The Chemistry of Heterocycles

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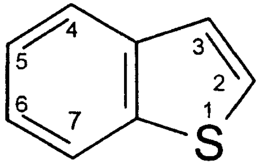
By Theophil Eicher and Siegfried Hauptmann, Wiley-VCH Veriag GmbH, 2003

5.7 Benzo[*b*]thiophene

[A] Benzo[*b*]thiophene was previously named thionaphthene. It has the following spectroscopic data:



UV (ethanol)
λ (nm) (ε)

227 (4.40)
249 (3.83)
258 (3.83)
265 (3.63)
289 (3.22)
296 (3.50)

^{1}H-NMR (CCl_4)
δ (ppm)

H-2: 7.33
H-3: 7.23
H-4: 7.72
H-5: 7.25
H-6: (7.23)
H-7: (7.29)

^{13}C-NMR ($CDCl_3$)
δ (ppm)

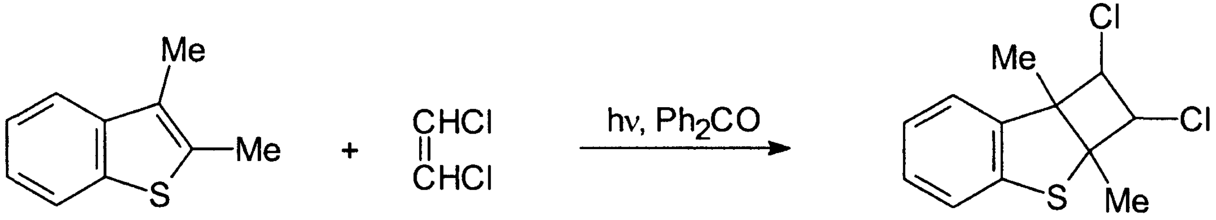
C-2: 126.2
C-3: 123.8
C-4: 123.6
C-5: 124.1
C-6: 124.2
C-7: 12
C-3a: 139.6
C-7a: 139.7

The NMR chemical shift values hardly differ from those of benzo[*b*]furan.

[B] Benzo[*b*]thiophene is somewhat less reactive in electrophilic substitutions than thiophene, and also less reactive than benzo[*b*]furan. Moreover, regioselectivity is poor, giving rise to mixtures.

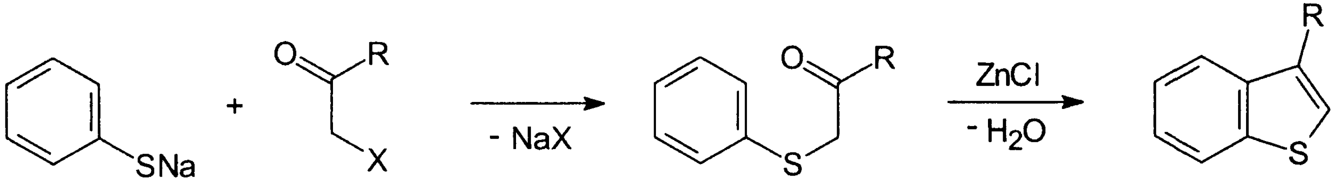
Frequently, the 3-position is attacked preferentially over the 2-position, e.g. in halogenation, nitration and acylation. Only the reaction with *n*-butyllithium is regioselective, giving 2-lithiated benzo[*b*]-thiophene.

Benzo[*b*]thiophenes undergo photochemical [2+2] cycloaddition, for instance with 1,2-dichloroethene in the presence of benzophenone as sensitizer:



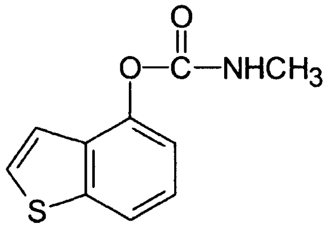
Oxidation of benzo[*b*]thiophene with peroxy acids leads to the 1,1-dioxide.

