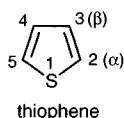
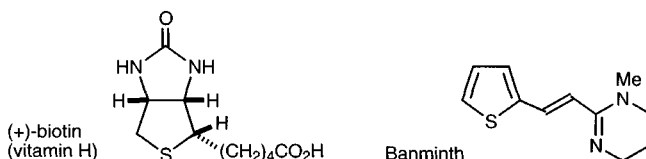


14 Thiophenes: reactions and synthesis



The simple thiophenes¹ are stable liquids which closely resemble the corresponding benzene compounds in boiling points and even in smell. They occur in coal tar distillates – the discovery of thiophene in coal tar benzene provides one of the classic anecdotes of organic chemistry. In the early days, colour reactions were of great value in diagnosis: an important one for benzene involved the production of a blue colour on heating with isatin (section 14.1.1.7) and concentrated sulfuric acid. In 1882, during a lecture-demonstration by Viktor Meyer before an undergraduate audience, this test failed, no doubt to the delight of everybody except the professor, and especially except the professor's lecture assistant. An inquiry revealed that the lecture assistant had run out of commercial benzene and had provided a sample of benzene which he had prepared by decarboxylation of pure benzoic acid. It was thus clear that commercial benzene contained an impurity and that it was this, not benzene, which was responsible for the colour reaction. In subsequent investigations, Meyer isolated the impurity *via* its sulfonic acid derivative and showed it to be the first representative of a then new ring system, which was named thiophene from *theion*, the Greek word for sulfur, and another Greek word *phaino* which means shining, a root first used in phenic acid (phenol) because of its occurrence in coal tar, a by-product of the manufacture of illuminating gas.



Aromatic thiophenes play no part in animal metabolism; biotin, one of the vitamins, is a tetrahydrothiophene, however aromatic thiophenes do occur in some plants, in association with polyacetylenes with which they are biogenetically linked. Banminth (Pyrantel), a valuable anthelmintic used in animal husbandry, is one of the few thiophene compounds in chemotherapy.

14.1 Reactions with electrophilic reagents

14.1.1 Substitution at carbon

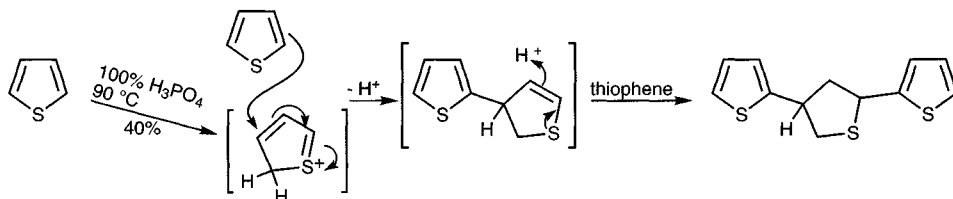
14.1.1.1 Protonation

Thiophene is stable to all but very strongly acidic conditions so many reagent combinations which lead to acid-catalysed decomposition or polymerisation of furans and pyrroles, can be applied successfully to thiophenes.

Measurements of acid-catalysed exchange, or of protonolysis of other groups, for example silicon,² or mercury,³ show the rate of proton attack at C-2 to be about 1000 times faster than at C-3.⁴ The pK_a for 2,5-di-*t*-butylthiophene forming a salt by protonation at C-2, is -10.2 .⁵

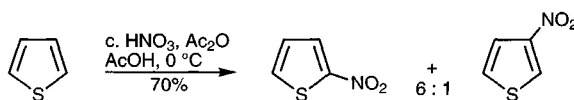
Reactions of protonated thiophenes

The action of hot phosphoric acid on thiophene leads to a trimer;⁶ its structure suggests that, in contrast with pyrrole (section 13.1.8), the electrophile involved in the first C–C bonding step is the α -protonated cation.



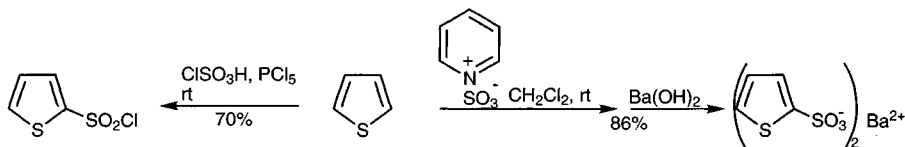
14.1.1.2 Nitration

Nitration of thiophene needs to be conducted in the absence of nitrous acid which can lead to an explosive reaction;⁷ the use of acetyl nitrate⁸ or nitronium tetrafluoroborate⁹ are satisfactory. Invariably the major 2-nitro-product is accompanied by approximately 10% of the 3-isomer.¹⁰ Further nitration of either 2- or 3-nitrothiophenes¹¹ also leads to mixtures – equal amounts of 2,4- and 2,5-dinitrothiophenes from the 2-isomer, and mainly the former from 3-nitrothiophene.¹² Similar, predictable isomer mixtures are produced in other nitrations of substituted thiophenes, for example 2-methylthiophene gives rise to 2-methyl-5- and 2-methyl-3-nitrothiophenes,¹³ and 3-methylthiophene gives 4-methyl-2-nitro- and 3-methyl-2-nitrothiophenes,¹⁴ in each case in ratios of 4:1.



14.1.1.3 Sulfonation

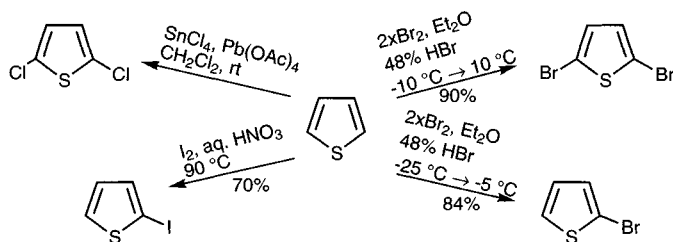
As discussed in the introduction, the production of thiophene-2-sulfonic acid by sulfuric acid sulfonation of the heterocycle has been long known;¹⁵ use of the pyridine-sulfur trioxide complex is probably the best method.¹⁶ 2-Chlorosulfonation¹⁷ and 2-thiocyanation¹⁸ are similarly efficient.



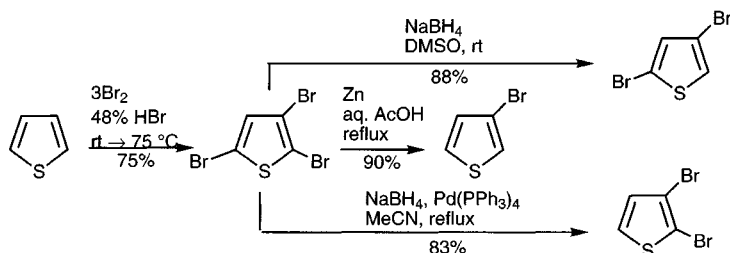
14.1.1.4 Halogenation

Halogenation of thiophene occurs very readily at room temperature and is rapid even at -30°C in the dark; tetrasubstitution occurs easily.¹⁹ The rate of halogenation of

thiophene, at 25 °C, is about 10^8 times that of benzene.²⁰ Both 2,5-dibromo- and 2,5-dichlorothiophenes²¹ and 2-bromo-²² and 2-iodothiophene²³ can be produced cleanly under various controlled conditions. Controlled bromination of 3-bromothiophene produces 2,3-dibromothiophene.²⁴



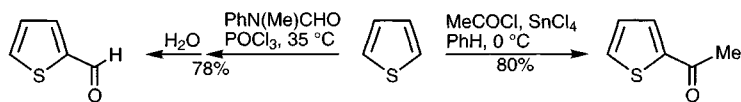
2,3,5-Tribromination of thiophene goes smoothly in 48% hydrobromic acid solution.²⁵ Since it has long been known that treatment of polyhalogenothiophenes with zinc and acid brings about selective removal of α -halogen, this compound can be used to access 3-bromothiophene²⁶ just as 3,4-dibromothiophene can be obtained by reduction of the tetrabromide.²⁷ One interpretation of the selective reductive removal is that it involves first, electron transfer to the bromine, then subsequently, transient 'anions', thus halogen can be selectively removed from that position where such an anion is best stabilised – normally an α position (section 14.4.1). The use of sodium borohydride, respectively with and without palladium(0) catalysis, converts 2,3,5-tribromothiophene into 2,3-dibromothiophene and 2,4-dibromothiophene.²⁸



