The Chemistry of Heterocycles

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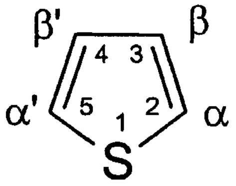
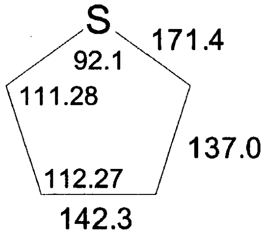
By Theophil Eicher and Siegfried Hauptmann, Wiley-VCH Veriag GmbH, 2003

5.6 Thiophene

[A] The univalent radical from thiophene is called thienyl. The ring atoms of thiophene are coplanar, as in furan. The greater atomic radius of sulfur causes the bond between the heteroatom and one of the α-C-atoms to be longer by 35.2 pm than in furan.





Structure of thiophene
(bond lengths in pm, bond angles in degrees)

The ionization potential of thiophene is 8.87 eV which is, according to KOOPMAN'S theorem, equal to the negative orbital energy of π_3. Because of the lower electronegativity of sulfur compared with oxygen, the dipole moment of 0.52 D is even smaller than that of furan. The chemical shifts in the NMR spectrum lie in the typical aromatic regions, as is the case with furan:

UV (95% ethanol)	^{1}H-NMR (CS_2)	^{13}C-NMR (acetone-d_6)
λ (nm) (ε)	δ (ppm)	δ (ppm)
215 (3.80)	H-2/H-5: 7.18	C-2/C-5: 125.6
231 (3.87)	H-3/H-4: 6.99	C-3/C-4: 127.3

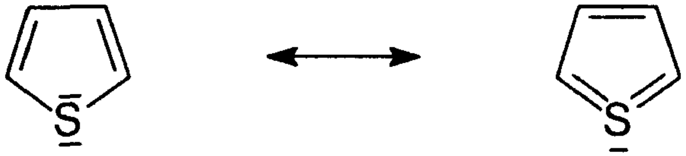
Thiophene is aromatic. Thiophene is a π-excessive heterocycle, i.e. the electron density on each ring atom is greater than one. The value of the empirical resonance energy of thiophene is approximately 120 kJ mol^{-1}; the DEWAR resonance energy is quoted as 27.2 kJ mol^{-1}.

The aromaticity of thiophene is thus less than that of benzene but greater than that of furan.

There are two possible explanations to account for the difference between thiophene and furan:

- Because of the lower electronegativity of sulfur compared with oxygen, the electron pair on sulfur is more effectively incorporated into the conjugated system, i.e. its delocalization produces more energy. This assumption is consistent with the dipole moments.

- Sulfur, as an element of the second short period, is capable of expanding its octet. Thus, its 3d-orbitals can take part in the conjugated system. This can be demonstrated by its resonance structures:



Spectroscopic measurements and MO calculations have shown, however, that the involvement of the 3d-orbitals in the aromatic system is negligible, certainly in the electronic ground state of the thiophene molecule.

[B] Thiophene prefers reactions with electrophilic reagents. Additions and ring-opening reactions are less important than with furan, and substitution reactions are dominant. Some additional reactions, such as oxidation and desulfurization, are due to the presence of sulfur and are thus confined to thiophenes.

Electrophilic substitutions

Thiophene reacts more slowly than furan but faster than benzene. The S_EAr reactivity of thiophene corresponds approximately to that of anisole. The reaction mechanism is the same as described for furan. Substitution is regioselective in the 2- or in the 2,5-position.

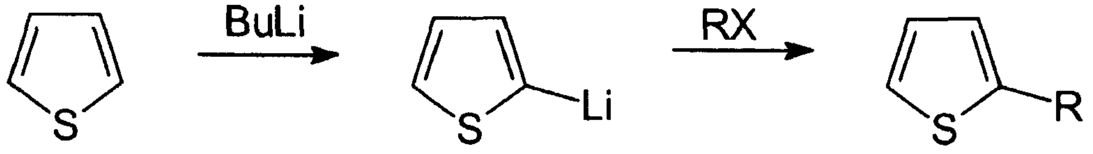
Thiophene is chlorinated by Cl_2 or SO_2Cl_2. Bromination occurs by Br_2 in acetic acid or with *N*-bromosuccinimide. Nitration is effected by concentrated nitric acid in acetic acid at 10 °C. Further substitution predominantly yields 2,4-dinitrothiophene. Sulfonation with 96% H_2SO_4 occurs at 30 °C within minutes.

Benzene reacts extremely slowly under these conditions. This provides the basis for a method to remove thiophene from coal tar benzene. Alkylation of thiophenes often gives only poor yields. However, more efficient procedures are the VILSMEIER-HAACK formylation, which yields thiophene-2-carbaldehyde, and acylation with acyl chlorides in the presence of tin tetrachloride, to give 2-acylthiophenes.

Like furan, thiophene is mercurated with mercury(II) chloride.

