*-heterocyclic carbene precursor **49** [69]



Scheme 52 Synthesis of a 1,2-di(thien-3-yl)ethene with a 2,5-dihydrothiophene bridge [70]

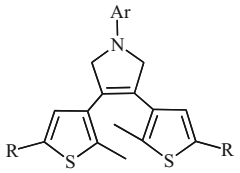
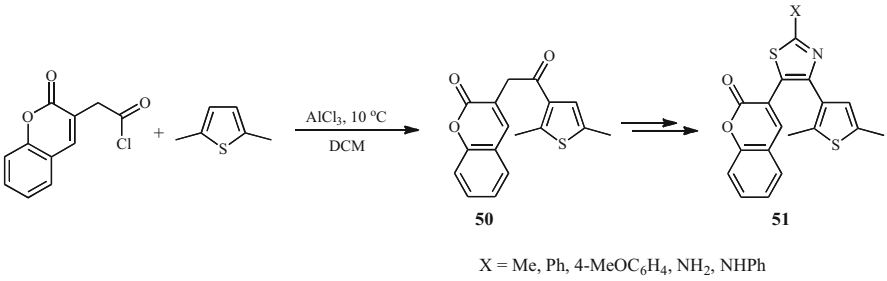
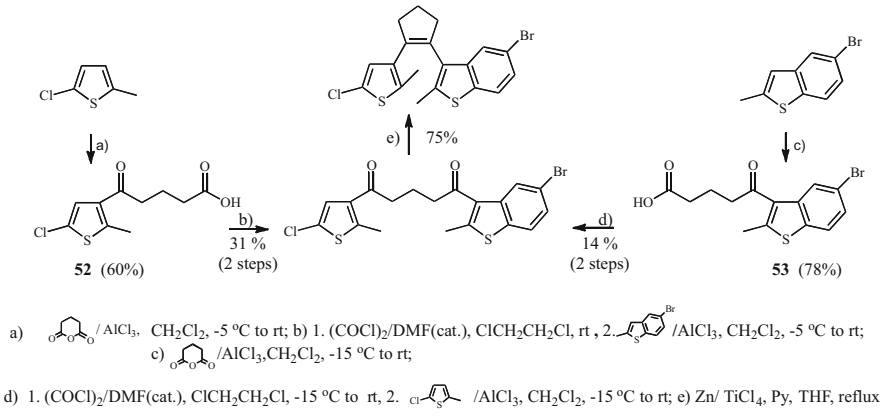


Fig. 2 A di(thien-3-yl)ethene with a 2,5-dihydropyrrole bridge [71]



Scheme 53 Synthesis of a 5-(coumarin-3-yl)-4-(thien-3-yl)thiazole **51** [72]



Scheme 54 Synthesis of nonsymmetric thien-3-yl/benzo[*b*]thien-3-yl cyclopentenes [73]

coumarin-3-ylacetyl chloride, producing ethanone **50** in 71% yield which was taken on to produce a thiazole **51** (Scheme 53) [72].

The synthesis of nonsymmetric cyclopentenes, containing both thien-3-yl and benzo[*b*]thien-3-yl units, was aimed at more sophisticated photochromic molecules (Scheme 54) [73]. By the application of glutaric anhydride with 2-chloro-5-methylthiophene and 5-bromo-2-methylbenzo[*b*]thiophene in the presence of $AlCl_3$, keto acids **52** and **53** were obtained. Conversion of the keto acids into acid anhydrides then Friedel–Crafts acylations produced the desired diketone albeit in only 31% yield (over 2 steps) in the first case and in 14% yield (over two steps) in the second case (Scheme 54) [73].

2.3 Thiophene Halogenation

Halogenated thiophenes are undoubtedly the most often used thiophene derivatives. They can be further converted into various substituted thiophenes through metal–halogen exchange reactions, electrophilic or nucleophilic substitutions or any of several types of palladium(0)-catalysed chemistry [21, 22, 74–76].

Soon after thiophene was discovered by Victor Meyer, reports from his group gave the first examples of halogenated thiophenes – dibromothiophene (now known to be 2,5-dibromothiophene) and monoiodothiophene [77]. Monoiodothiophene (now known to be 2-iodothiophene) was synthesised from a mixture with benzene isolated from coal tar containing 50–60% of thiophene ('raw thiophene'). Here the higher reactivity of thiophene in comparison to benzene in halogenations was observed and used. Thus for benzene, iodination requires elevated temperatures, but thiophene was iodinated at room temperature. It was found that 2-iodothiophene can be synthesised either by the treatment with a mixture of iodine and iodic acid or

with a mixture of iodine and mercuric oxide [77]. The exact structure of thiophene was not known at that time, and a reaction equation was written as follows:

$$2C_4H_4S + 2I_2 + HgO = 2C_4H_3IS + HgI_2 + H_2O \quad (1)$$

Equation 1 Treatment of thiophene with iodine in the presence of mercuric oxide [77].

It was reported [77] that thiophene should not be left in the mixture with iodine without the presence of mercuric oxide on account of a resulting exothermic reaction which led to the formation of polymer and hydrogen sulfide.

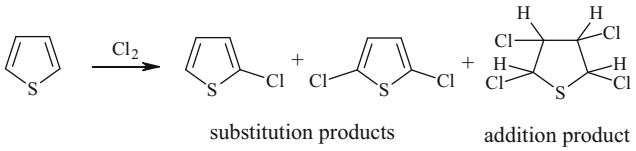
The application of monoiodothiophene for the synthesis of alkylthiophenes by Wurtz–Fittig reaction was later described, again by Meyer [77]; thus treatment of iodothiophene with alkyl bromides in dry ether in the presence of sodium led to the synthesis of 2-methylthiophene (already isolated from coal tar) and 2-ethyl-, 2-*n*-propyl and 2-*n*-butylthiophenes. The synthesis of diiodothiophene was also described in the same paper, albeit without any applications.

Dibromothiophene and also monobromothiophene were both obtained directly from the benzene fraction of coal tar by its reaction with bromine. It is significant that the preparation of bromo derivatives was very soon developed on a multigram scale at the Farbwerke Hoechst AG. From 1 kg of raw benzene fraction, 360 g of pure 2,5-dibromothiophene could be produced together with some monobromothiophene [78].

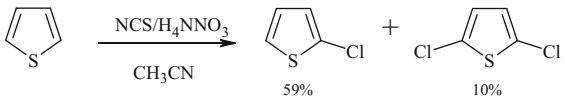
Dibromothiophene was further used as precursor for the synthesis of tetrachlorothiophene [79] via its reaction with chlorine. The mixture obtained by treatment of raw thiophene with chlorine contained both mono- and dichlorothiophenes which were separated by distillation [79].

The first example of alkylthiophene bromination was also demonstrated at that time. Methylthiophene which was obtained from coal tar as a mixture with toluene was reacted with bromine, and dibromo(methyl)thiophene separated from toluene. Its further bromination led to the synthesis of fully substituted tribromo(methyl) thiophene. 2-Iodo-5-methylthiophene was obtained by the same iodination procedure as iodothiophene. Deiodination with sodium allowed for the isolation of pure methylthiophene [80].

It is relevant that nowadays many differently substituted halogenated thiophenes are commercially available. Widely used chloro-, bromo- and iodo-substituted thiophenes can be easily obtained by direct methods [81]. Though halogenation of thiophene is well explored, nevertheless, methods addressing better regioselectivity for differently substituted thiophenes, acceleration of the process, making halogenations via more green chemical processes, have recently appeared. Moreover, the application of nontrivial techniques such as ultrasound irradiation [82] or reactions in microreactors [83] has been called upon to convert thiophene and substituted thiophenes cleanly and selectively into brominated thiophenes with good to excellent yields.



Scheme 55 Substitution and addition products from reaction of thiophene with chlorine [84]



Scheme 56 Use of NCS in the presence of ammonium nitrate for chlorination of thiophene [89]

When thiophene is treated with chlorine at an equimolar ratio, a mixture of 2-chlorothiophene and 2,5-dichlorothiophene, along with several addition products, is obtained [84]. For the successful isolation of both substitution products, it is necessary to eliminate addition products. This can be done by heating with solid sodium hydroxide or potassium hydroxide, prolonged pyrolysis or steam distillation of the reaction mixture from aqueous alkali or from a suspension of zinc or iron powder in water. As a result, the formation of mixtures containing mono-, di-, tri- and tetrachlorinated thiophenes is observed. The ratio of products is dependent on the reagents ratio, reaction temperature and dehydro-halogenation method (Scheme 55) [84].

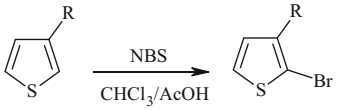
Investigations led to the conclusion that *N*-chlorosuccinimide (NCS) in acetic acid is the reagent of choice for the selective monochlorination of various thiophenes [85]. Other chlorinating agents such as sulfuryl chloride, hypochlorous acid [86], benzyltrimethylammonium tetrachloroiodate [87] or tin(IV) chloride in the presence of lead(IV) acetate [88] were shown to be useful reagents for thiophene chlorination.

Ammonium nitrate can be usefully added to NCS for selective aromatic chlorination reactions; thus, 2-chlorothiophene (59% yield) and 2,5-dichlorothiophene (10%) were obtained after treatment of thiophene with NCS/NH_4NO_3 in acetonitrile (Scheme 56) [89].

For the bromination of thiophene, bromine and *N*-bromosuccinimide (NBS) are the most useful reagents [90]. As in any electrophilic substitution of thiophene, halogenations take place preferentially at α-positions. 2-Substituted thiophenes are usually halogenated at C-5, and 3-substituted thiophenes are halogenated either at C-2 or at C-5 depending on the substituent.

N-Bromosuccinimide in a mixture of chloroform and acetic acid (1:1) was shown to brominate various 3-substituted thiophenes exclusively at C-2 [91, 92] in yields of 60–97% in 5–30 min (Scheme 57) [93].

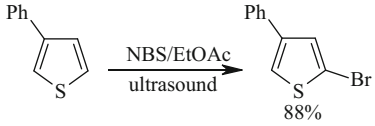
In contrast, the bromination of 3-phenylthiophene under ultrasound irradiation gave exclusively 2-bromo-4-phenylthiophene even with a twofold excess of NBS (Scheme 58) [82]:



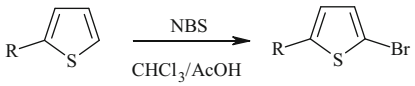
R = Me (84%) [91], (82-98%) [93], Ph (94%) [91], Br (80%) [91],

PhS (91%) [91], *n*-Hex (92%) [93], *n*-octyl (89%) [93], *n*-BuS (60%) [92]

Scheme 57 Use of NBS for bromination of 3-substituted thiophenes [91–93]

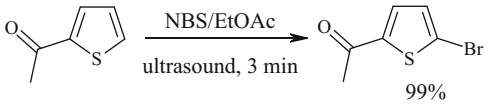


Scheme 58 Use of ultrasound irradiation for bromination of 3-phenylthiophene [82]

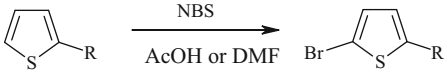


R = Me (99%), Ph (95%), PhS (90%), *t*-Bu (95%)

Scheme 59 C-5 Bromination of 2-substituted thiophenes [91]



Scheme 60 Use of ultrasound irradiation for the bromination of 2-acetylthiophene [82]



R = C_6H_{13} (82%) [94]

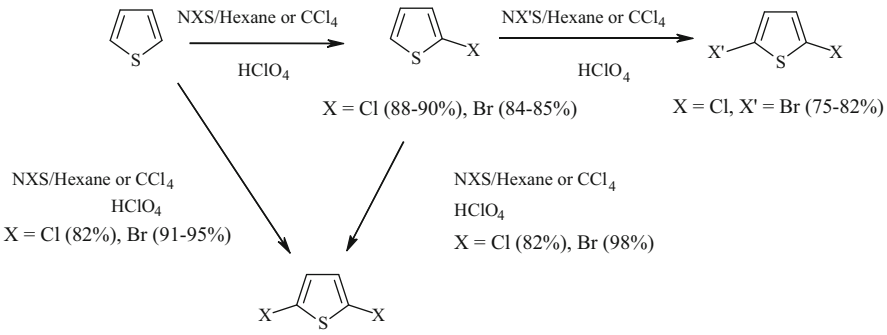
R = $C_{12}H_{25}$ (81-87%) [94, 95]

Scheme 61 Bromination of 2-long-chain-alkyl thiophenes with NBS [94, 95]

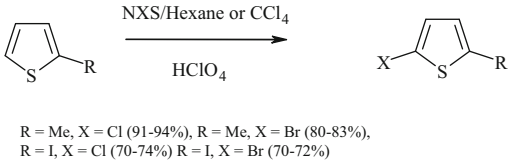
The treatment of various 2-substituted thiophenes with NBS in acetic acid/chloroform led to 5-brominated thiophenes (Scheme 59) [91].

Attempted bromination of 2-acetylthiophene using NBS in $CHCl_3$/AcOH did not proceed [91]. However, when the reaction was performed with ultrasound irradiation, 2-acetyl-5-bromothiophene was isolated in 99% yield (Scheme 60) [82].

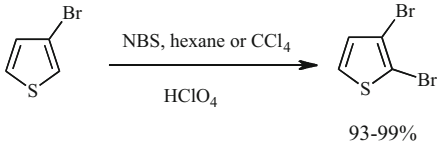
5-Bromination of thiophenes possessing long alkyl chains at C-2 was achieved with NBS, in either acetic acid or DMF (Scheme 61) [94, 95].



Scheme 62 Use of a biphasic system for thiophene halogenations [96]



Scheme 63 Halogenation of 2-substituted thiophenes under biphasic conditions [96]

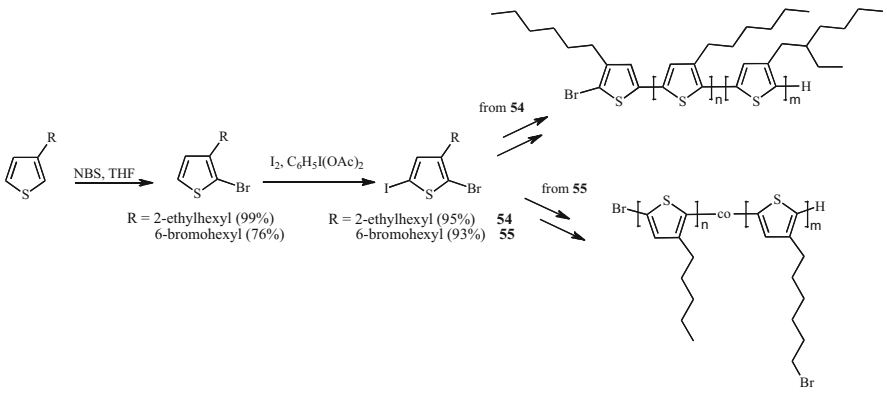


Scheme 64 Bromination of 3-bromothiophene [96]

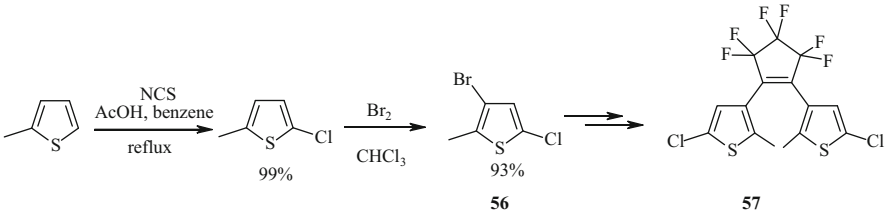
Usually halogenation with NXS (X=Cl, Br) needs polar solvents or catalytic amounts of Lewis acids. It was shown that perchloric acid can catalyse halogenation; moreover, a polar solvent was not needed. NBS or NCS suspended in hexane or in carbon tetrachloride forms a biphasic system. The perchloric acid serves as a phase-transfer agent to transport halonium species formed in situ into the bulk organic phase [96]. Application of one equivalent of NXS cleanly gave monohalogenated thiophenes; if two equivalents of NXS were used, 2,5-dihalogenated compounds resulted (Scheme 62).

Thiophenes substituted at C-2 were selectively halogenated at C-5 under biphasic conditions, though in the case of 2-methylthiophene, 10% of isomeric 2-methyl-3-chlorothiophene was also identified [96]. In this way, thiophenes with mixed halogens can be obtained. Chlorination and bromination of 2-iodothiophene gave 2-chloro-5-iodothiophene and 2-bromo-5-iodothiophene, respectively (Scheme 63).

The bromination of 3-bromothiophene under biphasic conditions gave selectively 2,3-dibromothiophene (Scheme 64) [96].



Scheme 65 Synthesis of regioregular poly(3-alkylthiophene)-based copolymers [97, 98]

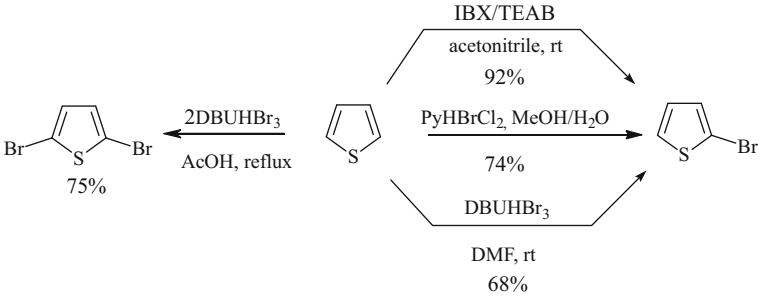


Scheme 66 Synthesis of a photochromic 1,2-di(thien-3-yl)perfluorocyclopentene [99, 100]

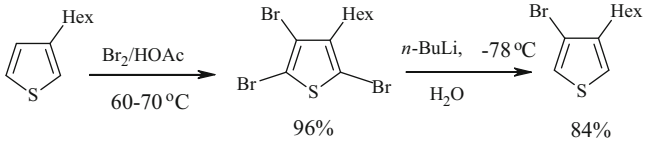
The synthesis of mixed halogenated compounds is of special interest because it allows the use of the differential reactivity of C–Cl, C–Br and C–I bonds for further regioselective modifications. C–I or C–Br bonds are more reactive than C–Cl. The syntheses of 2-bromo-3-(2-ethylhexyl)-5-iodothiophene **54** (R=2-ethylhexyl) [97] and 2-bromo-5-iodo-3-(6-bromohexyl)thiophene **55** (R=6-bromohexyl) [98] are nice recent examples of selective monobromination followed by selective monoiodination. The mixed halogenated thiophenes were further used for the synthesis of regioregular poly(3-alkylthiophene)-based copolymers by Grignard metathesis (GRIM) polymerisation via a quasi-living chain growth mechanism (Scheme 65) [97, 98].

3-Bromo-5-chloro-2-methylthiophene (**56**) was an intermediate for the synthesis of the photochromic diaryl perfluorocyclopentene **57** (Scheme 66) [99, 100]. 2-Methyl-thiophene was selectively chlorinated by NCS at C-5, followed by bromination *ortho* to the alkyl group. Subsequent selective reaction at the C–Br bond finally gave **57**, which in turn could be further modified at the thiophene ring by substitution of chlorine (Scheme 66) [99, 100].

Other brominations of thiophene have involved a hypervalent iodine reagent – *o*-iodoxybenzoic acid (IBX) with tetraethylammonium bromide (TEAB) – reaction proceeding at room temperature in 92% yield (Scheme 67) [101].



Scheme 67 Use of nonconventional reagents for thiophene brominations [101–103]



Scheme 68 Synthesis of 3-bromo-4-hexylthiophene [106]

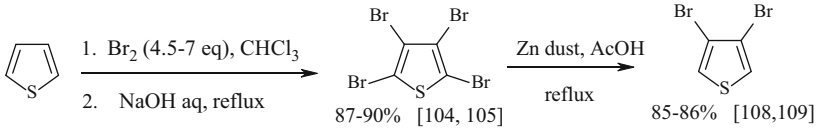
The use of pyridinium dichlorobromate ($PyHBrCl_2$) gives 2-bromothiophene in 74% yield (Scheme 67) [102]. The non-nucleophilic base, 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU), in combination with HBr and bromine gives a stable complex $DBUHBr_3$ that is able to brominate aromatic compounds; thus, 2-bromo- and 2,5-dibromothiophenes were obtained in good yields (Scheme 67) [103].

Direct bromination by bromine in acetic acid or in chloroform allows the synthesis of 2-bromo-, 2,5-dibromo-, 2,3,5-tribromo- and 2,3,4,5-tetrabromothiophenes [104, 105]. Microwave-assisted mono-, di-, tri- and tetrabrominations of thiophene have been described [83]. An example of 2,4,5-tribromination of 3-hexylthiophene using bromine in acetic acid is shown in Scheme 68 [106].

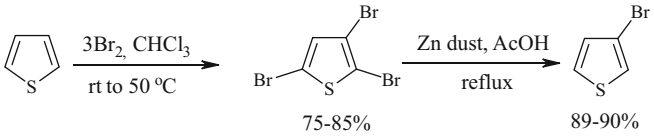
β-Halogenated thiophenes unsubstituted at α-positions are not directly accessible by substitution. However, exhaustive bromination, with regioselective dehalogenation at α-positions is often used as a means to prepare β-halothiophenes. In the example in Scheme 68, the 3,4-disubstituted thiophene was obtained via reaction with *n*-BuLi then water [106].

The debromination of tetrabromothiophene at α-positions with Grignard reagents was performed as early as 1934 [107]; later, Zn dust in acetic acid was shown to be the method of choice to prepare 3,4-dibromothiophene from 2,3,4,5-tetrabromothiophene [108] (Scheme 69), and this is still the method usually applied (see for example: [109]).

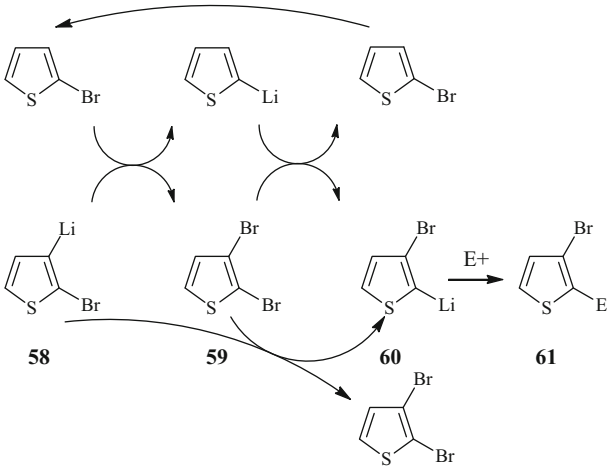
Similarly, a clean synthesis of 3-bromothiophene from 2,3,5-tribromothiophene can be achieved (Scheme 70) [108, 110]. The reductive removal of one or more α-halogens happens because the intermediate 'anion' (α-metallated species) is better stabilised and therefore preferentially formed [111].



Scheme 69 Exhaustive bromination of thiophene [104, 105] followed by α,α′-debromination [108]



Scheme 70 Synthesis of 3-bromothiophene [110]

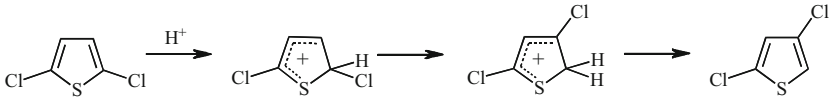


Scheme 71 The mechanism of base-catalysed halogen dance (BCHD) reaction [112]

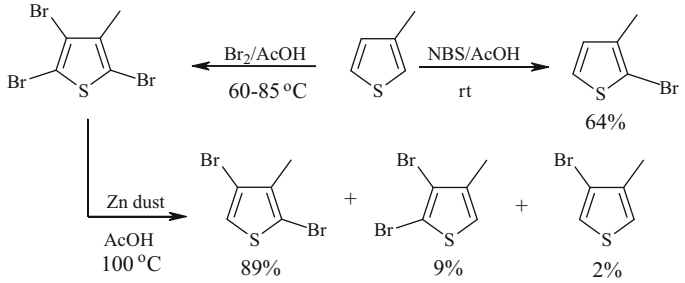
The base-catalysed halogen dance reaction (BCHD) can also be very useful in this case (Scheme 71) [112].

Briefly, initial lithiation by LDA takes place at C-3 of 2-bromothiophene (**58**), and the lithiated species can then react with the original compound by metal–halogen exchange. The so-formed lithiated and unlithiated intermediates **60** and **59** can further react with each other. The most stable metallated intermediate **60** will predominate, and after its treatment with an electrophile (or a proton from water), the 3-bromo-2-substituted product **61** will be formed (Scheme 71) [112].

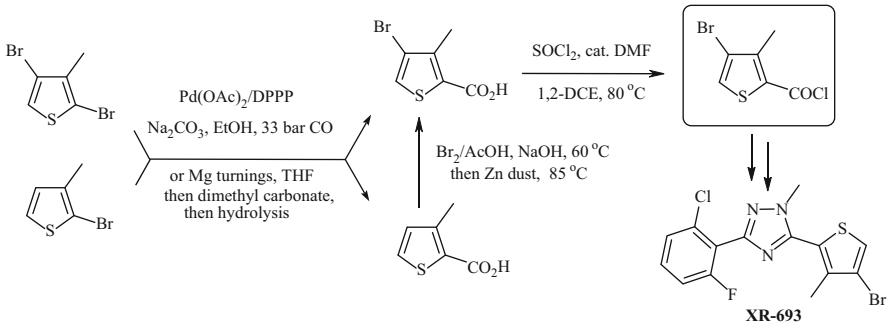
Another method for halogen atom position change on a thiophene [25] was demonstrated for 2,5-dichlorothiophene. Under acidic conditions, this was converted into the isomeric 2,4-dichlorothiophene. Formation of a 2,5-dichloro-2*H*-thiophenium ion then successive 1,2-migrations of chlorine and a proton lead to



Scheme 72 Conversion of 2,5-dichlorothiophene into 2,4-dichlorothiophene [25]



Scheme 73 Synthesis of 2-bromo-3-methylthiophene and 2,4-dibromo-3-methylthiophene from 3-methylthiophene [113]

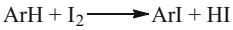


Scheme 74 Two syntheses of 4-bromo-3-methylthiophene-2-carbonyl chloride [113]

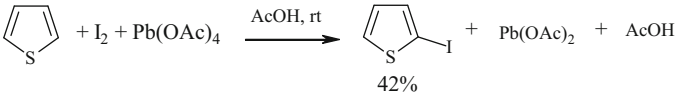
the 2,4-dichloro-2*H*-thiophenium ion, and neutralisation finally results in 2,4-dichlorothiophene (Scheme 72) [25].

4-Bromo-3-methylthiophene-2-carbonyl chloride was required as an intermediate for the synthesis of an insecticide, 5-(4-bromo-3-methylthien-2-yl)-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-1,2,4-triazole (XR-693) [113]. 3-Methylthiophene was selected as a starting material: it could be selectively 2-brominated with NBS or exhaustively brominated by bromine to 2,3,5-tribromo-4-methylthiophene as shown in Scheme 73 [113].

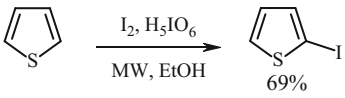
The polybrominated compound after treatment with Zn dust gave mainly 2,4-dibromo-3-methylthiophene, which was easily separated from the mixture (Scheme 73) [113]. The higher reactivity of C-2–Br in comparison to C-4–Br was utilised for carbonylation at C-2 (Scheme 74) [113].



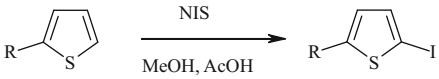
Scheme 75 Formation of aryl iodide along with by-product hydrogen iodide by direct arene iodination [114]



Scheme 76 Use of I_2 in the presence of $Pb(OAc)_4$ for iodination of thiophene [114]



Scheme 77 Use of I_2 in the presence of H_5IO_6 for iodination of thiophene [115]



R = Me (69%), Ph (68%)

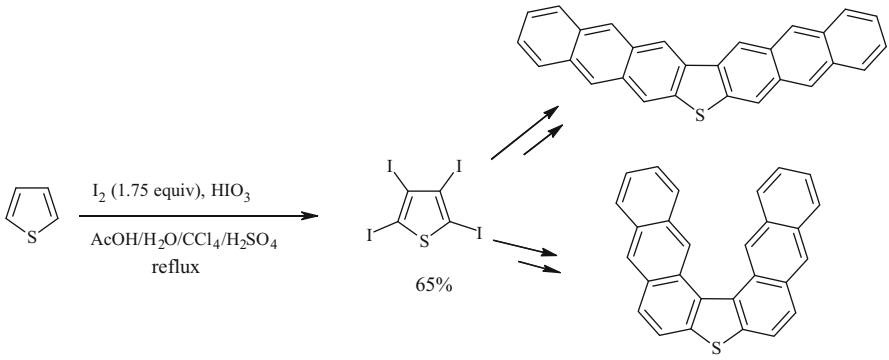
Scheme 78 Use of NIS in MeOH–AcOH for iodination of 2-substituted thiophenes [117, 118]

The serious drawback of electrophilic iodination of heterocycles with iodine is the formation of hydrogen iodide, which is both a strong reducing agent and a strong acid (Scheme 75) [114].

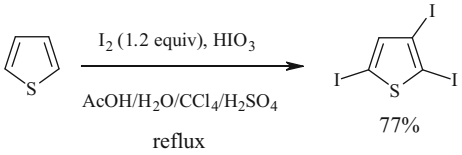
The destruction of thiophene by its treatment with iodine was noted already by Meyer in 1884 [77]. Application of HgO to capture HI has been known from Meyer's time and is still applied nowadays. Several other oxidants which can convert hydroiodic acid into iodine have been described. Lead(IV) acetate serves as useful oxidant to support iodination of thiophene with iodine (Scheme 76) [114]. The lead acetate was obtained in this case in situ from commercial red lead (minium), Pb_3O_4 [114].

Iodination of thiophene with iodine in the presence of orthoperiodic acid H_5IO_6 used as oxidant was performed either with conventional heating, giving 2-iodothiophene (60°C, 69%), or with microwave irradiation in only 5 min (Scheme 77) [115].

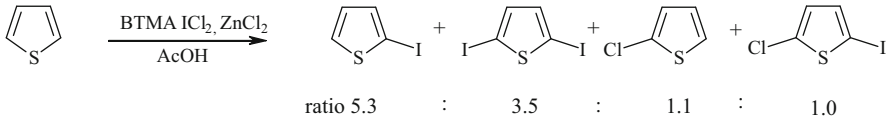
Thiophene was converted into 2-iodothiophene in 58% yield in only 10 min using iodine in the presence of silica-supported bismuth(III) nitrate pentahydrate under solvent-free conditions at room temperature [116]. *N*-Iodosuccinimide (NIS) in acetic acid and methanol is also an effective agent for iodination of thiophenes (Scheme 78) [117, 118].



Scheme 79 Synthesis of 2,3,4,5-tetraiodothiophene [121]



Scheme 80 Synthesis of 2,3,5-triiodothiophene [122]



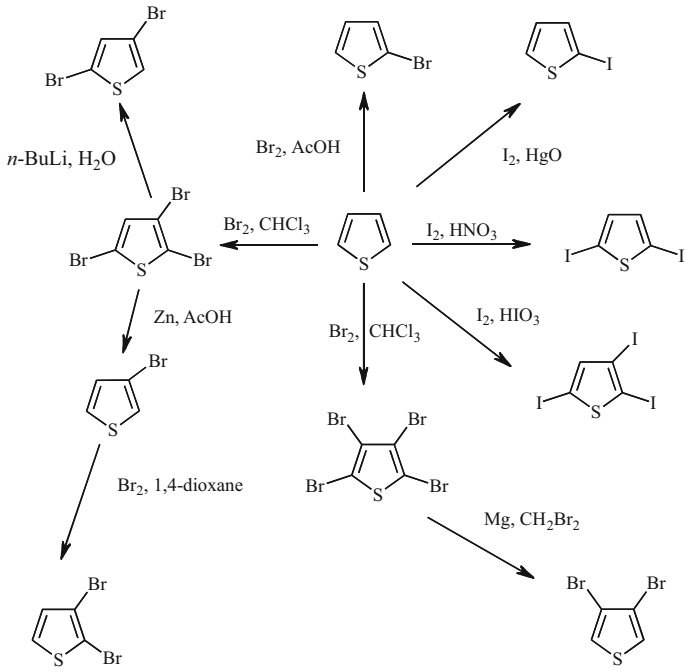
Scheme 81 Use of benzyltrimethylammonium dichloroiodate for chlorination/iodination of thiophene [123]

Diiodination with iodine proceeds effectively in the presence of nitric acid, which takes the role of an oxidant [119]. Addition of nitric acid also helped the effective mono-5-iodination of 2-substituted thiophenes. Another useful oxidant for thiophene diiodination is hydrogen peroxide [120].

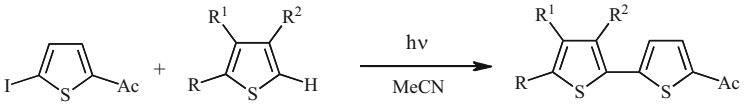
2,3,4,5-Tetraiodothiophene was obtained from thiophene by applying iodine together with iodic acid in a mixture of acetic acid, water, carbon tetrachloride and sulfuric acid in ratio 5:2:1:0.1 (Scheme 79) [121]. The yellow solid was isolated in 65% yield and was used for the synthesis of sulfur-containing acenes [121].

The same iodination approach was used to obtain also 2,3,5-triiodothiophene (Scheme 80) [122].

Benzyltrimethylammonium dichloroiodate (BTMA ICl_2) in the presence of zinc chloride in acetic acid was shown to form mixtures of both chlorinated and iodinated thiophenes (Scheme 81) [123].



Scheme 82 Practical approaches to the synthesis of various bromo- and iodo-substituted thiophenes [124]



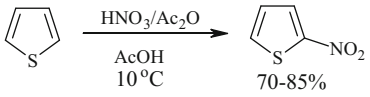
R, R^1, R^2=H, or Br, or I

Scheme 83 Photochemical arylation 2-acetyl-5-iodothiophene with mono- and polyhalogenated thiophenes [124]

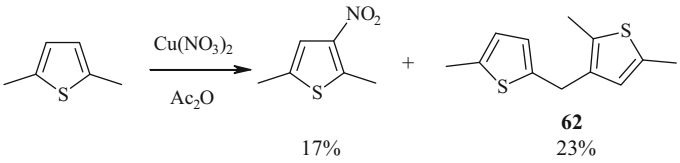
As a conclusion to this thiophene halogenation section, we cite Scheme 82 demonstrating practical syntheses of a whole array of bromo- and iodothiophenes [124]. These compounds were applied for photochemical coupling with 2-acetyl-5-iodothiophene [124] (Scheme 83).

2.4 Nitration of Thiophene

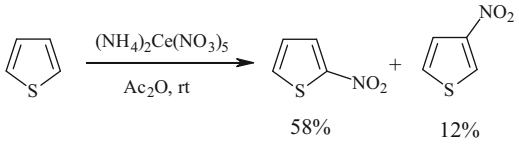
Nitro derivatives of thiophene are of considerable interest: some are biologically active; others are useful synthetic intermediates for chemical modifications and for the synthesis of biologically active compounds.



Scheme 84 Use of HNO_3 with Ac_2O in AcOH for nitration of thiophene [127]



Scheme 85 Use of $Cu(NO_3)_2$ in Ac_2O for nitration of 2,5-dimethylthiophene [132, 133]



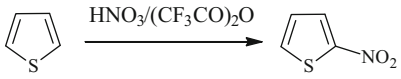
Scheme 86 Use of CAN in Ac_2O for nitration of thiophene [135]

Early attempts to nitrate thiophene and to reduce a nitro-product, in analogy with benzene chemistry, were unsuccessful until the conditions for nitration of thiophene were found. Eventually, rather special conditions were developed: thiophene vapour mixed with air was passed for several hours through fuming nitric acid. After work-up, mononitrothiophene and a dinitrothiophene were isolated [125].

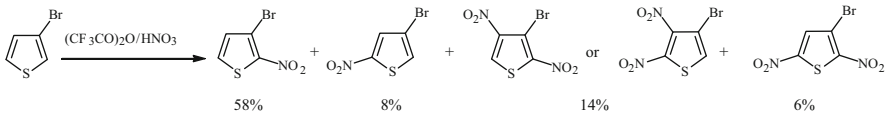
Later it became clear that the failure in thiophene nitration with nitric acid is due to the presence of nitrous acid that led to the formation of nitrosothiophene, which is prone to decomposition [126]. A mixture of nitric acid with acetic anhydride in glacial acetic acid can mononitrate thiophene very effectively (Scheme 84) [127].

Other useful thiophene-nitrating reagents include copper(II) nitrate in acetic anhydride and aluminium nitrate in acetic anhydride [128, 129]. Nitration of substituted thiophenes is subject to the usual mesomeric and inductive effects of the substituents [130]. Nitration can also take place at already substituted positions, replacing bromine or iodine (see, e.g. [131]). The nitration of 2,5-dimethylthiophene using copper(II) nitrate in acetic anhydride led to 2,5-dimethyl-3-nitrothiophene along with a product containing two thiophene rings – 3-(5-methylthien-2-ylmethyl)-2,5-dimethylthiophene **62** (Scheme 85) [132, 133]. Apparently, the cation $ThCH_2^+$ was formed under the reaction conditions which reacted as electrophile towards a second molecule of starting thiophene.

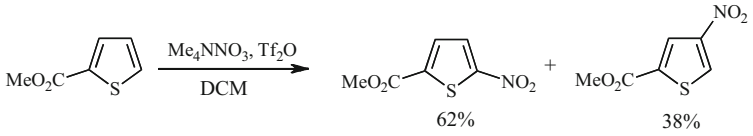
Cerium(III) ammonium nitrate (CAN) in acetic anhydride is also an efficient nitrating reagent for aromatic compounds [135]. The nitration of thiophene by CAN gave a mixture of 2-nitro- (58%) and 3-nitrothiophene (12%) (Scheme 86) [134].



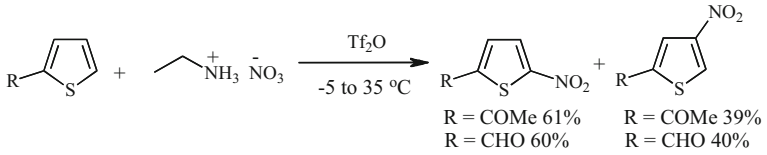
Scheme 87 Use of HNO_3 in $(CF_3CO)_2O$ for nitration of thiophene [136]



Scheme 88 Nitration of 3-bromothiophene [136]



Scheme 89 Use of Me_4NNO_3 in Tf_2O for nitration of methyl thiophene-2-carboxylate [137]



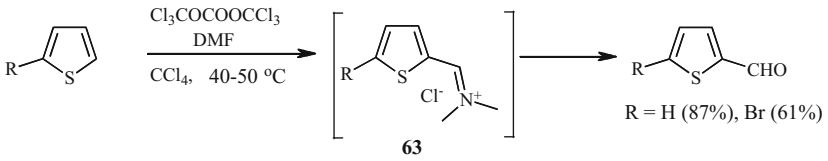
Scheme 90 Use of ionic liquid $EtNH_3^+NO_2^-$ promoted by Tf_2O for nitration of 2-acyl thiophenes [138]

A mixture of nitric acid and trifluoroacetic anhydride nitrated thiophene in 78% yield (Scheme 87) [136].

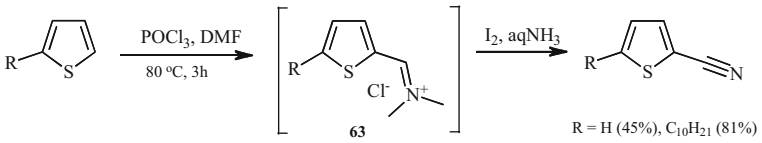
3-Bromothiophene under these conditions gave a mixture with the main product being 2-nitro-3-bromothiophene (58%) together with 2-nitro-4-bromothiophene (8%), and two products of dinitration (Scheme 88) [136].

Nitronium triflate ($TfONO_2$) which is readily generated in dichloromethane from tetramethylammonium nitrate ($Me_4N^+NO_3^-$) and triflic anhydride, can be used as a nitrating agent. Its application for the nitration of methyl thiophene-2-carboxylate afforded 5-nitro- and 4-nitro-substituted isomeric products in 91% combined yield (Scheme 89) [137].

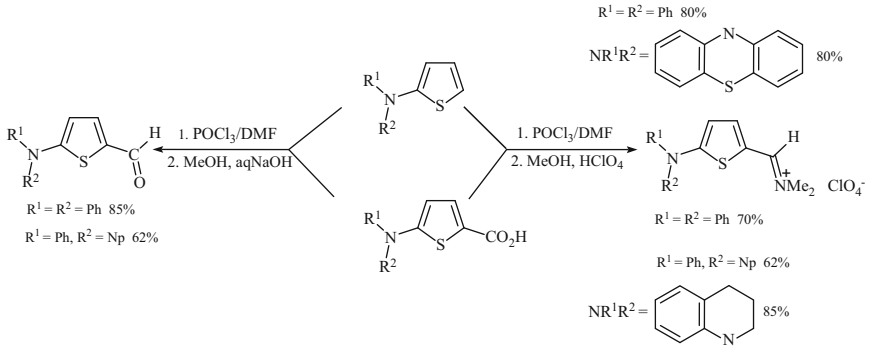
Nitration of 2-acetylthiophene and thiophene-2-carbaldehyde in ionic liquid $EtNH_3^+NO_2^-$ promoted by Tf_2O gave very high yields of mixtures containing 5-nitrated and 4-nitrated thiophenes in a ratio of 3:2 (Scheme 90) [138]. Formed in situ, nitronium triflate ($TfONO_2$) provides efficient nitration under mild conditions, and, moreover, the ionic liquid can be recovered and reused.



Scheme 91 Use of triphosgene in DMF for formylation of thiophene and 2-bromothiophene [142]



Scheme 92 Synthesis of thiophene nitriles via Vilsmeier–Haack intermediates [143]



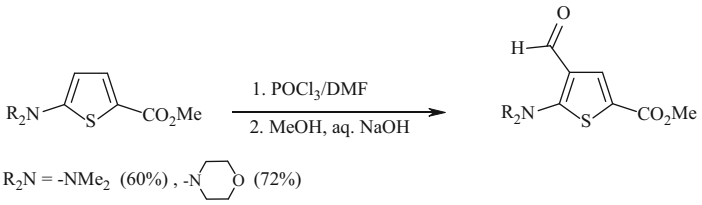
Scheme 93 Reaction of 2-aminothiophenes with $POCl_3$/DMF [141]

2.5 *Formylation of Thiophene*

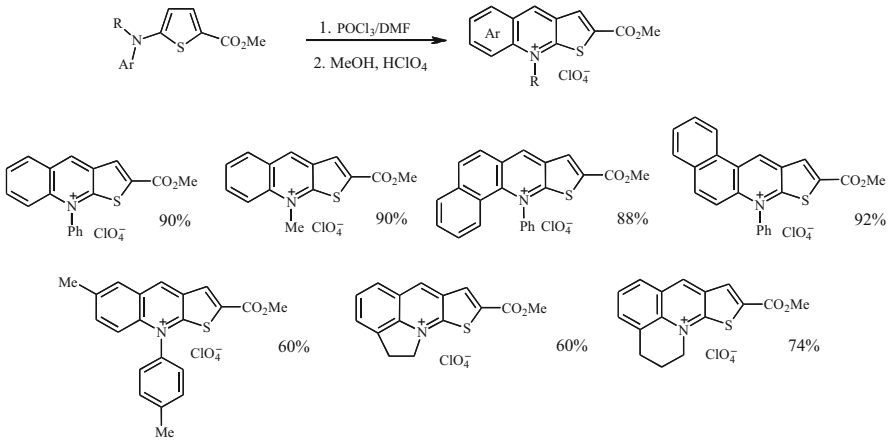
The Vilsmeier–Haack reaction leads to the formation of aromatic aldehydes starting from reactive aromatic compounds. The usual reagent combination is phosphoryl chloride or phosgene together with *N*-methylformanilide (MFA) or *N*,*N*-dimethylformamide (DMF) [139, 140]. First, a *N*,*N*-dimethyliminium salt, e.g. **63**, is formed which, after basic hydrolysis, gives carbaldehyde.

Bis(trichloromethyl) carbonate (triphosgene) in combination with DMF (Scheme 91) was demonstrated to be the useful and convenient-to-handle alternative to the traditional formylation reagents phosphoryl chloride and DMF [142].

Aromatic nitriles can be obtained by treating the usual Vilsmeier–Haack final product **63**, before hydrolysis, with molecular iodine and aq NH_3, and thus thiophene-2-nitrile can be obtained starting from thiophene (Scheme 92) [143].



Scheme 94 Formylation of 2-aminothiophene-5-carboxylates [141]



Scheme 95 Synthesis of 2-methoxycarbonyl-substituted thieno[2,3-*b*]quinolinium salts [141]

Application of the Vilsmeier procedure to *N*,*N*-disubstituted 2-aminothiophenes and work-up with perchloric acid gave isolable iminium salts in high yields (Scheme 93) [141]. The same kind of product was obtained from *N*,*N*-disubstituted 2-aminothiophene 5-carboxylic acids with yields of 62–85%, thus showing that *ipso*-displacement of the carboxylic acid group had occurred (Scheme 93) [141]. Work-up in the usual way with aq NaOH gave the aldehydes.

If an *N*,*N*-disubstituted 2-aminothiophene-5-carboxylate was used, the product resulted from Vilsmeier reaction *ortho* to the amine and *meta* to the ester groups (Scheme 94) [141].

When one of the groups on nitrogen of *N*,*N*-disubstituted 2-aminothiophene-5-carboxylates is a benzene ring, 2-methoxycarbonyl-substituted thieno[2,3-*b*] quinolinium salts were formed via a further cyclising condensation involving the introduced electrophile (Scheme 95) [141].

2.6 Sulfonation of Thiophene

Sulfonation of thiophene by sulfuric acid is very well known [144]. Thiophene-2-sulfonic acid was one of the first isolated compounds in the thiophene family

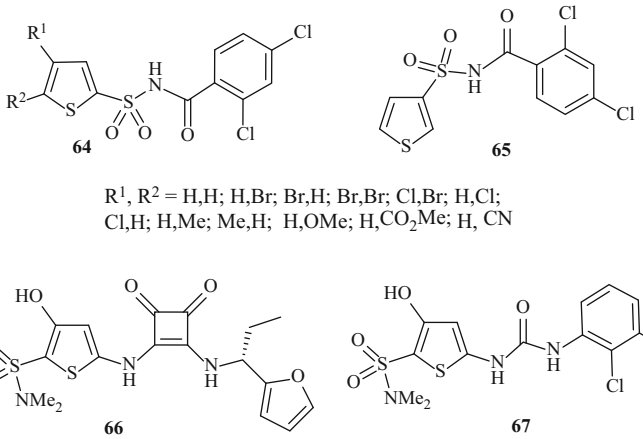
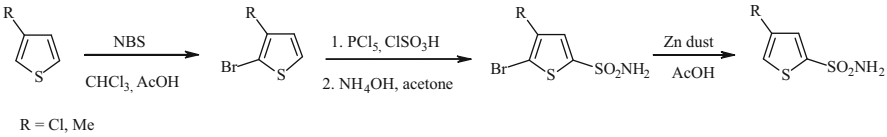
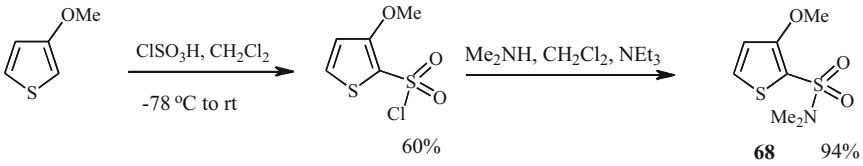


Fig. 3 Potentially biologically active thiophene-2-sulfonamides and thiophene-3-sulfonamides [150, 151]



Scheme 96 Synthesis of 4-substituted thiophene-2-sulfonamides [150]



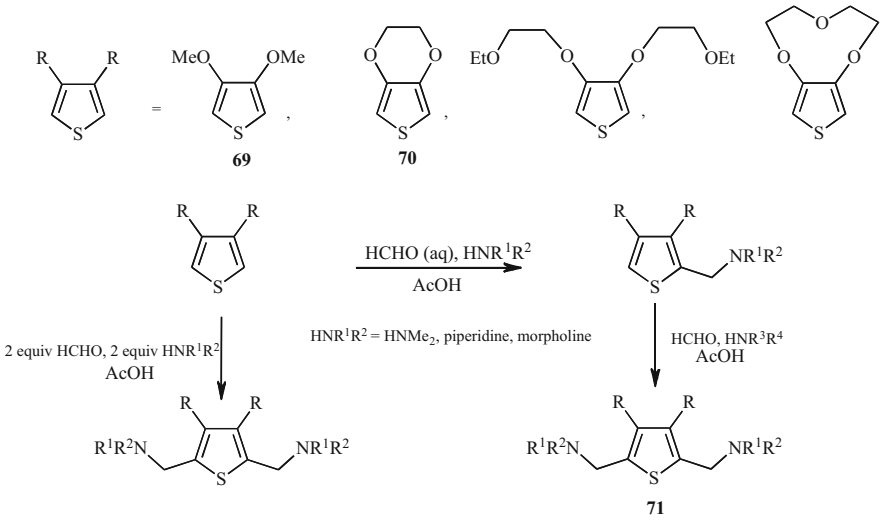
Scheme 97 Synthesis of 3-methoxythiophene-2-sulfonamides [151]

[145]. Later also thiophene-2-sulfonyl chloride and thiophene-3-sulfonamide were synthesised in the laboratory of Victor Meier [146, 147].

Various reagents for sulfonation are described in reviews [21, 22]. Nowadays the most usual method for thiophene sulfonation is application of chlorosulfonic acid, in many cases together with PCl_5 [148].

Several thiophene-2- and thiophene-3-sulfonamides were synthesised and investigated as potent compounds against HCT116 tumour cells (compounds **64** and **65** in Fig. 3) [150]. Thiophene-2-sulfonamides **66** and **67** were obtained as bioisosters for investigation of CXCR2 and CXCR1 chemokine receptor antagonists [151].

As precursors for several compounds **64** (Fig. 3), two 4-substituted thiophene-2-sulfonamides were synthesised after blocking the C-2 position with bromine (direct sulfonation would occur at C-2) (Scheme 96) [150]. The blocking group was later removed by treatment with zinc dust (Scheme 96) [150].



Scheme 98 Mannich reactions of 3,4-dialkoxythiophenes [153]

For the synthesis of compounds **66** and **67** (Fig. 3), 3-methoxythiophene was treated with chlorosulfonic acid initially at −78°C. Reaction with dimethylamine gave the sulfonamide **68** (Scheme 97), which was further converted through several steps into final products [151].

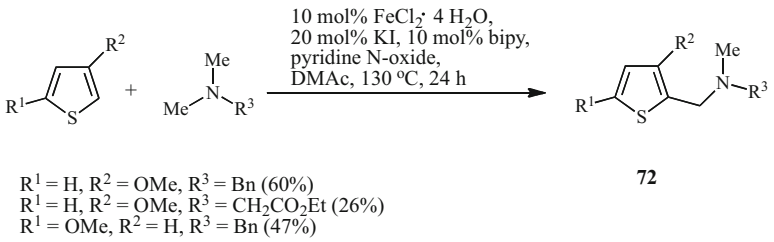
2.7 *Aminoalkylation of Thiophene: The Mannich Reaction*

Thiophene was successfully aminoalkylated for the first time [152] by heating thiophene with formaldehyde and ammonium chloride in 45% yield, together with several side products [21].

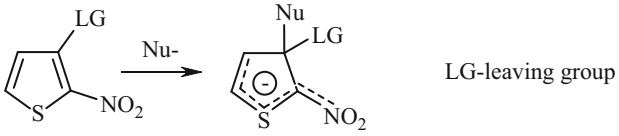
The Mannich reaction of 3,4-dialkoxy-thiophenes was investigated [153]: several Mannich bases and bis-Mannich bases were obtained under standard conditions: secondary amine and aqueous formaldehyde (37%) in glacial acetic acid (Scheme 98) [153].

It was shown that thiophene **70** is the most reactive and thiophene **69** is the least reactive in Mannich reactions [153]. Moreover, mixed aminomethyl thiophenes **71** could also obtained by this simple method [153].

Thiophenes reacted with methylamines through oxidative C–H/C–H cross-coupling in the presence of iron(II) chloride tetrahydrate, KI, and 2,2′-bypyridine [154], giving products **72** in moderate to good yields (Scheme 99).



Scheme 99 Oxidative C–H/C–H cross-coupling of thiophenes with dimethylamines [154]



Scheme 100 Formation of Meisenheimer adduct of a 2-nitrothiophene

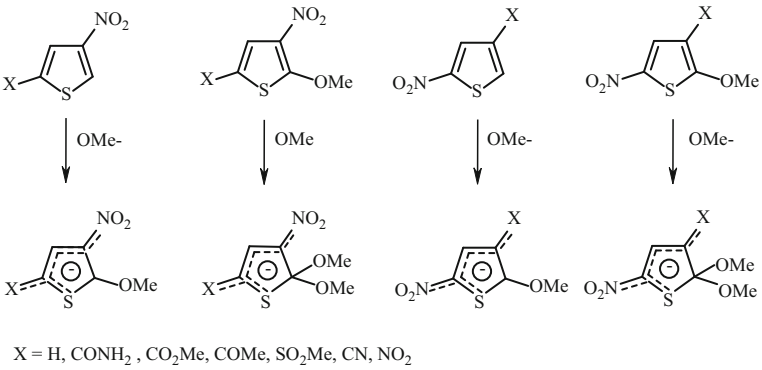
3 Nucleophilic Substitution

Direct nucleophilic substitution on a thiophene ring is rather limited. It proceeds only with highly reactive substrates – thiophenes possessing strong electron-withdrawing groups like nitro – or with highly reactive nucleophiles.

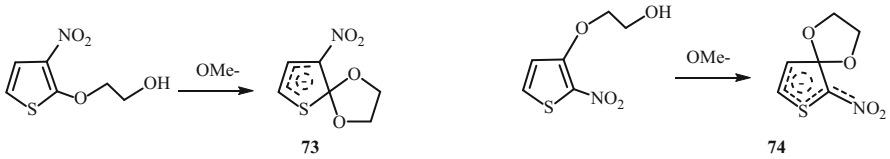
It was recognised early that halogenonitrothiophenes possess a higher reactivity to nucleophiles than the corresponding benzene derivatives [155]. Since then, nucleophilic substitutions of thiophenes have been well studied [156–161].

Aromatic nucleophilic substitution proceeds by an addition–elimination mechanism, where one of the vacant π* orbitals of aromatic ring is used for bonding interaction with the nucleophile [162]. In this way, the addition of nucleophile to the aromatic ring occurs with the formation of σ-complexes – Meisenheimer adducts – without displacement of any of the existing substituents (Scheme 100). The leaving group is then expelled in the second step [162].

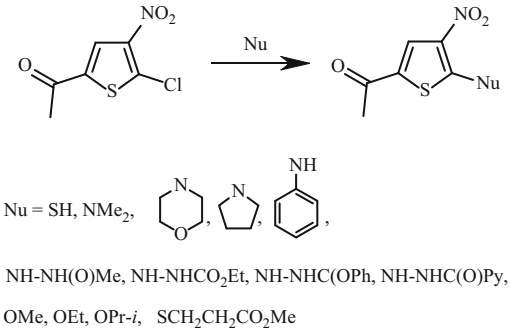
The Meisenheimer adducts of thiophenes have received lot of attention, as models for the σ-complexes that are intermediates in nucleophilic aromatic substitutions occurring through the classic S_NAr mechanism [156]. They have been investigated by ^1H and ^{13}C NMR, UV–visible and IR spectroscopy. The stability constants of some Meisenheimer adducts produced from differently substituted nitrothiophenes were determined by competition experiments and correlated with their ^{13}C NMR shifts [163]. The stability constants of σ-adducts resulting from nitrothiophenes attacked by MeO^- as nucleophile were estimated using NMR spectroscopy. It was shown that stability constants of thiophenes containing a methoxy group at C-2 are higher than for compounds with unsubstituted C-2 in each series of compounds. The stability constant is larger when a lower π-electron distribution change is necessary for adduct formation (Scheme 101) [163].



Scheme 101 The Meisenheimer adducts of several thiophenes formed by attack by MeO^- [163]



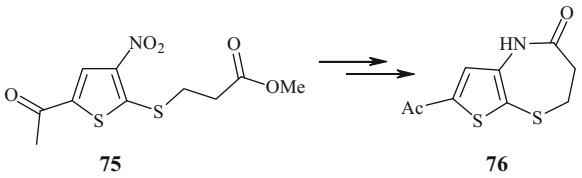
Scheme 102 Synthesis of spiro-Meisenheimer adducts [163]



Scheme 103 Nucleophilic substitutions of 5-acetyl-2-chloro-3-nitrothiophene [164]

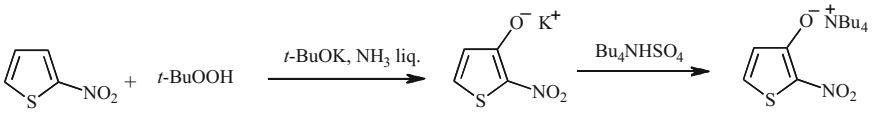
Spiro-Meisenheimer adducts **73** and **74** are formed from 2-(2-hydroxyethoxy)-3-nitrothiophene and 3-(2-hydroxyethoxy)-2-nitrothiophene, respectively, with sodium methoxide (Scheme 102) [163]. The stability constant of the adduct **74** is lower in comparison to that of **73** [163].

In most cases, nitrothiophenes or bromo-substituted nitrothiophenes have been used as the substrates for aromatic nucleophilic substitution. Both bromo and nitro groups can be substituted by oxygen, nitrogen or sulfur nucleophiles [156].

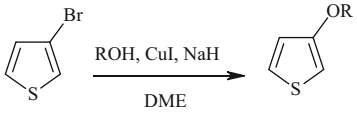


75 **76**

Scheme 104 Synthesis of a 6,7-dihydrothieno[2,3-*b*][1,4]thiazepin-5(4*H*)-one [164]



Scheme 105 Hydroxylation of 2-nitrothiophene with *tert*-butyl hydroperoxide [165]



R = Me, CH_2CF_3, $CH_2(CF_2)_2CF_3$, $CH_2(CF_2)_3CF_3$

Scheme 106 Synthesis of 3-alkoxythiophenes from 3-bromothiophene [166]

Nice examples of nucleophilic substitution on a thiophene ring are represented by nucleophilic substitutions of 5-acetyl-2-chloro-3-nitrothiophene (Scheme 103) [164].

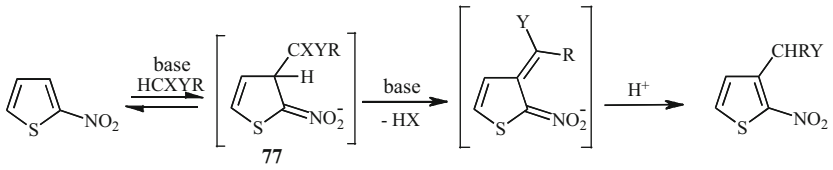
The acetyl group, as a second electron-withdrawing group, in addition to the nitro group, was necessary to support successful nucleophilic substitution. Various nucleophiles were effective, including aliphatic and aromatic *N*-nucleophiles, aliphatic *O*-nucleophiles as well as aliphatic *S*-nucleophiles (Scheme 103) [164].

The reduction of the nitro group in **75** allowed for cyclisation to bicyclic thiophenolactam **76** (Scheme 104) [164].

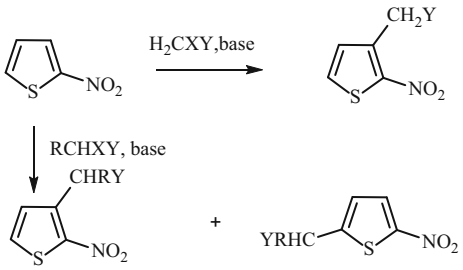
3.1 Reactions with Oxygen Nucleophiles

2-Nitrothiophene undergoes nucleophilic hydroxylation by applying potassium *tert*-butyl hydroperoxide, probably via a vicarious nucleophilic substitution (VNS) process. The only product was a rather unstable 3-hydroxy-2-nitrothiophene potassium salt, which could be converted into the more stable tetrabutylammonium salt (Scheme 105) [165].

It was shown that 3-alkoxy- and various 3-fluoroalkoxythiophenes can be easily obtained from 3-bromothiophene by applying the alcohol as nucleophile in the presence of CuI and NaH, in 60–71% yields (Scheme 106) [166].



Scheme 107 The general scheme of VNS on thiophene with CH-acidic compounds [168]



R = Me, Et, *i*-Pr, Ph; X (leaving group) = Cl, PhS, PhO;
Y (carbanion stabilizing group) = SO_2Ph, SO_2*p*-Tol, SO_2NMe_2, CO_2*t*-Bu, CN, COPh, 2-NCC_6H_4, 4-NCC_6H_4, 4-$PhSO_2C_6H_4$

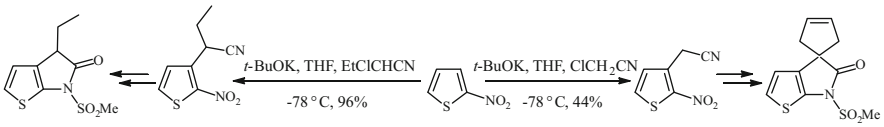
Scheme 108 Reaction of 2-nitrothiophene with CH-acids under basic conditions (VNS) [168]

3.2 Reactions with Carbon Nucleophiles

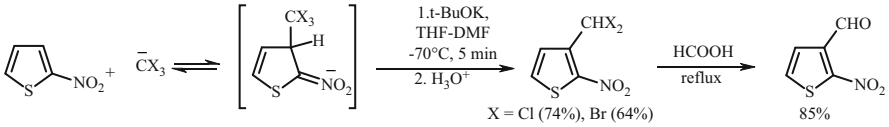
Active carbanions are prone to substitute hydrogen of nitroaromatic compounds; the substitution usually takes place either *ortho* or *para* to the nitro group. The anionic σ_H-adduct generated as a result of nucleophilic addition can be converted into the final product by various mechanisms [167]. Most often exemplified are vicarious nucleophilic substitution (VNS) and oxidative nucleophilic substitution of hydrogen (ONSH).

Vicarious nucleophilic substitution of hydrogen is described in several reviews [158, 159, 161]. The special character of vicarious nucleophilic substitution of hydrogen (VNSH) is that the nucleophile is a carbanion that must contain a leaving group X attached to the carbanionic centre. The first step is a fast reversible addition of carbanion to the nitroaromatic ring, followed by base-induced β-elimination of HX from the intermediate σ-adduct **77**. Protonation is then necessary to restore the aromaticity of the compound. Two equivalents of base must be used, the first to deprotonate the CH-acidic compound to form the carbanion; the second is responsible for the HX elimination (Scheme 107) [168].

Usual bases for VNS on thiophenes are *t*-BuOK or KOH in liquid ammonia or polar aprotic solvents. A variety of CH-acids of general formula RCHXY have been used in VNS reactions involving nitrothiophenes (Scheme 108) [168].



Scheme 109 Synthesis of 5,5-fused thiophene γ-lactams initiated by 3-cyanoalkylation of 2-nitrothiophene [169]



Scheme 110 3-Dihalomethylation of 2-nitrothiophene with either chloroform or bromoform [170]

The 3-cyanoalkylation of 2-nitrothiophene (Scheme 109) was applied for the synthesis of 5,5-fused thiophene γ-lactams as templates for serine protease inhibition [169].

The regioselectivity of the VNS process is dependent on substituents on the thiophene ring, the structure of the carbanion and the reaction conditions. Nucleophilic addition to 2-nitrothiophene can occur at two positions: C-3 and C-5, but the strong preference is for attack at C-3 [168].

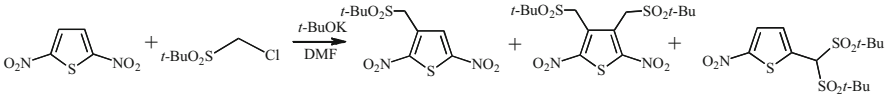
All secondary anions react at C-3 of 2-nitrothiophene; tertiary carbanions give mixtures of 3- and 5-substituted 2-nitrothiophenes, but still the major substitution occurs at C-3 [168]. It is instructive to compare with nitrobenzenes: tertiary carbanions replace only *para*-hydrogens from nitrobenzenes. Moreover, nitrobenzene is not as reactive under the conditions suitable for the substitution on a thiophene ring: *t*-BuOK as the base in THF [168].

2-Nitrothiophene readily undergoes dihalomethylation using chloroform or bromoform in basic medium via the VNS mechanism [170]. The actual nucleophile in this reaction is the trihalomethyl anion. Either 3-dichloromethyl- and 3-dibromomethyl-2-nitrothiophenes are obtained [170] (hydrolysis of 3-dichloromethyl-2-nitrothiophene with boiling formic acid produces the corresponding aldehyde) (Scheme 110) [170].

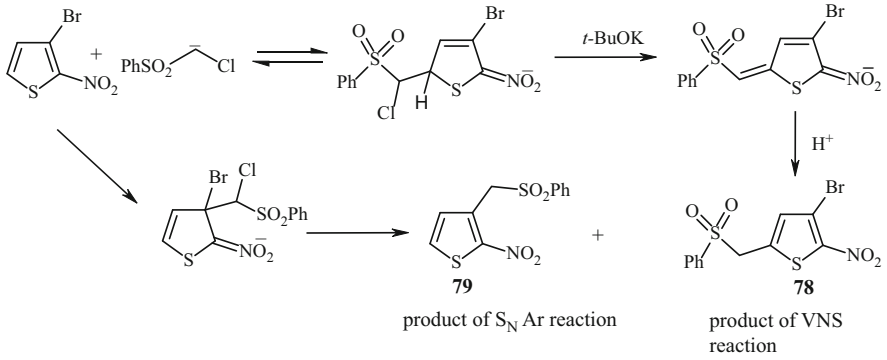
2-Nitrothiophenes with a substituent at C-5 also react smoothly under VNS conditions. Even when the substituent at C-5 is Br or I and a low base concentration was used (conditions favouring the S_NAr), no products of halogen substitution by S_NAr were observed [168].

2,5-Dinitrothiophene reacted with chloromethyl *tert*-butyl sulfone with *tert*-BuOK in DMF producing a mixture of 3-substituted and 3,4-disubstituted products (58% and 6%, respectively). When two equivalents of nucleophile were used, a 3,4-disubstituted product was major (54% with 5% of monosubstituted product). Some degree of substitution of one of the nitro groups by the nucleophile was also observed in both cases (3–4%) (Scheme 111) [168].

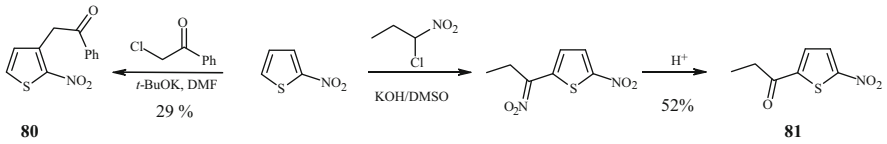
A VNS variation involves 2-nitrothiophenes which are already functionalised at C-3 [161]. Thus 2-nitro-3-bromothiophene with chloromethyl phenyl sulfone



Scheme 111 Reaction of 2,5-dinitrothiophene with chloromethyl *tert*-butyl sulfone [168]



Scheme 112 Nucleophilic substitution of 3-bromo-2-nitrothiophene [161]

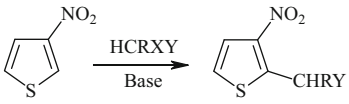


Scheme 113 Nucleophilic substitution of 2-nitrothiophene with α-chloroacetophenone and α-chloronitronate [159, 168, 171]

underwent carbanion VNS displacement of hydrogen at C-5 but was also attacked at C-3 with displacement of bromide. A high concentration of base in the reaction media led to the fast elimination of HCl from the C-5-σ-complex and thus to the predominant formation of C-5-substituted VNS product **78**. However, nucleophile addition to C-5 is a reversible process, and the slow addition of base did not support the shift of the reaction equilibrium to the C-5-substitution product; in this case, the product **79** of S_NAr was formed (Scheme 112) [161].

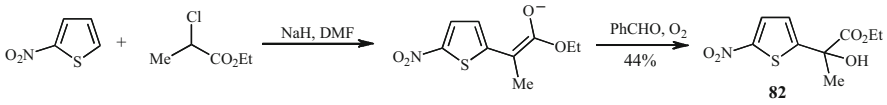
When one carries out a VNS of 2-nitrothiophene with α-chloroacetophenone in the presence of *t*-BuOK, (2-nitrothien-3-yl)methyl phenyl ketone **80** is formed [159, 171], but the reaction with α-chloronitronate anion in the presence of KOH, instead of the expected nitroalkane, gave the ketone **81**. The substitution in this case took place at C-5 [159, 168]. Nitroarylnitronate was formed as an intermediate in this reaction, and it was transformed into the final ketone probably by a Nef reaction during work-up (Scheme 113).

The nitro group in 3-nitrothiophene strongly activates C-2 for attack by a nucleophile, and as the result, only 2-substituted 3-nitrothiophenes are formed

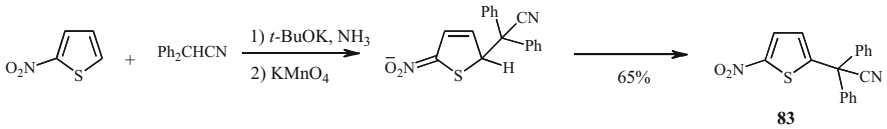


HCXYR = $ClCH_2SO_2Ph$ (96%), $ClCH_2SO_2NMe$ (40%),
$PhSCH_2CN$ (9%),$ClCH(Me)SO_2Ph$ (94%), $ClCH(Et)SO_2Ph$ (38%)
Base = KOH/NH_3 or $MeONa/NH_3$

Scheme 114 Reaction of 3-nitrothiophene with CH-acids [168]



Scheme 115 The synthesis of the ester of a nitrothienyl alkanoic acid [172]



Scheme 116 ONHS of 2-nitrothiophene with diphenylacetonitrile carbanion [173]

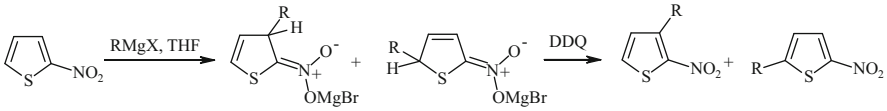
through nucleophilic substitution (Scheme 114). If C-2 in a 3-nitrothiophene is blocked by some substituent, no products of nucleophilic substitution are observed, and starting materials are completely recovered [168].

The ester of 5-nitrothien-2-ylalkanoic acid was obtained through VNS of 2-nitrothiophene with a 2-chloropropionate. Following oxidation of the anion formed in the course of the reaction in the presence of benzaldehyde, with molecular oxygen, led to α-hydroxyester **82** (Scheme 115) [172].