[C] By analogy with benzo[*b*]furans, benzo[*b*]thiophenes can be obtained from thiophenolates and α-halo ketones:

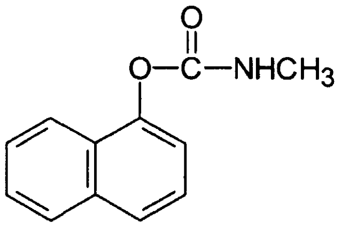


[D] Benzo[*b*]thiophene, colorless crystals, mp 32 °C, bp 221 °C, has a smell similar to that of naphthalene. It is present in the naphthalene fraction of coal tar and can be prepared from sodium thiophenolate and bromoacetaldehyde diethyl acetal. Benzo[*b*]thiophene occurs in roasted coffee beans.

Various Pharmaceuticals and biocides are derived from benzo[*b*]thiophene, and it is found to be bioisosteric with naphthalene and indole. Mobam **1** [4-(*N*-methylcarbamoyl)benzo[*b*]thiophene] is an insecticide which is as effective as carbaryl **2**. Both compounds inhibit the enzyme acetylcholinesterase.

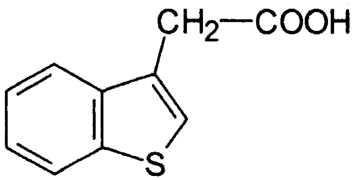


1



2

Benzo[*b*]-3-thienylacetic acid **3** promotes plant growth, as does the corresponding indole compound. 3-(2-Aminoethyl)benzo[*b*]thiophene **4** has an even stronger action on the central nervous system than tryptamin.



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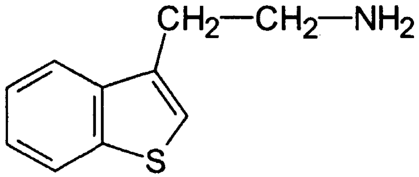
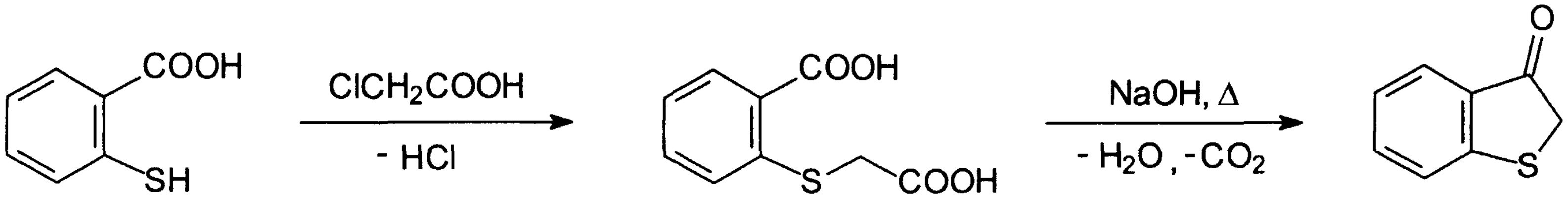
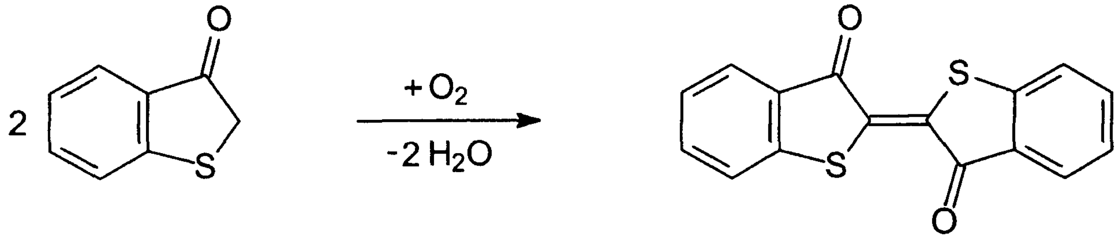


4

Several compounds which are known as thioindigo dyes are derived from benzo[*b*]thiophene. Thioindigo **6** itself is made from 2-sulfanylbenzoic acid via benzo[*b*]thiophen-3(2*H*)-one **5** (thioindoxyl) by the following steps (FRIEDLANDER 1905):