Metalation

Thiophene is metalated by butyllithium in the 2-position. 2-Alkylthiophenes are prepared from 2-lithiothiophenes by alkylation with haloalkanes:

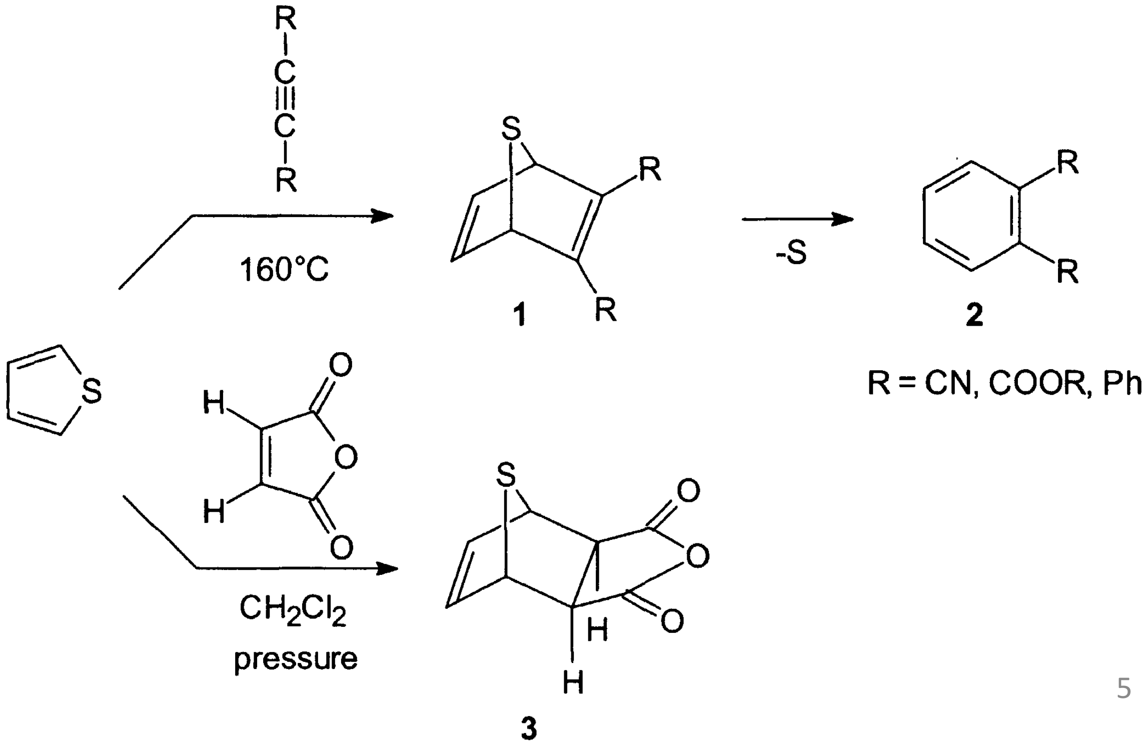


Addition reactions

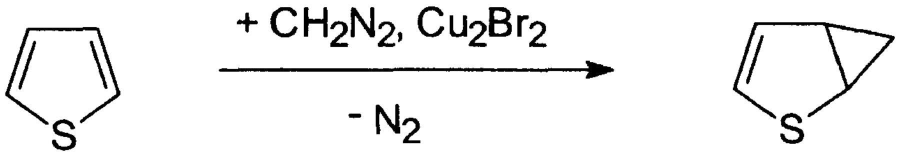
The palladium-catalyzed hydrogenation of thiophene yields thiolanes (tetrahydrothiophenes). Thiophenes undergo DIELS-ALDER reactions, but their diene reactivity is lower than that of furans.

The [4+2] cycloaddition occurs, therefore, only with very reactive dienophiles (arynes and alkynes with acceptor substituents) or under high pressure.

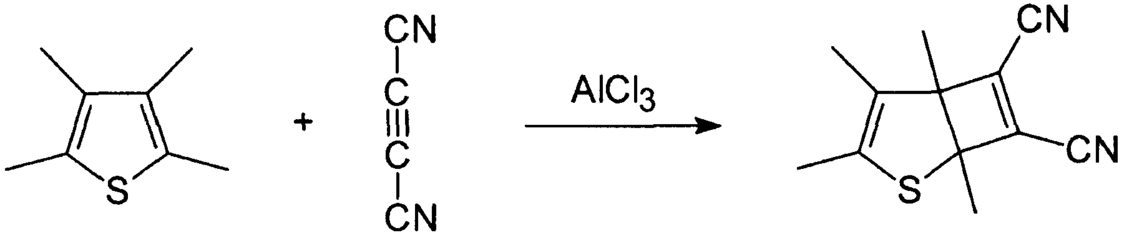
1,2-Disubstituted benzene derivatives **2** are formed with alkynes, as the primary DIELS-ALDER adduct **1** eliminates sulfur:



Thiophenes undergo [2+1] cycloadditions with carbenes across the C-2/C-3 bond, e.g.



and [2+2] cycloadditions with active alkynes. For example, tetramethylthiophene reacts with dicyanoacetylene under $AlCl_3$ catalysis as shown:



With 3-aminothiophenes (e.g. **4**), which are potential enamines, the [2+2] cycloaddition is considerably facilitated and occurs even below 0 °C. The cycloadducts (e.g. **5**) are converted thermally into 3-aminophthalic acid derivatives (e.g. **7**).

