Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Recent trends in the chemistry of aminobenzo[*b*]thiophenes

Mohamed A. Metwally[a]; Mohamed E. Khalifa[a]; Gamal A. El-Hiti[b]
[a] Department of Chemistry, Faculty of Science, Mansoura University, Mansoura, Egypt [b] School of Chemistry, Cardiff University, Cardiff, UK

Online publication date: 26 May 2010

To cite this Article Metwally, Mohamed A. , Khalifa, Mohamed E. and El-Hiti, Gamal A.(2010) 'Recent trends in the chemistry of aminobenzo[*b*]thiophenes', Journal of Sulfur Chemistry, 31: 3, 205 — 229
To link to this Article: DOI: 10.1080/17415991003721266
URL: http://dx.doi.org/10.1080/17415991003721266

Journal of Sulfur Chemistry
Vol. 31, No. 3, June 2010, 205–229

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Recent trends in the chemistry of aminobenzo[*b*]thiophenes

Mohamed A. Metwally[a], Mohamed E. Khalifa[a] and Gamal A. El-Hiti[b]*

[a]*Department of Chemistry, Faculty of Science, Mansoura University, Mansoura, Egypt;* [b]*School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, UK*

(*Received 16 October 2009; final version received 22 February 2010*)

The chemistry of aminobenzo[*b*]thiophenes has gained increased interest in both synthetic organic chemistry and biological fields and has considerable value. Some of the reactions have been successfully applied for the production of various fused heterocycles. The present review covers the literature up to date for the synthesis, reactions and applications of such compounds.

Keywords: aminobenzo[*b*]thiophenes; reactions; synthesis; heterocycles; biological activities

1. Introduction

Aminobenzo[*b*]thiophenes have been widely recognized as biologically useful systems and have been found to exhibit a range of biological activities. They are important intermediates in the synthesis a variety of valuable heterocyclic compounds (*1–4*). The chemistry related to benzothiophene derivatives was previously reviewed (*5*).

2. Synthesis

The main objective of this section is to provide a comprehensive account for the synthesis of various aminobenzo[*b*]thiophenes. The synthesis of aminobenzo[*b*]thiophenes may be carried out in several ways regardless of the position of the amino group either on the homocyclic or on the thiophene ring. The most versatile and economical methods involve Willgerodt–Kindler routes using primary and secondary amines, nucleophilic reaction followed by Thorpe–Ziegler cyclization and arylation reactions with electron-deficient aryl halides. Various syntheses involve a nitro group displacement of benzonitriles by a thiol anion followed by cyclization. The palladium catalytic systems have been used successfully to produce aminobenzo[*b*]thiophenes via Buchwald–Hartwig coupling. Also, such compounds were obtained via hydrogenation of the corresponding nitro

*Corresponding author. Email: el-hitiga@cardiff.ac.uk

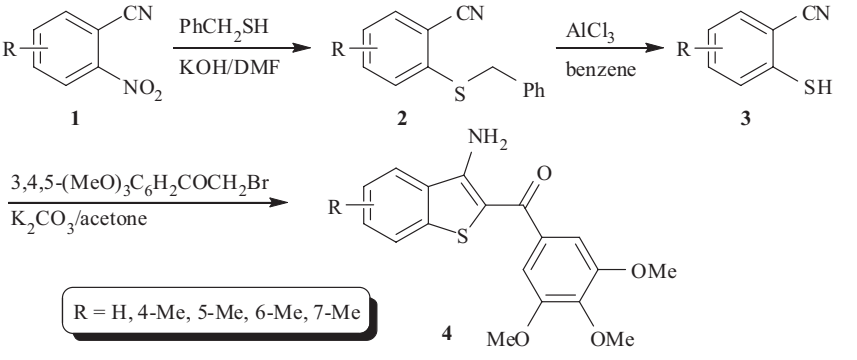
ISSN 1741-5993 print/ISSN 1741-6000 online

DOI: 10.1080/17415991003721266
http://www.informaworld.com

derivatives. The most common synthetic methods of aminobenzo[*b*]thiophenes are reported in the following sections.