Another mechanism of nucleophilic substitution which is relevant to thiophenes is oxidative nucleophilic substitution of hydrogen (ONSH). An example is the reaction of 2-nitrothiophene with the carbanion originating from diphenylacetonitrile. This carbanion forms σ_H-adducts only at a position *para* to a nitro group for steric reasons. Thus, after addition of an oxidant $KMnO_4$, the final product is **83** (Scheme 116) [173].

All the nitrile α-carbanions explored gave mostly the products of *para*-substitution. Only if C-5 in a 2-nitrothiophene was substituted with bromine did *ortho*-substitution through ONSH take place [173]. 3-Nitrothiophene gave exclusively the product of 2-substitution with 2-phenylpropanenitrile [173].

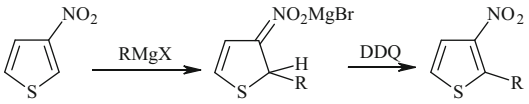
The very effective alkylation of 2-nitrothiophene with Grignard reagents is illustrated in Scheme 117 [174]. The σ-adducts formed by addition of alkylmagnesium bromide to the 2-nitrothiophene at both activated 3- and 5-positions can be oxidised by DDQ (Table 2) [174].



Scheme 117 Alkylation of 2-nitrothiophene with Grignard reagents [174]

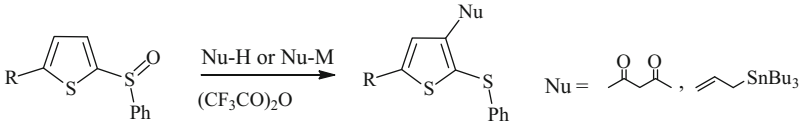
Table 2 Alkylation of 2-nitrothiophene with Grignard reagents [174]

R	Overall yield (%)	Ratio of 3-alkyl:5-alkyl
Me	67	87:13
Bu	55	83:17
i-Pr	52	78:22
C_6H_{11}	52	64:36

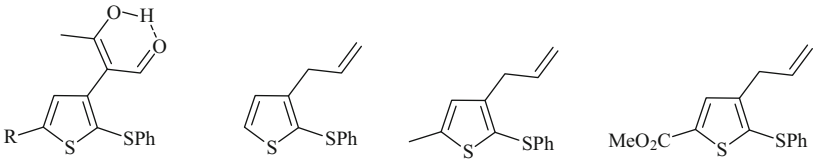


R = Me (70%), *i*-Pr (74%)

Scheme 118 Alkylation of 3-nitrothiophene with Grignard reagents [174]



R = H, CO_2Me, Me

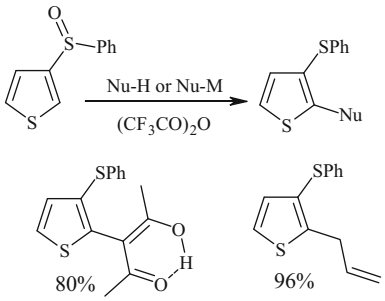


78% 88% 63% 50%

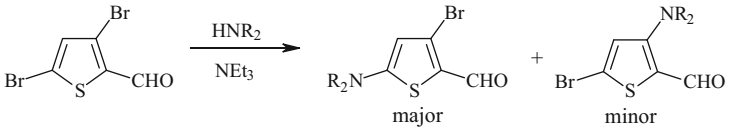
Scheme 119 Pummerer-type reactions of 2-sulfinylthiophenes [175]

The alkylation of 3-nitrothiophene with alkyl Grignard reagents (Scheme 118) was regioselective and led to the formation of 2-alkyl-3-nitrothiophenes [174].

Another activating and directing group for successful nucleophilic reactions on a thiophene ring is the sulfinyl group (Scheme 119) [175]. In this Pummerer-type reaction, nucleophilic attack of acetylacetone or allyltributyltin(IV) on 2-sulfinylthiophenes in the presence of trifluoroacetic anhydride gave regioselectively the products of substitution at C-3 [175].



Scheme 120 Pummerer-type reactions of 3-sulfinylthiophenes [175]



Scheme 121 Nucleophilic amination of 3,5-dibromothiophene-2-carbaldehyde [177]

Table 3 Nucleophilic amination of 3,5-dibromothiophene-2-carbaldehyde [177]

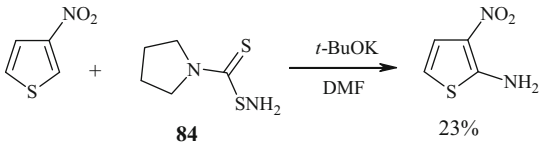
Amine	Product ratio major–minor	Yield of major product (%)
morpholine	71:29	42
piperidine	74:26	31
$(CH_3)_2NH$	81:19	28
$BnNHCH_3$	80:20	46

3-Sulfinylthiophenes also react in a regioselective manner to give C-2-substituted products (Scheme 120) [175]. The sulfur functional group which remained in the products allows for further transformations [175].

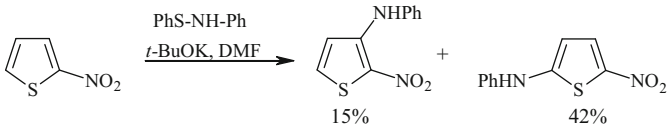
3.3 Reactions with Nitrogen Nucleophiles

Though nitrothiophenes are the main substrates for nucleophilic substitution on thiophene, thiophenes substituted by other electron-withdrawing groups can also be substituted by nucleophiles. As an example, the behaviour of thiophenes with a carbonyl group at C-2 and bromine at C-3 and C-5 as leaving groups was investigated (Scheme 121) [177].

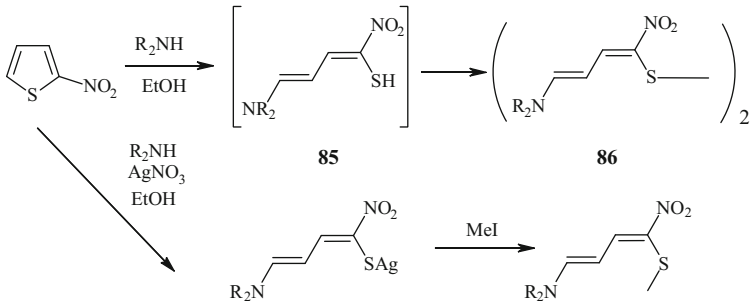
No matter which amine nucleophile was used, the major reaction product was a 5-aminated thiophene in yields of 28–46%, contaminated with a minor product. Double substitution was not observed. Changing the solvent (water, DMF, benzene), reagents ratio and concentration or the reaction temperature (50, 85 and 110°C) did not affect the regioselectivity of the reaction (Table 3) [177].



Scheme 122 VNS amination of 3-nitrothiophene by a sulfenamide **84** [176]



Scheme 123 Amination of 2-nitrothiophene by *N*-phenylbenzenesulfenamide [176]



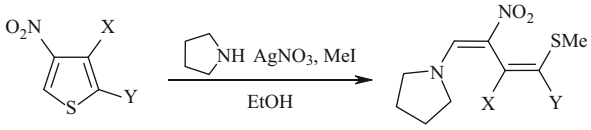
Scheme 124 Ring opening of 2-nitrothiophene upon treatment with aliphatic secondary amines [178]

Amination with a sulfenamide **84** is another example of a VNS reaction. Thus, 2-amino-3-nitrothiophene, albeit in only 23% yield, was obtained from 3-nitrothiophene (Scheme 122) [176].

2-Nitrothiophene was aminated by *N*-phenylbenzenesulfenamide giving a mixture of *ortho*- and *para*-substituted products, with the latter being the major product (Scheme 123) [176].

2-Nitrothiophene under attack by aliphatic secondary amines undergoes ring opening [178]; the C-5–S bond is broken, finally giving nitrobutadienedisulfide **86**, which is the product of oxidation of an unstable intermediate, thiol **85**. Addition of $AgNO_3$ to the initial reaction media furnished the silver(I) thiolate, which was successfully trapped giving the methylthio derivative by reaction with MeI (Scheme 124) [178]. The ring opening proceeded in a diastereoselective way giving exclusively the 1*E*,3*Z* configuration [178].

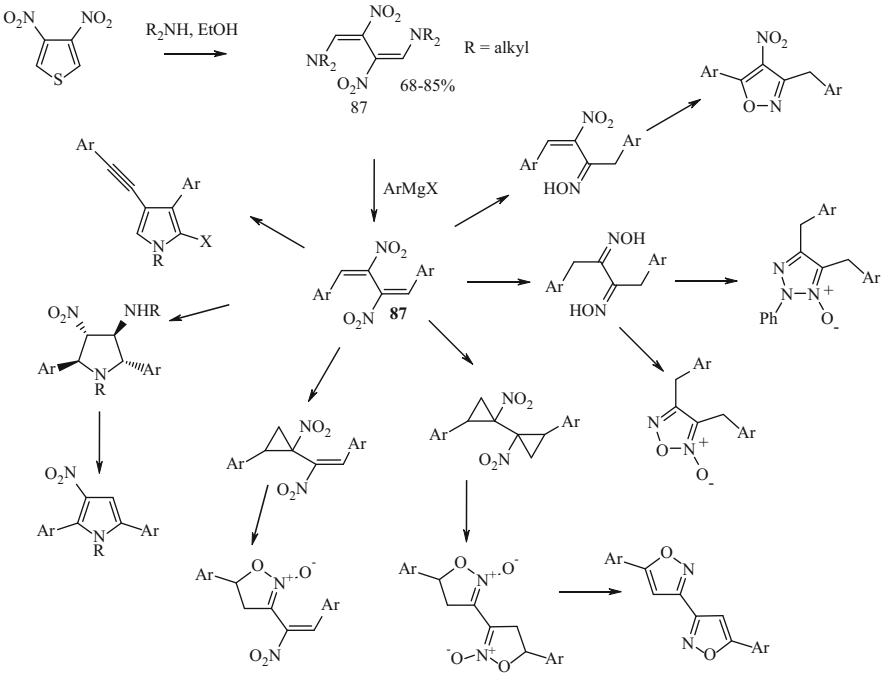
3-Nitrothiophene in reactions with aliphatic amines also gave the products of ring opening through cleavage of the C-5–S bond, though in lower yields (15–57%) [179]. In contrast to 2-nitrothiophene, the presence of silver nitrate was essential – no reaction was observed in its absence. The ring opening reaction was further extended to 2,3-disubstituted-4-nitrothiophenes (Scheme 125) [180].



X = Y = H; X,Y =  ; X =PhS, Y = H; X = $PhSO_2$, Y = H;

X = MeS, Y = H; X = $MeSO_2$, Y = H; X = MeCO, Y = H; X = CO_2Me, Y = H; X = CN, Y = H

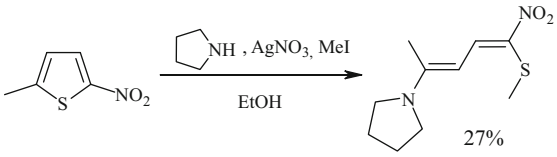
Scheme 125 Ring opening reaction of 2,3-disubstituted-4-nitrothiophenes on treatment with pyrrolidine in the presence of silver nitrate [180]



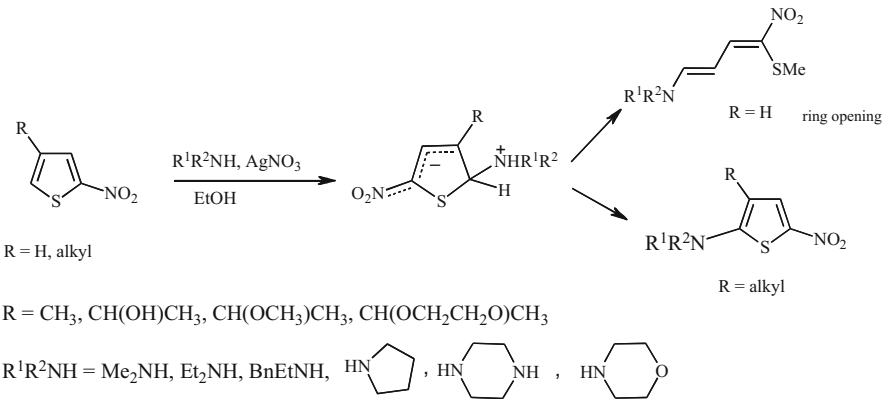
Scheme 126 3,4-Dinitrothiophene ring opening under attack by secondary aliphatic amines, and some synthetic applications of the 1,4-bis(dialkylamino)-2,3-dinitro-1,3-butadienes thus formed

3,4-Dinitrothiophenes also undergo ring opening, breaking both C–S bonds with extrusion of sulfur and formation of 2,3-dinitro-1,3-butadiene-1,4-diamines **87** – valuable compounds for further synthesis [181], for example, open-chain poly-functionalised molecules, homocyclic and heterocyclic derivatives and compounds with possible pharmacological applications (Scheme 126) [182].

5-Methyl-2-nitrothiophene also underwent ring opening under the action of pyrrolidine (Scheme 127) [183].



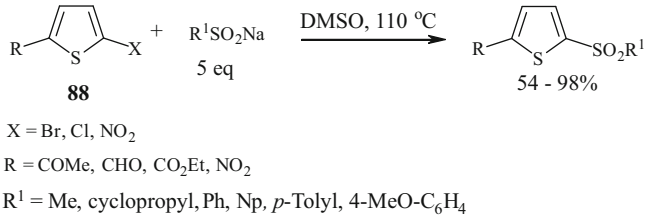
Scheme 127 Ring opening of 2-methyl-5-nitrothiophene [183]



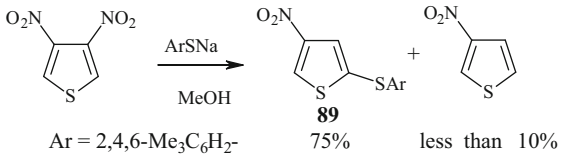
Scheme 128 Ring opening reactions of 2-nitrothiophenes versus nucleophilic substitution at C-5, in reactions with secondary amines [183]

However, 4-methyl-2-nitrothiophene under the same reaction conditions, and with various amines, gave only 3-methyl-2-amino-5-nitrothiophenes – products of oxidative nucleophilic substitution of hydrogen (ONSH) at C-5, in good yields with no trace of ring opening (Scheme 128) [183].

Substitution at C-5, and not ring opening, also occurred with other C-4–alkyl-substituted thiophenes (Scheme 128) [183]. The reaction is regioselective, as it occurs at the quasi-*para* (C-5) position, with no detectable substitution product at the quasi-*ortho* (C-3)-carbon and no detectable ring opening. The yields in the substitution reactions were rather low with dimethylamine (10–15%) but satisfactory in other cases (20–75%) [183]. Also, in these substitution reactions, 5–10% of starting material was always recovered. The surprising difference in the reaction course of 2-nitrothiophene in comparison to 4-alkyl-2-nitrothiophene was explained by a higher stability of the Meisenheimer-type adduct formed in the first step from 4-alkyl-2-nitrothiophenes (Scheme 128). This was proved in competition experiments and investigated by ^{13}C NMR, with sodium methoxide as nucleophile [183]. These revealed that the 4-methyl-group stabilises the Meisenheimer adduct by redirecting its polarisation effect from C-5 in starting compound to C-3 in the σ-complex. Thus the σ-adduct, produced from 4-methyl-2-nitrothiophene, has a longer lifetime and survived until the attack by oxidising reagent, finally giving the 5-amino-substituted thiophene [183].



Scheme 129 5-Nucleophilic sulfonylation of 2-substituted thiophenes [184]



Scheme 130 *cine*-Substitution of 3,4-dinitrothiophene with sodium 2,4,6-trimethylbenzenethiolate [186]

3.4 Reactions with Sulfur Nucleophiles

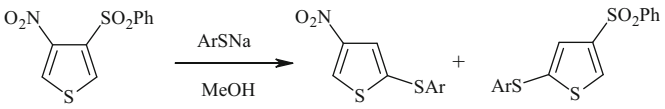
Thiophene sulfonation can be achieved by electrophilic substitution (see Sect. 2.6). Nucleophilic sulfonylation of thiophene, with displacement of a leaving group, is illustrated in Scheme 129 [184].

Thiophenes substituted at C-2 by electron-withdrawing groups (COMe, CHO, CO_2Et and NO_2) were suitable substrates. No reaction was observed for the compounds **88** (R=H). Leaving groups such as Br, Cl and NO_2 were successfully replaced by various sulfonyl groups (Scheme 129). In 2-bromo-5-nitrothiophene, both functional groups were substituted by methylsulfonyl or *p*-tolylsulfonyl groups giving 2,5-bis-sulfonylthiophenes [184].

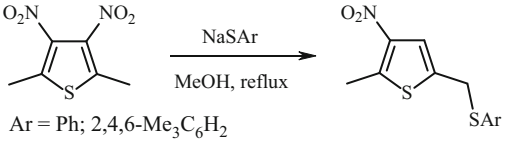
3.5 cine- *and* tele-*Substitution Reactions*

The examples of nucleophilic substitution discussed in Sect. 3.4 belong to the *ipso*-type [185]. In *cine*-substitution, the leaving group departs from the position adjacent to the nucleophile addition site, and in *tele*-substitution, the leaving group departs from a more remote position on the ring or even from a side-chain [159]. *cine*- and *tele*-substitutions of various nonaromatic, aromatic and heteroaromatic compounds, including thiophene, have been reviewed [185].

An example of *cine*-substitution on a thiophene is the reaction of 3,4-dinitrothiophene with thiophenolate anion in methanol, in a multistep sequence, to produce 2-arylsulfanyl-4-nitrothiophene **89** (Scheme 130) [186].



Scheme 131 *cine*-Substitution of 3-nitro-4-phenylsulfonylthiophene [187]



Scheme 132 *tele*-Substitution at 2,5-dimethyl-3,4-dinitrothiophene [188]

In the asymmetrically substituted 3-phenylsulfonyl-4-nitrothiophene, either or both functional groups can play the role of leaving group. *cine*-Substitution is operative also in this case; thus, both 4-nitro-2-arylsulfanylthiophene and 2-arylsulfanyl-4-phenylsulfonylthiophene are formed (Scheme 131) [187].

2,5-Dimethyl-3,4-dinitrothiophene is not able to form *cine*-substitution products and undergoes *tele*-substitution in its reaction with arylthiolates (Scheme 132) [188].

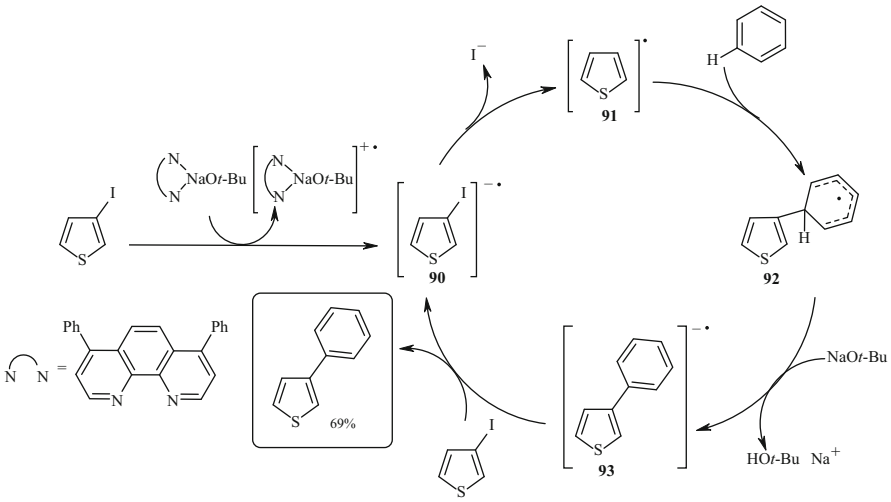
4 Substitution in Thiophenes Through Radical Reactions

Radical substitution reactions and their mechanisms and applications have been reviewed several times [189, 190]. Thiophene participates well in radical reactions. There are reviews describing both unimolecular radical nucleophilic substitutions ($S_{RN}1$) [191] and homolytic aromatic substitutions (HAS) of thiophenes [192]. The formation of thiophene radicals from peroxides, thienylamines and iodothiophenes has been discussed [192].

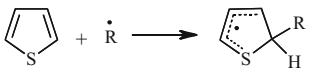
Radical substitutions are chain reactions involving single-electron transfer (SET). They proceed through initiation, propagation and termination stages. The following procedures can be used for the initiation step [193]: photostimulation [194, 195], the addition of solvated electrons or electron transfer by electrochemical methods [196].

Among the various methods of generation of radicals able to attack thiophene, aprotic diazotisation of heterocyclic amines and the photolysis of iodoheteroarenes in thiophene [197] give moderate to excellent yields of substituted thiophenes. Both methods have their advantages and disadvantages and lead to mixtures of 2- and 3-substituted thiophenes with the ratio dependent on the reaction conditions and the substrate [197].

Though radical arylations of thiophene have been largely replaced in recent years by transition metal-catalysed arylation processes, modern demands for



Scheme 133 Mechanism of thiophene arylation initiated by electron transfer from a complex of *t*-BuONa with 4,7-diphenyl-1,10-phenanthroline to 3-iodothiophene [198]



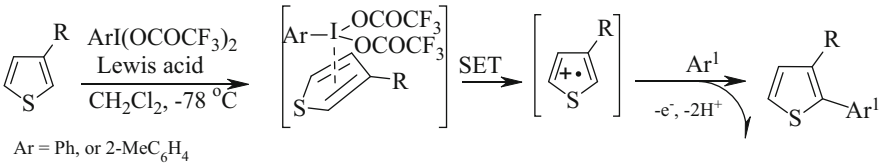
R = MeS, Et_3Si, PhCOO, Ph

Scheme 134 Formation of radical σ-complexes of thiophene [200]

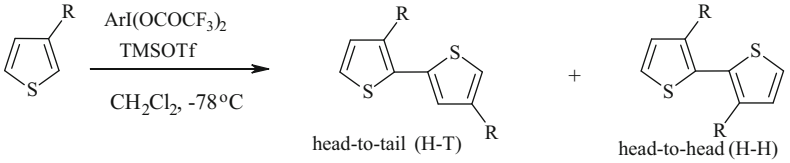
cheaper and environmentally friendly methods have revived an interest in radical reactions, which proceed without involving transition metals. Several recent examples are presented here.

Halothiophenes are usually substrates for reactions initiated by electron transfer. As an example, arylation of thiophene with unsubstituted benzene by an $S_{RN}1$ mechanism was demonstrated [198]. The reaction was initiated by electron transfer from a complex of *t*-BuONa with 4,7-diphenyl-1,10-phenanthroline to 3-iodothiophene (Scheme 133). The radical anion **90** formed disproportionates to give radical **91** and I^-. Addition of radical **91** to benzene gives rise to a new radical **92** which after deprotonation proceeds to anion radical **93**. This, in turn, transfers the electron to the next molecule of substrate, giving the final product and thus propagating the chain reaction (Scheme 133) [198].

In homolytic aromatic substitution, a radical attacks an aromatic ring leading to the formation of a σ-complex, which, after the loss of a leaving group, usually hydrogen ($H^{\cdot}$), is converted into the substitution product. In many cases, the oxidation step is also involved in the process: the radical σ-complex is oxidised to give a cationic σ-complex, which, in turn, loses a proton thus forming the final product [199]. The formation of radical σ-complexes (Scheme 134) upon attack of a radical on thiophene was confirmed by ESR spectroscopy [200].



Scheme 135 The general mechanism of thiophene arylation by a hypervalent iodine(III)-induced oxidation [201]



Scheme 136 Oxidative dimerisation of 3-substituted thiophenes [203]

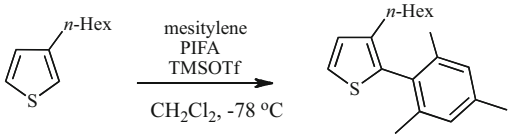
Table 4 Selective oxidative coupling reactions of 3-substituted thiophenes [203]

R	Yield (%)	(H–T) + (H–H)
n-hexyl	41	94:6
n-heptyl	52	92:8
n-octyl	30	95:5
methyl	72	80:20
n-butyl	88	77:23
isobutyl	98	87:13
cyclohexyl	67	90:10
$(CH_2)_6Br$	62	82:18
$SiMe_3$	46	1:99

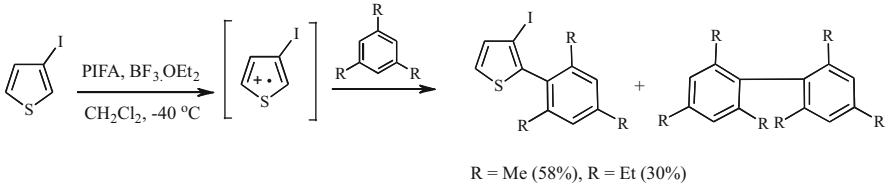
Numerous reports describe the arylation of thiophenes at unsubstituted positions under single-electron transfer (SET) conditions [201]. Application of a hypervalent iodine(III) compound [202], for example, phenyliodine bis(trifluoroacetate) (PIFA) in the presence of a Lewis acid, leads to the formation of a charge transfer complex which by further SET proceeds to a cation radical of thiophene (Scheme 135) [203]. This cation radical is reactive enough to react with a nucleophile. Following oxidation and deprotonation, the final product is formed (Scheme 135) [201].

The process has been employed for the synthesis of dimers starting from 3-substituted thiophenes (Scheme 136) [203]. Using TMSOTf as Lewis acid, it was possible to obtain good to excellent yields together with rather high selectivity. Thus, head-to-tail isomers were formed predominantly with almost all 3-substituted thiophenes. The only exception to this rule was 3-trimethylsilylthiophene which gave a head-to-head product (Scheme 136, Table 4) [203].

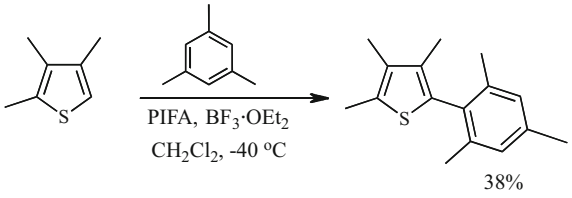
The capture of a cation radical, formed by hypervalent iodine(III)-induced oxidation of a 3-hexylthiophene, with mesitylene, present in 10-times excess, gave the product of ‘cross-coupling’, rather surprisingly at C-2 of the thiophene (Scheme 137) [203].



Scheme 137 3-*n*-Hexylthiophene coupling with mesitylene initiated by hypervalent iodine(III) oxidation [203]



Scheme 138 Radical reactions of 3-iodothiophene with 1,3,5-trialkylbenzenes [204]



Scheme 139 Reaction of 2,3,4-trimethylthiophene with 1,3,5-trimethylbenzene under SET oxidation conditions [204]

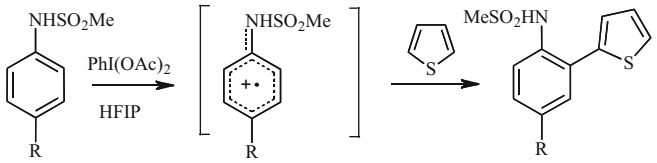
3-Iodothiophene, under rather similar conditions, reacts with trialkylbenzenes to give the biaryl product 58% (R=methyl) and 30% (R=ethyl) (Scheme 138) [204]. In this case, $BF_3 \cdot OEt_2$ was used as Lewis acid and some trialkylbenzene dimer was also produced. PIFA was later superseded by $C_6F_5I(OCOCF_3)$ [FPIFA] which suppressed the formation of homocoupling products [204].

2,3,4-Trimethylthiophene is also a suitable substrate for SET oxidation giving a cation radical and subsequently the product of coupling with 1,3,5-trimethylbenzene in 38% yield (Scheme 139) [204].

The reaction of thiophene with the cation radicals formed from *N*-aryl methanesulfonamides after treatment with iodobenzene diacetate by a SET mechanism led to biarylic compounds (Scheme 140) [205]. Hexafluoroisopropanol (HFIP) was used as a solvent for these reactions.

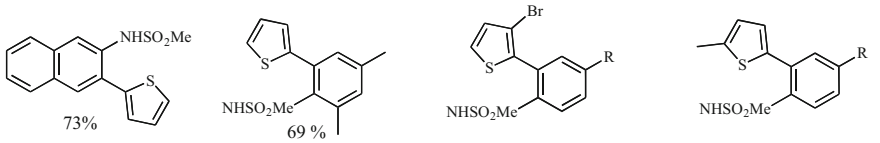
Several other compounds containing an aryl-thienyl fragment were obtained by the same method (see example in Scheme 141) [205].

3-Bromothiophene was also a suitable partner in this reaction. Substitution was regioselective and took place at C-2 of 3-bromothiophene (Scheme 141) [205]. Substitution of 2-methylthiophene was also regioselective, and the products of substitution at C-5 were isolated in 58–64% yields (Scheme 141). If 3-methylthiophene was



R = Me (76%), *n*-Pr (84%), *i*-Pr (74%), CH_2CH_2OH (75%), Cl (72%)

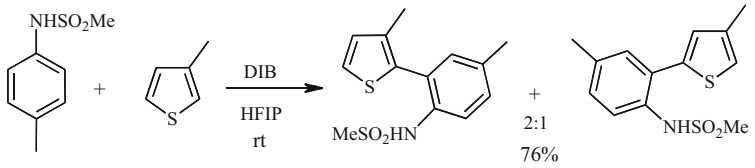
Scheme 140 Reaction of thiophene with the cation radical formed from *N*-aryl methanesulfonamide [205]



R = Me (67%), *n*-Pr (63%), *i*-Pr (62%), CH_2CH_2OH (64%), Cl (64%)

R = Me (58%), *n*-Pr (63%), *i*-Pr (64%)

Scheme 141 Various arylthiophenes obtained by the reaction of thiophenes with the cation radical formed from *N*-aryl methanesulfonamides [205]

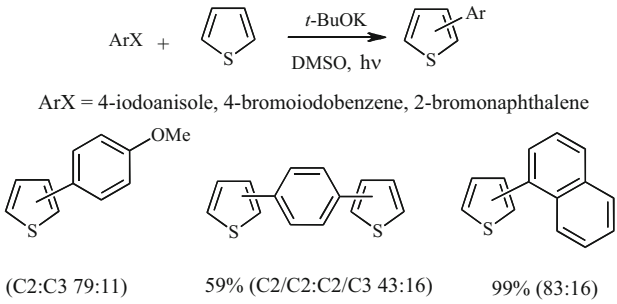


Scheme 142 Reaction of 3-methylthiophene with the cation radical formed from an *N*-aryl methanesulfonamide [205]

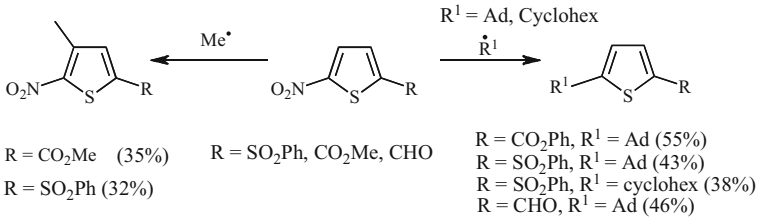
applied, a mixture of C-2- and C-5-arylated products in a ratio of 2:1 was formed (Scheme 142) [205].

Another approach to functionalisation of thiophene itself, where thiophene is attacked by another aryl radical, was performed using only *t*-BuOK in DMSO as the reagent [206]. Under photostimulation, aryl halides were converted into aryl anion radicals $[Ar\text{-}X]^{\bullet-}$, and these disproportionated to halide anion (X^-) and aryl radical ($Ar^\bullet$). The reaction of thiophene (Th-H) with radical $Ar^\bullet$ gave the new radical ($Ar\text{-}Th\text{-}H^\bullet$). Here *t*-BuOK was called upon to deprotonate the radical and to produce a new anion radical ($Ar\text{-}Th^{\bullet-}$), which by SET to starting halide is converted into a neutral compound – final product Ar-Th. Using this sequence, several products in good or excellent yields were obtained albeit with low regioselectivity (examples in Scheme 143) [206].

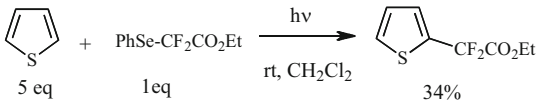
An investigation concerning the *ipso*-substitution of a nitro group in 2-nitrothiophenes demonstrated that l-adamantyl radical ($Ad^\bullet$) and cyclohexyl radical ($Cyclohex^\bullet$) selectively attack the *ipso*-positions of thiophenes bearing



Scheme 143 Thiophene arylation by ArX (X=Br, I) in the presence of *t*-BuOK in DMSO under photostimulation [206]



Scheme 144 The reaction of 2-nitrothiophenes with various aliphatic radicals [207]



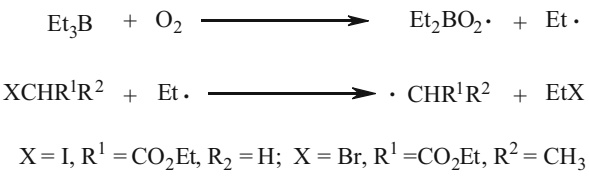
Scheme 145 Thiophene reaction with the radicals generated by photo-induced Se–C bond cleavage [209]

nitro groups and lead to denitration. However, the methyl radical (Me•) gave rise exclusively to products derived from addition at the unsubstituted ring positions (Scheme 144) [207].

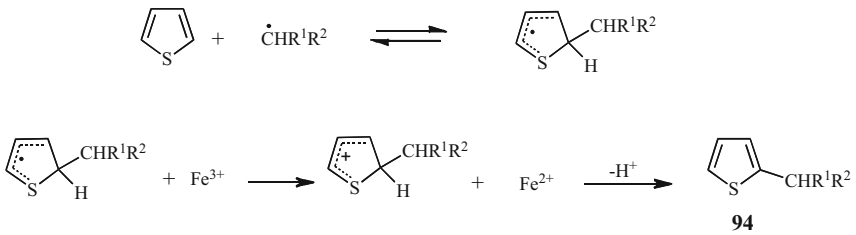
Radical *n*-perfluorobutylation of thiophene gave the mixture of 2-(*n*-perfluorobutyl)thiophene (86.5 %) and 3-(*n*-perfluorobutyl)thiophene (13.5 %) in 97 % overall yield [208]. For this purpose, the (*n*-perfluorobutyl)-radical was obtained by the reaction of (*n*-perfluorobutyl)-iodide with methyl radical which, in turn, was generated from different sources: *t*-BuOOH and $Fe(OAc)_2OH$, MeCOMe and H_2O_2 or DMSO/H_2O_2/Fe(II) [208].

Difluoromethyl radicals were produced by photo-initiated Se–CF_2 bond cleavage of ethyl α,α-difluoro-α-(phenylseleno)acetate. Their reaction with thiophene gave the product of 2-difluoromethylation (Scheme 145) [209].

Carbon radicals generated as a result of triethylborane autooxidation (Scheme 146) react with ICH_2CO_2Et or $BrCH(CH_3)CO_2Et$ in DMSO to produce new radicals capable of reacting with thiophene [210].



Scheme 146 Autooxidation of triethylborane thence formation of reactive electrophilic carbon radicals [210]



Scheme 147 Radical substitution of thiophene with electrophilic •CHR^{1}R^2 [210]

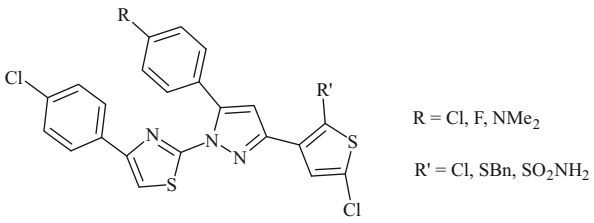


Fig. 4 Thiophene-containing compounds as potential radical scavengers [149]

In this way, ethyl esters **94** of thien-2-ylacetic acids were formed (Scheme 147) [210]. The presence of oxidant $Fe_2(SO_4)_3 \cdot H_2O$ was necessary for the oxidation of the intermediate σ-complex and thus for reaction progress (Scheme 147) [210].

Concluding this radical substitution section, one can cite examples of thiophene-containing molecules which were assessed for their antioxidant potential and free radical scavenging activity, in work seeking a good xanthine oxidase inhibitor [149].

It was demonstrated that both activities are dependent on substituents on the thiophene ring (R^1). The best compound had R=NMe$_2$ and R^1=SBn (Fig. 4) [149]. Thus, the capability of a thiophene ring to accept electrons from radicals was confirmed again.

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Thiophene Metallation and Cross-Coupling Chemistry

Jürgen Schatz and Ina Hoffmann

Abstract This chapter reviews the metallation of thiophenes, the utilization of the resulting organometal species as nucleophiles and as cross-coupling partners, and the cross-coupling reactions of halothiophenes and thiophenes. The main focus lies on transition metal-catalyzed carbon-carbon bond formations.

Keywords Alkynylation · C-H activation · Dehydrogenative cross-coupling · Desulfinylative cross-coupling · Direct arylation · Formylation · Gomberg-Bachmann reaction · Halogen-lithium exchange · Heck reaction · Hydrogen-deuterium exchange · Hydrogen-lithium exchange · Hypervalent diaryliodonium salts · Hypervalent iodine-induced SET oxidation · Kumada-Corriu-Tamao reaction · Metallation · Negishi reaction · Organocuprates · *ortho*-Olefination · Oxidative cross-coupling · Reductive dehalogenation · Rieke manganese · Sonogashira reaction · Stille reaction · Suzuki–Miyaura reaction · Thienyllithium · Thiophenediazonium salts · Transition metal-catalyzed cross-coupling · Ullmann reaction · Vinylation · Wenkert arylation

Contents

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1 Introduction

Thiophenes are recurring structural motifs found in many natural products and are frequently utilized as building blocks giving rise to a wide range of applications [1, 2]. Their scope reaches from bi(hetero)aryls, which represent a predominant substructure for biologically active molecules, through oligothiophenes and polymers, widely used in light-emitting diodes, photovoltaics, and semiconducting devices, up to supramolecular chemistry and optoelectronics making use of push-pull substituted thiophenes and photochromic dithienylethene derivatives.

Preparations of all these organic materials involve the construction of new carbon-carbon bonds and have prompted the development of many catalytic cross-coupling reactions. One of the most reliable synthetic methods to form carbon-carbon bonds is transition metal-catalyzed cross-coupling between organometallic nucleophiles and electrophilic organic halides or pseudohalides, respectively (Scheme 2a). The mechanisms of common cross-coupling reactions such as the Suzuki, Negishi, or Stille catalysis can be described by a catalytic cycle, differ in detail, but all include three main steps in the order: oxidative addition, transmetallation, and reductive elimination (Scheme 1).

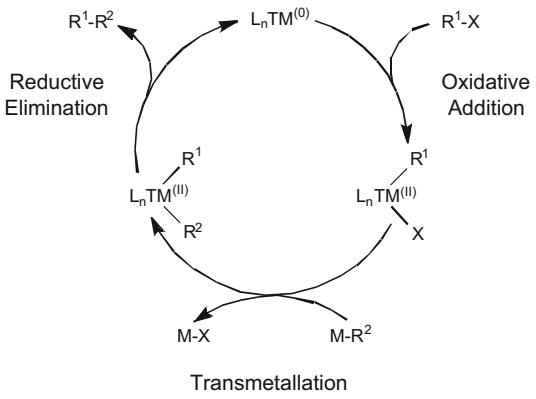
Although synthetically valuable, these methods suffer from intrinsic limitations in terms of atom and step economy. The pre-functionalization of the organometallic coupling partners is often expensive and time consuming. Also, traditional cross-coupling reactions generate stoichiometric amounts of organometallic by-products, with some of them even being toxic.

In this context, direct transition metal-catalyzed C-H activation of one non-functionalized coupling partner and reaction with another bearing a leaving group represents a suitable alternative for the formation of carbon-carbon bonds (Scheme 2b). The replacement of the organometallic reagent with a simple unsubstituted organic coupling partner eliminates the need for pre-functionalization.

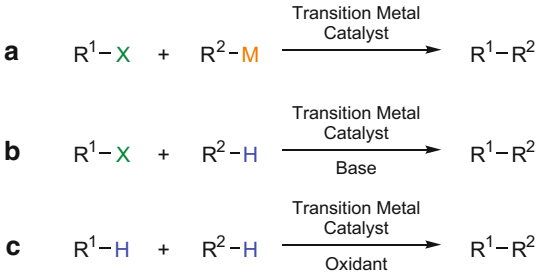
Oxidative cross-coupling reactions through twofold carbon-hydrogen bond cleavage are possible using transition metal catalysts with stoichiometric amounts of an oxidant (Scheme 2c). This method is highly atom economical regarding the non-functionalized substrates, but challenges in terms of selectivity and atom economy of transition metal oxidants still remain.

Additionally, in some cases, special metal complexes lead to degradation of the thiophene skeleton by activation of the carbon-sulfur bond [3–5].

Scheme 1 Catalytic cycle of traditional transition metal-catalyzed cross-coupling reactions



Scheme 2 Cross-coupling reactions: (**a**) traditional cross-coupling, (**b**) C-H activation, (**c**) oxidative cross-coupling



2 Synthesis by Substituent Modification

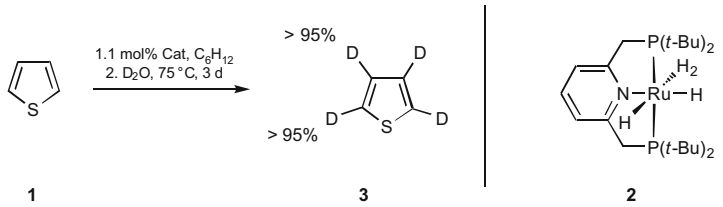
2.1 Substitution of Hydrogen

2.1.1 Hydrogen-Deuterium Exchange

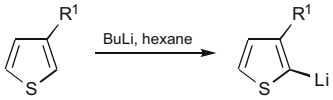
Catalytic hydrogen-deuterium exchange of thiophenes is possible utilizing D_2O as an environmentally benign and cheap deuterium source and a ruthenium dihydrogen complex **2** as the catalyst (Scheme 3) [6]. The exchange proceeds in a two-phase mixture of D_2O and cyclohexane. Cyclohexane, which serves as solvent for thiophene and the catalyst, was not deuterated under these reaction conditions. The hydrogen-deuterium exchange is quantitative at both α- and β-positions using 1 mol% catalyst at 75 °C for 3 days.

2.1.2 Metallation by Hydrogen-Lithium Exchange

The most common organolithium reagent for the metallation of thiophene is BuLi or BuLi/TMEDA, respectively. Alternative applicable reagents are lithium metal/naphthalene [7], alkyllithium/amine complexes [8], or lithiated polystyrene [9]. In the case



Scheme 3 Transition metal-catalyzed H/D exchange [6]



Scheme 4 Selective 2-lithiation

Table 1 Selective 2-lithiation

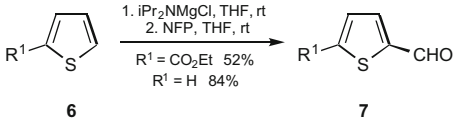
R^1	Ref.
H	[16]
OMe	[17]
O*t*-Bu	[18, 19]
F	[20]
CN	[21]
CH_2NMe_2	[22]
CO_2Li	[23, 24]

of halogenated thiophenes, LDA is the metallating agent of choice because its weak nucleophilicity allows the selective substitution of hydrogen with lithium instead of a possible halogen-metal exchange [10]. Next to chemoselectivity issues, substituents on the thiophene skeleton also have a strong influence on the regioselectivity of the hydrogen-lithium exchange process [11, 12]. Thus, thiophenes bearing substituents at the 2-position usually form 2,5-disubstituted products with organolithium compounds, whereas metallation of 3-alkyl thiophenes leads to a mixture of 2- and 5-lithiated products [13–15]. The selective 2-lithiation, which gives rise to 2,3-disubstituted derivatives (Scheme 4, Table 1), is possible with substituents at C-3 such as alkoxy, fluoro, cyano, carboxylate, or dimethylaminomethyl [17–23, 25, 26]. The last can direct the lithium atom into a specific position due to coordination with nitrogen. The dianionic lithium 2-lithiothiophene-3-carboxylate comprises a useful tool for the further synthesis of thiophenecarboxylic acid or ester derivatives [24].

2.1.3 Introduction of Formyl Groups by Metallation and Subsequent Reaction with *N*-Formylpiperidine

The application of hydrogen-lithium exchange reactions is limited due to possible reactions of nucleophilic organolithium reagents or aryllithium intermediates with

Scheme 5 Metallation of thiophenes followed by formylation with *N*-formylpiperidine [27]



Scheme 6 Vinylation of thiophene [28, 29]

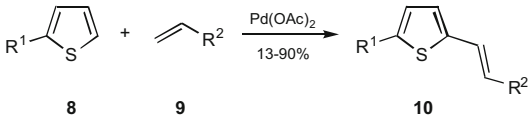


Table 2 Vinylation of thiophene [28, 29]

R^1	R^2	Yield[a] (%)	Ref.
H	CN	24 (2:1)[b]	[28]
H	Ph	13	[28]
H	CO_2Me	33	[28]
H	CO_2Bu	83	[29]
Me	CO_2Bu	87	[29]
OMe	CO_2Bu	62	[29]
Ph	CO_2Bu	80	[29]
4-$MeOC_6H_4$	CO_2Bu	87	[29]
H	CO_2t-Bu	90	[29]
4-$MeOC_6H_4$	CO_2t-Bu	78	[29]
H	$CONMe_2$	85	[29]
Me	CONMe	90	[29]
OMe	CONMe	70	[29]
OMe	CN	46 (2:1)[b]	[29]

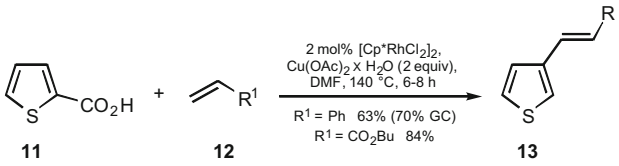
[a]Isolated yield of *E*-isomers
[b]Ratio of *E*- to *Z*-isomers in parentheses

electrophilic directing groups. Therefore, the metallation of thiophenes with organomagnesium compounds is a suitable alternative methodology.

For instance, the hydrogen-magnesium exchange of ethyl thiophene-2-carboxylate **6** is viable using (diisopropylamino)magnesium chloride, without a side reaction at the ester functionality with either the organomagnesium reagent or the arylmagnesium intermediate (Scheme 5) [27]. The metallation occurs selectively at the 5-position of the thiophene ring. The subsequent reaction of the thienylmagnesium intermediate, as nucleophile, for example, with *N*-formylpiperidine (NFP) gives the aldehyde **7**.

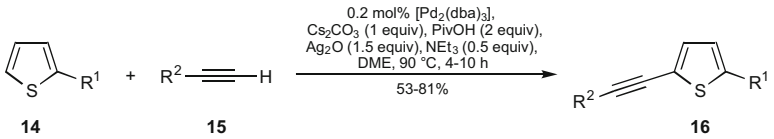
2.1.4 Introduction of Allyl, Alk-1-enyl, or Alk-1-ynyl Groups

Vinylthiophenes **10** can be synthesized by direct introduction of alk-1-enyl or alk-1-ynyl groups using equimolar amounts of palladium(II) chloride or palladium (II) acetate (Scheme 6, Table 2) [28, 30, 31]. A convenient method for the preparation of mono-alkenylated thiophenes is direct alkenylation with catalytic amounts of



11 12 13

Scheme 7 Coupling of thiophene-2-carboxylic acid derivatives with alkenes [32]



14 15 16

Scheme 8 Oxidative coupling of thiophenes with terminal alkynes [33]

palladium(II) acetate in the presence of silver acetate and pyridine (Scheme 6, Table 2) [29].

Alternatively, 3-vinylthiophenes **13** can be prepared through regioselective oxidative coupling of thiophene-2-carboxylic acid derivatives **11** with different alkenes **12** in the presence of a rhodium catalyst ($[Cp^*RhCl_2]_2$) and copper (II) acetate monohydrate as oxidant (Scheme 7) [32]. Thereby, the carboxylic group facilitates *ortho*-olefination and is subsequently removed by decarboxylation in a one-pot sequence. Additionally, benzo[*b*]thiophenes can equally be coupled effectively with butyl acrylate giving rise to the vinylated product in a yield of 70%.

The most common method for the introduction of alkyne groups is the catalytic Sonogashira cross-coupling reaction. However, the direct alkynylation of thiophenes represents a suitable alternative, not least due to its step, and atom economy. The palladium-catalyzed oxidative cross-coupling between differently functionalized thiophenes **14** and a variety of terminal alkynes **15** proceeds efficiently with extremely low catalyst loadings of 0.2 mol% (Scheme 8, Table 3) [33]. Notably, the reaction is compatible with thiophenes bearing various substituents such as ketone, aldehyde, ester, alkenyl, or halide. Of particular note is the iodo group, which is actually extremely reactive towards Sonogashira coupling reactions. Additionally, the utilization of terminal aryl alkynes with either electron-withdrawing or electron-donating groups also furnishes the corresponding products **16** in good yields.

2.1.5 Introduction of Aryl Groups

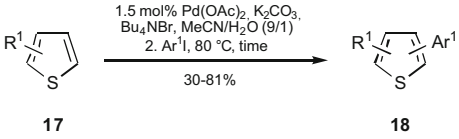
Transition Metal-Catalyzed Direct Arylation of Thiophenes with Aryl Halides

The most convenient method for the preparation of arylated thiophenes is palladium-catalyzed direct arylation [34–36]. This methodology is an atom-economical

Table 3 Oxidative coupling of thiophenes with terminal alkynes [33]

R^1	R^2	Time (h)	Yield (%)
COMe	Ph	4	81
COMe	4-*t*-BuC_6H_4	10	73
COMe	4-MeC_6H_4	10	64
COMe	4-$MeOC_6H_4$	10	68
COMe	4-FC_6H_4	6	70
COMe	3-BrC_6H_4	10	61
COMe	4-$CF_3C_6H_4$	5	56
COMe	3-$MeO_2CC_6H_4$	10	60
COMe	3-py	5	70
Me	Ph	5	73
Me	4-ClC_6H_4	10	72
Me	4-NCC_6H_4	10	55
Me	Si*i*-Pr_3	10	53
Br	Ph	5	68
Cl	Ph	5	76
I	Ph	5	63
CHO	Ph	5	67
CO_2Et	Ph	10	75
$CH{=}CHCO_2Me$	Ph	10	71
COPh	Ph	6	81
CO(4-FC_6H_4)	Ph	6	80
$COCF_3$	Ph	10	70
Ph	Ph	10	77
2-(5-phenylethynyl)thienyl	4-$MeOC_6H_4$	10	60

Scheme 9 Palladium-catalyzed coupling of thiophenes with aryl iodides [37]



17 **18**

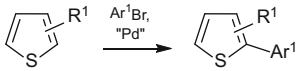
alternative to standard cross-coupling reactions requiring organometallic substrates. Thus, thiophenes **17**, which are activated by an electron-withdrawing substituent at position C-2 or C-3, can be directly arylated with aryl iodides by a Heck-type reaction with palladium(II) acetate and tetrabutylammonium bromide as catalytic system (Scheme 9, Table 4) [37–39]. The reaction of 2-substituted thiophenes is regioselective for C-5. In contrast, thiophenes bearing substituents at C-3 form 2,3-disubstituted products **18**; however, the formation of 2,4-disubstituted thiophenes is observed in some cases, for instance, treatment of 2-substituted thiophenes with arenes in the presence of a PhPdIbipy complex and a metal salt as additive forms the 2,4-disubstituted products regioselectively [40].

Aryl bromides can equally be coupled effectively with thiophenes **19** using the catalytic system tetrakis(triphenylphosphine)palladium and potassium acetate (Scheme 10, Table 5) [39]. The use of highly dispersed palladium-polypyrrole

Table 4 Palladium-catalyzed coupling of thiophenes with aryl iodides [37]

R^1	Ar^1	Time (h)	Yield (%)
2-CHO	5-Ph	7	30
2-NO_2	5-(4-$MeOC_6H_4$)	54	37
2-CN	5-(4-$MeOC_6H_4$)	4	77
2-CN	5-(4-$F_3CC_6H_4$)	3.25	79
2-CN	5-(2-$F_3CC_6H_4$)	3	81
3-CHO	2- Ph	3.50	35
3-CN	2-(4-$MeOC_6H_4$)	2.50	30

Scheme 10 Palladium-catalyzed coupling of thiophenes with aryl bromides



19 **20**

nanocomposites (Pd@pPy) enables an efficient coupling of *n*-butyl thiophenes **19** with either electron-rich or electron-poor bromoarenes [41], and the catalytic Pd@pPy nanocomposite can be easily recovered by filtration. Other palladium-catalyzed C-H arylations involve the treatment of 2-substituted thiophenes with *N*-(bromobenzyl)alkylamides [45] or the specific synthesis of thiophenes **20** for organic electronic materials [42]. Alternatively, an aryl group can be introduced into a thiophene **19** by a prior metallation of thiophene at an α-position, with catalytic amounts of an amine and ethylmagnesium chloride, i.e., the Grignard reagent, followed by palladium- or nickel-catalyzed arylation with an aryl bromide [43, 44]. Notably, the catalysts PEPPSI-SIPr and $NiCl_2$(dppe) can also be used to couple less reactive aryl chlorides effectively with both thiophenes and benzo[*b*] thiophenes according to this reaction protocol [44]. However, the nickel-catalyzed Wenkert arylation of thiophenes with an arylmagnesium halide in toluene gives rise to symmetrical (*E*,*E*)-1,4-diaryl-1,3-butadienes [46].

The direct arylation of 2-chlorothiophene **21** with both electron-neutral and electron-poor 4-substituted aryl bromides leads to the corresponding biaryls **22** in high yields, even using highly sterically hindered aryl bromides (Scheme 11, Table 6) [47]. However, arylation with deactivated aryl bromides is less successful, though more reactive aryl iodides bearing the same electron-rich substituents lead to higher conversions.

The preparation of polyfluoroarene-thiophene structures is of great interest, due to their role as active materials in electronic devices. The dehydrogenative cross-coupling of electron-deficient polyfluoroarenes and thiophenes is possible utilizing palladium(II) acetate as catalyst and silver(I) carbonate as oxidant [48]. However, the requirement for transition metal oxidants in stoichiometric amounts limits the atom economy of the direct arylation. Alternatively, molecular oxygen can be used as terminal oxidant for the palladium-catalyzed cross-coupling of polyfluoroarenes **24** with various functionalized thiophenes **23** (Scheme 12, Table 7) [49]. The reaction proceeds via twofold C-H functionalization, which is initiated by the C–H cleavage of polyfluoroarenes, giving rise to the corresponding polyfluoroarylated

Table 5 Palladium-catalyzed coupling of thiophenes with aryl bromides

R^1	Ar^1	Conditions	Yield (%)	Ref.
H	Ph	$Pd(PPh_3)_4$, KOAc, DMA, 150°C, 12 h	69	[39]
H	4-$MeOC_6H_4$	$Pd(PPh_3)_4$, KOAc, DMA, 150°C, 12 h	46	[39]
H	4-$OHCC_6H_4$	$Pd(PPh_3)_4$, KOAc, DMA, 150°C, 12 h	63	[39]
H	4-$Me(O)CC_6H_4$	$Pd(PPh_3)_4$, KOAc, DMA, 150°C, 12 h	47	[39]
H	4-$MeO_2CC_6H_4$	$Pd(PPh_3)_4$, KOAc, DMA, 150°C, 12 h	38	[39]
H	4-NCC_6H_4	$Pd(PPh_3)_4$, KOAc, DMA, 150°C, 12 h	52	[39]
H	4-$O_2NC_6H_4$	$Pd(PPh_3)_4$, KOAc, DMA, 150°C, 12 h	66	[39]
H	2-$O_2NC_6H_4$	$Pd(PPh_3)_4$, KOAc, DMA, 150°C, 12 h	53	[39]
2-*n*-Bu	4-NCC_6H_4	Pd@pPy, KOAc, DMAc, 150°C, 20 h	100	[41]
2-*n*-Bu	4-$Me(O)CC_6H_4$	Pd@pPy, KOAc, DMAc, 150°C, 20 h	100	[41]
2-*n*-Bu	Ph	Pd@pPy, KOAc, DMAc, 150°C, 20 h	90	[41]
2-*n*-Bu	2-quinolinyl	Pd@pPy, KOAc, DMAc, 150°C, 20 h	100	[41]
2-CHO	4-$EtOC_6H_4$	$Pd(OAc)_2$, PCy_3HBF_4, PivOH, K_2CO_3, PhMe, 110°C, 16 h	99	[42]
2-CHO	4-$C_6H_4N(4\text{-}BrC_6H_4)_2$[a]	$Pd(OAc)_2$, PCy_3HBF_4, PivOH, K_2CO_3, PhMe, 100°C, 16 h	89	[42]
2-thienyl	4-$TBSOC_6H_4$	$Pd(OAc)_2$, PCy_3HBF_4, PivOH, K_2CO_3, PhMe, 100°C, 16 h	52	[42]
2-CHO	4-$Ph_2NC_6H_4$	$Pd(OAc)_2$, PCy_3HBF_4, PivOH, K_2CO_3, PhMe, 100°C, 16 h	91	[42]
2-thienyl	4-*n*-$HexC_6H_4$[b]	$Pd(OAc)_2$, PCy_3HBF_4, PivOH, K_2CO_3, PhMe, 100°C, 16 h	87	[42]
H	4-$Ph_2NC_6H_4$	$Pd(OAc)_2$, PCy_3HBF_4, PivOH, K_2CO_3, PhMe, 100°C, 16 h	86	[42]
2-CN	4-$MeOC_6H_4$	$Pd(OAc)_2$, PCy_3HBF_4, PivOH, K_2CO_3, PhMe, 100°C, 16 h	97	[42]
H	4-(4-BrC_6H_4)C_6H_4[c]	$Pd(OAc)_2$, PCy_3HBF_4, PivOH, K_2CO_3, PhMe, 110°C, 48 h	66	[42]
2-Cl, 3-Hex	4-$F_3CC_6H_4$	1. DMP, EtMgCl, THF; 2. Ar^1Br, $PdCl_2dppf$, rt, 10 h	51	[43]
2-Cl, 3-Hex	4-FC_6H_4	1. DMP, EtMgCl, THF; 2. Ar^1Br, $PdCl_2dppf$, rt, 18 h	68	[43]
2-Cl, 3-Hex	Ph	1. DMP, EtMgCl, THF; 2. Ar^1Br, $PdCl_2dppf$, rt, 14 h	76	[43]
2-Cl, 3-Hex	2-naphthalenyl	1. DMP, EtMgCl, THF; 2. Ar^1Br, $PdCl_2dppf$, rt, 14 h	83	[43]
2-Cl, 3-Hex	4-$MeOC_6H_4$	1. DMP, EtMgCl, THF; 2. Ar^1Br, $PdCl_2dppf$, rt, 22 h	86	[43]
2-Cl, 3-Hex	$Me_2NC_6H_4$	1. DMP, EtMgCl, THF; 2. Ar^1Br, $PdCl_2dppf$, rt, 20 h	25	[43]
2-Me	4-MeC_6H_4	1. Cy_2NH, EtMgCl, THF; 2. Ar^1Br, $NiCl_2$(dppe), THF, rt, 24 h	99	[44]
2-Me	4-$MeOC_6H_4$	1. Cy_2NH, EtMgCl, THF; 2. Ar^1Br, $NiCl_2$(dppe), THF, rt, 24 h	79	[44]
2-Me	Ph	1. Cy_2NH, EtMgCl, THF; 2. Ar^1Br, $NiCl_2$(dppe), THF, rt, 24 h	97	[44]

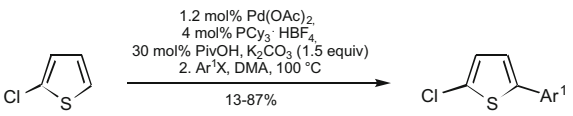
(continued)

Table 5 (continued)

R^1	Ar^1	Conditions	Yield (%)	Ref.
2-Me	4-FC_6H_4	1. Cy_2NH, EtMgCl, THF; 2. Ar^1Br, $NiCl_2$(dppe), THF, rt, 24 h	98	[44]
2-Me	4-$F_3CC_6H_4$	1. Cy_2NH, EtMgCl, THF; 2. Ar^1Br, $NiCl_2$(dppe), THF, rt, 23 h	76	[44]
2-Me	2-naphthalenyl	1. Cy_2NH, EtMgCl, THF; 2. Ar^1Br, $NiCl_2$(dppe), THF, rt, 23 h	75	[44]
2-Me	$Me_2NC_6H_4$	1. Cy_2NH, EtMgCl, THF; 2. Ar^1Br, $NiCl_2$(dppe), THF, rt, 23 h	38	[44]
2-CCC_6H_{13}	4-MeC_6H_4	1. Cy_2NH, EtMgCl, THF; 2. Ar^1Br, PEPPSI-SIPr, THF, rt, 22 h	75	[44]
2-CCC_6H_{13}	4-$MeOC_6H_4$	1. Cy_2NH, EtMgCl, THF; 2. Ar^1Br, PEPPSI-SIPr, THF, rt, 24 h	86	[44]
H	4-MeC_6H_4	1. Cy_2NH, EtMgCl, THF; 2. Ar^1Br, PEPPSI-SIPr, THF, rt, 24 h	95	[44]
H	4-$MeOC_6H_4$	1. Cy_2NH, EtMgCl, THF; 2. Ar^1Br, PEPPSI-SIPr, THF, rt, 24 h	75	[44]
H	4-$Me_2NC_6H_4$	1. Cy_2NH, EtMgCl, THF; 2. Ar^1Br, PEPPSI-SIPr, THF, rt, 24 h	70	[44]

[a]Threefold reaction based on aryl bromide; product is 5,5′,5″-(nitrilotris(benzene-4,1-diyl))tris (thiophene-2-carbaldehyde)
[b]Twofold reaction based on bisthiophene; product is 5,5′-bis(4-hexylphenyl)-2,2′-bithiophene
[c]Twofold reaction based on aryl bromide; product is 4,4′-di(thiophen-2-yl)-1,1′-biphenyl

Scheme 11 Direct arylation of 2-chlorothiophene [47]

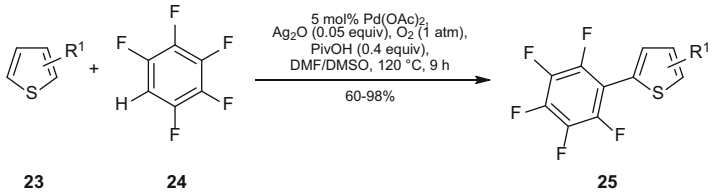


21 **22**

Table 6 Direct arylation of 2-chlorothiophene [47]

Ar^1	X	Time (h)	Yield (%)
4-$O_2NC_6H_4$	Br	8	87
4-MeC_6H_4	Br	8	72
4-ClC_6H_4	Br	8	68
4-$F_3CC_6H_4$	Br	16	56
2-MeC_6H_4	Br	8	72
2-$MeO_2CC_6H_4$	Br	14	74
4-$MeOC_6H_4$	Br	14	13
4-$MeOC_6H_4$	I	14	58
2-$MeOC_6H_4$	Br	14	37
2-$MeOC_6H_4$	I	14	59

products **25** in yields up to 98%. Variously substituted fluoroarenes can be effectively coupled with a selection of thiophenes under the same aerobic reaction conditions.



23 24 25

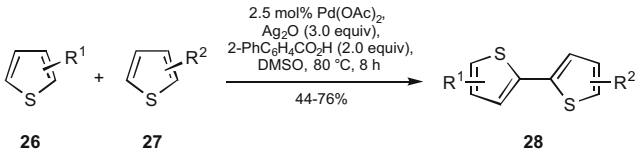
Scheme 12 Aerobic dehydrogenative cross-coupling of pentafluorobenzene with thiophene derivatives [49]

Table 7 Aerobic dehydrogenative cross-coupling of pentafluorobenzene with thiophene derivatives [49]

R^1	Yield (%)
2-CO_2Me	90
2-$CONMe_2$	94
2-CHO	68
2-Cl	60
2-Me	80
2-C_6F_5	86
2-(4-$MeOC_6H_4$)	88
2-(4-$F_3CC_6H_4$)	81
2-(3-$O_2NC_6H_4$)	98

Transition Metal-Catalyzed Direct Arylation of Thiophenes with Heteroarenes

Transition metal-catalyzed C-H activation can also be utilized for the dehydrogenative cross-coupling of thiophenes with heteroarenes giving rise to the ubiquitous biheteroaryl motif found in biologically active compounds and semiconducting materials. For instance, thiophenes and their benzo-annulated analogs can be successfully cross-coupled with various *N*-containing heterocycles, such as xanthines, azine *N*-oxides, imidazoles, and benzoxazoles by palladium-catalyzed dual C–H bond cleavage [50, 51]. For this intermolecular regioselective carbon-carbon bond formation, 2.5 mol% palladium(II) acetate as catalyst and copper (II) acetate monohydrate as oxidant are used. Bromo-substituted pyrimidines can react with thiophenes either by microwave-assisted palladium-catalyzed direct arylation or by nucleophilic aromatic substitution of the pyrimidine in the presence of a Lewis acid, such as trifluoroacetic acid, followed by oxidation with potassium hexacyanoferrate(III) in an aqueous solution of potassium hydroxide [52, 53]. Notably, the latter leaves the pyrimidine C–Br bond intact, following a dual C–H/C–H cross-coupling reaction pathway. The dehydrogenative cross-coupling of thiophenes and benzo[*b*]thiophenes with furans can be achieved utilizing a rhodium(III) complex ($[RhCp^*Cl_2]_2$) as catalyst and copper(II) 2-ethylhexanoate as oxidant [54]. Polythiophenes are accessible by direct heteroarylation polymerization.



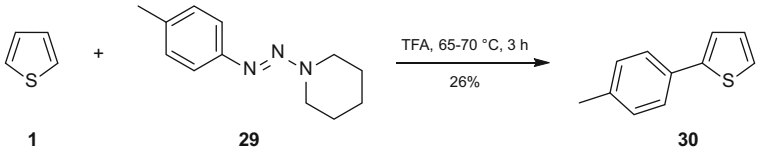
Scheme 13 Palladium-catalyzed cross-coupling between two differently substituted thiophenes [56]

Table 8 Palladium-catalyzed cross-coupling between two differently substituted thiophenes [56]

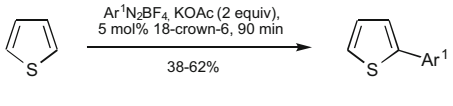
R^1	R^2	Yield[a] (%)
2-$CONMe_2$	2-Br, 3-*n*-Hex	71 (25)
2-CO_2Me	2-Br, 3-*n*-Hex	70 (28)
2-CO_2Me, 3-Me	2-Br, 3-*n*-Hex	64 (32)
2-COMe	2-Br, 3-*n*-Hex	76 (20)
2-CHO	2-Br, 3-*n*-Hex	72 (23)
2-CN	2-Br, 3-*n*-Hex	53 (14)
2-CO_2Me	2-Br, 3-Me	71 (25)
2-CO_2Me	2-Br	62 (31)
2-CO_2Me	2-Cl, 3-Me	70 (28)
2-CO_2Me	2-Cl	61 (31)
2-CO_2Me	2-Me	53
2-$CONMe_2$	2-Ph	64 (33)
2-CHO	2-Ph	65 (30)
2-$CONMe_2$	2-CCPh	52 (22)
2-CO_2Me	2-$CONMe_2$	69 (27)
2-$CONMe_2$	2-C_6F_5	60
2-OMe	2-Br, 3-*n*-Hex	56 (18)
2-Me	2-OMe	44 (37)
2-Ph	2-Br, 3-*n*-Hex	66 (27)
2-benzo[*b*]thienyl	2-(4-$Ph_2NC_6H_4$)	53 (27)
2-(5-CHO-thienyl)	2-Br, 3-*n*-Hex	71, 68

[a]Yield of homocoupling product of **27** observed

Most of these arylations are palladium promoted, using catalysts such as the highly stable Herrmann-Beller catalyst, palladium(II) acetate, or palladium(II) acetate in combination with pivalic acid, which aids the C-H activation [36]. Another technique involves the iterative growth of oligomers, which is accomplished by regioselective metallation of 3-substituted thiophenes at the α-position by means of the Knochel-Hauser base (TMPMg·LiCl) and subsequent nickel-catalyzed cross-coupling with bromothiophene [55]. The preparation of biheteroaryls **28** from differently functionalized thiophenes **26** and **27**, which is challenging due to possible homocouplings, is feasible in the presence of palladium(II) acetate and silver (I) oxide (Scheme 13, Table 8) [56]. Thiophenes bearing functionalities with various electronic characters as well as thiophenes with similar electronic groups can be efficiently coupled with one another giving rise to the corresponding bithiophenes **28** in yields up to 76%.



Scheme 14 Arylation of thiophene by reaction with an aryltriazene [57]



Scheme 15 Gomberg-Bachmann coupling of diazonium salts [61]

Table 9 Gomberg–Bachmann coupling of diazonium salts [61]

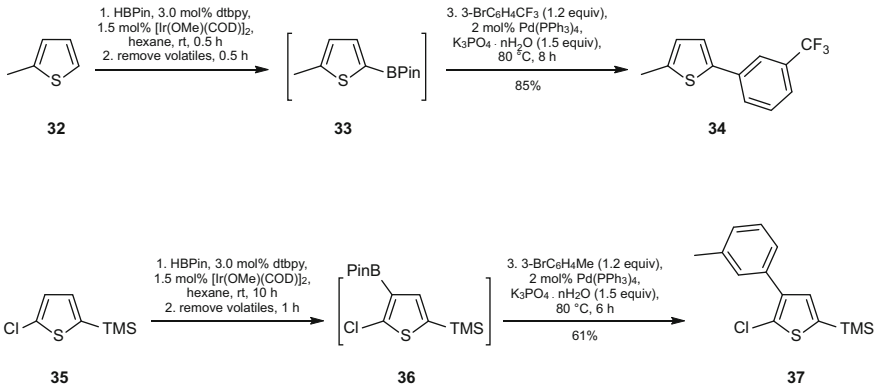
Ar^1	Conditions	Yield (%)	Ref.
4-ClC_6H_4	KOAc, 18-crown-6	62	[62, 63]
4-ClC_6H_4	KOAc	33	[64]
4-BrC_6H_4	KOAc, 18-crown-6	56	[63]
4-BrC_6H_4	KOAc	20	[58]
4-$O_2NC_6H_4$	KOAc, 18-crown-6	38	[62]
4-$O_2NC_6H_4$	KOAc	23	[58]

Direct Arylation of Thiophenes Without a Palladium Catalyst

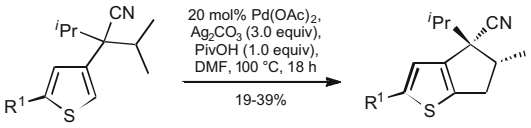
The synthesis of arylated thiophenes without the requirement for a palladium catalyst is possible using aryltriazenes (Scheme 14) [57] or aromatic diazonium salts (Gomberg-Bachmann reaction) [58]. The usually low to moderate yields of this type of arylation can be improved by adding phase-transfer catalysts to the reaction medium [59–61]. Phase-transfer agents like crown ethers or quaternary salts enhance the reactivity of the Gomberg-Bachmann reaction (Scheme 15, Table 9) [62]. Hypervalent iodines, such as phenyliodine(III) bis(trifluoroacetate) (PIFA), can also be utilized to promote the metal-free cross-coupling between thiophenes and nucleophilic alkylbenzenes [65]. The cross-coupling proceeds via a thiophene cation radical, which is generated by hypervalent iodine-induced SET oxidation.