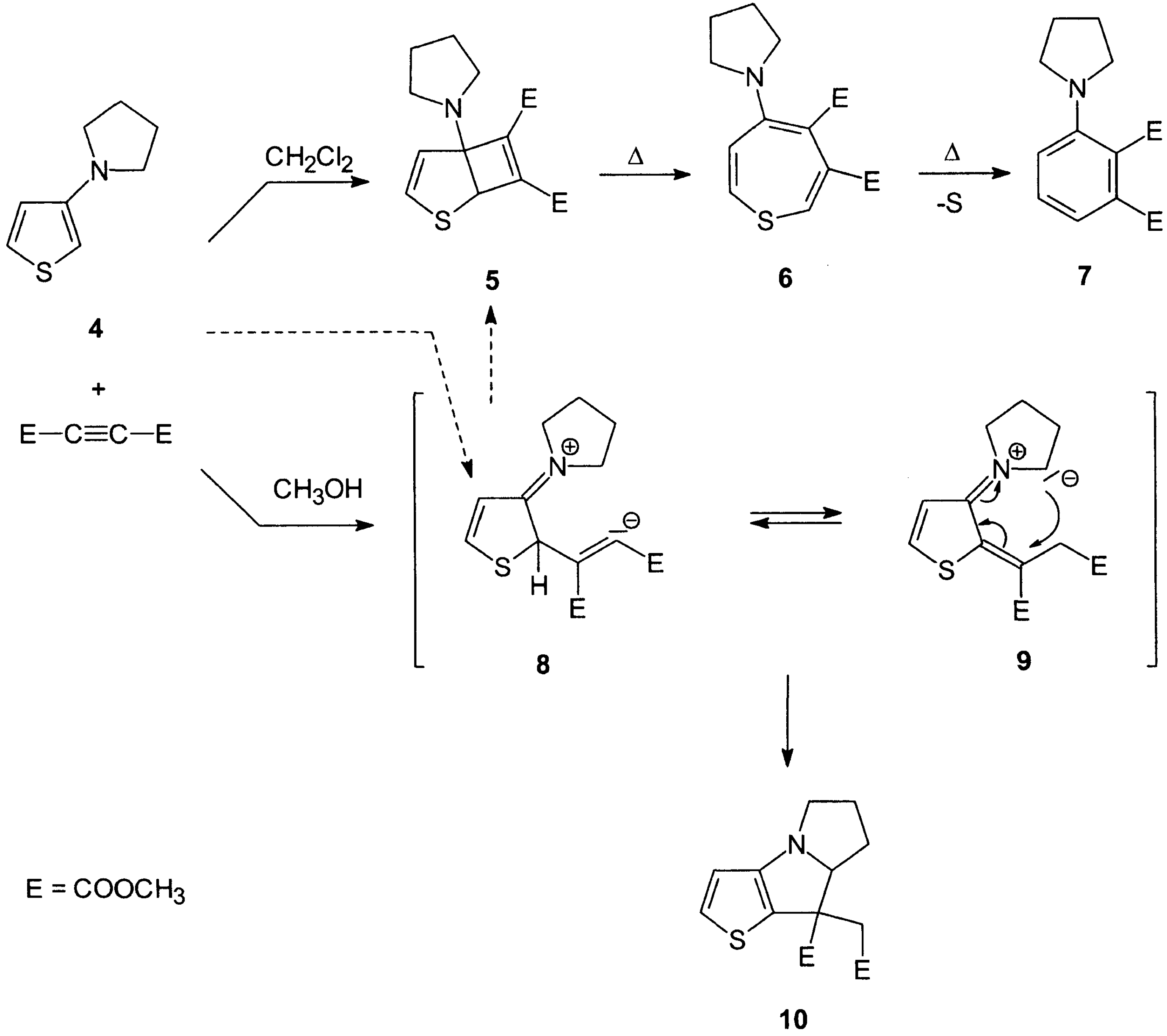
This occurs with electrocyclic ring-opening of the cyclobutene ring via a thiepine (e.g. **6**) and the extrusion of sulfur.

The solvent dependence of this cycloaddition is remarkable.

The formation of **5** requires an aprotic medium, whereas in a protic medium (e.g. CH_3OH), the thieno[2,3-*b*]-5,6,7,7*a*-tetrahydro-1*H*-pyrrolizine **10** is formed.

As the rate of product formation is the same in both media, it is plausible that the same primary product **8** of a dipolar [2+2] cycloaddition is formed first.

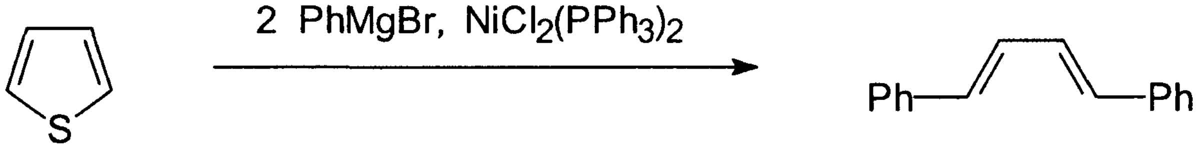
The reaction then proceeds to give **5** in the nonpolar medium and **10** via the ylide **9** in the polar medium.