2.1. *From benzonitriles*

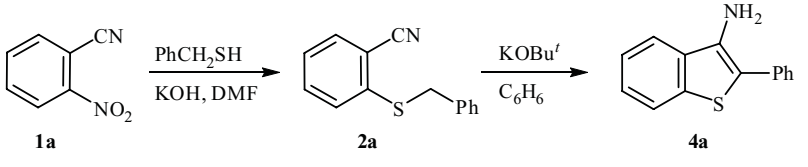
Various substituted aminobenzo[*b*]thiophenes were synthesized efficiently starting from substituted benzonitriles in which the nitro group of benzonitriles was displaced by a thiol anion followed by cyclization (*6–18*). A three-step synthesis of 3-aminobenzo[*b*]thiophenes **4** (R = H, Me) was reported (Scheme 1). The first step involves reaction of 2-nitrobenzonitriles **1** (R = H, Me) with the potassium salt of phenyl methanethiol in cold aqueous DMF (*6*) to give the corresponding thiol ethers **2** (*7, 8*) by replacing the nitro group. The second step involves *S*-debenzylation of **2**, using aluminum chloride in benzene, to give the corresponding thiol **3** (*7, 8*). The third step involves condensation of **3** with 1-(3,4,5-trimethoxyphenyl)-2-bromoethanone, in the presence of potassium carbonate in refluxing acetone, followed by cyclization to afford **4** (Scheme 1) in excellent yields (*7, 8*).



Scheme 1. Synthesis of 3-aminobenzo[*b*]thiophenes **4**.

Compounds of the general formula **4** (R = OMe, 5,6-di-OMe) were also obtained in excellent yields from 2-aminobenzonitriles. 2-Mercaptobenzonitriles **3** (R = OMe, 4,5-di-OMe) were synthesized by the Leuckart reaction (*9*).

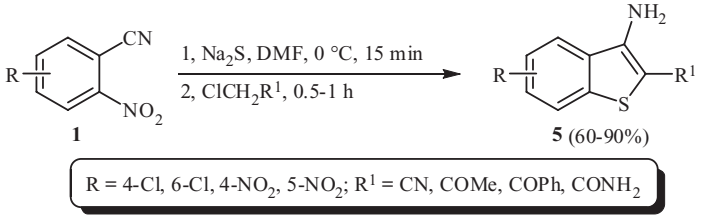
Beck has developed a two-step synthesis of 3-amino-2-arylbenzo[*b*]thiophenes (*6*). For example, the first step involves reaction of 2-nitrobenzonitrile (**1a**; *i.e.* **1** where R = H) and benzyl thiol in the presence of KOH in DMF to give 2-(benzylthio)benzonitrile (**2a**; Scheme 2) (*6*). The second step involves cyclization of **2a** in the presence of potassium *tert*-butoxide in benzene to give 3-amino-2-phenylbenzo[*b*]thiophene (**4a**; Scheme 2).



Scheme 2. Synthesis of 3-amino-2-phenylbenzo[*b*]thiophene (**4a**).

A series of 2-substituted 3-aminobenzo[*b*]thiophenes **5** was obtained in a one-step reaction from 2-nitrobenzonitriles **1** (*10*). Reactions of **1** with sodium sulphide in DMF at 0°C for 15 min

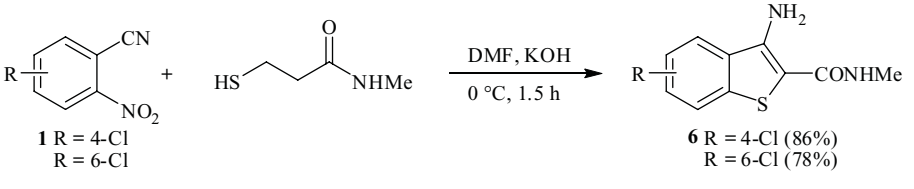
followed by alkylation afforded **5** in 60–90% yields (Scheme 3) (*10*). The reaction again involves a nitro group displacement to produce the corresponding 2-mercaptobenzonitrile followed by alkylation and cyclization.



Scheme 3. Synthesis of 2-substituted 3-aminobenzo[*b*]thiophenes **5**.

