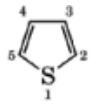
Kirk-Othmer Encyclopedia of Chemical Technology.

THIOPHENE AND THIOPHENE DERIVATIVES

Thiophene [110-02-1] and a number of its derivatives are significant in fine chemical industries as intermediates to many products for pharmaceutical, agrochemical, dyestuffs, and electronic applications. This article concentrates on the industrial, commercial, and economic aspects of the production and applications of thiophene and thiophene derivatives and details the main synthetic schemes to the parent ring system and simple alkyl and aryl derivatives. Functionalization of the ring and the synthesis of some functional derivatives that result, not from the parent ring system, but by direct ring cyclization reactions are also considered. Many good reviews on the chemistry of thiophene and thiophene derivatives are available (1–7).

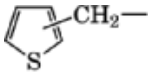
1. Nomenclature, Numbering, and Structure

The basic nomenclature of the thiophene ring system and its derivatives is indicated by the following: the sulfur atom is number 1, positions 2 and 5 are equivalent in the parent ring, as are the 3 and 4 positions.

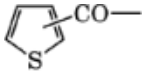


thiophene

thienyl



thenyl



thenoyl

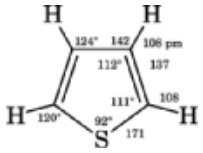
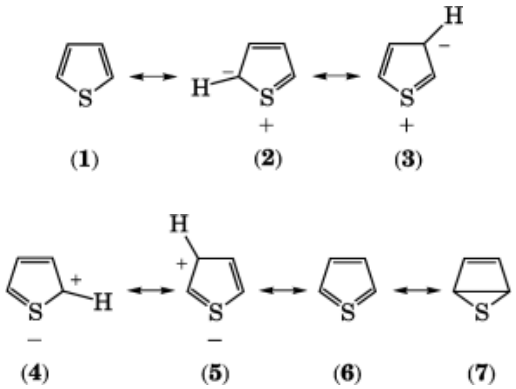


Fig. 1. Bond lengths and bond angles in thiophene.

The structure of the parent ring has been studied by numerous techniques. The precise data from microwave studies (8) on the dimensions and bond angles is given in Fig. 1.

In valence bond terms the mesomers indicated by (**1–7**) reflect the ground-state position of thiophene. Mesomer **(1)** is the principal contributor to the ring structure; **(2)** and **(3)** are significant; **(4–7)** contribute in a minor way to the structure.



With its sextet of π electrons, thiophene possesses the typical aromatic character of benzene and other similarly related heterocycles. Decreasing orders of aromaticity have been suggested to reflect the strength of this aromatic character: benzene $>$ thiophene $>$ pyrrole $>$ furan (9); and benzene $>$ thiophene $>$ selenophene $>$ tellurophene $>$ furan (10).

2. Physical Properties and Spectroscopy

Table 1 indicates the significant physical properties of thiophene and 2- and 3-methylthiophene; Table 2, the toxicological and ecotoxicological properties.

2.1. Uv Spectroscopy

The commonly used solution uv spectrum of thiophene consists of a broad band, 220–250 nm ($\log\epsilon = 3.9$), caused by an overlap of transition states and two low intensity bands at 313 and 318 nm. Alkyl derivatives and similarly related $+\mathrm{M}$ substituents, at the 2-position, give a single band; similar 3-substituents give a double peak. Negative, ie, $-\mathrm{I}$, $-\mathrm{M}$, substituents at the 2-position give two absorptions, whereas 3-substituents of this type give only one band of lower intensity. A useful bathochromic shift is noted for thiophene derivatives compared to benzene analogues, thus making certain thiophene derivatives of significant commercial interest as dyes and optical brightening agents.

Table 1. Physical Properties of Thiophene and Methylthiophenes[a]

Property	Thiophene	2-Methylthiophene	3-Methylthiophene
CAS Registry Number	[110-02-1]	[554-14-3]	[616-44-4]
freezing point, °C	−38.3	−63.4	−68.9
boiling point at 101.3 kPa[b], °C	84.16	113	115
flash point, °C	−7	16	15.5
density, d_4^0, kg/m^3	1087.3	1025.0	1025.0
density, d_4^{25}, kg/m^3	1057.3	1014.0	1016.2
refractive index, n_D^{25}	1.52572	1.5174	1.5172
viscosity at 25°C, mPa·cP)	0.621	0.669	0.642
surface tension at 20°C, mN/m(=dyn/cm)	31.34	30.95	32.37
vapor pressure, kPa[b], at			
0°C	2.86		1.33 at 11°C
20°C	8.36	2.66 at 21°C	3.99 at 31°C
50.1°C	31.16	10.66 at 49.1°C	10.66 at 51.5°C
84.16°C	101.3	101.3 at 112.6°C	101.3 at 115.4°C
95.9°C	143.3	133.3 at 122.4°C	133.3 at 125.4°C
119.8°C	270.1	199.9 at 138°C	199.9 at 141°C
critical constants			
temperature, °C	306.2	335.8	339.8
pressure, MPa[c]	5.70	4.91	4.91
volume, mL/mol	219	275	276
density, kg/m^3	385		
heat of vaporization at bp, kJ/mol[d]	31.47	33.90	34.25
heat of formation at 298.16 K, kJ/mol[d]			
liquid	81.67	45.44	43.89
gaseous	115.44	84.35	83.43
heat of combustion at 101.3 kPa[b] and 25°C, kJ/mol[d]	−2435.2	−3471.3	−3469.0
dielectric constant at 20°C	2.74		

[a] Ref. 11.
[b] To convert kPa to mm Hg, multiply by 7.5.
[c] To convert MPa to psi, multiply by 145.
[d] To convert kJ/mol to kcal/mol, divide by 4.184.

2.2. Ir Spectroscopy

Significant absorptions can be identified as characteristic of particular substitutions within families of thiophene derivatives. The most widely studied in this connection are probably the halothiophenes, where absorption bands have been characterized. This is useful for qualitative analysis, but has also been used quantitatively in association with the standard spectrum of materials of known purity.