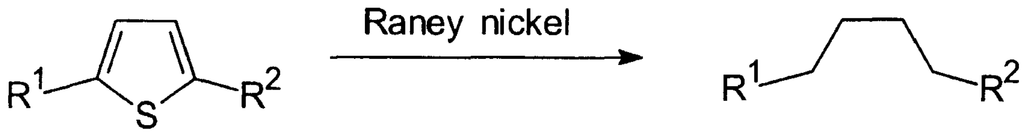
E = $COOCH_3$

Ring-opening reactions

Thiophenes are neither polymerized nor hydrolyzed by moderately concentrated BRÖNSTED acids. Ring-opening demands special reagents, e.g. phenylmagnesium bromide in the presence of dichlorobis(triphenylphosphane)nickel(II):



Another ring-opening reaction of thiophene is the reductive desulfurization with RANEY nickel in ethanol to give alkanes:



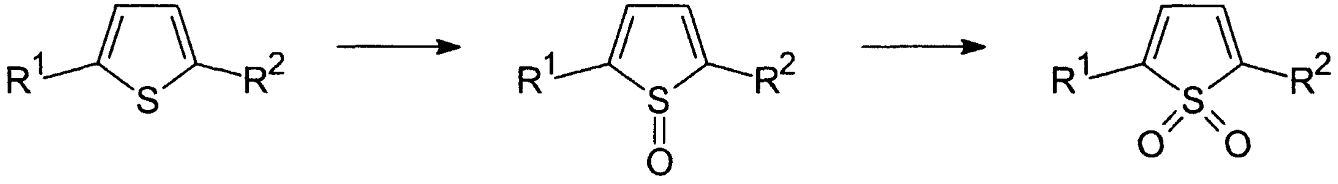
RANEY nickel adsorbs hydrogen during its preparation, which effects the reduction.

In an alternative reaction, hydrogen is used in the presence of molybdenum or tungsten as a catalyst.

This hydrodesulfurization is of great industrial importance for the removal of thiophenes and other sulfur compounds from petroleum.

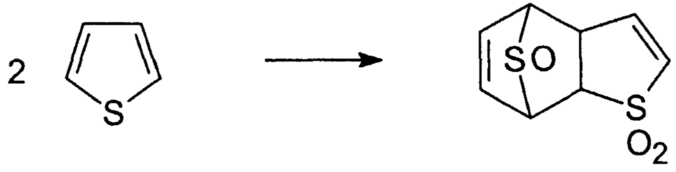
Oxidation

Thiophenes are oxidized by peroxy acids to give thiophene 1-oxides **11**, which can proceed further to thiophene 1,1-dioxides **12**:



11 **12**

These compounds have a much stronger tendency than thiophene to undergo addition reactions. Thus, in the oxidation of thiophene with an excess of 3-chloroperoxybenzoic acid, the product **13** is produced. It results from a [4+2] cycloaddition of thiophene 1-oxide to the C-2/C-3 bond of thiophene 1,1-dioxide.



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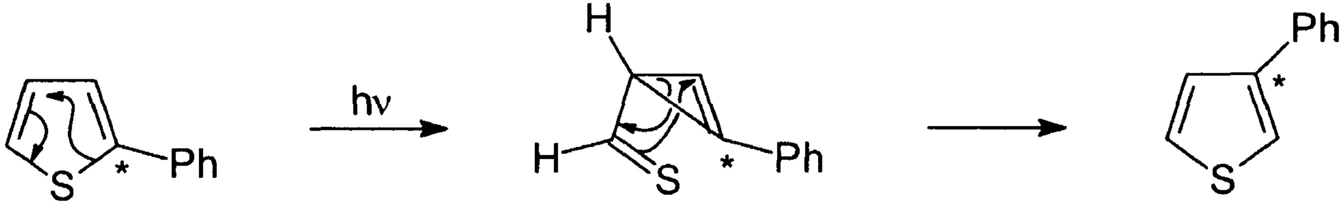
Photoisomerization

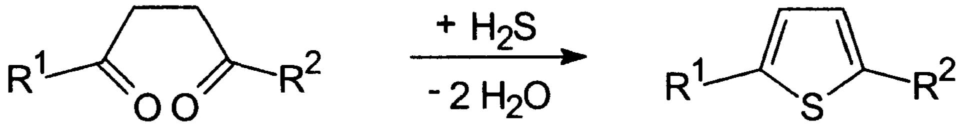
On irradiation of 2-phenylthiophene, 3-phenylthiophene is formed. Photoisomerizations of numerous substituted thiophenes, as well as of furans and pyrroles, are known.



By using ^{14}C-labelled compounds, it can be shown that the phenyl substituent remains bonded to the C-atom of the thiophene ring. One suggestion has postulated cyclopropene-3-thiocarbaldehyde as intermediate as shown above.

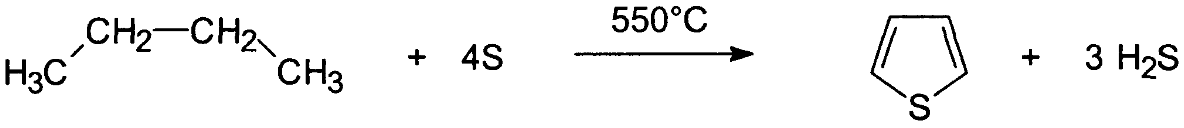
[C] The retrosynthesis of thiophene can be worked out in principle by analogy to that of furan. A number of syntheses for thiophene can be deduced.