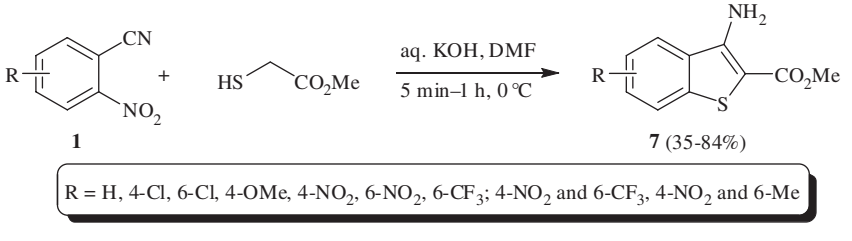
It was found that the reaction of 2-nitrobenzonitrile (**1a**; *i.e.* **1** where R = H) or 2-methoxy-6-nitrobenzonitrile (**1b**; *i.e.* **1** where R = 2-OMe) with Na_2S did not take place even at a higher temperature (100°C) for a longer reaction time. This limitation was overcome by the use of 3-mercaptopropionitrile (*11*) instead of Na_2S, in the presence of potassium hydroxide. The reaction proceeded via a nitro group displacement and an equilibrium mixture was formed involving the cyanoethyl thioether and the corresponding 2-mercaptobenzonitrile anion. The alkylation with chloroacetonitrile or chloroacetone following ring closure gave the corresponding **5** (R = H, 4-OMe; R^1 = CN, COMe) in 50–70% yields (*10*).

Similarly, 3-amino-*N*-methylbenzo[*b*]thiophene-2-carboxamides **6** were obtained in high yields from reactions of nitriles **1** (R = 4-Cl, 6-Cl) with 3-mercapto-*N*-methylpropanamide in DMF and in the presence of KOH at 0°C for 1.5 h (Scheme 4) (*12*). However, in the case of 2-nitrobenzonitrile (**1a**; Scheme 2), only 8% yield of the desired product **6** (R = H; Scheme 4) was obtained.



Scheme 4. Synthesis of 3-amino-*N*-methylbenzo[*b*]thiophene-2-carboxamides **6**.

Methyl 3-aminobenzo[*b*]thiophene-2-carboxylates **7** were prepared in 35–84% yields from reactions of 2-nitrobenzonitriles **1** with methyl thioglycolate in the presence of aqueous KOH in DMF at 0°C for 5 min to 1 h (Scheme 5) (*13*). The reaction was successfully applied for



Scheme 5. Synthesis of methyl 3-aminobenzo[*b*]thiophene-2-carboxylates **7**.

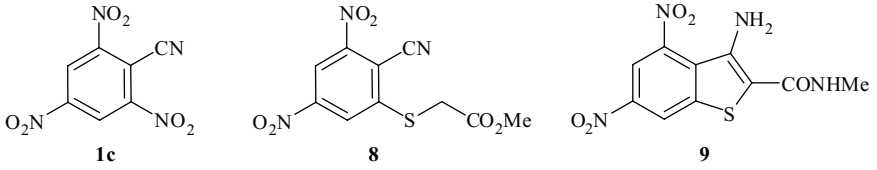
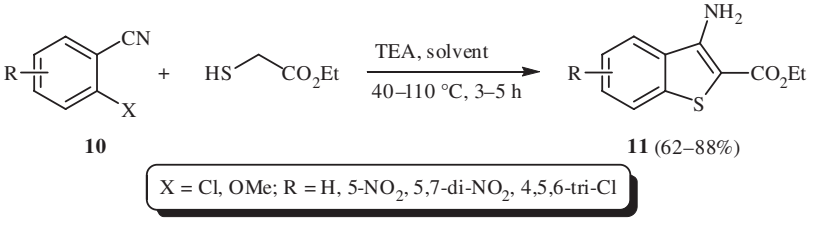


Figure 1. Structures of compounds **1c**, **8** and **9**.

the preparation of compounds **7** that have substituents in the 4 and/or 6-positions. However, no reaction took place when 2-chlorobenzonitrile was used as the starting material under similar conditions even after a longer reaction time of up to 2 days at room temperature.