One-Pot C–H Borylation/Suzuki–Miyaura Cross-Coupling

An alternative method for the direct arylation of thiophenes via C–H bond functionalization is a one-pot C–H borylation/Suzuki–Miyaura reaction sequence (Scheme 16) [66]. The first step is the generation of the organoboron intermediates **33** and **36** from the thiophenes **32** and **35** by means of an iridium catalyst. The second step, the Suzuki–Miyaura cross-coupling, can be accomplished subsequently by adding an aryl bromide to the solution of crude boronate esters without the necessity to remove the spent iridium catalyst beforehand.



Scheme 16 One-pot C–H borylation/Suzuki–Miyaura cross-coupling [66]



Scheme 17 Intramolecular C-H/C-H activation [67]

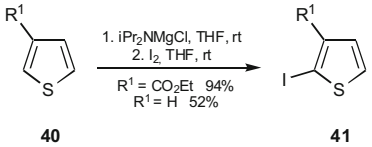
Table 10 Intramolecular C-H/C-H activation [67]

R^1	dr	Yield (%)
2-MeC_6H_4	30:1	33
2-$F_3CC_6H_4$	19:1	31
2-NCC_6H_4	>98:2	36
2-$O_2NC_6H_4$	>98:2	35
Ph	23:1	24
3-$MeOC_6H_4$	26:1	30
3-NCC_6H_4	19:1	19
4-MeC_6H_4	23:1	35
2-FC_6H_4	23:1	39
H	–	<5

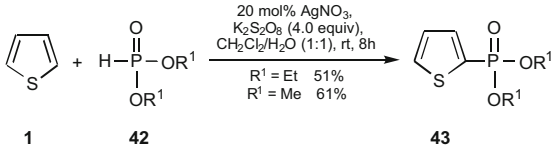
2.1.6 Introduction of Alkyl Groups via Intramolecular Palladium-Catalyzed Dehydrogenative Coupling

Fused thiophene-cyclopentanes **39** can be synthesized by intramolecular dual C-H activation of 2-arylthiophenes **38** (Scheme 17, Table 10) [67]. The cross-coupling proceeds moderately well using palladium(II) acetate as catalyst and silver (I) carbonate as oxidant. When the thiophene moiety is not substituted at position 2, homocoupling occurs easily. However, in contrast to this direct route, a two-step sequence consisting of a prior bromination and a subsequent palladium-catalyzed arylation is much more effective forming the fused thiophene-cyclopentane **39** in a yield of 83%.

Scheme 18 Iodination of thiophene [27]



Scheme 19 Dehydrogenative cross-coupling of thiophenes with dialkyl phosphites [69]



2.1.7 Halogenation

The halogenation of thiophenes is an important synthetic step for the further formation of variously functionalized thiophenes. The reactions of halogenated thiophenes are described in detail in Sect. 2.3 (Substitution of Heteroatoms). Iodinated thiophenes can be prepared by the selective metallation of ethyl thiophene-3-carboxylate with the base (diisopropylamino)magnesium chloride at C-2 (Scheme 18) [27]. The resulting thienylmagnesium intermediate can react with iodine giving rise to 2-iodothiophene **41** in 94% yield. Analogously, chlorothiophenes react with ethylmagnesium chloride under deprotonative metallation in the presence of catalytic amounts of *cis*-2,6-dimethylpiperidine and can give iodo-products by subsequent reaction with iodine [43].

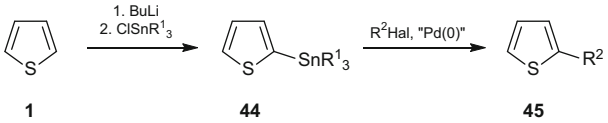
2.1.8 Introduction of Dialkyl Phosphite

Heteroaryl phosphonates are common motifs in biological compounds and have stimulated the development of transition metal-catalyzed methodologies for C–P bond formation [68]. Phosphonated thiophenes **43** are accessible via silver-catalyzed dehydrogenative cross-coupling of thiophene **1** with dialkyl phosphites **42** (Scheme 19) [69]. The reaction is performed in aqueous dichloromethane, proceeds regioselectively at the α-position, and utilizes silver(I) nitrate as catalyst and the oxidant potassium persulfate.

2.2 Substitution of Metals

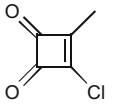
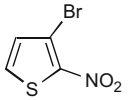
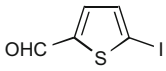
2.2.1 Substitution Reactions Involving Organostannanes (the Stille Reaction)

Transition metal-catalyzed cross-coupling reactions between organometallic reagents and organic electrophiles are one of the most powerful tools for forming

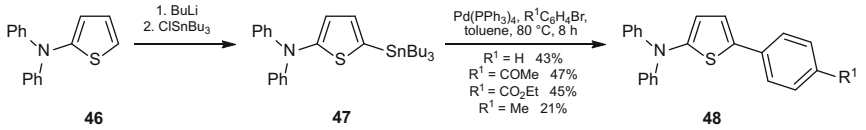


Scheme 20 Stille coupling of 2-(trialkylstannyl)thiophenes

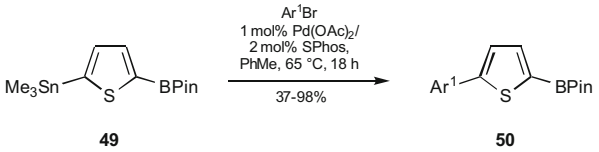
Table 11 Stille coupling of 2-(trialkylstannyl)thiophenes

R^1	R^2Hal	Yield (%)	Ref.
Bu		65	[105]
Me	*trans*-$EtO_2CCH{=}CHI$	74	[106]
Bu	2-iodothiophene	80	[107]
Bu		29	[108]
Bu		71	[107]
Bu	*trans*-PhCH=CH–COCl	86	[109]
Me	$H_2C{=}CH{-}CH_2{-}Cl$	40	[110]
Bu	$MeCOC_6H_4I$	80	[102]
Bu	C_6F_5Br	81	[42]

carbon-carbon bonds. One of a number of those catalytic methods is the Stille reaction, which is readily used for the synthesis of both mixed aryl-thienyl oligomers and bi- and terthiophenes [42, 70–86]. Typical thienylstannanes **73** such as (tributylstannyl)- or (trimethylstannyl)thiophene can be prepared from the corresponding thienyllithiums [87–90]. Though tributylstannyl compounds are less reactive compared to the respective trimethylstannyl compounds, their utilization is more common, because of their lesser toxicity [91]. However, the general toxicity of the organotin substrates and by-products remains a major drawback of the Stille reaction. The cross-coupling of thienylstannanes **73** is possible with aryl, acyl, alk-1-enyl, or allyl halides or triflates as well as terminal alkynes via palladium(0)-catalysis [92]. The reaction rate decreases dependent on the halide in the sequence $R^2I{>}R^2Br{>}R^2Cl$. Like other cross-coupling reactions, the mechanism of the Stille reaction can be described by a catalytic cycle involving the three main steps: oxidative addition, transmetallation, and reductive elimination. At the outset of the catalytic cycle, the active Pd(0) species either is formed in situ via reduction of a Pd(II) pre-catalyst like dichloro(triphenylphosphine)palladium(II) or can be obtained by the loss of two ligands of preformed Pd(0) species such as tetrakis(triphenylphosphine)palladium(0) [93–100]. The efficiency of the Stille coupling can be improved by adding cocatalysts such as Cu(I) salts [101–104]. Usually, Stille reactions are performed in tetrahydrofuran, 1,4-dioxane,



Scheme 21 Stille coupling of *N*,*N*-diphenyl-5-(tributylstannyl)thiophene-2-amine [114]



Scheme 22 Stille coupling of disubstituted thiophene with aryl bromides [115]

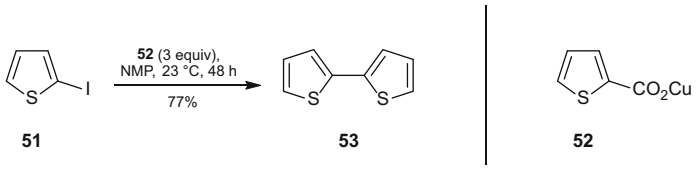
Table 12 Stille coupling of disubstituted thiophene with aryl bromides [115]

Ar^1	Yield (%)
4-$O_2NC_6H_4$	98
4-NCC_6H_4	84
4-$F_3CC_6H_4$	81
3-pyridinyl	81
5-(2-OHC-furanyl)	95
5-(2-MeO_2C-furanyl)	76
4-$MeOCC_6H_4$	87
Ph	83
1-naphthalenyl	91
4-$Me_2NC_6H_4$	37
3-$MeOC_6H_4$	89
2,5-$(MeO)_2C_6H_3$	66

dimethylformamide, or *N*-methyl-2-pyrrolidone as solvent. In contrast to reactions such as Suzuki, Kumada, or Heck couplings that are run under basic conditions, the Stille reaction can proceed under neutral conditions. However, often, basic conditions (e.g., lithium carbonate, sodium carbonate, trialkylamine, pyridine) are also applied (Scheme 20, Table 11) [79, 111–113].

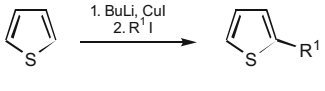
2-(*N*,*N*-Diphenylamino)thiophene **46** can be lithiated and subsequently reacted with tributylstannyl chloride giving rise to a 2,5-disubstituted thienylstannane intermediate **47** (Scheme 21) [114]. The 5-tributylstannylated thiophene **47** can thus be utilized in a Stille reaction coupling effectively with neutral, activated, as well as deactivated bromobenzenes. The reaction takes place in anhydrous toluene, using catalytic amounts of tetrakis(triphenylphosphine)palladium(0).

The cross-coupling reaction of differently functionalized aryl halides with a 2,5-disubstituted thiophene **49** bearing a trimethylstannyl as well as a boronic acid ester pinacolate (BPin) group shows high nucleophile selectivity (Scheme 22, Table 12) [115]. The biaryls **50** are chemoselectively formed via Stille coupling in the presence of a catalytic system consisting of palladium(II) acetate and SPhos



51 53 52

Scheme 23 Synthesis of 2,2′-bithiophene by Ullmann-like reductive coupling [120]



1 54

Scheme 24 Coupling of thiophenes via 2-thienylcopper [121]

Table 13 Coupling of thiophenes via 2-thienylcopper [121]

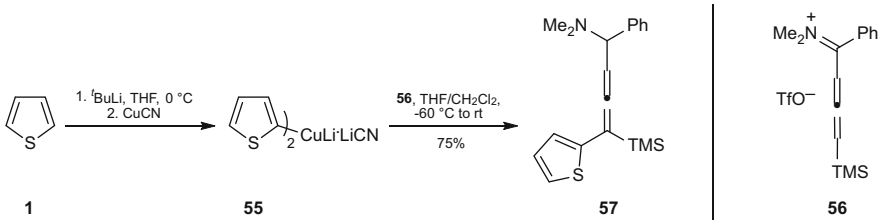
R^1	Yield (%)
Ph	41
4-Tol	36
2,6-$(MeO)_2C_6H_3$	28
2-thienyl	2

indicating the significance of the base for a successful Suzuki–Miyaura reaction. The addition of a second aryl halide in combination with potassium phosphate to the reaction pot leads to a subsequent Suzuki–Miyaura cross-coupling reaction.

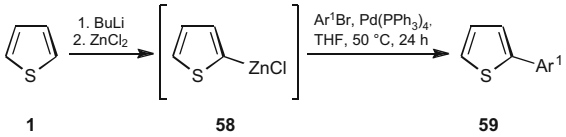
2.2.2 Substitution Reactions Involving Organocopper Derivatives

The synthesis of symmetrical bithienyls is possible via the Ullmann reaction [116–119]. Here, halogenated thiophenes are coupled with one another at elevated temperatures via copper catalysis forming the corresponding biaryls in low to moderate yields. 2,2′-Bithiophene **53** can as well be generated at room temperature through an Ullmann-like reductive coupling of 2-iodothiophene **51**, which is promoted by copper(I) thiophene-2-carboxylate **52** (Scheme 23) [120]. The high reaction temperatures required for an Ullmann reaction are achieved using high boiling solvents such as nitrobenzene, quinoline, or *N*,*N*-dimethylformamide; however, the use of the last increases the chance of a dehalogenation side reaction (ArX → ArH) [117]. In order to avoid the replacement of halogen by hydrogen, the synthesis of bithienyls via copper intermediates is a more convenient method [121–128]. For instance, the synthesis of 2-arylthiophenes **54** is possible via the initial preparation of 2-thienylcopper by the reaction between 2-thienyllithium and copper(I) salts (Scheme 24, Table 13) [121]. 2-Thienylcopper subsequently reacts with various iodoarenes giving rise to the corresponding products **54** in moderate yields.

The utilization of organocuprates is another useful method for the formation of carbon-carbon bonds. Typical organocuprate-assisted reactions are conjugate



Scheme 25 Conjugate addition of thienylcuprates to propyniminium salts [132]



Scheme 26 Palladium-catalyzed cross-coupling of 2-thienylzinc chloride [83]

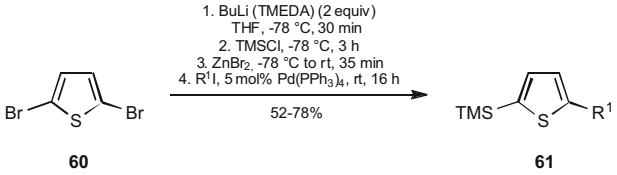
Table 14 Palladium-catalyzed cross-coupling of 2-thienylzinc chloride [83]

Ar^1	Yield (%)
Ph	80
4-$MeOC_6H_4$	88
3-ClC_6H_4	82
3-NCC_6H_4	80
4-$H_2C{=}CHC_6H_4$	26

addition, acylation, or alkylation of the organic ligand. Low-order thienylcuprates of the type (2-thienyl)Cu(CN)Li can be prepared by the reaction of 2-thienyllithium with copper(I) cyanide [129–131]. For instance, the synthesis of a 1-dialkylamino-3-(trimethylsilyl)allene **57** is possible via conjugate addition of the homocuprate $(2\text{-thienyl})_2CuLi{\cdot}LiCN$ **55** to a propyne iminium triflate **56** (Scheme 25) [132, 133]. However, mixed thienylcuprates of the type R_TR_RCuLi have not been widely applied yet, because the thienyl moiety R_R functions merely as dummy ligand, whereas R_T represents the transferable ligand [134].

2.2.3 Substitution Reactions Involving Organozinc Derivatives (the Negishi Reaction)

The Negishi reaction is another effective method for forming arylthiophenes via palladium-catalyzed cross-coupling of in situ generated thienylzinc halides with electrophilic aryl halides (Scheme 26, Table 14) [83, 87, 135–138]. Both mixed oligomers and polymers can be efficiently prepared via Negishi coupling [139–141]. The thienylzinc reagent is formed through the reaction of the corresponding thienyllithium with a zinc(II) halide. By analogy with the Stille coupling described above, the reaction proceeds via oxidative addition, transmetallation, and reductive elimination. As well as palladium catalysts, such as tetrakis(triphenylphosphine)



Scheme 27 One-pot, three-component synthesis of unsymmetrically substituted thiophenes from 2,5-dibromothiophene [143]

Table 15 One-pot, three-component synthesis of unsymmetrically substituted thiophenes from 2,5-dibromothiophene [143]

R^1	Yield (%)
4-Tol	64
3,5-$Me_2C_6H_4$	54
4-$MeOC_6H_4$	78
4-ClC_6H_4	57
4-FC_6H_4	56
4-$MeO_2CC_6H_4$	59
4-NCC_6H_4	52
3-pyridyl	67

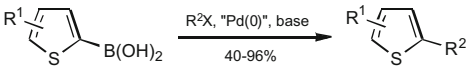
palladium(0), Negishi couplings can be effectively promoted by nickel complexes. For instance, the cross-coupling between a vinylic telluride and 2-thienylzinc chloride is catalyzed by dichloro(1,2-bis(diphenylphosphino)ethane)nickel(II) (Ni(dppe)Cl_2) forming the corresponding product in a high yield of 81% [142].

The transformation of a symmetrically disubstituted thiophene into an unsymmetrical target compound is an interesting synthetic device. The reaction of 2,5-dibromothiophene **60** giving rise to unsymmetrical 5-aryl-2-trimethylsilylthiophenes **61** proceeds in a one-pot three-component fashion forming thienylzinc bromides in situ, which are subsequently submitted to Negishi coupling (Scheme 27, Table 15) [143]. The initial step, the synthesis of 2,5-dilithiothiophene from 2,5-dibromothiophene **60**, uses a double bromine-lithium exchange with butyllithium in the presence of tetramethylethylenediamine (TMEDA). The dilithio intermediate is then electrophilically trapped first with trimethylsilyl chloride and then anhydrous zinc bromide, generating the organozinc derivative which is immediately transformed via a palladium-catalyzed Negishi coupling into an unsymmetrically substituted thiophene **61** in moderate to good yield.

2.2.4 Substitution Reactions Involving Organoboron Derivatives (the Suzuki–Miyaura Reaction)

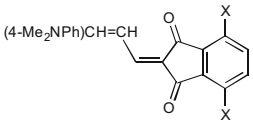
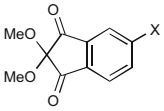
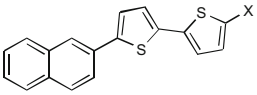
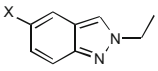
The palladium-catalyzed Suzuki–Miyaura reaction is an extremely effective and versatile approach for selective carbon-carbon bond formation. Thus, the coupling between arylboronic acids and aryl halides or triflates is frequently utilized for the preparation of biaryls [52, 81, 87, 88, 144–152] or fused heterocyclic systems [139–141, 153–157]. Other applications involve the synthesis of indazole-based thienyl

Scheme 28 Suzuki–Miyaura coupling reactions of 2-thienylboronic acids



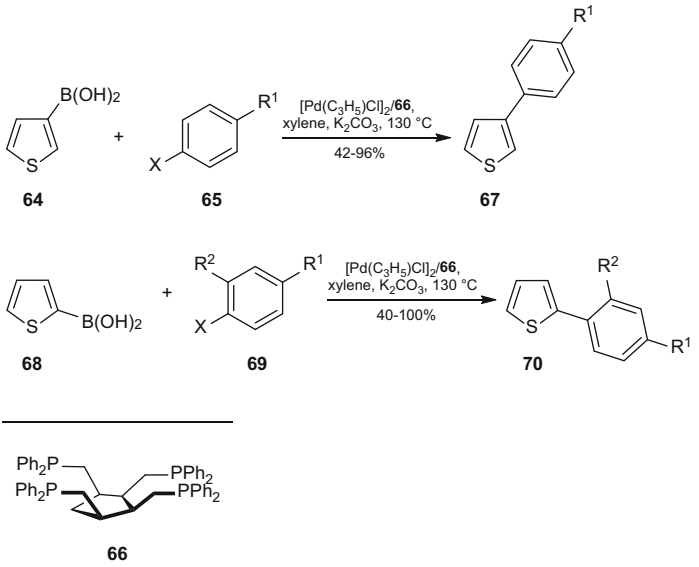
62 63

Table 16 Suzuki–Miyaura coupling reactions of 2-thienylboronic acid

R^1	R^2	X	Conditions	Yield (%)	Ref.
H	$ClC_4F_8CH_2CH_2$	I	$Pd(PPh_3)_4$, $NaHCO_3$	68	[162]
H	$C_{10}F_{21}CH_2CH_2$	I	$Pd(PPh_3)_4$, $NaHCO_3$	58	[162]
H		I	$PdCl_2(PPh_3)_2$, Na_2CO_3	82	[163]
H	4-ClC_6H_4CO	Cl	$Pd(PPh_3)_4$, Cs_2CO_3	78	[164]
H	MeCO	Cl	$Pd(PPh_3)_4$, Cs_2CO_3	47	[164]
H		Br	$Pd(PPh_3)_4$, Na_2CO_3	96	[165]
H	3-thienyl	Br	$Pd(PPh_3)_4$, Na_2CO_3	40–70	[147]
H	2-pyridyl	Br	$Pd(PPh_3)_4$, Na_2CO_3	67	[166]
H	5-pyrimidinyl	Br	$Pd(PPh_3)_4$, K_2CO_3	55[a]	[52]
5-CHO	4-$Ph_2NC_6H_4$	Br	$Pd(dppf)Cl_2$, K_2CO_3	75[a]	[42]
H	4-$Ph_2NC_6H_4$	Br	$Pd(PPh_3)_4$, $NaHCO_3$	51[b]	[42]
5-$C_{10}H_{21}$		Br	$Pd(PPh_3)_4$, Na_2CO_3	65[b]	[161]
H		Br	$Pd(dppf)Cl_2$, K_2CO_3	87	[158]

[a]Microwave assisted
[b]With 2-thienylboronic acid pinacol ester

compounds [158], which are valuable building blocks found in biologically active molecules, or the postmodification of polycyclic aromatic hydrocarbons, e.g., the construction of cyclopenta[*hi*]aceanthrylenes bearing thiophene-based functionalities on positions 2 and 7 [159]. Even oligothiophenes can be synthesized, for instance, by the polymer-supported coupling of thienylboronic acids with iodothiophenes [160, 161]. Next to the formation of aryl- and alkylthiophenes, the versatility of the Suzuki–Miyaura reaction is also displayed in the couplings of thienylboronic acids with diverse functional groups such as acid chlorides giving rise to ketones (Scheme 28, Table 16) [164] or amines/aldehydes forming aminomethylthiophenes [167, 168]. The reaction proceeds via the three-step catalytic cycle according to the general mechanism of metal-catalyzed cross-coupling reactions. However, the transmetallation step requires the activation of the boron by



Scheme 29 Suzuki–Miyaura coupling reactions of 3- and 2-thienylboronic acids with aryl halides [171]

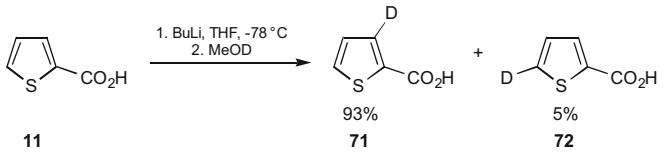
Table 17 Suzuki–Miyaura coupling reactions of 3- and 2-thienylboronic acids with aryl halides [171]

Boronic acid	R^1	R^2	X	Ratio(substrate/catalyst)[a]	Yield[b] (%)
68	COMe	–	Br	250:1	77 (82)
68	COMe	–	Br	1000:1	(55)
68	CHO	–	Br	250:1	81 (90)
68	CHO	–	Br	1000:1	(45)
68	CN	–	Br	250:1	85 (96)
68	CN	–	Br	1000:1	(77)
68	OMe	–	Br	250:1	84 (97)
68	OMe	–	Br	1000:1	(42)
64	H	H	I	100:1	82 (96)
64	H	H	Br	50:1	(47)
64	OMe	H	Br	50:1	81
64	H	Me	Br	20:1	87 (100)
64	H	Me	Br	50:1	(40)

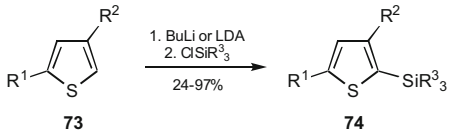
[a]Substrate/catalyst ratio based on aryl halide
[b]Isolated yields; GC and NMR yields in parentheses

a base. 2- and 3-Thienylboronic acids can be obtained by the reaction via the corresponding thienyllithiums [169, 170].

The Suzuki–Miyaura coupling of 3-thienylboronic acid **64** with aryl bromides **65** is possible with extremely low catalyst loadings of only 0.1% using the catalytic system



Scheme 30 Synthesis of deuterated thiophene-2-carboxylic acids [24]



Scheme 31 2-Silylation of thiophenes

Table 18 2-Silylation of thiophenes

R^1	R^2	$SiR^3{}_3$	Yield (%)	Ref.
H	H	$Si(CH{=}CH_2)(2\text{-thienyl})_2$	24	[191]
H	H	TMS	84	[192]
Me	H	TMS	72	[193]
Me	H	$SiMe_2CH_2Cl$	97	[194]
Me	H	TBDMS	83	[195]
H	Br	TMS	87	[196]

Tedicyp **66**/allylpalladium(II) chloride dimer (Scheme 29, Table 17) [171, 172]. In contrast, the reaction of 2-thienylboronic acid **68** with aryl halides **69** needs to be performed with 1–5% of the same catalytic system. Alternatively, cross-coupling can utilize arylboronic acids with thiophene halides: this yields better results in most cases.

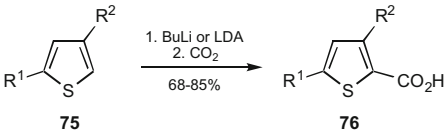
2.2.5 Substitution Reactions Involving Organolithium Derivatives

Replacement of Lithium by Hydrogen or Deuterium

The introduction of hydrogen or deuterium atoms into thiophenes is possible via the treatment of thienyllithiums with alcohols, water, deuterated alcohols, or deuterium oxide (Scheme 30) [24, 173, 174]. The combination of this method with a prior halogen-metal exchange reaction is a powerful tool for the regioselective partial dehalogenation of halogenated thiophenes [20, 174–190].

Replacement of Lithium by a Silyl Group

Silylated thiophenes **74** can be generated in moderate to high yields by the reaction of thienyllithiums with diverse chlorosilanes (Scheme 31, Table 18) [191–202]. The utilization of dichlorosilanes leads to the formation of dithienyl compounds bridged by a SiR_2 group.

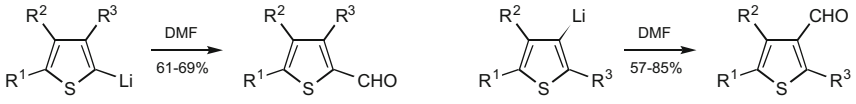


75 76

Scheme 32 Reaction of 2-thienyllithiums with carbon dioxide

Table 19 Reaction of 2-thienyllithiums with carbon dioxide

R^1	R^2	Yield (%)	Ref.
H	CN	68	[21]
$CONEt_2$	H	85	[25]
SMe	SMe	75	[203]
Ph	H	81	[204]



77 78 79 80

Scheme 33 Formylation of thienyllithiums

Table 20 Formylation of thienyllithiums

Thienyllithium	R^1	R^2	R^3	Yield (%)	Ref.
77	H	Me	H	61	[210]
77	Me	H	Me	69	[210]
79	H	H	H	70	[211]
79	Me	H	H	59	[212]
79	H	Me	H	57	[213]
79	Me	H	Me	85	[214]

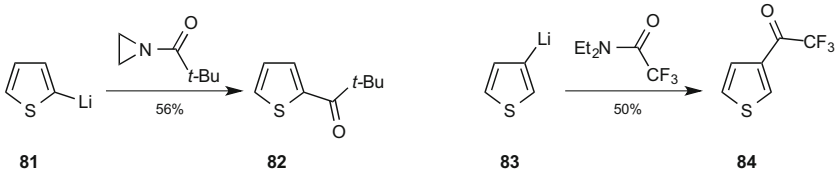
Replacement of Lithium by a Carboxy Group

The treatment of thienyllithiums with solid carbon dioxide gives rise to thiophene-2-carboxylic acids **76** in good yields (Scheme 32, Table 19) [13, 14, 16, 21, 25, 205–207].

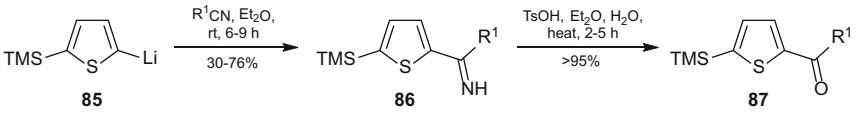
Replacement of Lithium by a Formyl or Acyl Group

Usually formylation of thiophenes is possible through a direct Vilsmeier-Haack reaction [208, 209]. Alternatively, thiophene-carbaldehydes, for example, **78** and **80**, can be prepared by the reaction of thienyllithiums with *N*,*N*-dimethylformamide (Scheme 33, Table 20) [210, 212, 213, 215–219]. Notably, thiophene-3-carbaldehyde derivatives are easily accessible using this formylation methodology.

The reaction of lithiothiophenes with acylating agents [220–223] offers a good alternative to Friedel-Crafts acylations. For example, acylthiophenes such as **82** and **84** can be generated by applying carboxamides (Scheme 34) [224, 225]**.** The



Scheme 34 Acylation of thienyllithiums [224, 225]



Scheme 35 Reaction of 2-thienyllithium with nitriles [226]

Table 21 Reaction of 2-thienyllithium with nitriles [226]

R^1	Yield (%)
4-ClC_6H_4	76
2-ClC_6H_4	51
4-$MeOC_6H_4$	54
3-pyridyl	30
4-pyridyl	56

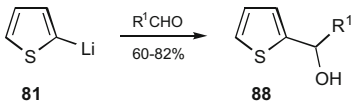
reaction of 2-lithio-5-trimethylsilylthiophene **85** with nitriles followed by hydrolysis gives rise to the corresponding acylated thiophenes **87** in moderate to high yields (Scheme 35, Table 21) [226]**.**

Replacement of Lithium by a Hydroxymethyl or Aminomethyl Group

The introduction of hydroxymethyl groups into thiophenes is possible by the reaction of thienyllithiums with ketones or aldehydes (Scheme 36, Table 22) [227–229]. Electron-rich heterocycles like 2-methylthiophene **32** can be treated with 1-[(triphenylphosphoranylideneamino)methyl]-1,2,3-benzotriazole **90**, which serves as aminomethylation agent, forming the corresponding product **91** in moderate yield (Scheme 37) [230].

Replacement of Lithium by an Alkyl, Alkenyl, Alkynyl, or Aryl Group

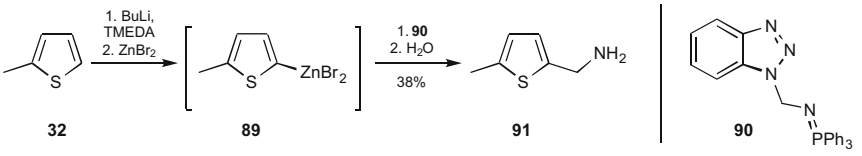
Various other carbon electrophiles will react with thienyllithiums (Scheme 38, Table 23). Alkylation of 2-thienyllithiums is possible with common alkylating reagents such as dimethyl sulfate, alkyl halides, or ethylene oxide [14, 199, 231, 232, 235–237]. Treating 2-thienyllithium with chlorotrifluoroethene gives rise to 2-(2-chloro-1,2-difluorovinyl)thiophene in high yield [232]. The introduction of



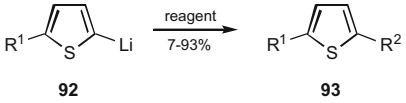
Scheme 36 Reaction of 2-thienyllithium with aldehydes [227]

Table 22 Reaction of 2-thienyllithium with aldehydes [227]

R^1	Yield (%)
H	60
Me	87
Et	82
Pr	74
Bu	76
$(CH_2)_4Me$	63



Scheme 37 Synthesis of a thiophene 2-methanamine by aminomethylation [230]

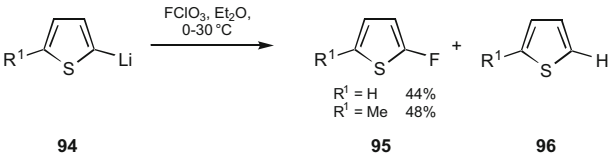


Scheme 38 Alkylation, alkenylation, alkynylation, and arylation using 2-thienyllithiums

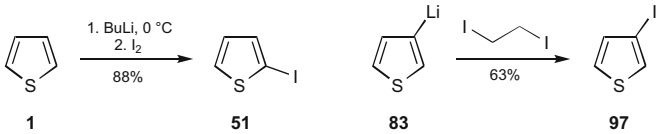
Table 23 Alkylation, alkenylation, alkynylation, and arylation using 2-thienyllithiums

R^1	R^2	Reagent	Yield (%)	Ref.
H	Me	Me_2SO_4	65	[14]
H	Et	EtBr	61	[14]
H	Bn	BnBr	63	[14]
H	$(CH_2)_2NMe_2$	$Me_2NCH_2CH_2Cl$	7	[231]
OMe	$(CH_2)_2NMe_2$	$Me_2NCH_2CH_2Cl$	40	[231]
SMe	$(CH_2)_2NMe_2$	$Me_2NCH_2CH_2Cl$	11	[231]
H	CF=CFCl	F_2C=CFCl	93	[232]
H	C≡CH	FC≡CH	55	[233]
H	C≡CBu	MeOC≡CBu	33	[234]
H	Ph	PhBr	31 (22)[a]	[14]

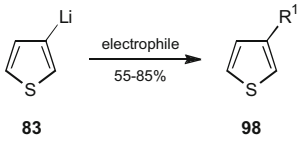
[a]Isolated yield of by-product 2,5-diphenylthiophene in parentheses



Scheme 39 Fluorination via 2-thienyllithiums [238]



Scheme 40 Iodination via thienyllithiums [246, 247]



Scheme 41 3-Sulfanylation and 3-sulfonylation of thiophene using 3-thienyllithium

alkyne groups into the thiophene moiety can proceed with alkynes bearing leaving groups such as fluorine or methoxy [233, 234]. The arylation of thienyllithium with bromobenzene takes place in tetrahydrofuran forming a mixture of 2-phenylthiophene (32%) and 2,5-diphenylthiophene (22%) [14].

Replacement of Lithium by a Halogen

Halogenated thiophenes, which are important intermediates for the synthesis of further substitution patterns, can be generated by the reaction of thienyllithium derivatives with sources of electrophilic halogens. Fluorination is possible using perchloryl fluoride forming the corresponding product **95** in moderate yield (Scheme 39) [20, 238–240]. Chlorine can be introduced by the reaction of thienyllithium with chlorine, hexachloroethane, trichloroacetonitrile, or sulfonyl chloride [20, 173, 180, 226, 229, 240–244]. Tetrabromomethane is used for brominations [245] and alkyl iodides for iodinations (Scheme 40) [24, 123, 246–250].

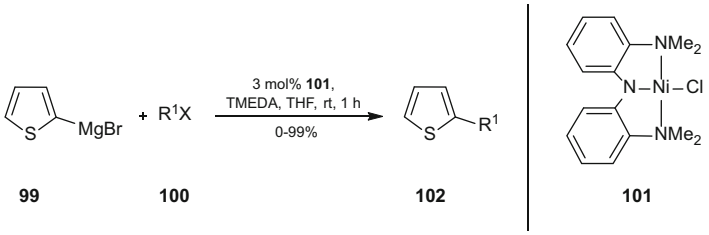
Replacement of Lithium by a Sulfanyl or Sulfonyl Group

Sulfanyl- [250–253], alkylsulfanyl- [247], arylsulfanyl- [254, 255], or sulfonyl-substituted [22, 213, 229, 256] thiophenes can be prepared by the reaction of thienyllithium with sulfur, disulfides, or sulfonic acid esters, respectively, in moderate to high yields (Scheme 41, Table 24).

Table 24 3-Sulfanylation and 3-sulfonylation of thiophene using 3-thienyllithium

Electrophile	R^1	Yield (%)	Ref.
BuSSBu	SBu	63	[247]
MeSSMe	SMe	71	[247]
S_8	SH	63	[250]
$TsOCH_2Cy$	Ts	55	[254]
$PhSO_2OPh$	SO_2Ph	85, 88[a]	[254]

[a]Reaction with 2-thienyllithium



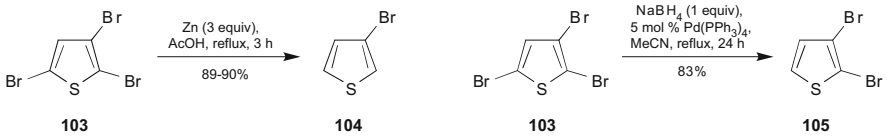
Scheme 42 Kumada-Corriu-Tamao coupling of alkyl halides with 2-thienylmagnesium bromide [260]

2.2.6 Substitution Reactions Involving Organomagnesium Derivatives (the Kumada-Corriu-Tamao Reaction)

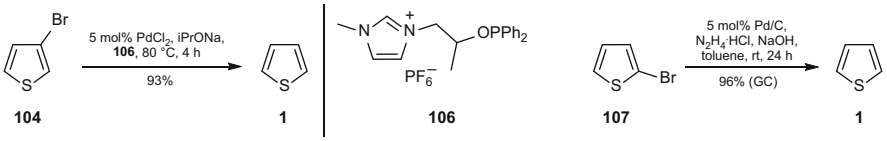
Another synthetic method to introduce substituents into a thiophene by carbon-carbon bond formation is the catalytic Kumada-Corriu-Tamao cross-coupling procedure [42, 136, 257, 258]. Usually, the reaction between nucleophilic thienylmagnesium derivatives, i.e., a Grignard reagent, and electrophilic organic halides is performed in the presence of a nickel or palladium catalyst. The cross-coupling reaction of two Grignard reagents, one of which is 2-thienylmagnesium bromide, can proceed via manganese catalysis in the presence of oxygen as oxidant giving rise to satisfactory yields [259]. However, as a consequence of the high reactivity of Grignard reagents, the Kumada-Corriu-Tamao procedure does not have the broad functional group tolerance associated with other cross-coupling methods. Nevertheless, Grignard reagents are easy to prepare, economical, and often commercially available. The nickel(II) pincer catalyst **101** is able to promote the Kumada-Corriu-Tamao coupling between 2-thienylmagnesium bromide **99** and a range of unactivated alkyl iodides **100** in good to high yields (Scheme 42, Table 25) [260]. However, the attempted coupling of the thienyl Grignard **99** with 1-bromooctane failed. A further alternative for an effective Kumada-Corriu coupling under mild reaction conditions is the palladium-catalyzed reaction of 2-thienylmagnesium bromide **99** with secondary benzylic bromides in the presence of the Xantphos ligand [261]. The Kumada cross-coupling reaction can also be utilized for the formation of organic electronic devices. For instance, poly (3-methylthiophene) films are accessible by a palladium-promoted surface-initiated Kumada catalyst transfer polycondensation [262]. For that, a (4-bromobenzyl)

Table 25 Kumada-Corriu-Tamao coupling of alkyl halides with 2-thienylmagnesium bromide [260]

R^1	X	Yield[a] (%)
$(CH_2)_2Ph$	I	99
Bu	I	93
Cy	I	54



Scheme 43 Reductive dehalogenation of bromothiophenes [302, 303]



Scheme 44 Dehalogenation of bromothiophenes [304, 305]

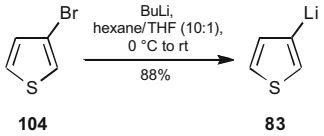
phosphonic acid-functionalized ITO layer is initially treated with (tri-*tert*-butylphosphine)palladium(0) and subsequently placed in a tetrahydrofuran solution of 2-bromo-5-chloromagnesio-3-methylthiophene.

2.3 Substitution of Heteroatoms

2.3.1 Substitution of Halogen by Hydrogen

The regioselective removal of halogen substituents attached to the thiophene ring is a convenient methodology for the further synthesis of thiophene derivatives. If dehalogenation is performed via a halogen-lithium exchange reaction, the thienyllithium intermediate can subsequently be reacted with various electrophiles. Usually, dehalogenation of halogen-substituted thiophenes is carried out using reducing agents such as Raney nickel [263–268], zinc/hydrochloric acid [174, 213, 214, 269–282], sodium amalgam [211, 283–285], as well as telluride [286, 287], copper metal [116, 288–292], phosphorous/hydrogen iodide [293], and others [214, 294–301] (Scheme 43).

Palladium-assisted dehalogenation reactions are another possibility for an efficient removal of bromine substituents, for example, 3-bromothiophene **104** is dehalogenated in the presence of an imidazolium-based phosphinite ionic liquid (IL-$OPPh_2$) **106** forming thiophene **1** in a yield of 93% (Scheme 44, left) [304]. The



Scheme 45 3-Thienyllithium via halogen-metal exchange with butyllithium [247]

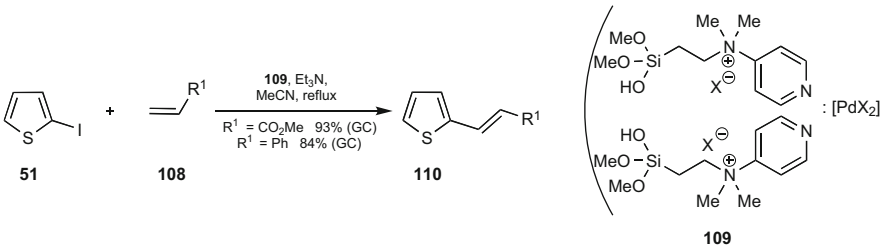
ionic liquid **106** serves both as ligand for palladium(II) and solvent and can be recovered along with the catalyst and reused several times. The combination of catalytic amounts of palladium-on-carbon and hydrazine hydrochloride, which serves as hydrogen donor, facilitates an effective dehalogenation of 2-bromothiophene **136** (Scheme 44, right) [305].

2.3.2 Substitution of Halogen by Metal

The selective lithiation of thiophenes is possible via halogen-lithium exchange reactions (Scheme 45) [306]. Potential side reactions are hydrogen-metal exchange or halogen-dance reactions at temperatures above -70°C [15, 214, 307–309]. That is why thiophenes bearing fluorine substituents are not suitable, because the substitution of fluorine with lithium is suppressed by a hydrogen-lithium exchange [20, 310]; thus, bromothiophenes are the starting material of choice, because bromine-lithium exchange is preferred over hydrogen-lithium exchange [176, 185, 211, 231, 249, 309, 311–315] and in addition their reactivity exceeds that of chlorothiophenes [316–319]. Considering multi-bromothiophenes, a stepwise halogen-lithium exchange occurs. Here the bromine at an α-position is replaced more readily than a bromine at a β-position [185, 320–322]. Iodothiophenes can undergo halogen-metal exchange reactions, but ring opening is possible [249, 323–328]. An alternative to the substitution of halogen by lithium is the formation of Grignard reagents from halogenated thiophenes [182, 321, 329–331].

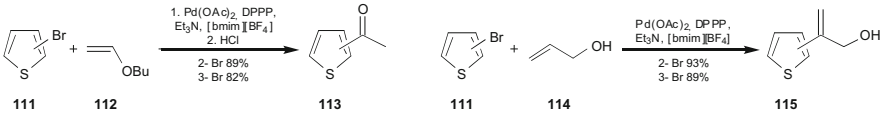
2.3.3 Palladium-Catalyzed Cross-Coupling of Halothiophenes with Alkenes

The palladium-catalyzed Heck reaction [38, 332, 333] is an efficient methodology for the cross-coupling of halothiophenes with various alkenes [334–336]. For instance, 2-iodothiophene **51** can be effectively coupled with alkenes **108** in the presence of a palladium containing nanostructured silica **109** (I-Pd) bearing trialkyl-(4-pyridyl)-ammonium binding sites forming the corresponding products **110** in high yields (Scheme 46) [337]. This Heck coupling proceeds most efficiently using triethylamine as base and acetonitrile as solvent. Additionally, the heterogeneous catalyst can be recovered and reused for five reaction cycles without losing its catalytic activity. Vinylated thiophenes are also readily accessible by Heck cross-coupling reactions between thienyl bromides and terminal alkenes in the presence of the highly active palladium-based dichloro[1-(dicyclohexylphosphanyl)piperidine] complex [338] or by a selective palladium-catalyzed



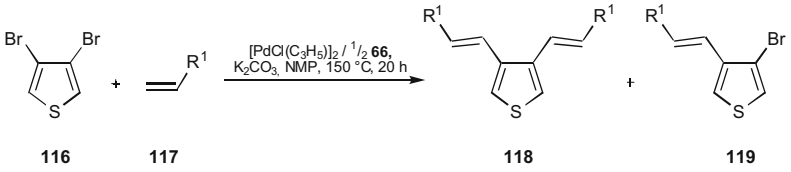
51 108 110 109

Scheme 46 Heck reaction of 2-iodothiophene with alkenes using catalyst I-Pd [337]



111 112 113 111 114 115

Scheme 47 Heck arylation of butyl vinyl ether and allyl alcohol in an ionic liquid [340]



116 117 118 119

Scheme 48 Palladium-catalyzed Heck reactions with 3,4-dibromothiophene [341]

cross-coupling reaction of 2,5-dibromothiophene with tristyrylindium as nucleophilic reagent [339].

The palladium-catalyzed Heck reactions of 3- and 2-bromothiophene **111** with the electron-rich olefins butyl vinyl ether **112** and allyl alcohol **114** proceed effectively in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate (Scheme 47) [340]. The special feature of this reaction is that only branched olefin products are formed using the imidazolium ionic liquid, whereas the utilization of normal solvents gives rise to a mixture of regioisomers.

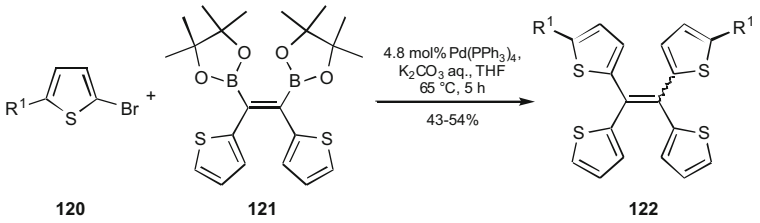
Alternatively, a catalytic system consisting of the tetrapodal phosphine ligand Tedicyp **66** and the allylpalladium chloride dimer ($[PdCl(C_3H_5)]_2$) can be used for efficient Heck vinylation reactions (Scheme 48, Table 26) [341]. The cross-coupling of 3,4-dibromothiophene **116** with various alkenes **117** gives rise to the corresponding vinylated products **118** and **119**.

Tetra(2-thienyl)ethylene (TTE) derivatives **122** can be synthesized by Suzuki–Miyaura reactions of a *cis*-boronic ester **121** with differently functionalized bromothiophenes **120** (Scheme 49, Table 27) [342]. *Vic*-bis(pinacolatoboryl)ethylene **121** can be isolated from the reaction of di(2-thienyl)acetylene with bis-pinacolato-diboron beforehand, but is subsequently employed as crude intermediate

Table 26 Palladium-catalyzed Heck reactions with 3,4-dibromothiophene [341]

R^1	Ratio(substrate/catalyst)	Ratio (**118**/**119**)	Yield (**118**) (%)
CO_2Bu	25	100/0	95
CO_2Bu	250	18/82	65
Ph	250	100/0	82
Ph	1000	48/52	100[a]
Ph	5000	0/100	20[a]
3-Tol	250	100/0	78
3-ClC_6H_4	250	100/0	80

[a]GC yield (mixture of mono- and diaddition products)

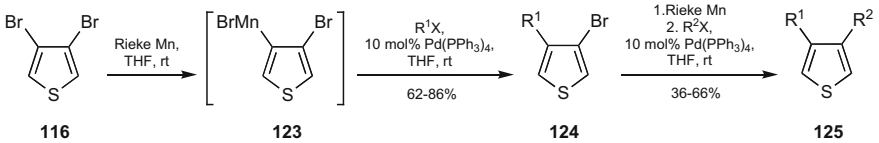


120 **121** **122**

Scheme 49 Palladium-catalyzed Suzuki–Miyaura reactions with bromothiophenes [342]

Table 27 Palladium-catalyzed Suzuki–Miyaura reactions with bromothiophenes [342]

R^1	Yield (%)
H	50
CHO	54
CH_3	49
NO_2	43



116 **123** **124** **125**

Scheme 50 Cross-coupling reactions of 3-thienylmanganese bromides [343]

to react with bromothiophenes **120** bearing either electron-withdrawing or electron-donating substituents under palladium catalysis.

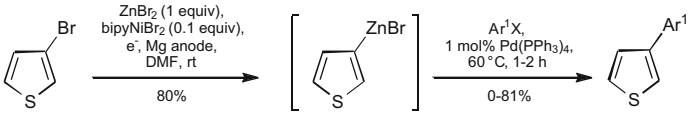
2.3.4 Metal-Assisted Cross-Coupling of Halothiophenes with Arenes

Manganese-Assisted Coupling Reactions

The preparation of 3-thienylmanganese bromide **123** is possible via the direct oxidative addition of Rieke manganese to 3,4-dibromothiophene **116** (Scheme 50)

Table 28 Cross-coupling reactions of 3-thienylmanganese bromides [343]

R^1	X	R^2	Y	Yield (**124**) (%)	Yield (**125**) (%)
Bz	Cl	–	–	80	–
4-BrC_6H_4CO	Cl	–	–	83	–
3-BrC_6H_4CO	Cl	–	–	62	–
Ph	I	Bz	Cl	65	66
4-$EtO_2C_6H_4$	I	Bz	Cl	86	46
4-$MeOC_6H_4$	I	Ph	I	69	36



Scheme 51 Electrochemical synthesis of 3-arylthiophenes [345]

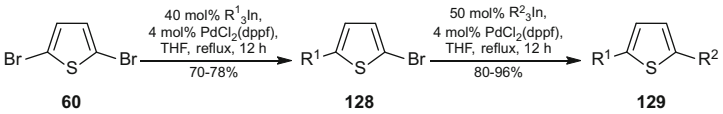
Table 29 Electrochemical synthesis of 3-arylthiophenes [345]

Ar^1	X	Yield (%)
Ph	I	81
4-NCC_6H_4	Br	47
2-$MeO_2CC_6H_4$	Br	40
4-$MeOC_6H_4$	Br	0

[136]. Notably, Rieke manganese is able to take part in oxidative addition even where Rieke zinc or Rieke magnesium is insufficiently reactive [258]. The 3-thienylmanganese bromide intermediate **123** can be coupled effectively with both aryl iodides and aroyl chlorides via palladium catalysis to give the products **124** and **125** in moderate to high yields (Scheme 50, Table 28) [343, 344].

Zinc-Assisted Coupling Reactions

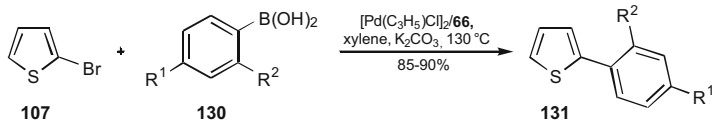
3-Thienylzinc bromide **126** can be generated from 3-bromothiophene **104** by a nickel-catalyzed electroreduction (Scheme 51, Table 29) [345]. Thereby 2,2′-bipyridyldibromonickel(II) is used as catalyst and magnesium as sacrificial anode. 3-Thienylzinc bromide **126** can be subsequently reacted with various aryl halides giving rise to the corresponding (hetero)biaryls **127** in moderate to good yields. The arylation is palladium catalyzed, because the nickel catalyst, which is still present in the reaction medium, is inactivated by electrochemical reduction to nickel(0).



Scheme 52 Selective and sequential cross-coupling with triorganoindium reagents [339]

Table 30 Selective and sequential cross-coupling with triorganoindium reagents [339]

R^1	R^2	Yield (**128**) (%)	Yield (**129**) (%)
2-thienyl	Ph	78	96
2-benzo[*b*]thienyl	2-thienyl	77	80
2-furanyl	–	70	–



Scheme 53 Suzuki–Miyaura-type coupling of arylboronic acids with 2-bromothiophene [171]

Palladium-Catalyzed Coupling Reactions

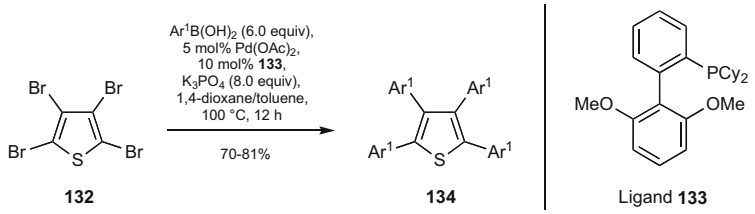
Palladium-Catalyzed Synthesis of Biheteroaryls and Oligothiophenes

The preparation of biheteroaryls, conjugated thienyl oligomers, and polymers is of great interest due to their potential applications in electronic and optoelectronic devices (see [346]). Especially appealing is the possibility to tune their physical and chemical properties through functionalization. Many oligothiophenes are accessible by palladium-catalyzed cross-coupling reactions based on halothiophenes. Frequently used catalysts are palladium(II) acetate, the Herrmann-Beller catalyst, and classical tetrakis(triphenylphosphine)palladium(0) [36, 42, 52, 161]. The synthesis of butadiene-thiophene or heteroaryl-thiophene copolymers, respectively, is possible through initial metallacycle transfer chemistry followed by Suzuki cross-coupling reactions in the presence of tris(dibenzylideneacetone)dipalladium(0) [347]. Alternatively, biheteroaryls and oligothiophenes can be prepared by selective and iterative cross-coupling reactions using indium organometallics as reagents (Scheme 52, Table 30) [339]. The selective cross-coupling of 2,5-dibromothiophene **60** with nucleophilic triorganoindium reagents forms the corresponding products **128** in high yields. These monocoupled products **128** can subsequently be treated additionally with indium organometallics to give bithiophenes **129**. Notably, the monocoupled products **128** can also be utilized as pronucleophiles in an iterative reaction sequence for the generation of oligothiophenes.

Table 31 Suzuki–Miyaura-type coupling of arylboronic acids with 2-bromothiophene [171]

R^1	R^2	Ratio(substrate/catalyst)[a]	Yield (%)
H	H	100000:1	88
COMe	H	1000:1	90
OMe	H	1000000:1	85
H	Me	100000:1	89

[a]Substrate/catalyst ratio based on aryl halide



Scheme 54 Synthesis of tetraarylthiophenes [348]

Table 32 Synthesis of tetraarylthiophenes [348]

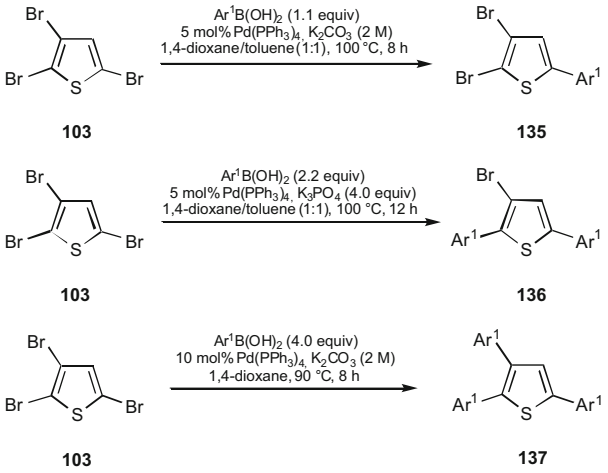
Ar^1	Solvent	Yields (A) (%)	Yields (B) (%)
Ph	toluene	37	70
4-$MeOC_6H_4$	1,4-dioxane	94	
2-$MeOC_6H_4$	1,4-dioxane	38	65
1-naphthalenyl	toluene	65	
4-MeC_6H_4	toluene	87	
4-ClC_6H_4	toluene	89	
4-FC_6H_4	toluene	93	
2-thienyl	toluene	–	81

Suzuki–Miyaura Cross-Coupling in the Presence of a Palladium/Tetraphosphine Catalyst

2-Arylthiophenes **131** can be prepared by the Suzuki–Miyaura cross-coupling reaction of 2-bromothiophene **107** with different arylboronic acids **130** in the presence of a Tedicyp **66** palladium complex (Scheme 53, Table 31) [171]. The arylation takes place with only 0.1–0.0001 mol% catalyst. The cross-couplings of thienylboronic acids and aryl halides under the same reaction conditions result in slightly poorer yields.

Suzuki–Miyaura Cross-Coupling in the Presence of a Biarylmonophosphine Ligand

Another efficient approach for the arylation of halothiophenes is the Suzuki–Miyaura cross-coupling reaction of tetrabromothiophene **132** with different arylboronic acids (Scheme 54, Table 32) [348]. One possibility to prepare fourfold



Scheme 55 Suzuki–Miyaura reactions of 2,3,5-tribromothiophene [350]

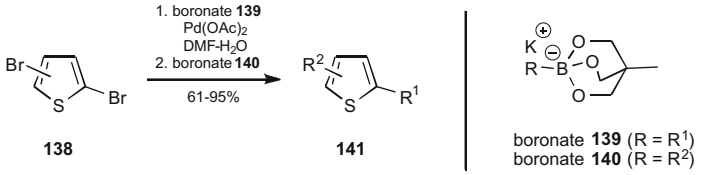
Table 33 Suzuki–Miyaura reactions of 2,3,5-tribromothiophene [350]

Ar^1	Yield (**135**)(%)	Yield (**136**) (%)	Yield (**137**) (%)
4-MeC_6H_4	47	55	92
4-EtC_6H_4	53	67	
3-FC_6H_4	40		
2,6-$(MeO)C_6H_3$	44		
2-ClC_6H_4		51	
3-ClC_6H_4		50	
4-*t*-BuC_6H_4			87
3,5-$Me_2C_6H_3$			78
4-$F_3CC_6H_4$			83

arylated thiophenes **134** is the palladium-promoted coupling using classical tetrakis (triphenylphosphine)palladium(0) catalyst (Procedure A). The utilization of palladium(II) acetate in combination with biarylmonophosphine ligand **133** gives rise to significantly improved results (Procedure B) [349]. Even the failed coupling of tetrabromothiophene **132** with 2-thienylboronic acid **68** can be successfully promoted using the catalytic system based on ligand **133** resulting in a yield of 81%.

Site-Selective Suzuki–Miyaura Cross-Couplings of 2,3,5-Tribromothiophene

5-Aryl-2,3-dibromothiophene **135**, 2,5-diaryl-3-bromothiophene **136**, and 2,3,5-triarylthiophene **137** can be prepared starting from the same trisubstituted bromothiophene **103** via site-selective palladium-catalyzed Suzuki–Miyaura cross-coupling reactions (Scheme 55, Table 33) [350, 351]. The regioselectivities are based on steric as well as electronic reasons. The most reactive carbon atom is C-5 due to its electron-deficient character. C-2 is electronically identical, but is



Scheme 56 Double boronate couplings of dibromothiophenes [353]

Table 34 Double boronate couplings of dibromothiophenes [353]

R^1	R^2	Yield (2,4-**141**) (%)	Yield (2,3-**141**) (%)
4-MeC_6H_4	4-FC_6H_4	95	85
4-FC_6H_4	4-MeC_6H_4	71	64
(*E*)-PhC=CH	Ph	64	70
Ph	(*E*)-PhC=CH	65	67
2-$MeOC_6H_4$	Ph	81	64
Ph	2-$MeOC_6H_4$	94	61
2-thienyl	Ph	77	62
Ph	2-thienyl	81	73

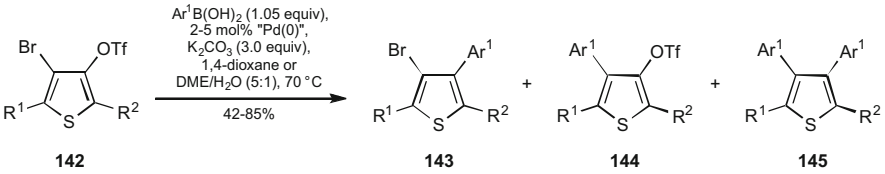
sterically hindered, because of the neighboring bromine on C-3. Thus, both the steric hindrance and the lower electron deficiency point to C-3 being the least reactive. In addition, multi-brominated thiophenes can also be utilized in Suzuki–Miyaura cross-coupling reactions with differently functionalized arylboronic acids giving rise to thiophene-core estrogen receptor ligands, which have superagonist activity [352].

Suzuki-Type Cross-Coupling in the Presence of Boronates

Stable boronate salts **139** and **140**, which were developed by Miyaura and coworkers, can be alternatively utilized in cross-coupling reactions with disubstituted bromothiophenes **138** (Scheme 56, Table 34) [353, 354]. The one-pot double boronate coupling of 2,4- or 2,3-dibromothiophene **138** proceeds under mild reaction conditions in aqueous solution giving rise to the corresponding products **141** in good to high yields. The application of arylboronic acids instead of the boronate salts results in poorer yields in most of the cases.

Chemoselective Suzuki–Miyaura Cross-Coupling of 3-Bromo-4-Triflyloxy-Thiophenes

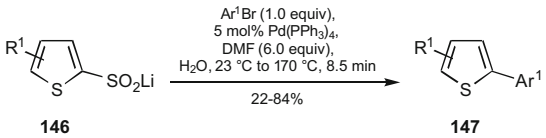
Using of 3-bromo-4-triflyloxy-thiophenes **142**, a ligand-dependent chemoselective Suzuki–Miyaura cross-coupling with diverse arylboronic acids mediated by different palladium catalysts can be achieved (Scheme 57, Table 35) [355]. When tetrakis (triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) is utilized, the triflate group (**143**) reacts preferentially. In contrast, couplings promoted by bis(tri-*tert*-



Scheme 57 Chemoselective coupling of 3-bromo-4-triflyloxy-thiophenes [355]

Table 35 Chemoselective coupling of 3-bromo-4-triflyloxy-thiophenes [355]

R^1	R^2	Ar^1	"Pd(0)"	Yield (**143**) (%)	Yield (**144**) (%)	Yield (**145**) (%)
H	CO_2Me	4-MeC_6H_4	$Pd(PPh_3)_4$	71	–	10
H	CO_2Me	4-MeC_6H_4	$Pd(PtBu_3)_2$	–	81	–
CO_2Me	CO_2Me	4-MeC_6H_4	$Pd(PPh_3)_4$	55	–	14
CO_2Me	CO_2Me	4-MeC_6H_4	$Pd(Pt\text{-}Bu_3)_2$	–	66	Traces
H	CH_2OH	4-$MeOC_6H_4$	$Pd(PPh_3)_4$	72	–	–
H	CH_2OH	4-$MeOC_6H_4$	$Pd(Pt\text{-}Bu_3)_2$	–	69	Traces
H	CH_2OH	4-pyridinyl	$Pd(PPh_3)_4$	65	–	–
H	CH_2OH	4-pyridinyl	$Pd(Pt\text{-}Bu_3)_2$	–	61	–
CH_2OH	CH_2OH	4-$MeOC_6H_4$	$Pd(PPh_3)_4$	85	–	–
CH_2OH	CH_2OH	4-$MeOC_6H_4$	$Pd(Pt\text{-}Bu_3)_2$	–	43	8
CH_2OH	CH_2OH	4-pyridinyl	$Pd(PPh_3)_4$	45	–	–
CH_2OH	CH_2OH	4-pyridinyl	$Pd(Pt\text{-}Bu_3)_2$	–	42	–



Scheme 58 Desulfinylative cross-coupling with 2-thienylsulfinates [356]

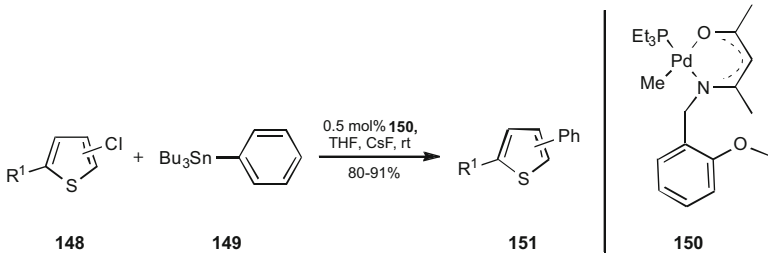
butylphosphine)palladium(0) ($Pd(Pt\text{-}Bu_3)_2$) give bromide-displaced product **144** selectively. The utilization of arylboronic esters instead of acids results in similar chemoselective product formation.

Desulfinylative Cross-Coupling of Thiophene Sulfinates

The environmentally benign synthesis of arylated thiophenes **147** in pure water is possible via desulfinylative cross-coupling between nucleophilic 2-thienylsulfinates **146** and differently substituted bromoarenes (Scheme 58, Table 36) [356]. The reaction proceeds efficiently within short reaction times in the presence of tetrakis (triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) without the need for additives, base, cocatalysts, or water-soluble ligands. Additionally, the application of a highly aqueous solvent mixture consisting of water and *N*,*N*-dimethylformamide at a ratio of 3:1

Table 36 Desulfinylative cross-coupling with 2-thienylsulfinates [356]

R^1	Ar^1	Yield (%)
benzo[*b*]	4-NCC_6H_4	78
5-Me	4-NCC_6H_4	64
4-Me	4-NCC_6H_4	57
3-Me	4-NCC_6H_4	27
H	4-NCC_6H_4	71
H	3-NCC_6H_4	65
H	2-NCC_6H_4	84
H	4-$F_3CC_6H_4$	44
H	4-$EtO_2CC_6H_4$	64
H	1-naphthalenyl	49
H	4-$MeOC_6H_4$	22



Scheme 59 Stille coupling of chlorothiophenes with organostannanes [357]

Table 37 Stille coupling of chlorothiophenes with organostannanes [357]

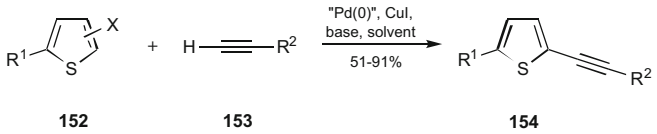
R^1	Chlorothiophene	Yield[a] (%)
H	2-Cl	88 (91)
H	3-Cl	80 (84)
CHO	5-Cl	91 (93)

[a]GC yield in parentheses

in combination with the catalyst precursors palladium(II) chloride and phosphine results in higher yields in almost all cases.

Stille Cross-Coupling in the Presence of a Phosphanyl-β-Ketoiminate Palladium Catalyst

Another approach for the synthesis of biaryls is the Stille cross-coupling reaction. For this, chlorothiophenes **148** can be coupled with tributyl(phenyl)stannanes **149** by means of a highly active phosphanyl-β-ketoiminate palladium complex **150** forming the arylated thiophenes **151** in high yields (Scheme 59, Table 37) [357]. It is noteworthy that the reaction works with unreactive, inexpensive, and readily available chlorothiophenes **148** at room temperature.



Scheme 60 Sonogashira cross-coupling reaction of halothiophenes with terminal alkynes

Table 38 Sonogashira cross-coupling reaction of halothiophenes with terminal alkynes

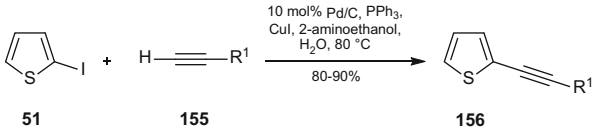
R^1	X	R^2	Conditions	Yield (%)	Ref.
H	2-I	Ph	$Pd(PPh_3)_4$, CuI, NEt_3, benzene, rt, 24 h	78	[358]
H	2-I	Ph	$PdCl_2(PPh_3)_2$, CuI, NBu_3, K_2CO_3, H_2O, rt, 24 h	80	[359]
H	3-Br	Ph	$Pd(PPh_3)_4$, CuI, NEt_3, benzene, rt, 24 h	75	[358]
H	2-I	Bu	$Pd(PPh_3)_4$, CuI, NEt_3, benzene, rt, 24 h	86	[358]
H	3-Br	Bu	$Pd(PPh_3)_4$, CuI, NEt_3, benzene, rt, 24 h	79	[358]
H	2-I	CH_2OTHP	$Pd(PPh_3)_4$, CuI, NEt_3, benzene, rt, 24 h	83	[358]
H	2-I	CH_2OTMS	$Pd(PPh_3)_4$, CuI, NEt_3, benzene, rt, 24 h	82	[358]
2-thienyl	5-I	Ph	$Pd(PPh_3)_4$, CuI, $NEt_2Bn^+Cl^-$, 2.5 M NaOH, benzene, rt, 24 h	77[a]	[360]
H	2-Br	Ph	Pd/C, PPh_3, K_2CO_3, EtOH, reflux, 48 h	78[b]	[361]
H	2-I	Ph	Pd/C, PPh_3, K_2CO_3, EtOH, reflux, 48 h	89[b]	[361]
H	2-Br	C_5H_{11}	Pd/C, PPh_3, K_2CO_3, EtOH, reflux, 48 h	59[b]	[361]
H	2-I	C_5H_{11}	Pd/C, PPh_3, K_2CO_3, EtOH, reflux, 48 h	91[b]	[361]
H	2-Br	$C(CH_3)_2OH$	Pd/C, PPh_3, K_2CO_3, EtOH, reflux, 48 h	72[b]	[361]
H	2-I	$C(CH_3)_2OH$	Pd/C, PPh_3, K_2CO_3, EtOH, reflux, 48 h	46[b]	[361]
2-Br	5-Br	TMS	$Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2NH, THF	90	[362]
2-Br	5-Br	TMS	$Pd(PPh_3)_4$, CuI, NEt_3, 75°C, 3 d	87	[362]
2-Br	5-Br	TMS	$Pd(PPh_3)_4$, CuI, NEt_3, 75°C, 3 d	78	[362]
2-I	5-I	TMS	$Pd(PPh_3)_4$, CuI, NEt_3, 75°C, 3 d	51	[362]

[a]Stoichiometric amounts of Pd(0)
[b]Copper-free cross-coupling

2.3.5 Palladium-Catalyzed Cross-Coupling of Halothiophenes with Alkynes

The preparation of (alk-1-ynyl)thiophenes **154** is possible via palladium-catalyzed Sonogashira cross-coupling reactions between iodo- or bromothiophenes **152** and terminal alkynes **153** (Scheme 60, Table 38) [309, 360, 363, 364]. Alkynylated thiophenes represent an important structural motif found in many π-electronic systems such as molecular rods or conjugated macrocycles [163, 362, 365, 366]. In the case of bromoiodo-substituted thiophenes, the more reactive iodine atom is replaced selectively [367]. Some coupling methods require stoichiometric amounts of palladium(0) [360, 368], whereas other methods proceed successfully under photochemical conditions without the need of a catalyst [369]. Recent

Scheme 61 Pd/C-mediated alkynylation of 2-iodothiophene in water [371]



51 155 156

Table 39 Pd/C-mediated alkynylation of 2-iodothiophene in water [371]

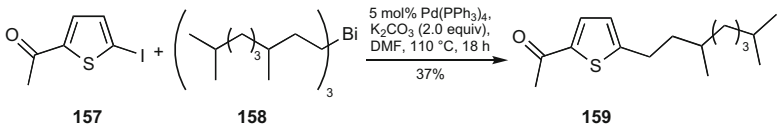
R^1	Yield (%)
$C(CH_3)_2OH$	87
$(CH_2)_3OH$	85
CH(OH)Me	90
CH_2OPh	90
CH_2SPh	86
CH_2NHPh	88
hexyl	87
4-Tol	87
1-indolyl	84
$(CH_2)_2OH$	80

efficient Sonogashira alkynylation techniques involve the use of catalytic systems such as palladium containing nanostructured silica [337] or a 2-(di-*tert*-butylphosphino)biphenyl palladium complex [370]. Another possibility to make alkynylated thiophenes is the palladium-catalyzed cross-coupling reaction of bromothiophenes with nucleophilic triorganoindium reagents [339].