(1) The simplest method is 'sulfurization' followed by cyclizing dehydration of 1,4-dicarbonyl compounds **14** analogous to the PAAL-KNORR synthesis of furans. This cyclocondensation is carried out with P_4S_{10} or H_2S, and furnishes 2,5-disubstituted thiophenes **15** (Paal synthesis):

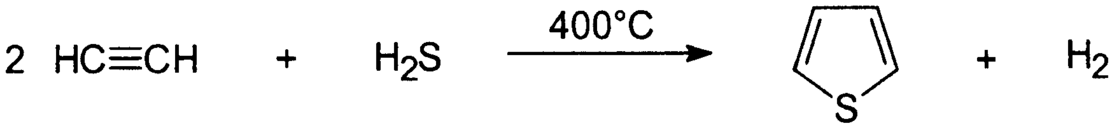


14 **15**

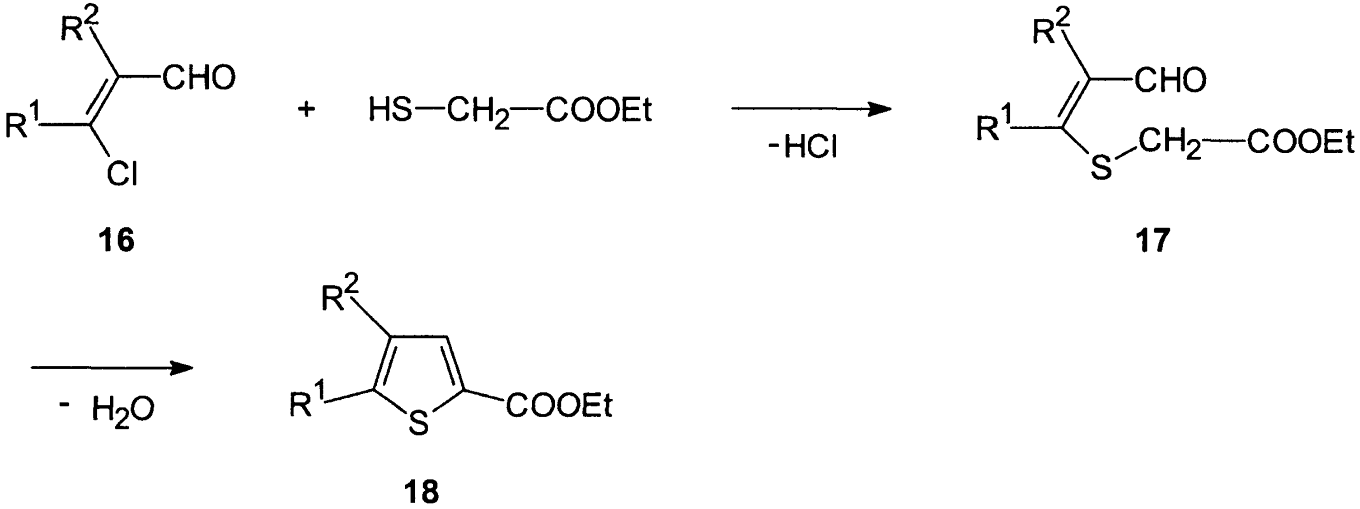
(2) Butane and higher alkanes, as well as corresponding alkenes and 1,3-dienes, undergo a cyclodehydrogenation with sulfur in the gas phase, with the formation of thiophenes, e.g.



Acetylene, as well as 1,3-diynes, also yield thiophenes with H_2S under similar conditions:

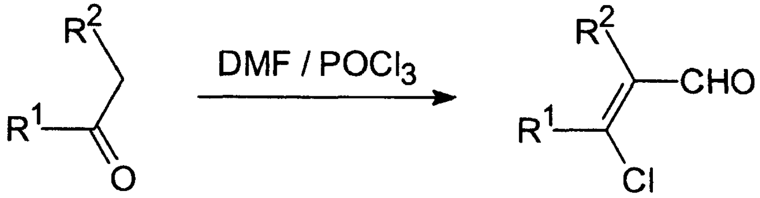


(3) 1,3-Dicarbonyl compounds or β-chlorovinyl aldehydes react with thioglycolates or other thiols possessing a reactive methylene group to give thiophene-2-carboxylic esters **18** in the presence of pyridine (Fiesselmann synthesis):