Similarly, methyl 3-amino-4,6-dinitrobenzo[*b*]thiophene-2-carboxylate (**7**; R = 4,6-di-NO_2) can be synthesized from 2,4,6-trinitrobenzonitrile (**1c**; Figure 1) (*14*). Indeed, a reaction of **1c** with methyl thioglycolate in the presence of KOH in acetonitrile gave methyl 2-(2-cyano-3,5-dinitrophenylthio)acetate (**8**; Figure 1) in which one of the *ortho*-nitro groups to CN group was again replaced. Intramolecular cyclization of **8** gave the corresponding **7** in 50% yield (*15*). Isolation of **8** followed by treatment with sodium methoxide in methanol afforded **9** (Figure 1) in higher yield (80%) (*15*).

Previous reactions have been applied for the preparation of various substituted 3-aminobenzo[*b*]thiophenes starting from 2-halo or 2-methoxybenzonitriles (*16, 17*). The process involves halogen or methoxy displacement by a thiol anion and subsequent base-catalyzed ring closure. For example, a series of ethyl 3-aminobenzo[*b*]thiophene-2-carboxylates **11** were synthesized successfully in high yields (62–88%) from reactions of 2-chloro- or 2-methoxybenzonitriles **10** with ethyl thioglycolate in the presence of triethylamine at 40–110°C for 3–5 h (Scheme 6) (*17*). Various solvents such as ethylene glycol monoethyl ether, benzene and ethanol were used. It seems that the combination of solvent and base play an important role for the success of the reaction in the case of 2-chlorobenzonitrile which was not successful using KOH in the presence of DMF.

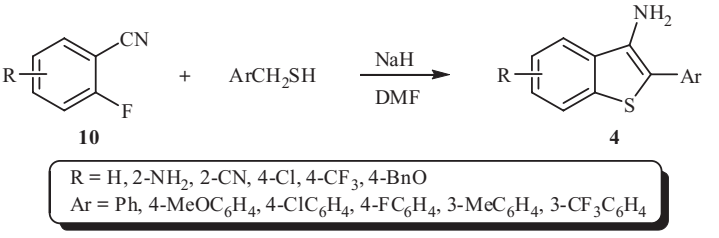


Scheme 6. Synthesis of ethyl 3-aminobenzo[*b*]thiophene-2-carboxylates **11**.

It was found that treatment of 2,4-difluorobenzonitrile with sodium methoxide gave a mixture of 2-fluoro-4-methoxybenzonitrile and 4-fluoro-2-methoxybenzonitrile, which were not separated and allowed to react with methyl thioglycolate in the presence of potassium *tert*-butoxide in DMF at room temperature to produce methyl 3-amino-6-methoxybenzo[*b*]thiophene carboxylate in a 14% overall yield (*16*). The reaction of 2-fluoro-4-nitrobenzonitrile with methyl thioglycolate in acetonitrile, in the presence of triethylamine as a base, gave methyl 3-amino-6-nitrobenzo[*b*]thiophenecarboxylate in a 47% yield (*16*).

More recently, the process of Beck (*6*) was modified in which a more general one-step process for the synthesis of 3-aminobenzo[*b*]thiophenes, substituted at the 2- and 6-positions with a variety of groups, was developed. A series of 2-aryl-3-aminobenzo[*b*]thiophenes (**4**) were synthesized in

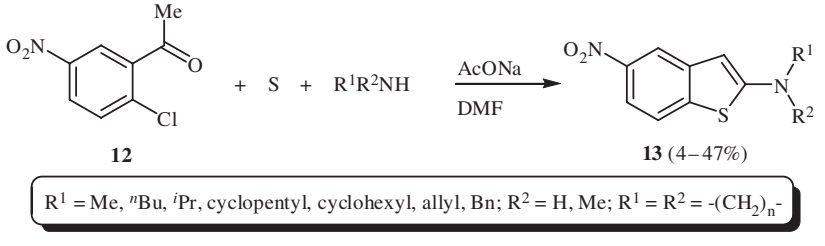
very high yields from the reactions of the appropriate substituted benzonitriles **10** (X = F) with substituted benzyl thiols in the presence of NaH in DMF at room temperature (Scheme 7) (*18*).