5

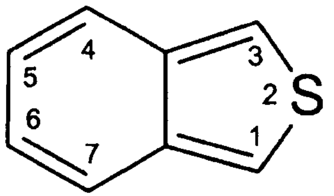


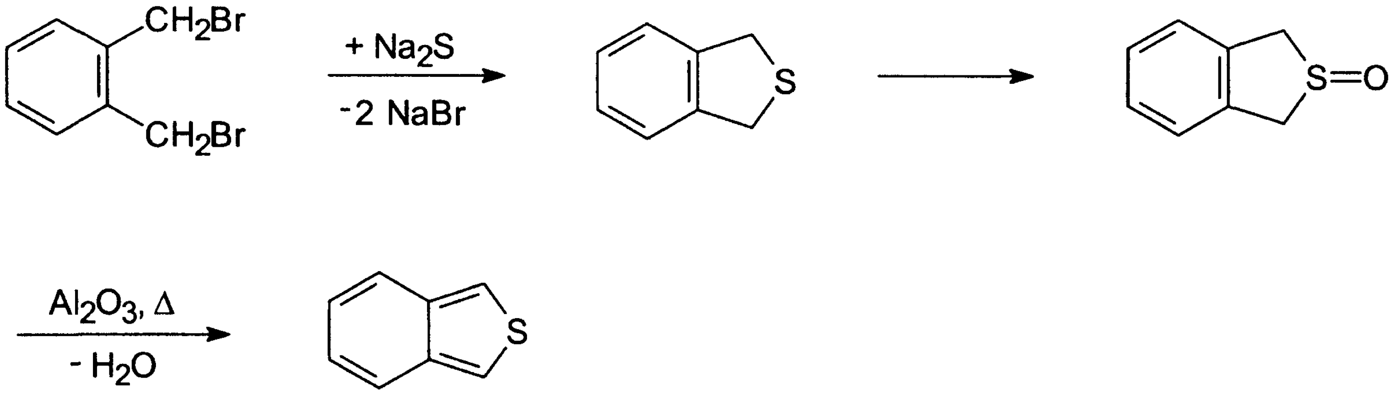
6

Thioindigo, a vat dye, forms red needles and its vat is bright yellow. As a dye, it has a blue-red color. Thioindigo dyes were produced in large quantities until the fifties, but since then they have become less important.

5.8 Benzo[*c*]thiophene

[A-D] This system lacks a benzene ring and has a *o*-quinonoid structure. Unlike benzo[*c*]furan, benzo[*c*]thiophene has been isolated. Its synthesis proceeded by the following route, starting from 1,2-bis(bromomethyl)benzene:

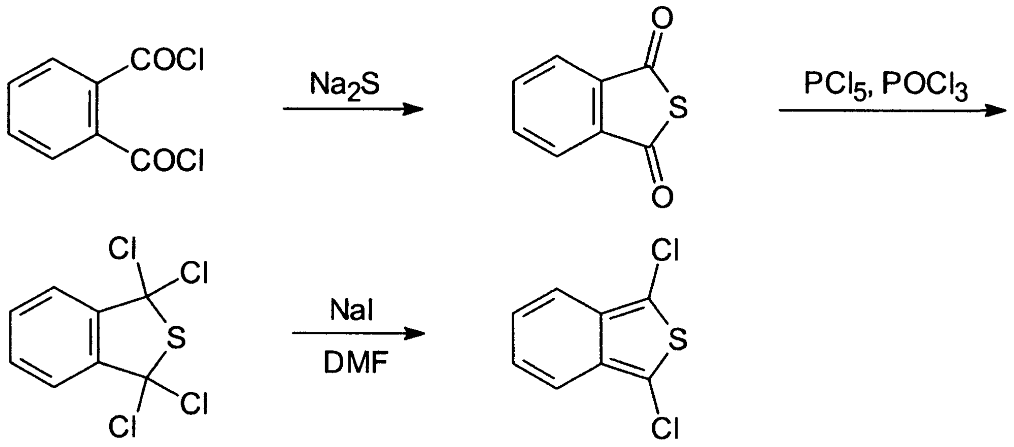




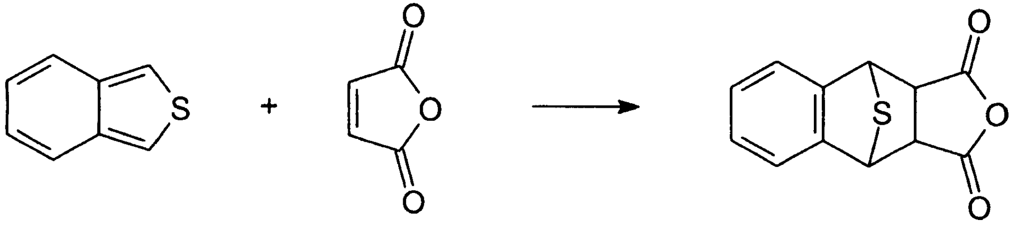
1,3-Dihydrobenzo[*b*]thiophene-2-oxide is heated in a sublimation apparatus with aluminium oxide in vacuo, resulting in the sublimation of benzo[*c*]thiophene. The compound is isolated as colorless crystals of mp 53-55 °C. It it thermally unstable and decomposes, even at -30 °C, under nitrogen within a few days. Its stability is increased by substituents in the 1,3-positions as in benzo[*c*]furan.

1,3-Diphenylbenzo[*c*]thiophene, yellow needles, mp 118 °C, is thermally stable. Its solution displays a green fluorescence. The compound can be prepared by ring transformation of 1,3-diphenyl-isobenzofuran with P_4S_{10} in CS_2.

1,3-Dichlorobenzo[*c*]thiophene, bright yellow crystals, mp 54 °C, was made from phthaloyl dichloride:

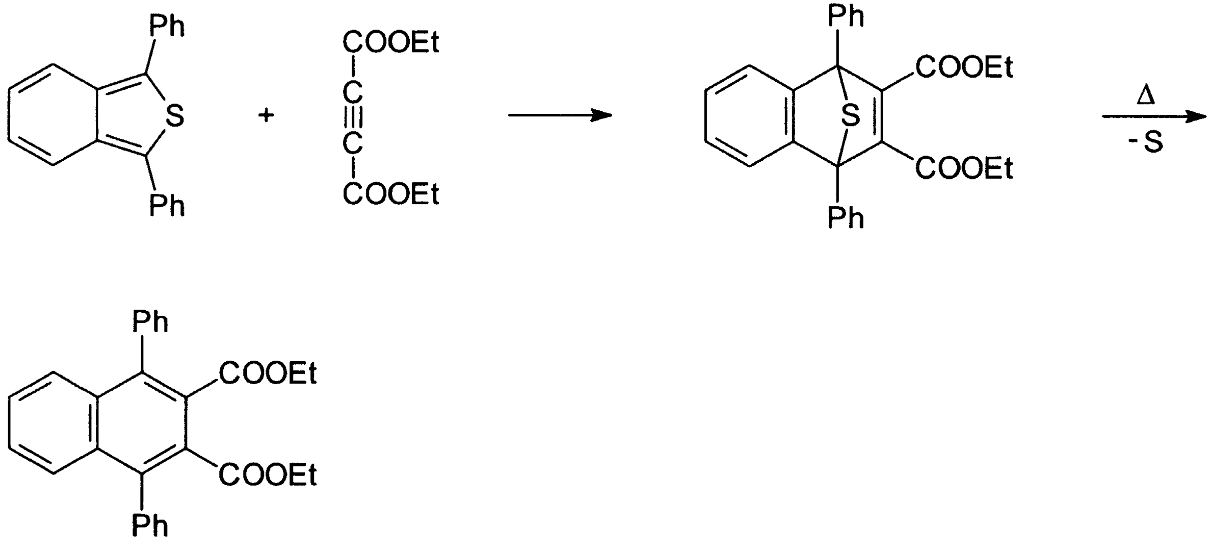


[4+2] Cycloadditions are typical for benzo[c]thiophenes, e.g.:



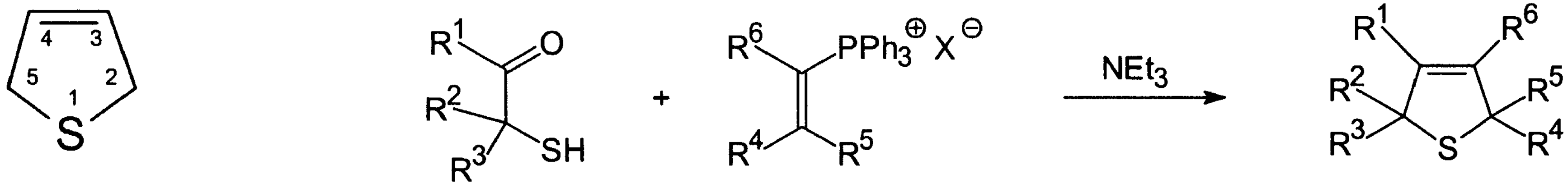
Mixtures of *endo*- and *exo*-diastereomers are usually formed. The reactivity of 1,3-diphenylbenzo[*c*]thiophene in [4+2] cycloadditions is distinctly lower.