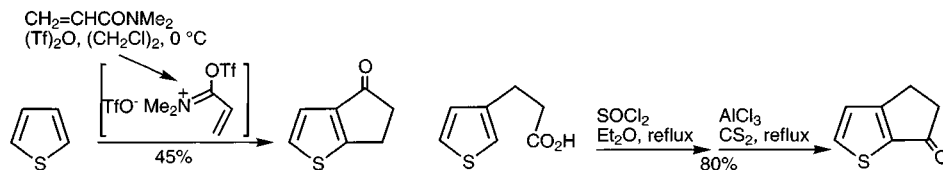
Monoiodination of 2-substituted thiophenes, whether the substituent is activating or deactivating, proceeds efficiently at the remaining α -position using iodine with iodobenzene diacetate.²⁹ 3-Alkylthiophenes can be monobrominated or monoiodinated at C-2 using *N*-bromosuccinimide³⁰ or iodine with mercury(II) oxide,³¹ respectively.

14.1.1.5 Acylation

The Friedel-Crafts acylation of thiophenes is a much-used reaction and generally gives good yields under controlled conditions, despite the fact that aluminium chloride reacts with thiophene to generate tars: this problem can be avoided by adding catalyst to the thiophene and the acylating agent;³² tin tetrachloride has been used most frequently. Acylation with anhydrides, catalysed by phosphoric acid³³ is an efficient method. Reaction with acetyl *p*-toluenesulfonate, in the absence of any catalyst produces 2-acetylthiophene in high yield.³⁴ Vilsmeier formylation of thiophene leads efficiently to 2-formylthiophene;³⁵ 2-formylation results when 3-phenylthiophene is subjected to Vilsmeier conditions.³⁶



In acylations, almost exclusive α -substitution is observed, but where both α -positions are substituted, β -substitution occurs easily. This is nicely illustrated by the synthesis of the isomeric bicyclic ketones shown below.³⁷

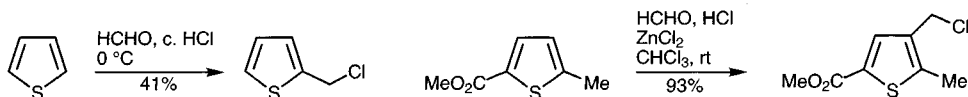


14.1.1.6 Alkylation

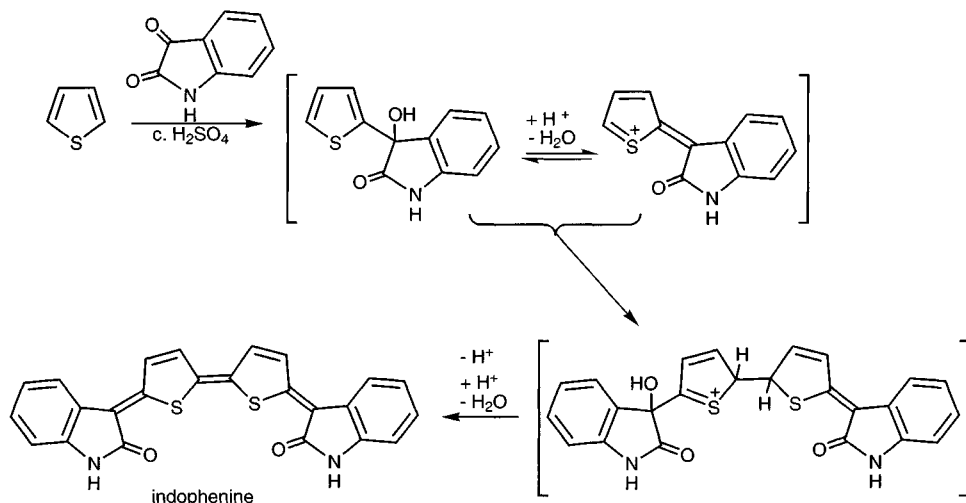
Alkylation occurs readily, but is rarely of preparative use; the efficient 2,5-bis-*t*-butylation of thiophene is one such example.³⁸

14.1.1.7 Condensation with aldehydes and ketones

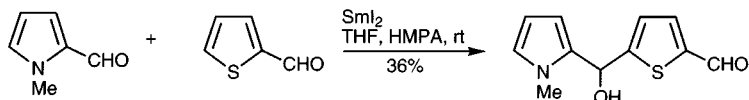
Acid-catalysed reaction of thiophene with aldehydes and ketones is not a viable route to hydroxyalkylthiophenes, for these are unstable under the reaction conditions. Chloroalkylation can however be achieved³⁹ and with the use of zinc chloride, even thiophenes carrying electron-withdrawing groups react.⁴⁰ Care is needed in choosing conditions; there is a tendency for formation of either di-2-thienylmethanes⁴¹ or 2,5-bis(chloromethyl)thiophene.⁴²



A reaction of special historical interest, mentioned in the introduction to this chapter, is the condensation of thiophene with isatin in concentrated sulfuric acid, to give the deep blue indophenine⁴³ as a mixture of geometrical isomers.⁴⁴

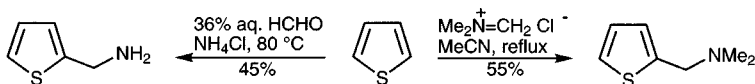


Hydroxyalkylation at the 5-position of 2-formylthiophene results from exposure of the thiophene aldehyde and a second aldehyde, to samarium(II) iodide; in the example shown below the other aldehyde is 1-methylpyrrole-2-aldehyde.⁴⁵

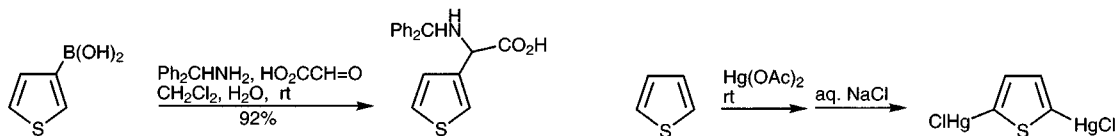


14.1.1.8 Condensation with imines and iminium ions

Aminomethylation of thiophene⁴⁶ was reported long before the more common Mannich reaction – dimethylaminomethylation, which, although it can be achieved under routine conditions with methoxythiophenes,⁴⁷ requires the use of $\text{Me}_2\text{N}^+ = \text{CH}_2 \text{Cl}^-$ ('Eschenmoser's salt' is the iodide) for thiophene and alkylthiophenes.⁴⁸



Another device for bringing thiophenes into reaction with Mannich intermediates is to utilise thiophene boronic acids, as illustrated below; primary aromatic amines can be used as the amine component.⁴⁹

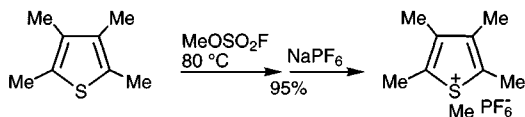


14.1.1.9 Mercuration

Mercuration of thiophenes occurs with great ease; mercuric acetate is more reactive than the chloride;⁵⁰ tetrasubstitution and easy replacement of the metal with halogen can also be achieved straightforwardly.⁵¹

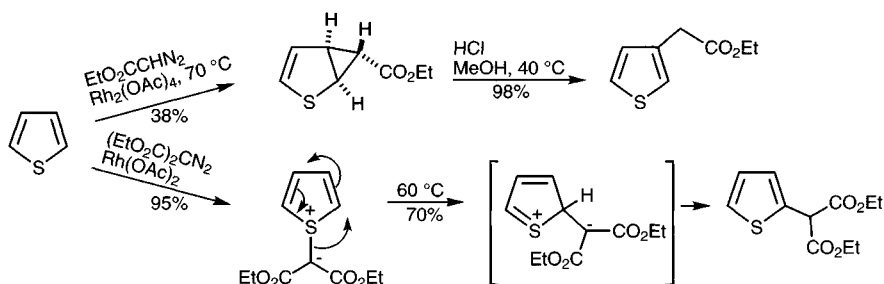
14.1.2 Addition at sulfur

In reactions not possible with the second row element-containing pyrrole and furan, thiophene sulfur can add electrophilic species. Thiophenium salts⁵² though not formed efficiently from thiophene itself, are produced in high yields with polyalkyl-substituted thiophenes.⁵³ The sulfur in such salts is probably tetrahedral,⁵⁴ i.e. the sulfur is sp^3 hybridised.