Scheme 7. Synthesis of 2-aryl-3-aminobenzo[*b*]thiophenes **4**.

2.2. *From Willgerodt–Kindler reaction*

Generally speaking, primary amines are usually more reactive than secondary amines in the classical Willgerodt–Kindler reaction (*19*). Reaction of 1-(2-chloro-5-nitrophenyl)ethanone (**12**), via Willgerodt–Kindler routes, using primary and secondary amines, resulted in a simple, efficient, three-component one-pot synthesis of 2-aminobenzo[*b*]thiophenes (**13**; Scheme 8) (*20*).



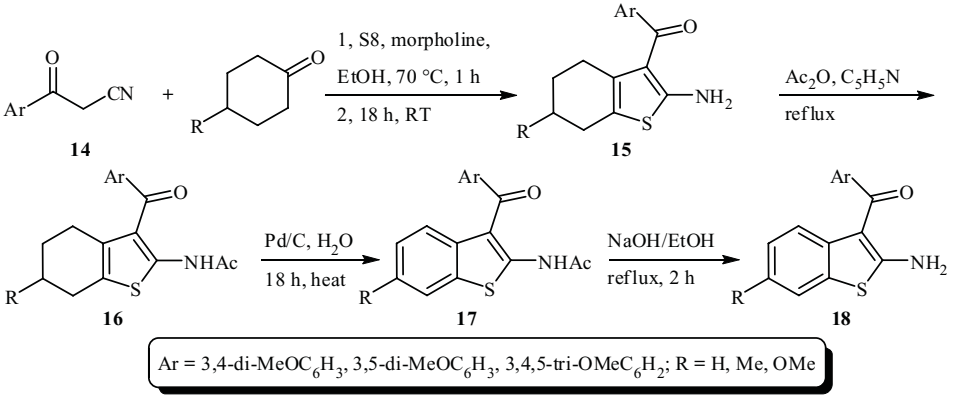
Scheme 8. Synthesis of 2-aminobenzo[*b*]thiophenes **13**.

However, the yields obtained were generally low (4–47%). It was found that the ratio of amine/S/base has not been optimized and various ratios were used based on the type of amine. Relatively better yields from primary amines (14–46%) were obtained at lower temperatures (35–60°C). On the other hand, higher temperature (60–100°C) worked better for the secondary amines (*e.g.* dimethylamine) but the yield of the product was only 4% (*20*). Cyclic amines produced low yields (10–31%) of the corresponding benzo[*b*]thiophenes. DMF was found to be the most favourable solvent. The reaction failed to produce any product when sterically hindered di-*N*-butylamine, diallylamine and diisopropylamine were used. Also, aromatic amines such as aniline and heterocyclic amines such as benzotriazole amines failed to react (*20*). However, the Willgerodt–Kindler reaction is not devoted to the synthesis of benzo[*b*]thiophene derivatives. The success of the reaction represented in Scheme 8 could be due to the effect of the nitro group which aids cyclization.

2.3. *From β-ketonitriles*

A series of 2-aminobenzo[*b*]thiophenes **18** were synthesized in four steps starting from *β*-ketonitriles **14** (Scheme 9) (*7, 8*). Reactions of aroylacetonitriles **14** and substituted

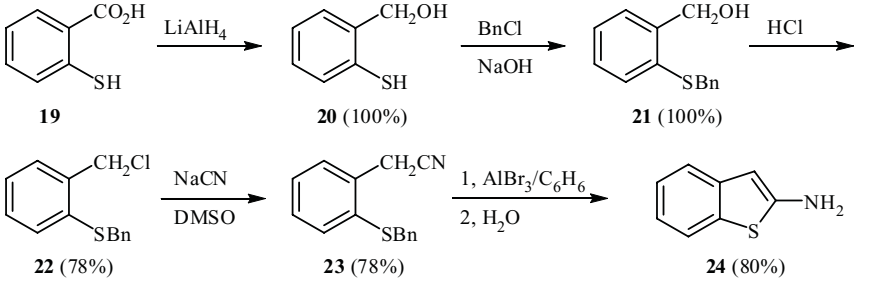
cyclohexanones in the presence of S_8 and morpholine (*21*) gave the corresponding 2-amino-3-aroyl-4,5,6,7-tetrahydrobenzo[*b*]thiophenes **15**. Acetylation of the amino group in compounds **15**, with a mixture of acetic anhydride and pyridine, provided the corresponding acetylamino derivatives **16**, which were converted to the corresponding benzo[*b*]thiophenes **17** by aromatization on heating with Pd/C (Scheme 9). Ethanolysis of **17** with ethanolic NaOH under reflux conditions for 2 h gave **18** (*7, 8*).