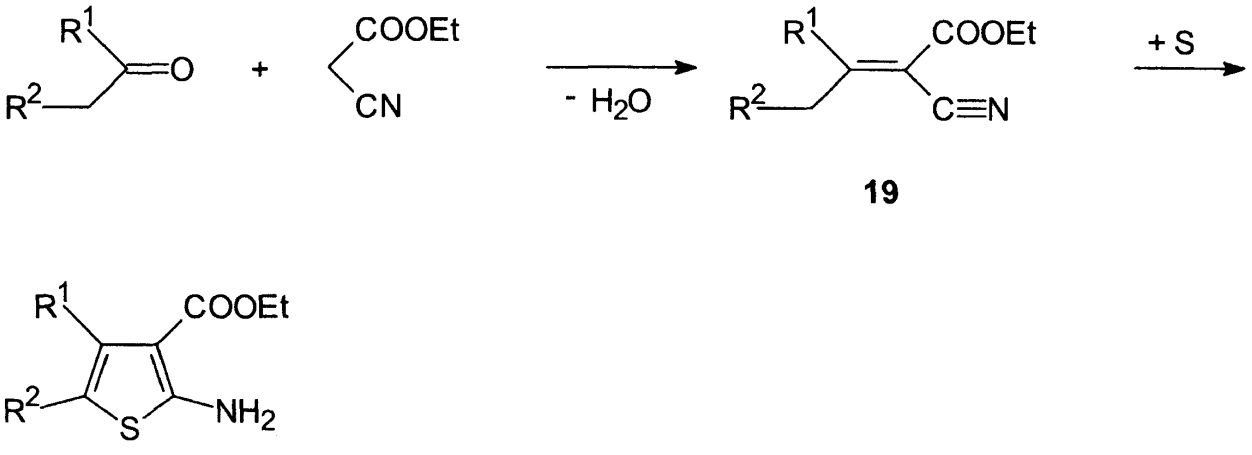


Initially, a formal vinyl substitution of the chlorine atom by MICHAEL addition takes place, followed by loss of HCl to give the intermediate **17**. Finally, cyclization occurs by an intramolecular aldol condensation.

β-Chlorovinyl aldehydes **16** result from α-methylene ketones by the action of DMF/$POCl_3$ (the VILSMEIER-HAACK-ARNOLD reaction):



(4) α-Methylene carbonyl compounds undergo cyclocondensation with cyanoacetic ester or malononitrile and sulfur in ethanol in the presence of morpholine to give 2-aminothiophenes **20** (Gewald synthesis):



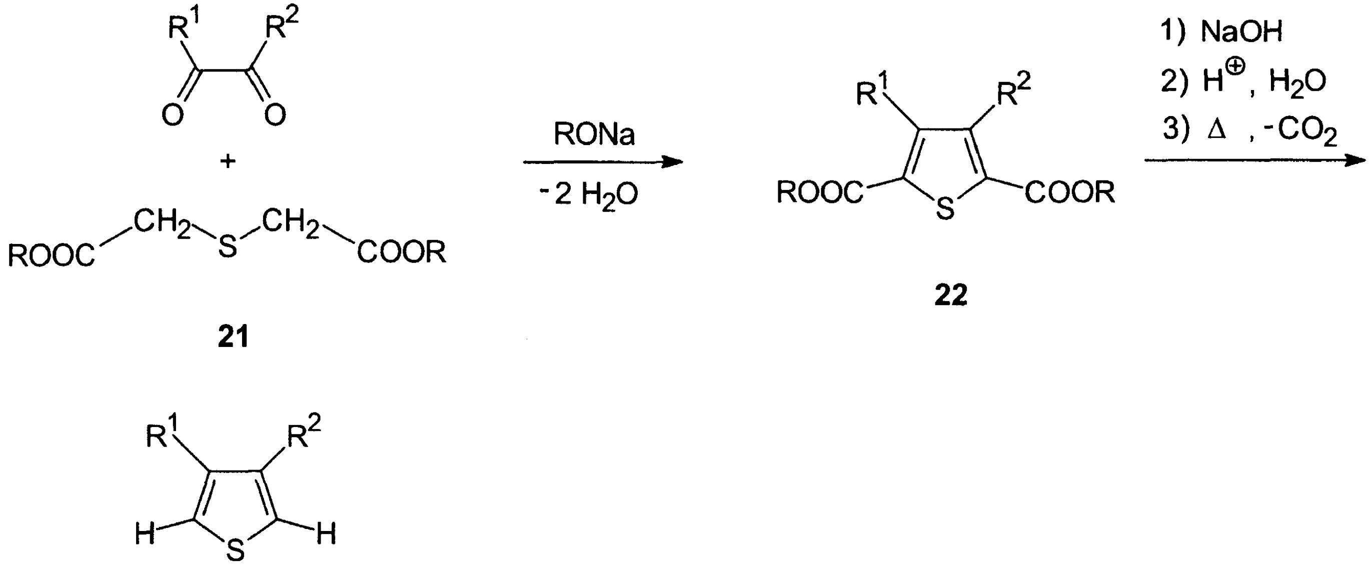
19

20

Initially, a KNOEVENAGEL condensation between the carbonyl compound and the reactive methylene group takes place. The α,β-unsaturated nitriles **19** that are formed are cyclized by the sulfur, probably via sulfanyl derivatives of **19** as intermediates.

(5) 1,2-Dicarbonyl compounds can be made to cyclize with esters of 3-thiapentanedioic acid **21** under base catalysis (Hinsberg synthesis).

This widely applicable and high-yield synthesis leads to substituted thiophene dicarboxylic esters **22** via a double aldol condensation, with the two CH_2 groups of **21**. Hydrolysis and decarboxylation of the esters yield 3,4-disubstituted thiophenes **23**:



21

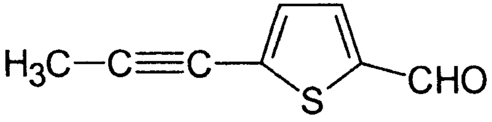
22

23

[D] Thiophene, a colorless, water-insoluble liquid, with an odor like benzene, mp -38 °C, bp 84 °C, occurs in coal tar. It remains in the benzene fraction (benzene: bp 80 °C) on distillation of coal tar, and can be removed by extraction with cold concentrated sulphuric acid.