2.3. Nuclear Magnetic Resonance Spectroscopy

Nmr is a most valuable technique for structure determination in thiophene chemistry, especially because spectral interpretation is much easier in the thiophene series compared to benzene derivatives. Chemical shifts in proton nmr are well documented; for thiophene ($CDCl_3$), δ = H_2 7.12, H_3 7.34, H_4 7.34, and H_5 7.12 ppm. Coupling constants occur in well-defined ranges: $J_{2-3} = 4.9 - 5.8$; $J_{3-4} = 3.45 - 4.35$; $J_{2-4} = 1.25 - 1.7$; and $J_{2-5} = 3.2 - 3.65$ Hz. The technique can be used quantitatively by comparison with standard spectra of materials of known purity. ^{13}C-nmr spectroscopy of thiophene and thiophene derivatives is also a valuable

Table 2. Toxicological and Ecotoxicological Properties of Thiophene and Methylthiophenes

Property	Thiophene	2-Methylthiophene	3-Methylthiophene
Log P_{ow}	1.81[a]		
LD_{50}, rat (oral), mg/kg	1400	3200 (mouse)	2300[b]
LD_0, rat (dermal), mg/kg	>2000		
LD_{50}, rabbit (dermal), mg/kg	830		>2000[b]
LC_0, rat (inhalation), 1 h mg/L	>27		
LC_{50}, mouse (inhalation), 2 h, mg/m^3	9500	>2000 (rat, 4 h)	>2000 (rat, 4 h)
skin irritancy	irritant		slight irritant[b]
eye irritancy	irritant		minimal irritant[b]
bacterial mutagenicity, Ames	negative[c]	negative	negative[b]
EC_{50}, *Daphnia magna*, mg/kg	13[d]		
LC_{50}, fish (*Oryzias latipes*), 48 h, mg/kg	15.6[e]		
biotic degradation	minimal[d]		
biological accumulation	no		
U.N. No.	2414	1993	1993
hazard symbol	F, T[f]	F	F

[a] Ref. 12.
[b] Ref. 13.
[c] Ref. 14.
[d] Ref. 15.
[e] Ref. 16.
[f] Toxic, only if >0.1% benzene is present.

technique that shows well-defined patterns of spectra. ^{13}C chemical shifts for thiophene, from tetramethylsilane (TMS), are C_2 127.6, C_3 125.9, C_4 125.9, and C_5 127.6 ppm.

3. Reactions of Thiophene and Alkylthiophenes

Electrophilic substitution of thiophene occurs largely at the 2-position and the reactivity of the ring is greater than that of benzene. 3-Substituted derivatives are generally prepared by indirect means or through ring cyclization reactions.

3.1. Alkylation

Thiophenes can be alkylated in the 2-position using alkyl halides, alcohols, and olefins. Choice of catalyst is important; the weaker Friedel-Crafts catalysts, eg, $ZnCl_2$ and $SnCl_4$, are preferred. It is often preferable to use the more readily accomplished acylation reactions of thiophene to give the required alkyl derivatives on reduction. Alternatively, metalation or Grignard reactions, on halothiophenes or halomethylthiophenes, can be utilized.

3.2. Acylation

To achieve acylation of thiophenes, acid anhydrides with phosphoric acid, iodine, or other catalysts have been widely used. Acid chlorides with $AlCl_3$, $SnCl_4$, $ZnCl_2$, and BF_3 also give 2-thienylketones. All reactions give between 0.5 and 2.0% of the 3-isomer. There has been much striving to find catalyst systems that minimize the 3-isomer content attempting to meet to customer specifications. The standard procedure for formylation is via the Vilsmeier-Haack reaction, using phosphorus oxychloride/*N*,*N*-dimethylformamide ($POCl_3$/DMF) or *N*-methylformanilide.

Table 3. Physical, Toxicological, and Ecotoxicological Properties of 2-Bromothiophene, 3-Bromothiophene, and 2-Bromo-3-Methylthiophene

Property	2-Bromo-thiophene	3-Bromo-thiophene	2-Bromo-3-methylthiophene
CAS Registry Number	[1003-09-4]	[872-31-1]	[14282-76-9]
description	liquid	liquid	liquid
flash point, °C	60	56	
boiling point at 101.3 kPa, °C	150	158	181–182
density at 20°C, kg/m^3	1684	1740	1571 (25°C)
refractive index, n_D^{25}	1.5860	1.5910	1.5680
LD_{50}, rat (oral), mg/kg	200–250[a]	66–160[a]	1923[a]
LD_{50}, rabbit (dermal), mg/kg	134[a]	173–694[a]	>2000[b]
LC_{50}, 4 h, mg/L	1.04[a]		
skin irritancy	irritant[a]	slight irritant[a]	moderate irritant[b]
eye irritancy	irritant[a]	slight irritant[a]	moderate irritant[b]
sensitization	no[a]		
Ames test	negative[a]	negative[a]	negative[c]
EC_{50}, *Daphnia magna*, 48 h, mg/L	5.0[d]		0.79[d]
hazard symbol	T, N	T	Xn, N
TSCA status	listed	listed	not listed
U.N. No.	2810	2810	3082

[a] Ref. 19.
[b] Ref. 20.
[c] Ref. 21.
[d] Ref. 22.

3.3. Halogenation

Many different halogenating reagents have been used to accomplish halogenation of the thiophene ring. Excess of reagent gives di-, tri-, and even tetrahalogenation of thiophene itself. The bromothiophenes are often the preferred target. Bromine in acetic acid or chloroform has been the traditional route, but utilizes just one of the atoms of bromine. Addition products are often observed, particularly when proceeding through to di- and tribromothiophenes.

N-Bromosuccinimide and *N*, *N*′-dibromo-5,5-dimethylhydantoin have also been used successfully, which makes possible recycling of succinimide or the hydantoin and utilizes all the bromine atoms. A mixture of sodium bromide–sodium bromate in aqueous acid has also been used commercially.

Introduction of a 3-bromosubstituent onto thiophene is accomplished by initial tribromination, followed by reduction of the α-bromines by treatment with zinc/acetic acid, thereby utilizing only one of three bromines introduced. The so-called halogen dance sequence of reactions, whereby bromothiophenes are treated with base, causing proton abstraction and rearrangement of bromine to the produce the most-stable anion, has also been used to introduce a bromine atom at position 3. The formation of 3-bromothiophene [872-31-1] from this sequence of reactions (17) is an efficient use of bromine. Vapor-phase techniques have also been proposed to achieve this halogen migration (18), but with less specificity. Table 3 summarizes properties of some brominated thiophenes.

Table 4. Reactions of 2-Thienyllithium

Reagent	Product	CAS Registry Number of product
carbon dioxide	2-thiophenecarboxylic acid	[527-72-0]
sulfur	thiophene-2-thiol	[7774-74-5]
N, *N*-dimethylformamide	2-thiophenecarboxaldehyde	[98-03-3]

3.4. Nitration

It is difficult to control nitration of thiophene, which yields 2-nitrothiophene [609-40-9]. The strongly electrophilic nitronium ion leads to significant yields (12–15%) of 3-isomer. A preferred procedure is the slow addition of thiophene to an anhydrous mixture of nitric acid, acetic acid, and acetic anhydride.