Scheme 9. Synthesis of 6-substituted 2-amino-3-aroylobenzo[*b*]thiophenes **18**.

2.4. *From thiosalicylic acid*

2-Aminobenzo[*b*]thiophene (**24**; Scheme 10) is obtained in an overall yield of 48% via a five-step reaction (*22*). The first step involves reduction of thiosalicyclic acid (**19**) to produce 2-mercaptobenzyl alcohol (**20**). Subsequent conversion of **20** to **24** gave the 2-aminobenzo[*b*]thiophene in an 80% yield. The final step involves cleavage of the carbon-sulfur bond in **23** based on the findings of Harnish and Tarbell (*23*). It might involve complexation with $AlBr_3$, disproportionation to form benzyl bromide and the desired product **24** as the bromoaluminum salt. Subsequent hydrolysis of such salt followed by a ring closure afforded **24** (*22*).

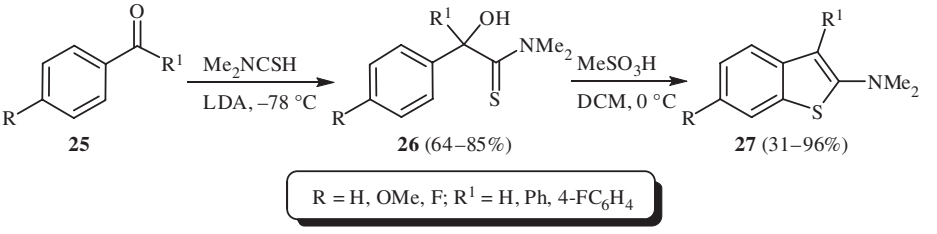


Scheme 10. Synthesis of 2-aminobenzo[*b*]thiophene (**24**).

2.5. *From benzaldehydes*

2-Dimethylaminobenzo[*b*]thiophenes were synthesized in high yields (*24, 25*). For example, the reaction of aryl aldehydes or ketones **25** with *N,N*-dimethylthioformamide in the presence of

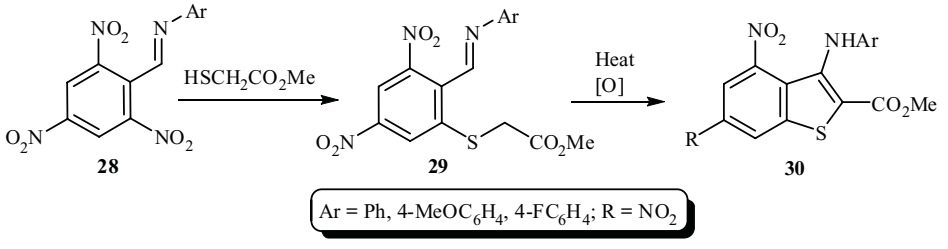
LDA at −78°C to produce the corresponding α-hydroxythioacetamides **26** in 64–85% yields (Scheme 11). Following cyclization–aromatization of **26** with $MeSO_3H$ in DCM at 0°C **27** was afforded in 31–96% yields (*25*).



Scheme 11. Synthesis of 2-dimethylaminobenzo[*b*]thiophenes **27**.