A solution of isatin (indole-2,3-dione) in concentrated sulphuric acid turns blue in the presence of thiophene (the indophenine reaction). This test is used to detect thiophene as an impurity in benzene. It was observed that when benzene is made by decarboxylation of benzoic acid, the indophenine reaction, which was originally thought to be caused by benzene, does not take place. This led to the discovery of thiophene by V. MEYER (1882).

Thiophenes occur in fungi and some higher plants, e.g. junipal **24** in the fungus *Daedeliajuniperina.* A number of thiophenes have been isolated from composite, e.g. the 2,2'-bithienyl derivative **25** from the roots *of Echinops spaerocephalus.* Such compounds are nematocidal.



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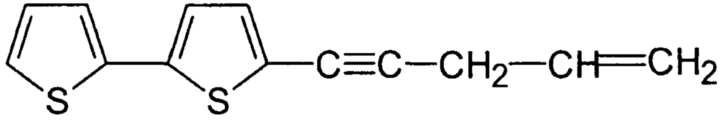

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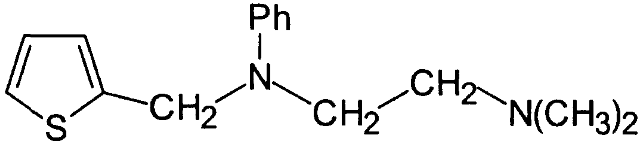
Many drugs are derived from thiophene. Examples are the antihistamine methaphenilene **26** ([2-(dimethylamino)ethyl]phenyl(2-thenyl)amine) and the anti-inflammatory tiaprofenic acid **27** (2-(5-benzoyl-2-thienyl)propionic acid):



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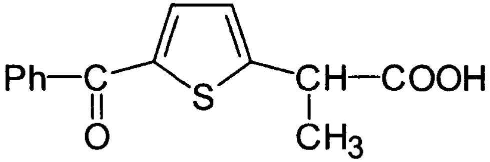

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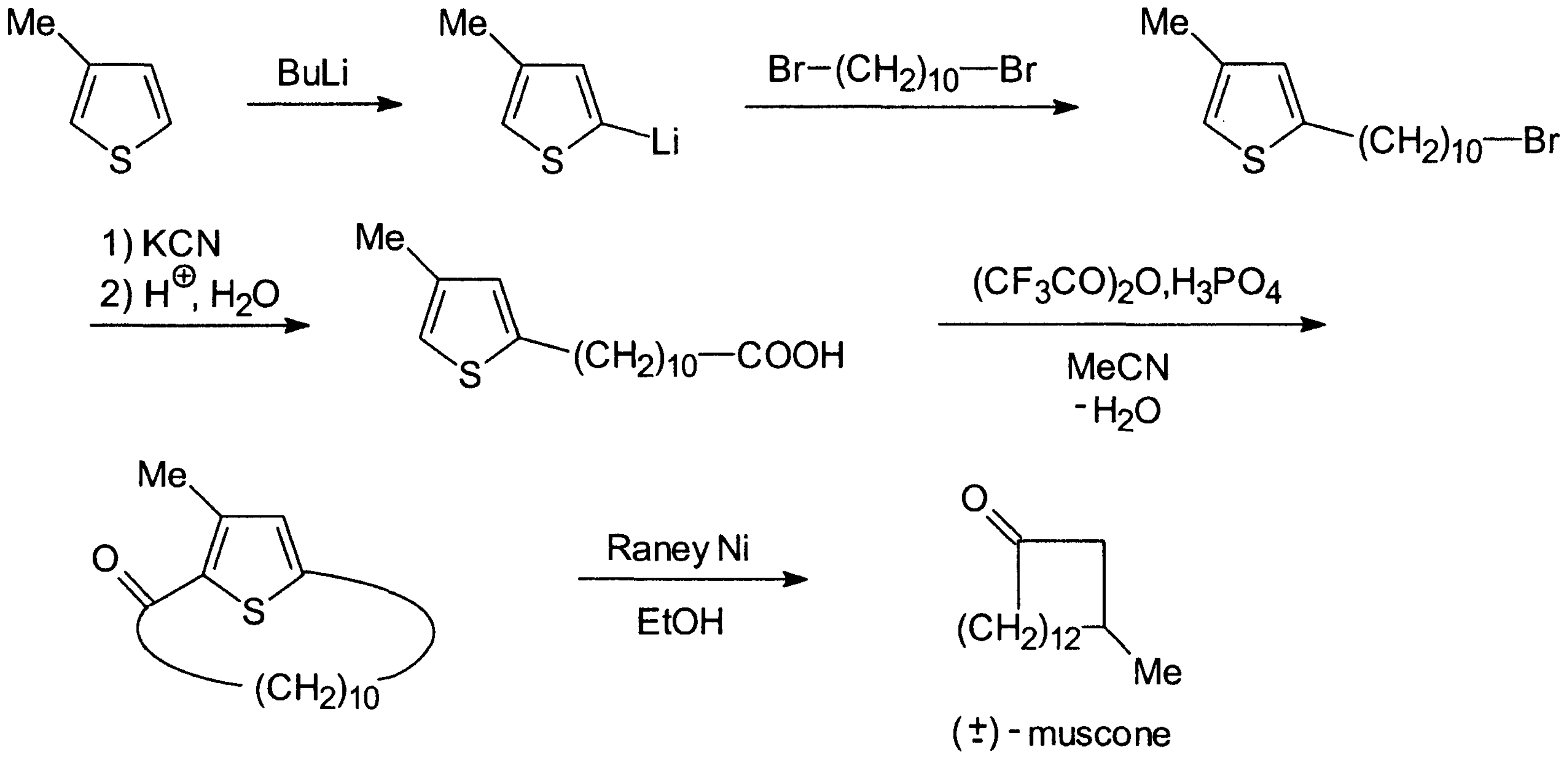
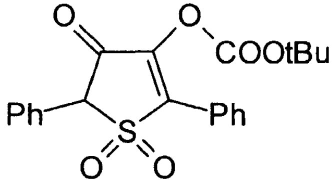
It is often observed that the pharmacological effect of a thienyl or thenyl substituent is the same or similar to that of a phenyl or benzyl substituent. This phenomenon is known as bioisosterism. Poly(thiophenes) can be used as electric conducting polymers.