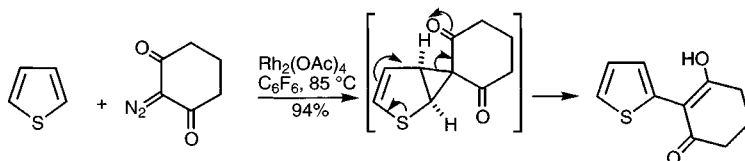


Even thiophene itself will react with carbenes, at sulfur, to produce isolable thiophenium ylides, and in these, the sulfur is definitely tetrahedral.⁵⁵ The rearrangement⁵⁶ of thiophenium bis(methoxycarbonyl)methylide to the 2-substituted thiophene provides a rationalisation for the reaction of thiophene with ethyl diazoacetate⁵⁷ which produces what appears to be the product of carbene addition to the 2,3-double bond; perhaps this goes *via* initial attack at sulfur followed by $\text{S} \rightarrow \text{C}-2$

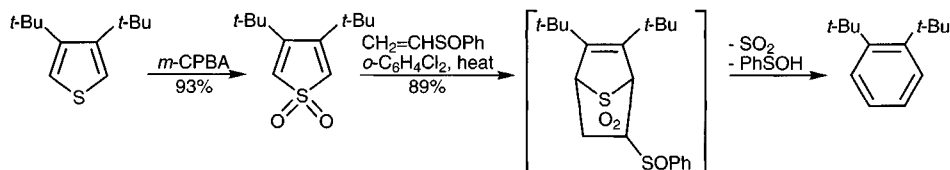
rearrangement then collapse to the cyclopropane. Acid catalyses conversion of the cyclopropanated compound into a thiophene-3-acetic ester.⁵⁸ 2,5-Dichlorothiophenium bis(methoxycarbonyl)methylide has been used as an efficient source of the carbene: simply heating it in an alkene results in the transfer of $(\text{MeO}_2\text{C})_2\text{C}$ to the alkene.⁵⁹



In a rhodium-promoted carbenoid reaction, a 2-substituted thiophene is the final isolated product; the sequence below shows how this can be understood as involving a cyclopropanated intermediate.⁶⁰



Uncontrolled *S*-oxidation of a thiophene leads to *S,S*-dioxides; that from thiophene itself has been isolated, but above -40°C it dimerises giving eventual products depending on concentration,⁶¹ but with substituted thiophenes the dioxides can be isolated. Peracids⁶² or 3,3-dimethyldioxirane⁶³ can be used, but do not succeed if there are electron-withdrawing substituents. A solution of fluorine in water (hypofluorous acid) will however achieve the objective even with thiophenes carrying electron-withdrawing groups.⁶⁴ The *S,S*-dioxides are no longer aromatic thiophenes and react as dienes in Diels-Alder reactions; generally sulfur dioxide is extruded from the initial adduct, leading to further reaction⁶⁵ – eventual aromatisation in the example shown.⁶⁶

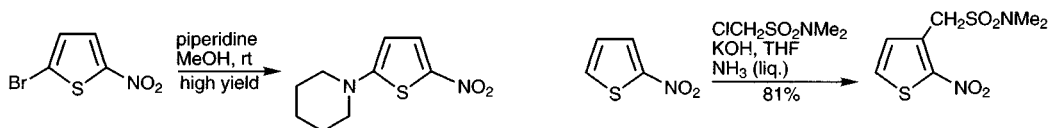


14.2 Reactions with oxidising agents

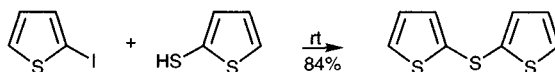
Apart from the *S*-oxidations discussed above, the thiophene ring system, unless carrying electron-releasing substituents, is relatively stable to oxidants; side-chains can be oxidised to carboxylic acid groups, though not usually in synthetically useful yields.

14.3 Reactions with nucleophilic reagents

Nitro-substituents activate the displacement of leaving groups like halide, as in benzene chemistry, and extensive use of this has been made in thiophene chemistry. It has been shown that such nucleophilic displacements proceed at least 10^2 times faster than for benzenoid counterparts, and this may be accounted for by participation of the sulfur in the delocalisation of charge in the Meisenheimer intermediate.⁶⁷ Nitro groups also permit the operation of VNS processes (section 2.3.3) as illustrated below.⁶⁸



Activation provided by the sulfur may also account for the extremely easy displacement of iodine from the thiophene 2-position using alkyl- or arylthiols as nucleophiles.⁶⁹



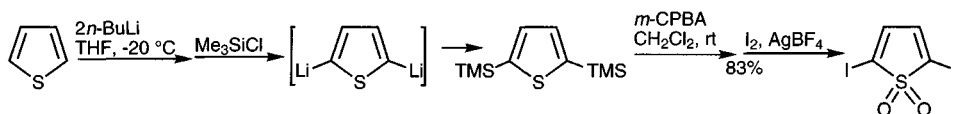
Copper and copper(I) salts have been used extensively in thiophene chemistry to catalyse displacement of bromine and iodine, but not chlorine, in simpler halothiophenes.⁷⁰



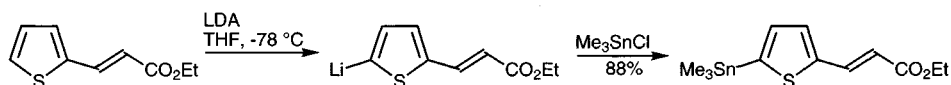
14.4 Reactions with bases

14.4.1 Deprotonation of C-hydrogen

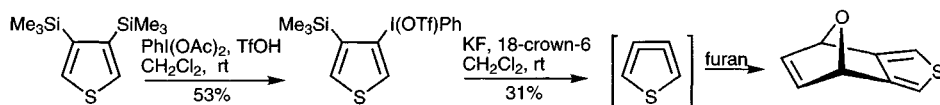
Monolithiation of thiophene takes place at C-2; two mol equivalents of lithiating agent easily produces 2,5-dilithiothiophene.⁷¹ 3-Lithiothiophene is unstable with respect to the 2-isomer at temperatures $> -25^\circ\text{C}$ in ether solution but is stable in hexane;⁷² the corresponding zinc and magnesium derivatives retain regio integrity even at room temperature.⁷³



Lithiation at a thiophene β -position, in the presence of a free α -position, has been achieved with the assistance of an *ortho*-directing substituent at C-2.⁷⁴ Thiophene-2-carboxylic acid lithiates at C-3, *via ortho* assistance, using *n*-butyllithium,⁷⁵ but at C-5, using lithium diisopropylamide.⁷⁶ 3-(Oxyalkyl)thiophenes, again with *ortho* assistance, are lithiated at C-2.⁷⁷ The lithiation of 2-chloro-5-methoxythiophene at C-4 and C-3, in a ratio of 2:1, is instructive⁷⁸ as is the deprotonation of 2- and 3-bromothiophenes at 5- and 2-positions respectively with LDA.⁷⁹ The conversion of 3-isopropylthiophene into the 2-aldehyde by Vilsmeier formylation but into the 5-aldehyde via lithiation presents a nice contrast.⁸⁰