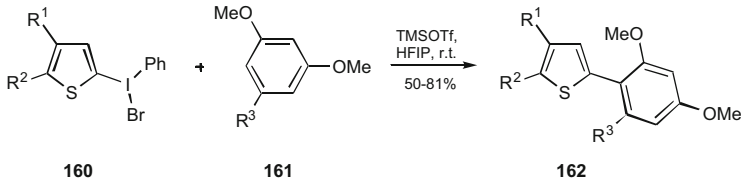
The utilization of water as a suitable, environmentally benign reaction medium has received increasing attention. Some Sonogashira cross-coupling reactions of halothiophenes with terminal alkynes run effectively in water [371, 372] or aqueous isopropanol [373]. For instance, the Pd/C-mediated coupling between 2-iodothiophene **51** and a selection of functionalized alkynes **155** proceeds highly efficiently in water giving rise to the corresponding alkynylthiophenes **156** with yields up to 90% (Scheme 61, Table 39) [371].

2.3.6 Palladium-Catalyzed Cross-Coupling of Halothiophenes with Trialkylbismuth Reagents

The introduction of alkyl groups into the thiophene moiety is possible via palladium-catalyzed cross-coupling of thienyl halides with trialkylbismuth reagents (Scheme 62) [374]. A catalytic system consisting of tetrakis(triphenylphosphine) palladium(0) ($Pd(PPh_3)_4$) and potassium carbonate is able to promote the reaction of 2-acetyl-5-iodothiophene **157** and tris(3,7-dimethyloctyl)bismuthine **158** forming the corresponding product **159** in a yield of 37%.



Scheme 62 Palladium-catalyzed cross-coupling of 2-acetyl-5-iodothiophene with trialkylbismuth reagent [374]



Scheme 63 Arylation using iodonium bromides [376]

Table 40 Arylation using iodonium bromides [376]

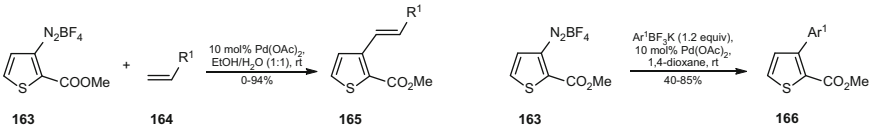
R^1	R^2	R^3	Yield (%)
Me	Me	H	77
Hex	Me	H	70
Me	$(CH_2)_5Br$	H	71
$(CH_2)_2$–$(CH_2)_2$		H	75
p-Tol	Me	Br	81
p-$MeOC_6H_4$	Me	Br	50

2.3.7 Cross-Coupling via Diaryliodonium Bromides

Hypervalent diaryliodonium salts are important arylating agents in organic synthesis [375, 376]. The arylation of thienyliodonium bromides **160** with methoxybenzenes as aromatic nucleophiles **161** is possible under mild reaction conditions in hexafluoroisopropanol (HFIP) and without the necessity for a metal catalyst (Scheme 63, Table 40). TMSOTf is a suitable additive for the direct *ipso* substitution.

2.3.8 Palladium-Catalyzed Cross-Coupling via Thiophenediazonium Salts

Thiophenediazonium salts **163** can be utilized as electrophilic coupling partners for differently functionalized alkenes **164** via a Matsuda-Heck (Scheme 64, left) as well as various potassium aryltrifluoroborates via Suzuki–Miyaura (Scheme 64, right) cross-coupling reactions giving rise to 3-substituted thiophenes **165** and **166**



163 164 165 163 166

Scheme 64 Palladium-catalyzed cross-coupling via thiophenediazonium salts [377]

Table 41 Palladium-catalyzed cross-coupling via thiophenediazonium salts [377]

R^1	Ar^1	Time (h)	Yield (**165**) (%)	Yield (**166**) (%)
CO_2t-Bu		5	86	
Ph		5	60	
4-$AcOC_6H_4$		24	60	
$PO(OEt)_2$		29	85	
CN		19	94	
CN		24	–	
	Ph	4		77
	4-FC_6H_4	0.75		69
	3-FC_6H_4	1		82
	2,4-$F_2C_6H_3$	1.25		41
	2,4-$F_2C_6H_3$	0.75		84
	2,4-$F_2C_6H_3$	0.5		85
	2,4-$F_2C_6H_3$	0.5		78
	2,4-$F_2C_6H_3$	5		79
	2-$MeOC_6H_4$	1.25		68
	2-MeC_6H_4	1.25		44
	2-MeC_6H_4	0.75		44
	2-MeC_6H_4	7		40
	3-thienyl	0.75		78

in high yields (Table 41) [377]**.** Both coupling methods are performed under aerobic conditions, without a base, and in the presence of ligandless palladium (II) acetate as catalyst. Also, benzo[*b*]thiophenes bearing the diazonium functionality can equally couple effectively with potassium aryltrifluoroborates.

3 Summary, Conclusions, Outlook

Transition metal-catalyzed cross-coupling reactions are the most utilized methods for the formation of carbon-carbon bonds, in particular for the synthesis of bihetaryls. The dehydrogenative, oxidative cross-coupling between both non-functionalized thiophenes and arenes seems to be the ideal strategy with regard to synthetical simplicity. However, transition metal-free cross-coupling reactions, which are promoted only by an oxidant, are less well developed and remain an interesting challenge that needs to be studied further.

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Fused Thiophenes and Some Oligomers and Polymers Therefrom

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Abstract The main methodologies for the synthesis of fused thiophenes (thienothiophenes, dithienothiophenes, and thienoacenes) and some of their oligomers and polymers are described. Such compounds are particularly important in materials chemistry. They have applications in organic light-emitting diodes (OLEDs), organic field effect transistors (OFETs), (dye-sensitized) solar cells, and electrochromic devices (ECDs).

Keywords Aldol condensation · Amberlyst 15 · Dithieno[2,3-*b*;2′,3′-*d*]thiophene · Dithieno[2,3-*b*;3′,2′-*d*]thiophene · Dithieno[3,2-*b*;2′,3′-*d*]thiophene · Dithieno[3,4-*b*;2′,3′-*d*]thiophene · Dithieno[3,4-*b*;3′,2′-*d*]thiophene · Dithieno[3,4-*b*;3′,4′-*d*]thiophene · Dithienothiophene (DTT) · EDOT · Ethyl thioglycolate · Friedel–Crafts acylation · ITO · Lawesson's reagent · McMurry reaction · Negishi cross-coupling · P_4S_{10} (pentaphosphorus decasulfide, Berzelius reagent) · Sonogashira cross-coupling · Stille cross-coupling · Thieno[2,3-*b*]thiophene · Thieno[3,2-*b*]thiophene · Thieno[3,2-*c*][1,2]dithiin · Thieno[3,4-*b*]thiophene · Thieno[3,4-*c*]thiophene · Thienoacene · Thienothiophene (TT) · Vilsmeier–Haack formylation · Wittig reaction

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Contents

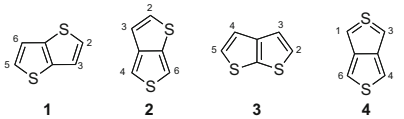
1 Introduction

Conjugated organic materials are the focus of intense interest due to their use as an active layer in organic-based thin film transistors [1, 2]. Organic materials have significant advantages over their silicon analogs in terms of time and cost, as their deposition from solution facilitates fast and large-area fabrication. The charge carrier mobility and the current on/off ratio define the performance of a fabricated device. Low conductivity in the off state, combined with high charge carrier mobility ($>1 \times 10^{-3}$ cm^2 V^{-1} s^{-1}), is desirable for a good organic semiconducting material. Stability to oxidation is a necessary criterion as oxidation can diminish device performance [3]. Extending the π system increases π stacking, resulting in increased charge carrier mobility and decreased band gap, to which most investigations have been dedicated, to tune the band gap of organic conductive polymers [4–6].

One of the convenient methods for tuning band gaps is the use of fused thiophene units [7]. In contrast to thiophenes, fused thiophenes have more rigid structures, with extended π-conjugation, which results in a lowering of the band gap and an increase in intermolecular interactions in the solid state [4, 6]. The simplest fused thiophenes contain two fused thiophene rings and are known as thienothiophenes (TTs). They have electron-rich structures, which make them useful building blocks for conjugated and low band gap organic semiconductors [4, 6, 7]. Fusing another thiophene unit gives tricycles known as dithienothiophenes (DTTs), which have also been extensively utilized to construct functional materials owing to their planar and rigid conjugated structures [8]. Further extension of DTTs produces systems known as thienoacenes, containing more than three fused thiophene rings [9–11]. In this chapter, selected and important synthetic routes to fused thiophenes made up solely of two or more thiophenes are described.

2 Thienothiophenes

Thienothiophenes (TTs) are the simplest fused thiophenes, with four isomers, namely thieno[3,2-*b*]thiophene (**1**), thieno[3,4-*b*]thiophene (**2**), thieno[2,3-*b*]thiophene (**3**), and thieno[3,4-*c*]thiophene (**4**) [4, 6, 7, 12, 13]. Syntheses and polymerizations of all the TTs, except unstable thieno[3,4-*c*]thiophene (**4**), have been studied extensively. The three TTs, **1**–**3** possess stable and electron-rich structures, which make them useful building blocks for conjugated and low band gap organic semiconductors [14].



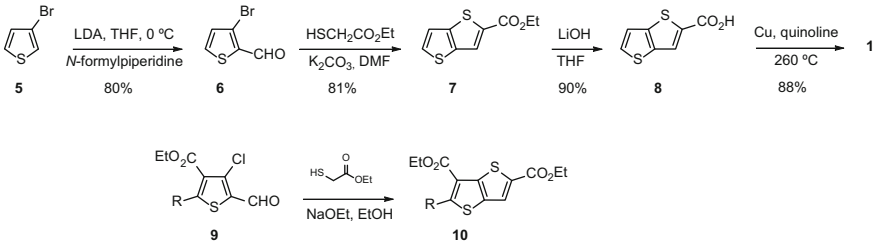
2.1 Thieno[3,2-b]thiophene (1)

2.1.1 Synthesis of Thieno[3,2-*b*]thiophenes

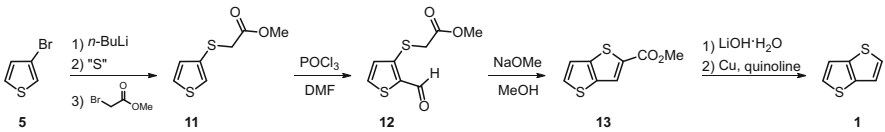
A practical four-step synthesis of thieno[3,2-*b*]thiophene (**1**) in an overall yield of 51% started from 3-bromothiophene (**5**) which was treated with LDA and then *N*-formylpiperidine to give 3-bromothiophene-2-carbaldehyde (**6**) [15]. Reaction with ethyl 2-sulfanylacetate in the presence of K_2CO_3 then produced ester **7**, saponification of which gave acid **8**. Efficient decarboxylation using Cu powder and quinoline at elevated temperature yielded **1** (Scheme 1) [17–21]. 2,6-Diesters **10** were prepared from **9** in high yields using the same ring closure strategy [16].

An alternative synthesis of **1**, also starting from 3-bromothiophene **5**, involved transmetallation, introduction of elemental sulfur, then S-alkylation with methyl 2-bromoacetate to give **11**. Regioselective Vilsmeier–Haack formylation led regioselectively to **12** and aldol cyclocondensation using NaOMe (or 1,5-diazabicyclo [4.3.0]-non-5-ene (DBN) [22]) afforded the bicyclic ester **13** ready for hydrolysis and decarboxylation (Scheme 2) [18].

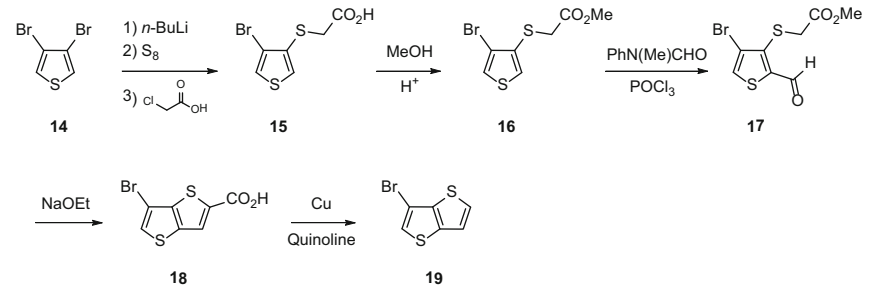
3-Bromothieno[3,2-*b*]thiophene (**19**) was made by monolithiation of 3,4-dibromothiophene (**14**), followed by consecutive addition of elemental sulfur and chloroacetic acid to form the acid **15** (Scheme 3). After esterification, a carbaldehyde unit was introduced regioselectively by Vilesmeier reaction to yield **17**. Treatment of **17** with sodium ethoxide induced ring closure and hence formation of **18**, decarboxylation with the assistance of copper powder and quinoline giving 3-bromothieno[3,2-*b*]thiophene (**19**) [23].



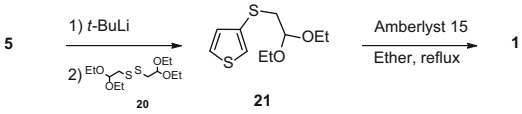
Scheme 1 Synthesis of thieno[3,2-*b*]thiophene (**1**) via 3-bromothiophene-2-carbaldehyde (**6**) [15], and preparation of 2,6-diester **10** [16]



Scheme 2 Synthesis of thieno[3,2-*b*]thiophene (**1**) starting from 3-bromothiophene (**5**) [18]

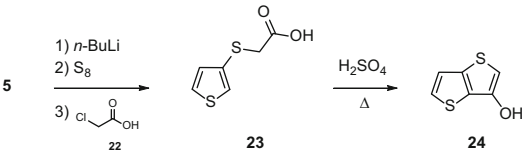


Scheme 3 Preparation of 3-bromo-TT (**19**) starting from 3,4-dibromothiophene (**14**) [23]

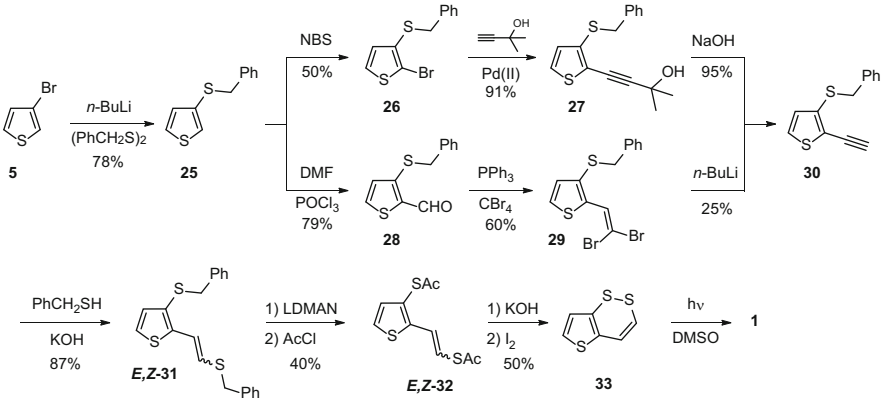


Scheme 4 Synthesis of thieno[3,2-*b*]thiophene (**1**) starting from 3-bromothiophene (**5**) in two steps [24]

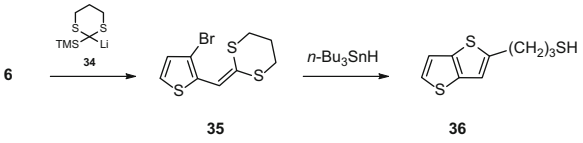
A two-step route in 67% overall yield again utilized 3-lithiothiophene, this time in reaction with 1,2-bis(2,2-diethoxyethyl)disulfide (**20**), producing the acetal **21**, electrophilic ring closure directly to **1** resulting from mild acid (Amberlyst 15) treatment (Scheme 4) [24].



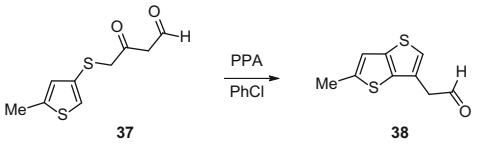
Scheme 5 3-hydroxythieno[3,2-*b*]thiophene (**24**) starting from 3-bromothiophene (**5**) [13]



Scheme 6 Synthesis of TT **1** via dithiin **33** [25]



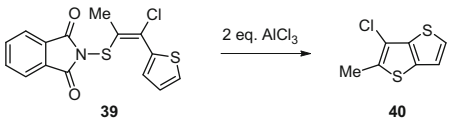
Scheme 7 Synthesis of TT (**36**) substituted by 3-mercaptoprop-1-yl at C-2 [26]



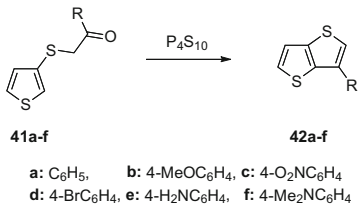
Scheme 8 Preparation of side-chain aldehyde **38** using PPA-promoted ring closure [13]

In a similar way, synthesis of 3-hydroxythieno[3,2-*b*]thiophene (**24**) required reaction of 3-lithiothiophene with elemental sulfur, then 2-chloroacetic acid (**22**) to give carboxylic acid **23**, which ring closed in hot acid (Scheme 5) [13].

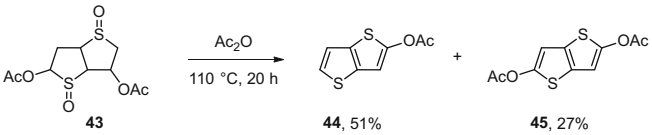
3-Lithiothiophene quenched with dibenzyl disulfide formed 3-(benzylthio) thiophene (**25**), which was used to obtain 3-benzylthio-2-ethynylthiophene (**30**) via two routes, as shown in Scheme 6 [25]. The alkyne **30** was now converted into thieno



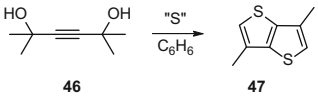
Scheme 9 3-Chloro-2-methylthieno[3,2-*b*]thiophene (**40**) via $AlCl_3$-catalysed ring closure [27]



Scheme 10 Synthesis of TTs **42a–f** possessing aryl units at C-3 [28]



Scheme 11 Pummerer rearrangement of disulfoxide (**43**) furnishing the TTs **44** and **45** [29]



Scheme 12 Synthesis of 3,6-dimethylthieno[3,2-*b*]thiophene (**47**) [30]

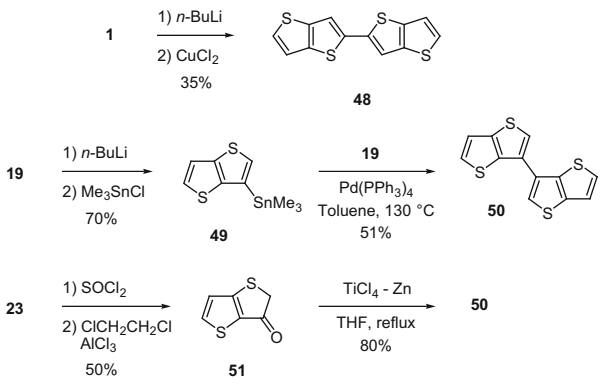
[3,2-*c*][1,2]dithiin (**33**). Daylight irradiation of **33** dissolved in DMSO finally gave **1**, in 120 min, though at the end of a rather long series of steps (Scheme 6).

The synthesis of the TT **36**, possessing a 3-mercaptoprop-1-yl unit at C-2 was achieved through the reaction of aldehyde **6** with lithium-2-trimethylsilyl-1,3-dithian-2-ide (**34**) and tributylstannane successively (Scheme 7) [26].

Another electrophilic cyclization involving methyl 4-(thien-3-yl)-1,3-keto-aldehyde **38** was effected using polyphosphoric acid (PPA) in chlorobenzene giving TT **38** (Scheme 8). It is significant that the cyclizing ring closure occurred at C-2 and not at C-4 [13].

Two equivalents of $AlCl_3$ were used to bring about cyclizing electrophilic substitution to make **40** from **39** (Scheme 9) [27].

A range of TTs **42a–f**, possessing *para*-substituted-aryl groups at C-3, were produced by ring closure of ketones **41a–f**, using P_4S_{10}, in moderate to good yields [28] (Scheme 10).



Scheme 13 Synthesis of 2,2′- and 3,3′-dimers **48** and **50**, respectively [32–34]

Pummerer rearrangement on disulfoxide **43** formed a mixture of 2-acetoxythieno[3,2-*b*]thiophene (**44**) and 2,5-diacetoxythieno[3,2-*b*]thiophene (**45**) (Scheme 11) [29].

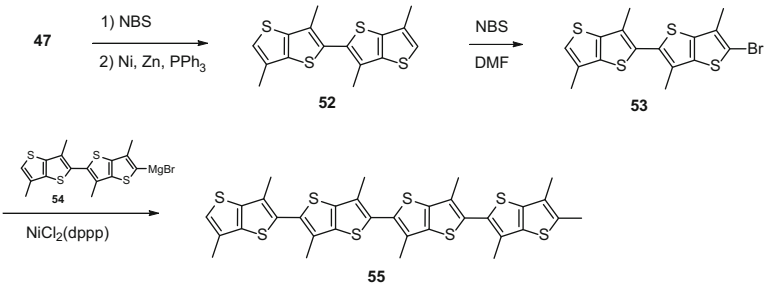
Commercially available 2,5-dimethylhex-3-yne-2,5-diol (**46**) reacts with elemental sulfur in hot benzene to give 3,6-dimethylthieno[3,2-*b*]thiophene (**47**) (Scheme 12) [30, 31].

2.1.2 Synthesis of Oligomers of Thieno[3,2-*b*]thiophene and Other Conjugated Derivatives

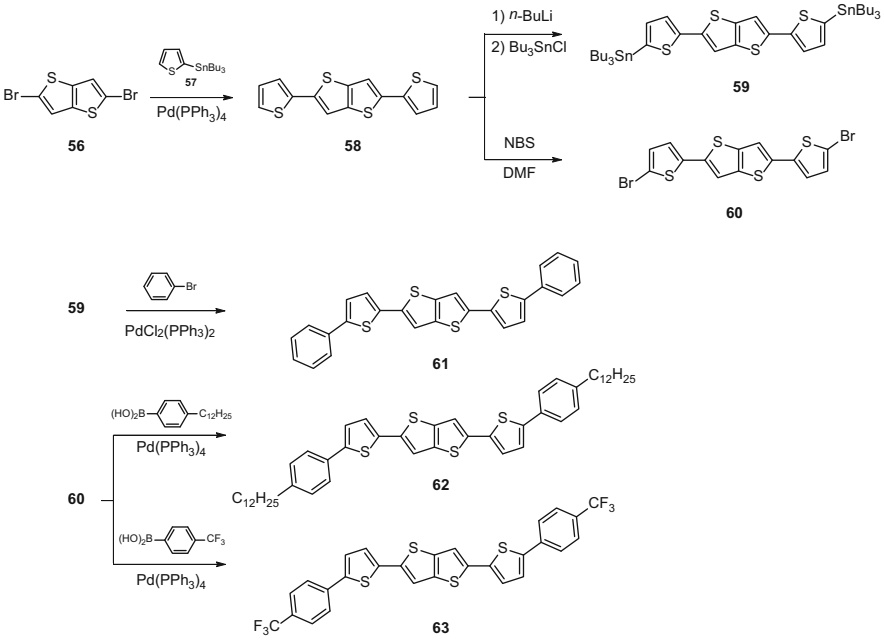
The 2,2-linked dimer **48** of **1** was prepared by 2-lithiation and then oxidation using $CuCl_2$ [32]. The 3,3-linked dimer **50** resulted from a combination of 3-bromothieno [3,2-*b*]thiophene (**19**) and 3-trimethylstannylthieno[3,2-*b*]thiophene (**49**) [33]. Another method for the synthesis of **50** involved a reductive coupling of two molecules of **51**, which was prepared from the reaction of **23** with thionyl chloride followed by intramolecular acylation in the presence of $AlCl_3$ (Scheme 13) [34].

The dimer **52** and the tetramer TT **55** were made from **47** (Scheme 14), thus bromination was followed by coupling using Ni as a catalyst to yield the dimer **52**. The tetramer **55** was obtained, following a similar methodology, via bromination of **52** then cross-coupling with its Grignard derivative **54** in the presence of $NiCl_2$(dppp) [35].

Various other mixed oligomers and modified [3,2-*b*]TTs have been prepared, and a selection is described in what follows. The reaction of 2,5-dibromothieno [3,2-*b*]thiophene (**56**) (easily prepared from TT (**1**) using two equivalents of NBS) with tributyl(thien-2-yl)stannane (**57**) in a Stille cross-coupling protocol resulted in the formation of 2,5-di(thien-2-yl)thieno[3,2-*b*]thiophene (**58**). The successive treatment of **58** with *n*-BuLi and Bu_3SnCl gave (**59**), which was Stille cross-coupled to obtain 2,5-bis(5-phenylthien-2-yl)thieno[3,2-*b*]thiophene (**61**). Dibromination of **88** furnished 2,5-bis(5-bromothien-2-yl)thieno[3,2-*b*]thiophene (**60**) and



Scheme 14 Synthesis of dimer **52** and tetramer **55** [35]

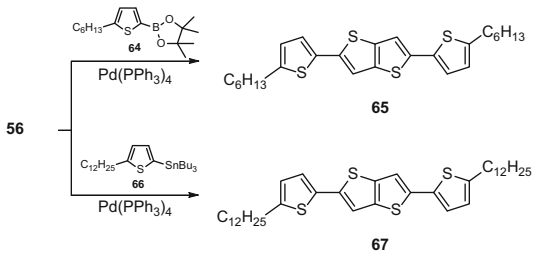


Scheme 15 Synthesis of oligomers **61–63** [36]

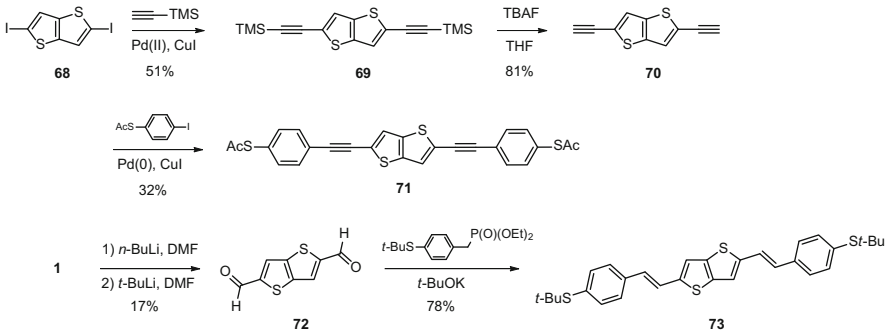
Suzuki cross-coupling reactions of **60** with aryl boronic acids produced 2,5-bis (5-(4-dodecylphenyl)thien-2-yl)thieno[3,2-*b*]thiophene (**62**) as yellow and 2,5-bis (5-(4-(trifluoromethyl)phenyl)thien-2-yl)thieno[3,2-*b*]thiophene (**63**) as orange crystals (Schemes 15 and 16) [36].

2,5-Bis(5-hexylthien-2-yl)thieno[3,2-*b*]thiophene (**65**) and 2,5-bis(5-dodecylthien-2-yl)thieno[3,2-*b*]thiophene (**67**) were prepared from 2,5-dibromo-TT (**56**), through Suzuki and Stille cross-couplings, respectively (Scheme 17) [37].

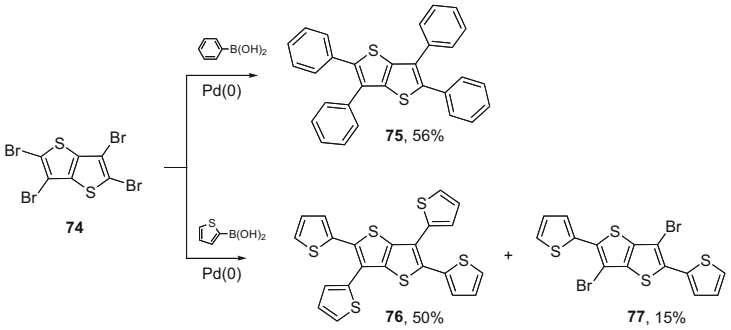
Rod-type oligomers oligo(*p*-phenylene-ethynylene) and oligo(*p*-phenylene-vinylidene), **71** and **73**, respectively, with sulfur units at each end to provide 'alligator clips' for the measurement of their single-molecule conductance through



Scheme 16 Synthesis of 2,5-bis(5-hexylthien-2-yl)-TT (**65**) and 2,5-bis(5-dodecylthien-2-yl)-TT (**67**) [37]



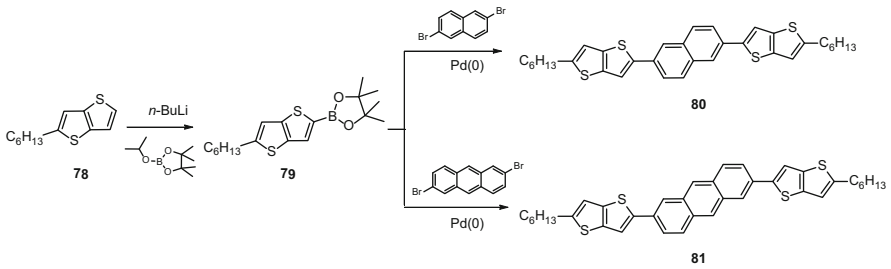
Scheme 17 Syntheses of rod-type oligomers **71** and **73** [38]



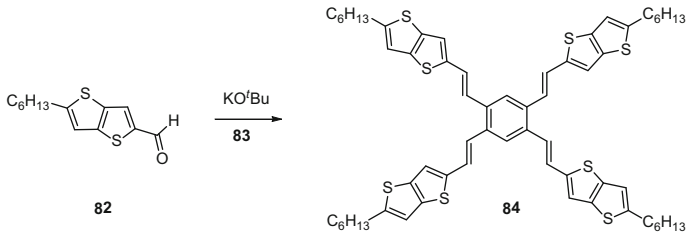
Scheme 18 Synthesis of tetrasubstituted TTs **75** and **76** [39]

a mechanically controllable break junction (MCBJ) technique, were achieved by applying Sonogashira cross-coupling and Horner–Wadsworth–Emmons-olefination protocols, respectively (Scheme 17) [38].

Thieno[3,2-*b*]thiophenes carrying either four phenyl (**75**) or four 2-thienyl groups (**76**) were constructed using Suzuki cross-couplings of tetrabromo-TT (**74**) with phenyl- or thiophene-2-boronic acids [39] Scheme 18).



Scheme 19 Preparation of oligomers **80** and **81** [40]



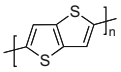
Scheme 20 Synthesis of star-shaped oligomer **84** [41]

Systems with two 2-hexylthieno[3,2-*b*]thiophenes connected via a π-conjugated spacer, naphthalene or anthracene, were built up via conversion of **78** into the 1,3,2-dioxaborolane **79** then Suzuki cross-coupling of this with 2,6-dibromonaphthalene or 2,6-dibromoanthracene (Scheme 19) [40].

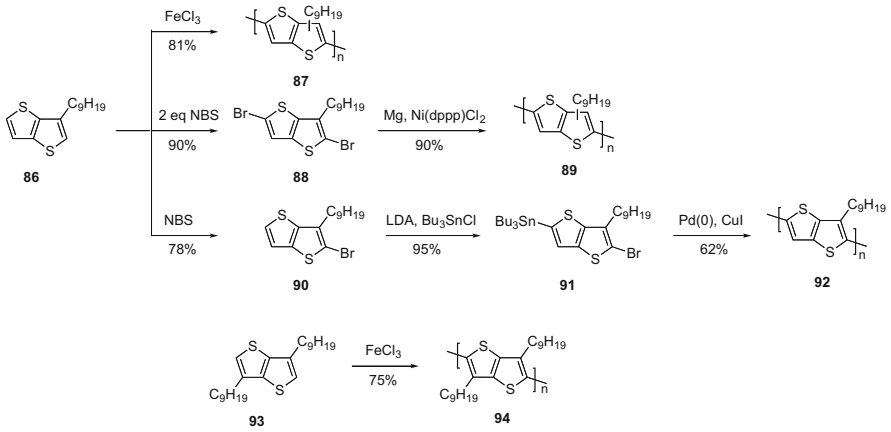
A system with four alkylated thieno[3,2-*b*]thiophenes, located around a benzene through ethylene linkages, depended for its synthesis on the reaction of aldehyde (**82**) with [1,2,4,5-tetra(diethoxyphosphorylmethyl)benzyl]phosphonic acid diethyl ester (**83**) (Scheme 20) [41].

2.1.3 Synthesis of Polymers Containing Thieno[3,2-*b*]thiophene Units

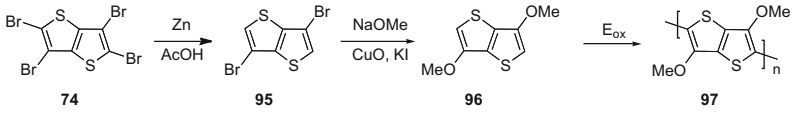
In contrast to thieno[3,4-*b*]thiophene (**2**), electropolymerization of which was not reported until 2001 [42], electrochemical and chemical polymerizations of thieno[3,2-*b*]thiophene (**1**) were conducted in the 1980s [18], thus electrochemical polymerization of thieno[3,2-*b*]thiophene (**1**), results in poly(thieneno[3,2-*b*]thiophene) (PTT, **85**) with the units linked through the 2- and 5-positions.



PTT, **85**



Scheme 21 Syntheses of regiorandom (**87** and **89**) and regioregular (**92**) polymers from mono-alkyl TT (**86**), and polymer **94** from di-alkyl TT (**93**) [43]

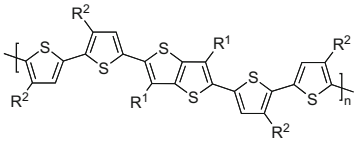


Scheme 22 Synthesis of polymer **97** from 3,6-dimethoxy-TT **96** [44]

Many more polymers and copolymers involving [3,2-*b*]-TT have been prepared and studied. A few of these are exemplified in this section. For example, polymerization of 3-nonylthieno[3,2-*b*]thiophene (**86**) was performed using three different pathways: (i) oxidatively with $FeCl_3$, (ii) 2,5-dibromination, followed by a Kumada cross-coupling, and (iii) preparation of the 2-bromo-5-stannane and its Stille cross-coupling (Scheme 21). The first two methods gave regiorandom polymers, the last was applied to prepare regioregular polymer. Polymerization of **93** was conducted with $FeCl_3$ giving polymer **94** [43].

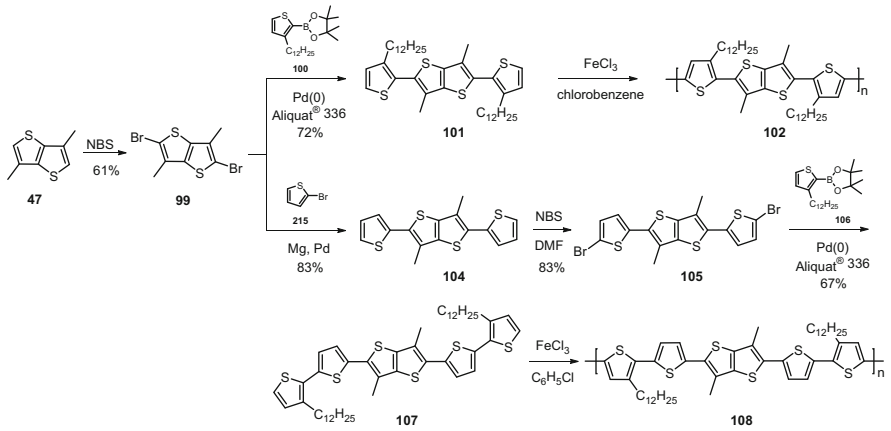
3,6-Dimethoxy [3,2-*b*]-TT **96** was synthesized from 3,6-dibromo-TT (**95**), itself obtained by reductive removal of the α-bromines from tetrabromo-TT, and polymerized electrochemically [44] (Scheme 22).

Copolymerization of **1** with 4,4′-dialkylbi(alkythiophenes) produced polymers **98a–d** possessing TT and bithiophene repeating units [45].

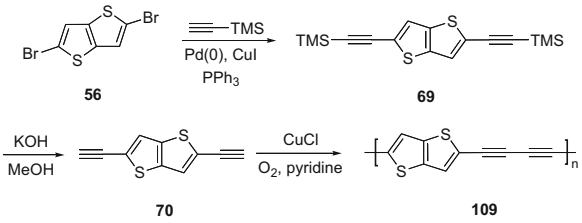


98a: R^1 = H, R^2 = $C_{10}H_{21}$
98b: R^1 = $C_{12}H_{25}$, R^2 = H
99c: R^1 = H, R^2 = $C_{12}H_{25}$
99d: R^1 = H, R^2 = $C_{14}H_{29}$

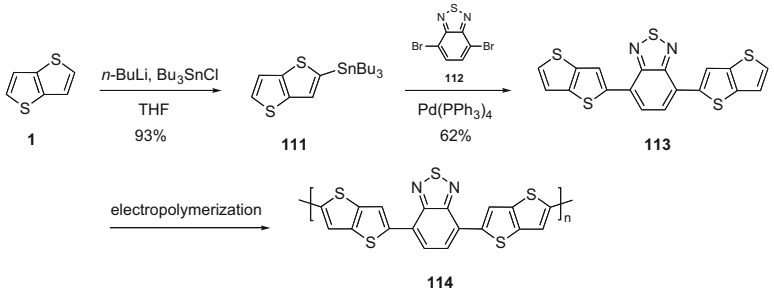
Solution-processable regioregular semiconductors, poly(2,5-bis(3-dodecylthien-2-yl)-3,6-dimethylthieno[3,2-*b*]thiophene) (**102**) and poly(2,5-bis(3′-dodecyl-



Scheme 23 Synthesis of copolymers **102** and **108** starting from 3,6-dimethyl-TT (**47**) [31]

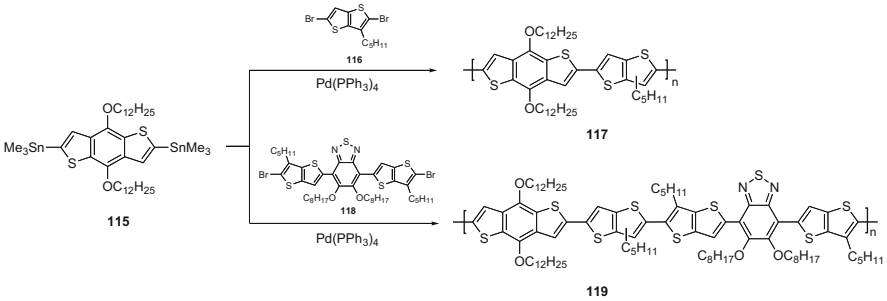


Scheme 24 Synthesis of the copolymer **109** [18]

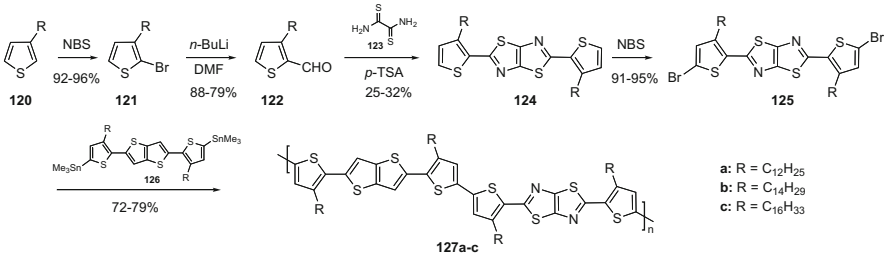


Scheme 25 Synthesis of TT-Btdaz (**113**) and its polymer **114** [47]

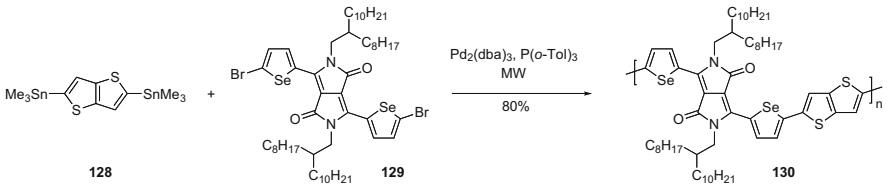
2,2′-bithien-5-yl)-3,6-dimethylthieno[3,2-*b*]thiophene) (**108**) were obtained as shown in Scheme 23, thus dibromination of **47** was followed by Suzuki cross-coupling with (**100**) to afford (**101**). $FeCl_3$-mediated oxidative polymerization at 65°C gave **102**. For the synthesis of the polymer **108**, dibrominated TT (**99**) was



Scheme 26 Synthesis of TT copolymers **117** and **119** [48]



Scheme 27 Synthesis of copolymers **127a–c** [49]



Scheme 28 Preparation of D-A copolymer **130** [50]

cross-coupled with 2-bromothiophene (**103**) to produce (**104**), dibromination of which provided (**105**) then Suzuki cross-coupling with (**106**) led to (**107**) which was polymerized to **108** with $FeCl_3$ [31].

Poly[2,5-ethynylene-(thieno[3,2-*b*]thiophenediyl)ethynylene] (**109**) was constructed from dibromo-TT (**56**) via Sonogashira cross-coupling with trimethylsilylacetylene providing **69** then, after desilylation, chemical polymerization of **70** using CuCl and O_2 gave **109** (Scheme 24) [18].

Asymmetric electrochemical polymerization of thieno[3,2-*b*]thiophene (**1**), 2,2′-bisthieno[3,2-*b*]thiophene (bis-TT, **48**), and 4,7-bis-thieno[3,2-*b*]thiophen-2-yl-benzo[1,2,5]thiadiazole (TT-Btdaz, **113**) [46], linked through the TT 2-positions, was carried out in cholesteric liquid crystals (CLCs) (Scheme 25) [47].

Stille cross-coupling was used to form the copolymers poly(4,8-didodecyloxybenzo[1,2-*b*:4,5-*b*′]dithiophene-alt-3-pentylthieno[3,2-*b*]thiophene) (**117**) and

poly(4,8-didodecyloxybenzo[1,2-*b*:4,5-*b*′]dithiophene-alt-5,6-bis(octyloxy)-4,7-bis (6-pentylthieno[3,2-*b*]thien-2-yl)benzo[*c*][1,2,5]thiadiazole (**119**) from benzo [1,2-*b*:4,5-b′]dithiophene (**115**) with **116** and benzothiadiazole (**118**), respectively (Scheme 26) [48].

Poly(3-alkylthiophene)s, having TT and electron-deficient thiazolo[5,4-*d*]thiazole rings, were assembled through Stille cross-couplings (Scheme 27) [49]. Treatment of the aldehydes **122** with dithiooxamide (**123**) provided thiazolo[5,4-*d*] thiazole oligomers (**124**). Dibromination and then copolymerization with bis-stannane **126** produced air-stable polymers **127a–c**.

A donor–acceptor (D-A) copolymer, poly(3-(2,2′-biselenophen-5,5′-yl)-2,5-di (2-octyldodecyl)-6-(thieno[3,2-*b*]thiophen-2,5-yl)-1,4-diketopyrrolo[3,4-*c*]pyrrole (**130**), was obtained as a dark green solid, through Stille cross-coupling of distannyl TT **128** and diselenophene-substituted DPP **129** as a dark green solid (Scheme 28) [50].

2.2 Thieno[3,4-b]thiophene (2)

2.2.1 Synthesis of Thieno[3,4-*b*]thiophenes

In 1967, Wynberg et al. reported the first synthesis of air-sensitive thieno[3,4-*b*] thiophene [51]. The sulfoxide (**131**) was converted into anhydride **133** in refluxing acetic anhydride (**132**). Hydrolysis to form thieno[3,4-*b*]thiophene-2-carboxylic acid (**134**) then copper/quinoline decarboxylation gave **2**, isolated initially as a picrate (Scheme 29).

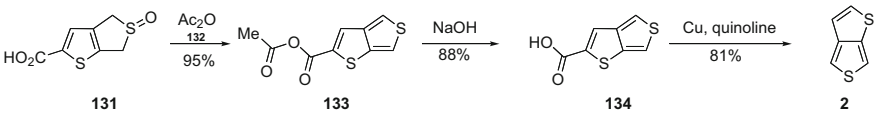
An analogous procedure gave **138**, containing ester and cyano groups at 2- and 3-positions (Scheme 30) [52].

Assisted 3-metallation of **139**, then trapping with carbon dioxide, produced diacid **140a**. Metallation at C-5 then addition of an alkyl bromide gave alkylated products **141b–e**. The carboxylic acid groups were reduced to primary alcohols, converted into bromides **143**, and reacted with Na_2S to give dihydro-TTs **144a–e**, which were aromatized, in this case using DDQ (Scheme 31) [53].

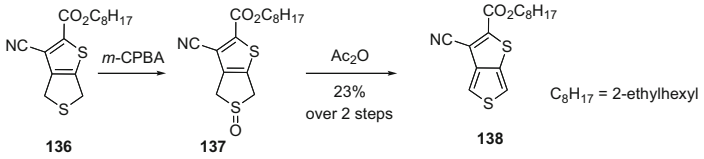
3,4-Dibromothiophene (**14**) can be converted into **2** in two steps in an overall yield of 39% (Scheme 32). Sonogashira cross-coupling with trimethylsilylacetylene provided **146**. Transmetallation then addition of elemental sulfur gave the corresponding thiolate, thermal cyclization of which afforded thieno[3,4-*b*]thiophene (**2**) as a colorless oil [55]. Using phenylacetylene instead of trimethylsilylacetylene led to 2-phenylthieno[3,4-*b*]thiophene in 19% yield from the dihalide [54].

3,4-Dibromothiophene (**14**) was also the starting material for the construction of 2-formylthieno[3,4-*b*]thiophene (**150**) (Scheme 33). Lithiation enabled formation of aldehyde **147** then reacted with ethyl mercaptoacetate in the presence of CuO nanoparticles and K_2CO_3 to give **148**, the ester group of which was reduced and the resulting alcohol oxidized to aldehyde [55].

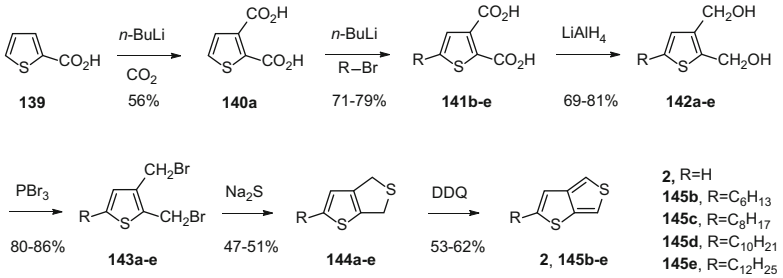
2-Decylthieno[3,4-*b*]thiophene (**145d**) was constructed from thiophene-2-carboxylic acid (**139**). 3-Metallation with *ortho* assistance using two equivalents



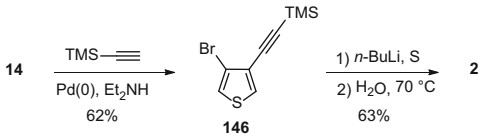
Scheme 29 Synthesis of thieno[3,4-*b*]thiophene (**2**) from sulfoxide **131** [51]



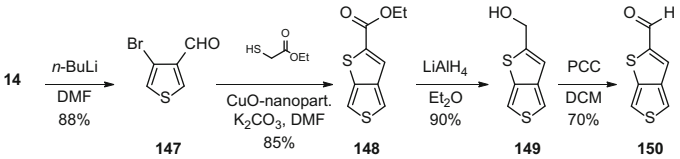
Scheme 30 Synthesis of **138** via dehydration of **137** [52]



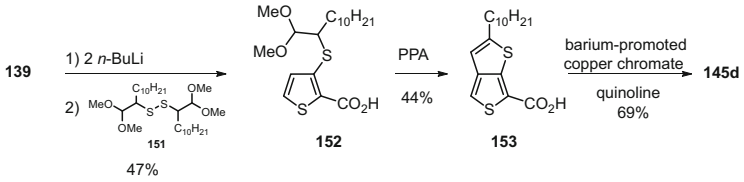
Scheme 31 Preparation of TT (**2**) and alkyl-substituted TTs (**145b–e**) [53]



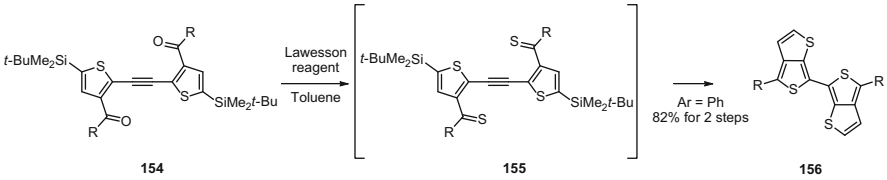
Scheme 32 Synthesis of **2** starting from 3,4-dibromothiophene (**14**) [54]



Scheme 33 Preparation of 2-formylthieno[3,4-*b*]thiophene (**150**) [55]



Scheme 34 Synthesis of alkyl-substituted TT, 2-decylthieno[3,4-*b*]thiophene (**145d**) [56, 57]



Scheme 35 Synthesis of diaryl-substituted bi(thieno[3,4-*b*]thiophene)s **156** [58]

of *n*-BuLi then trapping with 2,2′-bis(1,1-dimethoxydodecan-2-yl)disulfide (**151**) gave (**152**), which was followed by treatment with polyphosphoric acid (PPA) to obtain the bicyclic acid (**153**) via electrophilic ring closure at the available β-position. Removal of the carboxylic acid using barium-promoted copper chromite in quinoline at 200 °C furnished **145d** (Scheme 34) [56, 57].

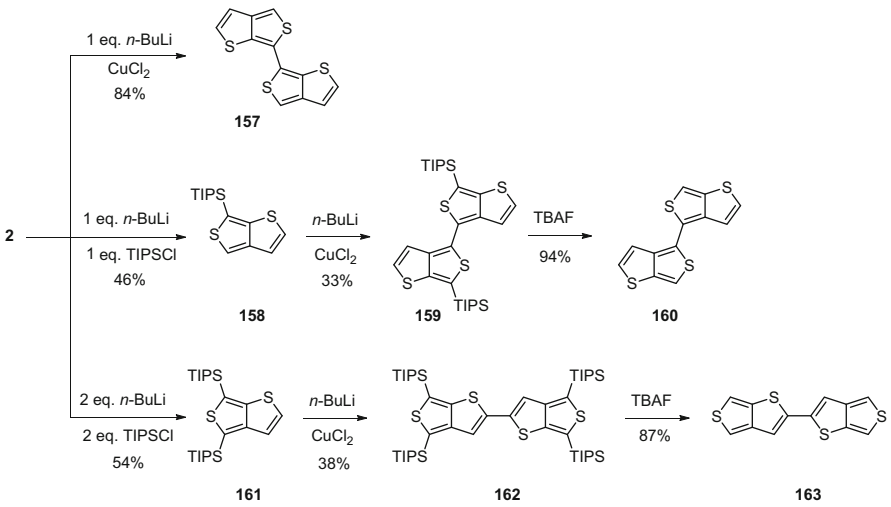
Diaryl-substituted bi(thieno[3,4-*b*]thiophene)s **156** were generated by intramolecular double 5-*exo-dig* cyclizations of bis[(arylthiocarbonyl)thien-2-yl]acetylenes **155** [58]. For example, the reaction of **154** with Lawesson's reagent in refluxing toluene led to thiocarbonyl compound (**155**), thermal 5-*exo-dig* cyclization of which furnished **156** in 82% yield (Scheme 35).

2.2.2 Synthesis of Oligomers of Thieno[3,4-*b*]thiophenes and Other Conjugated Derivatives

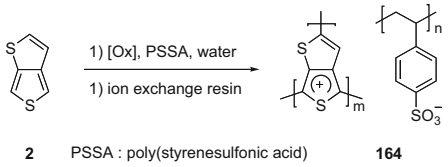
Three thieno[3,4-*b*]thiophene dimers, namely 2,2′-bis-(thieno[3,4-*b*]thiophene) (**163**), 4,4′-bis(thieno[3,4-*b*]thiophene) (**160**), and 6,6′-bis(thieno[3,4-*b*]thiophene) (**157**), were synthesized using $CuCl_2$-promoted coupling (Scheme 36) [59]. Note the subtle use of regioselective lithiation, lithiation then blocking and lithiation and double blocking, to reach **157**, **160**, and **163** respectively.

2.2.3 Synthesis of Polymers Containing Thieno[3,4-*b*]thiophene Units

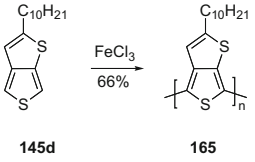
The first electrochemical polymerization of thieno[3,4-*b*]thiophene (**2**) [42] used a constant potential of 1.2 V applied on an indium tin oxide (ITO)-coated glass plate. Polymerization of **2** as an aqueous dispersion using a polyelectrolyte, such as poly(styrenesulfonate) (PSS), produced poly(thieno[3,4-*b*]thiophene)-poly (styrenesulfonic acid) (**164**) [42, 60] (Scheme 37).



Scheme 36 Synthesis of the dimers **157**, **160**, and **163** [59]



Scheme 37 Polymerization of **2** as an aqueous dispersion [42, 60]

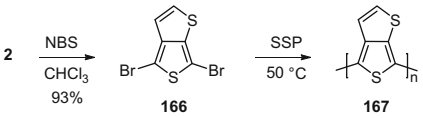


Scheme 38 Chemical polymerization of 2-decylthieno[3,4-*b*]thiophene (**145d**) [56, 57]

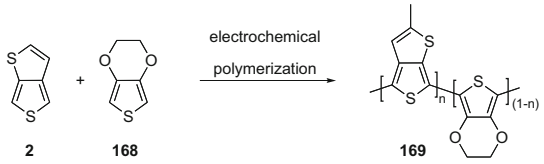
2-Decylthieno[3,4-*b*lthiophene was polymerized using $FeCl_3$ to obtain a blue-green polymer **165**, which was soluble in common organic solvents (Scheme 38) [56, 57].

Bromination of **2** gave 4,6-dibromothieno[3,4-*b*]thiophene (**166**) as a white crystalline solid in 93% yield, which was used for mild solid-state polymerization (SSP) at a temperature below the melting point (50 °C) resulting in a bromine-doped polymer **167**, which was insoluble in common organic solvents (Scheme 39) [54].

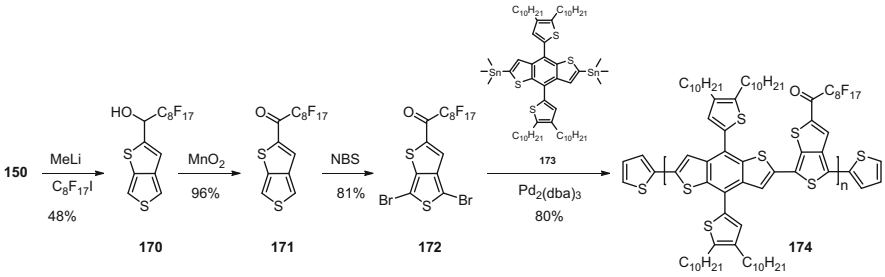
The copolymer **169** was constructed electrochemically from **2** and 3,4-ethylenedioxythiophene (EDOT) (**168**) [62] (Scheme 40).



Scheme 39 Solid state polymerization (SSP) of **166** [54, 61]



Scheme 40 Preparation of copolymer **169** [62]



Scheme 41 Preparation of copolymer **174** [63]

The copolymer **174** was prepared from dialkyl thienylated benzodithiophene (**173**) and perfluororalkyl-carbonyl substituted thieno[3,4-*b*]thiophene (**172**) monomers (Scheme 41). Thus, reaction of thieno[3,4-*b*]thiophene-2-carbaldehyde (**150**) with heptadecafluorooctyl iodide in the presence of methyllithium to form **170** was followed by oxidation with MnO_2 giving ketone **171**. Bromination with two equivalents of NBS furnished dibromide **172**, and this was Stille cross-coupled with **173** in the presence of $Pd_2(dba)_3$ to obtain the copolymer **174** [63].

Many other copolymers containing thieno[3,4-*b*]thiophene units have been made and some of them are shown in Fig. 1 [64–66].

2.3 Thieno[2,3-b]thiophene (3)

2.3.1 Synthesis of Thieno[2,3-*b*]thiophenes

Thieno[2,3-*b*]thiophene (**3**) is a cross-conjugated system, which can be used to decrease the conjugation length in a polymer in order to decrease the HOMO

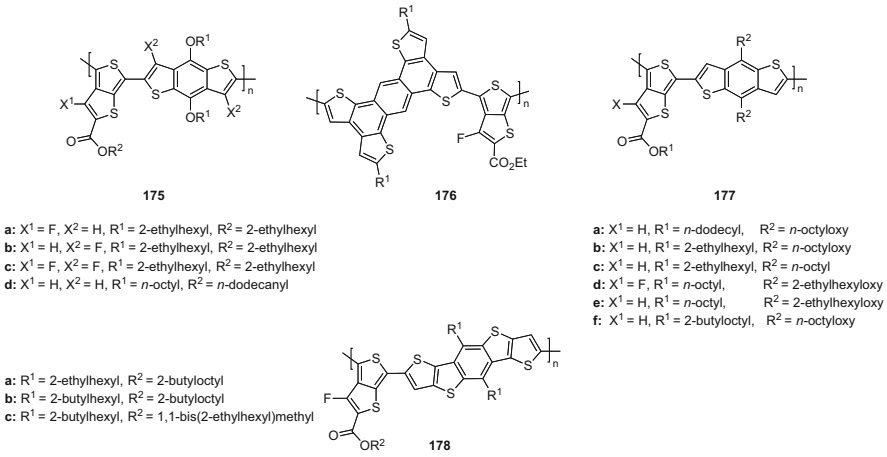
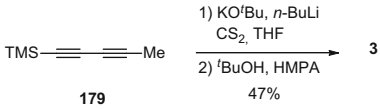


Fig. 1 Some copolymers containing thieno[3,4-*b*]thiophene units [64–66]



Scheme 42 Synthesis of **3** from trimethylsilylpenta-1,3-diyne (**179**) [67]

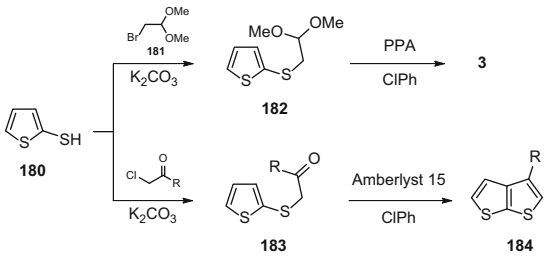
energy level. Several methods have been developed to synthesize **3** and its derivatives. [2,3-*b*]-TT (**3**) itself can be synthesized from 1-trimethylsilylpenta-1,3-diyne (**179**) simply by reaction with CS_2 and *n*-BuLi/KO*t*-Bu at −80 °C, followed by a solution of *t*-BuOH in HMPA at −30 °C [67] (Scheme 42).

2-Mercaptothiophene (**180**) S-alkylated with 2-bromoacetaldehyde dimethyl acetal (**181**) gave **182**, ring closed with PPA in refluxing chlorobenzene giving **3** (Scheme 43) [20, 68]. Similarly, 3-alkyl-TTs (**184**) are produced via S-alkylation of **180** with an α-chloroketone, then acid-catalyzed ring closure [69].

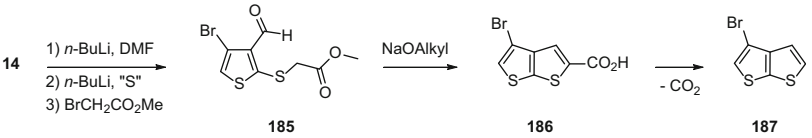
Monolithiation of 3,4-dibromothiophene (**14**) and addition of DMF, followed by treatment with *n*-BuLi again and then elemental sulfur, and methyl bromoacetate produced **185**. Aldol-type ring closure and a final decarboxylation of **189** give 3-bromothieno[2,3-*b*]thiophene (**187**) (Scheme 44) [18].

Condensation of thiophene-3-carbaldehyde (**188**) with 2-thioxothiazolidin-4-one (**189**) affords **191** via intermediate **190**. Treatment of **191** with two equivalents of iodine produces thieno[2,3-*b*]thiophene-2-carboxylic acid (**192**) in 70% yield (Scheme 45) [70].

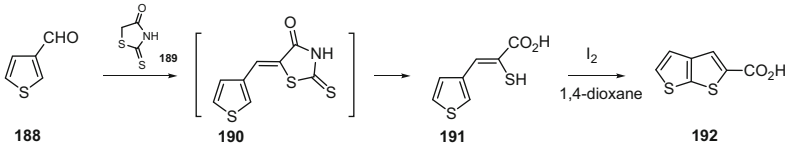
2,4,5-Tribromothiophene-3-carbaldehyde (**193**) with ethyl thioglycolate produces ethyl 4,5-dibromothieno[2,3-*b*]thiophene-2-carboxylate (**194**) in 58% yield



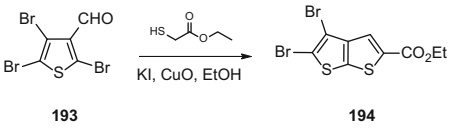
Scheme 43 Synthesis of **3** and **184** from 2-mercaptothiophene (**180**) [20, 68, 69]



Scheme 44 Synthesis of 3-bromothieno[2,3-*b*]thiophene (**187**) starting from 3,4-dibromothiophene (**14**) [18]



Scheme 45 Ring closure of **191** with I_2 giving thieno[2,3-*b*]thiophene-2-carboxylic acid (**192**) [70]

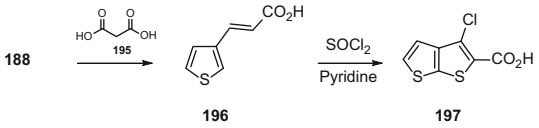


Scheme 46 Formation of ethyl 4,5-dibromothieno[2,3-*b*]thiophene-2-carboxylate (**194**) [21]

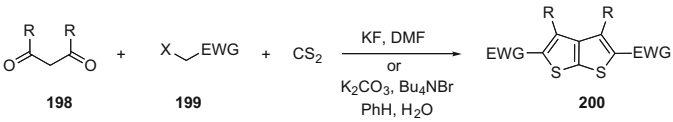
(Scheme 46) [21]. Ring closure can also be performed using 1,5-diazabicyclo [4.3.0]non-5-ene (DBN) [22].

Condensation of thiophene-3-carbaldehyde (**188**), with malonic acid (**195**) led to (*E*)-3-(thien-3-yl)acrylic acid (**196**), then, treatment with thionyl chloride in pyridine gave chloro-acid **197** in 51% yield [71, 72] (Scheme 47).

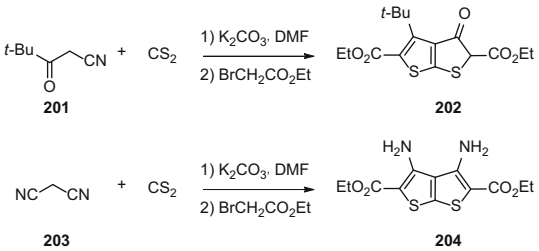
2,5-Disubstituted [2,3-*b*]-TTs (**200**) were synthesized through the reaction of 1,3-diketones **198** with α-halo-ketones, and similar, **199**, and carbon disulfide in the presence of KF as a promoter (Scheme 48). The synthesis can also be performed using phase-transfer catalysis [73, 74].



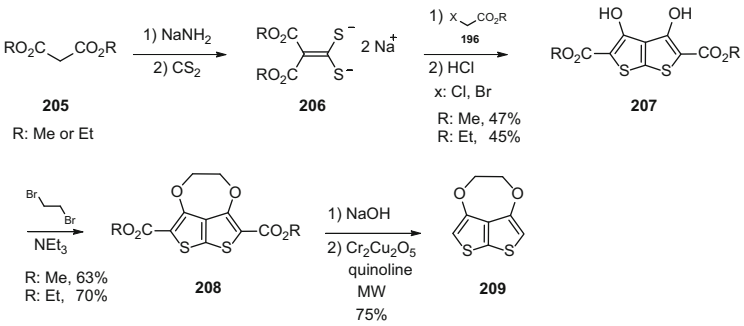
Scheme 47 Synthesis of **197** via a Doebner condensation [71, 72]



Scheme 48 Thieno[2,3-*b*]thiophenes (**200**) starting from 1,3-diketones (**198**) and halides (**199**) [73, 74]

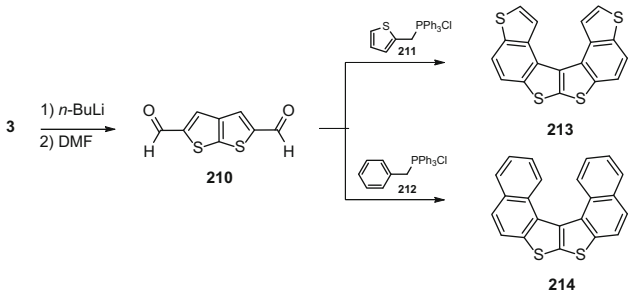


Scheme 49 Synthesis of oxo- and amino-substituted [2,3-*b*]-TTs, **202** and **204**, respectively [75]



Scheme 50 Synthesis of 3,4-ethylenedioxythieno[2,3-*b*]thiophene (**209**) [76]

Oxo- and amino-substituted [2,3-*b*]-TTs (**202** and **204**) result from the reaction of 3-keto esters, malononitrile, ethyl cyanoacetate, or 3-ketonitriles, with alkylating agents such as ethyl bromoacetate and bromoacetonitrile, as exemplified in Scheme 49 [75].



Scheme 51 Synthesis of heterohelicenes **213** and **214** [78]

Other examples of this theme, giving 3,4-dihydroxythieno[2,3-*b*]thiophenedicarboxylates (**207**) involve the intermediacy of **206**. Dialkylation of **207** with 1,2-dibromoethane leads to **208** saponification followed by decarboxylation then producing 3,4-ethylenedioxythieno[2,3-*b*]thiophene (**209**) (Scheme 50) [76].

2.3.2 Synthesis of Oligomers of Thieno[2,3-*b*]thiophenes and Other Conjugated Derivatives

Unlike the other TT isomers, incorporation of thieno[2,3-*b*]thiophene, a cross-conjugated system, into conjugated oligomers or polymers suppresses the effective conjugation length and hence increases its ionization potential, that is, lowers the HOMO energy level and increases the stability of the materials [77].

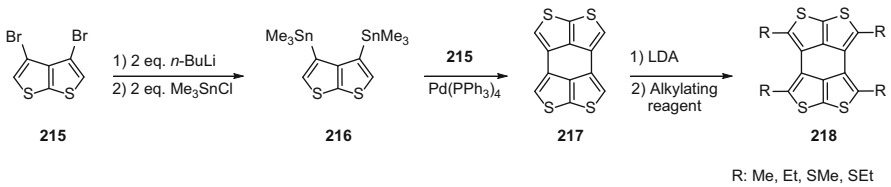
2-Lithiation of thieno[2,3-*b*]thiophene (**3**) followed by treatment with *N,N*-dimethylformamide gives the dialdehyde **210**, which on reaction with Wittig-reagents (**211** and **212**) produces heterohelicenes **213** and **214**, respectively [78] (Scheme 51).

2,3,6,7-Tetrathiabenzo[l,3-*cd*:4,6-*c′d′*]dipentalene (**217**), which is isoelectronic with perylene, was prepared via dimerization of thieno[2,3-*b*]thiophene (**3**) [79]. Another method for the synthesis of **217** involved the cross-coupling of 3,4-dibromo-TT (**212**) with 3,4-bis(trimethylstannyl)-TT (**216**) in the presence of a palladium catalyst giving **217** in 13% yield. Functionalization of **217** via lithiation with LDA, followed by addition of an alkyl iodide or a dialkyl disulfide leads to **218** [80] (Scheme 52).

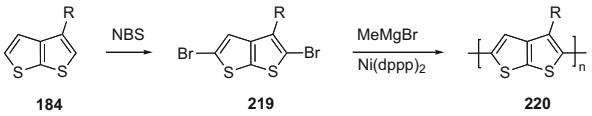
2.3.3 Synthesis of Polymers Containing Thieno[2,3-*b*]thiophene Units

The chemical polymerizations of TTs (**184**) were achieved via reaction of dibromo-TTs **219**, with MeMgBr and $Ni(dppp)_2$ (Scheme 53) [69].

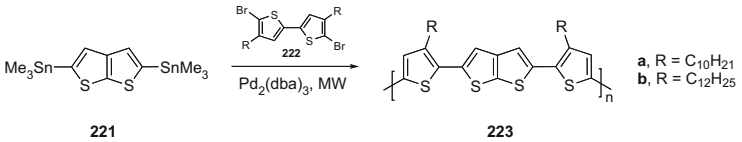
Synthesis of co-polymers **223a** and **223b** consisting of bithiophene and thieno[2,3-*b*]thiophene (**3**) units involved Stille cross-coupling polymerization of 2,5-bis(trimethylstannyl)thieno[2,3-*b*]thiophene (**221**) with 5,5-dibromo-4,4′-dialkyl-2,2′-bithiophenes (**222**) (Scheme 54) [77].



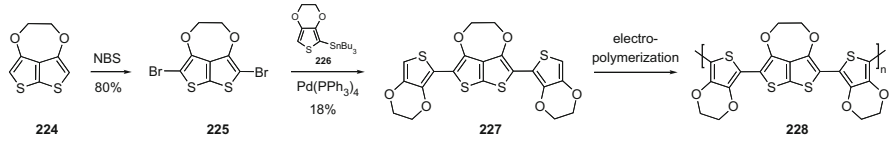
Scheme 52 Preparation of dipentalene **217** from **215** [80]



Scheme 53 Polymerization of a dibromo TT (**219**) using MeMgBr and $Ni(dppp)_2$ [69]



Scheme 54 Preparation copolymers **223a,b** [77]

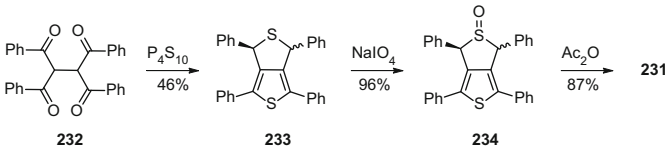


Scheme 55 Synthesis of oligomer **227** and its electropolymerization furnishing copolymer **228** [76]

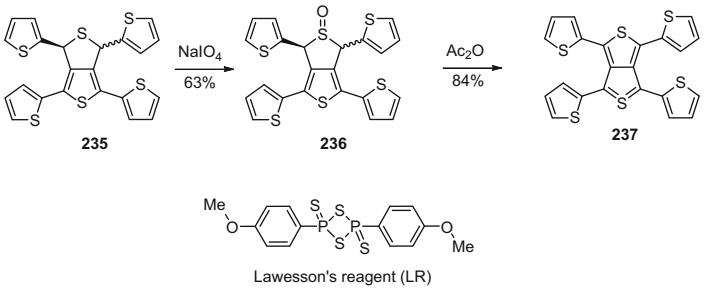
Dibromination of **224** provided 2,5-dibromo-3,4-ethylenedioxythieno[2,3-*b*]thiophene (**225**) as a pale yellow solid, Stille cross-coupling of which with 2-tributylstannyl-3,4-ethylenedioxythiophene (**226**) in the presence of $Pd(PPh_3)_4$ furnished 2,5-bis(3,4-ethylenedioxythiophene)-3,4-diethylenedioxythieno[2,3-*b*]thiophene (**227**) as a pale yellow solid, which was electropolymerized (Scheme 55) [76].