2.6. *From trinitrobenzylidenes*

Reactions of *N*-arylazometins **28** with methyl thioglycolate in the presence of potassium carbonate in acetonitrile at room temperature gave the corresponding sulfides **29**, replacing one of the *ortho*-nitro groups (*26*). Compounds **29** underwent intramolecular cyclization followed by oxidation to produce the corresponding methyl 3-(arylamino)-4,6-dinitrobenzo[*b*]thiophene-2-carboxylates (**30**, R = H; Scheme 12) (*26*). When the aryl group in compound **28** was replaced by a heterocyclic moiety, the reactions were not successful and only low yields of the corresponding **30** were produced (*ca*. 7%) (*26*). Instead, methyl 4,6-dinitrobenzo[*b*]thiophene-2-carboxylate was produced in moderate yields (40%) as a result of the heterocyclic fragment elimination (*26*).



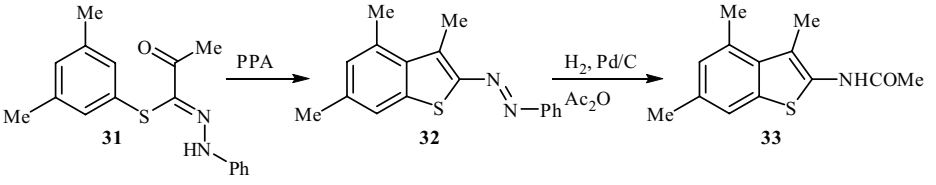
Scheme 12. Synthesis of methyl 3-(arylamino)-4,6-dinitrobenzo[*b*]thiophene-2-carboxylates **30**.

2.7. *From phenylazobenzo[***b***]thiophenes*

Catalytic hydrogenation of 2-(phenylazo)-3,4,6-trimethylbenzo[*b*]thiophene (**32**), obtained from **31** on treatment with polyphosphoric acid (PPA), with hydrogen in the presence Pd/C and acetic anhydride gave 2-acetamido-3,4,6-trimethylbenzo[*b*]thiophene (**33**; Scheme 13) but in low yield (*27*). Alkaline hydrolysis of **33** has produced 2-amino-3,4,6-trimethylbenzo[*b*]thiophene.

2.8. *From nitrobenzo[***b***]thiophenes*

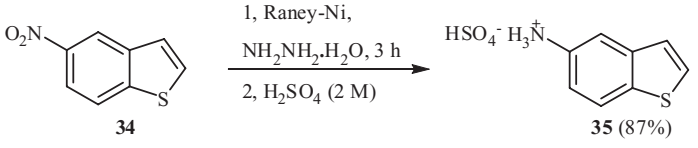
Nitration of benzo[*b*]thiophene itself with a mixture of fuming nitric and acetic acids at mild temperatures (60–70°C) gave a mixture of nitro derivatives in 85% yield (*28*). The mixture was



Scheme 13. Synthesis of 2-acetamido-3,4,6-trimethylbenzo[*b*]thiophene (**33**).

shown to contain 2-, 3- and 4-nitrobenzo[*b*]thiophenes in the ratio of *ca.* 1:6:2, respectively (*28*). Reduction of the nitro derivatives with hydrogen in the presence of platinium oxide under pressure for 1 h gave the corresponding aminobenzo[*b*]thiophenes in 81% yield (*28*). Similarly, nitration of benzo[*b*]thiophene-2-carboxylic acid with a mixture of nitric acid and acetic anhydride gave a mixture of the corresponding nitro derivatives in 75% yield. Such nitro derivatives were decarboxylated to give nitrobenzo[*b*]thiophenes in 62% yield which upon reduction with hydrogen in the presence of PtO_2 as a catalyst produce the corresponding amino derivatives in a 60% yield (*28*).