The formation of arynes has often been achieved by base-induced dehydrohalogenation but for the formation of 3,4-didehydrothiophene a fluoride-induced process can be used, following *ipso* electrophilic displacement of one of the silicons to generate the appropriate precursor.⁸¹

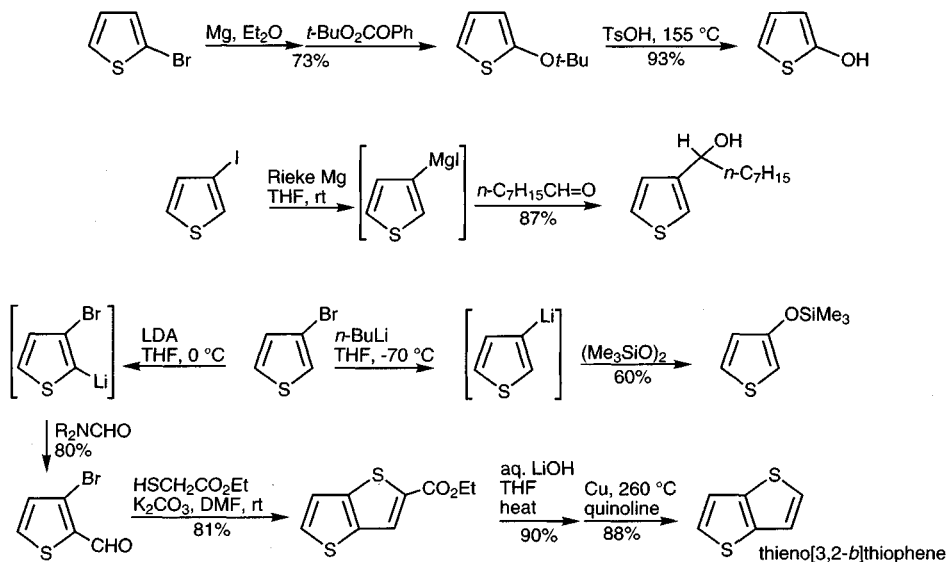


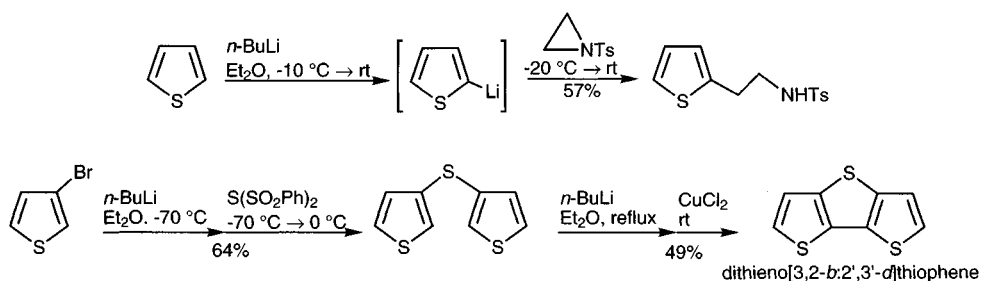
14.5 Reactions of C-metallated thiophenes

14.5.1 Lithium and magnesium derivatives

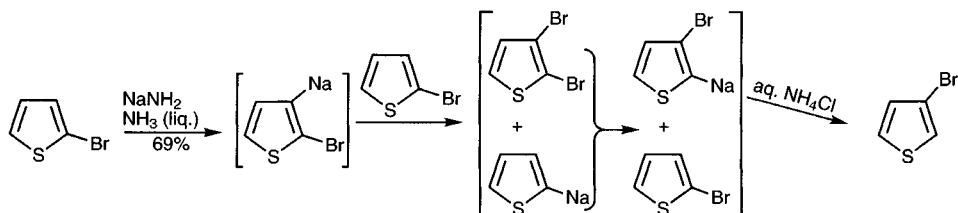
2-Bromo- and 2-iodothiophenes readily form thienyl Grignard reagents⁸² though 3-iodothiophene requires the use of Rieke magnesium.⁷³ Bromine and iodine at either α - or β -positions undergo exchange with alkylolithiums giving lithiated thiophenes. The reaction of 2,3-dibromothiophene with *n*-butyllithium produces 3-bromothien-2-ylolithium.⁸³

The use of thienyl Grignard reagents, and more recently lithiated thiophenes, has been extensive and can be illustrated by citing formation of oxythiophenes, either by reaction of the former with *t*-butyl perbenzoate⁸⁴ or the latter directly with bis(trimethylsilyl) peroxide⁸⁵ or *via* the boronic acid,⁸⁶ the synthesis of thiophene carboxylic acids by reaction of the organometallic with carbon dioxide,⁸⁷ the synthesis of ketones, by reaction with a nitrile,⁸⁸ or alcohols by reaction with aldehydes,⁷³ by the reaction of 2-lithiothiophene with *N*-tosylaziridine,⁸⁹ and by syntheses of thieno[3,2-*b*]thiophene⁹⁰ and of dithieno[3,2-*b*:2',3'-*d*]thiophene.⁹¹ Some of these are illustrated below.

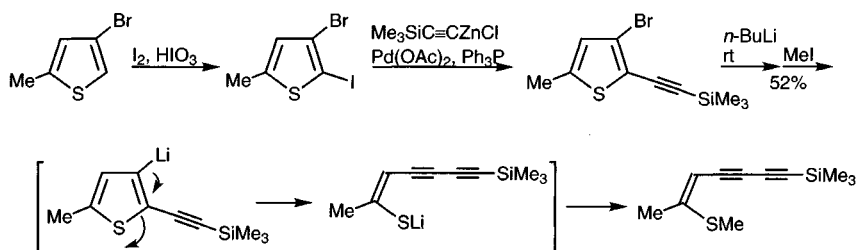




There are two complications which can arise in the formation and the use of lithiated thiophenes: the occurrence of a 'Base Catalysed Halogen Dance',⁹² and the isomerisation or ring opening of 3-lithiated thiophenes. As an example of the first of these, and one in which the phenomenon is put to good use, consider the transformation of 2-bromothiophene into 3-bromothiophene by reaction with sodamide in ammonia.⁹³ The final result is governed, in a set of equilibrations, by the stability of the final anion: the system settles to an anion in which the charge is both adjacent to halogen and at an α -position.



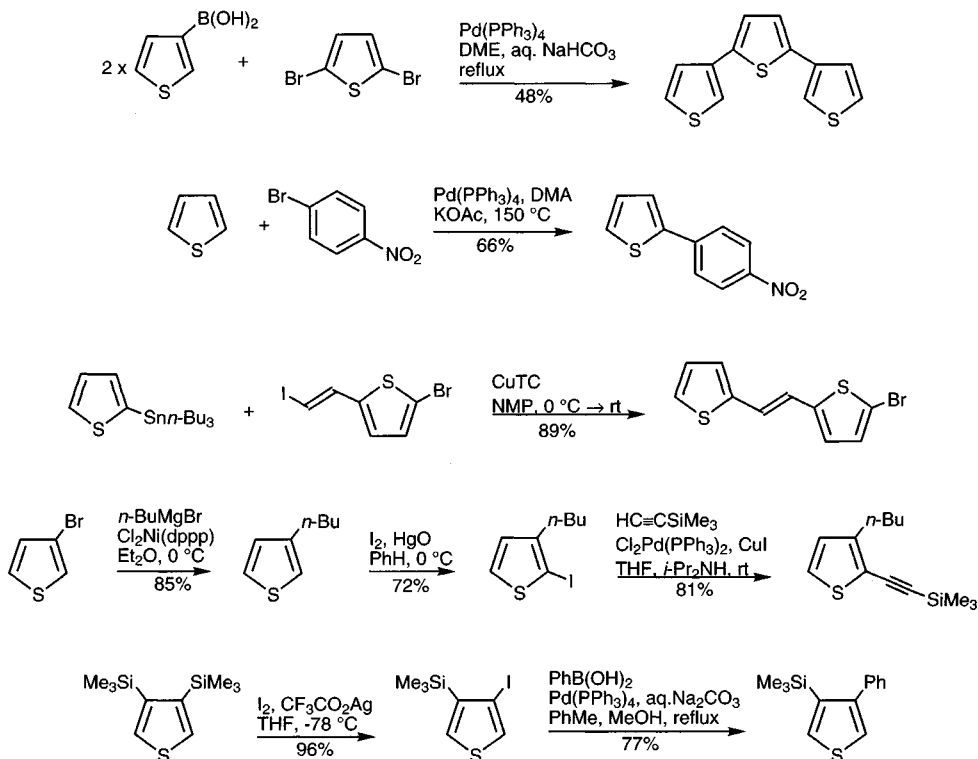
3-Lithiothiophene can be utilised straightforwardly at low temperature but if the temperature is increased, ring-opening can occur. The ring opening can be used to advantage in the synthesis of *Z*-enynes by trapping with an alkyl halide, as illustrated below.⁹⁴