2.4 Thieno[3,4-c]thiophene (4)

Unlike the other TTs, thieno[3,4-*c*]thiophene (**4**), possessing a 10-π-electron system and sulfur with oxidation state of +4, sometimes referred to as "nonclassical" thienothiophene, has not been studied extensively as it is unstable; its existence has

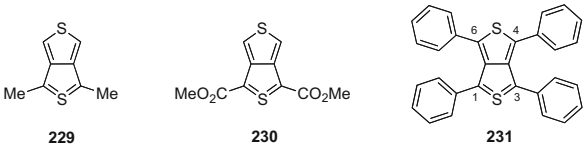


Scheme 56 The synthesis of 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene (**231**) [86, 87]



Scheme 57 Synthesis of tetra(thien-2-yl)thieno[3,4-*c*]thiophene (**237**) [12]

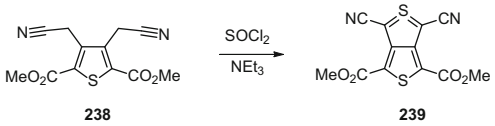
only been proved by trapping [81–84], for example **229** and **230** [85, 86]. Tetraphenylthieno[3,4-*c*]thiophene (**231**) was the first isolable [3,4-*c*]-TT, obtained as shiny reddish-purple needles with a melting point of 245–248 °C. It has a singlet ground state since its solution in benzene does not provide an ESR signal. It has an intense permanganate-like color in solution, with λ_{max} 553 nm [87, 88].



2.4.1 Synthesis of Thieno[3,4-*c*]thiophenes

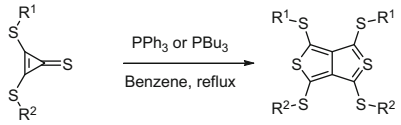
The synthesis of **231** was achieved in three steps starting from 1,1,2,2-tetrabenzoylethane (**232**) thus double ring closure using P_4S_{10} [89], produced **233**, treatment with $NaIO_4$ then yielding the sulfoxide **234** and dehydration with acetic anhydride furnished **231** (Scheme 56) [86, 87]. Tetra(thien-2-yl)thieno[3,4-*c*]thiophene (**237**), a dark purple (λ_{max} 576 nm), stable crystalline substance, was made in similar fashion (Scheme 57) [12].

A different route provided **239**, carrying four electron-withdrawing units: the sulfur was inserted into dinitrile (**238**) with thionyl chloride in the presence of triethylamine (Scheme 58) [90, 91].



238 239

Scheme 58 Synthesis of thieno[3,4-*c*]thiophene **239** possessing four electron-withdrawing units [90, 91]



240 241

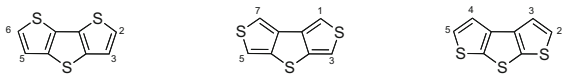
R^1 : ^{i}Pr, ^{t}Bu; R^2 : ^{i}Pr, ^{t}Bu, Me, Et

Scheme 59 Dimerization of 2,3-di(alkylthio)cyclopropenethiones (**240**) to form [3,4-*c*]-TT **241** [92, 93]

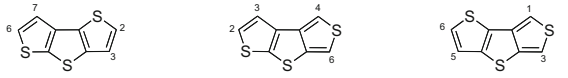
Dimerization of 2,3-di(alkylthio)cyclopropenethiones (**240**) in the presence of triphenyl- or tributylphosphine furnished 1,3,4,6-tetra(alkylthio)thieno[3,4-*c*]thiophenes (**241**) (Scheme 59) [92, 93].

3 Dithienothiophenes

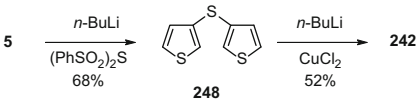
Compounds with three annulated thiophene rings, known as dithienothiophenes (DTTs), have been utilized extensively to construct functional materials, such as p-type semiconductors for OFETs, owing to their planar, sulfur-rich, rigid, conjugated, and highly thermal- and photo-stable structures [3, 7–9, 94]. Six isomers have been reported, namely dithieno[3,2-*b*;2′,3′-*d*]thiophene (**242**), dithieno[3,4-*b*;3′,4′-*d*]thiophene (**243**), dithieno[2,3-*b*;3′,2′-*d*]thiophene (**244**), dithieno[2,3-*b*;2′,3′-*d*]thiophene (**245**), dithieno[3,4-*b*;3′,2′-*d*]thiophene (**246**), and dithieno[3,4-*b*;2′,3′-d]thiophene (**247**) [8].



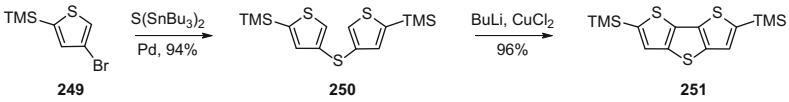
242 243 244



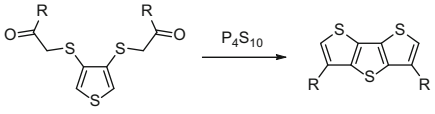
245 246 247



Scheme 60 Synthesis of dithieno[3,2-*b*;2′,3′-*d*]thiophene (**242**) from 3-bromothiophene (**5**) [95]



Scheme 61 Synthesis of 2,6-bis(trimethylsilyl)-DTT **251** from **249** using $S(SnBu_3)_2$ [33]



a: Ph, **b:** 4-$MeOC_6H_4$, **c:** 4-BrC_6H_4, **d:** 4-$NO_2C_6H_4$, **e:** 2-thienyl

Scheme 62 Reactions of 1,8-diketones (**252a–e**) in the presence of P_4S_{10} affording DTTs (**253a–e**) [96–98]

3.1 Dithieno[3,2-b;2′,3′-d]thiophene (242)

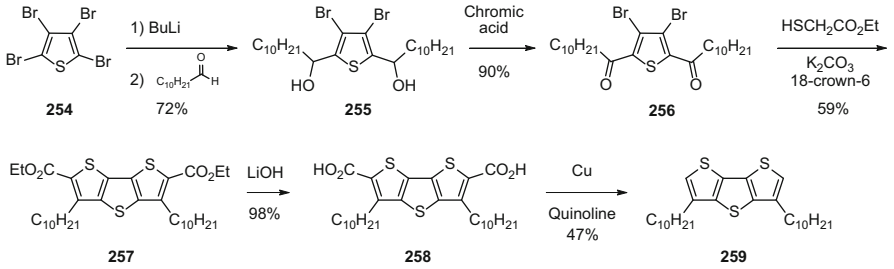
3.1.1 Synthesis of Dithieno[3,2-*b*;2′,3′-*d*]thiophenes

In 1971, the first synthesis of **242** used transmetallation of 3-bromothiophene (**5**) then reaction with the electrophilic sulfur source $(PhSO_2)_2S$. The resulting 3, 3′-dithienyl sulfide (**248**) was α,α'-dilithiated and the carbon–carbon bond made by oxidation with $CuCl_2$ [95] (Scheme 60).

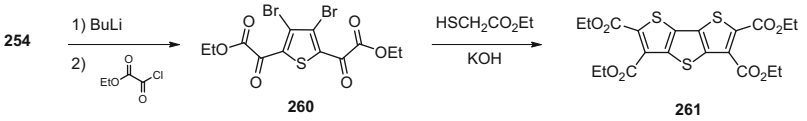
A synthesis of 2,6-bis(trimethylsilyl) substituted DTT (**251**), started from 4-bromo-2-trimethylsilylthiophene (**249**). Here the linking sulfur was supplied using $S(SnBu_3)_2$ and Pd(0) catalysis, providing **250** and the carbon–carbon link made using *n*-BuLi and then $CuCl_2$ (Scheme 61) [33].

1,8-Diketones (**252a–e**) reacted with P_4S_{10} in refluxing toluene produce DDTs **253** possessing 3,5-diaryl substituents, in 53–95% yields (Scheme 62) [8, 96–98].

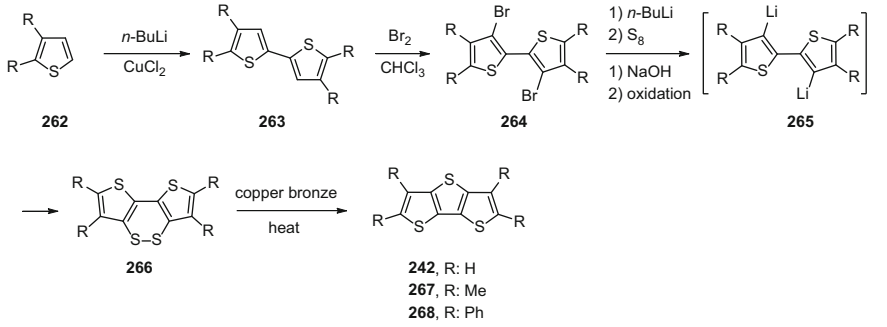
3,5-Didecyldithieno[3,2-*b*:2′,3′-*d*]thiophene (**259**) was made from tetrabromothiophene (**254**) in five steps [19]. 2,5-Dilithiation, followed by quenching with undecanal, produced **255**, oxidation then giving the dione **256**. Finally, ethyl 2-mercaptoacetate reacted to form the two thiophene rings. Hydrolysis and decarboxylation led to **259** (Scheme 63).



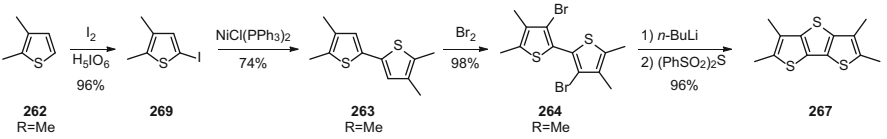
Scheme 63 Synthesis of didecyl DTT **259** from tetrabromothiophene (**254**) [19]



Scheme 64 Preparation of a DTT tetracarboxylate (**261**) [99]



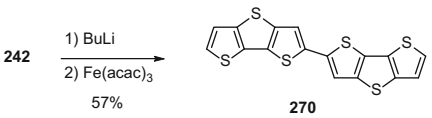
Scheme 65 The synthesis of DTTs **242, 267,** and **268** via a dithiin [25]



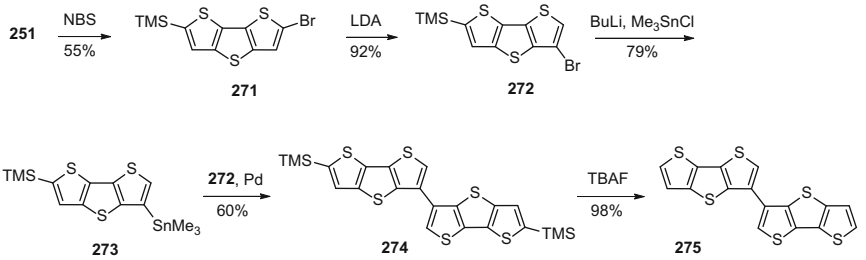
Scheme 66 Synthesis of DTT **267** [100]

If 3,4-dibromo-2,5-dilithiothiophene is trapped instead with ethyl chloroox-oacetate, subsequent reaction with ethyl 2-mercaptoacetate gives rise to the tetraethyl DTT-2,3,5,6-tetracarboxylate **261** (Scheme 64).

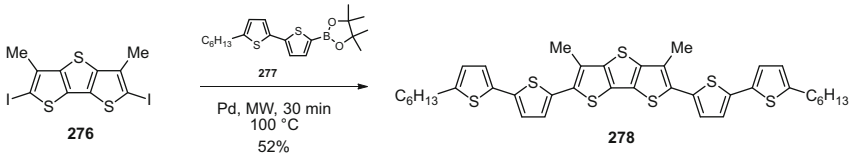
Oxidative coupling of a thiophene (2-lithiation then $CuCl_2$) gives a dimer **263** α,α′-dibromination of which, then transmetallation, allows introduction of sulfur in



Scheme 67 Dimerization of **242** giving α,α′-linked **270** [101]



Scheme 68 Synthesis of β,β′-linked dimer **275** [33]



Scheme 69 Preparation of DTT **278** possessing dithiophene units at 2- and 6-positions [102]

the form of a 1,2-dithiin, **266** which gives DTTs on strong heating [25] (Scheme 65).

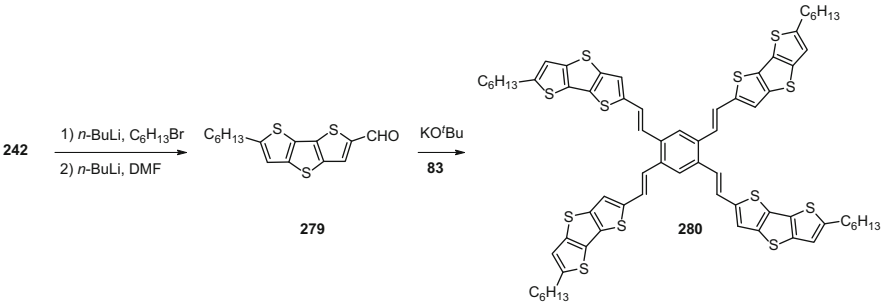
A dimer **263** formed using nickel(0) cross-coupling was dibrominated at the only available positions, then dilithiated, and reacted with $(PhSO_2)_2S$ to obtain the tetramethyl-DTT **267** (Scheme 66) [100].

3.1.2 Synthesis of Oligomers of Dithieno[3,2-*b*;2′,3′-*d*]thiophenes and Other Conjugated Derivatives

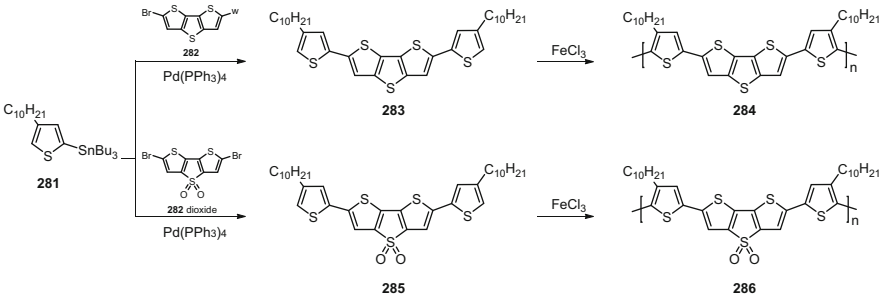
The DTT dimer (**270**) was made simply by *α*-metallation then oxidation with $Fe(acac)_3$ (Scheme 67) [101].

The *β*,*β*′-linked dimer (**275**) was synthesized as shown in Scheme 68 [33]. The key step was a halogen dance to force a bromine into a β-position (**271**→**272**) ready for transmetallation, stannation, and then cross-coupling.

Many other conjugated units have been linked to DTTs, often via cross-couplings – just two examples are shown in Schemes 69 and 70 [40, 102].



Scheme 70 Synthesis of star oligomer **280** [41]

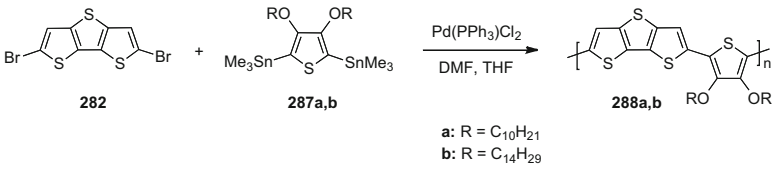


Scheme 71 Preparation of copolymers **284** and **286** [109, 110]

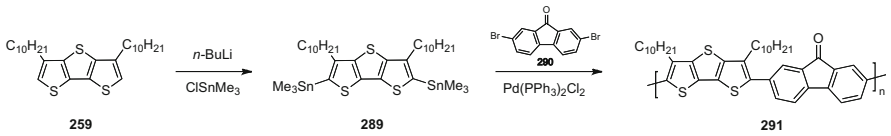
3.1.3 Synthesis of Polymers Containing Dithieno[3,2-*b*;2′,3′-*d*] thiophene Units

Electropolymerization of DTT **242** can be conducted on transparent conductive tin oxide covered glass [103]. Compound **253a** was polymerized using a potentiodynamic method [104]. DTTs **253b**, possessing a strong electron-donating MeO, and **253c** with a mild electron-withdrawing Br groups were electropolymerized. DTT **253e**, substituted with 2-thienyl, was electro-copolymerized with EDOT on a glassy carbon electrode (GCE) [105, 106]. The photochemical polymerization of **242** in the presence of an appropriate electron acceptor such as *p*-dinitrobenzene (DNB) involves photoinduced electron transfer from the singlet excited state of **242** to the DNB producing a radical cation of **242** and a radical anion of DNB [107, 108]. DTT and DTT-*S*,*S*-dioxides were copolymerized generating **284** and **286**: thien-2-yltributylstannane (**281**) was cross-coupled with dibromo-DTT (**282**) or dibromo-DTT-*S*,*S*-dioxide (**285**) to obtain the monomers **283** and **285**, respectively. Polymerization was performed using $FeCl_3$, which gave the soluble copolymers **284** and **286** (Scheme 71) [109, 110].

Highly soluble conjugated polymers poly(2,6-(dithieno[3,2-*b*:2′,3′-*d*] thiophenyl)-alt-2,5-(3,4-dialkoxy)thiophenyl) (**288a,b**) were produced by Stille cross-coupling of **282** with 2,5-bis(trimethyltin)-3,4-dialkoxythiophenes (**287a,b**) in moderate yields (Scheme 72) [111].



Scheme 72 Synthesis of copolymers **288a,b** possessing DTT and dialkoxythiophene units [111]



Scheme 73 Preparation of copolymer **291** composed of DTT and fluorenone units [112]

Soluble poly(3,5-didecanyldithieno[3,2-*b*:2′,3′-*d*]thiophene-alt-9-fluorenone (**291**) was prepared via Stille cross-coupling polymerization from bis(trimethylstannyl)-DTT (**289**) and dibromo-9-fluorenone (**290**) using in 57% yield (Scheme 73) [112].

Some other copolymers involving dithieno[3,2-*b*;2′,3′-*d*]thiophene are shown in Fig. 2 [113–117].

3.2 Dithieno[3,4-b;3′,4′-d]thiophene (243)

Dithieno[3,4-*b*;3′,4′-*d*]thiophene (**243**) was first prepared in 1971 starting from 3,4-dibromothiophene (**14**) [95]. Transmetallation then reaction with $(PhSO_2)_2S$ formed **300**, reaction of which with *n*-BuLi and then oxidative ring closure provided dithieno[3,4-*b*;3′,4′-*d*]thiophene (**243**). Alternatively, **243** can be accessed from **300** via the use of $Pd(PPh_3)_4$ and hexamethylditin (Scheme 74) [118, 119].

3.2.1 Synthesis of Oligomers of Dithieno[3,4-*b*;3′,4′-*d*]thiophenes and Other Conjugated Derivatives

Cyclic tetrathiophene **303** [120], which is planarized by the sulfur-bridge, thus possesses an antiaromatic cyclooctatetraene (COT) core. Double metallation of **301** then addition of $CuCl_2$ resulted in the dimerized product **302** in 45% yield. The TMS groups were removed with TBAF, producing the planar cyclic tetrathiophene **303** quantitatively (Scheme 75).

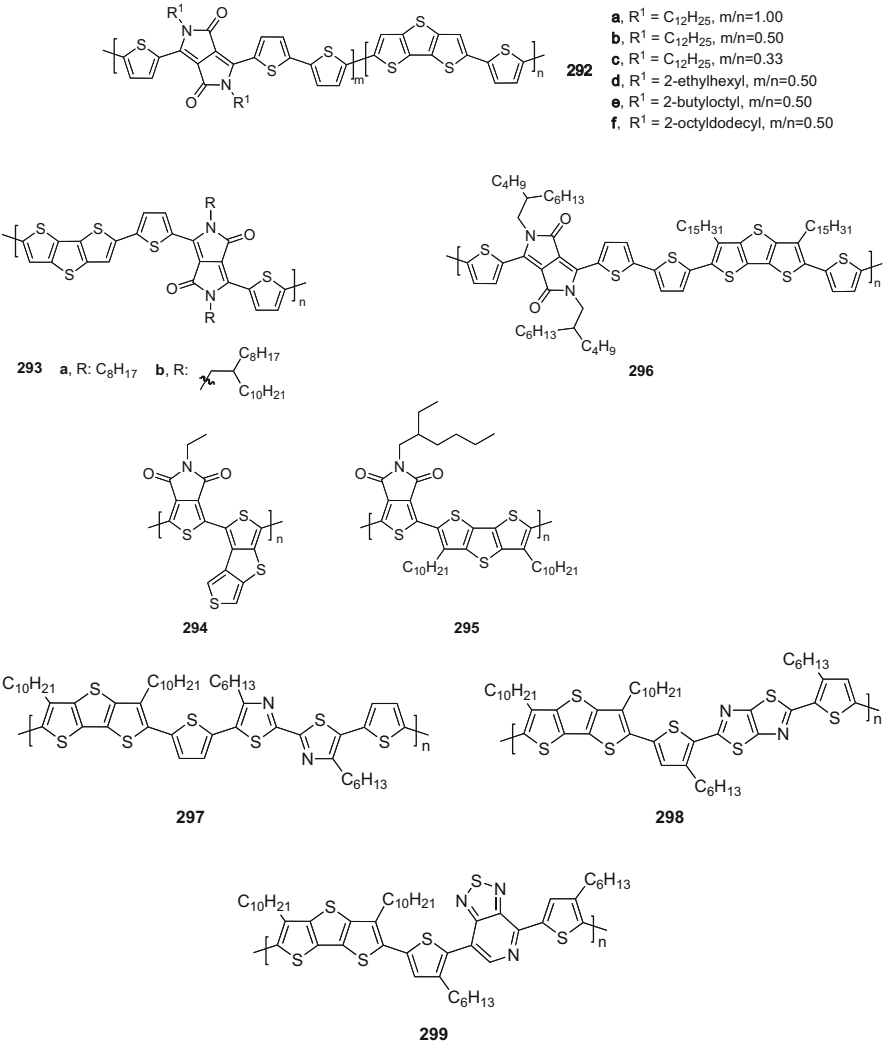
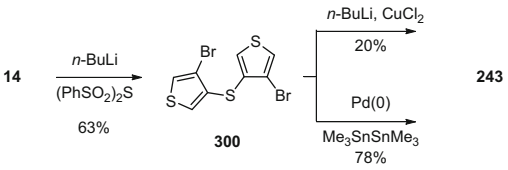
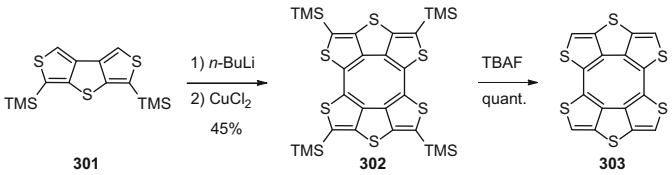


Fig. 2 Copolymers involving dithieno[3,2-*b*;2′,3′-*d*]thiophene units [113–117]



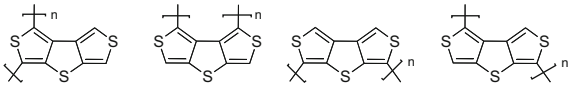
Scheme 74 Synthesis of **243** from 3,4-dibromothiophene (**14**) by two routes [95, 118, 119]



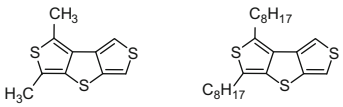
Scheme 75 Synthesis of cyclic tetrathiophene **303** [120]

3.2.2 Synthesis of Polymers Containing Dithieno[3,4-*b*;3′,4′-*d*] thiophene Units

The photochemical polymerization of **243** in the presence of an appropriate electron acceptor such as *p*-dinitrobenzene (DNB) and CCl_4 involves photoinduced electron transfer from the singlet excited state of **243** to the electron acceptor causing the formation of radical cation of **243** and radical anion of DNB. Electropolymerization of **243** gave a polymer with strong electrochromic properties. Structure **304** is considered to be the most probable of the four possible structures (**304–307**) [121–124].



Electropolymerization or $FeCl_3$-promoted chemical polymerization was applied to **308** and the 2,5-dioctyl-DTT **309** [125].

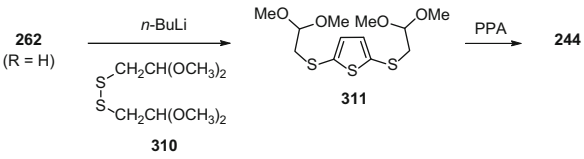


3.3 Dithieno[2,3-b;3′,2′-d]thiophene (244)

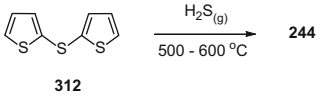
The DTT dithieno[2,3-*b*;3′,2′-*d*]thiophene (**244**) was prepared as early as 1958, starting from thiophene itself. 2,5-Dilithiation then reaction with disulfide (**310**) gave (**311**), which underwent a double ring closure promoted by PPA to furnish **244** (Scheme 76) [126].

Pyrolysis of 2,2′-dithienyl sulfide (**312**) at 500–600 °C under nitrogen and in the presence of hydrogen sulfide gives **244** [13] (Scheme 77).

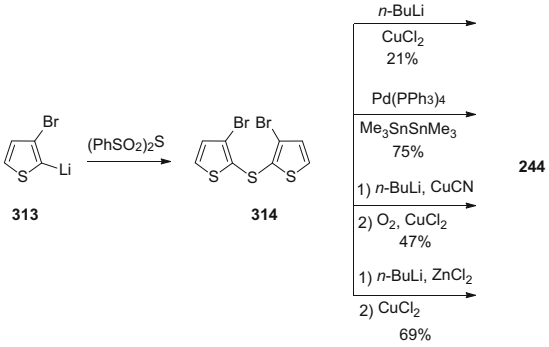
Reaction of 3-bromo-2-lithiothiophene (**313**) with $(PhSO_2)_2S$ provided **314**. The remaining bond can be formed in various ways, as shown in Scheme 78 [95, 118, 119].



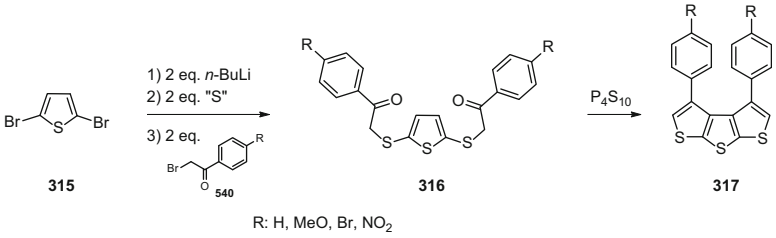
Scheme 76 Synthesis of **244** starting from thiophene (**262**, R=H) [126]



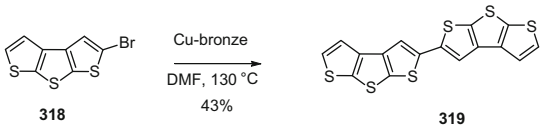
Scheme 77 Synthesis of **244** from 2,2′-dithienyl sulfide **312** [13]



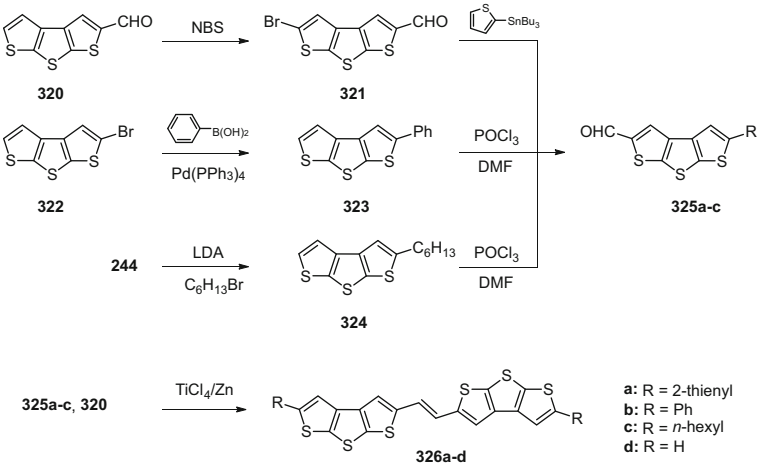
Scheme 78 Synthesis of **244** from **313** applying different methodologies [95, 118, 119]



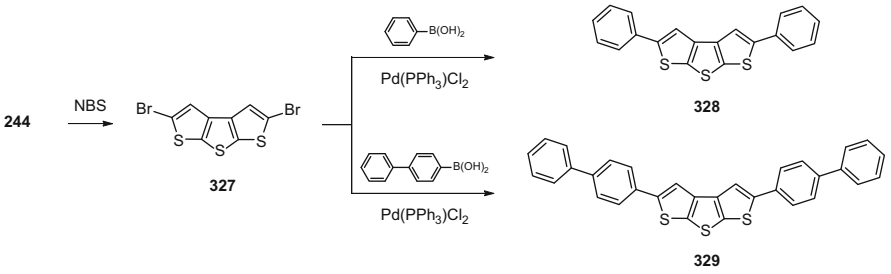
Scheme 79 Reaction of diketone (**316**) with P_4S_{10} furnishing DTTs (**317**) [127]



Scheme 80 Synthesis of DTT 2,2′-dimer **319** [128]



Scheme 81 Preparation of **326a–d** [128, 129]

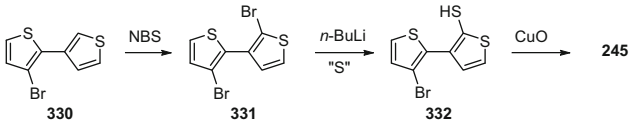


Scheme 82 Preparation of DTTs **328** and **329** with extended conjugation [130]

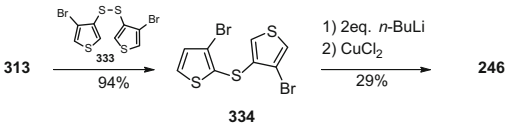
The DTTs (**317**), possessing *para* substituted phenyl groups at the 3- and 4-positions, were made available through ring closure of diketones (**316**) using P_4S_{10} [89] (Scheme 79) [127].

3.3.1 Synthesis of Oligomers of Dithieno[2,3-*b*;3′,2′-*d*]thiophenes and Other Conjugated Derivatives

A dimer of **244** can be produced by copper-promoted reaction of 2-bromo-DTT **318** (Scheme 80) [128].



Scheme 83 Synthesis of **245** [131]



Scheme 84 Synthesis of **246** [95]

Various other DTTs with extended conjugation have been reported, for example Scheme 81 shows how aldehydes **325** [129], themselves prepared by alternative routes, were used to prepared ethene-linked **326**. Schemes 81 and 82 illustrate the use of cross-couplings to add aryl units [130].

3.4 Dithieno[2,3-b;2′,3′-d]thiophene (245)

A three-step synthesis of the DTT dithieno[2,3-*b*;2′,3′-*d*]thiophene (**245**), started from 3-bromo-2-(thien-3-yl)thiophene (**330**) utilized bromination to **331**, then treatment with *n*-BuLi and finally elemental sulfur producing **332**; heating this thiol with CuO gave **245** (Scheme 83) [131].

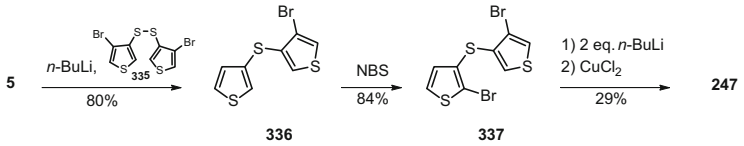
3.5 Dithieno[3,4-b;3′,2′-d]thiophene (246)

The synthesis of DTT dithieno[3,4-*b*;3′,2′-*d*]thiophene (**246**) starts with the reaction of 3-bromo-2-lithiothiophene (**313**) with disulfide **333** to give **334**. Dilithiation with *n*-BuLi and then oxidative ring closure using $CuCl_2$ lead to **246** [95] (Scheme 84).

DTT (**246**) has been electropolymerized [103, 132].

3.6 Dithieno[3,4-b;2′,3′-d]thiophene (247)

3-Lithiothiophene reacted with disulfide **335** gave **336**. Next, regioselective bromination produced dibromide **337**, reaction of which with two equivalents of



Scheme 85 Synthesis of **247** [131]

n-BuLi and then $CuCl_2$ treatment gave dithieno[3,4-*b*;2′,3′-*d*]thiophene **247** (Scheme 85) [131].

DTT (**247**) has been electropolymerized on ITO [103, 131, 133].

4 Thienoacenes

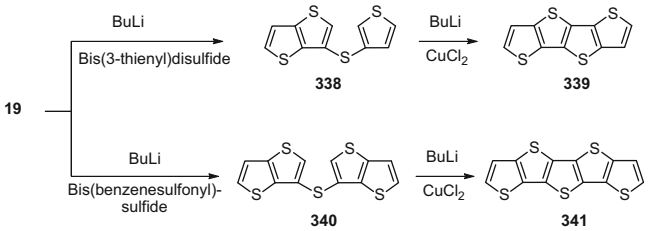
The formal insertion of a sulfur atom, to connect the β-positions of α,α′-linked thiophenes, or oligothiophenes, results in linear thienoacenes, which are planar, and rigid π-conjugated molecules with strong intermolecular S···S interactions, leading to an efficient molecular orbital overlap. Therefore, they are potential candidates for applications in optoelectronic devices [134].

For the syntheses of thienoacenes from TTs, two strategies have been applied, namely, connecting 3- and 3′-positions of thiophene moieties with a sulfur atom, and then joining the 2- and 2′-positions or, vice versa. The syntheses of tetrathienoacene (**339**) and pentathienoacene (**341**) (Scheme 86) illustrate the first of these [23, 135], thus, transmetallation of 3-bromothieno[3,2-*b*]thiophene (**19**), followed by reaction with bis(3-thienyl)disulfide gave **338**, which was then treated with *n*-BuLi and $CuCl_2$ successively to lead to tetrathienoacene (**339**). Similarly, using ((bis(benzenesulfonyl)sulfide) as a sulfur source, pentathienoacene (**341**) was obtained.

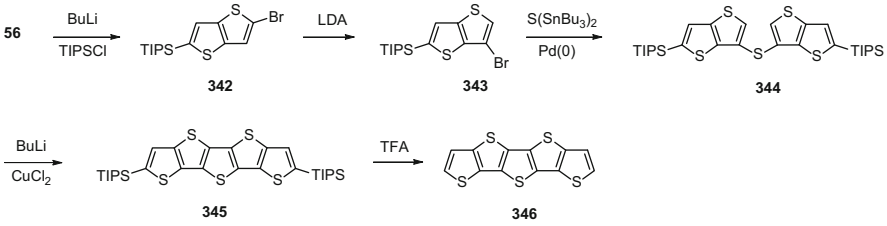
An alternative route to pentathienoacene (**346**) is shown in Scheme 87: bromide **343** is generated via a halogen dance, sulfur inserted with palladium(0) catalysis, and the final bond made in the usual way [134].

The heptathienoacene (**350**) was obtained in just five steps in an overall yield of 27% (Scheme 88). Note the use of a TIPS group not only to block the terminal α-positions but also to increase solubility before the halogen dance to generate **347** [134].

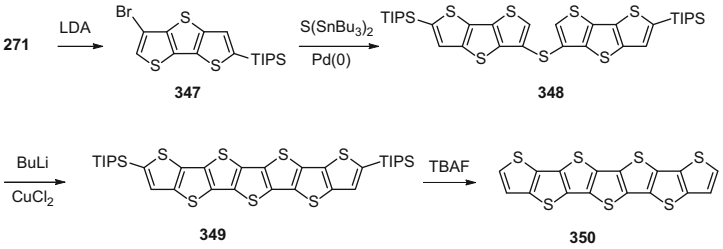
The tetradecanyl-substituted heptathienoacene (**358**) was produced in seven steps, starting from 3-bromo-6-decylthieno[3,2-*b*]thiophene (**352**). The key step, conversion of **355** into **356**, involved a halogen dance using LDA [135–137]. A comparable sequence was applied for the synthesis of nonathienoacene (**360**) in nine steps, starting from 3-bromo-5-decanyldithieno[3,2-*b*:2′,3′-*d*]thiophene (**359**) [138] (Scheme 89).



Scheme 86 Synthesis of tetrathienoacene (**339**) and pentathienoacene (**341**) starting from 3-bromo-TT (**19**) [23, 135]



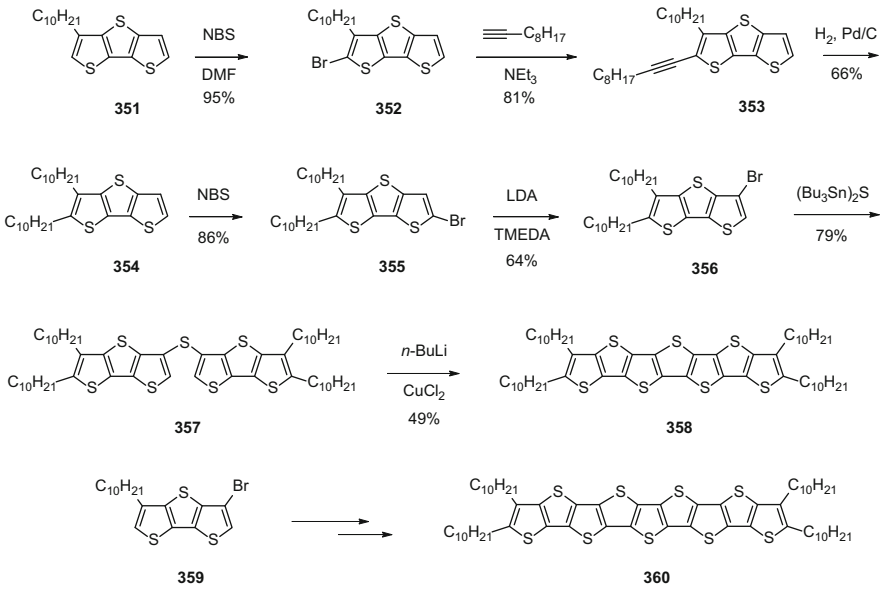
Scheme 87 Synthesis of pentathienoacene **346** using a halogen dance strategy [134]



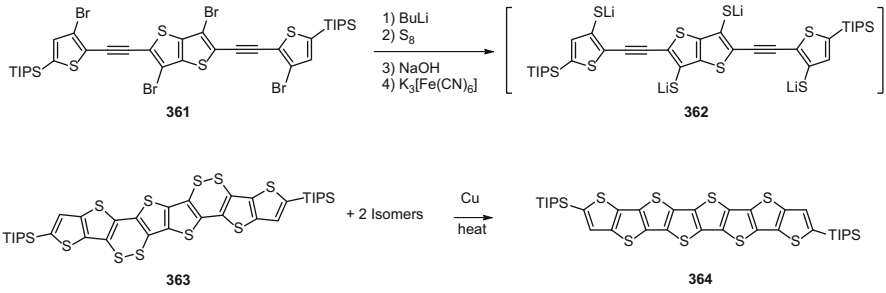
Scheme 88 Synthesis of heptathienoacene **350** [134]

Thienoacenes can also be prepared utilizing alkynes, and an intramolecular double sulfur–sulfur bonding of a dithienylacetylenedithiolate oxidative work-up with $K_3[Fe(CN)_6]$ forming a 1,2-dithiin. Thermolysis caused extrusion of sulfur and the formation of **364** [139] (Scheme 90).

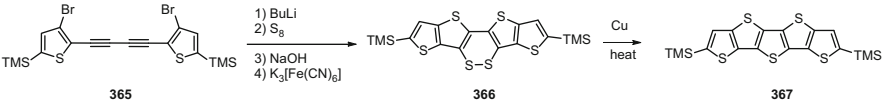
Diacetylene **365**, possessing *o*-bromothienyl subunits at both ends, underwent an intramolecular triple cyclization, resulting in pentathienoacene **367** in 22% yield (Scheme 91) [140, 141].



Scheme 89 Synthesis of **358** and **360** [135–138]



Scheme 90 Synthesis of **364** [139]



Scheme 91 Cyclization of a 1,3-diyne **365** to a pentathienoacene [140, 141]

5 Conclusions

Fused thiophenes are rigid, thermally stable, and easily processable compounds. They are promising candidates for applications in molecular electronics. In this chapter, based on the number of thiophene units, the principal synthetic routes to fused thiophenes are addressed in three sections, namely thienothiophenes, dithienothiophenes, and thienoacenes, which have two, three, and more-than-three annulated thiophenes, respectively. Important examples of the construction of oligomers, further conjugated analogs, and polymers of these systems are given.

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Thiophene in Conducting Polymers: Synthesis of Poly(thiophene)s and Other Conjugated Polymers Containing Thiophenes, for Application in Polymer Solar Cells

Francesco Livi, Jon E. Carlé, and Eva Bundgaard

Abstract Conducting polymers based on thiophene are described. The polymers include poly(thiophene) with and without side-chains and other conjugated polymers in general, based on thiophene. The synthesis and characteristics of the polymers are described along with the application of these as light-absorbing materials in polymer solar cells.

Keywords Applications of conjugated polymers · Low bandgap polymers · Polythiophene · Thiophene as electron donor

Contents

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1 Introduction

Research on conducting polymers gained great momentum in the late 1970s as a result of the pioneering work by Shirakawa, MacDiarmid, and Heeger, published in 1977 [1]. They showed that polyacetylene, which is the simplest conjugated polymer and therefore can be considered a prototype thereof, can become highly conductive through a chemical redox reaction using bromine or iodine. This finding prepared the ground for the development of organic electronics such as organic light-emitting diodes (OLEDs) [2], field-effect transistors (FETs) [3], photodiodes [4], and polymer solar cells (PSCs) [5]. Much of the research and development within these technologies is focused on the development of conducting materials with properties that match the requirements of the technology. Conjugated polymers are a group of materials that fulfill many of the requirements and, taken with possibilities for further modification of their properties, have become very popular. For a polymer to become a conducting material, it needs to have a system of delocalized electrons, as found in a polymer with conjugated double bonds [6]. In a conjugated polymer, p_z orbitals are oriented perpendicularly to the polymer backbone allowing electronic interaction between the double bonds. This interaction results in a delocalization which contributes to the conducting mechanism [7].

Conjugated polymers allow one to envision the possibility of high-volume solution processing of thin films on flexible substrates, by printing and coating techniques, which could enable fast and low-cost production of organic electronics [8]. This, from a manufacturing point of view, is a very attractive feature, and this is another reason that PSCs have been designated as a future low-cost alternative to the traditional inorganic solar cell [9]. State-of-the art PSCs rely on a bulk heterojunction active layer, comprising a light harvesting conjugated polymer (the donor) and a buckminsterfullerene derivative (the acceptor), sandwiched in between two electrodes, as illustrated in Fig. 1.

When light shines on a PSC device, it can produce electricity and the process, from light to current, is generally divided into four main steps: (1) The conjugated polymer in the active layer of the PSC absorbs light, which can result in the formation of electron–hole pairs, also known as excitons. When this happens, the electron is excited from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO). The difference between the HOMO and the LUMO of the polymer is known as the bandgap of the polymer. (2) The electron–hole pairs are bound to each other by the Coulomb attraction forces and their diffusion through the active layer is coupled. The exciton diffusion length in these materials is limited to 10–20 nm, which means that this is also the optimal physical dimension of the domains in the bulk heterojunction. (3) Dissociation of excitons takes place at the interface of the donor and the acceptor material, leaving the positively charged hole on the donor whereas the negatively charged electron is located on the acceptor material. (4) The charges are transported to the electrodes through the active layer. The donor polymer serves to transport the holes, while the electrons are transported in the acceptor material. This charge transport is

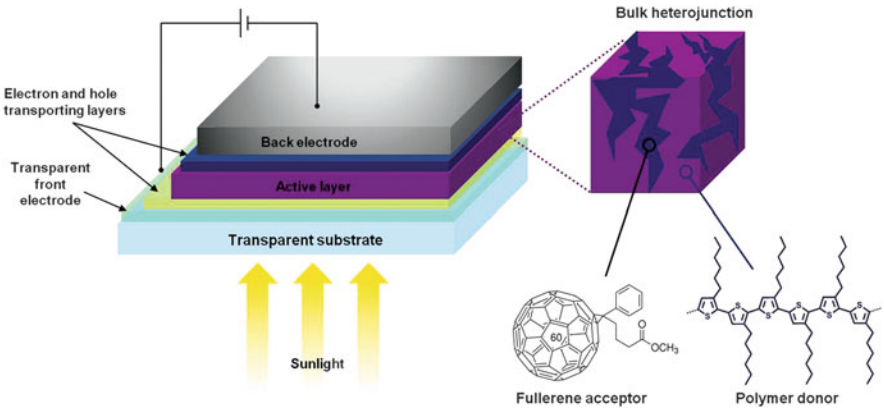


Fig. 1 A schematic representation of PSC devices with a bulk heterojunction active layer based on a conjugated polymer (e.g., poly(3-hexylthiophene), P3HT) and a buckminsterfullerene (e.g., phenyl-C61-butyric acid methyl ester, PCBM). The active layer is, in the simplest form, sandwiched between two electrodes

driven by an internal electric field caused by the different work functions of the electrodes [10, 11].

To ensure an efficient separation of the electrons and holes, transporting layers are often applied between the active layer and the different electrodes. As a hole-transporting layer (HTL), the highly conductive thiophene-based polymer poly (3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS) [12] has been the most utilized and as electron transporting layer (ELT), ZnO is often used [13].

In order to achieve large-scale production of PSCs with high efficiency and long lifetime, the conjugated polymer needs to have several important properties such as having an easy synthetic route, being large-scale solution-processable, and having broad absorption, high mobility, good miscibility with the acceptor material, and, of course, high stability.

Thiophene (see Fig. 2), a five-membered aromatic ring containing sulfur, is comparable in structure to pyrrole and furan, which contain nitrogen and oxygen, respectively, but it possesses some unique qualities. Sulfur is an electron-donating heteroatom and it contributes two electrons to the 6π electron-system of the ring and additionally has a lone pair of electrons in an sp^2-hybridized orbital, in the plane of the ring. Thiophene is thus an electron-rich aromatic heterocycle.

The application of polythiophene (PT) itself is limited due to its insolubility; however, by attaching alkyl or other side-chains to the polymer backbone, the solubility is increased and a wider application is possible. The alkyl group can be a straight or branched chain, though the most widely used is the *n*-hexyl group for the good performance of P3HT in PSCs. In general, all poly(thiophene)s with an alkyl chain with four or more carbon atoms are soluble in common organic solvents [14].

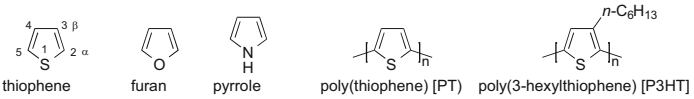


Fig. 2 Illustration showing thiophene, furan, pyrrole, poly(thiophene) (PT), and poly (3-hexylthiophene) (P3HT). Note: thiophene ring 2- and 5-positions are often referred to as α-positions and the 3- and 4-positions as β-positions

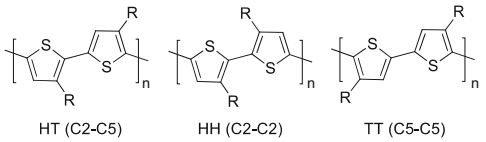


Fig. 3 Different coupling configurations of a poly(3-substituted-thiophene): HT, HH, and TT

When a thiophene carrying a 3-substituent, such as 3-*n*-hexylthiophene, is polymerized, links between the thiophene units can occur in three different configurations, i.e., head-to-tail (HT), tail-to-tail (TT), or head-to-head (HH), as shown in Fig. 3. When the coupling is HT-HT the polymer is said to be regioregular.

Within PSCs, an enormous amount of research has been dedicated to the P3HT:$PC_{61}BM$ system, and efficiencies of 4–5%, close to the optimal device performance for this system, have been achieved [15–18]. Highly regioregular P3HT has become the material of choice and is by far the most studied polymer in PSC as it is relatively easy to synthesize and process, relatively stable, and cheap/affordable [19].

The optical bandgap of a poly(alkylthiophene) (PAT) depends on the percentage of HT linkages; for regioregular P3HT, it is 1.9 eV. This is due to the lamella structure that is formed in a film of P3HT [20]. However, this relative large bandgap limits the light absorption to wavelengths below 650 nm. The development of polymers having a better overlap with the solar spectrum, and thus the potential to be more efficient at harvesting photons, has resulted in significant improvements in PSC performance [21, 22]. Such polymers are known as low bandgap (LBG) polymers, which are loosely defined as polymers with a bandgap below 2 eV, thus absorbing light with wavelengths longer than 620 nm [23]. In general, these polymers are based on two different monomers, one having an electron-rich (a donor) and one having an electron-deficient (an acceptor) motif, as seen in the examples shown in Fig. 4. This donor–acceptor approach creates a partial charge separation at the backbone of the polymer which results in a lowering of its bandgap [24]. The majority of LBG polymers are based on thiophene, a substituted thiophene, and/or a fused-thiophene system. The introduction of thiophene as a building block in the active material has had a major influence on the progress of PSCs, and it will continue to play an important role in further developments within this field.

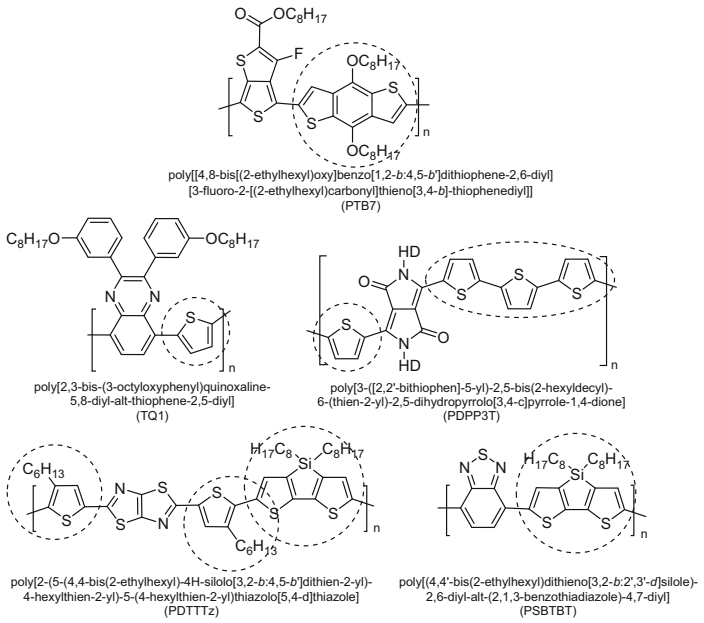


Fig. 4 Examples of low bandgap polymers based on thiophene. C_8H_{17} = 2-ethylhexyl, HD = 2-hexyldecyl. The donor motif is marked with a ring in the LBG polymers

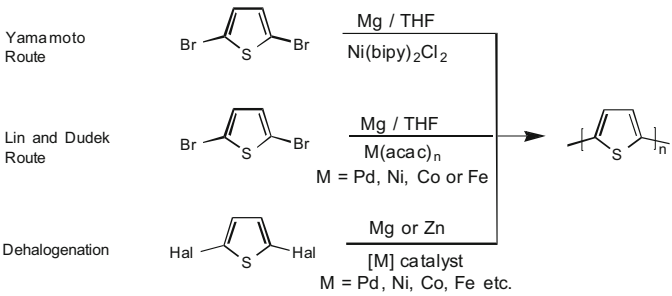
2 Synthesis

In this section is presented a short overview of the synthesis of thiophene-based conjugated polymers. Even though PT has not yet been shown to be useable in large-scale PSCs, due to insolubility, its potentially high stability, high conductivity, and cheap starting material suggest that this polymer may have a role in future PSCs, and thus, its synthesis is described briefly together with PATs and low bandgap and conjugated polymers in general.

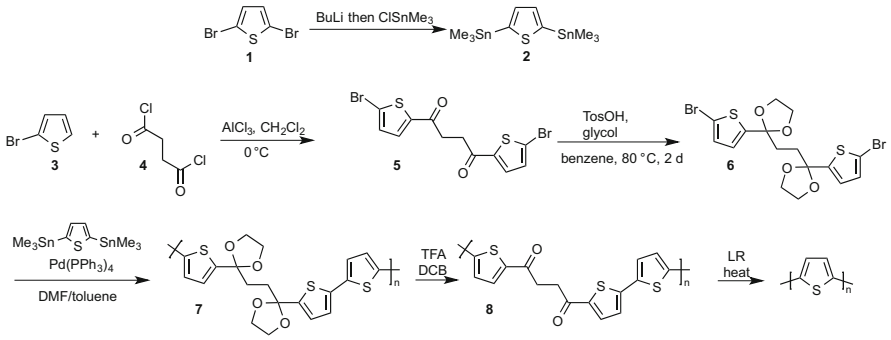
2.1 Synthesis of PT

The synthesis of PTs can be achieved via electrochemical or chemical methods. Three of the chemical methods are illustrated in Scheme 1. These are the Yamamoto route [25], the Lin and Dudek route [26], and other similar routes based on dehalogenation [27–30].

These routes are all organometallic polycondensations where two monomers are condensed, in the presence of a metal, such as Mg or Zn, and a transition metal catalyst, after elimination of a salt. The stoichiometry of the salt depends on what metal is used and what halogen is employed as leaving group on the thiophene



Scheme 1 Organometallic polycondensation of 2,5-dihalo-thiophenes



Scheme 2 Synthesis of high molecular weight PT from a soluble prepolymer obtained via Stille couplings [32]

($MgHal_2$, $ZnHal_2$, etc.). By changing the type of halogen, the catalyst employed, the metal, or the reaction conditions in general, different yields and molecular weights of the PT can be achieved; however, all these routes result in low molecular weight polymers (around 3,000–4,000 g mol^{-1}) due to the low solubility of PT, and thus efforts have been made to increase the molecular weight [31]. For example, the strategy shown in Scheme 2 was used to obtain high molecular weight PT [32]. The first monomer, 2,5-bis(trimethylstannyl)thiophene (**2**), was synthesized from 2,5-dibromothiophene (**1**) via metal–halogen exchange followed by reaction with trimethyltin chloride. For the synthesis of the second monomer **6**, 2-bromothiophene (**3**) was first subjected to a Friedel–Crafts acylation with succinyl chloride (**4**) to give the 1,4-dione **5**, which was then protected as a bis-acetal, **6**. The monomers were then combined in a Stille cross-coupling polymerization to give **7**, which was further treated with acid to reveal the 1,4-dicarbonyl system in PT precursor **8**. This was thiated through reaction with Lawesson's reagent to form a thiophene ring from the 1,4-dicarbonyl system and thus obtain PT with a high molecular weight (M_n of about 36,000 g mol^{-1}) [32].

Another method gives PT, from thiophene, as nanoparticles, by a chemical oxidative reaction in aqueous medium in the presence of surfactants and oxidants

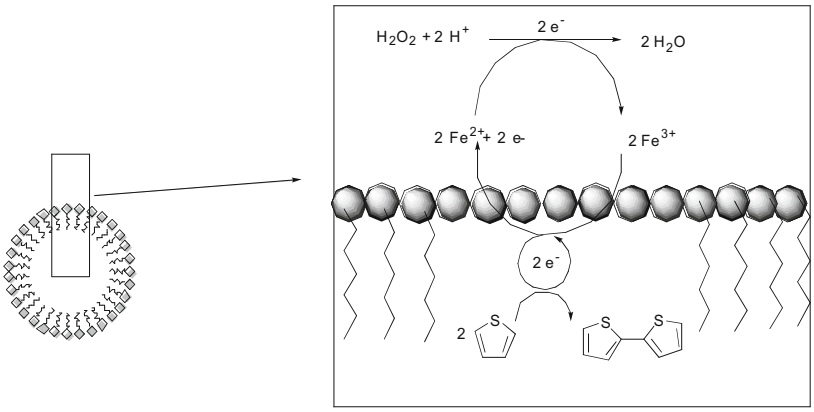
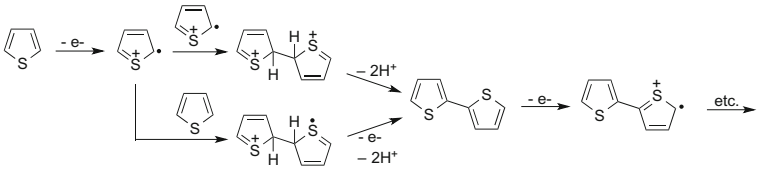


Fig. 5 Catalyzed oxidative polymerization of thiophene in micelles [34]



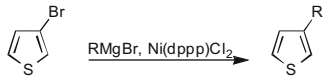
Scheme 3 The mechanism of electrochemical synthesis of PT [39]

like ammonium persulfate [33], Fe(III) [34, 35], or Cu(II) salts [36]. In these cases polymerization occurs within the micelles and starts after the metal cations diffuse into the micelles with subsequent thiophene oxidation [36] as shown in Fig. 5. After the thiophene oxidation, the reduced metal, i.e., Fe^{2+} or Cu^{+}, is usually reoxidized using hydrogen peroxide [34, 36].

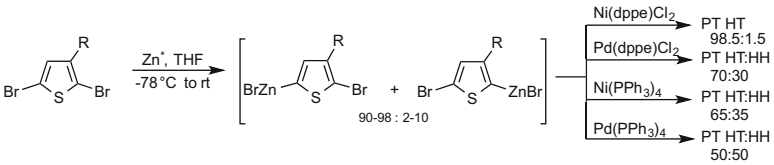
PT film has also been prepared by treating thiophene with $FeCl_3$ solution in anhydrous $CHCl_3$, a method known as ferric chloride oxidative polymerization [37].

PT conducting films can be generated through electrochemical polymerization of thiophene, where the monomer is oxidized at anodic potentials. Thiophene shows an oxidation potential peak of $E_{ox} = 1.6$ V ca. vs SCE ($CH_3CN + 10^{-1}M$ $N(Bu)_4ClO_4 + 10^{-2}$ M thiophene; sweep rate: 20 mV/s; H_2O: 10^{-2} mol l^{-1}) [38]; this means that poly(thiophene) can be oxidized to anodic potentials and deposited on an electrode.

The mechanism is quite complex; however, a largely accepted mechanism is shown in Scheme 3. Thiophene dimer formation is promoted by an electrochemical oxidation and coupling, followed by the loss of two protons. The neutral dimer is then oxidized and coupled with another unit producing a trimer; the mechanism is repeated and a polymer with n thiophene rings is formed [39]. Several studies have



Scheme 4 Synthesis of 3-alkylthiophenes by a Kumada cross-coupling [52]



Scheme 5 Rieke route to PATs [47]

been carried out in order to understand the mechanism, and the radical cation polymerization shown in Scheme 3 is the most accepted [40, 41].

Organic conducting polymers, including PT, have been formed on Pt, using thiophene or other heterocyclic compounds, acetonitrile and Bu_4NClO_4 [38].

PT has also been synthesized through anodic oxidation of thiophene or bithiophene in molten salts such as $AlCl_3$ and 1-methyl-3-ethylimidazolium chloride, and films have been deposited on Pt, W, and glassy carbon electrodes [42].

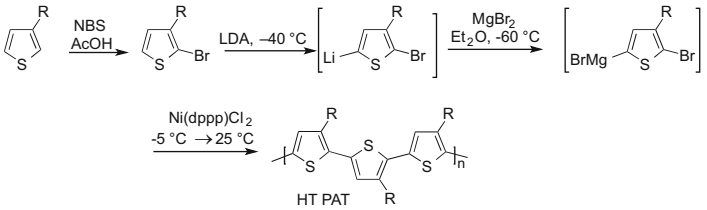
PT has been electrochemically synthesized by several groups, where the main conditions studied were the electrolytic medium, the monomer concentration, and the employed electrodes [40, 42–45].

2.2 Synthesis of PATs

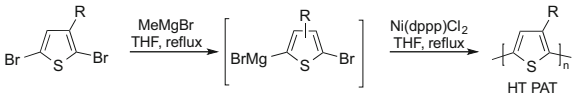
In the polymerization of alkylthiophenes, the reactivity and thus the routes that lead to PATs are almost the same as for PT, but the challenge here is not as much the solubility but the regioregularity. Great efforts have been put into preparing fully regioregular PATs (HT-HT) for their better performance in PSCs [46–51].

The synthesis of a 3-alkylthiophene monomer can be achieved in several different ways. One rather simple way involves Kumada cross-coupling of 3-bromothiophene (**9**) with an alkyl Grignard reagent, as seen in Scheme 4 [52].

A 3-alkylthiophene can be polymerized using various strategies. The Rieke strategy (see Scheme 5) produces 98.5% regioregular P3HT [48]. Various catalysts were used with 2,5-dibromo-3-alkylthiophenes [47]. Thus, reaction with Rieke zinc (Zn*) forms a mixture (90:10 or higher, up to 98:2) of (5-bromo-4-alkylthien-2-yl) zinc(II) bromide and its isomer (5-bromo-3-alkylthien-2-yl)zinc(II) bromide. The ratio depends on reaction temperature and/or the bulkiness of the alkyl group [47]. These isomeric intermediates polymerize to give PATs with a regioregularity that depends mainly on the catalyst employed; thus, totally regiorandom PATs are



Scheme 6 McCullough route for the synthesis of 100 % HT PATs. R = alkyl chain [46]



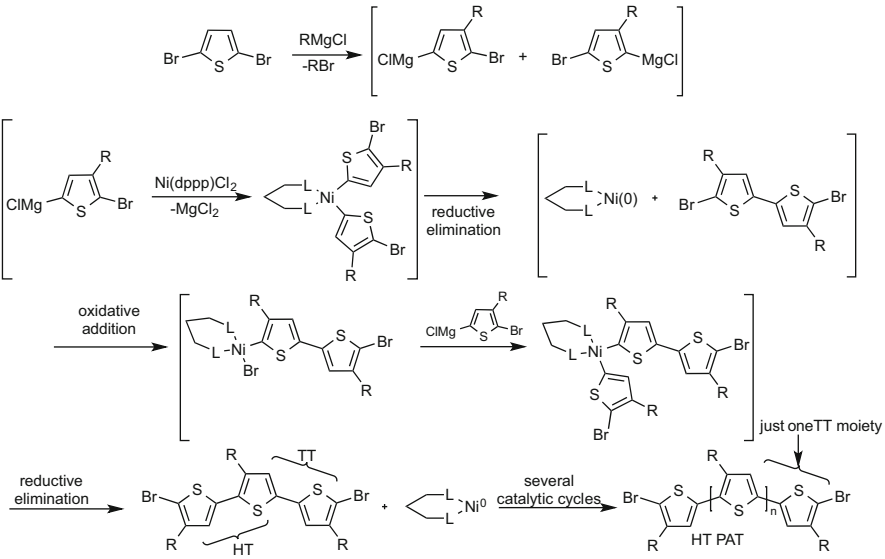
Scheme 7 GRIM method for HT PAT [50]

observed with $Pd(PPh_3)_4$, while the highest values of regioregularity, up to 98.5%, are achieved using $Ni(dppe)Cl_2$.

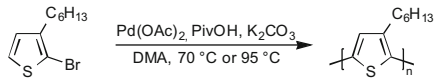
A variant on cross-couplings, the McCullough route, uses 1,3-bis(diphenylphosphino)propanenickel(II) chloride ($Ni(dppp)Cl_2$) giving a PAT (alkyl = $C_{12}H_{25}$) with 91% HT-HT [51], P3HT with a regioregularity of 98% [49] and various others with 100% regioregularity [46]. The starting material for all the PATs was a 2-bromo-3-alkylthiophene which was metallated at C5 using lithium diisopropylamide (LDA) to give a lithium derivative which was then converted into the corresponding magnesium compound by treatment with $MgBr_2$. $Ni(dppp)Cl_2$ catalyzed the cross-coupling polymerization of the 2-bromo-3-alkylthien-5-ylmagnesium bromide, to give regioregular PAT (Scheme 6) [46].

A Grignard metathesis (GRIM) method gave an HT PAT [poly(3-dodecylthiophene)], with regioregularity ≥99.9%. Here, a 2,5-dibromo-3-alkylthiophene is treated with CH_3MgBr in the presence of $Ni(dppp)Cl_2$ as catalyst, as shown in Scheme 7.

It is suggested that GRIM polymerization proceeds by a chain growth mechanism (where the monomer is added to the active chain end only and each step depends on the previous one to generate the active site) as shown in Scheme 8 and not by a step growth process (where the monomer can be added to any two molecular species – polymerization in each species can occur and a polymer with high M_n is formed only after a relatively long time) [53]. 2-Bromo-5-chloromagnesium-3-alkylthiophene is generated, together with its isomer, which, however, is not involved in the polymerization, due to steric hindrance at the 2-position, in a ratio of up to 85:15. 2-Bromo-5-chloromagnesium-3-alkylthiophene then reacts with $Ni(dppp)Cl_2$ forming a bis(organo)-nickel compound by oxidative addition. After reductive elimination, this leads to the formation of 5,5′-dibromo-2,2′-bithienyl (TT coupling) and Ni(0) [53]. The dimer now reacts



Scheme 8 Suggested mechanism for nickel(0)-catalyzed polymerization (GRIM) (R = alkyl chain) [53]



Scheme 9 Example of direct arylation polymerization (DARP) [54]

with the Ni(0) center through an oxidative addition generating a new organo-nickel intermediate and the cross-coupling is repeated. Just one TT defect is generated as a result of this mechanism [53].

A more eco-friendly strategy avoids prior thiophene functionalization, since just one position has to be functionalized with a leaving group such as bromine and mild conditions are employed. This strategy takes inspiration from the direct heteroarylation that allows the formation of a new C–C bond by cross-coupling between an organohalide (hetero)arene (or functionalized with other leaving groups) and the C–H bond of a second (hetero)aryl system, as seen in Scheme 9 [54–56].

This strategy, known as direct arylation polymerization (DARP), can be used for the synthesis of several organic systems and with a large variety of catalysts and co-catalysts [57–59]. Various mechanisms have been proposed, depending on the catalytic system employed; however, the metallation at the non-halogenated position of the monomer is believed to be concerted and base assisted [60].

The typical conditions used, in addition to the organohalide monomer and the unsubstituted monomer, (in the example in Scheme 9, the organohalide and the

unsubstituted reaction center are on the same molecule) are (1) Pd pre-catalyst such as palladium(II) acetate; (2) pivalic acid, which coordinates to the palladium forming the catalytically active species, after being deprotonated by a base such as potassium carbonate; and (3) *N*,*N*-dimethylacetamide as solvent [54, 56, 61]. This methodology has already been tested for many conjugated copolymers [54, 56, 61].

P3HT made using DARP and using Stille cross-coupling (below) can be compared. Yields from the DARP procedure are lower than those obtained through Stille cross-coupling, but molecular weights of the P3HTs obtained through the two coupling methods are comparable. P3HT synthesized through Stille cross-coupling exhibited an M_n of 15.2 kDa and 93% of regioregularity; P3HT synthesized by DARP had an M_n of 15.5 kDa and 88% of regioregularity [54]. An optimized DARP, following exploration of variables such as (1) reaction time, (2) temperature, (3) catalyst loading, and (4) use of a bulkier carboxylic acid (neodecanoic acid instead of pivalic acid), gave improved molecular weight, yield, and crystallization point, while the regioregularity was the same of that obtained through Stille cross-coupling (93.5%). Also, P3HT prepared in this way has almost the same physical properties as that prepared by Stille cross-coupling, i.e., it has limited structural defects [62].

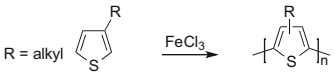
P3HT has also been synthesized following a dehydrohalogenative polycondensation from 2-bromo-3-hexylthiophene, using Herrmann's catalyst [*trans*-bis(acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II)], one phosphinic ligand, cesium carbonate, and THF as solvent. The yield was almost quantitative (99%) and the regioregularity was high (98%) as was the molecular weight (M_n = 30.6 kDa) [63].

A Heck-type polymerization method led to 3-alkylthiophene oligomers with up to 90% HT coupling in good yields. Heck-type polymerization of 2-bromo-3-octylthiophene using $Pd(OAc)_2$, *n*-Bu_4NBr, and K_2CO_3 as the catalytic system led to less pure materials with lower M_n; however, this methodology could be economically viable, used at a bulk level [64].

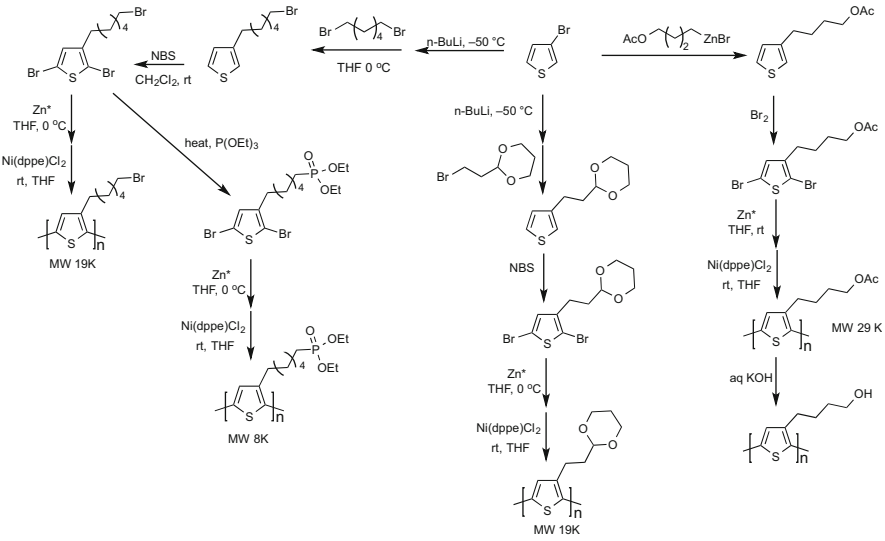
Polymerization employing chemical oxidants, in particular transition metal halides [65], such as $FeCl_3$, is one of the most common routes to synthesize PATs and is well described in the literature [31, 66], as is electrochemical deposition [31].

In Scheme 10 the synthesis of PAT through chemical oxidation is shown: high molecular weight PATs (M_n up to 55 kDa) with a regioregularity degree up to 80% (HT couplings) have been obtained by reaction with $FeCl_3$ in dry chloroform [67] following a similar procedure already tested [65]. The chemically synthesized PATs were more regular and crystalline than those electrochemically synthesized [67]. Regioregularity degrees up to 94% have been observed in the synthesis of phenyl-substituted PTs with $FeCl_3$. Regarding the mechanism, studies on different reaction conditions have been carried out, and multiple possibilities have been discussed, including radical polymerization [68], radical cation polymerization (the most probable) [69, 70], and polymerization via a carbocation mechanism [71].