Acetylene dienophiles yield adducts which, on heating, are converted into the corresponding substituted naphthalenes with loss of sulfur:



5.9 2,5-Dihydrothiophene

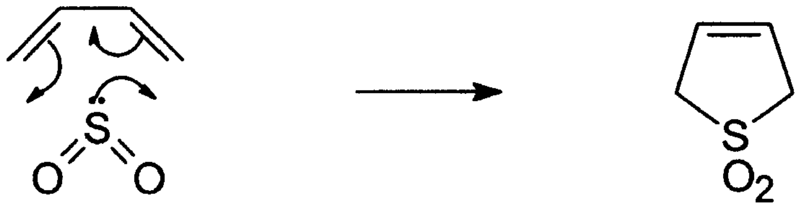
[A-D] The names Δ^3-thiole and 3-thiole have previously been used for 2,5-dihydrothiophene. A general synthesis for 2,5-dihydrothiophenes with different substituents is based on the MICHAEL addition of α-sulfanylcarbonyl compounds to vinyl phosphonium salts, followed by an intramolecular WITTIG reaction:



2,5-Dihydrothiophenes are oxidized to 1,1-dioxides by *m*-chloroperoxybenzoic acid.

These compounds are also accessible by [4+1] cycloaddition of 1,3-dienes and sulfur dioxide.

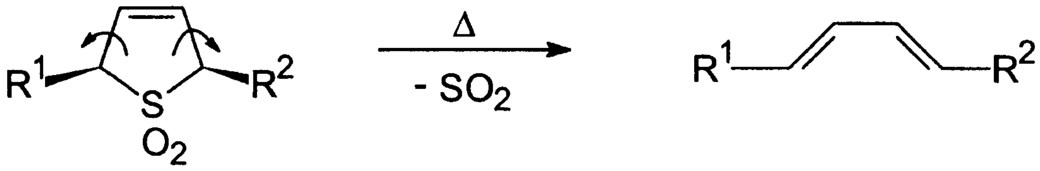
For instance, butadiene reacts even at room temperature with liquid sulfur dioxide to give an adduct 2,5-dihydrothiophene 1,1- dioxide, commonly known by the trivial name 3-sulfolene:

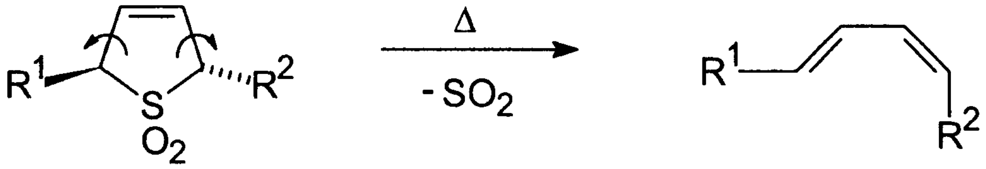


Following WOODWARD, such conversions are called **cheletropic reactions**. The LUMO of the 1,3-diene surrounds the nonbonding electron pair of sulfur like the claws of a crab (Greek: chele).

3-Sulfolenes are **masked** 1,3-dienes. At about 150 °C they undergo [4+1] cycloreversion (cyclo-elimination) into 1,3-dienes and sulfur dioxide.

As this is a thermal concerted reaction, it proceeds in a **dis-rotatory** manner according to the WOODWARD-HOFFMANN rules. Thus a *cis*-2,5-disubstituted 3-sulfolene stereospecifically yields an *(E,E)*-1,3-diene, while the *trans*-diastereomer gives an (*E*,*Z*)-1,3-diene:





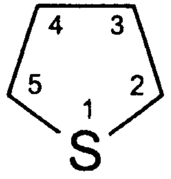
For multistep syntheses that include a DIELS-ALDER reaction, corresponding 1,3-dienes are necessary. They can be prepared by the method described. In many cases, the 1,3-diene is not isolated, but the DIELS-ALDER reaction is carried out with 3-sulfolene and dienophile in boiling xylene.