14.5.2 Palladium-catalysed reactions (also nickel- and copper-catalysed reactions)

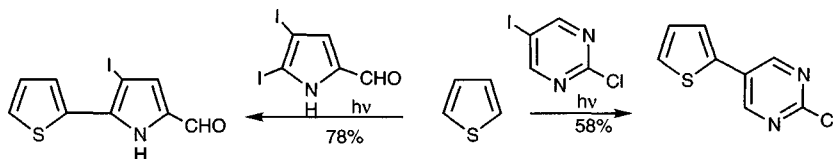
There are by now many examples involving palladium(0)-catalysed couplings using halothiophenes, thiophene boronic acids, thienylstannanes, and thienylzinc reagents.⁹⁵ In substrates where there is halogen at both thiophene α - and β -positions, the former enters into reaction. Representative examples, some of which are illustrated below, include the production of arylthiophenes using thiophene-2- and -3-boronic acids⁹⁶ and thiophene stannanes,²⁴ and directly from the heterocycle with an aryl halide leading to 2-substitution;⁹⁷ the formation of thienyl-alkynes,^{81,98} thienyl-alkenes from thienyl halides and from thienyl stannanes,⁹⁹ the formation of fused ring systems from bromo-amino-thiophenes or formylthiophene boronic

acids,¹⁰⁰ and the nickel(0)-catalysed couplings of thienylzinc, -magnesium and -manganese compounds generated using the Rieke (activated) metals.¹⁰¹

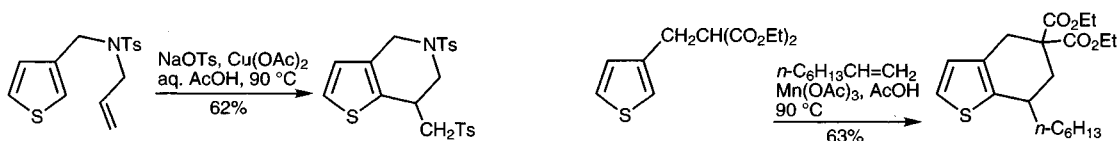


14.6 Reactions with radical reagents

The production of arylthiophenes by radical substitution was never a particularly efficient procedure and has now been superseded by palladium-catalysed coupling processes. Aryl radicals generated by a variety of methods,¹⁰² the most effective of which are aprotic diazotisation¹⁰³ and photolysis of iodoarenes, particularly iodohetarenes,¹⁰⁴ give 2-substituted thiophenes.

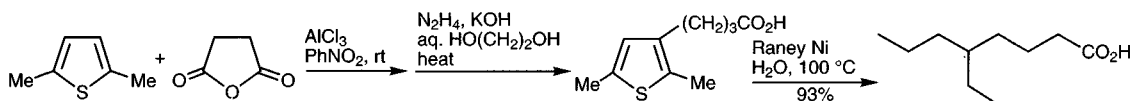


Radicals generated in various ways have been utilised in elaborating thiophenes and in ring closing reactions; examples are shown below.^{105,106}



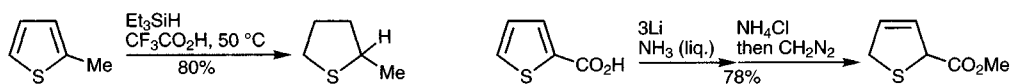
14.7 Reactions with reducing agents

Catalytic reductions of the thiophene ring, or of substituents attached to it, are complicated by two factors: poisoning of the catalyst, and the possibility of competing hydrogenolysis – reductive removal of sulfur, particularly with Raney nickel – indeed the use of thiophenes as templates on which to elaborate a structure, followed finally by desulfurisation is an important synthetic strategy (for another example see section 14.13.2.3). This has been developed extensively for thiophene acids, where the desulfurisation can be achieved very simply by dissolving Raney nickel alloy in an alkaline aqueous solution of the acid,¹⁰⁷ and for long chain hydrocarbons,¹⁰⁸ and large-ring ketones.¹⁰⁹



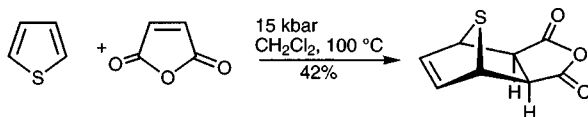
Sodium/ammonia¹¹⁰ treatment also causes disruption of the ring in thiophene and simple thiophenes, however thiophene-2-carboxylic acid and 2-acylthiophenes can be converted into the 2,5-dihydro-derivatives using lithium in ammonia followed by protonation or trapping with an alkyl halide.¹¹¹ Side-chain reductions can be carried out with metal hydrides, which do not affect the ring.

Simple saturation of the ring can be achieved using ‘ionic hydrogenation’,¹¹² i.e. a combination of a trialkylsilane and acid, usually trifluoroacetic; the reduction proceeds *via* a sequence of proton then ‘hydride’ additions¹¹³ and consequently requires electron-releasing substituents to facilitate the first step. 2,5-Dihydro-products accompany tetrahydrothiophenes as products of reductions with zinc and trifluoroacetic acid.¹¹⁴

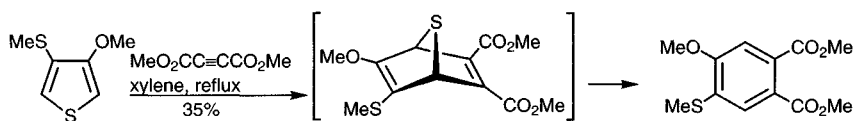


14.8 Electrocyclic reactions (ground state)¹¹⁵

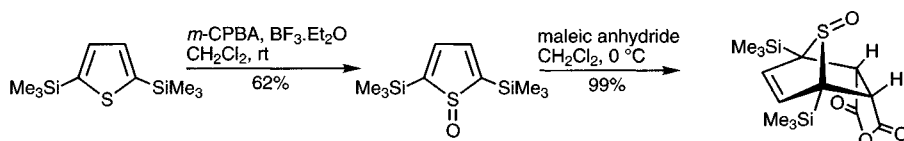
Unactivated thiophenes show little tendency to give products as 4 π components in a Diels-Alder sense, for example even at 15 kbar, only maleic anhydride, of the common, electron-deficient dienophilic partners, gives an adduct.¹¹⁶ Electrophilic alkynes will react with thiophenes under vigorous conditions,¹¹⁷ though the initial adduct extrudes sulfur and substituted benzenes are obtained as products.