Oxidative polymerization of 3-alkylthiophenes and electrochemical synthesis of PATs are widely used, but they lead to polymers containing a variable amount of irregularities; electrochemically synthesized PATs show more 2,4-linkages than the



Scheme 10 Chemical oxidation of a 3-alkylthiophene [31]



Scheme 11 Synthesis of functionalized PTs [76]

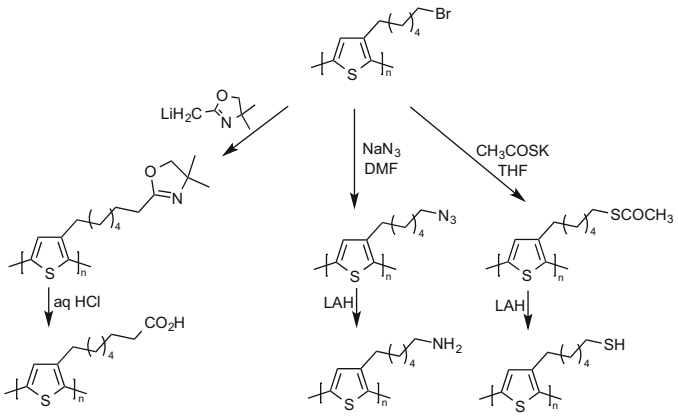
polymer from chemical polymerization where essentially only 2,5-couplings were observed [72].

Stille cross-couplings can also be employed in order to obtain PATs [73, 74] as well as Suzuki cross-couplings [75]. These two types of polymerization are described in detail below.

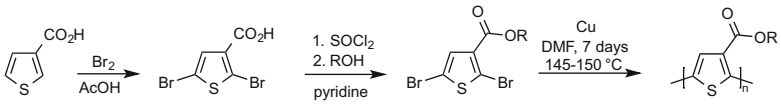
Other types of functionalized poly(3-alkylthiophene)s can be prepared in order to obtain polymeric materials with different chemical, optical, and electronic properties and different solubilities. The organozinc route has been used to synthesize polythiophenes bearing a phosphonic ester functionality or functional groups such as bromine, ester, alcohol, and acetal-protected aldehyde as terminal groups of C-3-substituents, as illustrated in Scheme 11 [76].

Regioregular HT poly(3-(6-bromohexyl)thiophene) was obtained via the GRIM method and post-polymerization functionalizations carried out thus obtaining PATs with carboxylic acid, amine, or thiol, as terminal groups on the side-chains as shown in Scheme 12 [77].

Poly(alkyl thiophene-3-carboxylates) with the carbonyl group directly attached to the thiophene ring were synthesized via an Ullmann reaction with copper powder (Scheme 13) [78]. This was further optimized yielding regioregular materials (HH-TT) [79].



Scheme 12 Synthesis of PATs with functionalized side chains [77]



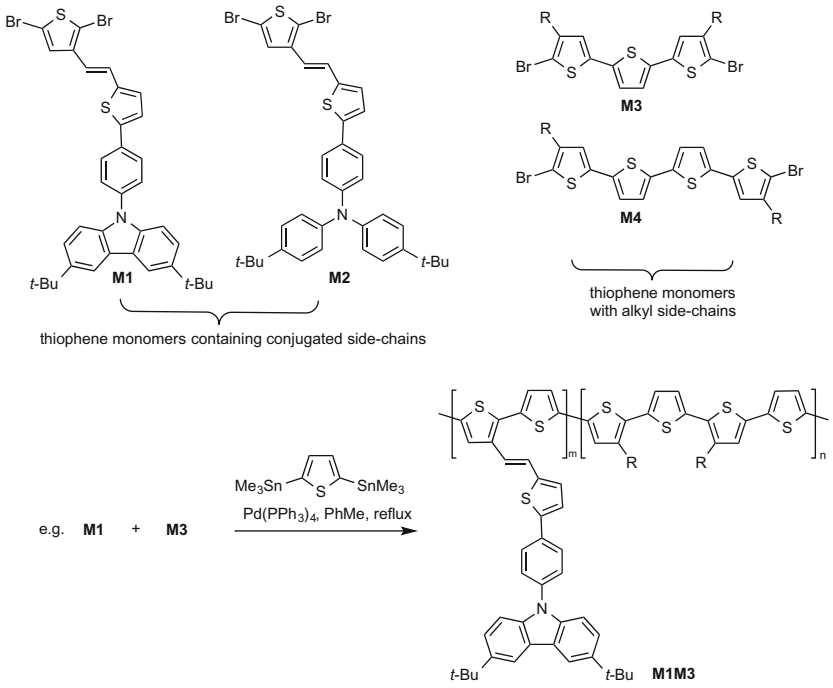
Scheme 13 Synthesis of PTs with carbonyl groups at C-3 (R = alkyl chain) [79]

Novel polythiophene derivatives having conjugated side-chains containing triphenylamine and carbazole were prepared [80]. Firstly, thiophene monomers with aromatic amine conjugated chains at C-3 and other monomers comprising three or four thiophenes with alkyl side-chains were prepared in order for the polymer to be soluble in organic solvents; the corresponding copolymers were obtained via Stille cross-couplings, as shown in Scheme 14.

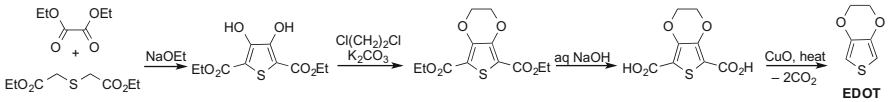
As shown above, thiophene-based polymers can have several different side chains and thus different characteristics. An important polymer for PSC based on thiophene is PEDOT:PSS which functions as an ETL as described above. PEDOT:PSS was developed in the late 1980s at Bayer AG laboratories to be a soluble conducting polymer which did not have undesirable couplings such as α–β or β–β [12]. Without the counterion, the polymer was highly crystalline, insoluble, and brittle, but it formed a transparent oxidized thin film that showed a conductivity of 300 S/cm. To ensure solubility, the polymer was prepared with a counterion, and this also resulted in highly conductive films, which were highly transparent and showed high stability [12, 81].

A synthesis of the monomer for PEDOT:PSS, i.e., 3,4-ethylenedioxythiophene (EDOT), is shown in Scheme 15 (other routes are detailed in [82–84]).

PEDOT:PSS can be synthesized by (1) oxidative, (2) electrochemical, or (3) transition metal-mediated coupling polymerizations in the presence of a monomeric or polymeric counterion. The synthesis of PEDOT:PSS by oxidative polymerization



Scheme 14 Synthesis of the copolymer M1M3 by Stille cross-coupling [80]



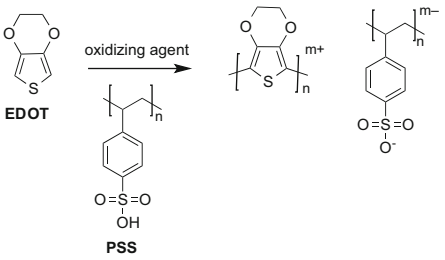
Scheme 15 A synthesis of EDOT [83, 84]

in aqueous media in the presence of the commercially available water-soluble polystyrene sulfonic acid as counterion is illustrated in Scheme 16 [85].

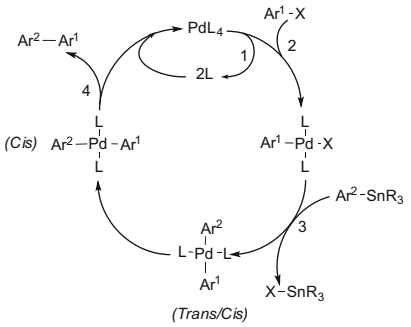
2.3 Synthesis of Other Conjugated Polymers

The synthesis of low bandgap and conjugated polymers can be carried out through various organometallic syntheses; however, Stille and Suzuki palladium-catalyzed cross-coupling polymerizations have been the most frequently employed.

In the Stille cross-coupling, an organotin compound, such as a trimethylstannyl or tributylstannyl species, is coupled with an sp^2-hybridized halide in the presence of a catalytically active complex of Pd(0). The mechanism has been well



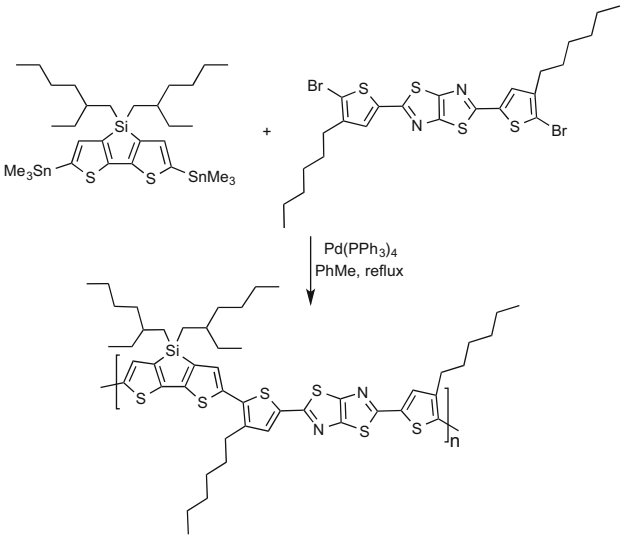
Scheme 16 Polymerization of EDOT to PEDOT:PSS using polystyrene sulfonic acid as counter ion. The oxidizing agent can be, e.g., sodium peroxodisulfate [85]



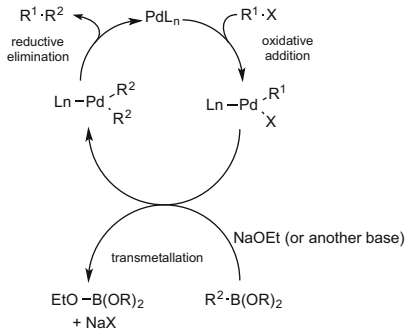
Scheme 17 A simplified catalytic cycle of the Stille cross-coupling, showing the four generally accepted steps: (*1*) ligand dissociation, (*2*) oxidative addition, (*3*) transmetallation, and (*4*) reductive elimination. The product can enter the cycle repeatedly and thereby is polymerized. Ar^1 and Ar^2 = aryl; R = methyl or butyl; X = Cl, Br, I, OTf [86]

investigated, and the four steps in the catalytic cycle shown in Scheme 17 are generally accepted [86]. The reaction cycle starts with (1) a ligand dissociation where the palladium goes from being coordinatively saturated (PdL_4) to become the more reactive PdL_2 [87]. This is followed by (2) an oxidative addition of the organic halide to the Pd(0) active species. The resulting Pd(II) complex undergoes a transmetallation (3) from the stannane leading to an intermediate that may be cyclic or open [88, 89]. After the formation of the product by (4), reductive elimination, the Pd(0) active species is regenerated and a new cycle can start. Typical catalytic systems used for this coupling are $Pd(PPh_3)_2Cl_2$ [90, 91], $Pd_2(dba)_3$ with P(o-Tol)$_3$ [92] or with tricyclohexylphosphine (PCy_3) [93], and Pd $(PPh_3)_4$ [94, 95].

In poly[2-(5-(4,4-bis(2-ethylhexyl)-4*H*-silolo[3,2-*b*:4,5-*b*′]dithien-2-yl)-4-hexylthien-2-yl)-5-(4-hexylthien-2-yl)thiazolo[5,4-*d*]thiazole] (PDTSTTz), the thiophene rings are part of the repetitive unit of the polymer. Dithienylthiazolo [5,4-*d*]thiazole (acceptor monomer) was reacted with a dithienosilole unit (donor



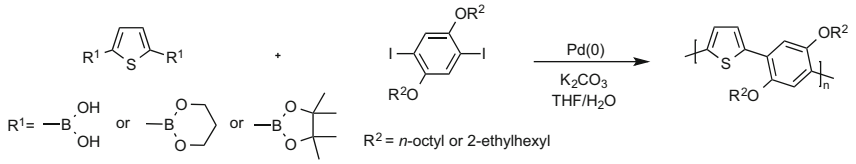
Scheme 18 Synthesis of dithieno[3,2-*b*:20,30-*d*]silole-alt-dithienylthiazolo[5,4-*d*]thiazole copolymer [95]



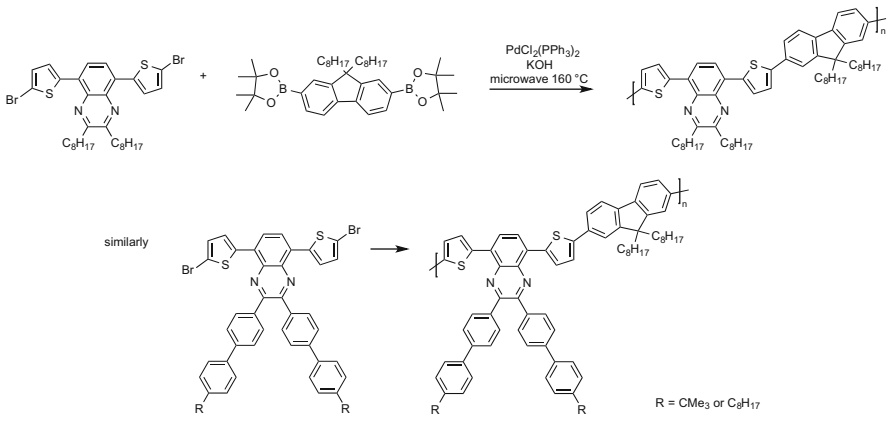
Scheme 19 Suzuki cross-coupling catalytic cycle [96, 97]

monomer) by Stille cross-coupling, obtaining an LBG polymer containing thiophene units shown in Scheme 18.

Suzuki cross-coupling polymerization is also often used to synthesize conjugated polymers. In this case, a halide (or triflate) monomer is cross-coupled with an organo-borane monomer under basic conditions and in the presence of a Pd(0) catalyst. The mechanism, shown in Scheme 19, is similar to Stille cross-coupling: the first step is the oxidative addition of the organic halide (electrophile) to the Pd (0) complex, generating a Pd(II) complex, which undergoes transmetallation with the organometallic monomer. Reductive elimination of the product allows a new cycle to start [96, 97]. The step that differs in the two cross-couplings is the



Scheme 20 Synthesis of thiophene–phenylene copolymers through Suzuki polycondensation [98]

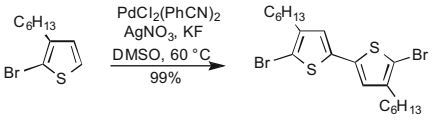


Scheme 21 Fluorene-di(thiophene)quinoxaline copolymers [99]

transmetallation step [97]. In a Suzuki coupling, a base is needed to accelerate the transmetallation step: this is ascribed to coordination of the base to the boron atom (Lewis acid), i.e., by the formation of an ate complex with a higher nucleophilic reactivity.

Alternating thiophene–phenylene copolymers were synthesized through Suzuki polycondensation (Scheme 20). Analysis of different thiophenebisboronic derivatives and of the pre-catalysts $Pd(PPh_3)_4$ and $Pd(OAc)_2$ [98] showed that the thiophenebisboronic pinacol diester is more stable than either the thiophenebisboronic acid or the thiophenebisboronic 1,3-propanediol diester. Using the more stable derivative means that deboronation is less likely, leading to higher molecular weight polymers [98]. Moreover, $Pd(PPh_3)_4$ was not as effective as Pd $(OAc)_2$ for the synthesis of the polymers from the bisboronic acid or the bisboronic 1,3-propanediol diester. However, using $Pd(PPh_3)_4$ as catalyst, the number of different end groups (boronic, iodo, and hydrogen) was lower than those observed using $Pd(OAc)_2$ [98]. There can be a problem of aryl–aryl exchange in the presence of $Pd(PPh_3)_4$, but using branched chains in the aryl unit leads to a defect-free polymer, since their presence deters aryl–aryl exchange [98].

Fluorene-di(thiophene)quinoxaline copolymers were synthesized through Suzuki reactions of a dibromo-di(thiophene)quinoxaline monomer (donor–acceptor–donor system) carrying various substituents on the quinoxaline system, with a fluorene diboronate, as shown in Scheme 21 [99].



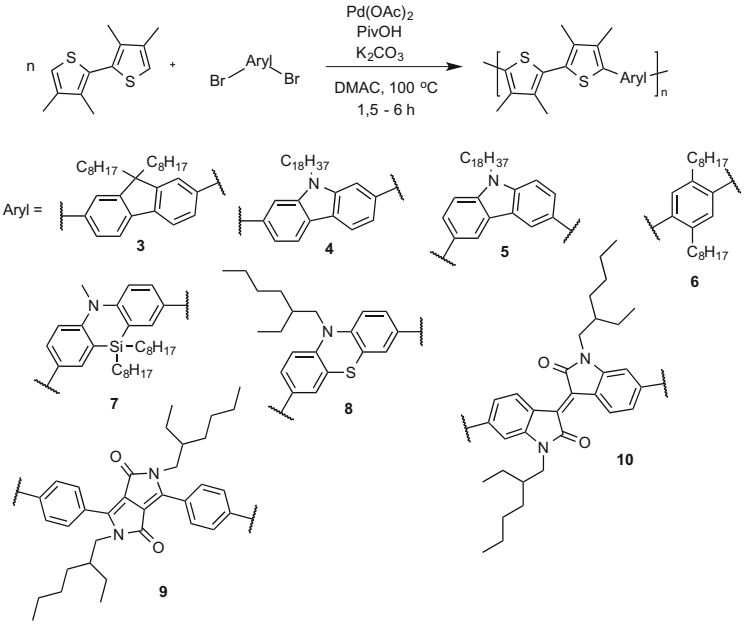
Scheme 22 Synthesis of 5,5′-dibromo-4,4′-dihexyl-2,2′-bithiophene [55]

Low bandgap and conjugated polymers in general need to be used and therefore synthesized on a large scale for them to be relevant for PSC. For this reason, the conventional routes, using Stille and Suzuki cross-couplings, are limited for industrial production because the monomers need specific leaving groups. Additionally, the monomers, especially tin compounds used in Stille cross-couplings, are highly toxic and inorganic waste is produced in both cross-coupling methods. Transition-metal-catalyzed C–H homocoupling can be used to synthesize a bi-(hetero)-aryl monomer unit which can be coupled with another monomer to give a conjugated polymer. One example is the synthesis of 5,5′-dibromo-4,4′-dihexyl-2,2′-bithiophene shown in Scheme 22 [55]. This TT bithiophene unit, with alkyl or other side-chains, can be employed as a donor unit and coupled to an acceptor unit to obtain a copolymer containing thiophene [100, 101].

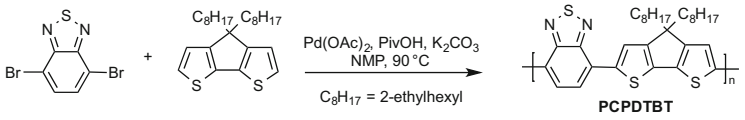
Thiophene- and bithiophene-based alternating materials were synthesized through direct heteroarylation, as described earlier for the synthesis of P3HT, yielding six different kinds of thiophene-based copolymers in good yields [61]. The catalytic system required the presence of $Pd(OAc)_2$, pivalic acid, and potassium carbonate in *N*,*N*-dimethylacetamide. The synthesis was optimized and eight polymers, as shown in Scheme 23, were produced, without the presence of cross-linked structures, in good to excellent yields. It was found that the reaction time has a strong influence on the presence of cross-linked structures [56].

In conjugated polymers, the physical and electrical properties change according to the different monomeric units employed, since the chemical structure influences the electronic configuration of the polymer. Different optical properties and optical energy gaps were reported for all the polymers shown in Scheme 20: λ_{max} (thin film) varies from 310 nm for polymer **8** to 585 nm for polymer **10** while Eg_{opt} varies from 1.74 eV for polymer **10** to 3.25 eV for polymer **6** [56].

The polymers made with the units **9** and **10** through DARP were tested as the active layer for PSC and gave PCEs of 0.89% and 0.39%, respectively [56], which are relatively low for a PSC. A similar polymer, but with the unit **9**, without methyl groups on the thiophene rings, showed higher power conversion efficiency (1.67%) [102], and this difference is probably due to the additional alkyl groups [56]. The reason why the bithiophene unit, with that conformation and the methyl substituents at the β-positions, shown in Scheme 23, was employed as the monomeric unit is because of the lack of DARP selectivity and thus to prevent side reactions (two positions of each thiophene are not available for the polymerization due to the presence of methyl group thus meaning that polymerization can occur only at the available α-positions). Further development of this methodology is therefore



Scheme 23 Thiophene-based copolymers synthesized through DARP [56]

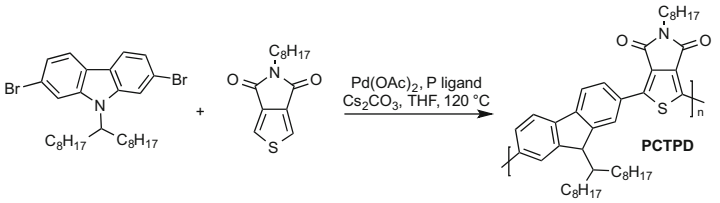


Scheme 24 Synthesis of PCPDTBT via DARP [103]

necessary, in order to improve C–H bond selectivity and obtain low bandgap polymers for PSC [56].

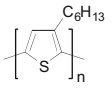
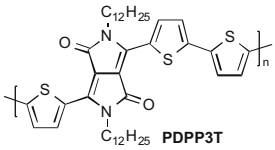
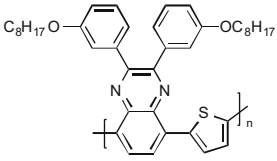
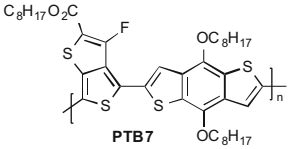
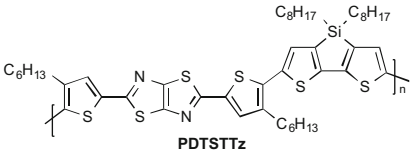
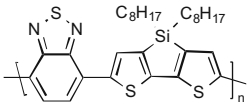
DARP has been used to synthesize low bandgap polymers containing thiophene-fused rings, such as poly(cyclopentadithiophene-*alt*-benzothiadiazole) (PCPDTBT) and other copolymers based on cyclopentadithiophene as donor unit [103]. The polymerization conditions have been optimized for the synthesis of PCPDTBT: M_n up to 70 kDa was achieved, whereas a slightly longer wavelength absorption maximum and a moderate improvement of photovoltaic performances than those of the Suzuki-coupled PCPDTBT (the maximum PCE was 2.24% vs. 2.01% achieved with Suzuki coupling) were observed when the monomers were coupled in the presence of pivalic acid, $Pd(OAc)_2$, and K_2CO_3 in *N*-methylpyrrolidone (Scheme 24) [103]. This can be contrasted with the synthesis of PCPDTBT, through DARP, which produced an M_n of 40 kDa when the monomers were polymerized with $Pd(OAc)_2$ and K_2CO_3 in DMA at 110°C for 24 h [104].

A polymer based on carbazole as donor unit and thieno[3,4-*c*]pyrrole-4,6-dione (PCTPD) as acceptor unit was also synthetized by DARP: the polymer exhibited an



Scheme 25 Synthesis of PCTPD via DARP [105]

Table 1 Examples of thiophene-based conjugated polymers from Fig. **4** applied in PSC. C_8H_{17} = 2-ethylhexyl; $C_{12}H_{25}$ = 2-hexyldecyl

Polymer structure and name	Bandgap (eV)	Efficiency of PSC (%)	References
 P3HT	1.9	~5	[106]
 PDPP3T	1.36	3.8	[107]
 TQ1	1.7	7.1	[108, 109]
 PTB7	1.63	8.50	[110]
 PDTSTTz	1.76	5.88	[95]
 PSBTBT	1.45	5.1	[94]

M_n of 34 kDa and showed an absorption maximum at slightly longer wavelength than that of the same polymer obtained through Suzuki coupling (Scheme 25) [105].

3 Application of Thiophene-Based Polymers in Polymer Solar Cells

As described in the introduction, thiophene-based conjugated polymers are often used as light-absorbing materials in the active layer of PSCs. In Table 1 a list of polymers (from Fig. 4) based on thiophenes is given along with the bandgap and the reported efficiency of the PSC. From Table 1 it can be seen that the PCE can be increased when applying an LBG polymer compared to P3HT.

4 Summary

In this chapter we have described conjugated polymer systems based on thiophene. The thiophene unit is a unique aromatic heterocycle that is electron rich. When it is coupled with itself or other aromatic units, conjugated polymers are achieved and these can be applied in organic electronics such as polymer solar cells. The synthesis of polythiophenes with various side chains can be carried out via different strategies. For the McCullough and Rieke routes, highly regioregular poly (3-alkylthiophenes) can be achieved. The low bandgap polymers based on thiophene are often synthesized by Stille or Suzuki cross-coupling polymerizations. Direct arylation polymerization has shown great potential since it does not require any activation groups and thus is favorable for application to the synthesis of both low bandgap polymers and poly(thiophene)s.

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Thiophene Oxidation and Reduction Chemistry

Yuzhi Lu, Ze Dong, Pengcheng Wang, and Hai-Bing Zhou

Abstract The oxidation of thiophenes to various thiophene 1-oxides and thiophene 1,1-dioxides and the Diels–Alder reactions of these oxides are reviewed. Progress on partial and complete reduction of thiophenes is described.

Keywords Birch reduction · Diels–Alder reaction · Dienes · Dienophiles · Dimerization · Ionic hydrogenation · Oxidation · Reduction · Reductive desulfurization · Thiophene 1,1-dioxides · Thiophene 1-oxides · Transition metal complexes

Contents

1 Introduction

Thiophene 1-oxides (thiophene *S*-oxides) and thiophene 1,1-dioxides (thiophene *S*, *S*-dioxides) are compounds of great importance in the field of heterocyclic and heteroatom chemistry from both synthetic and mechanistic points of view.

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Thiophene 1-oxides are more reactive and thermally labile than the corresponding thiophene 1,1-dioxides, making them difficult to prepare, but also widely used in the field of medicinal chemistry [1–3] and synthetic chemistry to prepare some key intermediates. Thiophene 1-oxides are also the key intermediates in the metabolism of the corresponding parent thiophenes in living organisms, rendering them of significant importance in drug metabolism studies [4]. Compared with thiophene 1-oxides, thiophene 1,1-dioxides have been more extensively investigated. In Diels–Alder reactions of thiophene 1,1-dioxides, they can act as either 2π or 4π components and undergo a range of cycloadditions with 4π or 2π components to construct a variety of compounds such as highly congested aromatic compounds that are otherwise hard to prepare. Oxidation of thiophenes to their 1,1-dioxides can also be applied in oxidative desulfurization (ODS) processes [5], which remove the sulfur compounds in light oil and therefore attract considerable attention in environment conservation. Moreover, thiophene 1,1-dioxides have been widely used in preparing photoelectric materials [6].

The hydrogenation of thiophenes and benzo[*b*]thiophenes, including ionic hydrogenation, Birch reduction, reductive desulfurization and reduction assisted by transition metal complexes, etc., has been well documented. Like oxidative desulfurization, reductive desulfurization of sulfur-containing compounds, especially the hydrogenation of thiophenes and their derivatives to generate sulfur-free products [7], has also attracted considerable attention. In the perspective of organic synthesis, reductive desulfurization of thiophenes represents a convenient pathway to synthesize long-chain or branched-chain compounds, especially carboxylic acids. In addition, reduction of thiophenes makes it possible to prepare polyalicyclic systems with various substituents [8].

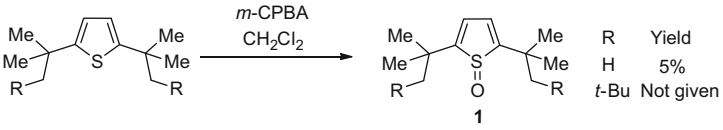
This chapter discusses the common and/or recent methods to prepare thiophene oxides and their Diels–Alder reactions, as well as the reduction chemistry of thiophenes.

2 Thiophene Oxidation Chemistry

2.1 Oxidation of Thiophenes to Thiophene 1-Oxides and Their Diels–Alder Reactions

2.1.1 Oxidation of Thiophenes to Thiophene 1-Oxides

The oxidation of thiophenes to thiophene 1-oxides is actually a process in which the aromaticity of a thiophene is lost. Direct oxidation of thiophenes provides the most straightforward way to the corresponding thiophene 1-oxides; however, the oxidation is always difficult to stop at the 1-oxide stage and is generally much slower than the further oxidation to thiophene 1,1-dioxides. Furthermore, the resulting thiophene 1-oxides are very reactive species and sometimes undergo a rapid



Scheme 1 Oxidation of 2,5-di-*tert*-butyl- and 2,5-di(2,4,4-trimethylpentan-2-yl)thiophene to corresponding thiophene 1-oxides by *m*-CPBA [9]

cyclodimerization through a Diels–Alder reaction that is even faster than oxidation of thiophene 1-oxides to thiophene 1,1-dioxides. Therefore, in order to achieve high yields and selectivity, various oxidants for the synthesis of thiophene 1-oxides have been investigated.

The first synthesis of isolable monocyclic thiophene 1-oxides was carried out by Whitten in 1970 [9]. In this case, 2,5-di-*tert*-butyl- and 2,5-di(2,4,4-trimethylpentan-2-yl)thiophenes were oxidized with *m*-chloroperbenzoic (*m*-CPBA), which afforded the kinetically stable thiophene 1-oxides **1**, though in low yields (Scheme 1).

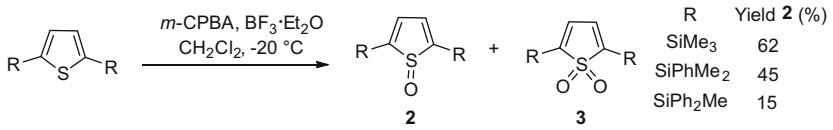
A more useful method uses *m*-CPBA in the presence of $BF_3 \cdot Et_2O$; thus, 2,5-bis (trimethylsilyl)thiophene and related thiophenes afforded the corresponding thiophene 1-oxides **2** in moderate yields, with only trace amounts of the corresponding thiophene 1,1-dioxides **3** [10, 11]. It should be noted that when this reaction was carried out with *m*-CPBA in the absence of $BF_3 \cdot Et_2O$, the reaction gave solely thiophene 1,1-dioxides **3** (in up to 27% yield), and no corresponding thiophene 1-oxides **2** were obtained at all. In this method, $BF_3 \cdot Et_2O$ may play a role not only in preventing further oxidation of the 1-oxides but also in increasing the reactivity of *m*-CPBA, probably through coordination to both the sulfide oxygen of **2** and the oxygen of the peracid (Scheme 2).

Typical applications of this route to synthesize thiophene 1-oxides are shown in Schemes 3 and 4.

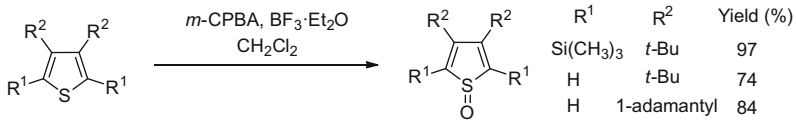
S-Oxidation of a di(thien-3-yl)methane provided a mixture of the mono *S*-oxide **4** and the double *S*-oxide **5**, in a ratio that depended on the number of equivalents of *m*-CPBA used (Scheme 5) [15].

The thiophenophane 1-oxides **6** and **7** could also be obtained in reasonable yields, and for the latter, the competing product, thiophenophane 1,1-dioxide **8**, can also be formed in 38% yield [16] (Scheme 6). Interestingly, when 1,11-dibromo [8](2,5)thiophenophane was oxidized under the same reaction conditions, an alternative reaction took place to give compounds **10** and **11** (Scheme 7). The formation of an $OH^{\bullet}$ radical plays a key role in the proposed mechanism (Scheme 7).

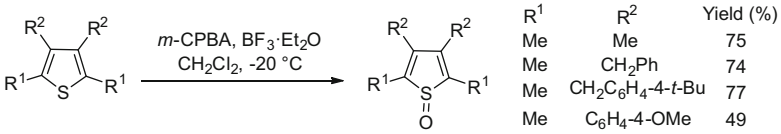
A H_2O_2-CF_3CO_2H system was developed for oxidizing some highly congested thiophenes to the corresponding thiophene 1-oxides, while other oxidants (e.g., dimethyldioxirane, *m*-CPBA, etc.) afforded thiophene 1,1-dioxides as products. For example, the oxidation of 2,3,4,5-tetraphenylthiophene with H_2O_2 in CF_3CO_2H-CH_2C1_2 gave tetraphenylthiophene 1-oxide in 30% yield (Scheme 8) [17]. Importantly, this method is also applicable for the preparation of benzo[*b*] thiophene 1-oxide derivatives in moderate to high yields (Scheme 9) [18].



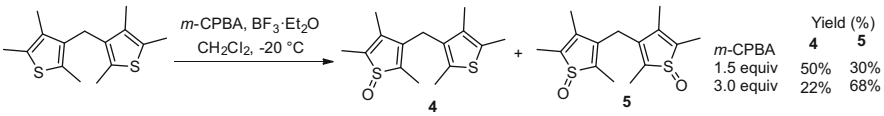
Scheme 2 Oxidation of 2,5-bis(trimethylsilyl)thiophene and related thiophenes to the corresponding thiophene 1-oxides [10, 11]



Scheme 3 Oxidation of highly congested thiophenes by *m*-CPBA in the presence of $BF_3 \cdot Et_2O$ [12]



Scheme 4 Oxidation of tetrasubstituted thiophenes to the corresponding thiophene 1-oxides [13, 14]

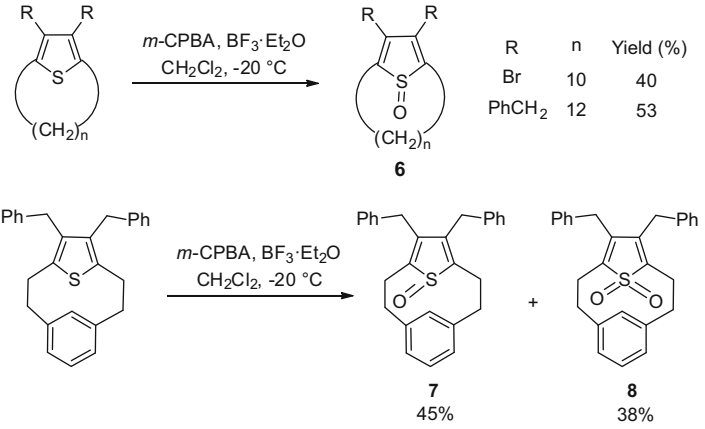


Scheme 5 Oxidation of a di(thien-3-yl)methane by *m*-CPBA in the presence of $BF_3 \cdot Et_2O$ [15]

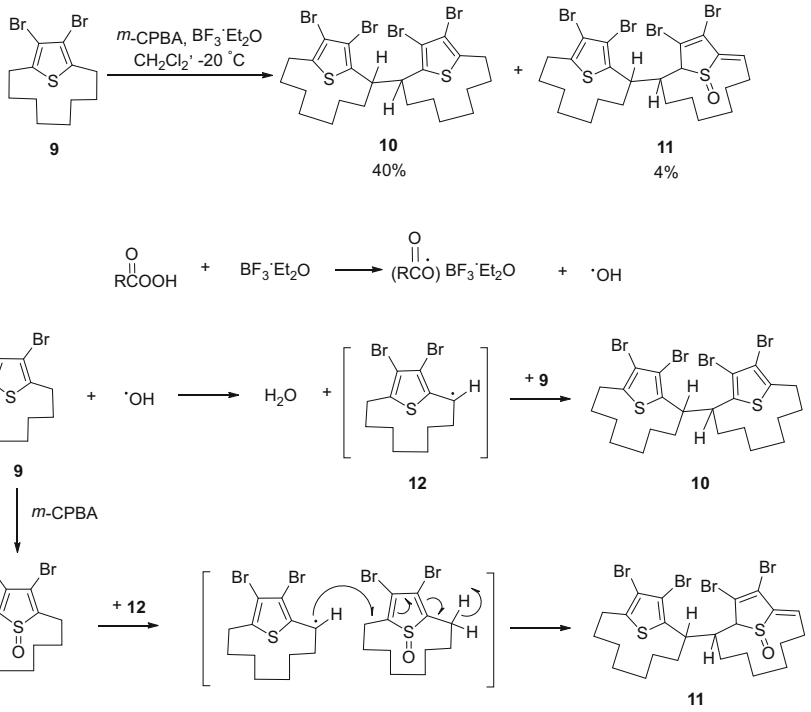
Compared with other oxidising systems such as $NaIO_4$, DMD (dimethyldioxirane), and *m*-CPBA, the H_2O_2-CF_3CO_2H system gives the best conversion rate [19], for example, when compounds **13** were treated with H_2O_2-CF_3CO_2H at different reaction temperatures, benzo[*b*]thiophene 1-oxides and benzo[*b*]thiophene 1,1-dioxides were obtained exclusively in good yields (Scheme 10).

One special example using O_2 as oxidant in an oxidative desulfurization (ODS) process should be noted. In a visible light-induced desulfurization technique for light oil [20], dibenzothiophene was oxidized to dibenzothiophene sulfoxide and dibenzothiophene sulfone gradually in CH_3CN in the presence of 9,10-dicyanoanthracene (DCA) with high yield; the resulting sulfoxides or sulfones can be removed by polar extractants, thus producing ultralow sulfur fuels (Scheme 11).

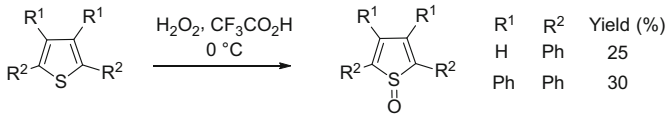
Very recently, a catalyst-free approach for solvent-dependent selective oxidation of organic sulfides, including thiophene, with Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)



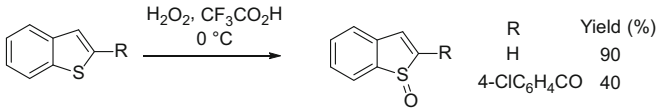
Scheme 6 Oxidation of thiophenophanes to the corresponding thiophene 1-oxides [16]



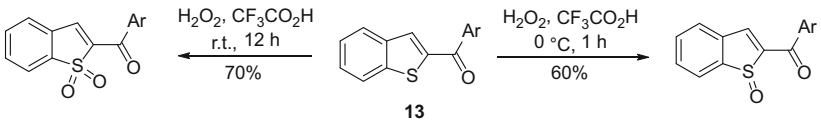
Scheme 7 Oxidation of 1,11-dibromo[8](2,5)thiophenophane by *m*-CPBA in the presence of $BF_3 \cdot Et_2O$ and the proposed mechanism [16]



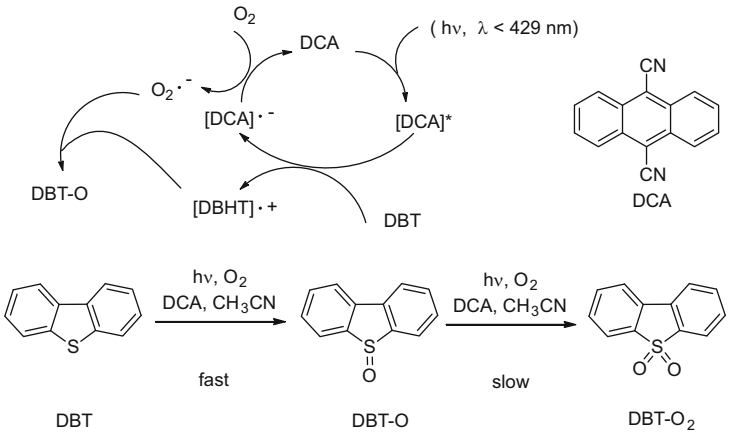
Scheme 8 Oxidation of 2,3,4,5-tetraphenylthiophene to the 1-oxide using H_2O_2-CF_3CO_2H complex [17]



Scheme 9 Oxidation of benzo[*b*]thiophene and 2-(4-chlorobenzoyl)benzo[*b*]thiophene to the corresponding thiophene 1-oxides by H_2O_2-CF_3CO_2H complex [18]

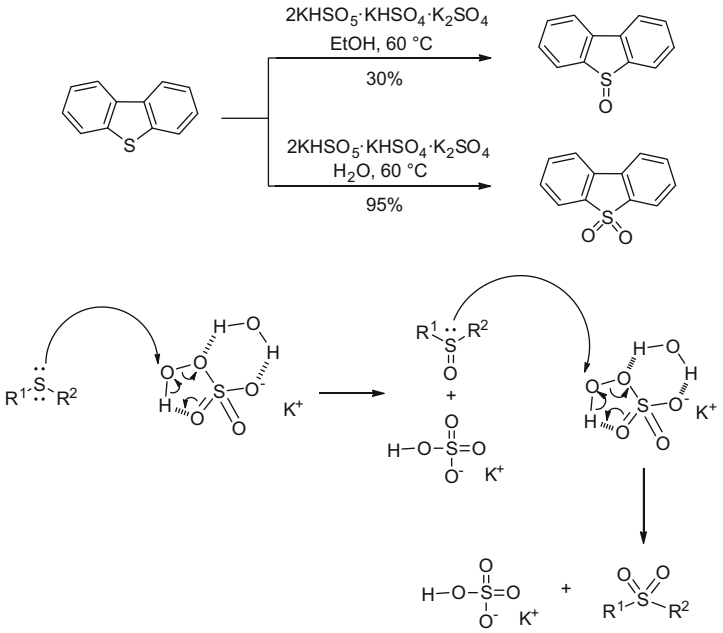


Scheme 10 Preparation of benzo[*b*]thiophene 1-oxides and benzo[*b*]thiophene 1,1-dioxides [19]



Scheme 11 Oxidative desulfurization of dibenzothiophene using O_2 as oxidant [20]

was developed [21]; notably, the reaction can be controlled by choice of solvent. When ethanol was used, sulfoxides were generally obtained in good yields, except that from dibenzothiophene, which was isolated in a relatively low yield (30%); however, sulfone was produced almost exclusively when the reaction was performed in water. The proposed reaction mechanism for the water-promoted oxidation of sulfide is shown in Scheme 12.



Scheme 12 Preparation of dibenzothiophene 1-oxide and dibenzothiophene 1,1-dioxide by Oxone® in different solvents and the proposed reaction mechanism [21]

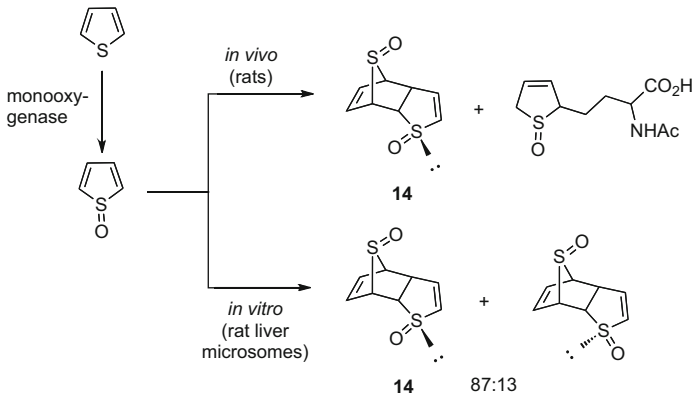
A specific approach to thiophene 1-oxides is the biological oxidation of thiophene, which is considered to be involved in the metabolism of thiophenes in organisms. The process uses mild operating conditions in the presence of water and oxygen.

The involvement of thiophene 1-oxide as the key intermediate in the metabolism of the parent thiophene was directly validated by the isolation of thiophene 1-oxide dimers both in vitro (oxidation of thiophene with rat liver microsomes) and in vivo (isolation of **14** from rat urine) (Scheme 13) [22].

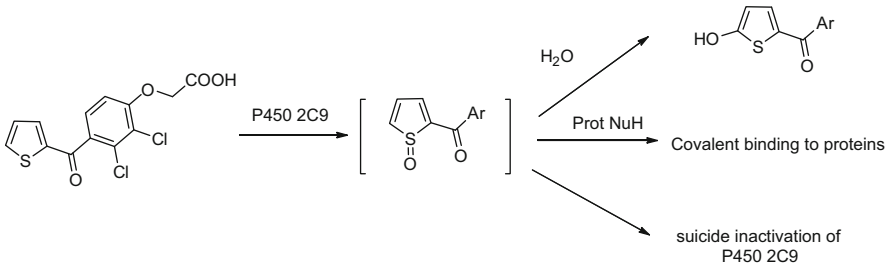
The metabolism of tienilic acid provides further evidence. Tienilic acid, a diuretic drug that is involved in the appearance of rare cases of immunoallergic hepatitis, leads to 5-hydroxytienilic acid as a major metabolite in vivo and in vitro (Scheme 14) [4, 23, 24].

Substituted chiral thiophene 1-oxides **15** and their Diels–Alder cycloadducts of variable enantiopurity have been isolated as products of dioxygenase-catalyzed sulfoxidation of the corresponding thiophenes using intact cells of *Pseudomonas putida* (Scheme 15) [25, 26].

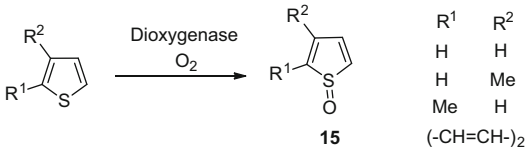
Oxidation of benzo[*b*]thiophene by rat liver microsomes in the presence of NADPH led to benzo[*b*]thiophene 1-oxide **16** as a major metabolite [27]. Identification of **16** and **17** was achieved by comparison with authentic samples prepared by oxidation of benzo[*b*]thiophene with H_2O_2 in CF_3CO_2H and further treatment of **16** with $HOCH_2CH_2SH$ in CH_3OH. Toluene dioxygenase (TDO) and naphthalene dioxygenase (NDO), which are present in *P. putida* mutant and *Escherichia coli*



Scheme 13 Isolation of thiophene 1-oxide dimers both in vitro and in vivo in rats [22]



Scheme 14 Thiophene 1-oxide as the intermediate in the metabolic oxidation of tienilic acid [4, 23, 24]



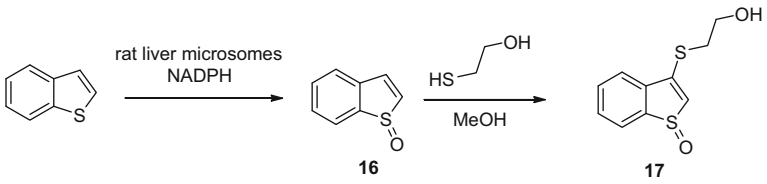
Scheme 15 Preparation of substituted chiral thiophene 1-oxides catalyzed by dioxygenase [25, 26]

recombinant whole cells, were also able to catalyze the oxidation of benzo[*b*] thiophene (Scheme 16) [28].

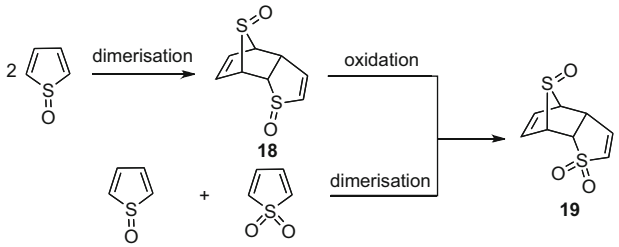
2.1.2 Diels–Alder Reactions of Thiophene 1-Oxides

Self-Dimerization

As described above, the oxidation of thiophenes to thiophene 1-oxides is much slower than the oxidation of thiophene 1-oxides to the corresponding thiophene



Scheme 16 Benzo[*b*]thiophene 1-oxide as an intermediate in the oxidation of benzo[*b*]thiophene by rat liver microsomes [28]



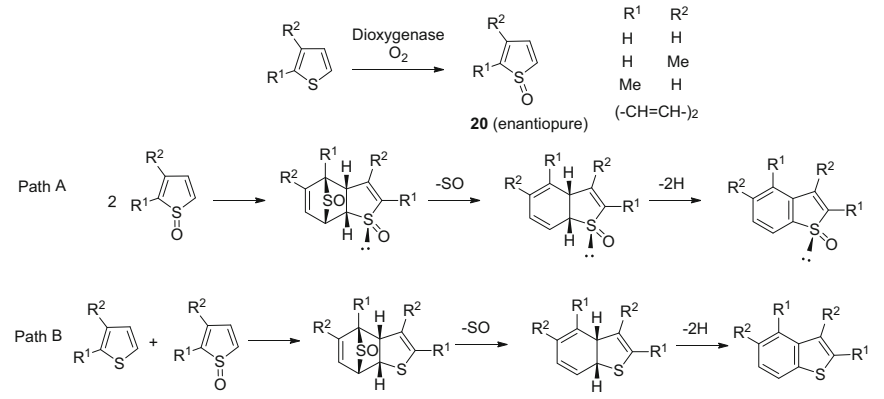
Scheme 17 Preparation of thiophene sesquioxide via thiophene 1-oxide [2+4] cyclodimerization with thiophene 1,1-dioxides or itself [29, 30]

1,1-dioxides. Therefore, thiophene 1-oxides are more reactive and thermally labile species than the corresponding thiophene 1,1-dioxides, rendering them more reactive as dienes compared to the corresponding 1,1-dioxides in Diels–Alder reactions.

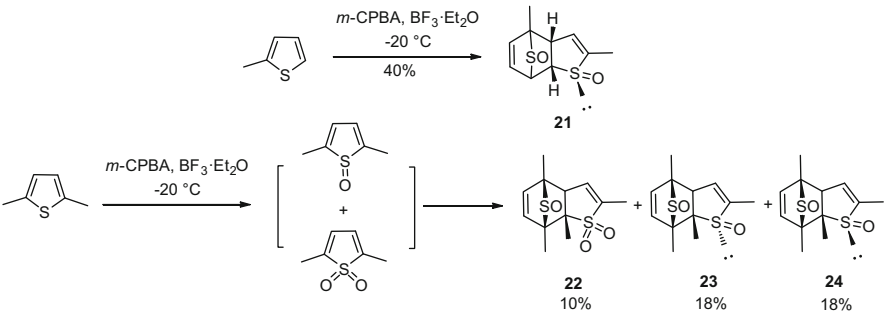
Upon oxidation, a 2,3-double bond of the thiophene ring takes part in a rapid [2+4] cyclodimerization with thiophene 1,1-dioxide, or with itself, to give the corresponding thiophene sesquioxides **18** and **19** (Scheme 17) [29, 30]. The structure and stereochemistry of **19** were elucidated via a detailed NMR spectroscopic study [31].

Thiophene 1-oxide dimers that were isolated from rat liver microsomes and urine demonstrated that thiophene 1-oxides are the key intermediate in the metabolism of the corresponding thiophene in living organisms. Substituted chiral thiophene 1-oxides **20** and their cycloadducts of variable enantiopurity were isolated as products of dioxygenase-catalyzed sulfoxidation of the corresponding thiophenes using intact cells of *P. putida*. Cycloadducts such as benzo[*b*]thiophene l-oxide and benzo[*b*]thiophene derivatives were formed through path A and path B respectively, among them thermal racemization ($\Delta G = 25.1$ kcal mol^{-1}) of the enantiopure ($ee > 98\%$) metabolite (l*R*)-2-methylbenzo[*b*]thiophene l-oxide has been observed (Scheme 18) [25].

Oxidation of 2-methylthiophene by *m*-CPBA in the presence of $BF_3 \cdot Et_2O$ gave a single dimer **21** – the dimerization product of 2-methylthiophene 1-oxide [15, 32]. However, under the same reaction conditions, 2,5-dimethylthiophene yielded three dimers: **22**, **23**, and **24** (Scheme 19). The adduct **22** results from the Diels–Alder reaction of thiophene 1-oxide acting as both diene and dienophile. The difference between **23** and **24** is the stereochemistry at one of the sulfur atoms.



Scheme 18 [2+4] Cyclodimerization of substituted chiral thiophene 1-oxides [25]

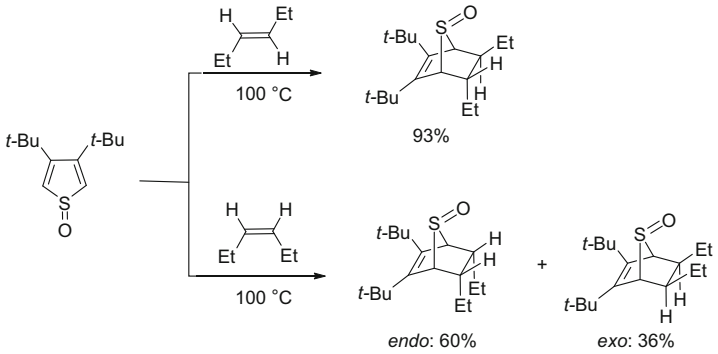


Scheme 19 Cyclodimerization of 2-methylthiophene 1-oxide and 2,5-dimethylthiophene 1-oxide [15, 32]

Reactions with Alkenes

The stereochemistry of the Diels–Alder reaction was investigated by the reactions of 3,4-di-*tert*-butylthiophene 1-oxide with *cis*- and *trans*-3-hexenes. The reactions occur on heating 3,4-di-*tert*-butylthiophene 1-oxide and an excess of the alkene at 100°C in a sealed tube and demonstrated that Diels–Alder reactions take place exclusively at the *syn*-π-face of 3,4-di-*tert*-butylthiophene 1-oxide (Scheme 20) [33].

The Diels–Alder reactions of 3,4-di-*tert*-butylthiophene 1-oxide with oxygen-(or sulfur)-substituted dienophiles or with simple cycloalkenic dienophiles, which are classified as inverse electron-demand Diels–Alder reactions on the basis of DFT calculations, took place exclusively at the *syn*-π-face of the diene with respect to the S=O bond, providing the corresponding adducts in high yields (Table 1) [15, 34, 35].



Scheme 20 Diels–Alder reaction of 3,4-di-*tert*-butylthiophene 1-oxide with *cis*- and *trans*-3-hexenes [33]

Using Lewis acid $BF_3 \cdot Et_2O$ as catalyst enhances the yield of oxidative cycloaddition of thiophenes with mono-activated dienophiles, a reaction that gives poor yields of cycloaddition products under uncatalyzed conditions [13].

Application of *m*-CPBA/$BF_3 \cdot Et_2O$ to synthesize thiophene 1-oxides from **25** and then 7-thiabicyclo[2.2.1]hept-2-en-7-oxides **26** through Diels–Alder reaction with dienophiles was carried out in generally moderate yields in one pot [3]; the 7-thiabicyclic oxide-bridged compounds **26** had *endo* stereochemistry. Several compounds **27–29** demonstrated high binding affinities (the affinities are presented as relative binding affinity (RBA) values, where estradiol has an affinity of 100%) with excellent ERα selectivity, and most thiabicyclic compounds are potent, ER-α-selective agonists in luciferase assays which were conducted in human liver cancer (HepG2) cells transfected with full-length human ERα or ERβ (Scheme 21).

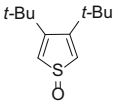
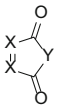
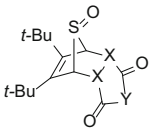
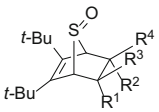
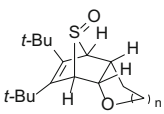
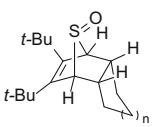
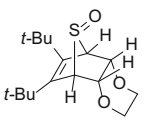
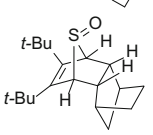
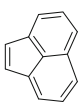
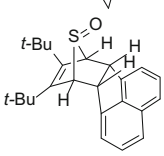
The Wittig olefination of cyclopropanone hemiacetal to generate the intermediate methylenecyclopropanes **30** and the subsequent cycloaddition with tetra-substituted thiophene 1-oxides can be carried out in a one-pot operation with overall good yields. X-Ray diffraction analysis of **31** and **32**, two of the cycloadducts, confirmed that their relative configurations were *endo*, *syn* (Scheme 22) [14].

Reactions with Quinones, Lactones, and *N*-Phenylmaleimide (NPM)

Quinones, cyclic lactones, and *N*-phenylmaleimide, which are typical dienophiles, undergo Diels–Alder reactions with thiophene 1-oxides. Oxidation of thiophene or thiophene derivatives with *m*-CPBA in the presence of quinones gives sulfoxide-bridged adducts and naphtho- or anthraquinone derivatives.

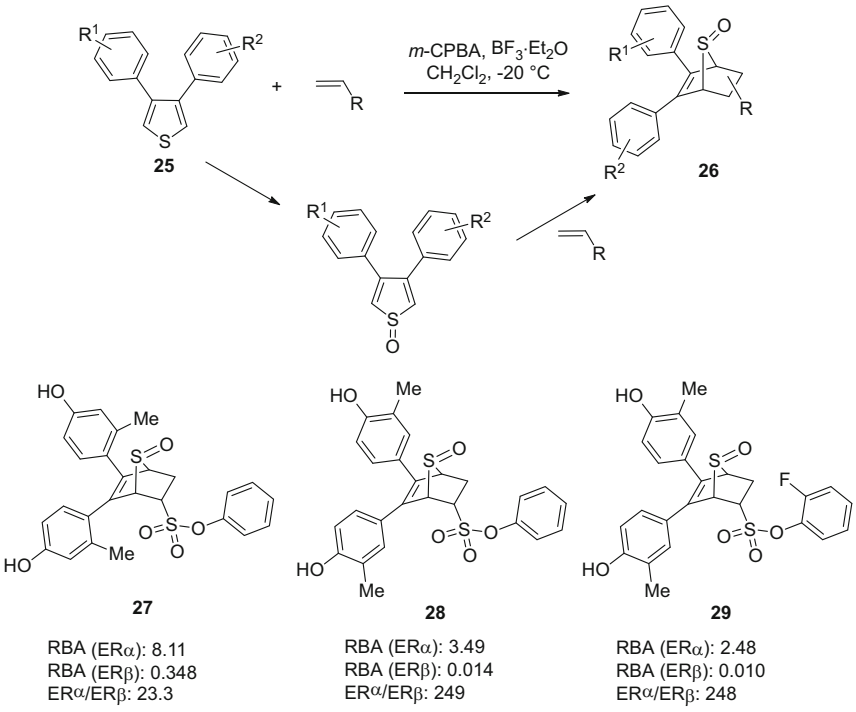
The Diels–Alder reactions of 2,5-bis(trimethylsi1yl)thiophene 1-oxide with dienophiles such as maleic anhydride and 1,4-benzoquinone are exclusively *endo* orientated and *syn* directed with respect to the S–O bond (Scheme 23) [36]. This stereochemistry is in good agreement with the results obtained from RHF and MP2 MO calculations using the 6-31G(*) basis set [37].

Table 1 Diels–Alder reaction of 3,4-di-*tert*-butylthiophene 1-oxide with various dienophiles

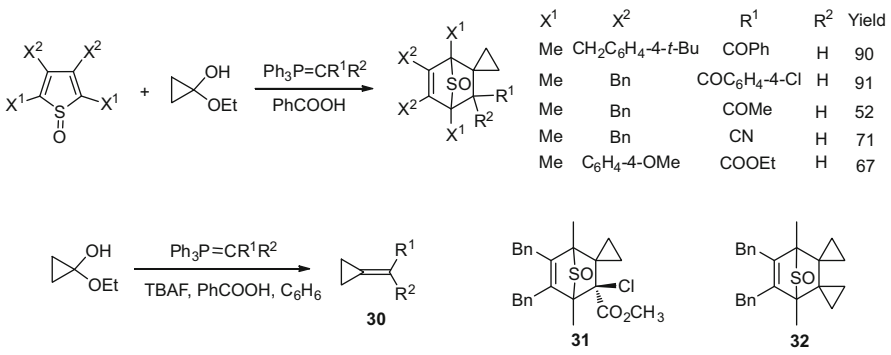
Diene	Dienophiles	Products	Yields
			X=CH, Y=O, 83% X=CH, Y=NMe, 100% X=CH, Y=NPh, 99% X=N, Y=NPh, 94%
			R^1=R^2=R^4=H, R^2=CN, 100% R^1=R^2=R^3=R^4=CN, 99% R^1=R^2= R^3=H, R^4=SOPh, 96% R^1=R^2=R^3=R^4=SO_2Ph, 98% R^1=R^2=Cl, R^3=R^4=H, 100% R^1=R^2=R^3=H, R^4=OEt, 100% R^1=R^2=R^3=H, R^4=SPh, 100%
			*n* = 1, 93% *n* = 2, 91%
			*n* = 1, 98% *n* = 2, 61% *n* = 4, 100%
			87%
			96%
			84%

Reaction of 3,4-di-*tert*-butylthiophene-1-oxide in ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4) with dienophile parasorbic acid afforded the Diels–Alder product **33** in 91% yield. But the resulting oxidation products **34** and **35** showed no significant photoreactivity, rendering it an inappropriate strategy for the synthesis of a two-stage photobase generator (PBG) based on photoinduced aromatization (Scheme 24) [38].

Tetrasubstituted thiophene 3,4-di-*tert*-butyl-2,5-dimethylthiophene 1-oxide reacted with maleic anhydride to give the Diels–Alder adduct quantitatively



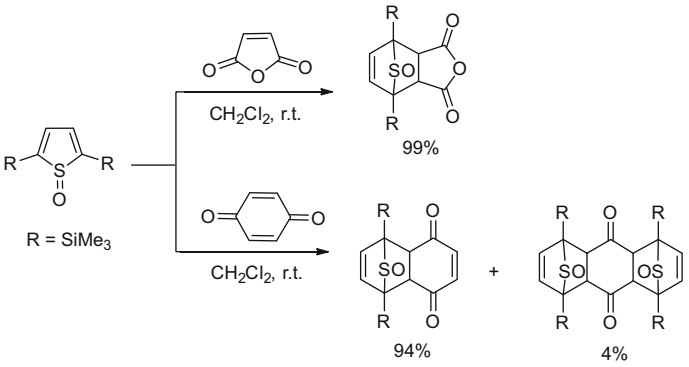
Scheme 21 Preparation of 7-thiabicyclo[2.2.1]hept-2-en-7-oxides through oxidative Diels–Alder reaction from 3,4-diarylthiophenes and representative compounds for selective activity to ERα [3]



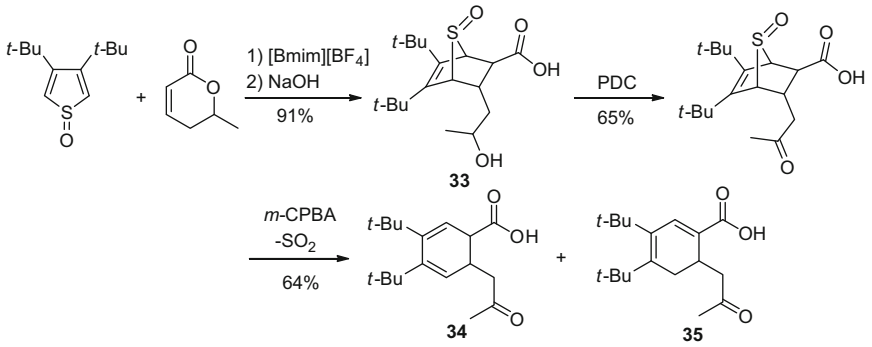
X^1	X^2	R^1	R^2	Yield
Me	$CH_2C_6H_4$-4-*t*-Bu	COPh	H	90
Me	Bn	COC_6H_4-4-Cl	H	91
Me	Bn	COMe	H	52
Me	Bn	CN	H	71
Me	C_6H_4-4-OMe	COOEt	H	67

Scheme 22 One-pot Diels–Alder reaction of tetrasubstituted thiophene 1-oxides and cyclopropylalkenes derived from cyclopropanone hemiacetal [14]

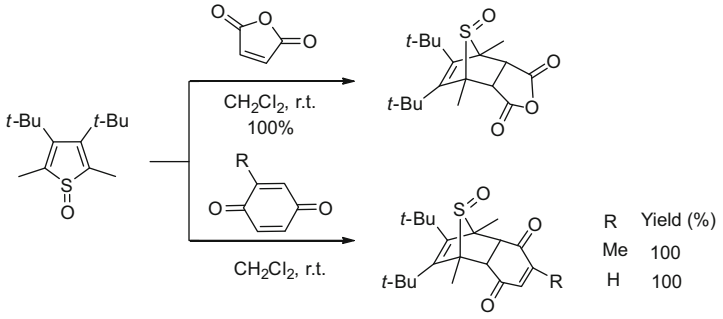
[39]. Similar reactions with 1,4-benzoquinone and substituted 1,4-benzoquinones also proceeded smoothly and provided the corresponding products in very high yields (Scheme 25) [13].



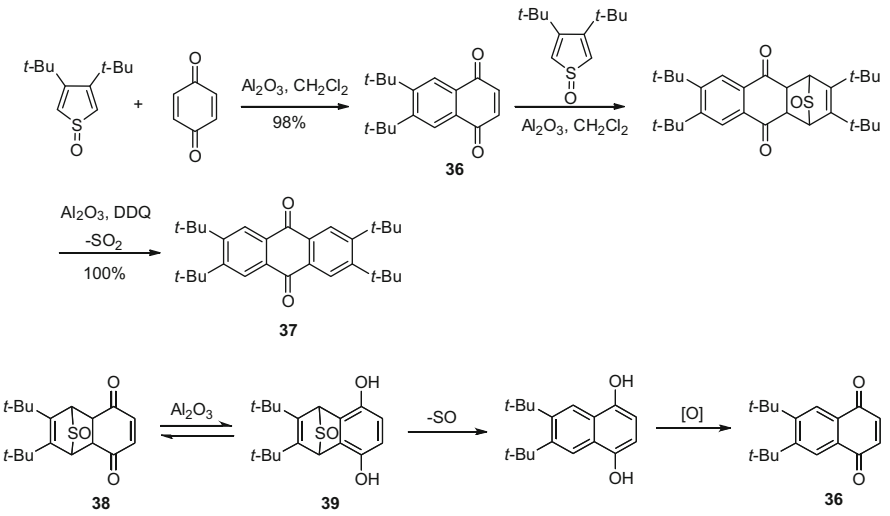
Scheme 23 Diels–Alder cycloaddition of 2,5-bis(trimethylsi1yl)thiophene 1-oxide with maleic anhydride and benzoquinone [36]



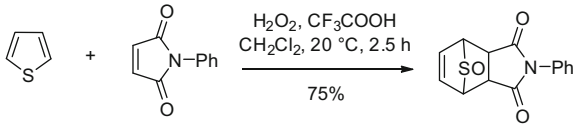
Scheme 24 Diels–Alder cycloaddition of 3,4-di-*tert*-butylthiophene-1-oxide and parasorbic acid [38]



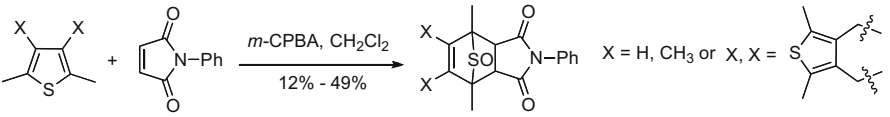
Scheme 25 Diels–Alder cycloaddition of 3,4-di-*tert*-butyl-2,5-dimethylthiophene 1-oxide with maleic anhydride, 1,4-benzoquinone, and 2-methyl-1,4-benzoquinone [13, 39]



Scheme 26 Preparation of 2,3,6,7-tetra-*t*-butylanthraquinone by using a Diels–Alder reaction catalyzed by silica gel (alumina) and the proposed mechanism [40]



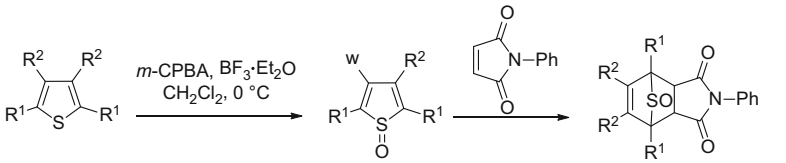
Scheme 27 Oxidative Diels–Alder cycloaddition of thiophene with *N*-phenylmaleimide using H_2O_2/CF_3CO_2H as oxidant [41]



Scheme 28 Oxidative Diels–Alder cycloaddition of thiophene derivatives with *N*-phenylmaleimide using *m*-CPBA as oxidant [22, 42]

Silica gel or alumina was used as catalyst for the Diels–Alder reaction of 3,4-di-*tert*-butylthiophene 1-oxide with 1,4-benzoquinone to produce 6,7-di-*tert*-butyl-1,4-naphthoquinone **36** and bis-adduct 2,3,6,7-tetra-*tert*-butylanthraquinone **37** [40]. The silica gel (alumina)-catalyzed enolization of **38** to form **39** may play an important role in the formation of **36** (Scheme 26).

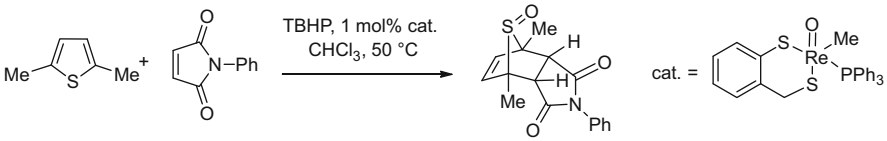
Oxidation of thiophene or thiophene derivatives with various oxidants in the presence of dienophile *N*-phenylmaleimide always leads to the Diels–Alder cycloaddition products. Typical oxidants H_2O_2/CF_3CO_2H [41], *m*-CPBA [22, 42], *m*-CPBA/$BF_3 \cdot Et_2O$ complex [13], and TPHP (*tert*-butyl hydroperoxide) [43] are shown in Schemes 27, 28, 29, and 30. The rhenium-catalyzed reactions are of



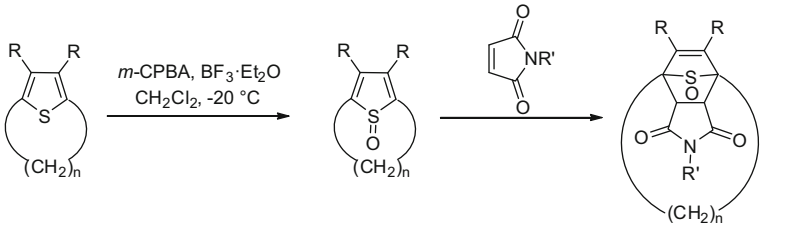
R^1	R^2	Yield (%)
CH_3	H	not isolated
CH_3	CH_3	75
CH_3	CH_2Ph	74

R^1	R^2	Yield (%)
CH_3	H	78
CH_3	CH_3	98
CH_3	CH_2Ph	95

Scheme 29 Oxidative Diels–Alder cycloaddition of 2,5-di- and tetrasubstituted thiophenes with *N*-phenylmaleimide using *m*-CPBA/$BF_3 \cdot Et_2O$ complex as oxidant [13]



Scheme 30 Oxidative Diels–Alder cycloaddition of 2,5-dimethylthiophene with *N*-phenylmaleimide using TPHP as oxidant [43]



R	n	Yield (%)
Br	10	40
$PhCH_2$	12	53

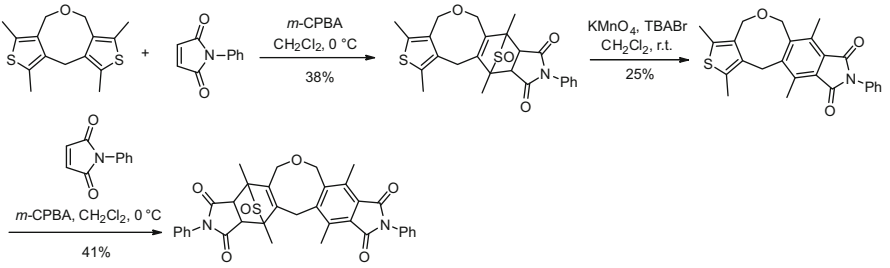
R	R'	n	Yield (%)
Br	Ph	10	70
$PhCH_2$	Me	12	56
$PhCH_2$	Ph	12	60

Scheme 31 Oxidative Diels–Alder cycloaddition of dibromo[n](2,5)thiophenophanes with *N*-phenylmaleimide [16]

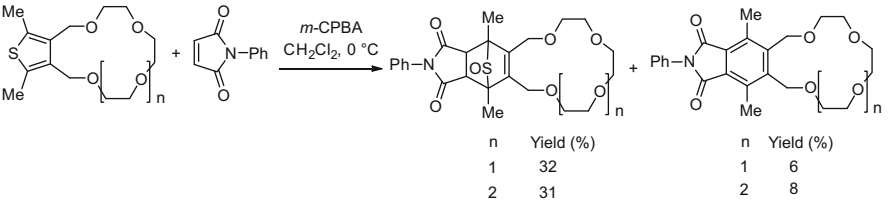
particular interest because they are rapid and yield clean sulfoxide-bridged adducts (Scheme 30).

