Chapter 10
Synthesis and Biological Evaluation of Some Polycyclic Aromatic Hydrocarbons

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10.1 Benzothiophene

10.1.1 Introduction

Because of their unique pharmacological and biological characteristics, heteroaromatic chemicals play crucial roles in identifying and advancing novel therapeutic candidates [1]. For many years, these substances have been utilized as anti-fungal, anti-oxidant, anti-bacterial, anti-inflammatory, anti-cancer, and anti-parasitic medications [2–5]. Benzothiophene has traditionally been produced using intramolecular cyclization and Claisen rearrangement processes. For instance, the intramolecular cyclization process of O-alkinylthioanisoles allowed for the regioselective synthesis of benzothiophene [6]. A recently described approach uses a Lewis acid catalyst to synthesize benzothiophene and dibenzothiophene from thiophenes and 2, 5-dimethoxy-THF [7].

Well-known candidates for heteroaromatic chemicals are benzothiophene and thiophenes, which are utilized in medications such as sertaconazole (**1**), raloxifene (**2**), and zileuton (**3**) (Fig. 10.1) [8–10]. Breast cancer patients are treated with raloxifene. Furthermore, compared to tamoxifen, a well-known anti-cancer medication with comparable biological characteristics, raloxifene has fewer side effects [11].

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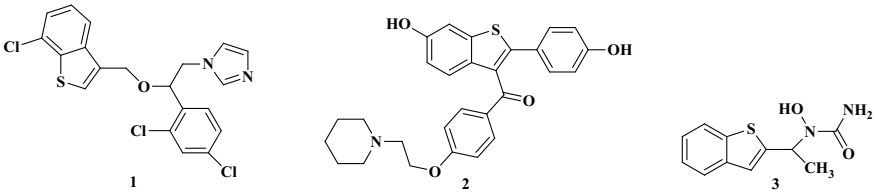


Fig. 10.1 Structure of sertaconazole **1**, raloxifene **2**, and zileuton **3**

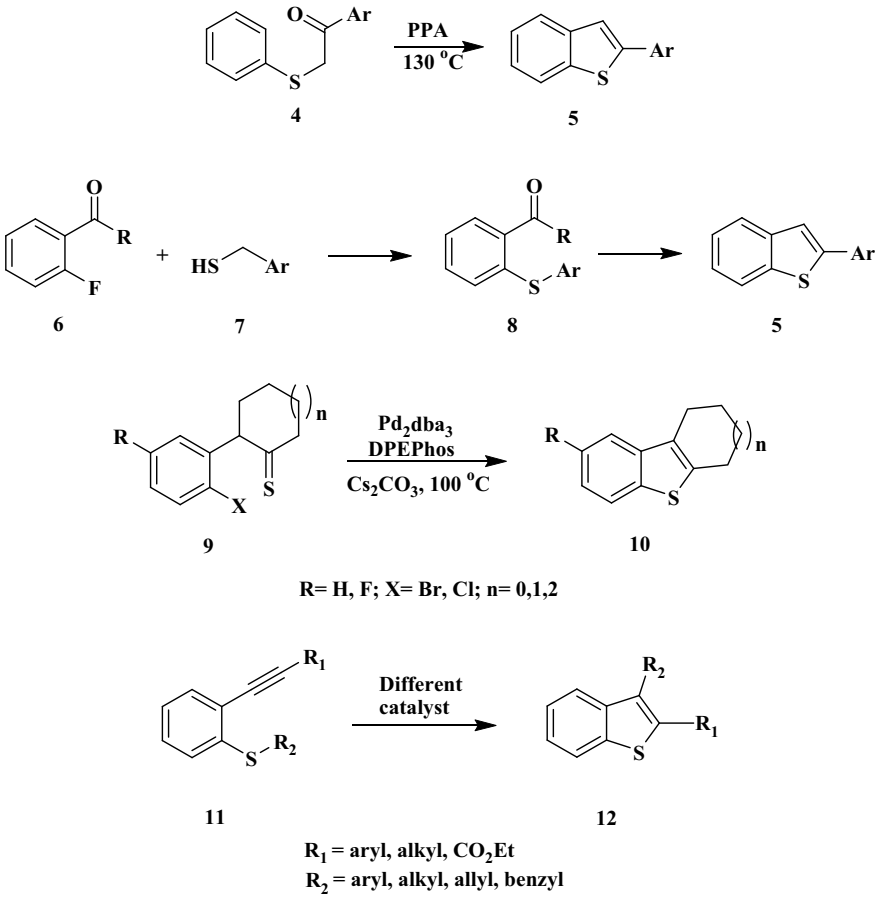
10.2 Synthesis

Several synthetic methods have been used and described to synthesize benzothiophene [12, 13]. Conventionally, 2-aryl benzothiophene (**5**) is produced using the widely recognized and applied domino cyclization/rearrangement reaction of a β-keto sulfide (**4**) catalyzed by acid [14]. An alternative approach makes use of the Knoevenagel condensation of an S-benzyl ortho-acylthiophenol (**8**), which is produced in situ from an ortho-fluoroketone (**6**) and a benzyl thiol (**7**) [12, 13]. A palladium-catalyzed method using an intramolecular C–S coupling reaction of an aryl halide with a thioketone was described [14, 15]. Originally designed to produce benzofurans from thioketone oxygen analogs (**9**), the authors discovered that the same circumstances could also be used for sulfur compounds, yielding moderate-to-good yields of fused benzothiophene (**10**). Recently, many theoretically distinct methods have been devised to break various bonds inside the benzothiophene ring (Scheme 10.1) [16–21].

10.2.1 Biological Activity

10.2.1.1 Benzothiophene: Anti-microbial Agents

Efforts have been made extensively over the last 10 years to create benzothiophene-based compounds that exhibit outstanding therapeutic efficacy and are active on many clinically approved therapeutic targets. Substitution at the heterocyclic thiophene ring rather than the aromatic component seemed more critical for the anti-microbial property of benzothiophene derivatives. In their study, Petsom et al. synthesized benzothiophene derivatives containing quinazoline-4-one. They then examined the anti-bacterial properties of these derivatives against two types of bacteria: Gram-positive ones, such as *Bacillus subtilis* (*BS*) and *Staphylococcus aureus* (*SA*), and Gram-negative ones, such as *Escherichia coli* (*EA*) and *Pseudomonas aeruginosa* (*PA*). Using a filter paper disc approach, the anti-fungal activity was evaluated against four distinct fungi: *Aspergillus niger* (*AN*), *Candida pinnacle* (*CP*), *Candida albicans* (*CA*), and *Rhizopus oryzae* (*RO*). The outcomes were compared with those of the standard medications, ampicillin and streptomycin. The effectiveness of compounds (**13**)

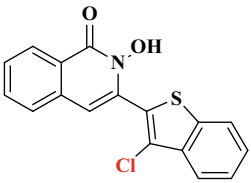


Scheme 10.1 General approaches for preparing benzo[b] thiophene derivatives

and (**14**) against *B. subtilis* and *E. coli* was demonstrated (Fig. 10.2) [22]. According to SAR research, benzothiophene's third-position chloro substituent boosts its anti-bacterial properties, and the attachment of fluoro and nitro groups in the phenyl groups linked to the quinazoline ring also enables anti-fungal properties [22].

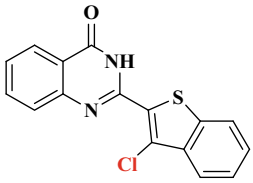
Anti-microbial Activity of Benzothiophene Derivatives: Structural Requirements

The benzothiophene nucleus has been discovered to have strong anti-microbial activity when substituted at all positions with various substituents; however, the first position is unsubstituted because it contains core sulfur. Benzothiophene's heterocyclic cores, such as oxadiazole, pyrazole, and thiazole, as well as groups like $–CH_2OH$ and $–CO_2CH_3$, boost the anti-microbial activity of the compound. The second position of the compound can be substituted with quinazoline and phenyl



13

IZ *(BS)* = 16mm
IZ *(EC)* = 12mm



14

IZ *(BS)* = 15 mm
IZ *(EC)* = 16 mm

Fig. 10.2 Anti-microbial properties of benzothiophene

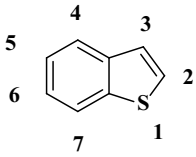


Fig. 10.3 Benzothiophene scaffold's structural requirements as anti-microbial agents

rings, including methoxy, methyl, and fluorine, or unsubstituted. In the same way, the substitutions for the pyrimidine, hydroxy group, and chloro group in the third position showed positive activity. Benzothiophene's fourth position can be replaced or left unsubstituted; substituents with hydroxyl and halogen groups have strong anti-bacterial properties. The benzo group connected to the first position of the benzimidazole core has also demonstrated anti-bacterial solid activity. The fifth or sixth position of the nucleus may be substituted with halogens or unsubstituted. For benzothiophene to show anti-bacterial action, it must contain nitro, halogens, and hydroxyl groups at positions 3, 4, and 6. It must also have fewer substituted benzothiophene at position 7 (Fig. 10.3).

10.2.1.2 Anti-cancer Agents

A tumor is a solid mass of cells that develops when one or more cells lose their ability to control their growth. This condition is known as cancer. Although there is genetic variation in the illness, malignant cells will always undergo metabolic modification [23]. It is one of the most significant risks to human existence and has received extraordinary attention globally. The creation of successful anti-cancer therapies, which incorporate the use of radiation therapy, chemotherapy, and surgery, has been the subject of extensive research [24]. Scientists have concentrated on numerous facets of cancer biology to create novel, effective medications with these properties. When developing anti-cancer drugs, medicinal chemists paid close attention to benzothiophene derivatives. Two anti-cancer medications, arzoxifene (**15**) and raloxifene (**16**), are the product of modifications made to the benzothiophene nucleus (Fig. 10.4) [25]. Compared to raloxifene, arzoxifene is much more potent in preventing mammary cancer in rats that have been caused by the carcinogen nitroso

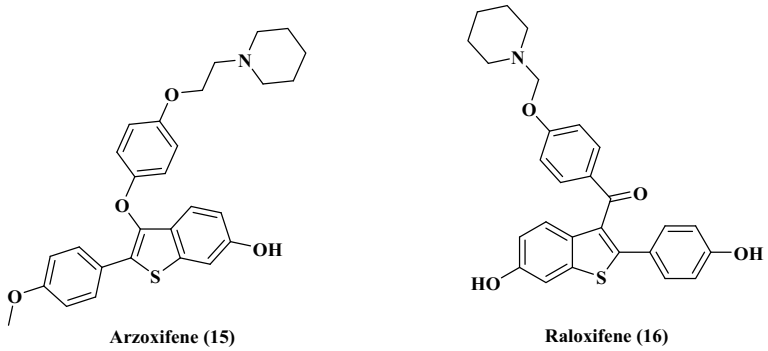


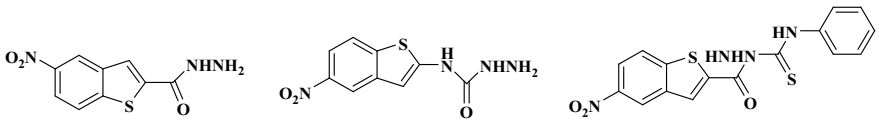
Fig. 10.4 Benzothiophene-based anti-cancer drugs

methyl ureave [25]. In postmenopausal women who have osteoporosis and high risk of breast cancer, raloxifene is used to treat osteoporosis and lower the risk of invasive breast cancer [26]. Perhaps more significantly, ongoing efforts have been focused on creating novel benzothiophene-based anti-cancer drugs targeting various enzymes and receptors.

10.2.1.3 Anti-inflammatory and Analgesic Agents

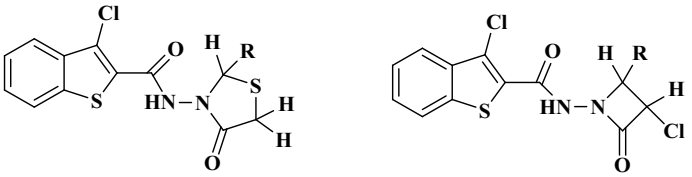
Many diseases have inflammation as their primary cause. An essential part of the immune system's reaction of the human body to pathogens, wounds, or trauma is inflammation. While inflammation is not the direct cause of many conditions, it frequently exacerbates pain and suffering [27]. According to recent research, inflammation plays a crucial role in infection and cancer but also in autoimmune diseases like multiple sclerosis, retinitis, psoriasis type I diabetes, atherosclerosis, rheumatoid arthritis, and Crohn's disease [28, 29]. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of several inflammatory disorders has proven to be highly beneficial.

After reviewing the above discussion, we summed up the following strategy for boosting the compounds' analgesic and anti-inflammatory properties: adding phenylthiosemicarbazide, semicarbazide, carbohydrazide, and pyrazole with p-anisyl and p-chlorophenyl substitutions at the third and fifth positions. The benzothiophene molecule exhibits good activity at the 3-position, where methyl and bromo replacements are introduced, leaving the remaining positions unsubstituted (Fig. 10.3). The anti-inflammatory and anti-nociceptive effects of compounds (**17–19**) were more potent than those of piroxicam (30% at 1 h, 25 mg/kg) at doses of 25 or 50 mg/kg. The action of semicarbazide (**18**), carbohydrazide (**17**), and phenylthiosemicarbazide (**19**) systems is more effective than that of carbohydrazide derivatives, according to SAR research (Fig. 10.5) [30].



(17) (18) (19)

Fig. 10.5 Benzothiophene-based anti-inflammatory and analgesic drugs



(20) (21)

R = 3-Cl-C_6H_4; R = 3-Br-C_6H_4; R = 4-OCH_3-C_6H_4; 3,4,-$(OCH)_3$-C_6H_3; 3-OCH_3-4-OH-C_6H_3; 3-OC_6H_5-C_6H_4; 4-N,N $(CH_3)_2$-C_6H_3

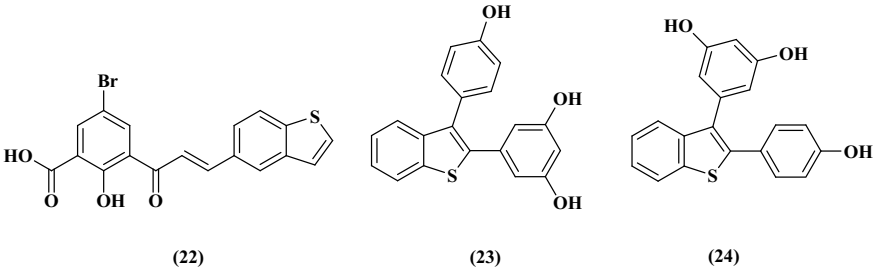
Fig. 10.6 Benzothiophene as anti-tubercular drugs

10.2.1.4 Anti-tubercular Agents

One of the fatal infectious diseases that has added to humanity's problems is tuberculosis (TB), a lung infection. Most tuberculosis cases are caused by *Mycobacterium tuberculosis* (*Mtb*), a pathogenic bacterial species of *Mycobacterium* [31]. Presently, 8.9–9.9 million new and recurring cases of tuberculosis are reported annually, and one-third of the world's population is afflicted with *Mtb* [26]. The current course of treatment involves a multi-drug regimen that must be followed for at least six months, but there is no assurance that the infection will be eradicated. Therefore, it is imperative to create novel anti-tubercular medications with quick action against mycobacteria in the intracellular environment that are less toxic and successfully kill MDR strains [32]. Using thiazolidinones (**20**) and azetidinones (**21**), which have a benzothiophene nucleus, Narute et al. conducted a quantitative structure–activity relationship (QSAR) analysis (Fig. 10.6) [33]. They concluded that the molecules bulky substitution and high nucleophilicity nature are conducive to their anti-tubercular action [33].

10.2.1.5 Anti-HIV Agents

Human immunodeficiency virus (HIV) infection causes the deadly disease known as acquired immune deficiency syndrome (AIDS). HIV infection impairs the body's defenses, making people more vulnerable to other diseases [34]. Over 30 million



(22) (23) (24)

Fig. 10.7 Benzothiophene as anti-HIV drugs

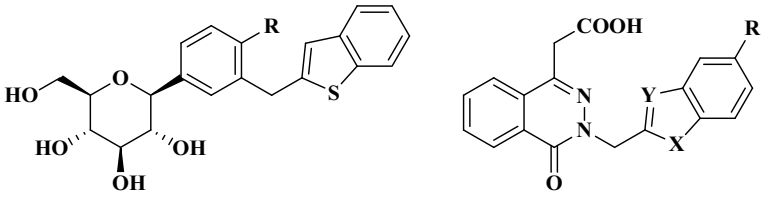
people are thought to be infected with HIV globally, and treatment of the virus continues to pose a significant challenge. Therefore, it is still crucial to find and develop newer anti-HIV drug candidates to address the issues surrounding this illness. Bioisosteric substitution of the phenyl ring with heteroaromatic and polycyclic rings is revealed by SAR study: enhanced action when thiophene or benzothiophene (**22**) was substituted for phenyl. Compounds (**23**) and (**24**) exhibit enhanced cytotoxicity potency (Fig. 10.7) [31, 35]. Combined with decitabine, a mutagenic nucleoside possessing anti-HIV-1 properties, these compounds limit HIV-1 replication.

10.2.1.6 Anti-diabetic Agents

The most prevalent chronic illness in the modern world, diabetes mellitus (DM), is characterized by high blood glucose levels brought on by either an absolute or relative inefficiency of circulating levels of insulin [36]. DM is a serious health concern. Diabetes may eventually result in retinopathy, neuropathy, and nephropathy due to microvascular damage in essential tissues. There is still a great demand for better anti-diabetes medications even though there are currently around a dozen kinds of anti-diabetes medicines on the market [37]. Ipragliflozin, ASP1941, (**25**), a benzothiophene derivative, is being researched to treat type-2 diabetes [38]. This section discusses compounds of benzothiophene, which show some anti-diabetic properties. Within the benzothiophene series, compound (**26**) exhibited good efficacy without any substitution, but compound (**27**) with fluorine substitution suppressed sorbitol accumulation in vivo (Fig. 10.8) [38, 39].

10.2.2 Conclusion

The synthesis of a wide range of multi-substituted benzothiophene, which is challenging by conventional methods, was made possible by the broad scope of benzothiophene synthesis and the adaptable C2-functionalizations. In summary, these molecules exhibit significant potential as effective active agents in medical chemistry.



(25 a, b)

a) = R = H
b) = R = F

(26-27)

X = S, Y= N, R = CF_3

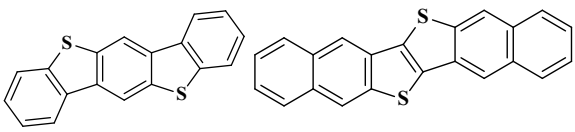
Fig. 10.8 Benzothiophene as anti-diabetic agents

10.3 Dibenzothiophene

10.3.1 Introduction

Stenhouse first synthesized dibenzothiophene in 1870 by heating diphenyl sulfide in the presence of iron nails. This compound was mistakenly identified as an isomer of diphenyl sulfide [40, 41]. Gilman et al. reported the synthesis of dibenzothiophene in 1938, employing $AlCl_3$ as a catalyst and biphenyl and sulfur as raw ingredients [42]. Dibenzothiophene is a flexible aromatic tricyclic molecule with a sulfur base. Organic and medicinal chemistry is the fundamental building block of beneficial organic compounds, including pharmaceutical medications and biologically active chemicals. Materials chemistry is a significant component of functional materials like organic semiconductors [43]. Dibenzothiophene is flexible heterocyclic sulfur-containing molecules typically essential to a wide range of significant organic substances, such as medicines, liquid crystals, photoactive chemicals, dyes, and conducting polymers (Fig. 10.9) [44–46]. Naphtho [2,3-b]-naphtho [2′,3′:4,5] thieno[2,3-d] thiophene (DNTT) and benzo [1,2-b:5,4-b′] bis [1] benzothiophene (BBBT) are two examples of sulfur-containing conjugated benzoheterocyclic compounds that show promise as materials for thin-film transistors.

Fig. 10.9 Benzo-fused thiophenes as organic electronics



BBBT

(28)

DNTT

(29)

10.3.2 Synthesis

Owing to the thiophene motif's vital role in a wide range of organic molecules across several sectors, several facile and effective synthesis techniques for dibenzothiophene have been developed recently. These techniques for creating dibenzothiophene and its derivatives include cyclizing C–S and C bonds to create a sulfur heterocycle with five members.

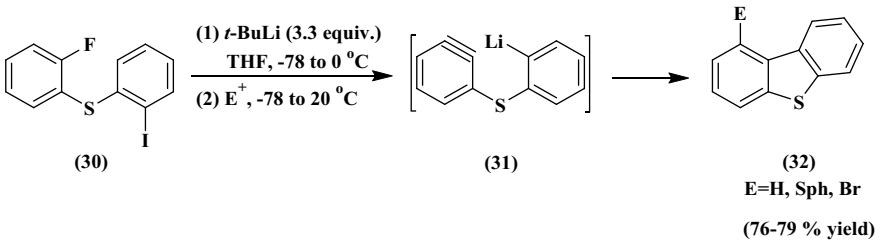
10.3.2.1 Transition Metal-Free C–S Bond Formation for Dibenzothiophene

10.3.3 C-X Cleavage for Dibenzothiophene Synthesis

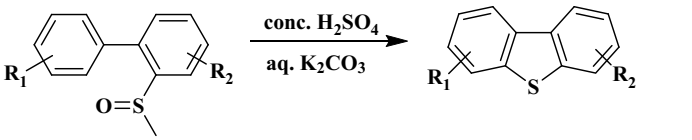
In 2006, Fanana's group discovered that C-X cleavage for dibenzothiophene synthesis produced functionalized dibenzothiophene derivatives by treating 2-fluorophenyl 2-iodophenyl thioether with 3.3 equiv. of *t*-BuLi. These derivatives then reacted with specific electrophiles (Scheme 10.2). An anionic cyclization on an aryl lithium intermediate tethered to benzyne is the process's mechanism [47].

10.3.3.1 C-H Functionalization for Dibenzothiophene

The Patel group disclosed a practical and effective process for generating unsymmetrical dibenzothiophene derivatives in 2012 (Scheme 10.3) [48]. Intramolecular cyclization of biaryl sulfoxides with sulfuric acid under low-temperature conditions yields dibenzothiophene with a very short reaction time. It is interesting to note that any position of dibenzothiophene can be reached by using this procedure. For instance, this method makes it simple to manufacture 1-substituted dibenzothiophene, which is hard to acquire by direct substitution reaction on dibenzothiophene.



Scheme 10.2 Dibenzothiophene-tethered aryllithiums via anionic cyclization



(33)

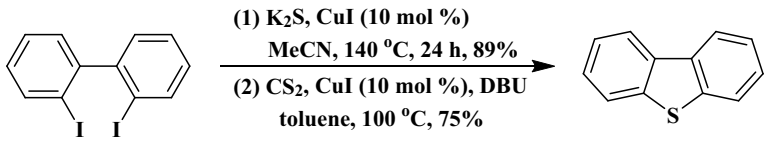
(34)

$R_1 = H; R_2 = H$ (94 %)

$R_1 = F; R_2 = H$ (92 %)

$R_1 = NO_2; R_2 = H$ (49 %)

Scheme 10.3 Biaryl methyl sulfoxides are intramolecularly cyclized for dibenzothiophene through acid-mediated processes



(35) (36)

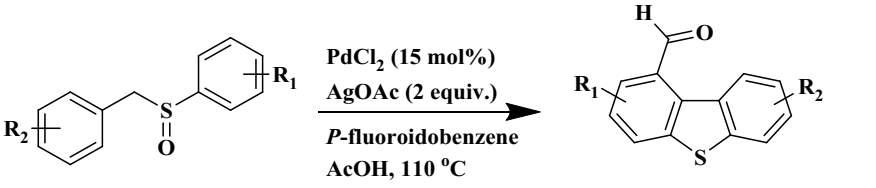
Scheme 10.4 Ullmann process with Cu catalyst for dibenzothiophene synthesis

10.3.3.2 Transition Metal-Catalyzed C–S Bond Formation for Dibenzothiophene

The Ullmann reaction of 2,2′-iodo substituted biphenyl with K_2S producing dibenzothiophene at 140 °C was reported by the Xi group in 2010. They developed a different one-pot process in 2013 for the very efficient preparation of dibenzothiophene [49]. This technique works well for building cyclic sulfur-containing molecular structures when 2,2′-iodine-substituted biphenyls are used as the substrate, and easily accessible, low-cost CS_2 is used as the sulfur source (Scheme 10.4) [49].

10.3.3.3 Transition Metal-Catalyzed C–C Bond Formation for Dibenzothiophene

Palladium-catalyzed double C–H bond activation of simple benzyl phenyl sulfoxides to produce dibenzothiophene (Scheme 10.5) [50]. Four hydrogen atoms are abstracted, and the products are created in a cascade reaction that is highly selective due to the reaction's well-regulated order. By using the palladium catalyst at a 15% molar ratio, this technique produced a range of dibenzothiophene derivatives in medium-to-good yields that were resistant to an extensive range of substrates. As a result, this approach has a significant innovative impact on organic synthesis [50].



(37)

(38)

R_1 = Me; R_2 = H (67-74 %)
R_1 = F; R_2 = H (53 %)
R_1 = Cl; R_2 = (51 %)
R_1 = H; R_2 = Cl (69 %)
R_1 = H; R_2 = Ph (46 %)

Scheme 10.5 Double C–H activation for dibenzothiophene, catalyzed by palladium and directed by sulfoxides

10.3.4 Conclusion

Numerous techniques have been established for the synthesis of dibenzothiophene and its derivatives by the production of C–S bonds, which bases, acids, or other non-metallic species can accelerate. Unfortunately, most of these techniques suffer from multi-step processes and pre-functionalization of synthesis precursors, making them neither environmentally friendly nor atom-economic. Transition metal-catalyzed coupling reactions have been a potent technique for synthesizing dibenzothiophene during the last ten years. For instance, it has been extensively documented that dibenzothiophene with a wide variety of functional groups at various positions can be synthesized by intramolecular C–H/S–H and C–H/C–S coupling processes, which are catalyzed by palladium and other transition metals.

10.4 Thienothiophene

10.4.1 Introduction

Conversely, thienothiophenes (TTs), which are composed of two annulated thiophene rings, ultimately form the planar system, and their incorporation into a molecular structure has the potential to significantly enhance or modify the essential characteristics of organic materials that are π-conjugated. Four main TT isomers differ from one another in the mutual orientation of the two cycles (Fig. 10.10) [51]. In comparison, thieno[3,4-b] thiophene (**41**) and the extremely unstable thieno[3,4-c] thiophene (**42**) are the least stable derivatives, whereas thieno[3,2-b] thiophene (**39**) and thieno[2,3-b] thiophene (**40**) are the most durable. The primary barrier to the

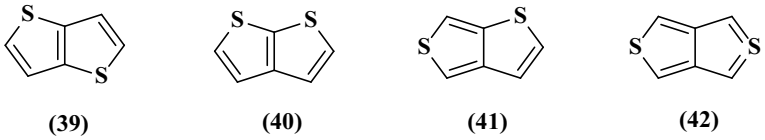
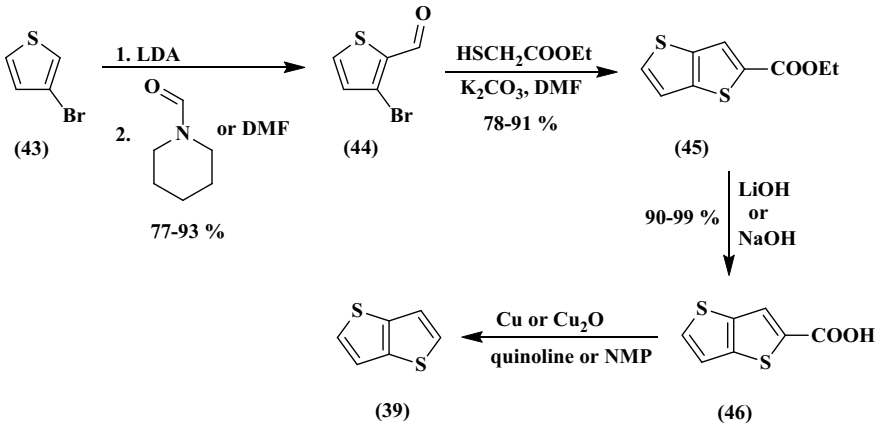


Fig. 10.10 Structure of four possible TT isomers (**39–42**)

simple manufacture of thienothiophene is the instability of the unsubstituted isomers (**41**) and (**42**). Furthermore, the obtained total yield, the number of reaction steps, and the availability of the employed starting materials are the primary determinants of a successful synthetic approach toward TTs (**39**) and (**40**). The procedure should follow stable intermediates and be simple to implement [52, 53].

10.4.2 Synthesis

A four-step reaction is used in the first synthetic technique, which is shown in Scheme 10.6 [54–58]. 3-bromothiophene (**43**) was selectively lithiated at position 2 using LDA. The generated lithium species was trapped by the reaction with N-formylpiperidine or N, N-dimethylformamide (DMF). This resulted in aldehyde (**44**) [54–56]. It then underwent cyclization with potassium carbonate acting as a base and ethyl thioglycolate. The C=C and C–S bonds in (45) were formed in this stage. Ester (**45**) was hydrolyzed to carboxylic acid (**46**) using lithium or sodium hydroxide. The final decarboxylation process used Cu/quinoline or CuO/N-methyl-2-pyrrolidone (NMP) [54]. This particular reaction sequence has a yield of approximately 50% overall.

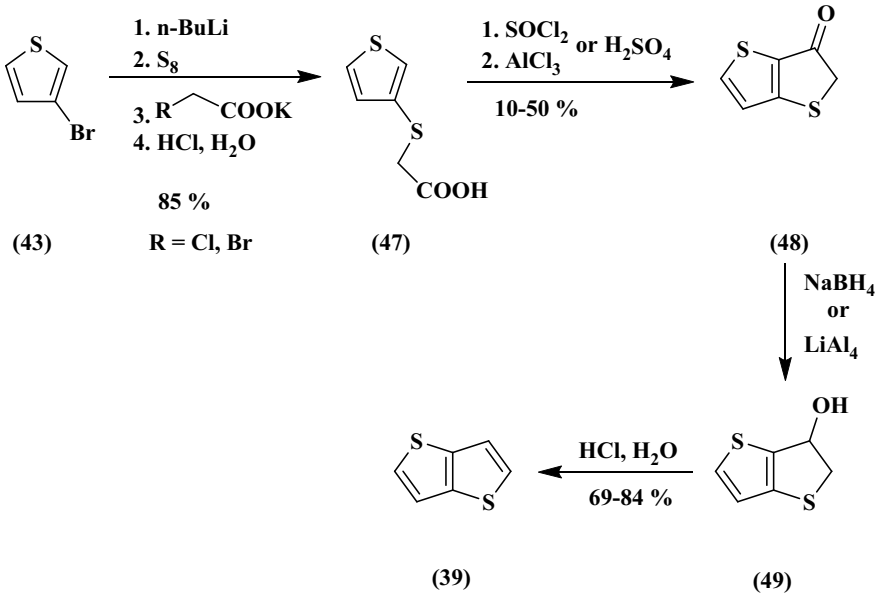


Scheme 10.6 Four-step method

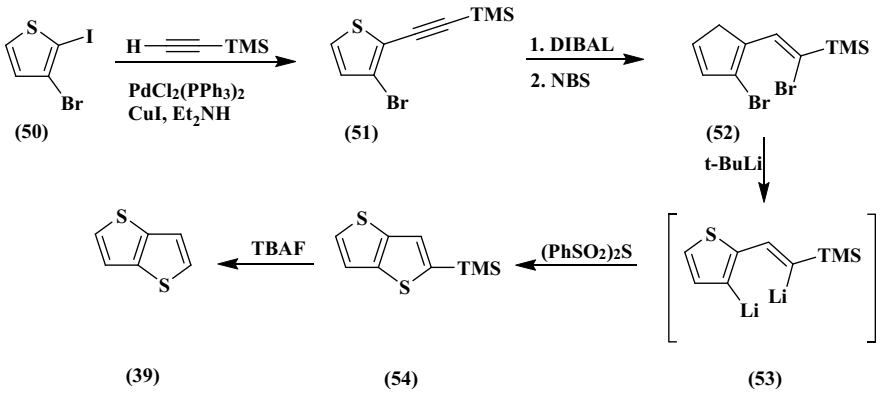
Three primary reaction steps are involved in this approach, which likewise begins with 3-bromothiophene (**43**) (Scheme 10.7) [59, 60]. The lithiation of (**43**) and the subsequent reaction with elementary sulfur produced an in vivo thiolate intermediate. This intermediate further substituted a halogen atom in either potassium chloroacetate or bromoacetate to yield carboxylic acid (**47**). There are two methods for carrying out the cyclization that follows. The first is an acid-catalyzed (H_2SO_4) cyclization; the corresponding acyl chloride was initially synthesized by Leriche et al. and then subjected to the intramolecular Friedel–Crafts acylation [60]. $NaBH_4$ or $LiAlH_4$ converted the ketone (**48**) produced to the intermediate alcohol (**49**) [59, 60]. By the following acid workup, alcohol (**49**) has (**39**). This series of reactions yields (**39**) out of the total 36% yield.

Trimethylsilyl (TMS) acetylene and 3-bromo-2-iodothiophene (**50**) are selectively cross-coupled in the final six synthesis routes leading to TT (**39**) (Scheme 10.8) [61]. Di(iso-butyl) aluminum hydride (DIBAL) reduction and NBS bromination were applied to the TMS-terminated alkyne (**51**). Following its lithiation to (**53**), the resultant dibromo derivative (**52**) underwent a reaction with bis(phenylsulfonyl)sulfide. (**39**) resulted from the last TMS-group elimination using tetrabutylammonium fluoride (TBAF). The literature does not provide the yields of the specific chemical steps.

This procedure, which works with acetal (Scheme 10.9), uses acetal (**56**). In sodium ethanolate or potassium carbonate, the bromine atom in 1,1-dimethoxyethylbromide was substituted by the beginning 2-sulphanylthiophene (**55**)



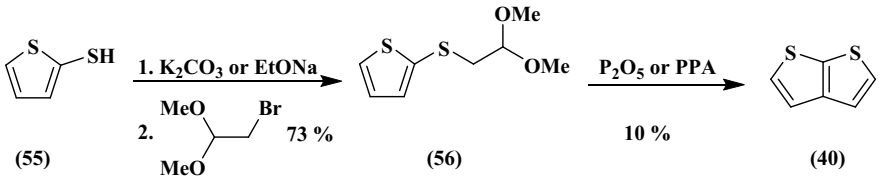
Scheme 10.7 Synthesis of (**39**)



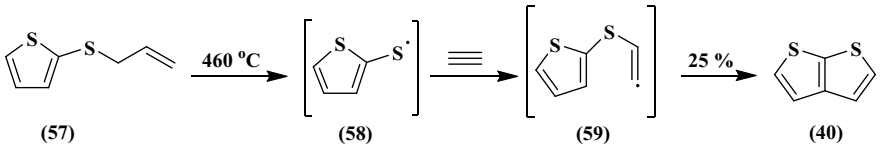
Scheme 10.8 Sonogashira cross-coupling in the production of (**39**)

as an S-nucleophile. Using polyphosphoric acid (PPA) or phosphorous oxide, the generated acetal (**56**) was cyclized to (**40**) [62, 63]. This chemical sequence has a 7% total yield.

Scheme 10.10 depicts the one-step gas phase production beginning from allyl(thiophene-2-yl) sulfide (**57**) [64]. The radical (**58**) was produced by the thermal cleavage of the sulfide (**57**), and it then interacted with acetylene. The last stage involved the formation of the (thiophene-2-yl) vinyl sulfide radical (**59**), which at 460 °C cyclized to produce thieno[2,3-b] thiophene (**40**) as a primary product with a 25% yield.



Scheme 10.9 Cyclization of acetal (**56**)



Scheme 10.10 Allyl(thiophene-2-yl) sulfide's gas phase reaction to TT (**40**)

10.4.3 Biological Activity

Prominent biological activities of thieno[2,3-b] thiophenes include anti-microbial, analgesic, anti-inflammatory, and anti-proliferative properties; they also oppose α_1-adrenoceptors and prevent cartilage degradation in articular diseases [65–71]. Nonetheless, because of the numerous uses for pyrazoles in the agrochemical and pharmaceutical industries and their analgesic, anti-pyretic, herbicidal, and anti-inflammatory qualities, the preparation of pyrazoles continues to be of significant interest [72, 73]. Because of their strong biological activity, pyridazine compounds are frequently used as anti-bacterial, anti-tuberculosis, anti-cancer, and anti-hypertensive drugs [74–81].

10.4.4 Conclusion

With a variety of therapeutic potentials, including anti-convulsant, anti-malarial, anti-bacterial, anti-mycobacterial, anti-depressant, anti-viral, anti-hypertensive, anti-cancer, anti-inflammatory, and anti-oxidant properties, thiophene and its derivatives constitute a significant class of chemicals in the medical profession.

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