However, both α - and β -methoxy-substituted thiophenes react with dimethyl acetylenedicarboxylate in xylene to give modest yields of phthalates resulting from sulfur extrusion from initial adducts; in acetic acid as solvent only substitution products are obtained.¹¹⁸



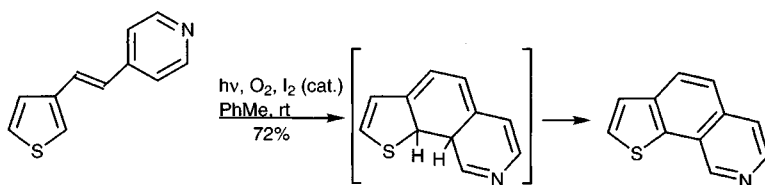
The strong tendency for thiophene-*S,S*-dioxides to undergo cycloaddition processes (section 14.1.2) is echoed, to a lesser degree by thiophene *S*-oxides. Thus, when thiophenes are oxidised with *meta*-chloroperbenzoic acid and boron trifluoride (without which *S,S*-dioxides are formed), in the presence of a dienophile, adducts from 2 + 4 addition can be isolated.¹¹⁹ Thiophenes 2,5- or 3,4-disubstituted with bulky groups can be converted into isolable *S*-oxides¹²⁰ which undergo cycloadditions as shown below.¹²¹



14.9 Photochemical reactions

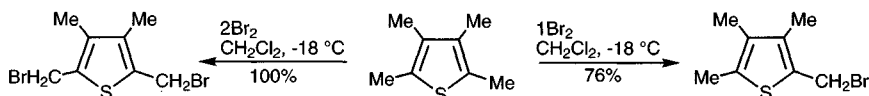
The classic photochemical reaction involving thiophenes is the isomerisation of 2-arylthiophenes to 3-arylthiophenes;¹²² the aromatic substituent remains attached to the same carbon and the net effect has been shown to involve interchange of C-2 and C-3, with C-4 and C-5 remaining in the same relative positions; scrambling of deuterium labelling is however observed and the detailed mechanism for the rearrangement is still a matter for discussion.

There are an appreciable number of examples in which photochemical ring closure of a 1-thienyl-2-aryl (or heteroaryl) ethene, carried out in the presence of an oxidant (often oxygen) to trap/aromatise a cyclised intermediate, leads to polycyclic products; an example^{123,124} is shown below.



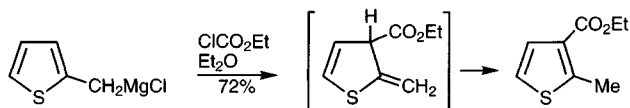
14.10 Thiophene-C-X compounds: thenyl derivatives

The unit – thiophene linked to a carbon – is termed thenyl, hence thenyl chloride is the product of chloromethylation (section 14.1.1.7); thenyl bromides are usually made by side-chain radical substitution,¹²⁵ substitution at an α -methyl being preferred over a β -methyl.¹²⁶



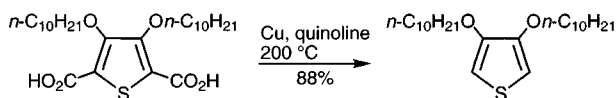
Relatively straightforward benzene-analogue reactivity is found with thenyl halides, alcohols (conveniently preparable by reducing aldehydes) and amines,

from for example, reduction of oximes. One exception is that 2-thenyl Grignard reagents usually react to give 3-substituted derivatives, presumably *via* a non-aromatic intermediate.¹²⁷



14.11 Thiophene aldehydes and ketones, and carboxylic acids and esters

Here, the parallels with benzenoid counterparts continue, for these compounds have no special properties – their reactivities are those typical of benzenoid aldehydes, ketones, acids, and esters. For example, in contrast to the easy decarboxylation of α -acids observed for pyrrole and furan, thiophene-2-acids do not easily lose carbon dioxide nevertheless, high temperature decarboxylations are of preparative value (see also 14.13.1.2).¹²⁸

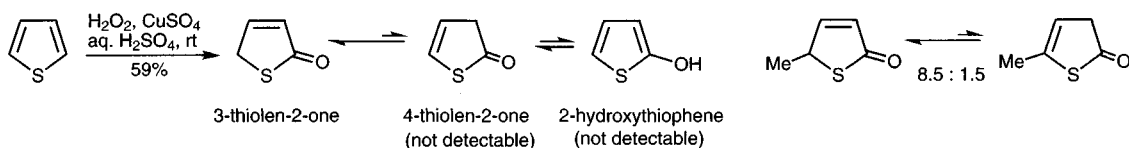


Just as in benzene chemistry, Wolff-Kischner or Clemmensen reduction of ketones is a much-used route to alkylthiophenes, hypochlorite oxidation of acetylthiophenes a good route to thiophene acids, Beckmann rearrangement of thiophene oximes is a useful route to acylaminothiophenes and hence aminothiophenes, and esters and acids are interconvertible without complications.

14.12 Oxy- and aminothiophenes

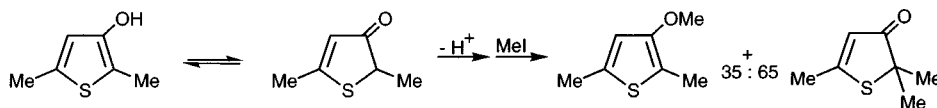
14.12.1 Oxythiophenes

These compounds are much more difficult to handle and much less accessible than phenols. Neither 2-hydroxythiophene nor its 4-thiolen-2-one tautomer are detectable, the compound existing as the conjugated enone isomer.¹²⁹ Thiophene can be converted directly into its 2-oxygenated derivative.¹³⁰

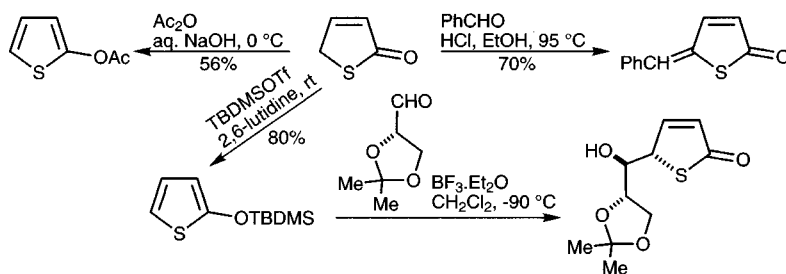


The inclusion of alkyl groups both stabilise the oxy-compounds and the double bond to which they are attached. In these more stable compounds alternative tautomers are found, thus 5-methyl-2-hydroxythiophene exists as a mixture (actually separable by fractional distillation!) of the two enone tautomers.¹³¹

β -Hydroxythiophenes are even more unstable than α -hydroxythiophenes; 3-hydroxy-2-methylthiophene exist as a mixture of hydroxyl and carbonyl tautomeric forms with the former predominating.¹³²



The acidities of the thienones are comparable with those of phenols, with pK_a s of about 10. Oxythiophene anions can react at oxygen or carbon and products from reaction of electrophiles at both centres can be obtained.¹³³ Silylation generates 2-silyloxy derivatives which react with aldehydes in the presence of boron trifluoride as shown below.¹³⁴



14.12.2 Aminothiophenes

Here again, these thiophene derivatives are much less stable than their benzenoid counterparts, unless the ring is provided with other substitution.¹³⁵ The unsubstituted aminothiophenes (thiophenamines) can be obtained by reduction of the nitrothiophenes,¹³⁶ but in such a way as to isolate them as salts – usually hexachlorostannates – or *via* Beckmann rearrangements¹³⁷ or Hofmann degradation,¹³⁸ as acyl derivatives which are stable. Many substituted amines have been prepared by nucleophilic displacement of halogen in nitro-halo-thiophenes. In so far as it can be studied, in simple cases, and certainly in substituted thiophenamines, the amino form is the only detectable tautomer.¹³⁹

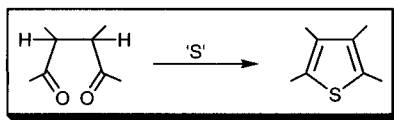
14.13 Synthesis of thiophenes¹⁴⁰

Thiophene is manufactured by the gas-phase interaction of C_4 hydrocarbons and elementary sulfur at 600 °C. Using *n*-butane the sulfur first effects dehydrogenation and then interacts with the unsaturated hydrocarbon by addition, further dehydrogenation generating the aromatic system.