A comparison of the *m*-CPBA oxidized Diels–Alder reaction of thiophene derivatives with *N*-phenylmaleimide, with or without Lewis acid, showed that the overall yields of Diels–Alder products in the presence of *m*-CPBA are much lower than those using *m*-CPBA/$BF_3 \cdot Et_2O$ complex, suggesting that the Lewis acid catalyst enhances the yield of the oxidative cycloaddition of thiophenes considerably [13].

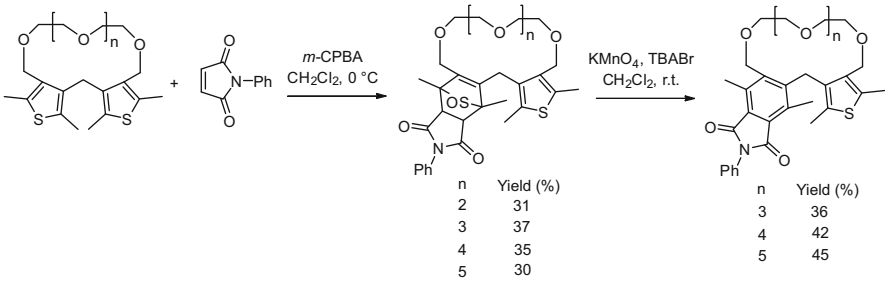
The oxidative Diels–Alder cycloaddition of a variety of intriguing thiophene derivatives such as thiophenophanes and thiopheno crown ethers with



Scheme 32 Oxidative Diels–Alder cycloaddition of a tricyclic bis(thien-3-yl)methane with *N*-phenylmaleimide [44]



Scheme 33 Oxidative Diels–Alder cycloaddition of thiopheno crown ethers with *N*-phenylmaleimide [44]

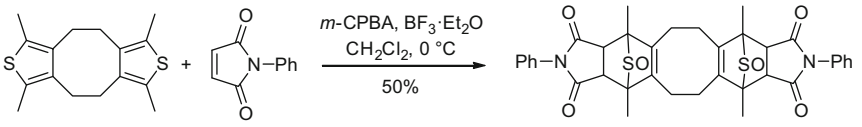


Scheme 34 Oxidative Diels–Alder cycloaddition of thiopheno crown ethers with *N*-phenylmaleimide [44]

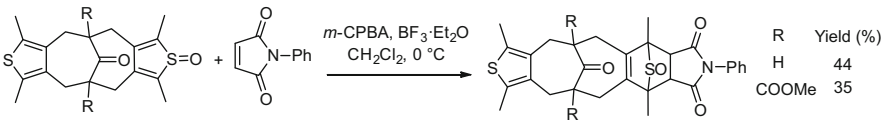
N-phenylmaleimide are shown in Schemes 31, 32, 33, 34, 35, 36, 44, and 45. In Schemes 32 and 34, the resulting S=O bridge is expelled under PTC conditions using $KMnO_4$ as oxidant and tributylbenzylammonium chloride (TBACl) as phase-transfer catalyst (PTC).

Reactions with Allenes

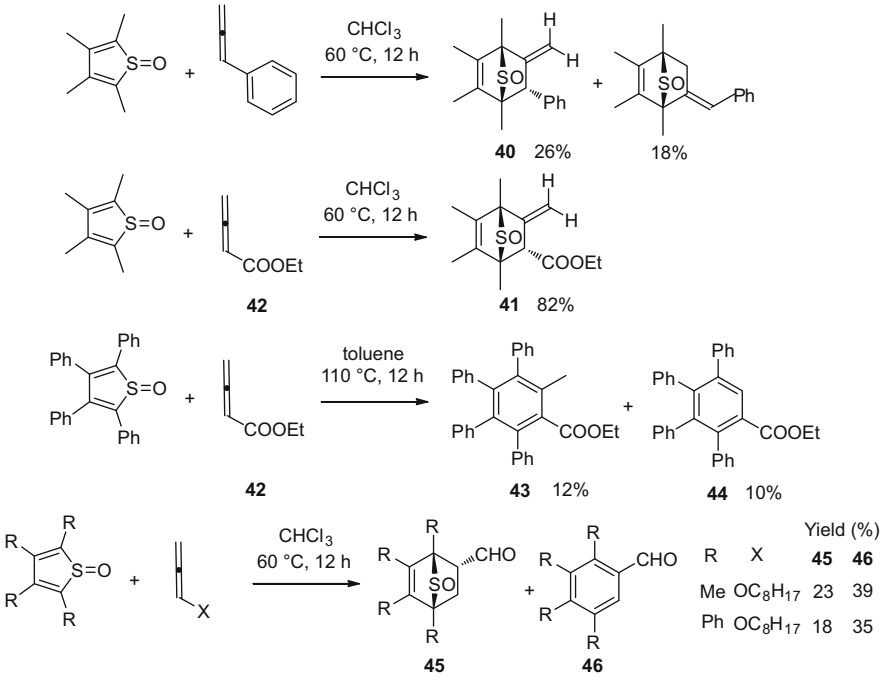
Reactions of tetrasubstituted thiophene 1-oxides with allenes afford thiabicyclo [2.2.1]heptene 1-oxides of types **40** and **41** along with aromatized products but in



Scheme 35 Oxidative Diels–Alder cycloaddition of an orthothiophenophane with *N*-phenylmaleimide [45]

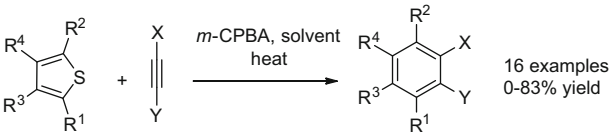


Scheme 36 Oxidative Diels–Alder cycloaddition of an orthothiophenophane with *N*-phenylmaleimide [45]

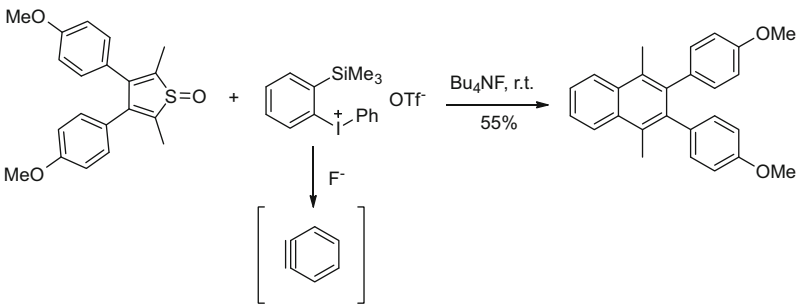


Scheme 37 Diels–Alder cycloaddition reactions of tetrasubstituted thiophene 1-oxides with allenes [47]

low yields. Interestingly, in the reaction of the tetraphenylthiophene 1-oxide with allene **42**, only the aromatized products **43** and **44** could be isolated, indicating that steric and electronic factors are important for the non-selectivity of the sequence (Scheme 37) [46].



Scheme 38 Oxidative cycloaddition of substituted thiophenes with alkynes [46]



Scheme 39 Preparation of 1,4-dimethyl-2,3-bis(*p*-methoxyphenyl)naphthalene through cycloaddition of a thiophene 1-oxide with benzyne [46]

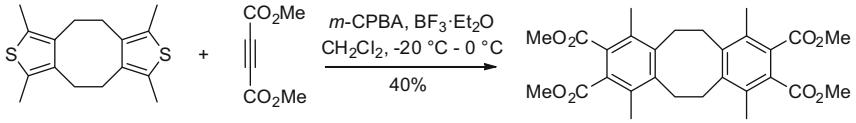
Reactions with Alkynes

The Diels–Alder reactions of a wide range of thiophene 1-oxides with different substituted alkynes under reflux conditions have been studied. It should be noted that some thiophene 1-oxides can react at temperatures as high as 140°C without decomposition, and only traces or very small amounts of deoxygenated products were obtained (Scheme 38). Thiophene 1-oxides can also react with benzyne to give cycloaddition products, for example, as shown in Scheme 39 [46].

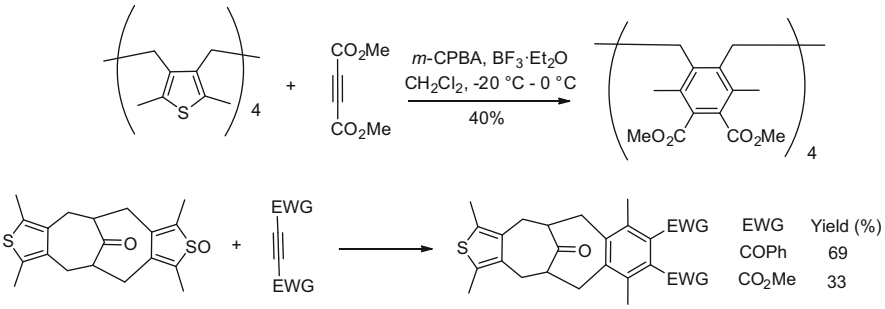
The oxidative Diels–Alder cycloaddition of molecules with multiple thienyl units to alkynes can proceed in the presence of *m*-CPBA/$BF_3 \cdot Et_2O$ complex; the yields can be increased upon the use of $BF_3 \cdot Et_2O$ compared with *m*-CPBA alone, as oxidant. The resulting SO-bridge in these bicyclic subunits can be expelled thermally or oxidatively under PTC conditions at room temperature (Schemes 40, 41, and 42) [16, 45].

Reactions with Sulfur Compounds

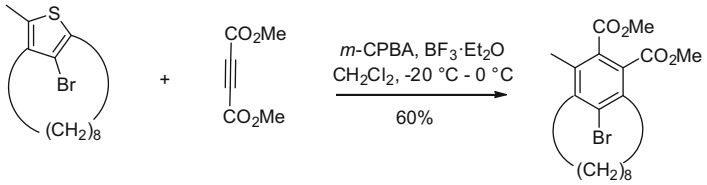
Thiophene 1-oxides can also react with sulfur compounds through Diels–Alder reactions to afford the corresponding sulfur-containing cycloaddition products. For example, disulfur monoxide (S_2O) can undergo a *syn*-π-face-selective Diels–Alder reaction with 3,4-di-*tert*-butylthiophene 1-oxide, leading to the sulfur-containing product **47** (Scheme 43) [47, 48].



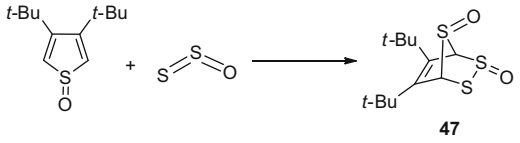
Scheme 40 Oxidative Diels–Alder cycloaddition of a tetramethylorthothiophenophane with dimethyl acetylenedicarboxylate [45]



Scheme 41 Oxidative Diels–Alder cycloaddition of four-thienyl-core cyclophane and an orthothiophenophane 1-oxide with alkynes [45]

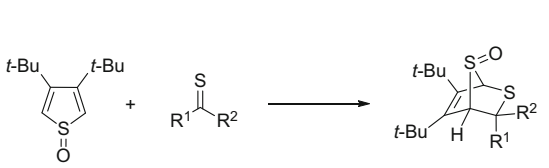


Scheme 42 Oxidative Diels–Alder reaction of 3-bromo-5-methyl[8](2,4)metathiophenophane with dimethyl acetylenedicarboxylate [16]



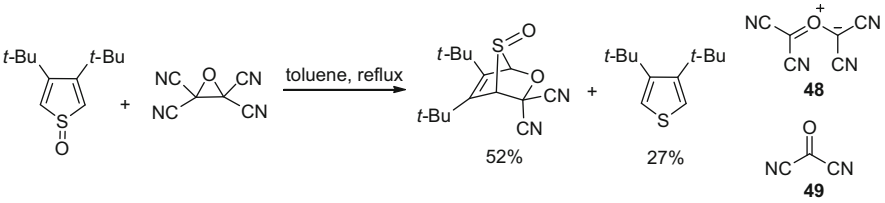
Scheme 43 *Syn*-π-face-selective Diels–Alder cycloaddition of 3,4-di-*tert*-butylthiophene 1-oxide with S_2O [47, 48]

Hetero Diels–Alder reactions of 3,4-di-*tert*-butylthiophene 1-oxide with thioaldehydes and thioketones take place exclusively at the *syn*-π-face with respect to the S=O bond, like the Diels–Alder reactions with ketones. Thiophosgene and adamantanethione can also react with 3,4-di-*tert*-butylthiophene 1-oxide to afford the corresponding *syn*-π-face products (Scheme 44) [49].

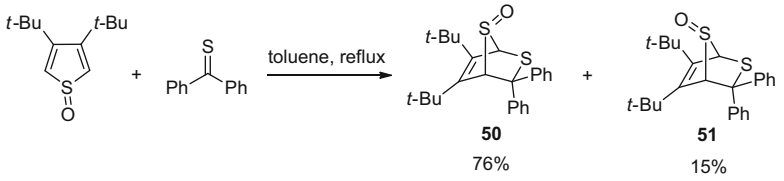


R^1	R^2	Yield (%)
Ph	H	79
Me	H	87
H	H	99
Me	Me	92
Cl	Cl	94
Ph	Ph	76
1-adamantyl		25

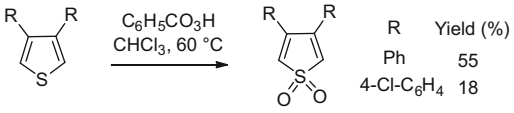
Scheme 44 *Syn*-π-face-selective Diels–Alder cycloaddition of 3,4-di-*tert*-butylthiophene 1-oxide with thioaldehydes and thioketones [49]



Scheme 45 Diels–Alder cycloaddition of 3,4-di-*tert*-butylthiophene 1-oxide with carbonyl cyanide [50]



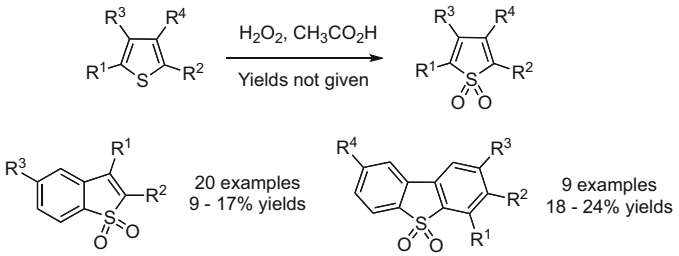
Scheme 46 *Syn*-π-face-selective Diels–Alder cycloaddition of 3,4-di-*tert*-butylthiophene 1-oxide with thiobenzophenone [49]



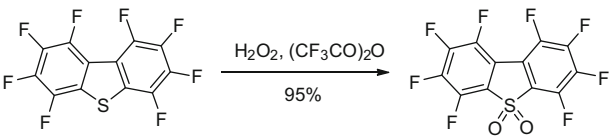
R	Yield (%)
Ph	55
4-Cl-C_6H_4	18

Scheme 47 Oxidation of 3,4-di-(*p*-chlorophenyl)thiophene and 3,4-diphenylthiophene by perbenzoic acid [51]

Tetracyanoethylene oxide can act to oxidize sulfides to sulfoxides but also reduces sulfoxides to sulfides with generation of two molecules of carbonyl cyanide. In its reaction with 3,4-di-*tert*-butylthiophene 1-oxide, the Diels–Alder adduct was found to be the major product, instead of the reduced product 3,4-di-*tert*-butylthiophene, because the reaction proceeded through intermediate **49** instead of **48** (Scheme 45) [50].



Scheme 48 Oxidation of thiophene derivatives by peracetic acid [52–56]



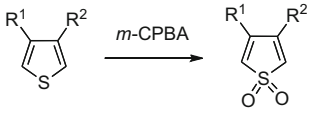
Scheme 49 Oxidation of perfluorodibenzothiophene by trifluoroperacetic acid [57]

Though normally, Diels–Alder reactions of 3,4-di-*tert*-butylthiophene 1-oxide and related compounds occur exclusively at the *syn*-π-face, exceptions have also been observed. For example, in its reaction with thiobenzophenone, two diastereomers **50** and **51** were obtained. The major diastereomer **50** was isolated in 76% yield, but the minor diastereomer **51** was also produced, in 15% yield, the conformation of which was established by X-ray diffraction analysis (Scheme 46). This example reveals that the reaction takes place predominantly at the *syn*-π-face to the S=O bond, though not exclusively. The π-face selectivity was explained in terms of the extent of conformational changes of 3,4-di-*tert*-butylthiophene 1-oxide that are brought about in progressing to the transition state [49].

2.2 Oxidation of Thiophenes to Thiophene 1,1-Dioxides and Their Diels–Alder Reactions

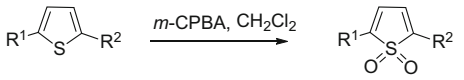
2.2.1 Oxidation of Thiophenes to Thiophene 1,1-Dioxides

Thiophene 1,1-dioxides (thiophene *S*,*S*-dioxides) are compounds of much importance from both synthetic and mechanistic points of view. The two lone pairs of electrons on the sulfur atom of thiophene are replaced by two oxygen atoms making the system no longer aromatic. Oxidation of thiophenes initially affords thiophene 1-oxides, which are further oxidized to give the corresponding thiophene 1,1-dioxides. This strategy is the most convenient way to synthesize thiophene 1,1-dioxides.



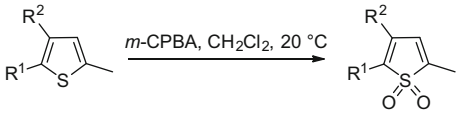
R^1	R^2	Yield (%)
tert-butyl		93
1-adamantyl		79
neopentyl		68
1-adamantyl	*tert*-butyl	80

Scheme 50 Oxidation of 3,4-disubstituted thiophenes with *m*-CPBA [59]



R^1	R^2	Yied (%)
Br	$SiMe_2$-*t*-Bu	59
Br	*n*-Hexyl	37
n-Hexyl	*n*-Hexyl	70
$SiMe_3$	$SiMe_3$	82

Scheme 51 Oxidation of 2,5-disubstituted thiophenes with *m*-CPBA [60–62]



R^1	R^2	Yield (%)
Me	Br	59
Me	$SiMe_3$	79
Me	H	39
Si-*t*-$BuMe_2$	H	74
$SiMe_3$	Br	74
i-Pr	Br	39

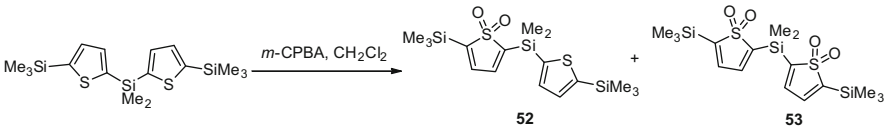
Scheme 52 Oxidation of 2,3,5-trisubstituted thiophenes by *m*-CPBA [63]

Perbenzoic acid was the earliest oxidant for the oxidation of thiophenes to thiophene 1,1-dioxides. Treatment of 3,4-di-(*p*-chlorophenyl)thiophene and 3,4-diphenylthiophene in the presence of perbenzoic acid in chloroform afforded the corresponding thiophene 1,1-dioxides in moderate yields (Scheme 47) [51].

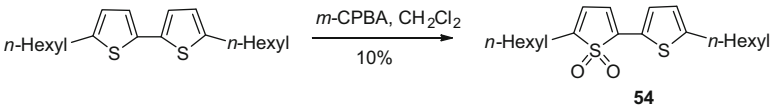
Another oxidizing reagent used in the early stage of thiophene 1,1-dioxides generation is peracetic acid. This oxidation is carried out by using a mixture of aqueous hydrogen peroxide and acetic acid, in which the peracetic acid intermediate is formed. A variety of thiophene derivatives were oxidized to the corresponding thiophene 1,1-dioxides using this method (Scheme 48) [52–56].

Perfluoroacetic acid, which is highly electrophilic, can even oxidize electron-deficient thiophenes such as perfluorodibenzothiophene (Scheme 49) [57] and related thiophenes [58] to thiophene 1,1-dioxides, which proved to be difficult using other oxidizing agents.

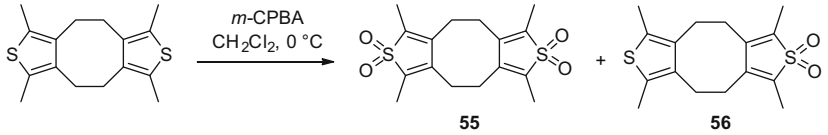
The most frequently used oxidizing reagent is *m*-chloroperbenzoic acid (*m*-CPBA). A great number of thiophenes and their derivatives including 3,4-disubstituted thiophenes (Scheme 50) [59], 2,5-disubstituted thiophenes (Scheme 51) [60–62], and 2,3,5-trisubstituted thiophenes (Scheme 52) [63] were oxidized to the corresponding thiophene 1,1-dioxides successfully.



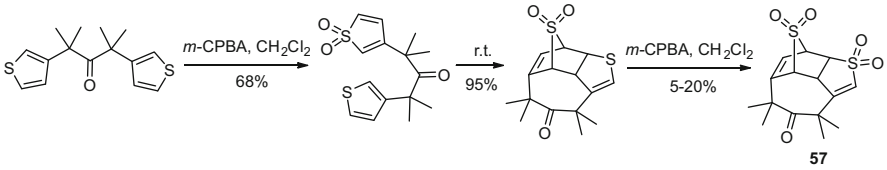
Scheme 53 Oxidation of dimethyl-bis-(5-trimethylsilyl-2-thienyl)silane with *m*-CPBA [64]



Scheme 54 Oxidation of 2,5′-bis(*n*-hexyl)-2,2′-bithiophene with *m*-CPBA [61]



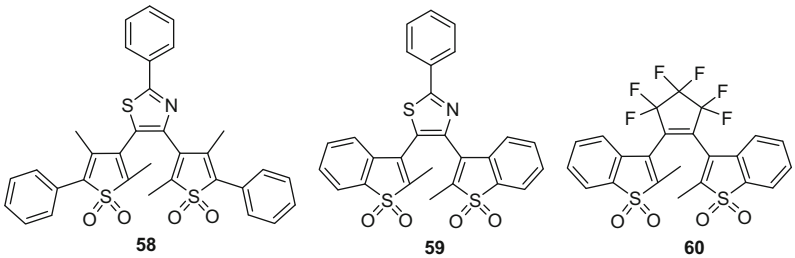
Scheme 55 Oxidation of tetramethylorthothiophenophanes with *m*-CPBA [65]



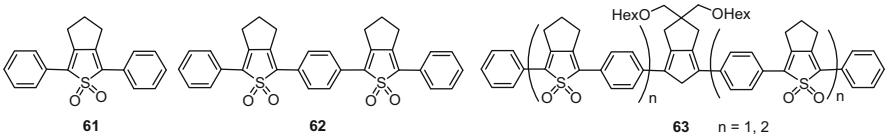
Scheme 56 Oxidation of 2,4-dimethyl-2,4-di(thien-3-yl)pentan-3-one with *m*-CPBA [66]

In the oxidation of dimethyl-bis-(5-trimethylsilyl-2-thienyl)silane, having two thiophene moieties, with one equivalent of *m*-CPBA, one thiophene ring was preferentially oxidized to afford only the mono-sulfone **52** in 36% yield. After further addition of *m*-CPBA, the corresponding mono-sulfone **52** and bis-sulfone **53** were obtained in 21 and 41% yields, respectively (Scheme 53) [64]. In another example, the oxidation of 2,5′-bis(*n*-hexyl)-2,2′-bithiophene was found to be difficult: the monodioxide **54** was obtained in low yield (10%), but no bis-*S*,*S*-dioxide was observed (Scheme 54) [61].

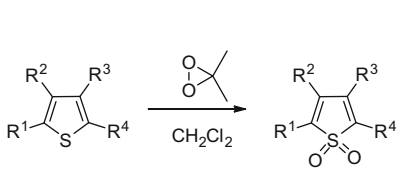
Oxidation of tetramethylorthothiophenophanes with *m*-CPBA gave a mixture of thiophene 1,1-dioxides **55** and **56** in a ratio depending on the amount of *m*-CPBA used (Scheme 55) [65]. The thiophene 1,1-dioxide **57** could also be easily obtained using this oxidant (Scheme 56) [66]. Application of this method produced novel photochromic compounds **58**–**60**, having relatively high fluorescence efficiencies (Scheme 57) [67], as well as the precursors **61**–**63** for electron-transporting materials (Scheme 58) [68].



Scheme 57 High fluorescence compounds produced using *m*-CPBA [67]



Scheme 58 Thiophene 1,1-dioxide oligomers and polymers produced using *m*-CPBA [68]



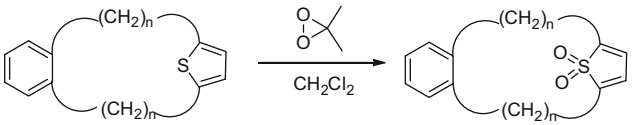
R^1	R^2	R^3	R^4	Yield (%)
H	H	H	H	99
CH_3	H	H	CH_3	93
CH_2Ph	H	H	CH_2Ph	93
Br	H	H	Br	27
COPh	Ph	Ph	COPh	76
$COCH_3$	H	H	$COCH_3$	53

Scheme 59 Oxidation of tetrasubstituted thiophenes by dimethyldioxirane (DMD) [69]

Dimethyldioxirane (DMD) is a useful reagent for oxidation of thiophenes to thiophene 1,1-dioxides, applicable to electron-rich thiophene derivatives, including sterically hindered thiophenophanes. For thiophenes with electron-withdrawing groups, which resist oxidation, dimethyldioxirane (DMD) is superior to other reagents such as *m*-CPBA and peracetic acid (Scheme 59) [69]. Similarly, orthothiophenophanes were converted into corresponding thiophene 1,1-dioxides **64** in good yields (Scheme 60) [70].

Inorganic oxidizing reagents have also been used frequently. Among these reagents, HOF · MeCN complex has shown its superiority (Scheme 61) [71]. This complex, made directly by bubbling fluorine through aqueous MeCN at −15°C, will oxidize various types of thiophenes to the corresponding thiophene 1,1-dioxides, including those which could not be oxidized by any other oxidant [72].

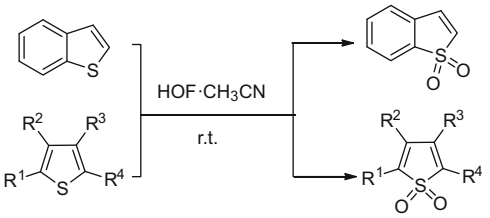
Comparison of the traditional oxidants with HOF · MeCN for various thiophene derivatives showed that the latter quickly converts them into the corresponding thiophene 1,1-dioxides in a few minutes with high yields, while traditional oxidants, e.g., *m*-CPBA, required hours or several days [73]. For some thiophene derivatives, HOF · MeCN complex is the only way to fully oxidize thiophenes to



n	Yield (%)
3	63
4	93

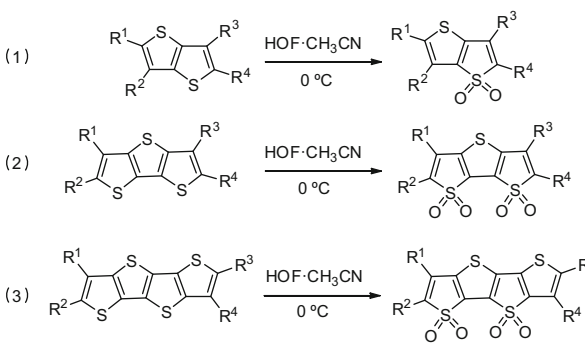
64

Scheme 60 Oxidation of orthothiophenophanes by dimethyldioxirane (DMD) [70]



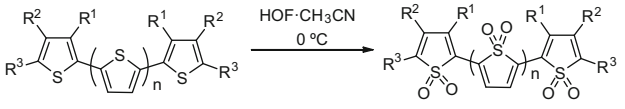
R^1	R^2	R^3	R^4	Yield (%)
Me	H	H	Me	95
Br	H	H	Br	95
Cl	H	H	Cl	70
Me	H	H	CO_2Et	90
Br	H	$C_{12}H_{25}$	Br	72
Br	H	CH_3	Br	76

Scheme 61 Oxidation of a wide variety of substituted thiophene derivatives by HOF · MeCN [71]



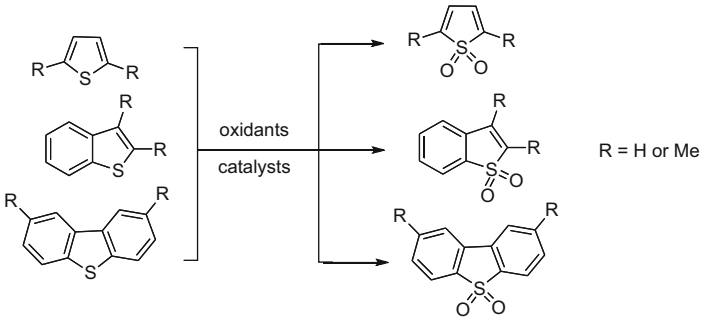
	R^1	R^2	R^3	R^4	Yield (%)
(1)	Br	Br	Br	Br	90
	H	Br	$(CH_2)_8CH_3$	H	85
	H	Br	$(CH_2)_8CH_3$	CO_2Et	70
(2)	H	Me	H	Me	45
	H	*t*-Bu	H	*t*-Bu	25
	H	CO_2Et	H	CO_2Et	0
(3)	CO_2Et	H	H	CO_2Et	83%

Scheme 62 Oxidation of fused oligothiophenes by HOF · MeCN [74]



R^1	R^2	R^3	n	Yield (%)
H	C_6H_{13}	Br	0	78
H	$C_{12}H_{25}$	Br	0	84
C_6H_{13}	H	Br	1	65
$C_{12}H_{25}$	H	Br	1	60
C_6H_{13}	H	C_6H_{13}	2	40

Scheme 63 Synthesis of oligothiophene-[all]-*S*,*S*-dioxides using HOF · MeCN as oxidant [6, 75, 76]



Scheme 64 Application of H_2O_2/catalyst systems in oxidative desulfurization (ODS) [5, 77–84]

thiophene 1,1-dioxides, one use for which is as precursors to prepare photoelectric materials (Schemes 62 and 63).

Much attention has been paid to the oxidative desulfurization (ODS) process, which can be carried out under very mild conditions for removing the sulfur compounds in light oil, of which many are thiophene derivatives. The oxidative desulfurization is usually carried out using stoichiometric H_2O_2 as oxidant accompanied by catalysts or acids; the resulting sulfones can be removed by polar extractants. The reagent combinations such as $H_2O_2/[(C_{18}H_{37})_2\ N^+(CH_3)_2]_3[PW_{12}O_{40}]$ [77], $H_2O_2/(NH_4)_2WO_4$/[Hnmp]BF_4 [78], $H_2O_2/NaWO_4$ [79], H_2O_2/(Cu/titanium silicate-1) [5], H_2O_2/CH_3ReO_3 [80], H_2O_2/[bmim]Cl/$FeCl_3$ [81], H_2O_2/[bmim]BF_4 [82], $H_2O_2/MoAl_2O_3$ [83], and $H_2O_2/WO(O_2)_2 \cdot Phen \cdot H_2O$ [84] have been used (Scheme 64).

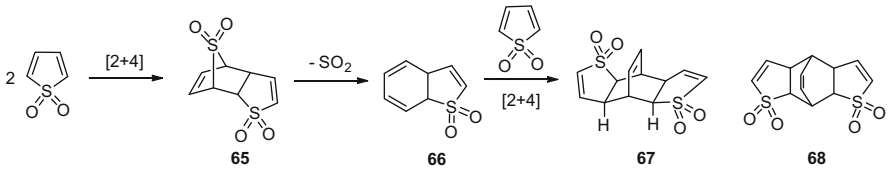
2.2.2 Diels–Alder Reactions of Thiophene 1,1-Dioxides

Diels–Alder reactions of thiophene 1,1-dioxides have been reviewed [85]; however, recent, and/or otherwise significant, examples of the applications of this reaction are discussed here.

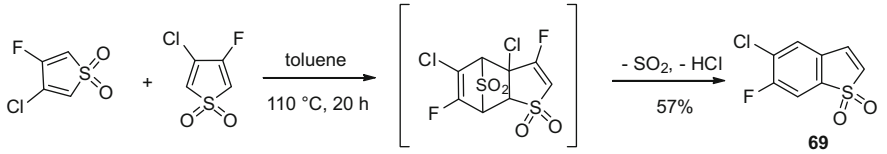
[2+4] Cyclodimerization

Thiophene 1,1-dioxides can undergo cyclodimerization via two distinct pathways. Many monocyclic thiophene 1,1-dioxides, which are thermally labile, undergo [2+4] cyclodimerization, while thermally stable thiophene 1,1-dioxides, particularly benzo [*b*]thiophene 1,1-dioxide and its derivatives, undergo [2+2] cyclodimerization upon photoirradiation. Herein, typical Diels–Alder [2+4] cyclodimerization is discussed.

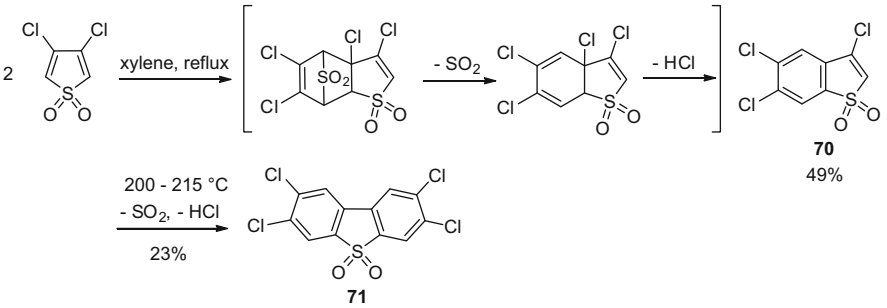
Thiophene 1,1-dioxide itself undergoes [2+4] dimerization to form dimeric product **66** with spontaneous loss of a SO_2 from the initial adduct **65** in highly dilute solution, and with increasing concentration, trimerization begins to occur, ^{13}C NMR spectroscopy showing that the trimer is **67** rather than **68** (Scheme 65) [70, 86, 87].



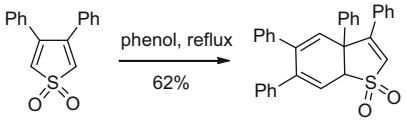
Scheme 65 [2+4] dimerization of thiophene 1,1-dioxide [60, 86, 87]



Scheme 66 Dimerization of 3-chloro-4-fluorothiophene 1,1-dioxide [88]

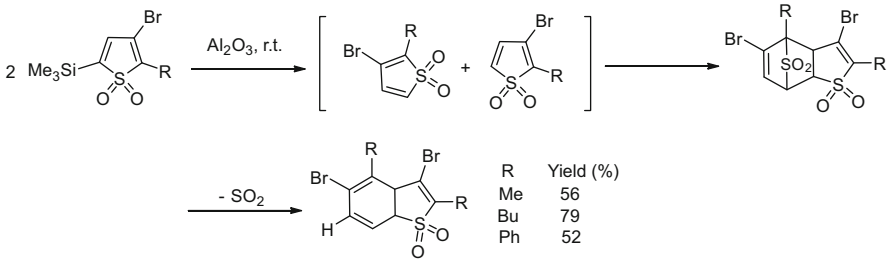


Scheme 67 Dimerization of 3,4-dichlorothiophene 1,1-dioxide [89]

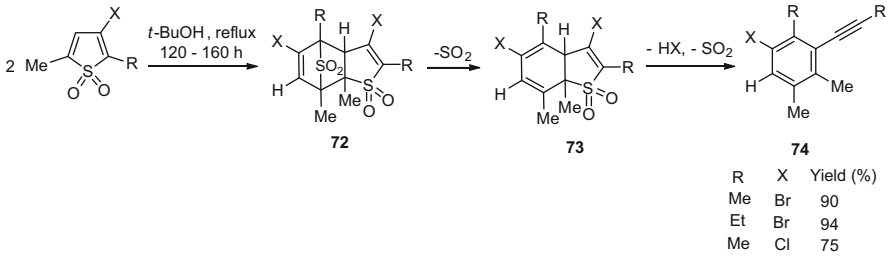


Scheme 68 Dimerization of 3,4-diphenylthiophene 1,1-dioxide [90]

Thermal stability of thiophene 1,1-dioxides increases with more substituents on the thiophene ring. For example, dimerization of 3-chloro-4-fluorothiophene 1,1-dioxide required heating in refluxing toluene for 20 h to give aromatic product **69** in 57% yield with release of one molecule of SO_2 and one molecule of HCl (Scheme 66) [88]. Similarly, the dimerization conditions for 3,4-dichlorothiophene 1,1-dioxide were also very harsh, and a mixture of products **70** and **71** was obtained. It should be noted that **71** could also be prepared from **70**, though the conditions were even harsher – reflux at 200–215°C (Scheme 67) [89].



Scheme 69 Dimerization of a trimethylsilyl-substituted thiophene 1,1-dioxides accompanied by desilylation [91]



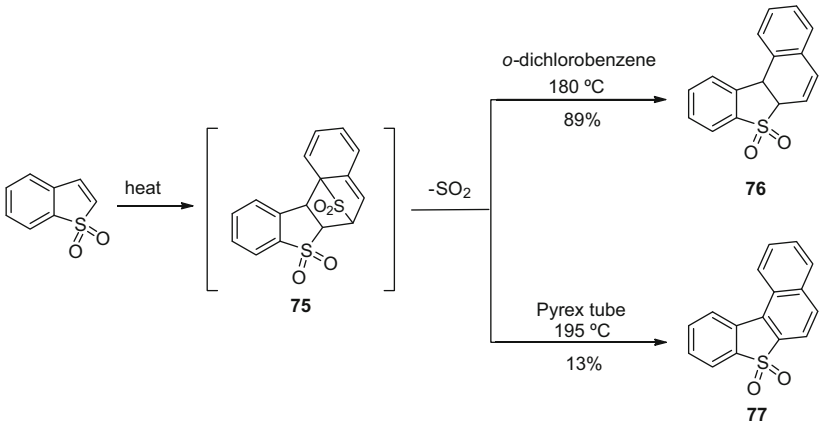
Scheme 70 Preparation of pentasubstituted-phenyl alkynes via dimerization of 2,3,5-trisubstituted thiophene 1,1-dioxides [92]

For more thermally stable thiophene derivatives such as 3,4-diphenylthiophene 1,1-dioxide, the dimerization requires more forcing conditions (Scheme 68) [90].

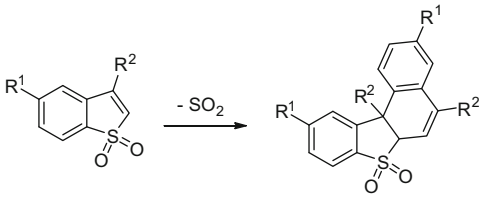
For a trimethylsilyl-substituted thiophene 1,1-dioxide, desilylation can take place in the presence of Al_2O_3 at room temperature, then dimerization and spontaneous loss of SO_2 give the product in 56% yield. Similar reactions of 3-bromo-2-butyl-5-trimethylsilylthiophene 1,1-dioxide and 3-bromo-2-phenyl-5-trimethylsilylthiophene 1,1-dioxide afford the corresponding products in moderate yields (Scheme 69) [91].

Interestingly, tandem cycloaddition and ring opening occur on heating 2,5-dialkyl-3-halothiophene 1,1-dioxides in refluxing *t*-BuOH for a prolonged period, affording a new short route to unsymmetrically pentasubstituted-phenyl alkynes **74** with spontaneous loss of SO_2 and HX (X=Cl, Br) from the adduct **73**, which was formed from the initial adduct **72** with the elimination of a SO_2 (Scheme 70) [92].

Even benzo[*b*]thiophene 1,1-dioxide and its derivatives of higher stability can undergo [2+4] dimerization under harsh conditions. For example, benzo[*b*]thiophene 1,1-dioxide dimerizes under forcing conditions to produce the unstable adduct **75**, which loses sulfur dioxide to give product **76** or **77**, depending upon the reaction conditions. This work clearly reveals the stabilizing effect of the benzene ring on the thiophene 1,1-dioxide ring (Scheme 71) [93–96]. Other typical examples are shown in Schemes 72 and 73.

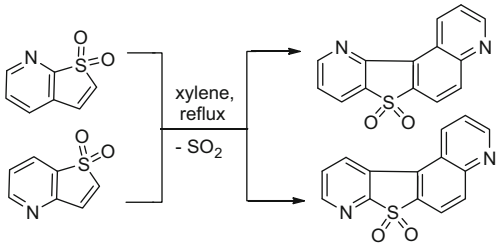


Scheme 71 Dimerization of benzo[*b*]thiophene 1,1-dioxide [93–96]



R^1	R^2	Condition	Yield (%)
Br	H	*o*-dichlorobenzene 180 °C	Not given
H	Br	Pyrex tube 290 - 300 °C	46
H	Cl	1-bromonaphthalene Pyrex tube, 280 °C	75

Scheme 72 Dimerization of 4-nitrobenzo[*b*]thiophene 1,1-dioxide and 5-bromobenzo[*b*]thiophene 1,1-dioxide [95]

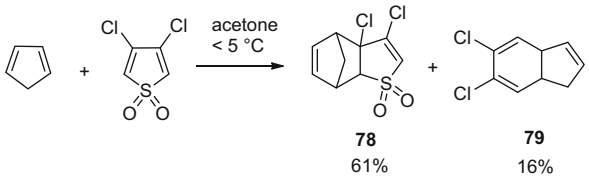


Scheme 73 Dimerization of thieno[2,3-*b*]pyridine 1,1-dioxide and thieno[3,2-*b*]pyridine 1,1-dioxide [97]

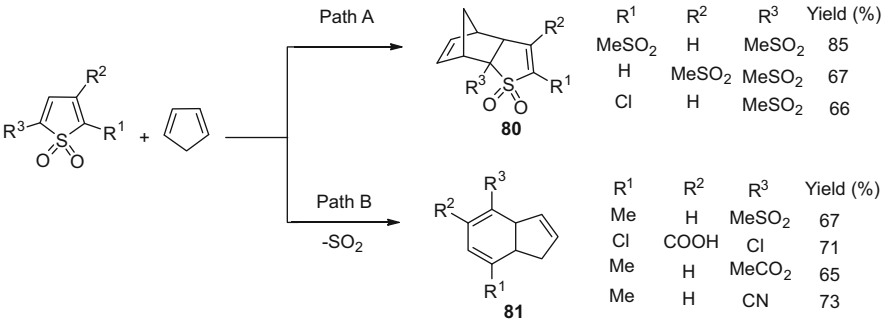
[2+4] Cycloaddition (Thiophene 1,1-Dioxides as 2π Components)

Under normal conditions, monocyclic thiophene 1,1-dioxides undergo Diels–Alder reactions acting as a diene (4π component); however, in some cases, thiophene 1,1-dioxides behave as a dienophile toward dienes.

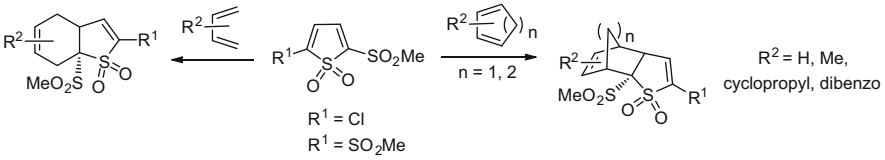
When 3,4-dichlorothiophene 1,1-dioxide is reacted with cyclopentadiene, two types of 1:1 adducts (exclusive of *exo-endo* isomerism) can result. Apart from the



Scheme 74 [2+4] and [4+2] cycloaddition of 3,4-dichlorothiophene 1,1-dioxide with cyclopentadiene [89]



Scheme 75 Cycloaddition of thiophene 1,1-dioxides act as a dual reactant with cyclopentadiene [98]



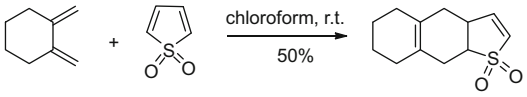
Scheme 76 [2+4] cycloaddition of 2-chloro-5-methylsulfonylthiophene 1,1-dioxide and 2,5-bis (methylsulfonyl) thiophene 1,1-dioxide with butadiene derivatives or cyclic dienes [99]

normal cycloaddition product **79**, adduct **78** is generated as well, in which 3,4-dichlorothiophene 1,1-dioxide served as a 2π component (Scheme 74) [89].

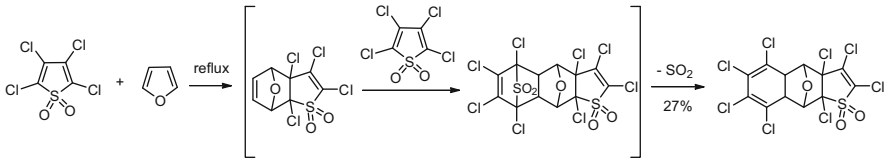
An interesting phenomenon emerged in the Diels–Alder reaction of thiophene 1,1-dioxides with two strong electron-withdrawing groups (EWG) with cyclopentadiene to give [2+4] cycloadducts **80**. In contrast, thiophene-1,1-dioxides with one EWG behave as dienes in an inverse electron-demand Diels–Alder reaction yielding dihydro-1*H*-indene derivatives **81** (Scheme 75). MP2 calculations successfully rationalized the contrasting regioselectivities of these cycloaddition reactions [98].

2-Chloro-5-methylsulfonyl-thiophene 1,1-dioxide or 2,5-bis(methylsulfonyl) thiophene 1,1-dioxide served as a 2π component when reacted with a series of butadiene derivatives or cyclic dienes (Scheme 76) [99].

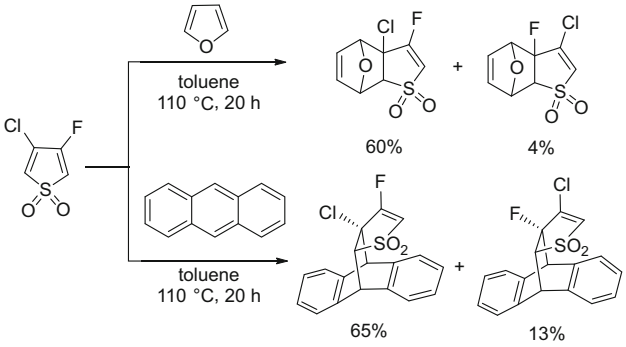
1,2-Bis(methylene)cyclohexane (Scheme 77) [100], furan (Schemes 78 and 79) [101], and anthracene (Scheme 79) [88] can also serve as 4π components when



Scheme 77 [2+4] cycloaddition of thiophene 1,1-dioxide with 1,2-bis(methylene)cyclohexane [100]



Scheme 78 [2+4] cycloaddition of tetrachlorothiophene 1,1-dioxide with furan [101]



Scheme 79 [2+4] cycloaddition of 3-chloro-4-fluorothiophene 1,1-dioxide with furan and anthracene [88]

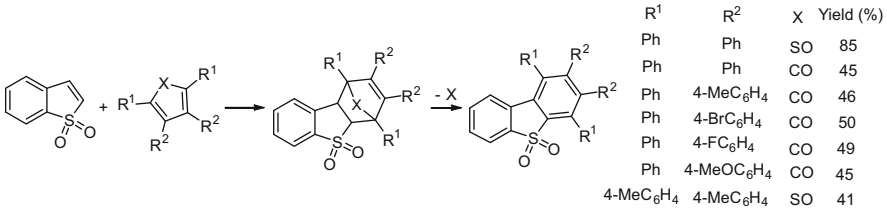
undergoing Diels–Alder reactions with thiophene 1,1-dioxides, affording the corresponding cycloaddition products in good yields.

Benzo[*b*]thiophene 1,1-dioxide or its substituted derivatives can also serve as 2π components in [4+2] cycloaddition reactions. Typical examples are shown below (Schemes 80 and 81).

[4+2] Cycloaddition (Thiophene 1,1-Dioxides as 4π Component)

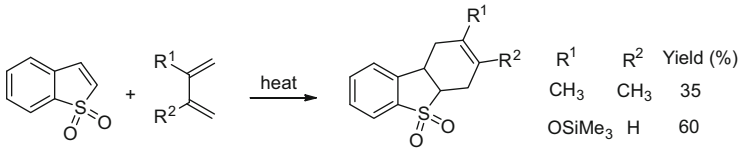
[4+2] Cycloaddition with Alkenic Dienophiles

Category A: *1,3-Cyclohexadiene-Forming Reactions*. Diels–Alder reactions of thiophene 1,1-dioxides and their derivatives usually lead to 1,3-cyclohexadiene derivatives with spontaneous loss of sulfur dioxide from the initial adducts. This type of reaction has been most extensively examined with tetrachlorothiophene 1,1-dioxide. A large variety of olefinic compounds reacted with tetrachlorothiophene 1,1-dioxide to form 1,2,3,4-tetrachloro-1,3-cyclohexadiene derivatives



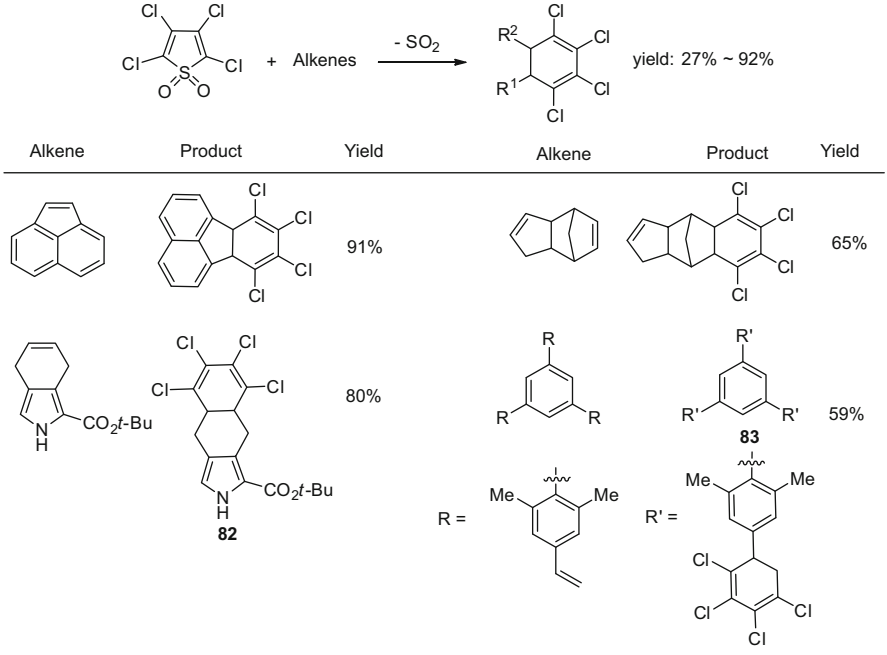
R^1	R^2	X	Yield (%)
Ph	Ph	SO	85
Ph	Ph	CO	45
Ph	4-MeC_6H_4	CO	46
Ph	4-BrC_6H_4	CO	50
Ph	4-FC_6H_4	CO	49
Ph	4-$MeOC_6H_4$	CO	45
4-MeC_6H_4	4-MeC_6H_4	SO	41

Scheme 80 [2+4] cycloaddition of benzo[*b*]thiophene 1,1-dioxide with thiophene 1-oxides and cyclopenta-2,4-dien-1-ones [102]

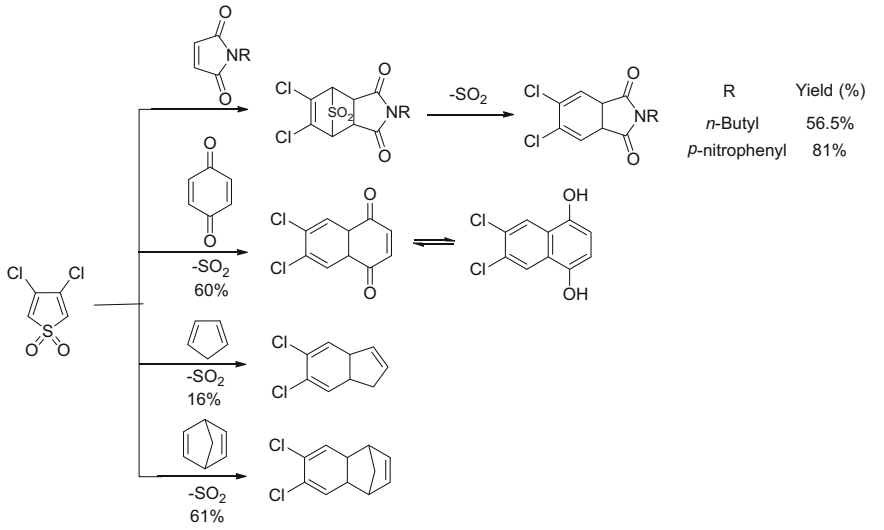


R^1	R^2	Yield (%)
CH_3	CH_3	35
$OSiMe_3$	H	60

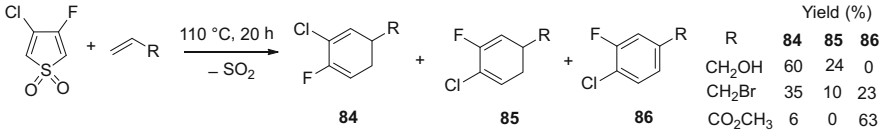
Scheme 81 [2+4] cycloaddition of benzo[*b*]thiophene 1,1-dioxide with 1,3-dienes [102]



Scheme 82 [4+2] cycloaddition of tetrachlorothiophene 1,1-dioxides with various olefinic compounds [103–108]



Scheme 83 Preparation of 1,3-cyclohexadiene derivatives from 3,4-dichlorothiophene 1,1-dioxide by [4+2] Diels–Alder cycloaddition [89]

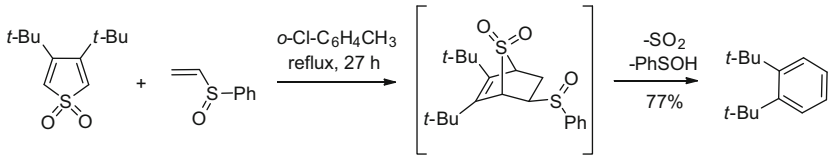


Scheme 84 Diels–Alder cycloaddition of 3-chloro-4-fluorothiophene 1,1-dioxide with alkenes [88]

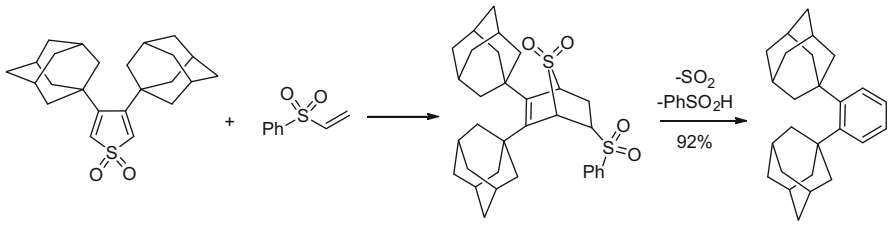
[103], and applications of this reaction were later reported by many other groups [104–106]. Typical applications of this reaction affording new compounds including a polychloro-substituted tetranaphthoporphyrin derived from **82** [107] and a hypothetical deciphenyl derived from **83** [108] (Scheme 82). Hypothetical deciphenyl is a $C_{60}H_{36}$-spheriphane, which has been envisaged as a potential precursor to C_{60}-fullerene.

3,4-Dichlorothiophene 1,1-dioxide can also react with olefinic compounds affording 1,3-cyclohexadiene derivatives in good yields (Scheme 83) [89].

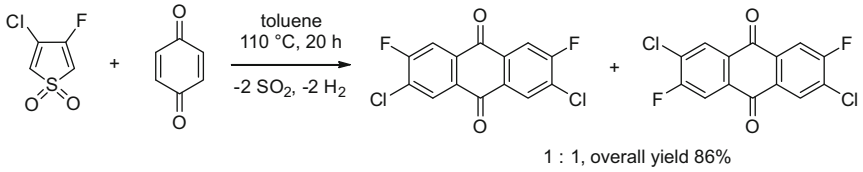
The reaction of 3-chloro-4-fluorothiophene 1,1-dioxide with simple alkenes proceeded with low regioselectivity; thus, a mixture of isomeric cyclohexadienes **84** and **85** was obtained, and when R=CH_2Br a considerable amount of aromatic compound **86** was also formed. It is likely that the aromatic products are formed as the result of slow thermal dehydrogenation of initially formed adducts, and the rate of dehydrogenation increases in the presence of electron-withdrawing substituents; thus, **86** was obtained as the main product when the alkene was methyl acrylate (Scheme 84) [88].



Scheme 85 Synthesis of 1,2-di-*tert*-butylbenzene from 3,4-di-*tert*-butylthiophene 1,1-dioxide with phenyl vinyl sulfone [109, 110]



Scheme 86 Synthesis of *o*-di-(1-adamantyl)benzene via Diels–Alder cycloaddition of 3,4-di-(1-adamantyl)thiophene 1,1-dioxide with phenyl vinyl sulfone [59]

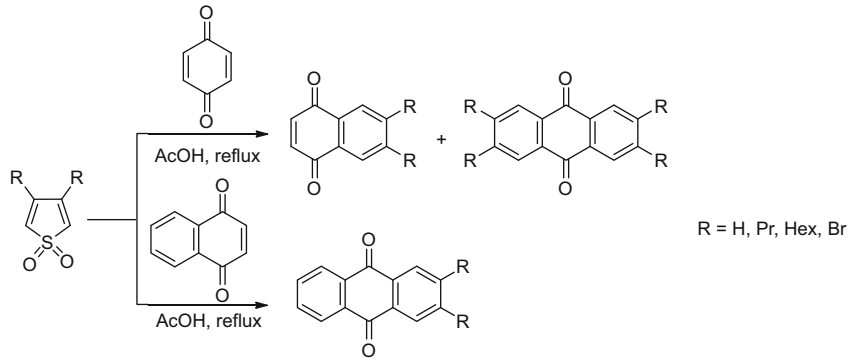


Scheme 87 Cycloaddition of 3-chloro-4-fluorothiophene 1,1-dioxide with 1,4-benzoquinone [88]

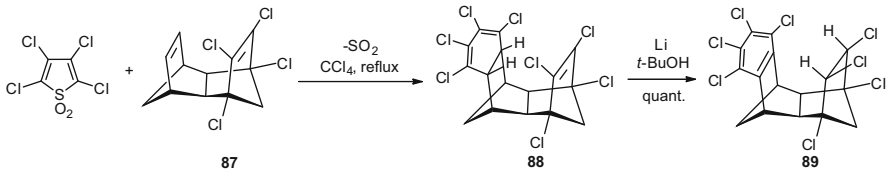
Category B: *Benzene Ring-Forming Reactions by Removal of a Small Molecule*. Cycloaddition of thiophene 1,1-dioxides with alkenic dienophiles often leads directly to the formation of a benzene ring by expulsion of a small molecule such as sulfur dioxide from the initial adducts. For example, 3,4-disubstituted thiophene 1,1-dioxides with bulky groups (Schemes 85 and 86) react with alkenic dienophiles such as phenyl vinyl sulfone followed by expulsion of a sulfur dioxide to afford the corresponding highly congested benzene ring products in high yields, which are difficult to prepare using other methods [109, 110].

3,4-Disubstituted thiophene 1,1-dioxides react with 1,4-benzoquinone or 1,4-naphthoquinone through Diels–Alder reactions followed by the loss of sulfur dioxide and oxidation, usually resulting in anthraquinone derivatives (Schemes 87 and 88).

The reaction of tetrachlorothiophene 1,1-dioxide with a dienophile **87** affords the primary product **88** in a stereospecific manner. In **88**, the cyclohexadiene ring protons are placed in close proximity to the double bond of the other ring. Upon dehalogenation of **88** with lithium/*tert*-butyl alcohol, the double bond is regenerated to give **89**, accompanied by a stereospecific hydrogen atom transfer.



Scheme 88 Diels–Alder cycloaddition of 3,4-disubstituted thiophene 1,1-dioxides with 1,4-benzoquinone or 1,4-naphthoquinone [111–113]



Scheme 89 Diels–Alder cycloaddition of tetrachlorothiophene 1,1-dioxide with a dienophile [114]

This Diels–Alder cycloadduct is a precursor of $C_{20}H_{20}$ [1.1.1.1]pagodane and variously substituted derivatives (Scheme 89) [114].

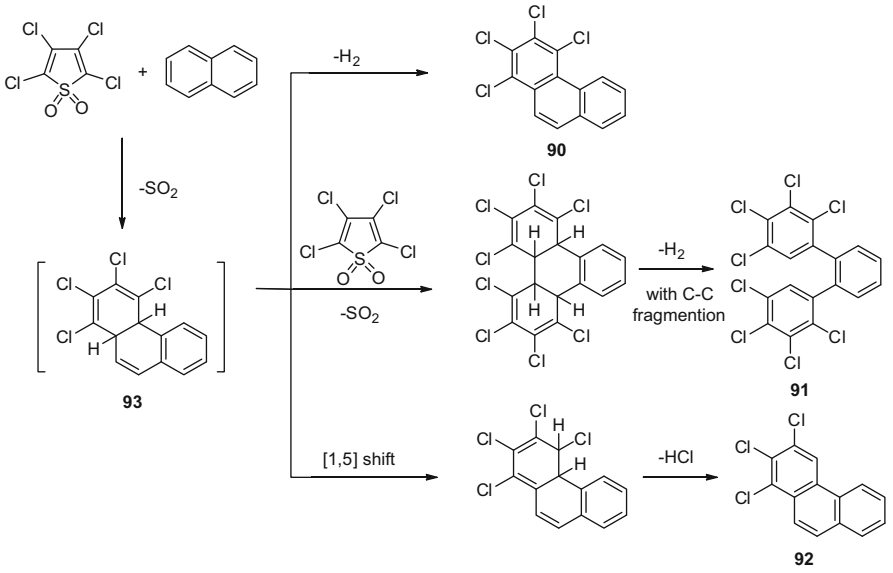
The reaction of tetrachlorothiophene 1,1-dioxide with naphthalene at 165–170°C gave a mixture of adducts **90–92**, because the first intermediate **93** can proceed via three pathways as shown in Scheme 90 [115].

Category C: *Benzene Ring-Forming Reactions by Ring Opening of Initial Adducts*. Halogenated thiophene 1,1-dioxides undergo addition–rearrangement reactions with furans to form halobenzyl carbonyl compounds. A variety of furan derivatives have been employed to give the halogenated benzyl ketones but not furan itself. More interestingly, 1:2 *cis*-:*trans*-2,5-dihydro-2,5-dimethoxyfuran **94** functioned like 2-methoxyfuran by loss of methanol in the reaction mixture, and methyl (2,3,4,5-tetrachlorophenyl)acetate **95** was produced in 51% yield (Scheme 91) [101].

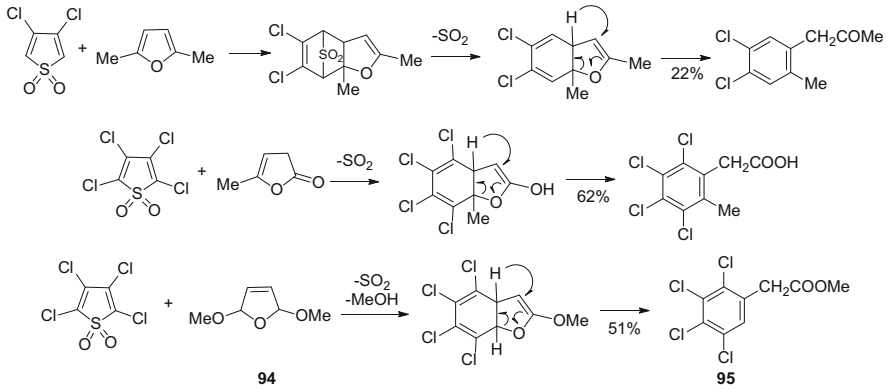
The reaction of 3,4-di-*tert*-butylthiophene 1,1-dioxide with 2,5-dimethylfuran gave a tetrasubstituted benzene **96** in 51% yield (Scheme 92) [109].

The observed 100% regiochemistry of the addition of 2-methylfuran and methyl furan-2-carboxylate to all thiophene 1,1-dioxides was explained in terms of the frontier orbital theory using the calculated orbital coefficients (Scheme 93) [116].

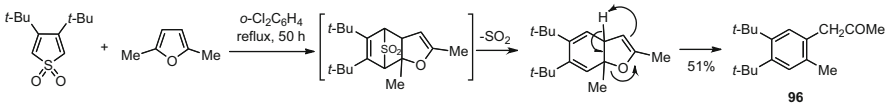
Category D: *Seven- and Eight-Membered Ring-Forming Reactions*. 2-Bromo-6-chlorocycloheptatriene was synthesized via cycloaddition of 1-bromo-2-chloro-cyclopropene to thiophene 1,1-dioxide and release of SO_2 from the adduct **97**,



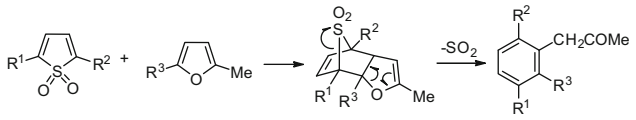
Scheme 90 Diels–Alder cycloaddition of tetrachlorothiophene 1,1-dioxide with naphthalene and further transformations [115]



Scheme 91 Addition–rearrangement reactions of furan derivatives with halogenated thiophene 1,1-dioxides [101]

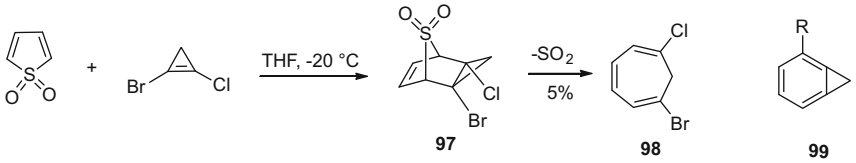


Scheme 92 Addition–rearrangement reactions of 3,4-di-*tert*-butylthiophene 1,1-dioxide with 2,5-dimethylfuran [109]

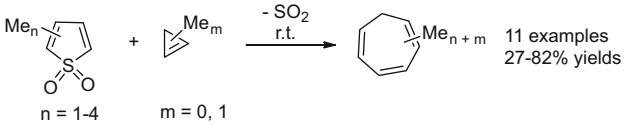


R^1	R^2	R^3	Yield (%)
Cl	Cl	H	91
Cl	SO_2Me	H	81
Br	SO_2Me	H	70
Br	CO_2Me	H	88
Me	SO_2Me	H	95
SO_2Me	SO_2Me	H	96
SO_2Me	SO_2Me	Me	93

Scheme 93 Addition–rearrangement reactions of 2,5-disubstituted thiophene 1,1-dioxides with 2,5-disubstituted furans [116]



Scheme 94 Preparation of dihalogeno-cycloheptatrienes from cycloaddition of 1-bromo-2-chlorocyclopropene to thiophene 1,1-dioxide [117]



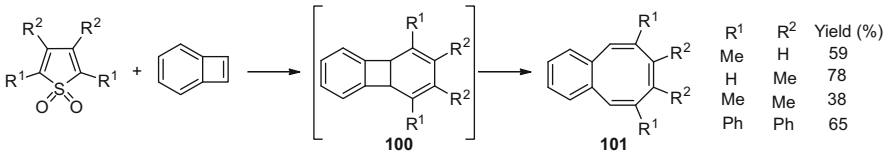
Scheme 95 Preparation of methylated cycloheptatrienes from methylated cyclopropenes and thiophene 1,1-dioxide [118]

thus providing access to dihalogeno-cycloheptatrienes **98** without generating the often undesirable cyclopropanes **99** (Scheme 94) [117].

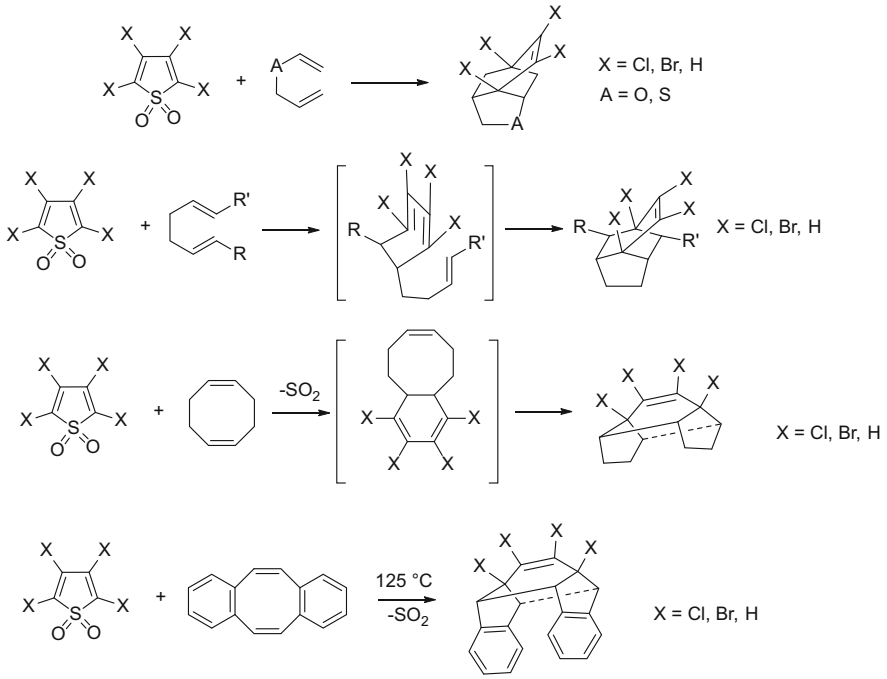
Methylated cycloheptatrienes were prepared by cycloaddition of methyl-cyclopropenes and thiophene 1,1-dioxides after expulsion of SO_2; the resulting cycloheptatrienes could be used to synthesize tropylium ions (Scheme 95) [118].