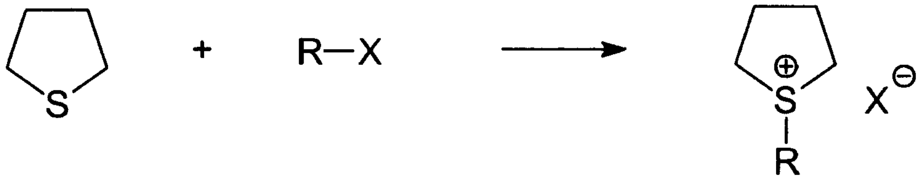
5.10 Thiolane

[A] The bond lengths in thiolane (tetrahydrothiophene) are the same as those in dialkyl sulfides. As in tetrahydrofuran, the ring is nonplanar and conformationally flexible. The twist conformation is preferred because of the larger heteroatom. The activation energy for pseudorotation is greater than that for tetrahydrofuran.

The chemical shifts in the NMR spectrum correspond to those observed for cycloalkanes and dialkyl sulfides.

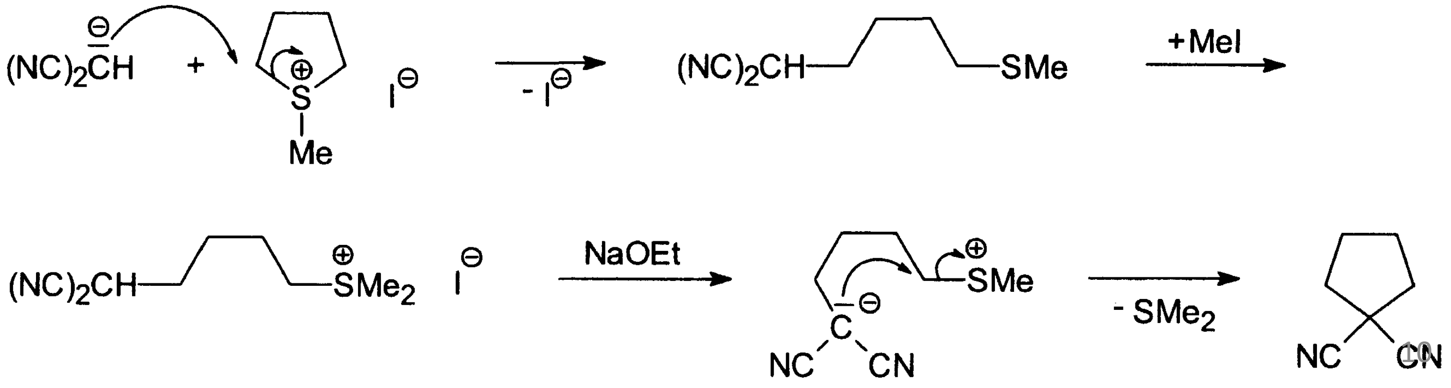
[B] Thiolanes behave like dialkyl sulfides. With haloalkanes or alcohols in the presence of BRÖNSTED acids, tertiary sulfonium salts are formed:





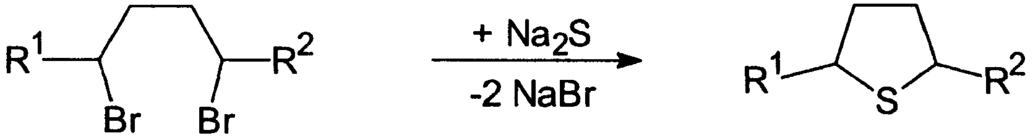
These compounds are good alkylation agents. Ring fission occurs with compounds possessing CH-acidity, e.g.:

Further methylation, followed by the action of sodium ethoxide in ethanol, leads to substituted cyclopentanes.