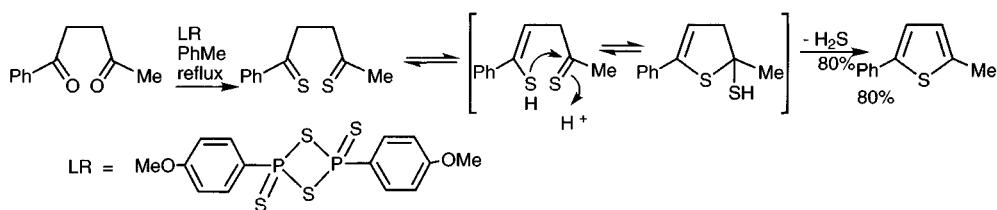
14.13.1 Ring synthesis

14.13.1.1 From 1,4-dicarbonyl compounds and a source of sulfur

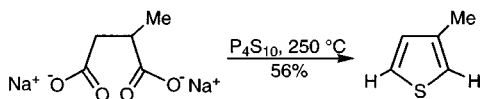
1,4-Dicarbonyl compounds can be reacted with a source of sulfur to give thiophenes.



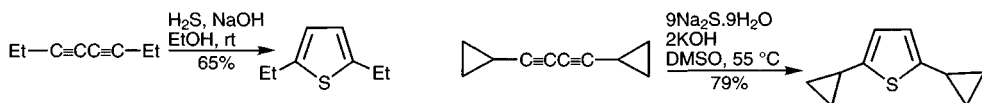
The reaction of a 1,4-dicarbonyl compound (see also 15.14.1.1) with a source of sulfur, traditionally phosphorus sulfides, latterly Lawesson's reagent (LR),¹⁴¹ or bis(trimethylsilyl)sulfide,¹⁴² gives thiophenes, presumably, but not necessarily, *via* the bis(thio ketone).



When the process is employed with 1,4-dicarboxylic acids, a reduction must occur at some stage, for thiophenes, and not 2,5-oxygenated thiophenes result.¹⁴³

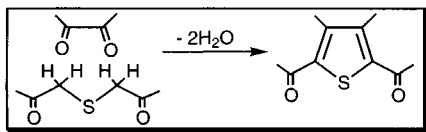


Much use has been made of conjugated diynes, also at the oxidation level of 1,4-dicarbonyl compounds, which react smoothly with hydrosulfide or sulfide, under mild conditions, to give 3,4-unsubstituted thiophenes. Unsymmetrical 2,5-disubstituted thiophenes can be produced in this way too.¹⁴⁴ Since nearly all naturally-occurring thiophenes are found in plant genera, and co-occur with polyynes, this laboratory ring synthesis may be mechanistically related to their biosynthesis.



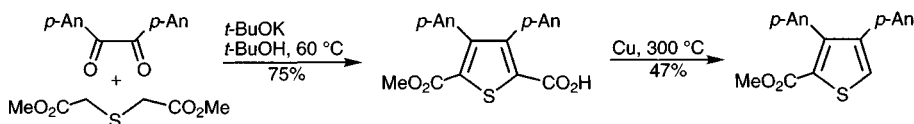
14.13.1.2 From thiodiacetates and 1,2-dicarbonyl compounds

1,2-Dicarbonyl compounds condense with thiodiacetates (or thiobismethyleneketones) to give thiophene-2,5-diacids (-diketones).



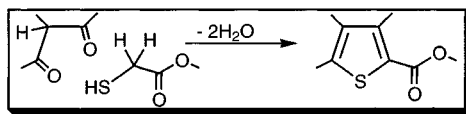
The Hinsberg synthesis

Two consecutive aldol condensations between a 1,2-dicarbonyl compound and diethyl thiodiacetate give thiophenes. The immediate product is an ester-acid, produced¹⁴⁵ by a Stobbe-type mechanism, but the reactions are often worked up *via* hydrolysis to afford an isolated diacid.

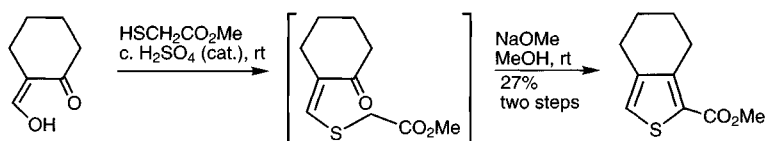


14.13.1.3 From thioglycolates and 1,3-dicarbonyl compounds

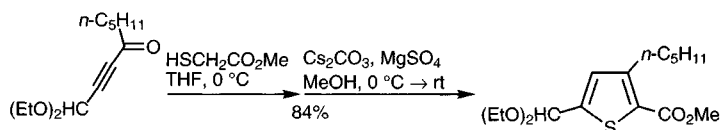
Thioglycolates react with 1,3-dicarbonyl compounds (or equivalents) to give thiophene-2-carboxylic esters.



In most of the examples of this approach, thioglycolates, as donors of an S–C unit, have been reacted with 1,3-keto-aldehydes, to give intermediates which can be ring closed to give thiophenes as exemplified below.¹⁴⁶

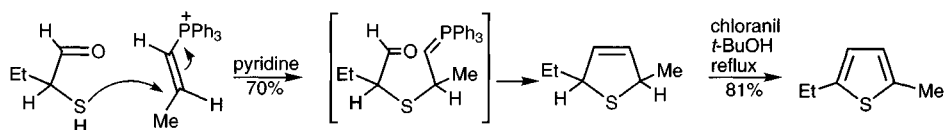


Alkynylketones react with thioglycolate to generate comparable intermediates by conjugate addition to the triple bond.¹⁴⁷



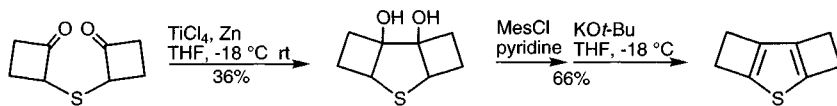
14.13.1.4 From α -thiocarbonyl compounds

2-Keto-thiols add to alkenylphosphonium ions, affording ylides which then ring close by Wittig reaction and give 2,5-dihydrothiophenes, which can be dehydrogenated.¹⁴⁸



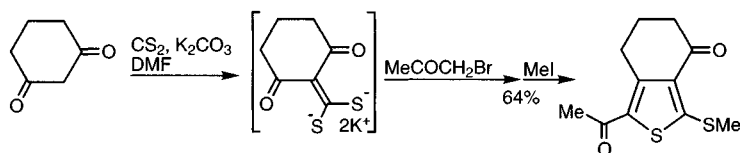
14.13.1.5 From thio-diketones

A route¹⁴⁹ in which the 3,4-bond is made by an intramolecular pinacol reaction is nicely illustrated¹⁵⁰ below by the formation of a tricyclic thiophene with two cyclobutane fused rings. The starting materials for this route are easily obtained from sodium sulfide and two mol equivalents of a 2-bromoketone.

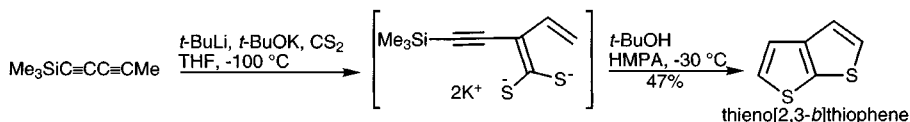


14.13.1.5 Using carbon disulfide

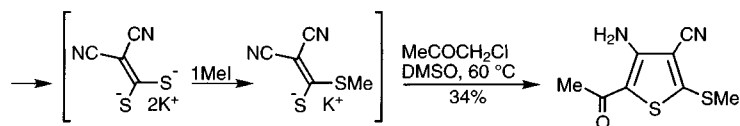
The addition of a carbanion to carbon disulfide with a subsequent *S*-alkylation provides a route to 2-alkylthiophenes.¹⁵¹ In the example below, the carbanion is the enolate of a cyclic 1,3-diketone.