Benzocyclobutene reacted with thiophene 1,1-dioxides at a relatively mild temperature to give the corresponding benzocyclo-octenes **101** in acceptable yields. For example 2,5-dimethyl-, 3,4-dimethyl-, 2,3,4,5-tetramethyl-, and 2,3,4,5-tetraphenylthiophene 1,1-dioxides gave the corresponding products in 38–78% yields. Elimination of sulfur dioxide took place under the reaction conditions, but the initial adducts **100** were not observed (Scheme 96) [119].

Category E: *[4+2] Cycloaddition Followed by Intermolecular [4+2] Cycloaddition*. 3,4-Dichloro-, tetrabromo-, and tetrachlorothiophene 1,1-dioxides react with a range of cyclic and acyclic non-conjugated dienes to give polycyclic compounds in good yields by [4+2] intermolecular cycloaddition followed by intramolecular [4+2] cycloaddition (Scheme 97) [103].



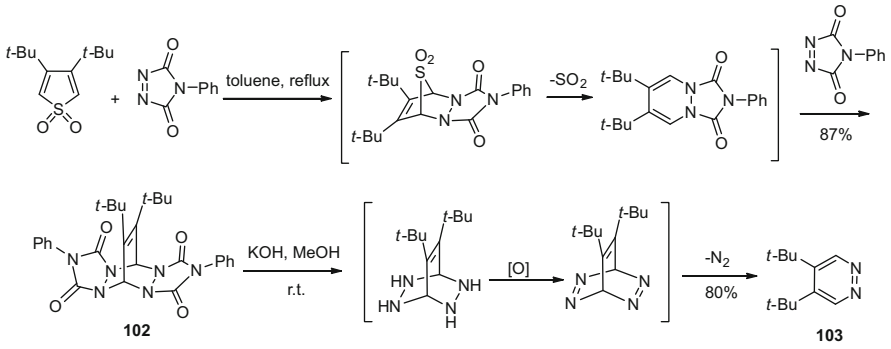
Scheme 96 Synthesis of benzocyclo-octenes through Diels–Alder cycloaddition of benzocyclobutene with thiophene 1,1-dioxides [119]



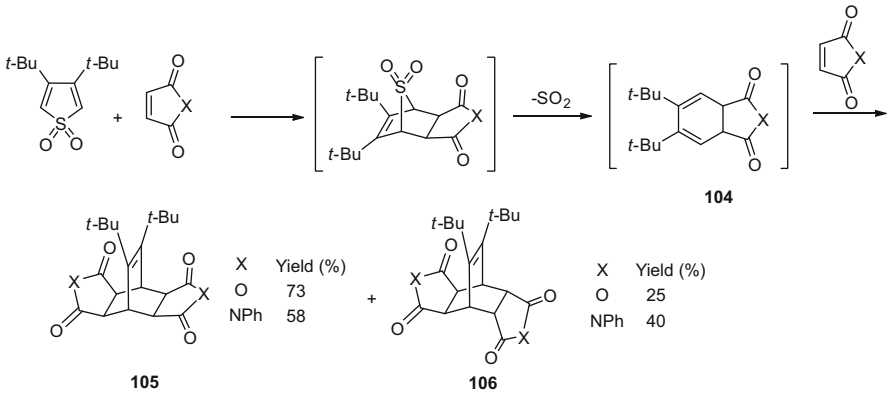
Scheme 97 [4+2] intermolecular Diels–Alder cycloaddition followed by intramolecular [4+2] cycloaddition of 3,4-dichloro-, tetrabromo-, and tetrachlorothiophene 1,1-dioxides with cyclic and acyclic non-conjugated dienes [103]

Category F: *Bis-Adduct Formation*. The primary adducts, cyclohexadiene derivatives, which are formed by Diels–Alder cycloaddition of thiophene 1,1-dioxides with dienophiles upon the loss of a SO_2, may undergo further Diels–Alder cycloaddition with the dienophile. Thus, the reaction of 3,4-di-*tert*-butylthiophene 1,1-dioxide with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) provides a unique pyridazine synthetic route since the bis-adducts **102** are converted into the corresponding pyridazine **103** in one pot and in good yield by treatment with KOH in methanol (Scheme 98) [120].

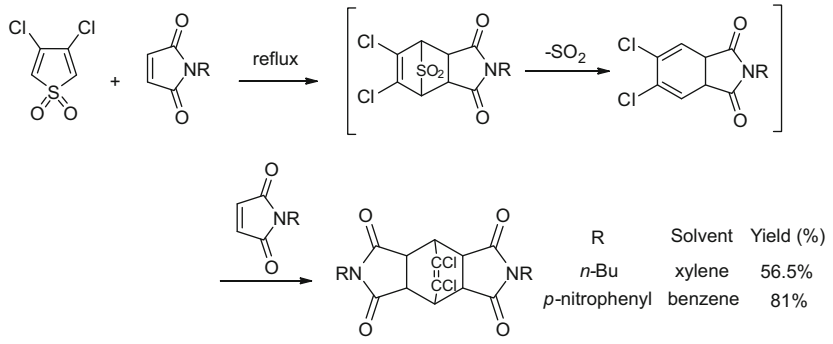
The reaction of 3,4-di-*tert*-butylthiophene 1,1-dioxide with two equivalents of *N*-phenylmaleimide or maleic anhydride afforded two major isomeric bis-adducts



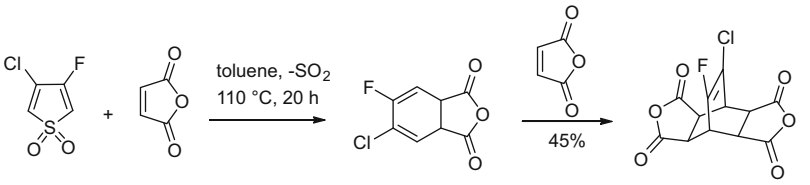
Scheme 98 Synthesis of 4,5-di-*t*-butylpyridazine through Diels–Alder cycloaddition of 3,4-di-*tert*-butylthiophene 1,1-dioxide with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) [120]



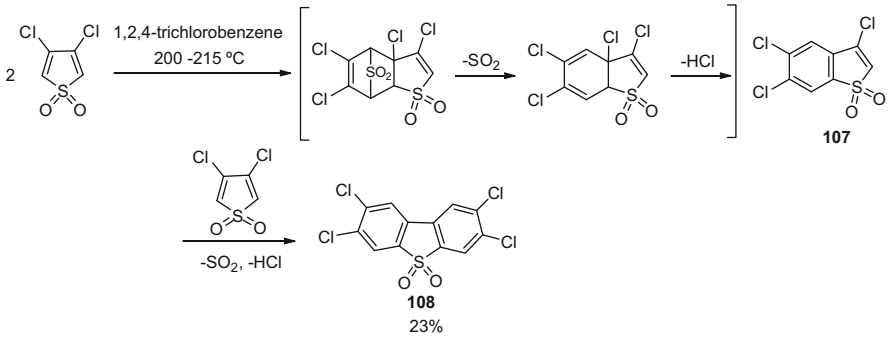
Scheme 99 Isomeric bis-adducts formed through Diels–Alder cycloaddition of 3,4-di-*tert*-butylthiophene 1,1-dioxide with maleic anhydride and *N*-phenylmaleimide [110]



Scheme 100 Bis-adducts formed through Diels–Alder cycloaddition of 3,4-dichlorothiophene 1,1-dioxide with *N*-butyl- and *N*-*p*-nitrophenyl maleimides [89]



Scheme 101 Bis-adduct formed through Diels–Alder cycloaddition of 3-chloro-4-fluorothiophene 1,1-dioxide with maleic anhydride [88, 121]



Scheme 102 Preparation of bis-adduct via oligomerization of 3,4-dichlorothiophene 1,1-dioxide [89]

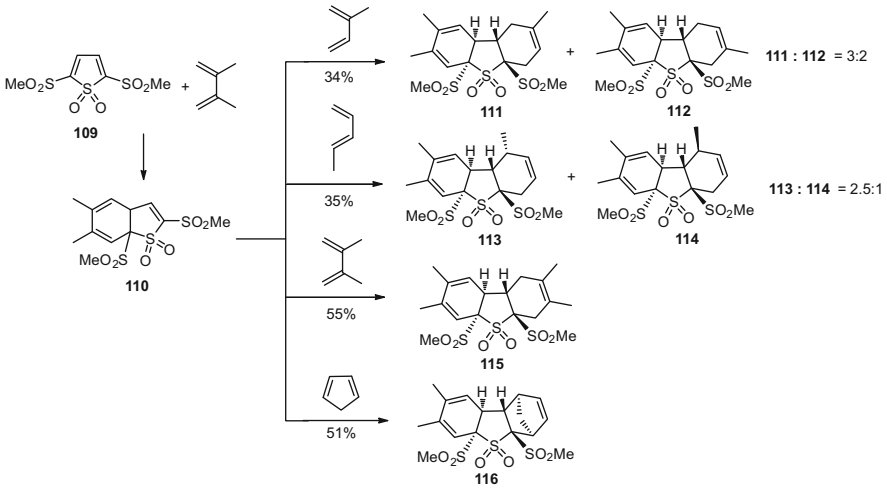
105 and **106** in moderate yields. These isomers are of the *endo–endo* and *endo–exo* type. It should be noted that monoadducts **104** could not be isolated even if one equivalent of a dienophile was used (Scheme 99) [110].

A similar phenomenon was also observed in the reaction of 3,4-dichlorothiophene 1,1-dioxide and 3-chloro-4-fluorothiophene 1,1-dioxide with dienophiles (Schemes 100 and 101). The thermal dimerization product **107** from 3,4-dichlorothiophene 1,1-dioxide reacted with another 3,4-dichlorothiophene 1,1-dioxide, providing the bis-adduct **108** in 23% yield (Scheme 102) [89].

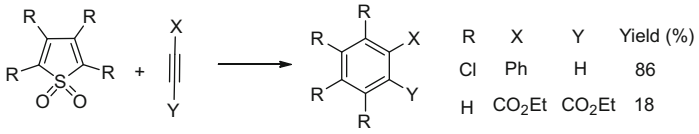
Thiophene 1,1-dioxides can behave as a dienophile toward 4π components and, therefore, can also be used for preparing bis-adducts through Diels–Alder reaction. Cycloaddition of dienes to thiophene 1,1-dioxide **109** afforded monoadducts **110**, which were reacted with other dienes to give bis-adducts **111**–**116**. The bis-adducts **111** and **112** and **113** and **114** were obtained as mixtures of stereoisomers, depending on the reaction conditions. Regio- and stereochemical features of the cycloaddition products were revealed by X-ray analyses (Scheme 103) [122].

[4+2] Cycloaddition with Alkynic Dienophiles

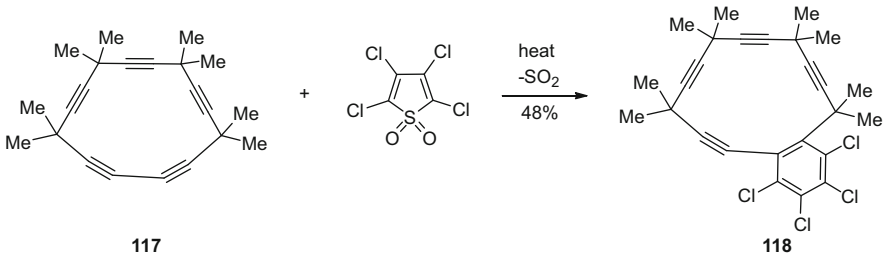
Diels–Alder cycloaddition of thiophene 1,1-dioxides with alkynic dienophiles leads to the formation of benzene derivatives directly via elimination of a sulfur dioxide.



Scheme 103 Preparation of bis-adducts using thiophene 1,1-dioxide as a dienophile toward dienes [122]

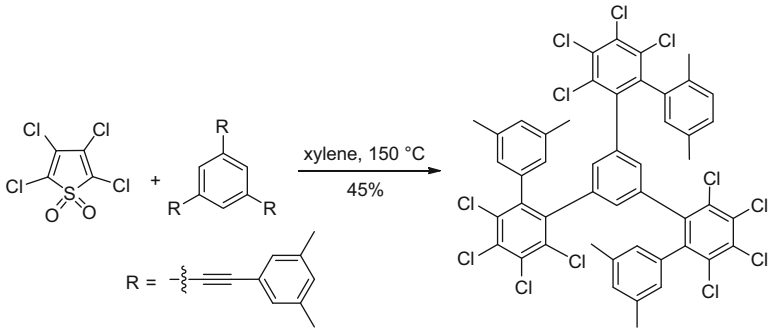


Scheme 104 Diels–Alder cycloaddition of tetrachlorothiophene 1,1-dioxide and thiophene 1,1-dioxide with alkynic dienophiles

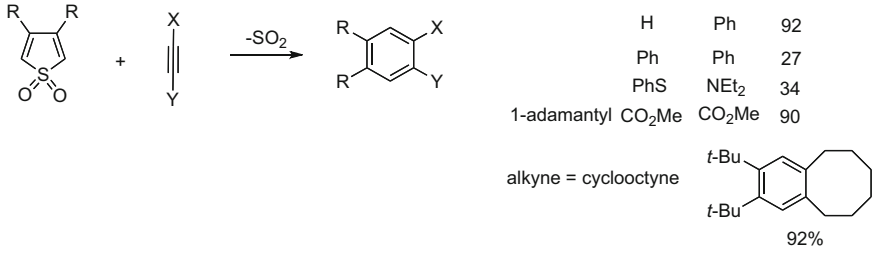


Scheme 105 Diels–Alder cycloaddition of tetrachlorothiophene 1,1-dioxide with a cyclic penta-alkyne [123]

Thus, unsubstituted or substituted thiophene 1,1-dioxides react with alkynes to form benzene derivatives with expulsion of sulfur dioxide (Scheme 104) [100, 103]. Tetrachlorothiophene dioxide reacted with a cyclic penta-alkyne **117** to give compound **118** in moderate yield (Scheme 105) [123]. The reaction of three-fold benzoannelation with tetrachlorothiophene gave dodecachloroseptiphenyl,

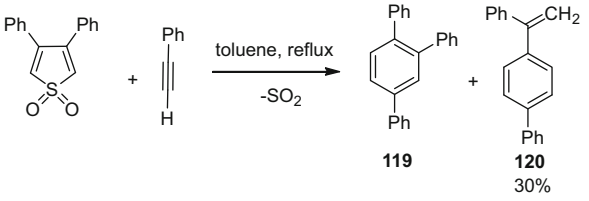


Scheme 106 Diels–Alder cycloaddition of tetrachlorothiophene 1,1-dioxide with threefold benzoannelation [108]



R	X	Y	Yield (%)
	CO_2Me	CO_2Me	100
	H	CO_2Me	72
	H	COMe	84
t-Bu	H	*n*-Bu	32
	H	Ph	92
	Ph	Ph	27
	PhS	NEt_2	34
1-adamantyl	CO_2Me	CO_2Me	90

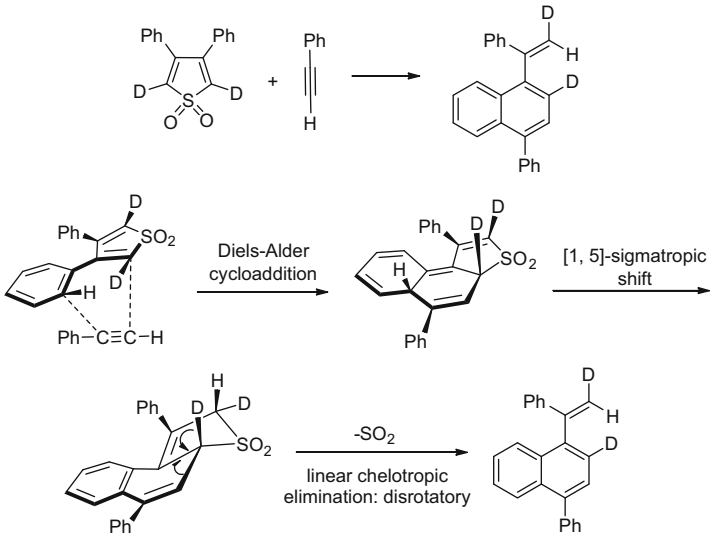
Scheme 107 Diels–Alder cycloaddition of highly congested thiophene 1,1-dioxides with various acetylenes [59, 109]



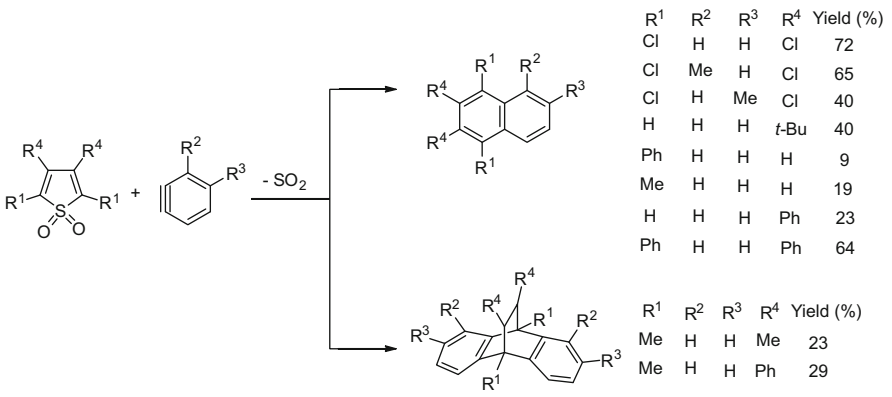
Scheme 108 [4+2] cycloaddition of 3,4-diphenylthiophene 1,1-dioxide with ethynylbenzene [124]

which could be further used to synthesize potential precursors to C_{60}-fullerene (Scheme 106) [108].

Construction of benzene derivatives bearing bulky substituents can be easily achieved by [4+2] cycloadditions of highly congested thiophene 1,1-dioxides with alkynic dienophiles (Scheme 107) [59, 109].



Scheme 109 Proposed mechanism and the geometric isomerism for [4+2] cycloaddition of 3,4-diphenylthiophene 1,1-dioxide with ethynylbenzene [124]



R^1	R^2	R^3	R^4	Yield (%)
Cl	H	H	Cl	72
Cl	Me	H	Cl	65
Cl	H	Me	Cl	40
H	H	H	*t*-Bu	40
Ph	H	H	H	9
Me	H	H	H	19
H	H	H	Ph	23
Ph	H	H	Ph	64

R^1	R^2	R^3	R^4	Yield (%)
Me	H	H	Me	23
Me	H	H	Ph	29

Scheme 110 [4+2] cycloaddition thiophene 1,1-dioxides with benzynes [109, 125]

The major product of the reaction of 3,4-diphenylthiophene 1,1-dioxide with ethynylbenzene was not 1,2,4-triphenylbenzene **119** as expected, but instead was an isomer, 1-phenyl-4-(1-phenylethenyl)naphthalene **120** (Scheme 108). Deuterium labeling was used to study the mechanism and the geometrical isomerism of this reaction (Scheme 109) [124].

Reactive alkynes such as benzyne and substituted benzynes react with a variety of thiophene 1,1-dioxides to produce naphthalene derivatives generally in moderate yields (Scheme 110) [109, 125].

3 Thiophene Reduction Chemistry

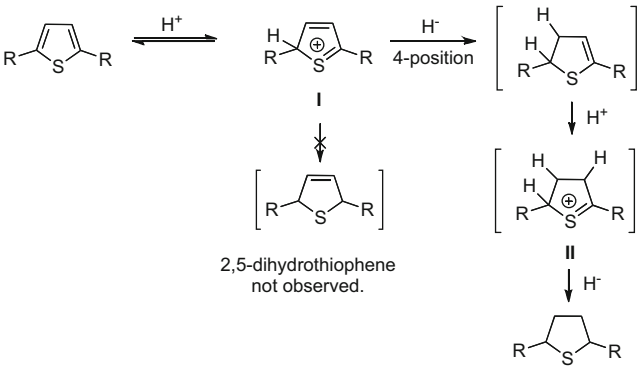
The reduced products of thiophenes including dihydrothiophene and tetrahydrothiophene derivatives play a crucial role in organic, biological, and medicinal chemistry and are widely distributed. The hydrogenation of thiophenes and benzo[*b*]thiophenes, including using ionic hydrogenation, Birch reduction, reductive desulfurization, reduction assisted by transition metal complexes, and other methodologies, has been well studied. Moreover, reductive desulfurization of sulfur-containing compounds, especially the hydrogenation of thiophenes and benzo[*b*]thiophenes to generate single products, has posed a challenge to synthetic chemists and attracted considerable attention. Due to the emerging concern on environment conservation, reductive removal of sulfur-containing compounds from gasoline and other fossil fuels becomes increasingly important.

3.1 Partial and Complete Reduction of Thiophenes

3.1.1 Ionic Hydrogenation of Thiophene and Benzo[*b*]thiophene

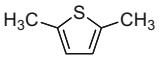
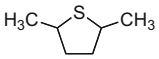
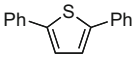
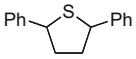
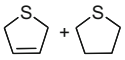
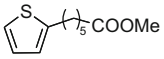
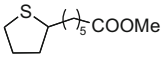
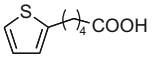
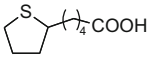
The ionic hydrogenation of thiophenes is similar to the acid-assisted hydrogenation of double bonds, in which the thermally favored carbonium ion is initially generated from the addition of a proton to double bond and subsequently irreversibly trapped by a hydride provided by a reducing agent. As illustrated in Scheme 112, in the ionic hydrogenation of thiophenes, the first step is addition of a proton from acid to the 2-position of the thiophene ring, giving a thiophenium cation **I**. Subsequently, a reducing reagent, most often a silane, is employed as the hydride-ion donor, and in principle two routes are possible. One is hydride-ion addition from silane to the 4-position affording a 2,3-dihydrothiophene. Then, additional protonation at the thiophene 3-position generates thiophenium cation **II** and this is followed by hydride attack at C-2, resulting in total reduction of the thiophene ring, i.e., providing a tetrahydrothiophene. Alternatively, the first hydride addition could occur at the 5-position, producing a 2,5-dihydrothiophene, although such partially reduced products are not observed [126, 127]. Comparison of the two possible routes shows that the former is fast to give the tetrahydrothiophene (Scheme 111).

The ionic hydrogenation of thiophenes employed $CF_3CO_2H \cdot HSiEt_3$ as the proton–hydride pair [126, 127]. Monosubstituted thiophenes, including 2-alkyl, 3-alkyl, 3-arylthiophenes, were smoothly reduced to the corresponding tetrahydrothiophenes, although the 3-alkylthiophenes at a much slower rate and in slightly poorer yields. 2,5-Dialkylthiophenes could also be converted completely into the reduced products, but in contrast, 2,5-diarylthiophenes showed no reactivity in this system. Thiophene itself underwent reduction more slowly and provided a mixture of tetrahydrothiophene and 2,5-dihydrothiophene. The presence of halide, carboxylic acid, or ester at the 2-position of the thiophene ring hindered



Scheme 111 The general mechanism of ionic hydrogenation of thiophenes [126, 127]

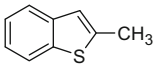
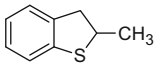
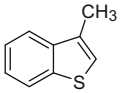
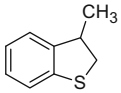
Table 2 Ionic hydrogenation of thiophenes with $CF_3CO_2H \cdot HSiEt_3$

Thiophene	Product	Ratio (thiophene:silane:acid)	Time	Yield (%)
		1:2:8	15	80
		1:2:9	80	60
		1:3:13	20	75
		1:2:8	25	80
		1:2:20	50	0
		1:3:11	35	20 + 30
		1:2:9	35	65
		1:2:7	40	65

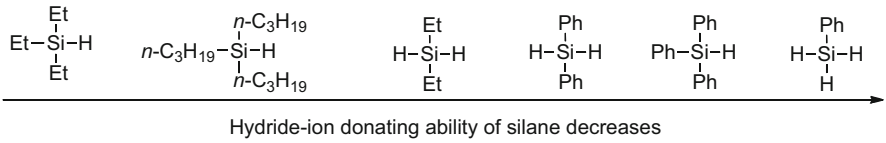
the hydrogenation; however, when these groups were positioned at the terminus of 2-substituted side-chains, no effect was observed and the ionic hydrogenation reaction proceeded successfully (Table 2).

Benzo[*b*]thiophene itself reacts slowly under ionic hydrogenation conditions to give 2,3-dihydrobenzo[*b*]thiophene, whereas 2-alkyl or 3-alkyl benzo[*b*]thiophenes are readily reduced. As shown in Table 3, the ionic hydrogenation of 3-methylbenzo[*b*]thiophene is a little faster than that of 2-methylbenzo[*b*] thiophene.

Table 3 Ionic hydrogenation of benzo[*b*]thiophenes with $CF_3CO_2H \cdot HSiEt_3$

Benzo[*b*]thiophene	Product[a]	Time	Yield (%)
		1.75 20	70 80
		1.75 20	85 90

[a]The molar ratio of benzo[*b*]thiophene: silane: $CF_3COOH = 1:1.1:1.7$



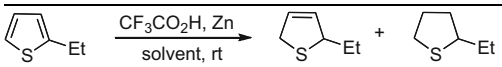
Scheme 112 Hydride-ion-donating ability of silanes [126]

The hydride-ion-donating ability of the silane depends on its structure. The most commonly used silane is triethylsilane, which exhibits the best hydride-ion donor ability. The hydride-donating ability of silanes has been proved to follow the order shown in Scheme 112 [126].

In the $CF_3CO_2H \cdot HSiEt_3$ system, although the detailed mechanism of the second step has not yet been ascertained, it is possible to consider that the effective hydride transfer is actually a result of transfer of two electrons and a proton, and thus, $HSiEt_3$ possesses dual donating functions, both electron donating and proton donating. Therefore, it seemed reasonable to develop a process in which these two donating functions would be divided between two separate donors, the first being the donor of electrons and the second supplying protons, especially since a proton donor is required for the first step of the sequence. Thus, the pairing $CF_3CO_2H \cdot Zn$ is in principle suitable [128]. Unfortunately, in contrast to the clean reduction products of substituted thiophenes, reduction of 2-ethylthiophene with a $CF_3CO_2H \cdot Zn$ system resulted in a mixture of the 2,5-dihydrothiophene and the tetrahydrothiophene and at a slow rate. From Table 4, one can see that replacement of $HSiEt_3$ with zinc leads to a variation of hydrogenation products such that instead of tetrahydrothiophenes, the predominant products were 2,5-dihydrothiophenes, which is a distinct difference from $HSiEt_3$ in acidic media.

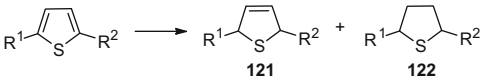
In other work on the concentrated $H_2SO_4 \cdot Zn$ system [129, 130], mono- and disubstituted thiophenes gave 2,5-dihydrothiophenes and thiophanes (2,3,4,5-tetrahydrothiophenes) with a significant preference for the former. The optimized conditions (thiophene:89% sulfuric acid:zinc = 1:30:110 in dichloromethane at 20°C) converted alkyl-substituted thiophenes into a mixture of 2,5-dihydrothiophenes and tetrahydrothiophenes with the former predominating. For 2-formyl- and 2-acetylthiophenes, under slightly modified conditions, 2,5-dihydro-

Table 4 Ionic hydrogenation of thiophene with $CF_3CO_2H \cdot Zn$



Molar ratio[a]	Time (h)	Solvent	Di-	Tetra-
1:50:100	3	–	41	11
1:92:50	2.5	Benzene	58	8
1:92:50	3	Toluene	61	8
1:92:50	3	Hexane	55	10
1:92:50	3	DCM	70	6
1:92:50	5	Ether	0	0

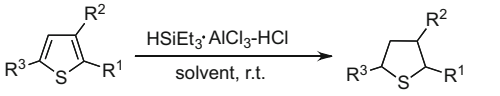
[a]The molar ratio of 2-ethylthiophene: Zn:CF_3COOH



Start material		Product		Yield (%)	
R^1	R^2	R^1	R^2	**121**	**122**
H	Et	H	Et	70	5
H	Me	H	Me	28	2
H	Pr	H	Pr	63	4
Me	Me	Me	Me	52	6
H	CHO	H	Me	35	5
H	COMe	H	Et	58	6

Scheme 113 Reduction of thiophenes with $H_2SO_4 \cdot Zn$ [129]

Table 5 Ionic hydrogenation of thiophene with $HSiEt_3 \cdot HCl\text{-}AlCl_3$

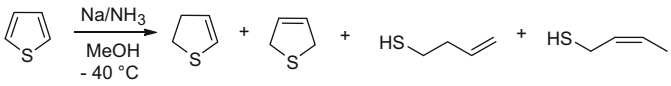


Substrate	Molar ratio[a]	Time (min)	Yield
R^1=Me, R^2=H, R^3=Me	1:3.2:0.3	90	76
R^1=Et, R^2=H, R^3=H	1:3.0:0.3	10	80
R^1=Ph, R^2=H, R^3=Ph	1:3.0:2.0	>10 h	66

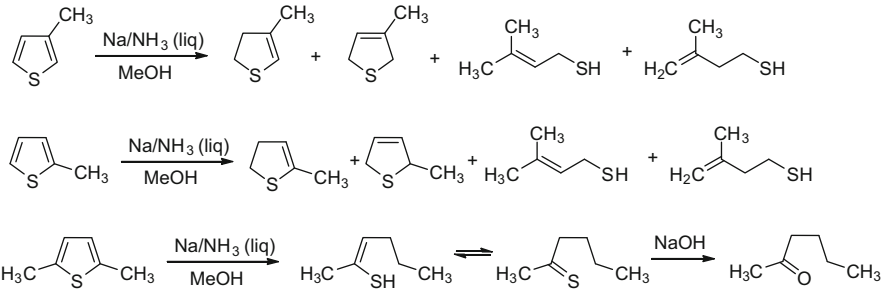
[a]The molar ratio of thiophene: $HSiEt_3$:$AlCl_3$

2-methylthiophene, 2-methylthiophane, and 2,5-dihydro-2-ethylthiophene, 2-ethylythiophane were obtained (Scheme 113).

2,5-Dimethyllthiophene forms a stable 2,5-dimethylthiophenium tetrachloro-aluminate salt on reaction with HCl-$AlCl_3$; thus, a novel reduction system of $HSiEt_3 \cdot HCl\text{-}AlCl_3$ was developed [131] for the complete reduction of substituted thiophenes to thiophanes. For 2,5-dimethylthiophene and 2-ethylthiophene, the completely hydrogenated tetrahydrothiophenes were obtained in 76 and 80% yields, respectively (Table 5). 2,5-Diphenylthiophene, which was a challenge for



Scheme 114 Birch reduction of thiophene [132, 133]



Scheme 115 Birch reduction of alkyl-substituted thiophenes [134]

$CF_3CO_2H \cdot HSiEt_3$, was reduced efficiently with this methodology, though over a prolonged reaction time, providing 2,5-diphenyltetrahydrothiophene in good yield.

The great advantage of the $HSiEt_3 \cdot AlCl_3$-HCl system is the introduction of Lewis acid $AlCl_3$ and the ability to adjust the medium "acidity" by varying the amount of $AlCl_3$. As a result, it has become possible in principle to reduce thiophenes that cannot be reduced by $CF_3CO_2H \cdot HSiEt_3$.

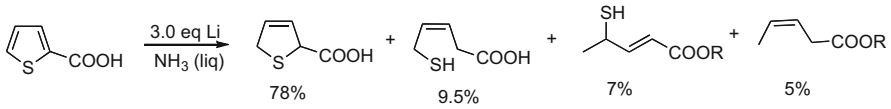
3.1.2 Birch Reduction of Thiophene

Birch reaction is the dearomatization of aromatic rings to unconjugated cyclohexadienes in the presence of alkali metals (Li, Na, K) in liquid ammonia, using alcohol as proton source. Compared to other heterocyclic compounds, including pyridines, furans, and pyrroles, the Birch reduction of thiophenes and their derivatives has been scarcely investigated.

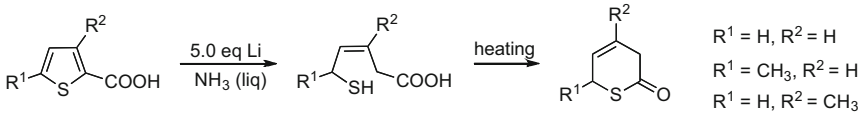
Treatment of thiophene in liquid ammonia at −40°C with sodium in the presence of methanol yielded a mixture of isomeric dihydrothiophenes as primary products together with ring cleavage products (Scheme 114) [132, 133].

The Birch reduction of substituted thiophenes, such as 3-methylthiophene, 2-methylthiophene, and 2,5-dimethylthiophene, also produced partially reduced and ring-opened products (Scheme 115) [134]. Substitution at the 3-position increased the proportion of dihydrothiophenes, whereas substitution at the 2-position inhibited the formation of dihydrothiophenes and favored complete reduction.

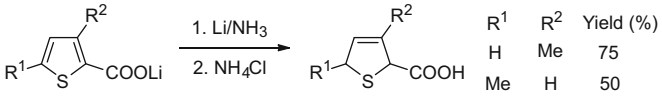
Birch reduction of thiophene-2-carboxylic acid did not afford a clean yield of standard Birch product even under modified conditions. Although 2,5-dihydrothiophene-2-carboxylic acid was the major product, the isolation of



Scheme 116 Birch reduction of thiophene-2-carboxylic acid [135]



Scheme 117 Ring opening of thiophene-2-carboxylic acids under Birch conditions [135]



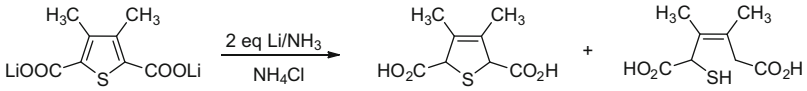
Scheme 118 Birch reduction of lithium thiophene carboxylate salts [136]

this compound was difficult, due to its susceptibility to further reduction or reductive cleavage under the reaction conditions. Therefore, a final mixture of partially reduced product and ring-opened compounds was obtained, as illustrated in Scheme 116 [135].

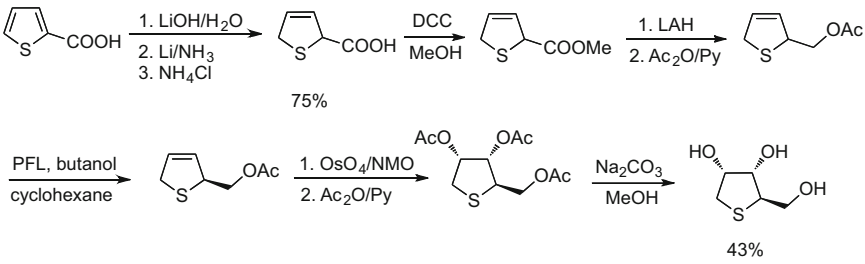
When five equivalents of lithium metal were employed in the Birch reduction of thiophene-2-carboxylic acid, ring-opened δ-mercapto product and β,γ-unsaturated carboxylic acid were obtained. Upon heating at 150–160°C, dehydration to the corresponding β,γ-unsaturated δ-thiolactone occurred. It is noteworthy that the double bond was in a *cis* conformation. Substituted thiophene-2-carboxylic acids exhibited similar behavior (Scheme 117).

Subsequently, it was found that the preparation of substituted 2,5-dihydrothiophenes can be conveniently realized by the lithium/ammonia reduction of the corresponding lithium thiophene carboxylate salts, instead of the acid [136]. As depicted in Scheme 118, the substituted thiophene-2-carboxylic acid was initially converted into the corresponding lithium salt by treatment with equivalent amount of lithium hydroxide, and then the reduction was accomplished with lithium/ammonia and ammonia chloride as the proton source. Through this procedure, the ultimate target products were obtained in yields of 75% and 50%, respectively, but as a mixture of approximately equal amounts of 2,5-*cis*- and -*trans*-isomers.

Birch reduction of more heavily substituted thiophene carboxylic acid salts proceeded readily to afford the corresponding substituted 2,5-dihydrothiophenes; however, the ring-opened by-product (*Z*)-5-mercapto-3-pentenoic acid was still detectable. Reduction of dilithium 3,4-dimethylthiophene-2,5-dicarboxylate also



Scheme 119 Birch reduction of dilithium thiophene 2,5-dicarboxylate salts [137]



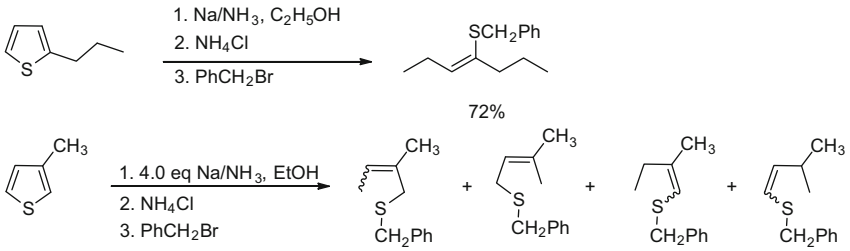
Scheme 120 The synthesis of (+)-l-deoxy-4-thio-D-ribose [138]

afforded a mixture of the corresponding dihydrothiophene and acyclic mercaptan [137] (Scheme 119).

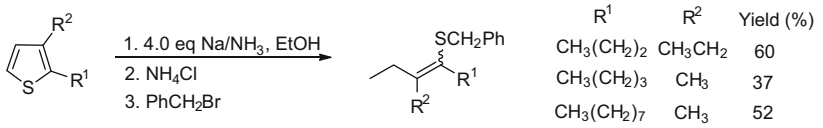
A synthesis of (+)-l-deoxy-4-thio-D-ribose as a sugar analogue employed thiophene-2-carboxylic acid as starting material, the crucial step being the generation of 2,5-dihydrothiophene-2-carboxylic acid via Birch reduction in 75% yield after recrystallization from hexane [138]. Subsequent esterification, reduction, enzymatic resolution, and final substrate-controlled dihydroxylation of the alkene, the thiosugar (+)-l-deoxy-4-thio-D-ribose was obtained with an enantiomeric excess of 92% by comparison with the specific rotation of (−)-l-deoxy-4-thio-L-ribose (Scheme 120).

As described above, under various Birch conditions, the reduced thiophenes are often contaminated by ring-opened by-products. The acyclic anions generated in situ can be trapped by adding an electrophile – benzyl bromide – leading to the isolation of ring-opened straight-chain compounds, efficiently, as the predominant products [139]. Thus, treatment of 2-propylthiophene, with four equivalents of sodium and subsequent alkylation with benzyl bromide, gave, regioselectively, (*Z*)-4-benzylthio-3-heptene in a 72% yield [140]. However, when 3-methylthiophene was subjected to Birch reduction and benzylation, a complex mixture of 1-benzylthio-2-methyl-2-butene, 1-benzylthio-3-methly-2-butene, 1-benzylthio-2-methyl-1-butene, and 1-benzylthio-3-methyl-1-butene was obtained in a ratio of 10:4:4:1. The ratio of the trisubstituted alkene to disubstituted alkene was 18:1, indicating that the product distribution depended on the thermodynamic stability of the products (Scheme 121) [139].

When 2,3-dialkyl-substituted thiophenes were employed, Birch reduction occurred smoothly leading to the expected tetrasubstituted alkenes. When 2-butyl-3-methylthiophene reacted with four equivalents of sodium by the procedure described above, 4-benzylthio-3-methyl-3-octene was obtained in 60% yield (Scheme 122) [139].

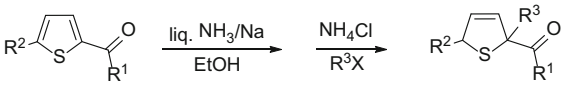


Scheme 121 Ring opening and trapping reactions of monoalkyl thiophenes [139, 140]



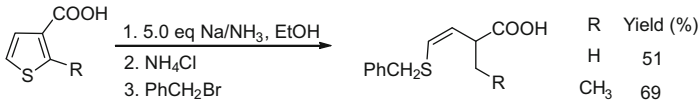
R^1	R^2	Yield (%)
$CH_3(CH_2)_2$	CH_3CH_2	60
$CH_3(CH_2)_3$	CH_3	37
$CH_3(CH_2)_7$	CH_3	52

Scheme 122 Ring-opening reaction of dialkylthiophenes [139]



R^1	R^2	R^3	Yield (%)
Me	H	Bn	73
n-Pr	H	Bn	82
n-Pr	H	allyl	68
n-C_9H_{19}	H	Bn	61
c-C_6H_{11}	H	Bn	80
n-C_7H_{15}	Me	Me	44
OH	H	Bn	68

Scheme 123 Cascade Birch reduction-alkylation of 2-acylthiophenes [141]

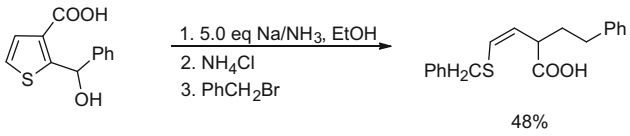


R	Yield (%)
H	51
CH_3	69

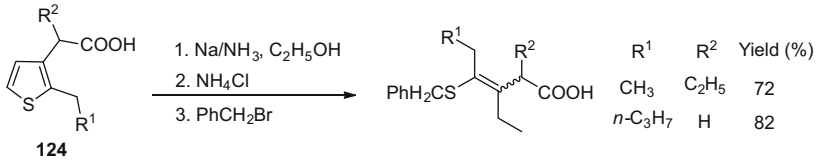
Scheme 124 Ring opening of thiophene-3-carboxylic acids [139]

Birch reduction of 2-acyl- or 2-acetyl-5-alkylthiophenes and subsequent alkylation with an alkyl halide gave 2-acyl-2-alkyl- or 2-acyl-2,5-dialkyl-2,5-dihydrothiophenes in moderate to good yields. As illustrated in Scheme 123, for a series of substrates, both 2-acylthiophenes and thiophene-2-carboxylic acid were tolerated in this process. The compounds **123** represent useful synthetic intermediates, which can be further converted into 1,3-dienes. Substituted dihydrothiophenes were subjected to *m*-CPBA, followed by thermolysis, and finally provided a series of 1,3-dienyl ketones [141].

Treatment of thiophene-3-carboxylic acid with five equivalents sodium in liquid ammonia and ethanol, and then benzyl bromide, produced a ring-opened product (*Z*)-4-benzylthio-2-methyl-3-butenoic acid in 51% yield. Similarly, the Birch



Scheme 125 Ring-opening reaction of 2-(α-hydroxylbenzyl)thiophene-3-carboxylic acid [140]



Scheme 126 Ring opening of thien-3-ylacetic acids [140]

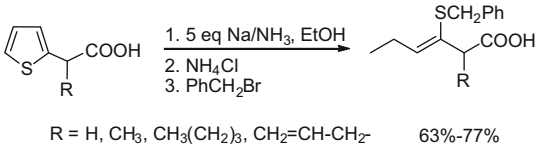
reduction/trapping of 2-methyl-3-thiophenecarboxylic acid gave (*Z*)-4-benzylthio-2-ethyl-3-butenoic acid in 69% yield (Scheme 124) [139].

A hydroxyl functional group can also be tolerated; thus, Birch reaction and alkylation of 2-(α-hydroxylbenzyl)thiophene-3-carboxylic acid resulted in the formation of the over-reduced product, (*Z*)-4-benzylthio-2-(2-phenylethyl)-3-butenoic acid, in 48% yield (Scheme 125) [140].

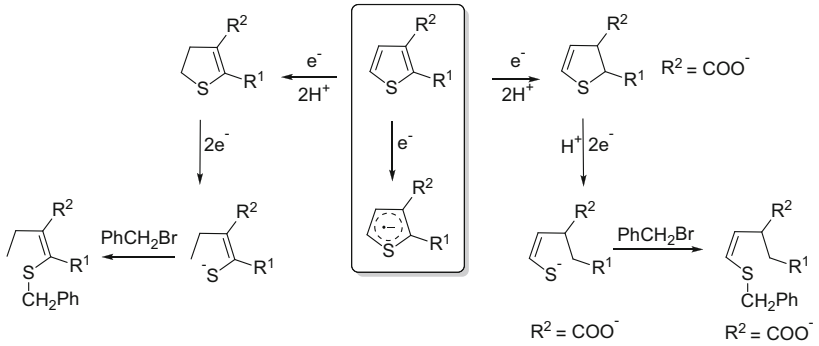
As depicted in Scheme 126, when substituted thien-3-ylacetic acid **124** was allowed to react with five equivalents of sodium in liquid ammonium in the presence of ethanol, to which three equivalents of ammonium chloride and benzyl bromide were added subsequently, 4-benzylthio-2,3-diethyl-3-hexenoic acid was obtained with a yield of 72%. In a similar manner, 4-benzylthio-3-ethyl-3-octenoic acid was obtained in 82% yield [140].

When thien-2-ylacetic acid was subjected to the abovementioned reaction conditions, similar ring opening was observed and the products consisted of (*Z*)-3-benzylthio-3-hexenoic acid and (*Z*)- and (*E*)-3-benzylthio-2-hexenoic acid with the ratio of 84:12:4. As illustrated in Scheme 127, the Birch reduction of 2-(thien-2-yl) propanoic acid with five equivalents of sodium in liquid ammonia in the presence of ethanol and a subsequent treatment with ammonium chloride and benzyl bromide led to the formation of (*Z*)-3-benzylthio-2-methyl-3-hexenoic acid in the yield of 63%. Additionally, under similar reaction conditions, 2-(thien-2-yl)hexenoic acid and 2-(thien-2-yl)-4-pentenoic acid also created the corresponding (*Z*)-3-benzylthio-2-butyl-3-hexenoic acid and (*Z*)-2-allyl-3-benzylthio-3-hexenoic acid with 77 and 76% yields, respectively [140].

To understand the differences between the two ring-opening modes, it is suggested that firstly the Birch reduction generates the thermodynamically stable dihydrothiophenes, and then the C–S bond cleavage occurs away from the double bond (Scheme 128) [139].



Scheme 127 Ring opening of thien-2-ylacetic acids [140]



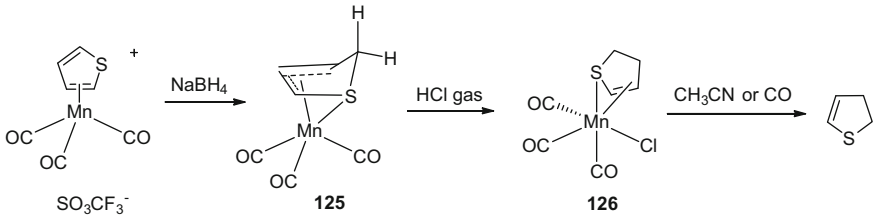
Scheme 128 The plausible mechanisms of ring-opening modes of substituted thiophenes [139]

3.1.3 Hydrogenation Using Transition Metals

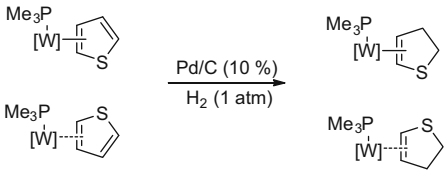
Reduction of thiophenes with the retention of its skeleton poses a challenge. Attempts to hydrogenate thiophenes via the usual hydrogenation procedures using transition metal catalysts such as nickel, platinum, and palladium almost inevitably fail, presumably owing to the powerful poisoning effect of this type of sulfur-containing compound. Some success with catalytic hydrogenation of thiophenes with molecular hydrogen could be achieved at an elevated temperature and pressure, though the products were often accompanied by hydrogen sulfide and hydrocarbons. Hydrogenation of thiophene to tetrahydrothiophene over a palladium catalyst was achieved with a very high catalyst-to-thiophene ratio to overcome the poisoning effect [142]. The yields of the tetrahydrothiophenes and hydrogenolysis products increase with the increase of contact time. Using a molybdenum sulfide catalyst, thiophene can be converted into thiophane and butanethiol at 350°C.

However, in contrast to heterogeneous hydrogenation, homogeneous reduction has attracted considerable attention. Furthermore, the coordination and reactivity of thiophenes on transition metal centers continue to attract considerable attention as model chemistry for the species and reactions that occur during heterogeneous hydrodesulfurization (HDS) of petroleum and other fossil fuels.

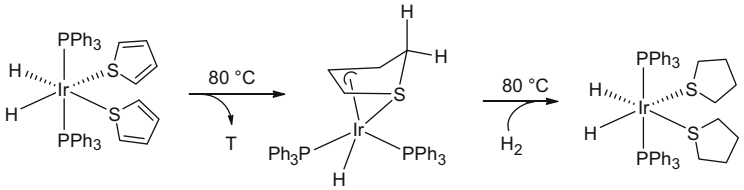
Investigations of Mn-thiophene complex (η-C_4H_4S)$Mn(CO)_3^+$ showed that bubbling HCl gas into a solution of **125** in hexane gave a yellow and air-stable precipitate **126**, then released the partially reduced product 2,3-dihydrothiophene



Scheme 129 Partial hydrogenation of thiophene with a Mn-complex [143]



Scheme 130 Partial hydrogenation of thiophene with W-complex [144]



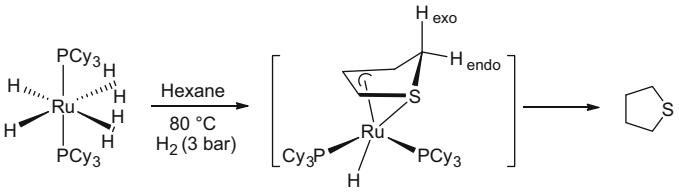
Scheme 131 Hydrogenation of thiophene with an Ir-complex [145]

through dissolution in acetonitrile or by bubbling carbon monoxide (Scheme 129) [143].

Reduction of TpW(NO)(PMe_3)(Br) (Tp=hydrido-tris(pyrazolyl)borate) with sodium in the presence of thiophene yielded a mixture of tungsten-containing complexes, exhibiting distinct chemical properties, which could be partially hydrogenated to dihydrothiophene complexes with combined yields of 22% in a 1:1 ratio of two diastereoisomers (Scheme 130). The η^2 coordinate binding fashion is less common for 16-electron metal complex than the η^1 or S-bound form [144].

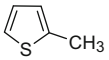
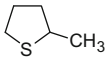
An iridium-2,3-dihydrothiophene complex can act as a homogeneous catalyst in the hydrogenation of thiophene to tetrahydrothiophene [145]. Thermolysis of bisthiophene dihydride $[(PPh_3)_2Ir(H)_2(\eta^1\text{-}SC_4H_4)_2]PF_6$ in 1,2-dichloroethane at 80°C provided an active intermediate $[(PPh_3)_2IrH\ (\eta^4\text{-}SC_4H_4)]PF_6$ through loss of one thiophene molecule. Then hydrogenation occurred, giving iridium complex $[(PPh_3)_2Ir(H)_2(\eta^1\text{-}SC_4H_8)_2]PF_6$ and another compound (Scheme 131). However, when the hydrogenation was conducted in the presence of excess thiophene, the iridium complex $[(PPh_3)_2Ir(H)_2(\eta^1\text{-}SC_4H_8)_2]PF_6$ was obtained exclusively.

The bis(dihydrogen) complex $[RuH_2(\eta^2\text{-}H_2)_2(PCy_3)_2]$, which contains two labile dihydrogen ligands and has been proven to be active and stable in a hydrogen



Scheme 132 Hydrogenation of thiophene with a Ru-complex [146]

Table 6 Hydrogenation catalyzed by [$RuH_2(\eta^2\text{-}H_2)_2(PCy_3)_2$]

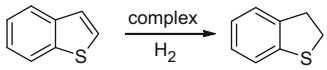
Entry	Substrate	Product	Conversion
1			85%
2			11%
3			86%

atmosphere, acts as the catalyst precursor for hydrogenation of thiophene and its derivatives [146]. The ligand-exchanged intermediate could be isolated, and the structure was determined by ^{1}H NMR. The active intermediate was formulated as a neutral Ru(II) complex, coordinated by one hydrogen, two tricyclohexylphosphines and one thioallyl ligand. It is noteworthy that this η^4 (S,C) complex mode is rarely found (Scheme 132).

Under the reducing conditions, thiophene and benzo[*b*]thiophene are readily and smoothly converted into tetrahydrothiophene and 2,3-dihydrobenzo[*b*]thiophene with conversion rates of 85% and 86%, respectively. However, for the 2-methylthiophene, the reaction went more slowly, and the conversion rate was only 11% under the same conditions (Table 6). Possible reasons for this are that substituents at C-2 or C-3 reduce the π-acceptor character of the olefin and sterically hinder the η^2-(C,C)-coordination mode as well. In addition, electron-donating alkyl groups enhance the donor ability of the sulfur atom, thereby favoring S-coordination.

Only reduction of the side-chain carbonyl to alcohol took place when 2-acetylthiophene and 2-formylthiophene were examined. This methodology showed no activity in attempted hydrogenation of dibenzo[*b*,*d*]thiophene, even when the hydrogen pressure was increased to 20 from 3 bar.

Compared to the hydrogenation of thiophene to tetrahydrothiophene, the homogenous regioselective hydrogenation of benzo[*b*]thiophene (BT) to 2,3-dihydrobenzo[*b*]thiophene (DHBT), which is a transformation of industrial interest in connection with the hydrodesulfurization, has been studied extensively assisted by transition metal precatalysts, including Os-, Ru-, Rh-, Ir-complexes (Scheme 133). Furthermore, the detailed mechanisms of the homogeneous regioselective hydrogenation of BT to DHBT have attracted intense attention. Several representative detailed catalytic cycles are discussed below, including transition metal complexes of Rh, Ir, Ru, and Os.



Scheme 133 Model hydrogenation reaction of benzo[*b*]thiophene by a transition–metal complex [147–151]

Study of the homogeneous catalytic hydrogenation of BT to DHBT in the presence of $[Rh(Cp^*)(MeCN)_3]^{2-}$ utilized deuteration experiments and detailed NMR studies to elucidate a catalytic cycle [147]. The main cycle starts with the η^2-coordination of BT to a rhodium polyhydrido species, followed by hydride transfer, hydrogenation, finally generating DHBT.

Further study of the homogeneous hydrogenation of BT to DHBT using the precatalysts $[M(COD)(PPh_3)_2]PF_6$, M=Rh, Ir] was conducted [148]. In the postulated catalytic cycle, BT initially binds η^1-S to a M(III) dihydride (M=Ir, Rh). Then dissociation of one BT molecule yields $Ir(H)_2(\eta^1\text{-S-DHBT})(PPh_3)_2]PF_6$, which is likely in equilibrium with the isomeric dihydrido-η^2-BT complex. Next, selective hydrogenation of the C-2–C-3 double bond occurs through a hydrido-2-benzo[*b*]thienyl species, yielding intermediates containing the hydrogenated product $[M(\eta^1\text{-S-DHBT})(PPh_3)_2]^+$. Displacement of DHBT by a new molecule of BT produces $[M(\eta^1\text{-S-BT})(PPh_3)_2]^+$, which reacts with hydrogen to restart the cycle.

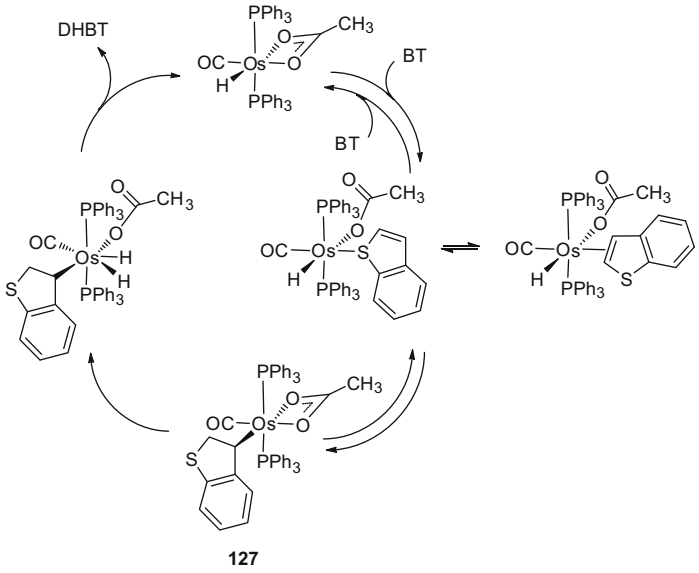
Regioselective hydrogenation of BT to DHBT with ruthenium(II) tris-acetonitrile complex $[(triphos)Ru(NCMe)_3](BPh_4)_2$ as catalyst in homogeneous phase takes place under mild reaction conditions [149].

It was found that $RuHCl(TPPMS)_2(THQ)_2$ and $RuHCl(TPPMS)_2(An)_2$ can be used as catalyst in a liquid-biphase hydrogenation of BT. The initial catalyst conditions were $T = 136°C$, P $(H_2) = 35$ atm, 1:1 mixture of water/decalin. Under these experimental conditions, the only product detected was DHBT with no evidence of C–S bond cleavage [150].

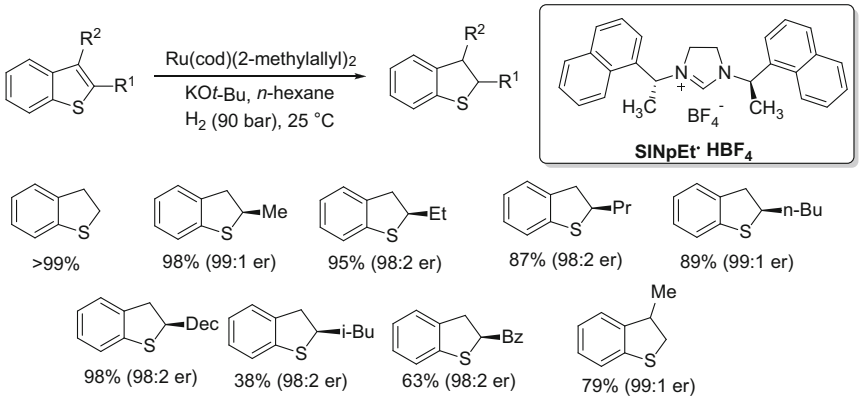
The complex $OsH(CO)(\kappa^3\text{-}OCOCH_3)(PPh_3)_2$ also catalyzes reduction of BT to DHBT under mild conditions. The proposed catalytic cycle, which is based on kinetic experiments, is shown in Scheme 134 [151]. Among the several elementary reactions, oxidative addition of hydrogen to **127** forms the dihydrido species $Os(H)_2(CO)(\kappa^1\text{-}OCOCH_3)(\eta^1\text{-}C_8H_7S)(PPh_3)_2$, which is considered to be the rate-determining step of the catalytic cycle. The fast reductive elimination of the 2,3-DHBT product regenerates the catalyst and restarts the cycle.

Optically active 2,3-dihydrobenzo[*b*]thiophene and tetrahydrothiophene derivatives play a crucial role in organic, biological, and medicinal chemistry and are widely distributed. The first homogeneous asymmetric hydrogenation of substituted thiophenes and benzo[*b*]thiophenes [152] utilized a Ru–NHC complex generated in situ from $[Ru(cod)(2\text{-methylallyl})_2]$ and $SINpEt \cdot HBF_4$ as the catalyst, the 2-substituted benzo[*b*]thiophene being converted into the corresponding 2,3-dihydrobenzo[*b*]thiophene smoothly with highly optical activity and in moderate to excellent yields (Scheme 135).

Inspired by the successful hydrogenation of substituted benzo[*b*]thiophenes, this catalytic system was applied to the reduction of mono- or disubstituted thiophenes

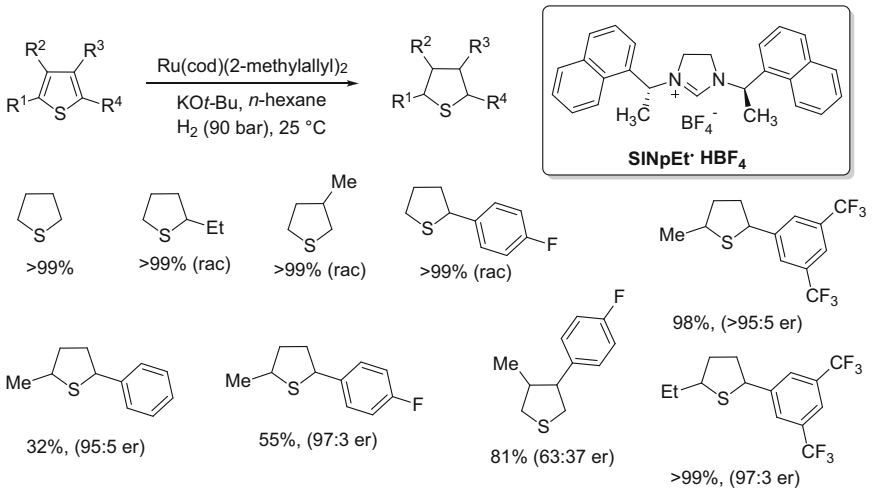


Scheme 134 Mechanism for the hydrogenation of BT catalyzed by an osmium complex [151]



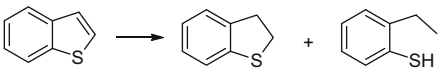
Scheme 135 Asymmetric hydrogenation of BTs using a Ru–NHC complex [152]

[152], and it was found that monosubstituted thiophenes such as 2-ethylthiophene and 2-(4-fluorophenyl)thiophene, 3-methylthiophene, and disubstituted thiophenes could be reduced quantitatively; however, all the monosubstituted tetrahydrothiophenes were obtained in racemic form only (Scheme 136). The rationale behind this phenomenon is poorly understood.



Scheme 136 Asymmetric hydrogenation of thiophenes by Ru–NHC complex [152]

Table 7 Birch-type reduction by electrochemical methodology



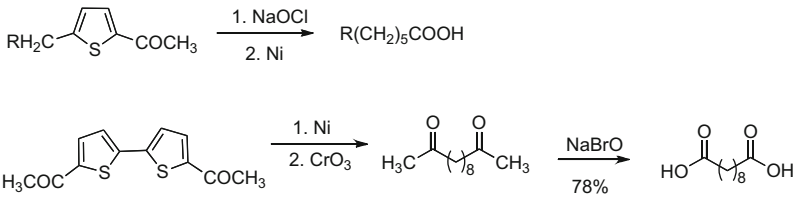
Electrolyte solution	Q. F	DHBT	ETP
2.1 M aqueous (TBA)OH, divided cell	2	68	15
as above, undivided cell	2	36	10
(TBA)BF_4, THF-H_2O (8%), divided cell	2	75	12

3.1.4 Other Methodologies of Hydrogenation

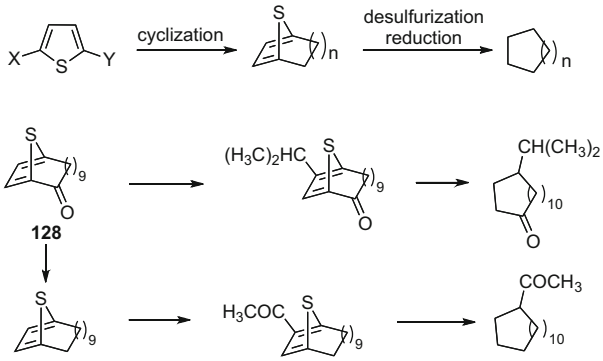
An electrochemical methodology brings about Birch-type reduction. The reduction of BT was carried out in either aqueous or a mixed THF-water media, and mercury pool was employed as the cathode. It was found that BT is initially reduced to DHBT, which is subsequently reductively cleaved to 2-ethylbenzenethiol. Under all conditions, DHBT is the major product obtained by the transfer of a charge equivalent to 2 F/mol (Table 7) [153].

3.2 Reduction of Thiophenes to Sulfur-Free Products

The history of reductive desulfurization is more than 70 years old, and the conversion of carbonyl group to methylene and the conversion of thioester to aldehyde are classical examples. The reductive desulfurization of thiophenes and derivatives



Scheme 137 Reductive desulfurization with Raney Ni [154]



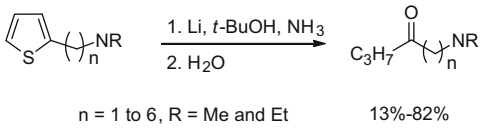
Scheme 138 Strategy for macrocycle construction through reductive desulfurization [8]

using either Raney nickel or nickel aluminum alloy has also garnered deserved consideration.

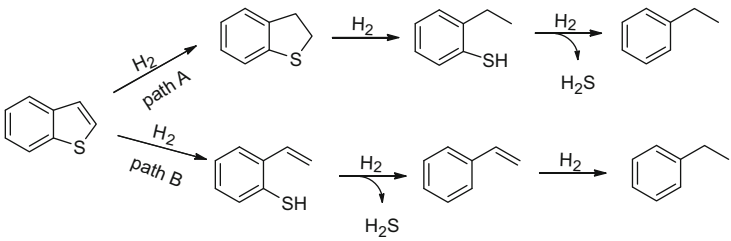
In the perspective of organic synthesis, the reductive desulfurization of thiophenes represents a convenient pathway to synthesize long (and branched)-chain compounds, especially fatty acids. For example, 2-acetyl-5-alkylthiophenes can be converted smoothly via hypohalite oxidation (to give the acid), followed by Raney nickel desulfurization, into the desired fatty acid [154]. Furthermore, this methodology could be expanded to the bisthiophenes. Owing to the insolubility of 5,5′-diacetyl-2,2′-bithienyl, desulfurization was carried out first, followed by oxidation to give 2,11-dodecanedione in high yield. The reductive desulfurization of substituted thiophenes with Raney nickel has proved to be effective in all cases and leads to the conversion of the thiophene rings to a hydrocarbon chain made up of the four carbon atoms of the ring, together with any associated substituents (Scheme 137).

Apart from the construction of long-chain bifunctional aliphatic compounds, reductive desulfurization can also be used in the synthesis of macrocycles [8] as illustrated in Scheme 138. Employing a thiophene as the starting material, the thiophene-containing bicyclic ketone **128** was prepared. From **128** one can reduce the ketone carbonyl group to diversify. Final reductive removal of thiophene cycle generates a series of macrocyclic products.

The use of thiophene as starting material in the synthesis of cyclic compounds not only simplifies construction of the final aliphatic carbon chain and facilitates the



Scheme 139 Reductive desulfurization under Birch conditions [155]



Scheme 140 The mechanisms of the regioselective hydrogenation of benzo[*b*]thiophenes [156]

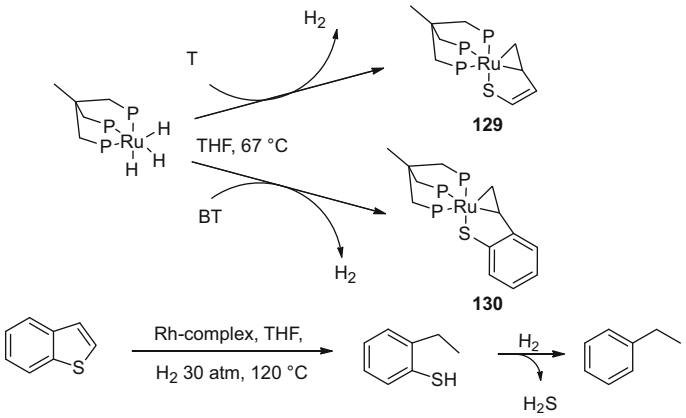
ring closing process but, as has already been pointed out, also makes it possible to prepare poly-alicyclic systems with various substituents that are difficult to incorporate in the preformed alicyclic molecule.

A reductive Birch desulfurization-hydrolysis of thiophene derivatives using lithium and alcohols in liquid ammonia on α-substituted thiophenes with subsequent hydrolysis of the products led to the conversion of the thiophene fragment of the molecule into a butyryl group [155]. A number of amino ketones of the aliphatic series were obtained from α-(ω-dialkylaminoalkyl)thiophenes. Scheme 139 shows how the yields increased dramatically from 13 to 82% as the length of the aliphatic side-chains increased, which presumably resulted from the remoteness of the functional group from the ring.

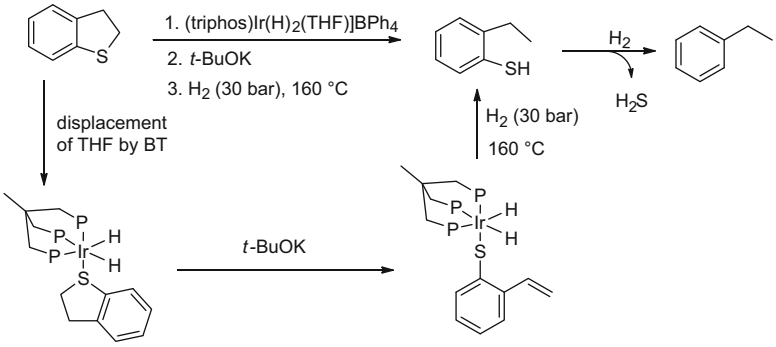
Coupled with the previous observations and further work, this methodology showed great substrate generality including α-alkyl-, α-(ω-hydroxyalkyl)-, and α-(ω-carboxyalkyl)-substituted thiophenes [155].

Another classification of reductive desulfurization concerns a technological process and is of extreme significance. These transformations often need noble metals as catalysts. Sulfur in fossil fuel feedstocks is contained in a variety of organic forms, including thiols, disulfides, and the more refractory thiophenes, benzo[*b*]thiophenes, and dibenzothiophenes. The reductive removal of sulfur from sulfur-containing compounds has enormous technological importance for several reasons, among which is a substantial contribution to the decrease of acid rain consequent upon fuel combustion. Accordingly, the desulfurization of thiophenes and benzo[*b*]thiophenes with catalysts has received a great deal of consideration.

The widely accepted mechanism of the regioselective hydrogenation of benzo[*b*] thiophenes over solid catalysts is shown in Scheme 140 [156]. Path A begins with the regioselective hydrogenation to 2,3-dihydrobenzo[*b*]thiophene prior to the C–S cleavage and subsequent desulfurization, while path B firstly breaks the C–S bond



Scheme 141 Reductive desulfurization of T and BT by [(triphos)RhH] [157]



Scheme 142 Reductive desulfurization of T and BT by Ir-complex [158]

followed by hydrogenation of the cleaved benzo[*b*]thiophene molecule. However, there are no reports that detail the catalytic opening and hydrogenation of BT assisted by transition metal complexes (Scheme 140).

The rhodium hydride, [(triphos)RhH], will react with thiophene and benzo[*b*] thiophene to yield complexes **129** and **130**, respectively, which yield other Rh-containing complexes when they were subjected to electrophilic reagents [7]. The catalytic transformation of BT into 2-ethylthiophenol can be achieved with this soluble rhodium complex (Scheme 141) [157].

DHBT can be readily converted into 2-ethylthiophenol on being reacted with an iridium complex [158]. The mechanism was assessed by in situ multinuclear NMR spectroscopy, allowing detection of a key intermediate of iridium η^1-DHBT complex, which had been reported rarely before (Scheme 142).

4 Conclusions and Perspective

The common and/or recent methods to prepare thiophene oxides and their Diels–Alder reactions, along with the reduction chemistry of thiophenes, are described in this chapter. Besides the methods which have been known for a long time, additional development of methods that involve thiophene oxidation and cycloaddition reactions as well as thiophene reduction reactions is also likely to continue to attract interest and research efforts. In addition, there is a huge potential for both applications and further methodological developments in the field of Diels–Alder cycloaddition reactions for preparing key compounds of importance.

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