3.5. Metalation

Direct reaction of thiophene and butyllithium in diethyl ether gives 2-thienyllithium [2786-07-4], a valuable intermediate and source of many further derivatives. Some examples are given in Table 4. Thienyllithiums can also be prepared by halogen exchange from bromothiophenes and butyllithium, but this requires low temperature to avoid any possible proton–lithium exchange, or rearrangement by the halogen dance mechanism. Thienyl Grignard reagents are also prepared from the bromothiophenes and can be used in reaction schemes to give many other derivatives.

3.6. Oxidation

Strong oxidizing agents can rupture the thiophene ring structure, eg, nitric acid gives maleic acid. In the vapor phase, oxidation can lead to loss of aromaticity, producing thiomaleic anhydride [6007-87-0]. Oxidation of alkylthiophenes can lead to carboxylic acids. A useful reagent for this is neutral sodium dichromate under autogenous pressure at 270°C (23). Oxidation at the sulfur atom with peroxides and peracids leads to the sulfone. This material readily undergoes Diels Alder reaction and a dimer has been isolated.

3.7. Reduction and Hydrodesulfurization

Reduction of thiophene to 2,3- and 2,5-dihydrothiophene and ultimately tetrahydrothiophene can be achieved by treatment with sodium metal–alcohol or ammonia. Hydrogen with Pd, Co, Mo, and Rh catalysts also reduces thiophene to tetrahydrothiophene [110-01-0], a malodorous material used as a gas odorant.

Rigorous hydrogenating conditions, particularly with Raney Nickel, remove the sulfur atom of thiophenes. With vapor-phase catalysis, hydrodesulfurization is the technique used to remove sulfur materials from crude oil. Chemically hydrodesulfurization can be a valuable route to alkanes otherwise difficult to access.

3.8. Side-Chain Derivatization

Reaction of thiophene with aqueous formaldehyde solution in concentrated hydrochloric acid gives 2-chloromethylthiophene [765-50-4]. This relatively unstable, lachrymatory material has been used as a commercial source of further derivatives such as 2-thiopheneacetonitrile [20893-30-5] and 2-thiopheneacetic acid [1918-77-0] (24). Similar derivatives can be obtained by peroxide, or light-catalyzed (25) halogenation of methylthiophenes, eg, *N*-bromosuccinimide/benzoylperoxide on 2-, and 3-methylthiophenes gives the corresponding bromomethylthiophenes.

3.9. Nucleophilic Reactions

Useful nucleophilic substitutions of halothiophenes are readily achieved in copper-mediated reactions. Of particular note is the ready conversion of 3-bromoderivatives to the corresponding 3-chloroderivatives with copper(I)chloride in hot *N*, *N*-dimethylformamide (26). High yields of alkoxythiophenes are obtained from bromo- and iodothiophenes on reaction with sodium alkoxide in the appropriate alcohol, and catalyzed by copper(II) oxide, a trace of potassium iodide, and in more recent years a phase-transfer catalyst (27).

4. Manufacture of Thiophenes

4.1. Preparative Methods

The thiophene ring system has been synthesized through numerous reaction types. A systematic review of these has been made (28) and is based on the number of components utilized in the construction of the ring. Some 19 combinations are possible, utilizing five method types. Not all combinations have been reported and some would be of only minor benefit.

Manufacture of thiophene on the commercial scale involves reactions of the two component method type wherein a 4-carbon chain molecule reacts with a source of sulfur over a catalyst which also effects cyclization and aromatization. A range of suitable feedstocks has included butane, *n*-butanol, *n*-butyraldehyde, crotonaldehyde, and furan; the source of sulfur has included sulfur itself, hydrogen sulfide, and carbon disulfide (29–32).

4.2. Process Description

Reactors used in the vapor-phase synthesis of thiophene and alkylthiophenes are all multitubular, fixed-bed catalytic reactors operating at atmospheric pressure, or up to 10^3 kPa and with hot-air circulation on the shell, or salt bath heating, maintaining reaction temperatures in the range of 400–500°C. The feedstocks, in the appropriate molar ratio, are vaporized and passed through the catalyst bed. Condensation gives the crude product mixture; noncondensable vapors are vented to the incinerator.

Reactions tend to deposit carbon on the catalyst, which ultimately leads to loss of activity. At this stage reactions are stopped, the catalyst purged and regenerated by a controlled oxygenating vapor. All the vapors from the regeneration process are also passed to the incinerator. A catalyst can undergo many regenerations before replacement becomes necessary.

4.3. Distillation System

The crude condensate consists of the desired product, some low boiling constituents, and a smaller quantity of high boiling tar. Distillation separates the low boiling components, which are invariably incinerated, followed by the product fraction. Tar accumulates in the still kettles, from which it is periodically removed, again to incineration. Stills work at atmospheric pressure and are vented to the incinerator.

4.4. Releases and Abatements

Organic chemical reactions under conditions as severe as 400–500°C are inherently less than completely selective. Although the synthesis of thiophene under such conditions is considered the best practical commercial environmental option, it nevertheless produces waste gases in quantities roughly equal to those of saleable products. It is generally not considered practical to treat the various off-gases individually. The scale and limited revenue of the process could not support the operation of such an ancillary plant. The incinerator

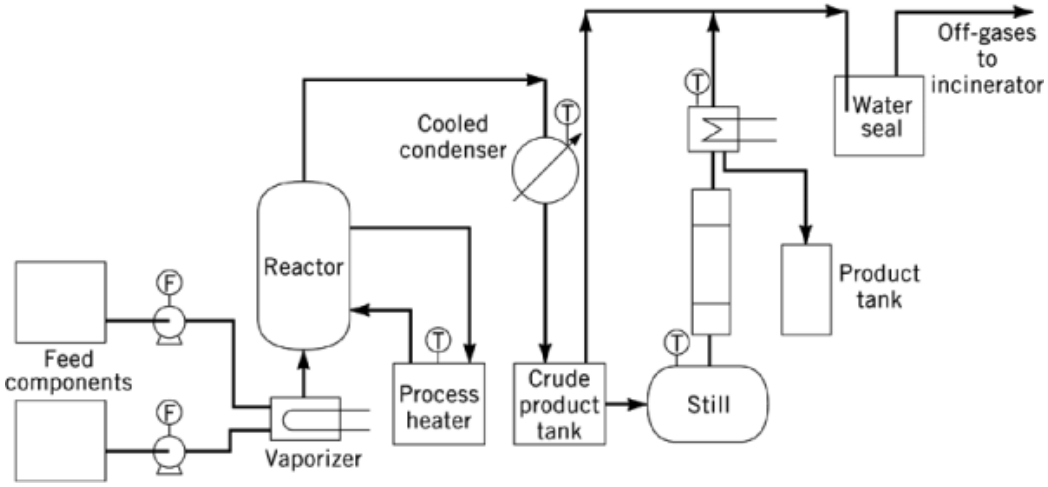


Fig. 2. Schematics of a vapor-phase process that generates thiophene and alkyl thiophenes, where the controlled parameters F=flow and T=temperature.

handles all vents. All the components of the streams are combusted under controlled conditions to give a single discharge, which is readily controlled and monitored. The overall environmental impact is minimal.

4.5. Quality

The plant operated by Synthetic Chemicals Ltd. operates within a quality management system, which complies with British Standard (BS) 5750 and ISO 9001, Part 1.

Dependent on the C-4 feedstock, the process outlined in Figure 2 gives a product containing low levels of benzene. The Elf Atochem process using the furan–H_2S route to give benzene-free material, but the process has the disadvantage of coproducing small amounts of mercaptans. Raw materials are not a problem for either process; market demand is the limiting factor in production capacity.

5. Manufacturing Processes for Thiophene Derivatives

5.1. Halothiophenes

The bromothiophenes, commercially the most important of the halothiophenes, are readily made and can be further derivatized. Manufacture of 2-bromothiophene involves the reaction of thiophene with a solution of sodium bromide/sodium bromate in acid solution. Such a reaction is controlled by the rate of addition of the acid. The two-phase system is stirred throughout the reaction; the heavy product layer is separated and washed thoroughly with water and alkali before distillation (Fig. 3). The alkali treatment is particularly important and serves not just to remove residual acidity but, more importantly, to remove chemically any addition compounds that may have formed. The washwater must be maintained alkaline during this procedure. With the introduction of more than one bromine atom, this alkali wash becomes more critical as there is a greater tendency for addition by-products to form in such reactions. Distillation of material containing residual addition compounds is hazardous, because traces of acid become self-catalytic, causing decomposition of the still contents and much acid gas evolution. Bromination of alkylthiophenes follows a similar pattern.

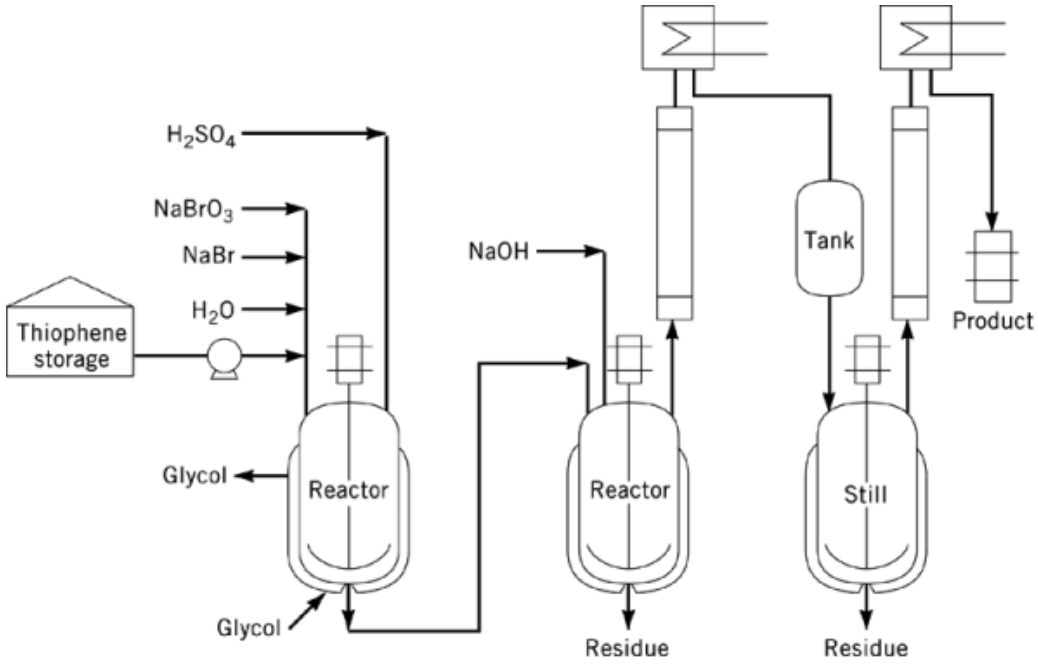


Fig. 3. Schematics of a liquid two-phase reactor system for 2-bromothiophene.

The route to 3-bromothiophene utilizes a variation of the halogen dance technology (17). Preferably, 2,5-dibromothiophene [3141-27-3] is added to a solution of sodamide in thiophene containing the catalyst tris(2-(2-methoxyethoxy)ethyl)amine (TDA-1) (33) at temperatures marginally below reflux. On completion, quenching exothermically liberates ammonia gas; the organic phase is separated, washed, and distilled, and forerunning thiophene is recycled. Material of 97–98% purity is isolated.

5.2. Acylthiophenes

Manufacturing methods introducing the carboxaldehyde group into the 2- or 5-positions of thiophene and alkylthiophenes utilize the Vilsmeier-Haack reaction. To synthesize 2-thiophenecarboxaldehyde (Table 5), a controlled addition of phosphorus oxychloride to thiophene in *N*, *N*-dimethylformamide is carried out, causing the temperature to rise. Completion of the reaction is followed by an aqueous quench, neutralization, and solvent extraction to isolate the product.

3-Thiophenecarboxaldehyde [498-62-4] has been commercially available (35) via carbonylation of 2,5-dimethoxy-2,5-dihydrofuran, followed by treatment with hydrogen sulfide, which introduces the sulfur atom with loss of methanol, inducing aromaticity and producing 3-thiophenecarboxaldehyde directly.

Manufacture of 2-acetylthiophenes involves direct reaction of thiophene or alkylthiophene with acetic anhydride or acetyl chloride. Preferred systems use acetic anhydride and have involved iodine or orthophosphoric acid as catalysts. The former catalyst leads to simpler workup, but has the disadvantage of leading to a higher level of 3-isomer in the product. Processes claiming very low levels of 3-isomer operate with catalysts that are proprietary, though levels of less than 0.5% are not easily attained.

The need for low levels of 3-isomer in 2-thiophenecarboxylic acid [527-72-0], which is produced by oxidation of 2-acetylthiophene [88-15-3] and used in drug applications, has been the driving force to find improved acylation catalysts. The most widely used oxidant is sodium hypochlorite, which produces a quantity of

Table 5. Physical, Toxicological, and Ecotoxicological Properties of 2-Thiophenealdehyde and 2-Acetylthiophene

Property	2-Thiophenecarboxaldehyde	2-Acetylthiophene
CAS Registry Number	[98-03-3]	[88-15-3]
description	liquid	liquid
melting point, °C		10–11
boiling point, °C	198	214
flash point, °C	77	96
density at 20°C, kg/m^3	1215 (21°C)	1171
refractive index, n_D^{25}	1.5920 (20°C)	1.5650
LD_{50}, rat (oral), mg/kg	1100	50 (mouse)
LD_{50}, rabbit (dermal), mg/kg	>2000	320 (rat)
LC_{50}, rat, 1 h, mg/m^3		1460[a]
skin irritancy	slight irritant	nonirritant
eye irritancy	slight irritant	slight irritant
sensitization	yes	
Ames test	negative	negative[a]
hazard symbol	none	T
TSCA status	listed	listed
U.N. No.	none	2810

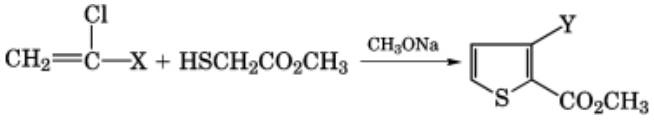
[a] Ref. 34.

chloroform as by-product, a consequence that detracts from its simplicity. Separation of the phases and acidification of the aqueous phase precipitate the product which is filtered off. Alternative oxidants have included sodium nitrite in acid solution, which has some advantages, but, like the hypochlorite method, also involves very dilute solutions and low throughput volumes.

The long-standing manufacturing route to 2-thiopheneacetic acid [1918-77-0] has also involved 2-acetylthiophene. Oxidation with potassium permanganate under controlled conditions leads to 2-thiopheneglyoxylic acid [4075-59-6], which may be isolated as ammonium salt. The salt is then carried through a reduction stage involving the Wolff-Kishner reaction in aqueous solution and utilizing hydrazine hydrate. Workup via acidification gives the unpleasant smelling 2-thiopheneacetic acid.

5.3. Methyl 3-aminothiophene-2-carboxylate

Synthesis of this amino ester [22288-78-4] has been variously described in the literature (see Table 6); it is a key intermediate to both pharmaceutical and agrochemical products. The main synthetic schemes use thioglycollate esters as starting materials. One reaction (38) employs 2,3-dichloropropionitrile (23DCPN) as the second component in early work, though this material was never commercialized. 2-Chloroacrylonitrile was available commercially for a time in the 1980s and was used to give this same product (39). This route was later upscaled by Synthetic Chemicals Ltd. following pharmaceutical and later agrochemical demand.



When X = CN, Y = NH_2; X = CO_2CH_3, Y = OH.

Chemical processing is carried out in the liquid phase, in glass-lined, stirred-batch reactors fitted with a heating/cooling jacket. The product is filtered off and dried. Handling the dry product requires grounded equipment to prevent static charges from building up, a particular hazard with this crystalline dust.

Table 6. Physical, Toxicological, and Ecotoxicological Properties of Methyl 3-Aminothiophene-2-Carboxylate and Methyl 3-Amino-4-Methylthiophene-2-Carboxylate

Property	Methyl 3-aminothiophene-2-carboxylate	Methyl 3-amino-4-methylthiophene-2-carboxylate
CAS Registry Number	[22288-78-4]	[85006-31-1]
description	detached crystals	detached crystals
melting point, °C	65	84
boiling point, °C	100–102 at 0.1 mm Hg	
flash point, °C	>100	>100
bulk density, kg/L	0.4	0.4
solubility in water	0.2% (18°C)	
LD_{50}, rat (oral), mg/kg	406[a]	2300[a]
LD_{50}, rabbit (dermal), mg/kg	>2000[a]	
skin irritancy	nonirritant[a]	nonirritant[a]
eye irritancy	slight mechanical irritant[a]	slight mechanical irritant[a]
sensitization	no[a]	
bacterial mutagenicity, Ames	negative[a]	negative[a]
LC_{50}, *Daphnia magna*, 48 h, mg/L	18[b]	
LC_{50}, fish (rainbow trout), 96 h, mg/L	43[b]	
biotic degradation	nonbiodegradable[b]	
transport classification	nonhazardous	nonhazardous

[a] Ref. 36.
[b] Ref. 37.

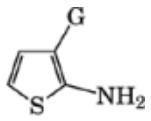
6. Economic Aspects

Sales of thiophene in the 1990s amount to hundreds of metric tons per year. Supplies are available worldwide from Synthetic Chemicals Ltd. (SCL) in the United Kingdom and Elf-Atochem SA in France. There is currently no U.S. producer of thiophene or the principal thiophene derivatives. At these levels of demand, material is shipped in 200-liter drums and in bulk quantities. Market price is dependent on the level of off-take. 3-Methylthiophene is also available from SCL, but demand is low and even lower in the case of 2-methylthiophene; lower production and lower market demand have led to higher prices for these derivatives.

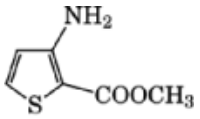
2-Bromothiophene is produced in Europe by Solvay and SCL, at up to 50 metric tons per year, with a 98%-pure specification and prices commensurate with production levels. 3-Bromothiophene is still a specialty product as of the mid-1990s, produced in multipurpose plant by SCL in hundreds of kilos per year, but at this level of market demand and also on account of the complexity of the synthesis, it commands a relatively high price.

The principal source of 2-thiophenecarboxaldehyde is Great Lakes Fine Chemicals Ltd. in the United Kingdom, whereas 2-acetylthiophene is produced by a number of manufacturers. Some of the 2-acetylthiophene producers continue derivatization to 2-thiophenecarboxylic acid and 2-thiopheneacetic acid.

The intermediates of type **(8)**, wherein G is an electron withdrawing group, which are used in the dyestuffs industry, are usually produced by the user companies themselves and used directly. The type **(9)** amino ester is another product from the SCL range of thiophene derivatives, produced in metric ton quantities for specific outlets.



(**8**)



(**9**)

7. Transport

Thiophene itself is classified as a highly flammable liquid for transportation, designated by U.N. No. 2414, Class 3, Packaging Group II, Hazard Symbol F. Classification for use is additionally exacerbated by a low volume of benzene found in commercial material. This is a component of manufacture from a cracking side reaction over the catalyst system. Although benzene levels are minimized in optimization of the process and in workup, typical product contains from 0.1 to $<0.3\%$ benzene. In Europe this demands the use of a risk phrase, R45: May Cause Cancer, being added to the label and included in the material safety data sheet. The subsidiary hazard symbol T, for toxic, is then also required. A benzene-free grade is available from Elf Atochem. The methylthiophenes are also highly flammable liquids; U.N. No. 1993, Flammable liquid, not otherwise specified (NOS) Class 3, Packaging Group II, Hazard Symbol F is again required. All of these products are regulated by the U.S. Department of Transport.

Bromothiophenes, if not stored and treated correctly, may decompose, liberate HBr gas, and lead to pressurizing of containers. Prior treatment with alkali, avoiding metal contaminants, and keeping a cool temperature can avert any problems. Acylthiophenes are transported under U.N. No. 2810, Toxic liquids, organic, N.O.S., Class 6.1, Packaging Group III.

8. Toxicity

Thiophene is harmful by inhalation, in contact with skin, or if swallowed; it is also a skin-irritant. Studies (40) indicate acute oral toxicity to rat in the range $1000 < LD_{50} < 3000$ mg/kg, and a dermal toxicity $LD_0 > 2000$ in rats. Thiophene may act as a central nervous system depressant; some evidence for liver damage in rats also exists. The methylthiophenes are irritating to skin, eyes, and the respiratory system. Thiophene and the methylthiophenes give a negative response in the Ames test for bacterial mutagenicity. Reports (41, 42) concerning neurotoxicity indicate that thiophene induces cerebellar degeneration, mediated via a disturbance of cerebellar blood vessels and hepatic injury. Thiophene is harmful in the aqueous environment and is non-biodegradable (see Table 2).

Thiophene and 3-methylthiophene are listed on the TSCA chemical substances inventory. Thiophene is regulated as a hazardous material under OSHA and also regulated under the Clean Air Act, Section 110, 40 CFR 60.489, but there are no exposure limits or controls set for 3-methylthiophene. Both materials are regulated under sections 311/312 of the Superfund Amendments and Reauthorization Act, 1986 (SARA), as

materials with an acute health and fire hazard, and under the Resource Conservation and Recovery Act, as ignitable hazardous wastes (D001).

Bromothiophenes are toxic materials by all routes. Inhalation toxicity of 2-bromothiophene is significant. Ecotoxicity is also noted for these materials, particularly for 2-bromo-3-methylthiophene. 2-Thiophenecarboxaldehyde and the 3-methyl derivative can cause minor irritation to the skin and eyes of rabbits. The former is a sensitizer to guinea pig skin, the latter is not. 2-Acetylthiophene is toxic in all modes of contact. Severe exposure causes serious inflammation of the lung, damage to many organs, and depression of the central nervous system.

9. Uses of Thiophene and Derivatives

9.1. Pharmaceuticals

Thiophene and its derivatives find applications in the pharmaceutical area over a wide range of drug types (43), which can be divided into four main groups.

9.1.1. Nonsteroidal Antiinflammatory Rheumatoid and Osteoarthritis Drugs

Of the many drugs in this area on the market, a number contain the thiophene moiety, and new ones are coming through trials, prior to entering the market. Tenoxicam [59804-37-4] (Hoffmann La Roche) (44), a cyclooxygenase/ lipoxygenase inhibitor developed as an antiinflammatory, is also used to treat arthritis. Although it has been launched in over 70 countries, it has not been introduced into the United States. A near relative, Lornoxicam [70374-39-9] (Haflund/Nycomed) (45), is in trials as a nonsteroidal antiinflammatory (NSAI) analgesic and for the treatment of post-operative pain. Lornoxicam is said to be 10 times more effective than tenoxicam and is to be marketed to control severe pain (see Analgesics, antipyretics, and antiinflammatory agents).

An established product, Surgam [33005-95-7] (Roussel UCLAF) (46), is still in production in the 1990s. One of the newer drugs coming into this area is Tenidap [100599-27-7] (Pfizer) (47), derived from 2-thiophenecarboxylic acid. The promising trial results of this drug indicate NSAI activity and disease-modifying effects, which minimizes joint damage by inhibiting the destruction mechanism. Its use would therefore constitute a novel arthritis treatment, however, continuing trials have indicated side effects and the drug has been withdrawn (Scrip No. 2169, 1996).

9.1.2. Hypertension and Heart Drugs

Heart disease and failure has a number of causes: hypertension, coronary artery disease, congestive heart failure, and arrhythmia of the heart. There are drugs that assist and control one or more of these conditions: angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, diuretics, and beta-blockers, respectively (see Cardiovascular agents). Eprosartan [133040-01-4] (SB) (48) in phase-three clinical trials is one of a new class of drugs that can be used to control both congestive heart failure and hypertension. Ticlopidine [55142-85-3] (Sanofi/Syntex) (49) and Clopidogrel [90055-48-4] (Sanofi/BMS) (50) are both antithrombotic drugs that prevent heart attacks, strokes, and peripheral arterial disease by acting as platelet aggregation inhibitors. Ticlopidine was the first such drug on the U.S. market following FDA approval in 1990. Clopidogrel is a similar product for the same purpose, with reported increased potency and fewer side effects. It is expected to have a bright future.

9.1.3. Antibiotics

Cephaloridine and Cephalothin (Glaxo) were early thiophene-containing, cephalosporin antibiotics. They have largely been replaced by later products, of which Cefoxitin [35607-66-0] (Merck) (51) is the principal thiophene-containing example (see Antibiotics).

Ticarcillin [34787-01-4] (SB) (52) is a significant penicillin antibiotic that incorporates the thiophene ring system. A number of routes to the required intermediate, 3-thiophenemalonic acid [21080-92-2], have been used over the years. Those from thiophene-based starting materials have involved 3-methylthiophene and 3-bromothiophene.

9.1.4. Other Pharmaceuticals

Other pharmaceutical products incorporating the thiophene ring include the antiasthmatic drug Ketotifen [34580-13-7] (Sandoz) (53), which is particularly marketed in Japan. The antifungal drug Tioconazole [65899-73-2] (Pfizer) (54) is based on 2-chloro-3-methylthiophene [14345-97-2]. The antiglaucoma drug Dorzolamide [120279-96-1] is made from a range of fused thiophene derivatives developed by Merck (55). A group of thiophene-containing drugs from the Japanese pharmaceutical industry includes Tipepidine [5169-78-8] (Tanabe) (56), an antitussive; Tiquizium Bromide [71731-58-3] (Hokuriku) (57), an antispasmodic; and Timepidium Bromide [35035-05-3] (Tanabe) (58), an anticholinergic.

9.2. Veterinary Products

Principal users of thiophene are the anthelmintics Pyrantel [15686-83-6] and Morantel [20574-50-9] (Pfizer) (59), based on 2-thiophenecarboxaldehyde and 3-methyl-2-thiophenecarboxaldehyde [5834-16-2], respectively. Tioconazole, one of a range of fungicidal products incorporating thiophene, has also found veterinary applications.

9.3. Agrochemical Products

The principal thiophene derivative in herbicidal protection, one of a range of sulfonylurea herbicides, is Harmony [79277-27-3] (Du Pont) (60), based on the intermediate methyl 3-aminothiophene-2-carboxylate **(9)**. The product is characterized by a rapid biodegradability in the soil. Many other thiophene derivatives have been shown to have agrochemical activity, but few of these have been developed to the commercial level.

9.4. Dyestuffs

The use of thiophene-based dyestuffs has been largely the result of the access of 2-amino-3-substituted thiophenes via new cyclization chemistry techniques (61). Intermediates of type **(8)** are available from development of this work. Such intermediates act as the azo-component and, when coupled with pyrazolones, aminopyrazoles, phenols, 2,6-dihydropyridines, etc, have produced numerous monoazo disperse dyes. These dyes impart yellow–green, red–green, or violet–green colorations to synthetic fibers, with excellent fastness to light as well as to wet- and dry-heat treatments (62–64).

9.5. Conjugated Polythiophenes

Because of their potential electrical conductivity, conjugated polythiophenes, along with other conjugated polymeric systems, have been extensively studied since the pioneering works in the early 1980s (65, 66) (see Electrically conductive polymers). Poly-3-alkylthiophenes, in particular, have attracted much attention. The use of 3-*n*-alkyl (C_{6--12}) side chains improves significantly the solubility and processibility of these polymers (67–73). Branched-chain-substituted thiophenes are difficult to polymerize and are generally less conductive. It is not surprising that many variations of the 3-substitution have been studied. In the laboratory this poses no significant problem, as synthetic routes to 3-substituted thiophenes are readily available (74). However, these routes tend to involve multistep syntheses, which add considerably to the cost of such monomers when scaleup is considered.

Applications of polythiophenes being considered utilize either the electrical properties of the doped conducting state with either anionic or cationic species, the electronic properties of the neutral material, or the electrochemical reversibility of the transition between the doped and undoped state of these materials (71).

The development of polythiophenes since the early 1980s has been extensive. Processible conducting polymers are available and monomer derivatization has extended the range of electronic and electrochemical properties associated with such materials. Problem areas include the need for improved conductivity by monomer manipulation, involving more extensive research using structure–activity relationships, and improved synthetic methods for monomers and polymers alike, which are needed to bring the attractive properties of polythiophenes to fruition on the commercial scale.

Another group of conjugated thiophene molecules for future applications are those being developed as nonlinear optical (NLO) devices (75). Replacement of benzene rings with thiophene has an enormous effect on the molecular nonlinearity of such molecules. These NLO molecules are able to switch, route, and modulate light. Technology using such materials should become available by the turn of the twenty-first century.

BIBLIOGRAPHY

"Thiophene" in *ECT* 1st ed., Vol. 14, pp. 95–102, by D. E. Badertscher and H. E. Rasmussen, Socony Mobil Oil Co., Inc.; in *ECT* 2nd ed., Vol. 20, pp. 219–226, by O. Meth-Cohn, University of Salford; "Thiophene and Thiophene Derivatives" in *ECT* 3rd ed., Vol. 22, pp. 965–973, by B. Buchholz, Pennwalt Corp.

Cited Publications

1. S. Gronowitz, ed., *Thiophene and Thiophene Derivatives*, Vols. **1–4**, Wiley-Interscience, New York, 1985.
2. H. D. Hartough, *Thiophene and Thiophene Derivatives*, Interscience Publishers, New York, 1952.
3. S. Gronowitz, *Adv. Heterocyclic Chem.* **1**, 1 (1963).
4. S. Gronowitz, *Org. Chem. Sulphur Selenium Tellurium*, London, **3**, 400 (1975); S. Gronowitz, *Org. Chem. Sulphur Selenium Tellurium*, **4**, 244 (1977).
5. O. Meth-Cohn, *Comp. Org. Chem.* **4**, 789 (1979).
6. R. M. Kellog, *Comp. Heterocyclic Chem.* **4**, 713 (1984); S. J. Rajappa, *Comp. Heterocyclic Chem.* **4**, 741 (1984); E. Campaigne, *Comp. Heterocyclic Chem.* **4**, 863 (1984).
7. J. B. Press and R. K. Russell, *Prog. Heterocyclic Chem.* **2**, 50 (1990); **3**, 70 (1991); **4**, 62 (1992); **5**, 82 (1993); **6**, 88 (1994); **7**, 82 (1995).
8. B. Bak, D. Christensen, and L. H. Nygaard, *J. Mol. Spectroscopy*, **7**, 58 (1961).
9. M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocyclic Chem.* **17**, 255 (1974).
10. F. Fringuelli and co-workers, *J. Chem. Soc. Perkin Trans. II*, (4), 332 (1974).
11. Data obtained on-line from *Beilstein Handbook of Organic Chemistry*, Beilstein Informationssysteme, Frankfurt, Germany.
12. K. Verschueren, *Handbook of Environmental Data on Organic Chemicals*, 2nd ed., Van Nostrand Reinhold, Co., Inc., New York, 1983, p. 1097.
13. Technical data, Synthetic Chemicals, Ltd., Huntingdon Research Centre Reports, July 1987.
14. Zeiger and co-workers, *Environ. Mutagen.* **9**(Suppl. 9), 1 (1987).
15. Technical data, Synthetic Chemicals Ltd., Binnie Environmental Report ENV161, 1994.
16. Technical data, Elf Atochem, Safety Data Sheet, November 4, 1994.
17. Eur. Pat. 299,586 (July 14, 1987), P. R. Grosvenor and L. S. Fuller (to Inspec Group plc).
18. Austral. Pat. 42,881 (Nov. 28, 1985), K. Eichler and E. I. Leupold (to Hoechst AG).
19. Technical data, Synthetic Chemicals Ltd, Huntingdon Research Centre Reports, 1979, 1986, 1988.
20. Technical data, Synthetic Chemicals Ltd, Safepharm Laboratories Ltd. Reports, 1994.
21. Technical data, Shell Japan Ltd, Hita Research Laboratories Report, T-3554, 1993.
22. Technical data, Synthetic Chemicals Ltd., Binnie Environmental Ltd. Reports, 1994.

23. L. Friedman, D. L. Fishel, and H. Schecter, *J. Org. Chem.* **30**, 1453 (1965).
24. B. F. Crowe and F. F. Nord, *J. Org. Chem.* **15**, 81 (1950).
25. Brit. Pat. 1,483,349 (Aug. 17, 1974), J. A. Clark and O. Meth-Cohn (to Synthetic Chemicals Ltd.).
26. S. Conde and co-workers, *Synthesis*, (6), 412 (1976).
27. S. Gronowitz, *Arkiv Kemi*, **12**, 239 (1958).
28. O. Meth-Cohn, *Org. Chem. Sulphur Selenium Tellurium*, **4**, 828 (1979).
29. U.S. Pat. 3,197,483 (July 27, 1965), B. Buchholz, T. E. Deger, and R. H. Goshorn (to Pennwalt Corp.).
30. U.S. Pat. 3,822,289 (July 2, 1974), Brit. Pat. 1,345,203, (Jan. 30, 1974), N. R. Clark and W. E. Webster (to Synthetic Chemicals Ltd.).
31. U.S. Pat. 3,939,179 (Feb. 17, 1976), T. R. Bell and P. G. Smith (to Pennwalt Corp.).
32. Brit. Pat. 1,585,647 (Mar. 11, 1981), J. Barrault, L. Lucien, and M. Guisnet (to Societe Nationale, Elf Aquataine).
33. Eur. Pat. 43,303 (July 1, 1980), G. Soula (to Rhone Poulenc Specialties Chimiques); G. Soula, *J. Org. Chem.* **50**, 3717, 1985.
34. Technical data, Synthetic Chemicals Ltd., Huntingdon Research Centre Reports, 1976.
35. Brit. Pat. 1,523,650 (Sept. 6, 1978), H. Koenig and U. Ohnsorge (to BASF AG).
36. Technical data, Synthetic Chemicals Ltd., Huntingdon Research Centre Reports, 1987.
37. Technical data, Synthetic Chemicals Ltd., Binnie Environmental Ltd., Reports, 1994.
38. Ger. Pats. 1,055,007 (Aug. 29, 1957) and 1,083,830, (Aug. 2, 1958); Brit. Pat. 837,086 (Aug. 29, 1958), H. Feisselmann (to Hoechst AG).
39. P. R. Huddleston and J. M. Barker, *Synthetic Comm.* **9**(8), 731 (1979).
40. Elf-Atochem, Springborn Labs. Report No., 3255.14, and 3255.15, 1994.
41. F. Mori and co-workers, *J. Toxicol. Pathol.* **5**, 21 (1992).
42. F. Mori and co-workers, *J. Toxicol. Pathol.* **6**, 213 (1993).
43. L. S. Fuller, J. W. Pratt, and F. S. Yates, *Manufactur. Chem. Aerosol News*, **49**(5), 67 (1978).
44. Ger. Pat. 2,537,070 (Mar. 18, 1976), O. Hromatka and co-workers (to Hofmann La Roche AG).
45. Eur. Pat. 313,935 (May 3, 1989), D. Binder, F. Rovenszky, and H. P. Ferber (to Hafslund Nycomed Pharma AG).
46. Ger. Pat. 2,055,264 (May 19, 1971), F. Clemence and O. Le Martret (to Roussel UCLAF).
47. U.S. Pat. 4,556,672 (Dec. 3, 1985), S. B. Kadin (to Pfizer Inc.).
48. Eur. Pat. 403,159 (Dec. 19, 1990), J. A. Finkelstein, R. M. Keenan, and J. Weinstock (to SmithKline Beecham Corp.).
49. U.S. Pat. 4,127,580 (Nov. 28, 1978), E. Braye (to Parcor/Sanofi).
50. Eur. Pat. 99,802 (June 13, 1982), D. Aubert, C. Ferrand, and J.-P. Maffrand (to Parcor/Sanofi).
51. Brit. Pat. 1,348,984 (Mar. 27, 1974), B. G. Christensen and co-workers (to Merck and Co. Inc).
52. Brit. Pat. 1,004,670 (Apr. 23, 1963), E. G. Brain and J. H. Naylor (to Beecham Group Ltd.).
53. Ger. Pat. 2,111,071 (Sept. 23, 1971), J. P. Bourquin, G. Schwarb, and E. Waldvogel (to Sandoz Ltd.).
54. U.S. Pat. 4,062,966 (Dec. 13, 1977), G. E. Gymer (to Pfizer Corp.).
55. Eur. Pat. 296,879 (Dec. 28, 1988), J. J. Baldwin, G. S. Ponticello, and M. E. Christy (to Merck and Co. Inc.).
56. Brit. Pat. 924,544 (Apr. 24, 1963), Y. Yamamoto (to Tanabe Seiyaku Co. Ltd.).
57. Belg. Pat. 866,988 (May 17, 1977), H. Kato and co-workers (to Hokuriku Pharmaceutical Co. Ltd.).
58. Brit. Pat. 1,358,446 (July 3, 1974), T. Kanno, S. Saito, and H. Tamaki (to Tanabe Seiyaku Co. Ltd.).
59. Brit. Pat. 1,120,587 (July 17, 1968), W. C. Austin, L. H. Conoverand, and J. W. McFarland (to Pfizer Ltd.).
60. Eur. Pat. 41,404 (Dec. 9, 1981), G. Levitt (to E. I. Du Pont de Nemours & Co., Inc.); *Proceedings of Meeting of Weed Society of America*, Seattle, Washington, 1980.
61. K. Gewald, *Chem. Ber.* **98**, 3571 (1965); *Org. Chem. Sulphur Selenium Tellurium*, **3**, 401 (1975).
62. Brit. Pats. 1,394,365 , 1,394,367, and 1,394,368 (May 14, 1975), D. B. Baird and co-workers (to ICI Industries Ltd.).
63. Brit. Pat. 1,434,654 (May 5, 1976), W. Groebke and A. Jotterand (to Sandoz AG).
64. Brit. Pat. 1,461,738 (Jan. 19, 1977), D. Von der Brueck and G. Wolfrum (to Bayer AG).
65. A. F. Diaz, *Chem. Scr.* **17**, 142 (1981).
66. G. Tourillon and F. Garnier, *J. Electroanal. Chem.* **135**, 173 (1982).
67. M. Sato, S. Tanaka, and K. Kaeriyama, *J. Chem. Soc. Chem. Commun.* (11), 873 (1986).
68. Fr. Pat. 2,596,566 (Oct. 2, 1987), F. Garnier and co-workers (to Solvay & Cie).
69. S. Hotta and co-workers, *Macromolecules*, **20**, 212 (1987).

70. G. Tourillon, in T. A. Skotheim, ed., *Handbook of Conducting Polymers*, Vol. **1**, Marcel Dekker, Inc., New York, 1986, p. 294.
71. J. Roncali, *Chem. Rev.* **92**, 711 (1992).
72. M. Schott and M. Nechtschein, in J.-P. Farges, ed., *Organic Conductors*, Marcel Dekker, Inc., New York, 1994, p. 495.
73. M. Schott, in Ref. 72, p. 539.
74. K. Schulz, K. Fahmi, and M. Lemaire, *Acros Organics Acta*, **1**, 10 (1995).
75. K. J. Drost, A. K.-Y. Jen, and V. P. Rao, *Chemtech.* **25**(9), 16 (1995).

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