[E] Thiophenes are not very important as preparative intermediates. Chiefly, they are used in the synthesis of a saturated C4 chain by reductive desulfurization. The synthesis of (±)-muscone from 3-methylthiophene serves as an example.



Partial reductive desulfurizations are also successful with 3-methoxythiophenes. This reaction was utilized for the synthesis of pheromones. The systems **28** and **29**, which are derived from thiophene 1,1-dioxide are used as reagents for the transfer of *N*-protective groups (**28**) and for the activation of carboxyl groups (**29**) in peptide synthesis.



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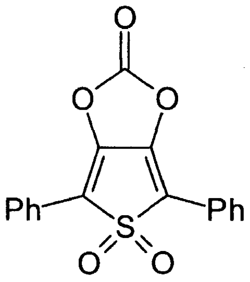

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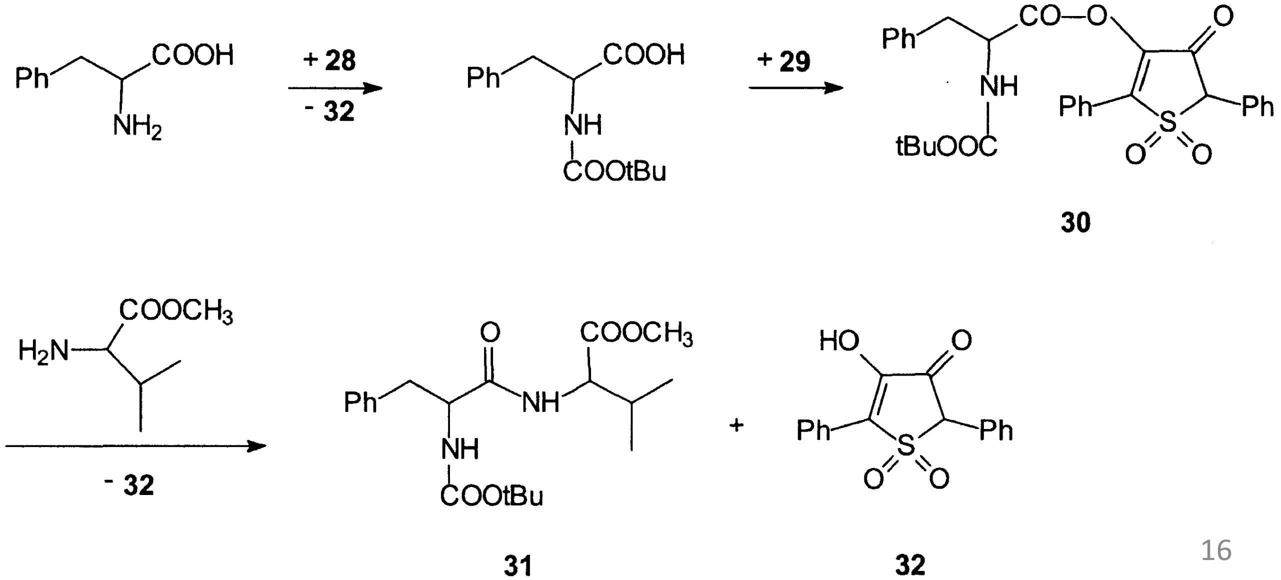
Their use is illustrated by the synthesis of the protected dipeptide Boc-$_{\text{L}}$-Phe-$_{\text{L}}$-Val-OCH$_3$ (**31**), which proceeds without racemization. The dipeptide **31** is prepared from Boc-protected $_{\text{L}}$-phenylalanine and $_{\text{L}}$-valine methyl ester:



The carboxyl activation proceeds via the enol ester **30**; in this case, as well as in the transfer of the *N*-protecting group, the easily accessible heterocycle **32** (from which the two reagents **28**/**29** are prepared) is reformed.