A truly delightful exploitation of this idea is a synthesis of thieno[2,3-*b*]thiophene in which a diyne is lithiated to give a lithio-allene which reacts with carbon disulfide.¹⁵²

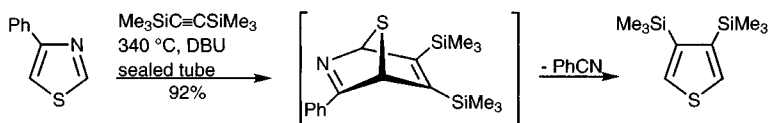


When the enolate is that derived from malononitrile,¹⁵³ 3-amino-4-cyanothiophenes are the result.¹⁵⁴



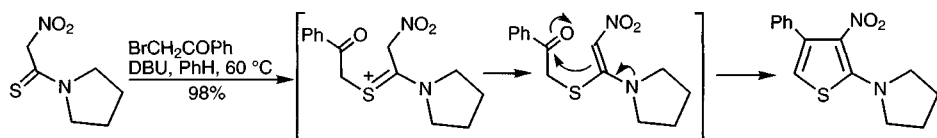
14.13.1.6 From thiazoles

The cycloaddition/cycloreversion sequence which ensues when thiazoles (the best in this context is 4-phenylthiazole) are heated strongly with an alkyne, generates 2,5-unsubstituted thiophenes. Though the conditions are vigorous, excellent yields can be obtained.⁸¹



14.13.1.7 From thio-nitroacetamides

The *S*-alkylation of thio-nitroacetamides with 2-bromoketones produces 2-amino-3-nitrothiophenes. The scheme below shows how the 3,4-bond making involves the intramolecular interaction of the introduced ketone carbonyl with an enamine/thioenol β -carbon.¹⁵⁵

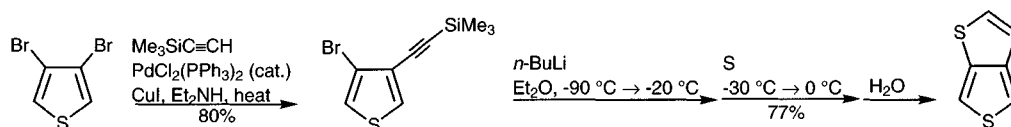


14.13.2 Examples of notable syntheses of thiophene compounds

14.13.2.1 Thieno[3,4-*b*]thiophene¹⁵⁶

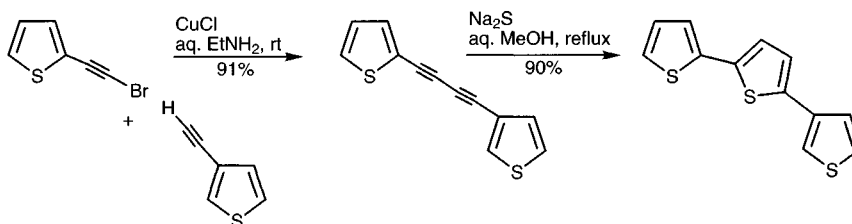
Thieno[3,4-*b*]thiophene was prepared from 3,4-dibromothiophene utilising the two halogens in separate steps: palladium-catalysed coupling and lithiation by

transmetallation followed by introduction of sulfur and intramolecular addition to the alkyne



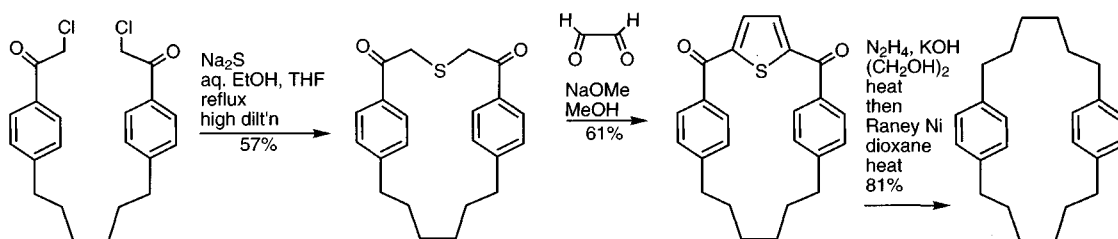
14.13.2.2 2,2':5',3''-Terthiophene¹⁵⁷

This sequence, for the regioselective synthesis of 2,2':5',3''-terthiophene uses the reaction of a diyne with sulfide to make the central ring.



14.13.2.3 [6.6]Paracyclophane¹⁵⁸

Here the thiophene rings were produced using the Hinsberg approach; hydrogenolytic removal of sulfur, having served its purpose to allow construction of the large ring, gave the cyclophane.



Exercises for chapter 14

Straightforward revision exercises (consult chapters 12 and 14)

- How could one prepare 2-bromo-, 3-bromo- and 3,4-dibromothiophenes?
- What would be the products of carrying out Vilsmeier reactions with 2-methyl- and 3-methylthiophenes?
- How could one convert 2,5-dimethylthiophene into (i) its *S*-oxide and (ii) its *S,S*-dioxide?
- What routes could one use to convert thiophene into derivatives carrying at the 2-position: (i) $\text{CH(OH)}t\text{-Bu}$; (ii) $(\text{CH}_2)_2\text{OH}$; (iii) Ph ?
- How could one prepare *n*-decane from thiophene?
- Draw the structures of the thiophenes which would be produced from the following reactant combinations: (i) octane-3,6-dione and Lawesson's reagent; (ii) dimethyl thiodiacetate $[\text{S}(\text{CH}_2\text{CO}_2\text{Me})_2]$, cyclopentane-1,2-dione and base; (iii) pentane-2,4-dione, methyl thioglycolate $[\text{HSCH}_2\text{CO}_2\text{Me}]$ and base.

More advanced exercises

1. Deduce the structure of the compound, $C_4H_3NO_2S$, produced from thiophene by the following sequence: $ClSO_3H$, then f. HNO_3 , then H_2O /heat; the product is isomeric with that obtained by reacting thiophene with acetyl nitrate.
2. Suggest structures for the major and minor, isomeric products, $C_5H_5NO_3S$, from 2-methoxythiophene with $HNO_3/AcOH$ at $-20^\circ C$.
3. What compounds would be formed by the reaction of (i) thiophene with propionic anhydride/ H_3PO_4 ; (ii) 3-*t*-butylthiophene with $PhN(Me)CHO/POCl_3$ then aq. $NaOH$; (iii) thiophene with $Tl(O_2CCF_3)_3$, then aq. $KI \rightarrow C_4H_3IS$; (iv) thiophene/succinic anhydride/ $AlCl_3 \rightarrow C_8H_8O_3S$, then N_2H_4/KOH /heat $\rightarrow C_8H_{10}O_2S$, then $SOCl_2$, then $AlCl_3 \rightarrow C_8H_8OS$.
4. Predict the principle site of deprotonation on treatment of 2- and 3-methoxythiophenes with *n*-BuLi.
5. Deduce structures for the compounds, C_4HBr_3S and $C_4H_2Br_2S$, produced successively by treating 2,3,4,5-tetrabromothiophene with Mg then H_2O and then the product again with Mg then H_2O .
6. Deduce the structure of the compound, $C_9H_6OS_2$, produced by the sequence: thiophene with BuLi, then $CO_2 \rightarrow C_5H_4O_2S$, then this with thiophene in the presence of P_4O_{10} .
7. Deduce the structure of the thiophenes: (i) $C_6H_4N_4S$, produced by reacting $(NC)_2C=C(CN)_2$ with H_2S ; (ii) $C_8H_8O_6S$ from diethyl oxalate, $(EtO_2CCH_2)_2S/NaOEt$, aq. $NaOH$, then Me_2SO_4 ; (iii) $C_{11}H_{16}S$ from 3-acetylcyclononanone with P_4S_{10} .

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