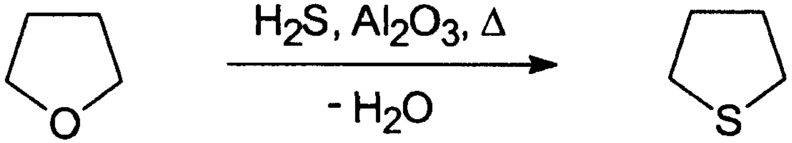


Thiolanes can be oxidized to sulfoxides and subsequently to sulfones.

[C] The reaction of 1,4-dibromo- or 1,4-diiodoalkanes with sodium or potassium sulfide provides thiolanes in good yield:



The ring transformation of tetrahydrofurans into thiolanes proceeds with hydrogen sulfide in the presence of aluminium oxide at 400 °C:



[D] Thiolane is a colorless, water-insoluble liquid of bp 121 °C. It has a distinctive odor similar to town gas. In combination with other compounds, it is responsible for the typical odor of urine after consumption of asparagus.

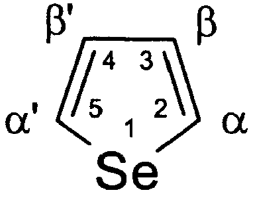
Thiolane 1,1-dioxide, known by the trivial name sulfolane, is obtained industrially by catalytic hydrogenation of 3-sulfolene. Sulfolane, colorless crystals, mp 27.5 °C, bp 285 °C, is water soluble.

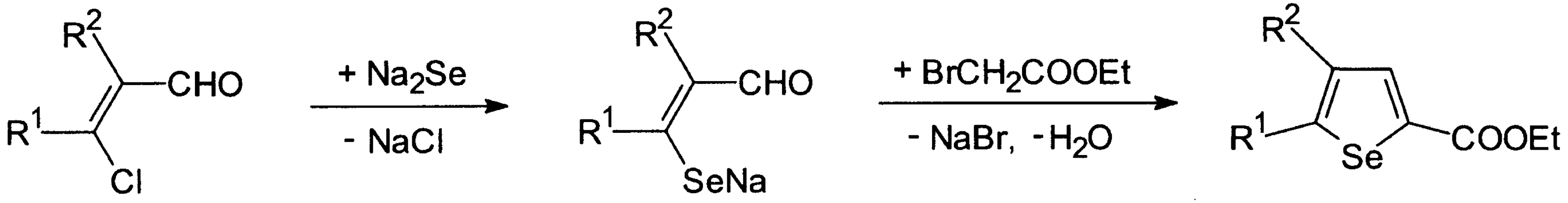
Sulfolane is a polar aprotic solvent and is used for the extraction of sulfur compounds from industrial gases and for the extraction of aromatic substances from pyrolysis fractions. It also serves as a solvent for cellulose acetate, polyvinyl chloride, polystyrene, and polyacrylonitrile.

5.11 Selenophene

[A-D] The selenophene molecule is planar. The chemical shifts in the NMR spectra are found in the region typical for aromatic compounds.

The synthesis of selenophenes uses a modified FIESSELMANN synthesis for thiophenes and proceeds as follows:





Acetylene reacts at 350-370 °C with selenium to produce selenophene. Ring transformation of furan into selenophene occurs with hydrogen selenide over aluminium at 400 °C.

Selenophene, a colorless liquid, which, in contrast to thiophene, has an unpleasant smell, has mp -38 °C and bp 110 °C and is insoluble in water.

Selenophene undergoes electrophilic substitution reactions typical of furan and thiophene. It reacts faster than thiophene but much more slowly than furan. Substitution occurs regioselectively in the 2- or 2,5-positions.

Tellurophenes have not been examined in great detail. Their synthesis is analogous to that described for selenophenes, but uses Na_2Te instead of Na_2Se. Tellurophenes are more sensitive towards acids than selenophenes or even thiophenes.

Benzo[*b*]selenophenes and -tellurophenes, as well as the corresponding dibenzo-condensed systems, are known.

Natural products derived from selenophene or tellurophene have so far not been discovered, which is in contrast to furan and thiophene.

Selenophene proves to be bioisosteric with benzene, thiophene and pyrrole, as in the case of 2-amino-3-(benzo[*b*]selenophen-3-yl)propionic acid and the proteinogenic amino acid tryptophan: