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RECENT ADVANCES IN THE SYNTHESIS AND APPLICATIONS OF BENZO[*b*]THIOPHENES

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Recent developments in the application and synthesis of benzo[*b*]thiophenes are reviewed, with an emphasis on various cyclization methodologies leading to the heterocyclic core structure.

Keywords: Applications; benzothiophenes; benzo[*b*]thiophenes; cyclization; synthesis; synthetic methodology

CONTENTS

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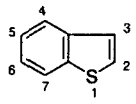
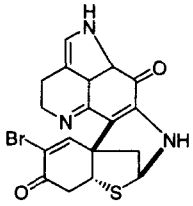
1. INTRODUCTION

Among bicyclic heteroaromatic compounds, benzo[*b*]thiophene **1** and its substituted derivatives occupy a unique place in organic chemistry. This class of compounds has been known for a long time since their isolation from coal tar distillates. Several synthetic methodologies have been developed in the intervening years. On the other hand, the practical applications of benzothiophenes, especially as pharmaceutical agents, pale when compared with their nitrogen cousins, i.e. indole alkaloids. However, growing interests in this area, especially those of medicinal applications, have rekindled research activities in this venerable field. This review will focus on the most recent developments in the synthesis and medicinal applications of benzo[*b*]thiophenes. Selected reactions unique to benzothiophene, that offer previously unmet synthetic needs, will also be discussed. For a systematic coverage of this heterocycle, including its chemical reactivities and physical properties, reviews that appeared in the last decade[1–4] and earlier are available.[5–11]



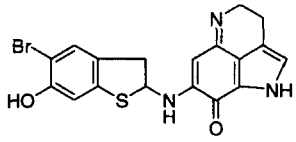
1

benzo[*b*]thiophene



2

(+)-discorhabdine A



3

(-)-makaluvamine F

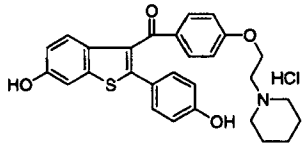
2. APPLICATIONS

Although alkylated benzo[*b*]thiophenes account for a large portion of the sulfur content in coal tar distillates and crude petroleum,[12–18] their origin has not been clearly elucidated and their presence in these products has largely been regarded as a nuisance to product quality. The isolation of pure benzothiophene derivatives from these sources posed a considerable technical challenge as many close analogs with similar physical characteristics often coexist. While there was some earlier interest of thioindigo as a dye, the commercial availability of benzothiophene and its derivatives has so far been very limited. Whereas indole plays a key role in protein chemistry as part of the essential amino acid L-tryptophan, and numerous natural products of important biological activities containing that heterocycle have been identified, synthesized, and commercialized, there is a relative scarcity of benzo[*b*]thiophene-containing compounds isolated from living organisms. However, the recent discovery of a novel class of antitumor and antimicrobial compounds from the Latrunculia sponge species of New Zealand is likely to elevate the interest level of benzothiophene in the natural products arena, as represented by a hexahydrobenzothiophene, (+)-discorhabdine A (prianosin A, **2**).[19,20] The benzothiophene moiety is better manifested in another member of the marine natural product family as the dihydro derivative (−)-makaluvamine F **3**.[21–24]

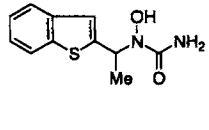
Undoubtedly, the major driving force behind advances in the chemistry of benzothiophene has to be their biological applications. It is within this domain of highly valued added products, either as pharmaceuticals or agrochemicals, that costly multi-step synthesis can be justified. Within the last two decades, benzothiophene has increasingly been recognized as a pharmacophore that offers advantages including

superior chemical and pharmacological stability, low intrinsic toxicity,[5,6,25,26] and, most importantly, a rich chemistry that enables medicinal chemists to explore molecular diversity in a rapid fashion using tools that have been developed concurrently and are recently gaining popularity, such as transition metal catalyzed carbon–carbon, and carbon-hetero bond formation and combinatorial chemistry.

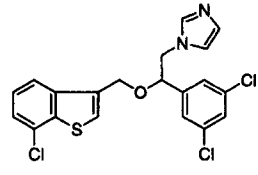
A large body of work related to benzothiophenes emerged with the development and introduction of three new chemical entities (NCE) containing this heterocycle as pharmaceuticals in recent years. Raloxifene (**4**, Evista®)[27,28] is a selective estrogen receptor modulator (SERM) that mimics the beneficial effects of estrogen in the skeletal and the cardiovascular systems, while lacking certain unpleasant side effects linked with traditional estrogen replacement therapies in reproductive tissues. This drug has been approved in the US and Europe for the prevention of osteoporosis in postmenopausal women. Zileutin® (**5**, Zyflo),[29–32] a 5-lipooxygenase inhibitor, has been approved and is on the market for anti-inflammatory indications. Sertaconale (**6**, Derfofix®, Zalain®)[33–36] has recently been introduced to the market as a broad spectrum antifungal reagent. The strategy of isosteric replacement of the indole nucleus by benzothiophene in medicinal chemistry has been widely used in other areas as well, for example, in SAR studies of GABA modulators, ergot alkaloids,[37,38] and opioid analgesics.[39]



4
raloxifene

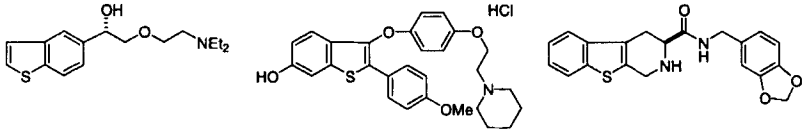


5
zileutin



6
sertaconazole

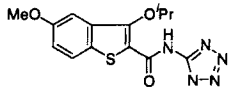
Several other molecular entities containing benzothiophene are at various stages of development. They include T588 (**7**),[40–42] a cognition enhancing agent with potential application for treating Alzheimer's dementia; LY353381 (**8**),[43] another SERM from Lilly; AP521 (**9**),[44] with potent $5Ht_{1A}$ receptor binding ability; CI959 (**10**),[45–47] an anti-inflammatory agent; and B428 (**11**),[48–52] a urokinase inhibitor. Another structurally interesting compound is PD 144795 (**12**),[53–57] an endothelial cell activation inhibitor as a benzothiophene oxide.



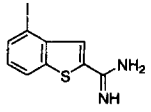
7
T588

8
LY353381

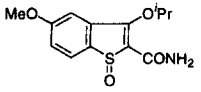
9
AP521



10
CI959

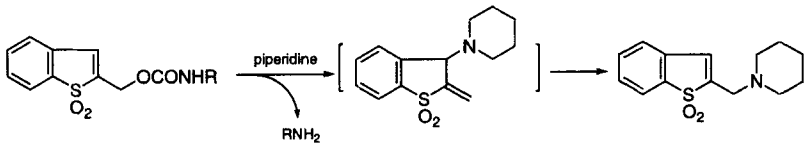


11
B428



12
PD144795

As a novel example of the applications of benzothiophene in synthesis, compound **13** (Bsmoc) has recently been introduced as a base- and nucleophile-sensitive amino protecting group amenable for peptide synthesis.[58] Treatment with a secondary amine such as piperidine initiates a Michael addition which is followed by elimination to release the free amino group, with the net effect of having the base capture the remaining protecting group in the form of sulfone **15**.



13 **14** **15**

SCHEME 1

3. RING MODIFICATIONS

A few possible pathways of introducing molecular diversity onto the benzothiophene core structure are illustrated in Figure 1. Naturally, functional groups on the benzene ring can be modified, eliminated, and introduced according to their individual activity pattern, as long as the vulnerability of the thiophene half of the molecule towards oxidation, electrophilic substitution, and proton abstraction is taken into consideration.

2-Lithiobenzothiophene **19**[59,60] can be obtained readily from treatment with *n*-BuLi and has proved to be invaluable for functionalization

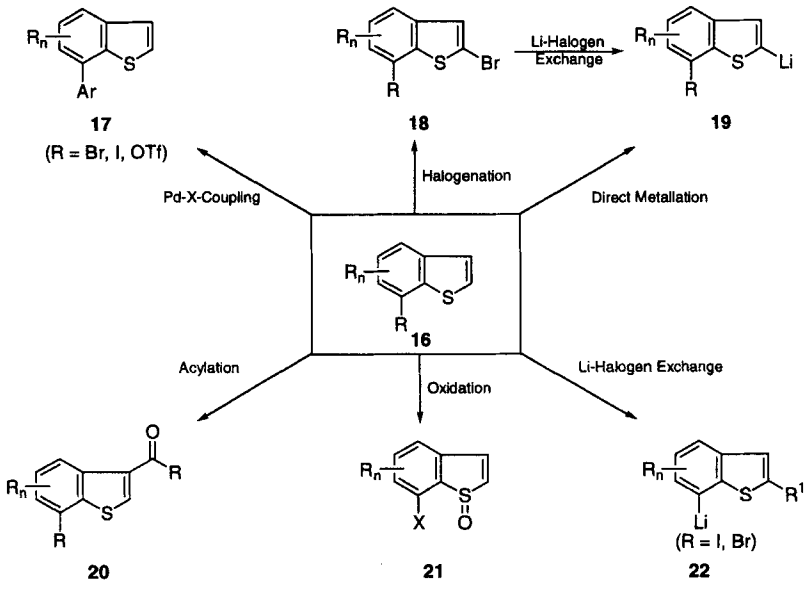
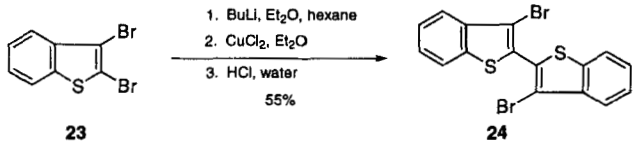


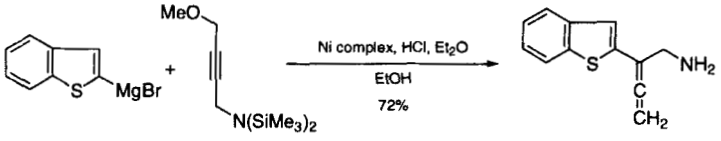
FIGURE 1

at that position by further reaction with appropriate electrophiles.[61] The 2-lithio species can also be transmetalated into other benzothiophenyl metals, such as Si,[62] Mg,[63] and Zn, which with attenuated activity can then be utilized in transition metal-catalyzed cross-coupling reactions. Lithio derivatives at 3- and other positions,[35,64,65] on the other hand, are most readily obtained by the much popularized metal-halogen (Br, I) exchange reaction from 3-halobenzothiophenes or other aryl halides at low temperature. The liability of 2-H towards deprotonation has to be considered in these cases. Interestingly, selective exchange of the 2-position bromine can be achieved on 2,3-dibromo derivatives (Eq. (1)).[66] Such an approach can be used to prepare 3-bromobenzothiophenes by quenching the resultant 2-lithio-3-bromo derivative with H_2O.[67] Benzothiophenyl Grignard reagents can be easily prepared from the corresponding bromides (Eq. (2)).[63] Unlike reactions involving organolithiums, 2-unsubstituted benzothiophenes can tolerate Grignard conditions without one having to protect the organolithium labile 2-H with removable groups such as $SiMe_3$. The 2-stannylbenzothiophene[68] **29** can also be obtained from the sulfone **28**

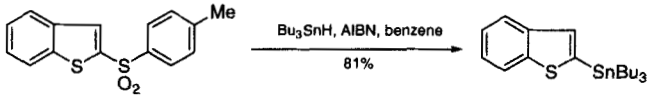
via an intermolecular radical substitution reaction (Eq. (3)) and served as a useful Stille coupling partner (Eq. (4)).[69]



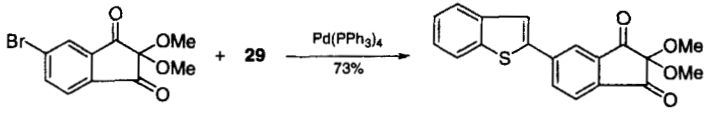
23 24 (1)



25 26 27 (2)

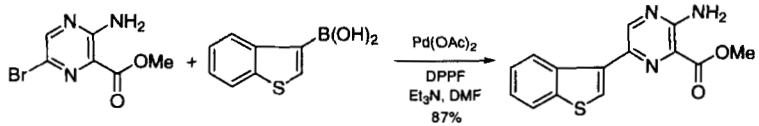


28 29 (3)

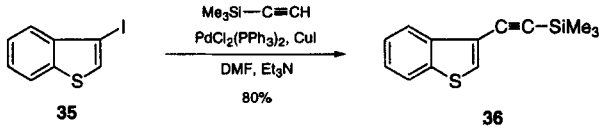


30 31 (4)

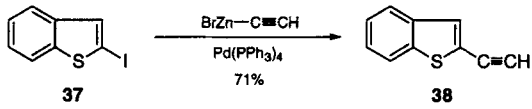
A Heck reaction has been applied to benzothiophen-4-yl triflate in the synthesis of a thioergoline.[38] Other recent examples of palladium catalyzed reactions involving benzothiophenes include Suzuki coupling of 3-benzothiophenylboronic acid (Eq. (5)),[70] Castro–Stevens–Sunogashira coupling of 3-iodobenzothiophene (Eq. (6)),[71] Negishi coupling of 2-iodobenzothiophene (Eq. (7)),[72] and, most interestingly, of benzothiophene itself with an aryl halide in the presence of CuI and Cs_2CO_3 (Eq. (8)).



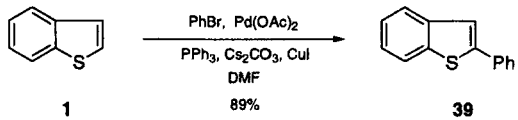
32 33 34 (5)



35 36 (6)

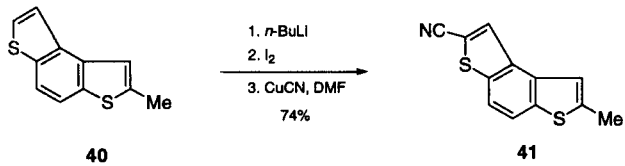


37 38 (7)

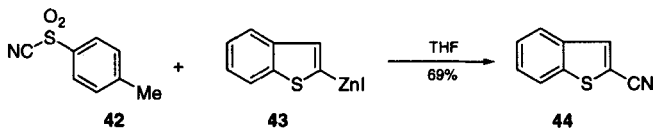


1 39 (8)

2-Cyano derivatives can be obtained either by treatment of a cyano nucleophile with a 2-iodo derivative (Eq. (9))[74] or of an electrophilic cyanide with the corresponding organozinc derivative **43** (Eq. (10)).[75]

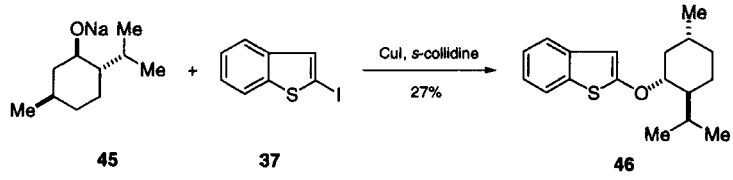


40 41 (9)



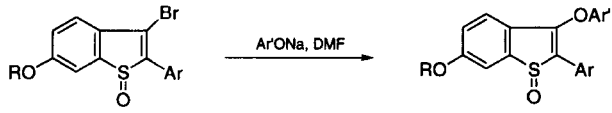
42 43 44 (10)

The 2-alkoxy derivatives can be obtained in low yield by an Ullmann reaction as shown in (Eq. (11)).[76] However, when the sulfide sulfur in the benzothiophene is oxidized to an electron withdrawing sulfoxide sulfur, substitution at the 3-position is a very facile event with phenolic nucleophiles, possibly via an addition–elimination mechanism (Eq. (12)).[43] The sulfoxides can be easily reduced back to benzothiophenes. 3-Aminobenzothiophene can be prepared by condensing the 3-oxo derivative with a secondary amine using $TiCl_4$ as dehydrating agent (Eq. (13)).[77]



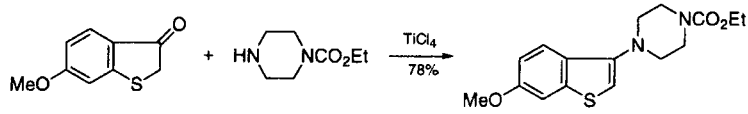
45 37 46

(11)



47 48

(12)



49 50 51

(13)

Evidently, direct metalation,[78–81] lithium-halogen exchange,[82] and the recently developed transition metal catalyzed cross-coupling processes[83–85] have played a crucial role in the advances of aromatic and heteroaromatic chemistry. The development of these synthetic methodologies, along with the increasing availability of various benzothiophene containing compounds from commercial sources, will undoubtedly fuel the growth of the application of benzothiophenes. It is very possible that in the next few decades, benzothiophene and, to some extent, benzofuran will join the ranks of privileged structure units such as indoles, β-lactams, and benzodiazepins in small molecule therapeutics.

4. BENZOTHIOPHENE RING SYNTHESIS

The reactivities of benzo[*b*]thiophenes resemble that of typical heteroaromatic compounds, depending on the substitution pattern and the functional groups present. Hence, we will focus mainly on the latest developments of ring synthesis of the bicyclic core of benzothiophene by

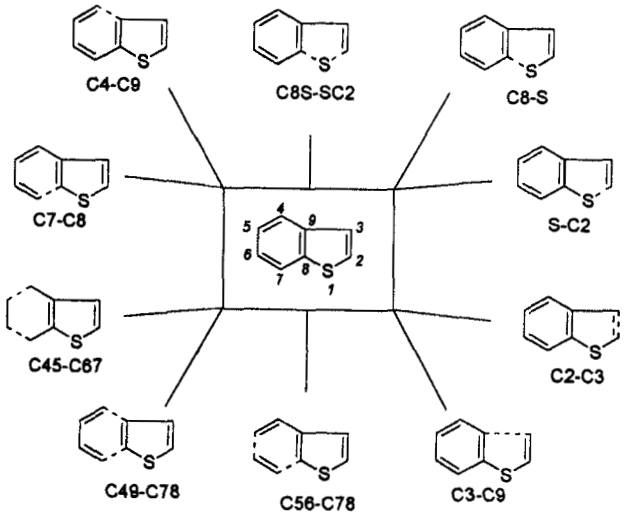
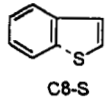


FIGURE 2

cyclization reactions. These reactions in turn can be divided into several categories according to which particular bonds are being formed upon cyclization (Figure 2): C8–S bond formation, S–C2 bond formation, C2–C3 bond formation, C3–C9 bond formation, C4–C9 bond formation, and C7–C8 bond formation. The simultaneous formation of two bonds, which is normally achieved by Diels–Alder reaction, is classified as C45–C67, C49–C67, or C49–C78 type cyclization. Syntheses via a formal insertion of the sulfur atom are often stepwise processes. However, for mere convenience, they are treated as a separate entity as type C8S–SC.

4.1. C8–S Bond Formation

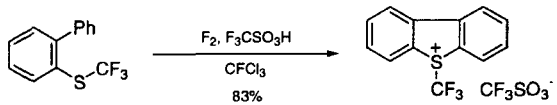


There are two possible modes of cyclization via the formation of an aryl-sulfur bond to construct the thiophene ring. One involves an

electrophilic sulfur species attacking the phenyl ring. The other requires an activated leaving group on the recipient carbon of the phenyl ring being displaced by a sulfur nucleophile. The latter mode of reaction has not received much attention, primarily for the reason that such aromatic nucleophilic substitution (S_{NAr}) would require a highly activated aryl halide, a thioenolate anion, photochemical activation, and/or transition metal catalysis. The preparation of these cyclization precursors may be time and effort consuming. Cyclization through the intermediacy of electrophilic sulfur, on the other hand, does not require a predisposed leaving group other than a proton at the C8 position. The transient sulfur cation, however, is unstable and could not be easily isolated, *vide infra*. In most cases the reaction is limited to forming benzothiophenes with an electron withdrawing group such as cyano or carboxylate at the 2-position and, more critically, the lack of such groups on the benzene ring.

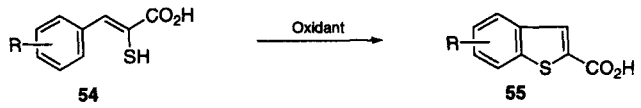
4.1.1. Electrophilic sulfur mediated cyclization

Despite the aforementioned limitations, electrophilic sulfur mediated cyclization has been widely used for the preparation of benzothiophenes. The intermediary sulfenium cations were usually not isolated. Sulfonium ions, on the other hand, can be induced to cyclize and isolated as stable salts (Eq. (14)).[86]



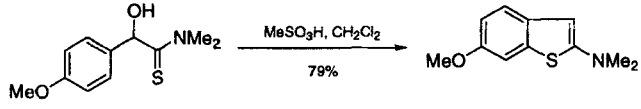
52 53 (14)

Owing to its simplicity, the procedure developed by Campaigne and Cline[87] continues to be the method of choice for synthesizing electron rich benzothiophenes (Eq. (15)) The α-mercaptocinnamic acid can be easily prepared by condensing the aromatic aldehyde with rhodanine, followed by hydrolysis. A major drawback to this method is the required absence of electron withdrawing groups on the phenyl ring, while an electron withdrawing group is needed to stabilize the enethiol moiety against decomposition. Decarboxylation at high temperature affords the parent compound.



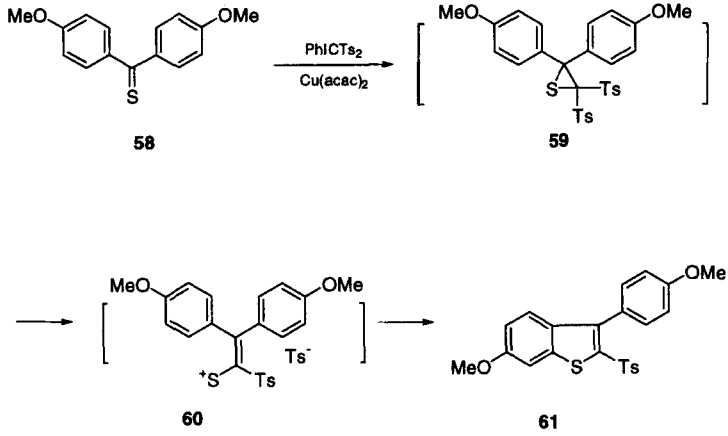
54 55 (15)

The electrophilic sulfur cation can also be generated via an internal electron shifting from sulfur to a carbocation and proceeds to afford benzothiophene in high yield (Eq. (16)).[88–90] The resulting 2-amino-benzothiophenes, with their electron-rich character, proved to be valuable intermediates for further synthetic manipulations and structure activity relationship studies.



56 57 (16)

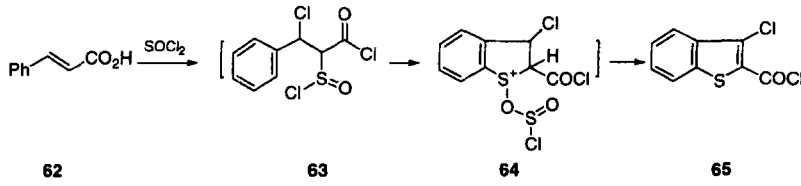
A novel cyclization pathway involving a sulfenium ion generated by Cu-catalyzed carbene insertion into a thiocarbonyl, followed by rearrangement, has been reported (Scheme 2).[91,92] Though the scope of the reaction appears to be limited to stable thioketones with ample steric bulk, this nonetheless serves as a novel venue to the unstable sulfenium cation intermediate.



58 59 60 61

SCHEME 2

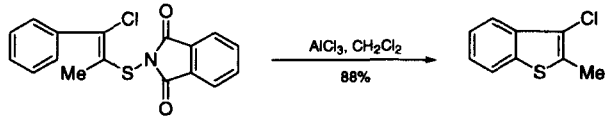
Several recent examples of using thionyl chloride mediated cyclization of styrene derivatives have been reported.[93–97] This reaction invariably afforded 3-chlorobenzothiophenes and works best for cinnamic acid derivatives. The reaction is likely to proceed through the intermediacy of the sulfinyl chloride **63** (Scheme 3).



62 **63** **64** **65**

SCHEME 3

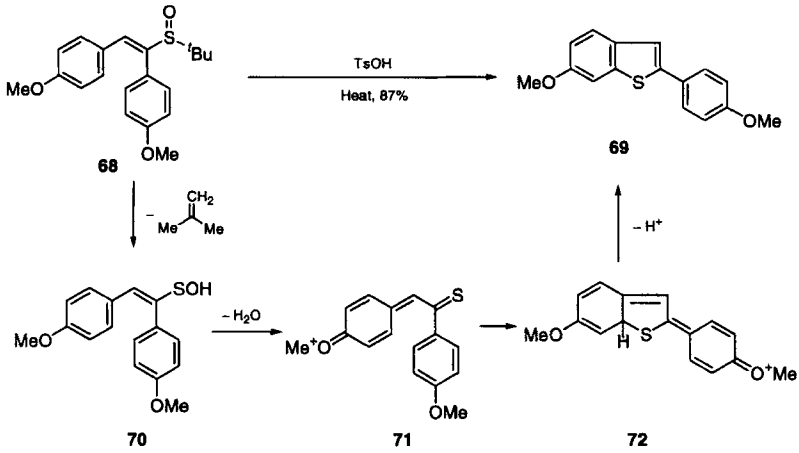
Addition of phthalimidosulfenyl chloride to diaryl- or alkyl(aryl)-acetylenes gave rise to chlorovinylsulfenamides, which cyclized upon treating with aluminum trichloride or other Lewis acids to give benzo[*b*]-thiophenes through an intramolecular electrophilic substitution (Eq. (17)).[98]



66 **67** (17)

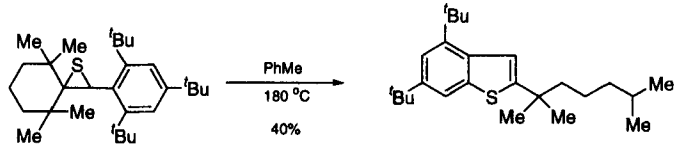
Generally, it holds true that benzothiophenes with an electron withdrawing group at the 2-position are formed in higher yield when sulfur cations are involved. One possible explanation is that the destabilizing effect of the adjacent electron withdrawing group confers higher stability to the thioenol structure and higher reactivity to the styrenyl sulfenium cation, hence less of a chance for it to undergo deleterious reactions, such as dimerization and other redox events.

In the context of raloxifene (**4**) synthesis, we have designed a new method for the construction of benzothiophene from a styrenyl sulfoxide. Specifically, when the sulfoxide **68** was heated in the presence of a Brønsted acid, fragmentation of the *tert*-butyl sulfoxide led to the sulfenic acid **70**, which then transformed into a sulfenium ion/thioketone in the acidic medium and cyclized onto the adjacent phenyl ring.[99,100]



SCHEME 4

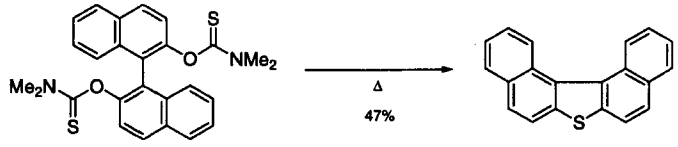
The reaction shown in (Eq. (18)) represents a unique rearrangement where a benzothiophene is produced from a sterically congested thiirane.[101] The thiiranes were synthesized by insertion of a sterically hindered diazo compound into the C=S double bond of (2,4,6-tri-*tert*-butyl)thiobenzaldehyde.



(18)

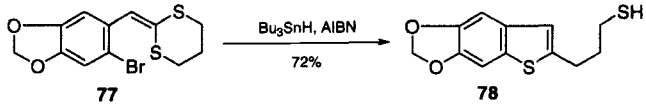
4.1.2. Nucleophilic and radical sulfur mediated cyclization

The Newman–Kwart reaction is a convenient way of converting an aryl-oxygen bond into an aryl-sulfur bond. As a rare example of nucleophilic sulfide cyclization, such a transformation has been taken advantage of in the synthesis of the symmetrical binaphthothiophene **76**.[102]



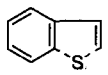
(19)

The reductive radical cyclization of an alkylidene dithiane attached to an aryl bromide (**77**) has been found to afford a mixture of benzothiophenes (Eq. (20)).[103] Direct addition of a sulfur radical to a phenyl ring to form benzothiophene is an unfavorable event thermodynamically and no example has been found.



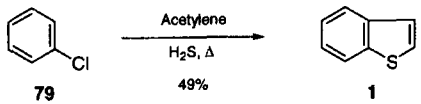
77 **78** (20)

4.2. Sulfur Insertion

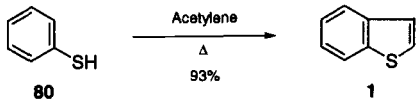


C8S-SC2

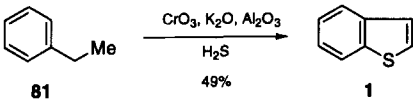
Direct synthesis of benzothiophene from chlorobenzene, H_2S and acetylene with yields reaching 70% can be carried out at 650–700 °C (Eq. (21)).[104,105] Thiophenol was also found to give benzothiophene upon treatment with acetylene at 400–700 °C (Eq. (22)). Alternatively, ethylbenzene has been converted into benzothiophene with H_2S over a mixed metal oxides catalyst (Eq. (23)).[107] These procedures along with the traditional synthesis from styrene were all carried out at high temperature under heterogeneous catalysis.



79 **1** (21)



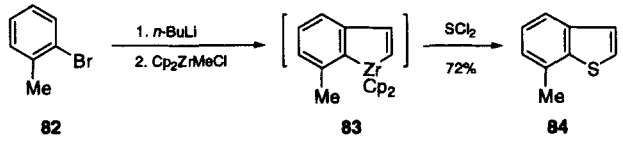
80 **1** (22)



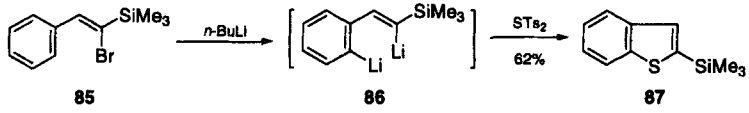
81 **1** (23)

All of these reactions require reasonable electron density on the phenyl ring in order for the reaction to proceed and these harsh

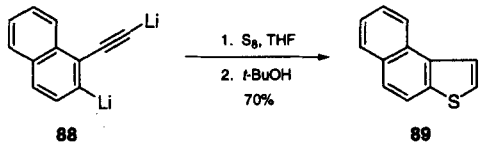
conditions preclude the presence of any heat sensitive functional groups. Special gas phase reactors are often required and, as a consequence, they have not been shown to be widely applicable in common laboratory settings. However, these restrictions do not apply to cases of displacement reactions of SCl_2 with *in situ* generated zirconacycles (Scheme 5).[108] In a similar fashion, the dilithio derivative **86** can be converted to benzothiophene in moderate yield.[109,110] Such an ortho directing effect is also observed with alkynyllithiums (Eq. (24)).[111] Thus, the treatment of (1-naphthyl)acetylene with superbase (*n*-BuLi/*t*-BuOK), followed by addition of sulfur, afforded naphthothiophene **89** in 70% yield. An obvious advantage of these methods is that the highly active bismetallated species can be generated from a simple aryl or alkenyl halide.



SCHEME 5

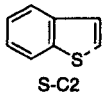


SCHEME 6



(24)

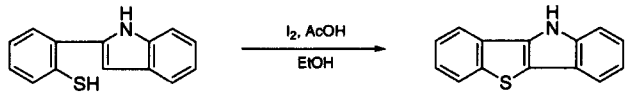
4.3. S–C2 Bond Formation



An obvious advantage of the S–C2 bond forming route to benzothiophene is that it would lead to only one regioisomer, as the outcome is predetermined by the substitution pattern of the 2-substituted thiophenol or derivative. Most of the reactions involve either condensation of a mercapto group with a carbonyl group or addition to an activated double or triple bond. A major drawback of this cyclization mode is the requirement for the availability of a thiophenol derivative with defined substitution pattern, whose synthesis often requires multi-step chemical maneuvers.

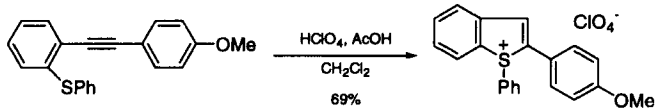
4.3.1. Electrophilic sulfur mediated S–C2 cyclization

In many cases the reaction mechanism of an electrophilic S–C2 cyclization resembles that of C8–S type reactions involving sulfonium or sulfenium ions, except that the sulfur cation in this scenario would attack an alkene instead of a phenyl group. However, these sulfur electrophiles are much more stable and precursors to them are a lot easier to procure than those discussed in Section 4.1, as they are no more than thiophenols with their ortho position substituted with an alkene, alkyne or an electron rich heterocycle. However, this has not been widely recognized and utilized. Consequently, few examples are found in the literature. Oxidation of the thiophenol **90** with iodine afforded the indolobenzothiophene **91**.[112] Similarly, the diaryl sulfide **92** cyclizes to give the sulfonium salt through the vinyl cation created by protonation of an acetylene unit with $HClO_4$.[113] Alternatively, electrons can also be removed from the system by using Br_2 as an oxidant (Eq. (27)).[114,115]



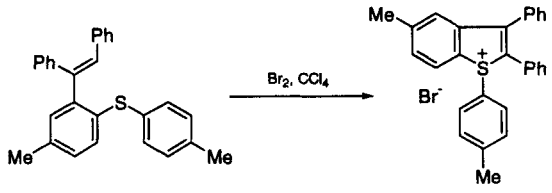
(25)

90 **91**



(26)

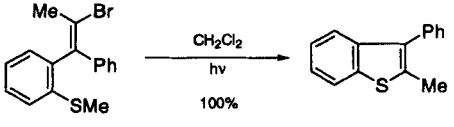
92 **93**



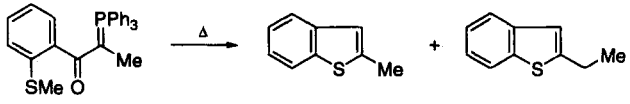
94 **95** (27)

4.3.2. Nucleophilic sulfur mediated S–C2 cyclization

Under photochemical conditions, the aryl alkyl sulfide **96** gave a benzothiophene in quantitative yield by displacement of a vinyl halide (Eq. (28)). The thermal reaction of compound **98** is thought to go through an arylacetylene upon pyrolysis.[117]

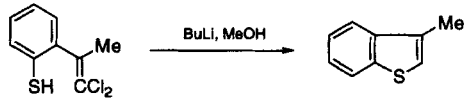


96 **97** (28)



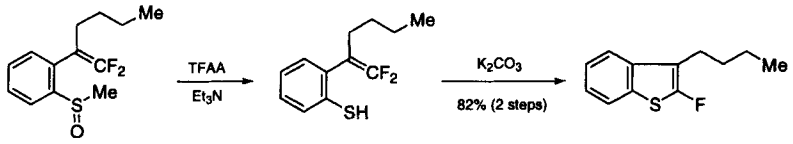
98 **99**: 14% **100**: 17% (29)

Vinylogous substitutions can be carried out on thiophenol derivatives, such as the case shown in Eq. (30).[118] Similarly, the 2-fluoro derivative **105** can be obtained from the sulfoxide **103** after deprotection and *in situ* cyclization.[118,119] It is noteworthy that these sulfur substitutions of alkenyl halides take place as 5-endo-trigonal processes and without transition metal catalysis.



101 **102** (30)

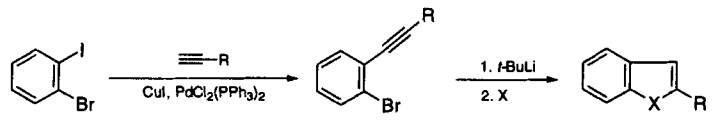
Palladium catalyzed cross coupling reactions between aryl halides and alkynes have broadened the horizon of heterocycle synthesis



103 104 105

SCHEME 7

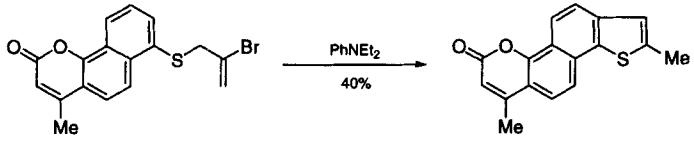
enormously. For example, *o*-bromoiodobenzene can be converted into an *o*-alkynylbromobenzene, which upon lithium-halogen exchange reacts with group VIB elements to afford the corresponding heterocycles in good yields (Scheme 8).[120]



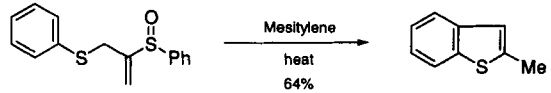
106 107 108

SCHEME 8

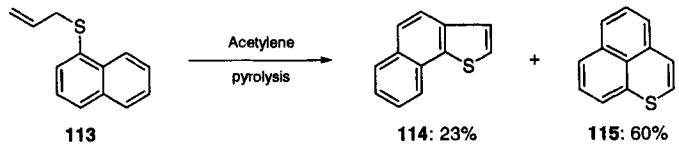
The 2-bromopropen-1-yl aryl sulfide **109** was found to give the naphthothiophene **110** upon being treated with a base. This reaction is likely to involve a thio-Claisen rearrangement followed by a mercapto addition to the resultant aryl allene.[121] A similar allene intermediate could also originate from a vinyl sulfoxide by loss of a sulfinic acid (Eq. (32)).[122] A thio-Claisen rearrangement of an allyl aryl sulfide, on the other hand, requires a much higher temperature (Eq. (33)).[123]



109 110 (31)

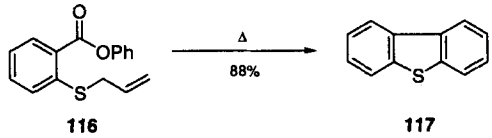


111 112 (32)



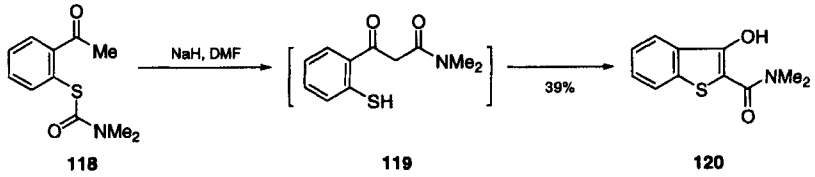
(33)

An efficient synthesis of dibenzothiophenes via flash vacuum pyrolysis of aryl salicylates **116** has been reported, which involves a novel rearrangement-CO_2 extrusion–cyclization sequence of *o*-substituted thiophenoxyl radicals.[124]



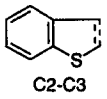
(34)

The reaction depicted in Scheme 9 is an interesting event where the deprotonated methyl ketone received the carbamoyl group and unmasked the thiophenol at the same time, which then underwent an oxidative cyclization to give a benzothiophene along with six-membered thiolactones.[125]



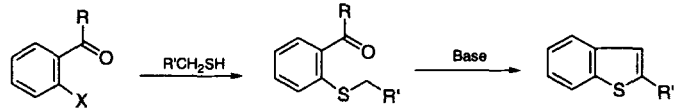
SCHEME 9

4.4. C2–C3 Bond Formation



The opportunities provided by formation of C2–C3 bond leading to benzothiophene are abundant. The reason may be two-fold. First, the methylene group adjacent to the sulfur in an aryl alkyl sulfide is

susceptible to deprotonation by a base to give a nucleophilic carbon, which can intercept an electrophile, such as a carbonyl group in the 3-position, in a very favorable intramolecular fashion. Secondly, a system such as compound **122** can be easily accessed by S_{NAr} reaction from compound **121** (Scheme 10). Thus the key requirement to this cyclization type is that an ortho disubstituted aryl sulfide be available to serve as the precursor for the condensation reaction.

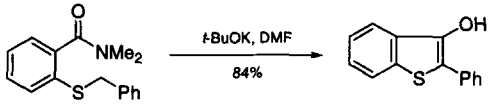


121 **122** **123**

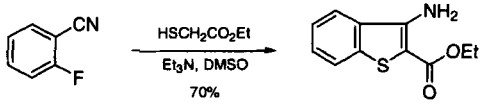
X = Cl, Br, I, F, SMe, OTf, NO_2, N_2^+

SCHEME 10

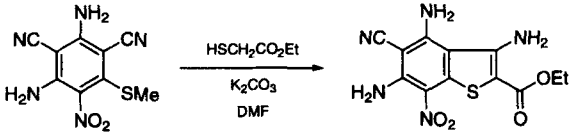
Electrophiles (RCO–) for the sulfur methyl anion include an amide to give a 3-hydroxybenzothiophene (Eq. (35)),[126] a nitrile to give a 3-aminobenzothiophene (Eqs. (36) and (37)),[127,128] a carboxylic acid to give a 3-chlorobenzothiophene (Eq. (38)),[129] and most commonly, an aldehyde to provide 3-unsubstituted derivatives (Eqs. (39)–(41)).[130–134] Such a reaction has also been successfully applied to the synthesis of the benzodithiophenes **137**.[135]



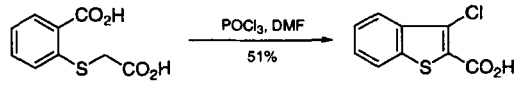
124 **125** (35)



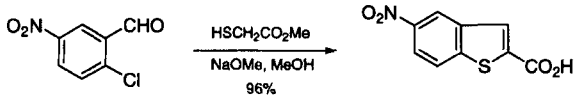
126 **127** (36)



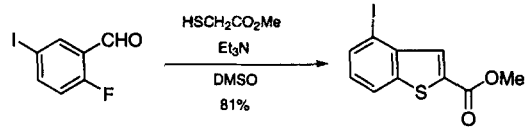
128 **129** (37)



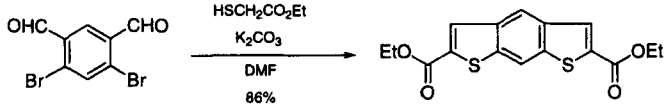
130 131 (38)



132 133 (39)

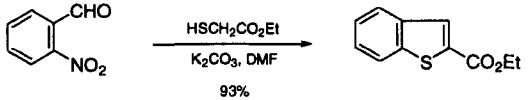


134 135 (40)

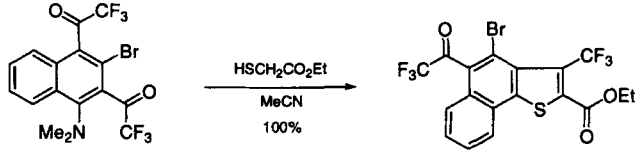


136 137 (41)

The leaving group *ortho* to the carbonyl for the incoming sulfur nucleophile can also be extended to a nitro group (Eq. (42)).[31] The benzo[*b*]thiophene 2-carboxylate (**139**) was synthesized from 2-nitrobenzaldehyde (**138**) in good yield and under convenient conditions. The carboxylate can be converted into an acetyl group by sequential treatment with DMSO/*t*-BuOK and Zn/NH_4Cl. Additionally, a dimethylamino group can be displaced by a sulfide anion when it is doubly activated by trifluoroacetyls (Eq. (43)).[136]

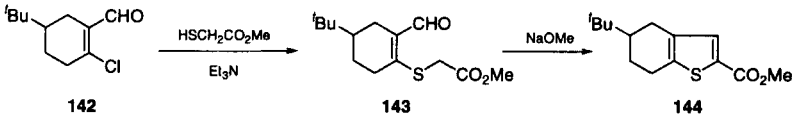


138 139 (42)



140 141 (43)

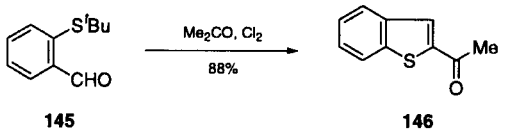
A tetrahydrobenzothiophene has been synthesized in a similar way (Scheme 11).[137] The starting material was obtained from 4-*tert*-butylcyclohexanone through Vilsmeier reaction and the resulting compound **143** can be aromatized by treatment with DDQ.



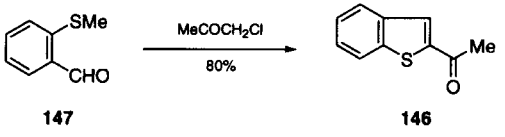
142 **143** **144**

SCHEME 11

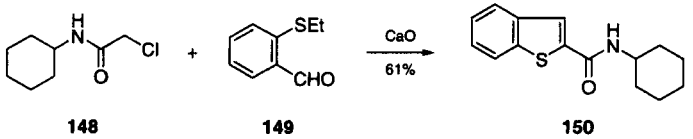
Alkyl aryl sulfides can also serve as sulfur donors by reacting with a halo ketone or acyl compound. *In situ* dealkylation commenced after the condensation to give benzothiophene.[138–140] Compound **146** is pivotal for the synthesis of zileutin **5**.[32]



145 **146** (44)

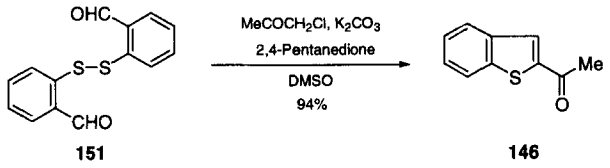


147 **146** (45)



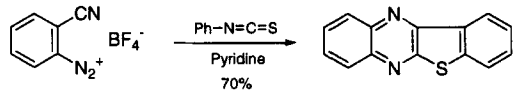
148 **149** **150** (46)

Disulfide **151** can be obtained by ozonolysis of benzothiophene and has been used as starting material for the preparation of more substituted analogs through a condensation reaction.[141] Alternatively, compound **151** can be obtained by condensation of 2-ClC_6H_4CHO and Me_3CSH, followed by treatment with HBr/DMSO. When stirred with $(MeCO)_2CH_2$ and $MeCOCH_2Cl$ in DMSO, the disulfide gave 2-acetylbenzo[*b*]thiophene in 94% yield (Eq. (47)). In this scenario both thiophenol molecules were utilized.[142] Much of this chemistry was developed in conjunction with the synthesis of zileutin **5**.

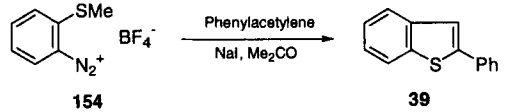


151 146 (47)

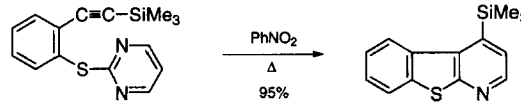
The formation of the quinoxaline fused benzothiophene **153** was realized by reaction of a diazonium salt with phenyl isothiocyanate.[143] Insertion of a diazonium salt into an acetylene also afforded a benzothiophene (Eq. (49)).[144] A reverse electron demand Diels–Alder reaction of **155** gave the tricyclic benzothienopyridine **156** in excellent yield after the extrusion of MeCN.[145]



152 153 (48)

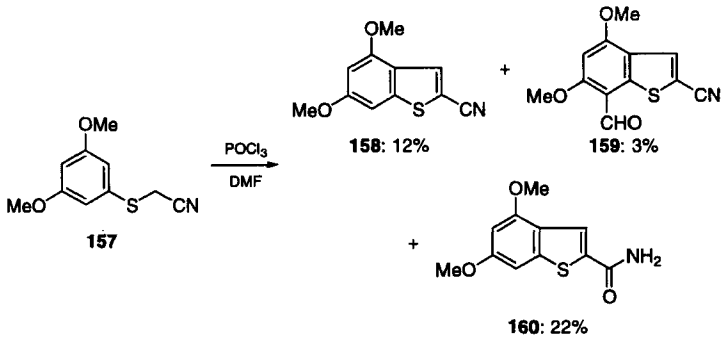


154 39 (49)

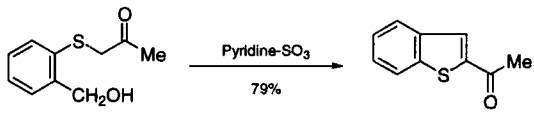


155 156 (50)

The aldehyde moiety can also be installed in the presence of an aryl sulfide by a Vilsmeier reaction (Eq. (51)),[146] or by oxidation of the benzylic alcohol **161** (Eq. (52)).[147]

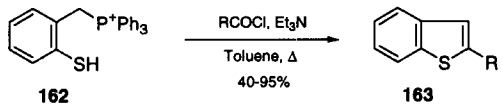


157 (51)



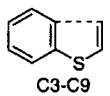
161 **146** (52)

It should be noted that current examples of this mode of cyclization are invariably limited to the synthesis of 2-substituted benzothiophenes, usually by an electron withdrawing group to render the position adjacent to the sulfur acidic enough to participate in the condensation reaction. A notable exception is the intramolecular Wittig reaction with an aryl thioester,[148] where R can be phenyl or alkyl groups (Eq. (53)).



162 **163** (53)

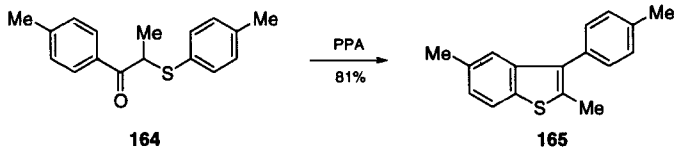
4.5. C3–C9 Bond Formation



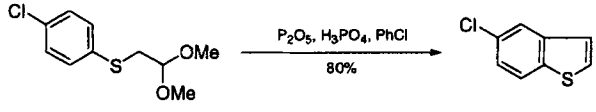
This is one of the most general, and widely used methods for preparing benzothiophene for a few reasons. First and foremost, the starting material could be a simple thiophenol, which in turn can be accessed from (1) reaction of an aryl Grignard or lithium reagent with elemental sulfur, (2) aromatic nucleophilic substitution of aryl halides or nitro compounds, and (3) Newman–Kwart rearrangement of the corresponding phenol. Secondly, the reaction is applicable to forming 2,3-unsubstituted benzothiophenes, where most other methods are hampered by low reactivity and yields, lack of available starting materials, and/or inherent limitation by reaction mechanism.

Usually an α-aryl thioketone, an aldehyde, or their protected forms such as an acetal, a ketal, or an enol ether (Eq. (56))[149] has been employed as starting material. A strong Lewis acid/dehydrating agent is needed to effect such a cyclization,[150,151] polyphosphoric acid (PPA) being the most frequently used reagent/solvent (Eq. (54)). A major

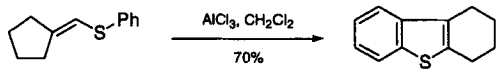
drawback of the C3–C9 type ring formation, as common with most electrophilic aromatic substitutions, is the low efficiency toward unactivated benzene rings.



164 165 (54)

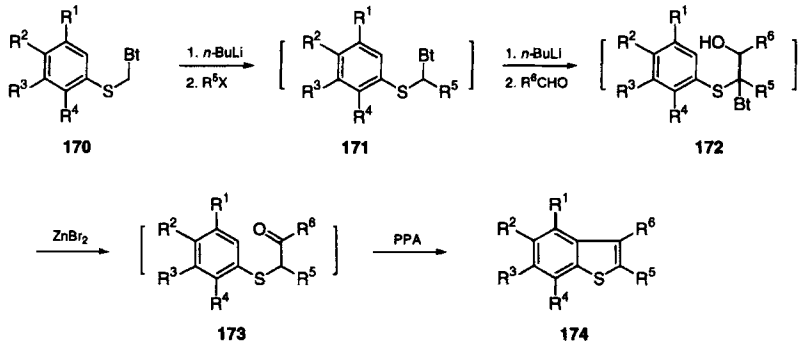


166 167 (55)



168 169 (56)

Katritzky's group has developed a very convenient method that allows the preparation of poly substituted benzothiophenes. Taking advantage of benzotriazole mediated metallation and Lewis acid promoted *in situ* generation of aryl thioketones **173**, a wide variety of benzothiophenes has been prepared. It should be noted that the whole sequence can be carried out in a one-pot fashion and that this procedure is quite amenable to parallel synthesis for exploration of molecular diversity.[150] De Groot *et al.* have precedented a similar synthetic sequence where a methoxy group was used in place of the benzotriazole.[152]

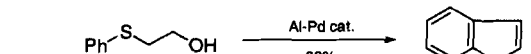


170 171 172

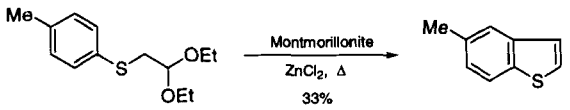
173 174

SCHEME 12

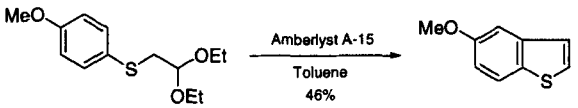
The synthesis of indoles, benzofurans, and benzothiophenes is possible at high temperature from $PhXCH_2CH_2OH$ (X = NH, O, S) catalyzed by palladium supported on aluminum orthophosphate through an oxidation–cyclization protocol.[153,154] Clark *et al.* have reported a gas phase reaction where zinc chloride impregnated montmorillonite was used as a catalyst for the cyclization of arylmercapto acetals.[155] This procedure eliminated several problems associated with the use of polyphosphoric acid as a solvent, including waste treatment issues. However, this procedure does require a very high temperature. We have disclosed a convenient method for accomplishing these reactions using the polymer-bound sulfonic acid resin Amberlyst A-15 as a catalyst in boiling toluene (Eq. (59)). While the yield with *p*-methoxyphenylthioacetal is only moderate, it compares favorably with the traditional PPA procedure where only a trace amount of product was obtained.[156]



175 1 (57)

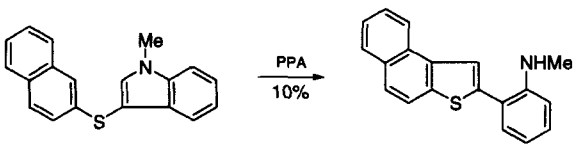


176 177 (58)



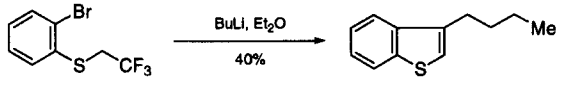
178 179 (59)

As a footnote to the earlier comparison between indoles and benzothiophenes was the conversion from an indole to a benzothiophene, albeit in low yield, reported by Hamel *et al.*[157] This transformation illustrates the reversible nature of these Friede–Crafts reactions (Eq. (60)).



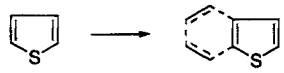
180 181 (60)

The trifluoroethyl sulfide **182** underwent cyclization upon being treatment with *n*-BuLi.[158] Unfortunately, the butyl group was also incorporated in the product.



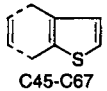
182 **183** (61)

4.6. Synthesis of Benzothiophenes via Benzoannulation



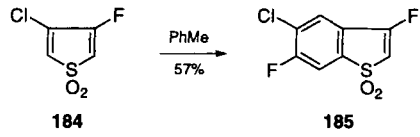
At first glance, synthesis of benzothiophenes via annulation onto an existing thiophene does not appear to be the most efficient disconnection in the retrosynthetic analysis, as two carbon–carbon disconnection would emerge from the 2,3-position of the thiophene ring, a seemingly very involved endeavor. In practice, however, this can be accomplished with relative ease and has served as a very quick entry into some highly substituted and polycyclic molecules with remarkable regioselectivity, and virtually all known benzene ring syntheses have been applied as a consequence. Often, the synthesis of precursors for such a benzoannulation is the major hurdle in the application of this approach.

4.6.1. Benzoannulation via simultaneous formation of C4–C5 and C6–C7

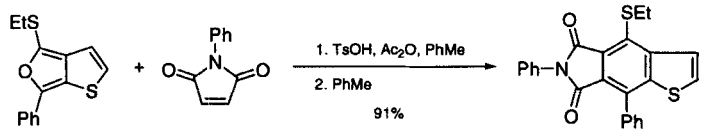


C45-C67

Among the approaches in this category, the Diels–Alder reaction is the most frequently used transformation. For example, the trihalogenated benzothiophene dioxide **185** can be formed where a thiophene dioxide serves as both a diene and dienophile after elimination of SO_2 and HCl.[159] Similarly, the benzothiophene **188** can be obtained from the furothiophene **186** by cycloaddition with succinimide **187**.[160–162]

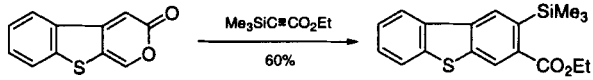


184 185 (62)



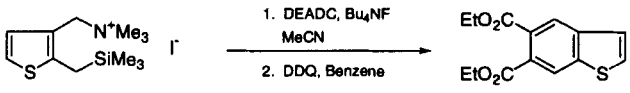
186 187 188 (63)

The synthesis of dibenzothiophenes can be attained by Diels–Alder reaction of the benzothienopyranone **189** with a dienophile, followed by extrusion of CO_2.[163]

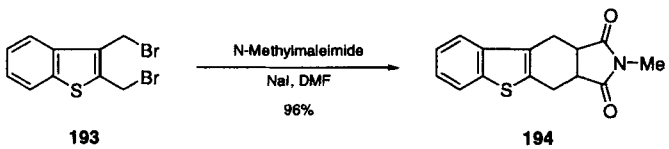


189 190 (64)

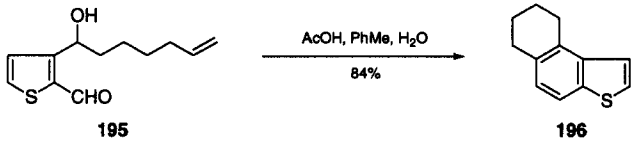
Dimethylenedihydrothiophene, generated *in situ* from 3-(trialkylamoniomethyl)-2-(trimethylsilylmethyl)thiophene iodide by fluoride induced 1,4-elimination, participates effectively in cycloadditions (Eq. (65)).[164] Alternatively the diene can be made available by reductive elimination of the dibromide **193**, as illustrated in Eq. (66).[165] These reactions resemble orthoquinonedimethide cycloadditions, as frequently used in polyaromatic synthesis, and have been applied in an intramolecular style (Eq. (67)).[166,167]



191 192 (65)

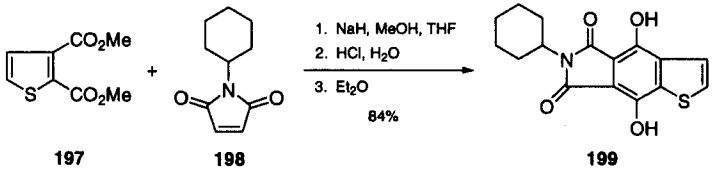


193 194 (66)

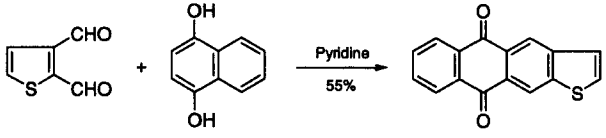


195 **196** (67)

The Dieckmann protocol has been applied to the synthesis of the imide **199** from the diester **197**.[168] Analogously, a thiophenoquinone was obtained by condensation of the dihydroquinone **201** with the dialdehyde **200** under very mild conditions (Eq. (69)).[169,170]

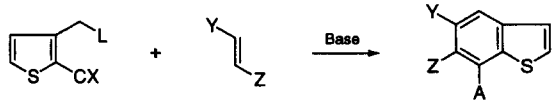


197 **198** **199** (68)



200 **201** **202** (69)

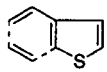
A large variety of 5,6,7-substituted benzothiophenes have been prepared by a tandem Michael addition–aldol condensation of 2,3-disubstituted thiophenes (Eq. (70)).[171] The reaction is initiated by deprotonation of a *p*-toluenesulfonylmethyl or a *p*-toluenesulfinylmethyl group and concluded by aromatization through elimination of either *p*-toluenesulfinic acid or the corresponding sulfenic acid, respectively, the overall yield ranging from 21–68%.



203 **204** **205** (70)

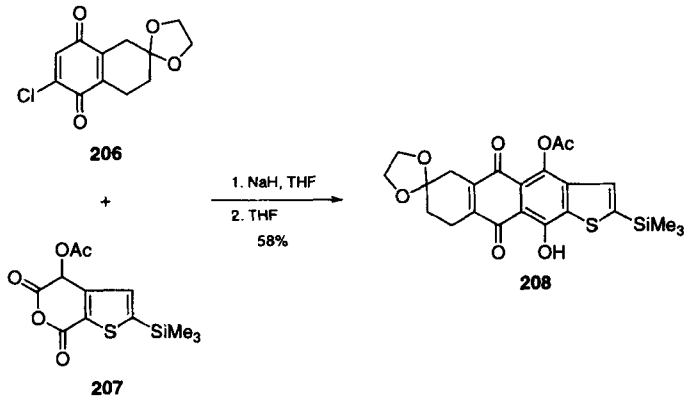
L = SO_nR, n = 1 or 2; CX = CHO, CN, CO_2Me
A = H, OH, or NH_2; Y = CO_2Me, Ar, Me, Z = CO_2Me, COPh

4.6.2. *Benzoannulation via simultaneous formation of C5–C6 and C7–C8*

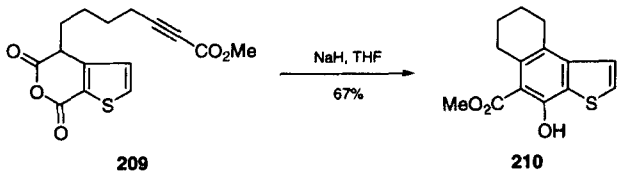


C56-C78

The Diels–Alder reaction of vinylthiophene equivalents generated by deprotonation of homophthalic anhydride **207**[172,173] has been applied to the synthesis of the thiophene analog of daunomycin, a potent antibiotic.[174–177] The homophthalic anhydride has also been cyclized with a tethered alkyne or alkene to afford a benzothienopyranone (Eq. (72)).[178,179]



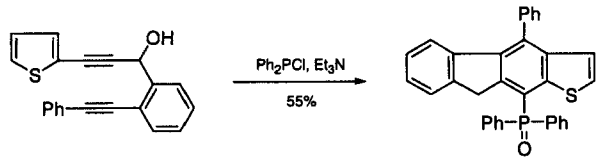
(71)



(72)

In a similar fashion, an intramolecular Diels–Alder reaction has been realized with an alkynylthiophene, to afford the polycycle **212**.[180,181] The [4 + 2] cycloaddition of 2-vinylthiophene with 1,2,3,4-tetrabromocyclopropene, followed by allyl cyclopropane isomerization, has been reported to give a benzothiophene in low yield (Eq. (74)).[182] Since hydrolysis of the dibromide gave the corresponding aldehyde,

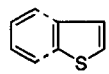
tetrabromocyclopropene **214** was regarded as a synthetic equivalent of bromoacetylenyl aldehyde.



211 **212** (73)

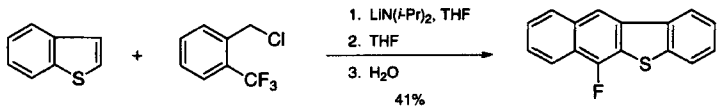
213 **214** **215** (74)

4.6.3. *Benzoannulation via simultaneous formation of C4–C9 and C7–C8*

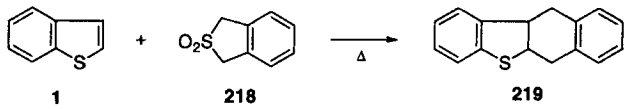


C49-C78

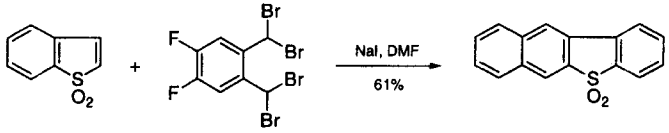
Kiselyov *et al.* have reported a novel synthesis of dibenzothiophenes where excess 2-benzo[*b*]thiophenyllithium was allowed to react with 2-(trifluoromethyl)benzyl chloride to yield 6-fluorobenzo[*b*]naphtho-[2,3-*d*]thiophene (Eq. (75)).[183] This can be interpreted as a cycloaddition of the *in situ* generated orthoquinonedimethide with the thiophene double bond, followed by elimination of HF. Benzothiophene itself participates as a dienophile at high temperature to afford the tetrahydrothionaphthacene **219**, which can be fully aromatized in an undisclosed yield by heating with sulfur.[184] Benzothiophene sulfone, on the other hand, proved to be a very good dienophile to trap the orthoquinonedimethide generated by reductive elimination from the tetrabromide **221** (Eq. (77)). The sulfone can be reduced to a benzothiophene by DIBAH.[185]



1 **216** **217** (75)

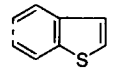


1 **218** **219** (76)



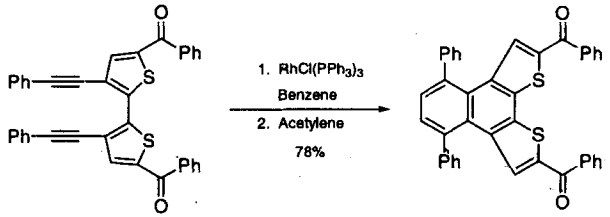
220 **221** **222** (77)

4.6.4. Benzene ring synthesis via formation of C5 and C6



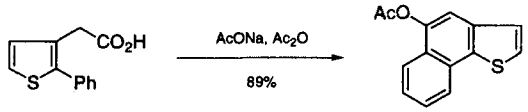
C5-C6

Rhodium-catalyzed trimerization of alkynes has been successfully applied to the synthesis of the unique benzobisthiophene **224** in 78% yield (Eq. (78)).[186]



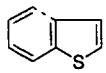
223 **224** (78)

Annulation onto an existing benzene ring was accomplished when an arylthienylacetic acid was refluxed with Ac_2O and NaOAc via an intramolecular acetylation to give the tricyclic compound **226**.[187]



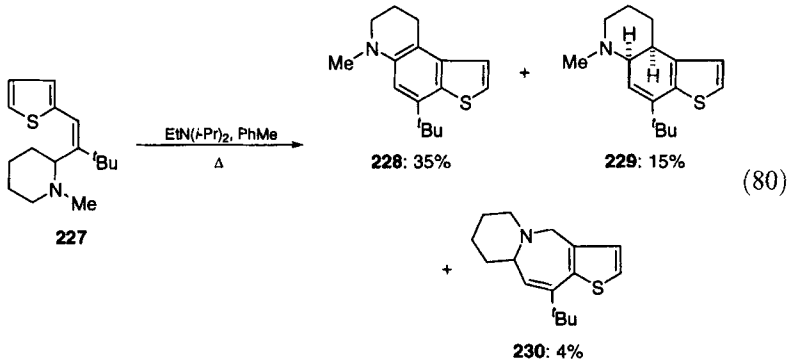
225 **226** (79)

4.6.5. *Benzene ring synthesis via formation of the C4–C9 bond*

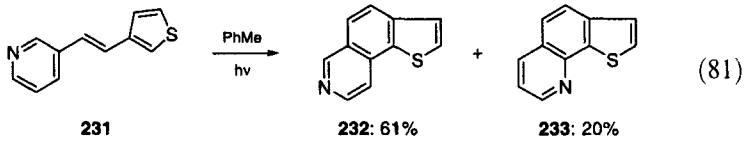


C4-C9

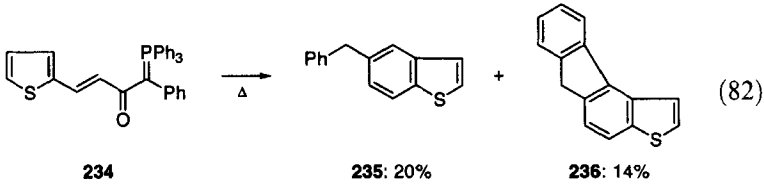
Thermal pericyclic reactions of **227** afforded benzothiophenes along with other isomers.[188] Such cyclizations have also been carried out photochemically with a pyridine ring (Eq. (81))[189] and with *in situ* generated acetylenes (Eq. (82)).[190]



(80)



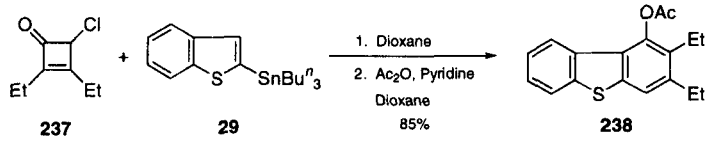
(81)



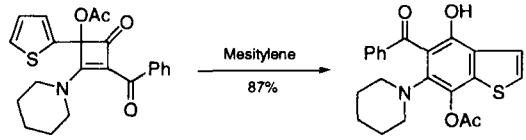
(82)

Liebeskind *et al.* have applied the cyclobutenone benzannulation strategy to benzothiophenes. The requisite cyclobutenones can be

obtained by a palladium-catalyzed cross-coupling reaction of organostannanes. Thermolysis led to the rearranged dibenzothiophenes in excellent yields.[191] A similar annulation has been reported with compound **239**.[192]

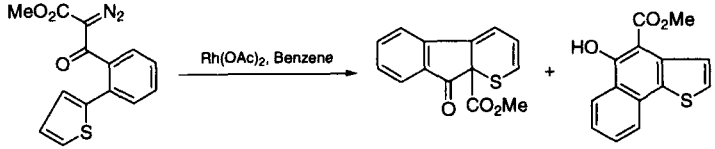


237 **29** **238** (83)

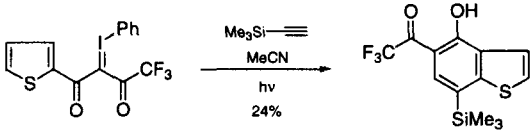


239 **240** (84)

Benzothiophene was formed as a minor product in the Rh-catalyzed carbene insertion into a C–H bond (Eq. (85)).[193] Photochemical carbene insertion into a silylated acetylene gave the benzothiophene **245** in similar yield.[194,195]

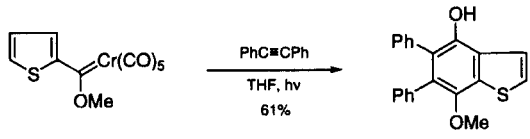


241 **242**: 68% **243**: 25% (85)

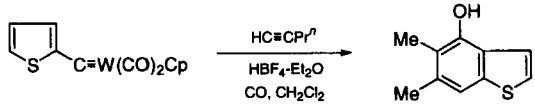


244 **245** (86)

Chromium[196,197] as well as tungsten[198] Fischer carbene chemistry has found application in the synthesis of benzothiophene by sequential acetylene and CO insertion reactions to a benzene ring (Eqs. (87) and (88)).

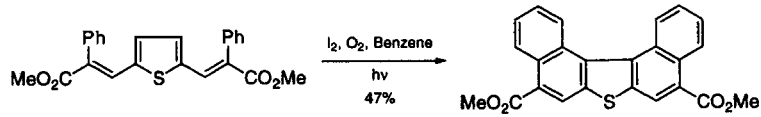


246 **247** (87)

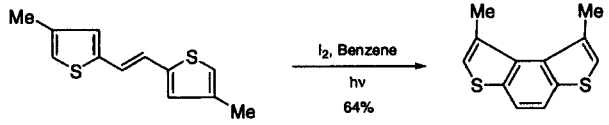


248 **249** (88)

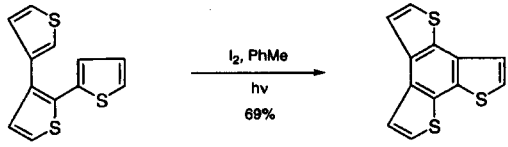
The photochemical oxidative cyclization of thiophene derivatives to form benzothiophene has been investigated quite extensively.[199–207] Annulation onto an indole ring has also been reported (Eqs. (89)–(93)).[208,209]



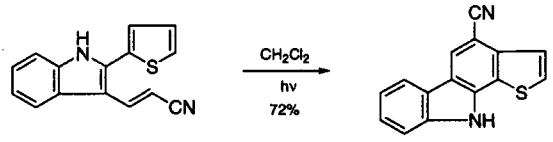
250 **251** (89)



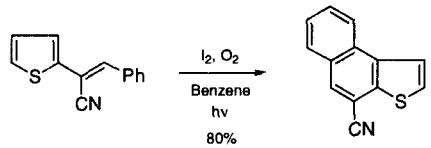
252 **253** (90)



254 **255** (91)

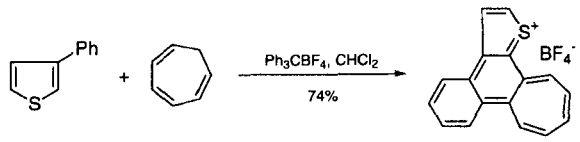


256 **257** (92)



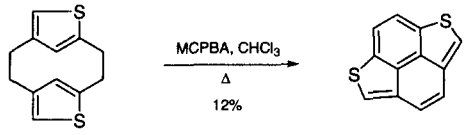
258 **259** (93)

A highly aromatic system (**262**) can be isolated as a stable salt from 3-arylthiophenes. This reaction is likely to proceed through alkylation of the thiophene by the aromatic carbocation generated *in situ*, followed by intramolecular cyclization (Eq. (94)).[210]

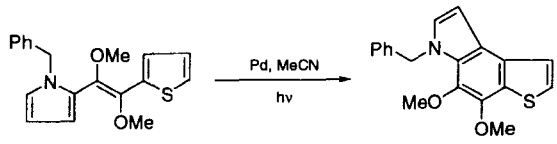


260 **261** **262** (94)

An interesting mode of cyclization at high temperature has been reported to give the condensed dimeric benzothiophene **264**, presumably through a Pummerer type mechanism.[211] In the synthesis of thiophene analogs of the antitumor agent CC-1065, a key step was a photochemical cyclization of the stilbenoid **265** in the presence of 5% Pd/C.[212–214]



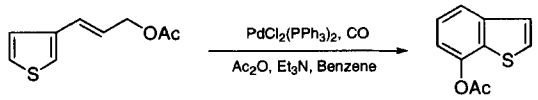
263 **264** (95)



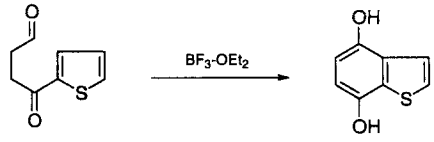
265 **266** (96)

A palladium-catalyzed carbonylative annulation of the allylic acetate **267** was implemented for the synthesis of compound **268**,[215,216] which is similar to the Lewis acid promoted cyclization of the keto

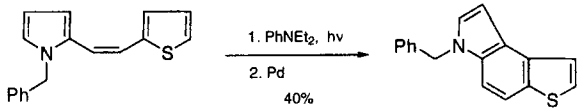
aldehyde **269**.[217,218] The indolobenzothiophene **272**, a CC-1065 intermediate, could be obtained by photolysis of **271**.[219]



267 **268** (97)

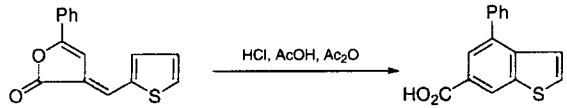


269 **270** (98)



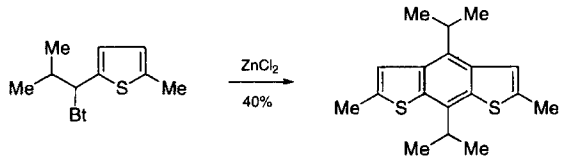
271 **272** (99)

The enol lactone **273**, obtained from condensation of 2-thiophenecarboxaldehyde with 3-aroylpropionic acids or their sodium salts in the presence of $NaOAc-Ac_2O$, was found to isomerize to 4-phenylbenzo[*b*]thiophene-6-carboxylic acid.[220]



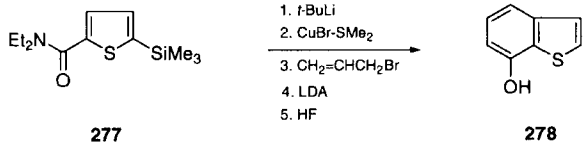
273 **274** (100)

Katritzky's group has disclosed a benzothiophene synthesis by Lewis acid catalyzed dimerization of benzotriazolylmethylthiophene. Intermolecular electrophilic alkylation, followed by autonomous aromatization, resulted in the formation of the benzodithiophene **276** in 40% yield.[221]



275 **276** (101)

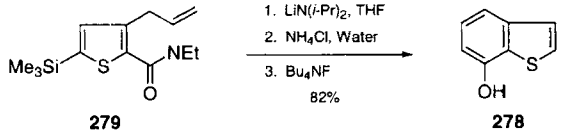
Snieckus *et al.* have developed a five-step sequence to 7-hydroxybenzothiophene via directed metallation of thiophene, followed by transmetallation, allylation, metallation and eventually cyclization.[217,222] The hydrogen atom on the other side of the thiophene has to be protected from these metallation steps.



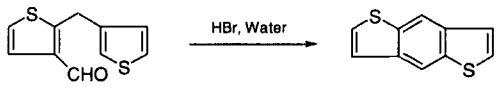
277 278 (102)

4.6.6. Other benzene ring syntheses

Lithiation of the allylic position of **279** affords 7-hydroxybenzothiophene in excellent yield, the necessity of protecting the 2-position of the thiophene ring notwithstanding.[223] The aldehyde **281** has been reported to give a benzodithiophene upon treatment with aqueous acid.[224]



279 278 (103)



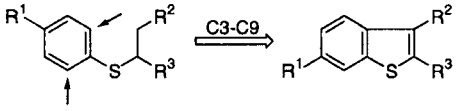
280 281 (104)

5. SUMMARY

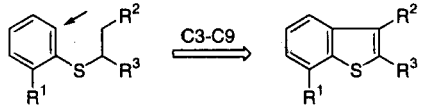
The last decade has witnessed the discovery of natural and synthetic compounds containing benzothiophenes of great pharmacological importance, with several of them already on the market and many more at various stages of clinical trial and preclinical development. Many new synthetic methodologies of this venerable heterocycle have

been reported, featuring high yields, high selectivities and use of organometallic reagents or catalysts. It is expected that building blocks containing benzothiophene, especially those which contain functional groups capable of being selectively derivatized to form new C–C bond or C–N, C–O bond, such as halogen, aldehyde, carboxylic acid, and amines will be highly sought after by medicinal chemists for structure-activity relationship studies.

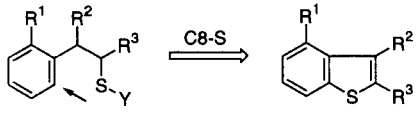
In the selection of a synthetic method for a particular benzothiophene, the electron density of the ring, the regioselectivity of the cyclization, and the substitution pattern of the desired compound must be taken into consideration. For example, adoption of a C9–C3 cyclization method is preferred for the making of C5 or C7 substituted benzothiophenes (Eqs. (105) and (106)). A C8–S cyclization would be preferred for the synthesis of a 4-substituted product (Eq. (107)), since in each case only one regioisomer is possible due to either symmetry or restriction of the reaction site.



(105)



(106)



(107)

In addition, the flexibility of the compounds toward further synthetic manipulations and the compatibility of the benzothiophene structure under the reaction conditions, e.g. the reactivity of the 2-H toward proton abstraction and of the sulfur toward oxidation, are also important factors in designing a synthesis. It is safe to say that no single method for the preparation of benzothiophenes is universally applicable, and in the synthetic repertoire there will always be a need for new

methods that address important issues including efficiency, selectivity, convenience, and environmental impact in the most positive manner.

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