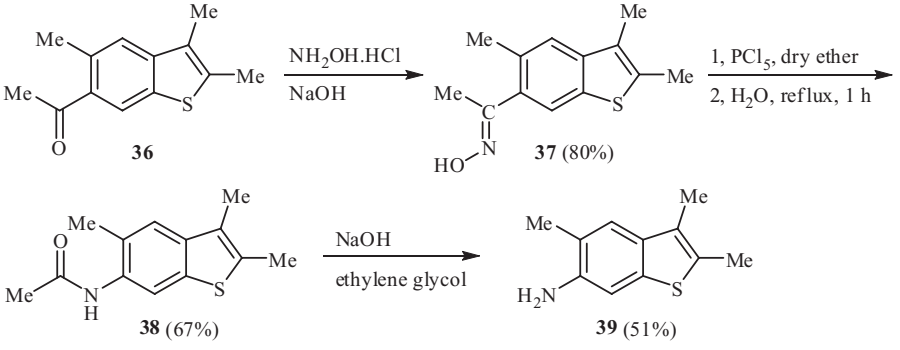
It is clear that nitration of benzo[*b*]thiophenes followed by a reduction provide a mixture of amino derivatives which are difficult to separate. This problem could be overcome by starting from nitrobenzo[*b*]thiophenes. 5-Aminobenzo[*b*]thiophene (**35**) was produced via reduction of 5-nitrobenzo[*b*]thiophene (**34**) (*29, 30*). Compound **34** (Scheme 14) was reduced with Raney nickel in the presence of hydrazine hydrate (85%), and the mixture was kept below its boiling point for 30 min (*30*). The residue obtained was treated with H_2SO_4 (2 M) and the product was isolated as the sulfate salt in 87% yield (*30*).



Scheme 14. Synthesis of 5-aminobenzo[*b*]thiophene (**35**).

2.9. *From benzo[*b*]thiophene amides*

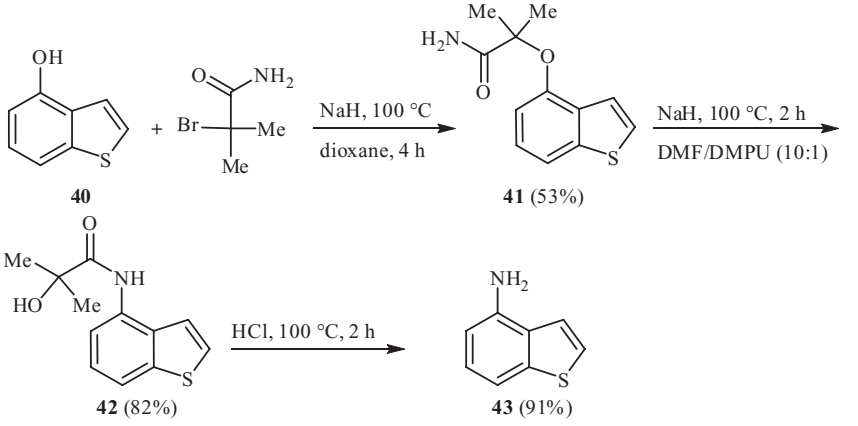
6-Amino-2,3,5-trimethylbenzo[*b*]thiophene (**39**) has been prepared starting from 6-acetyl-2,3,5-trimethylbenzo[*b*]thiophene (**36**; Scheme 15) (*31*). The reaction of **36** with hydroxylamine



Scheme 15. Synthesis of 6-amino-2,3,5-trimethylbenzo[*b*]thiophene (**39**).

hydrochloride in a basic medium gave the corresponding oxime **37** in 80% yield. 6-Acetamido-2,3,5-trimethylbenzo[*b*]thiophene (**38**) was obtained in 67% yield by the Beckmann rearrangement of **37**. Deprotection of **38** in a basic medium afforded **39** in 51% yield (*31*). Similarly, hydrolysis of 5-acetamido-4-nitrobenzo[*b*]thiophene with sodium hydroxide in ethanol gave 5-amino-4-nitrobenzo[*b*]thiophene in 97% yield (*32*).

Hydrolysis of *N*-(benzo[*b*]thiophen-4-yl)-2-hydroxy-2-methylpropanamide (**42**) in acidic medium using HCl (6 M) at 100°C for 2 h gave 4-aminobenzo[*b*]thiophene (**43**) in 91% yield (Scheme 16) (*33*). Compound **42** was initially produced from 4-hydroxybenzo[*b*]thiophene (**41**). Reaction of **40** with 2-bromo-2-methylpropanamide in the presence of sodium hydride in dry dioxane under reflux conditions for 4 h gave **41** in 53% yield (*33*). Compound **41** underwent the Smiles rearrangement on treatment with NaH in a mixture of DMF and DMPU (10:1), under reflux conditions for 2 h, to produce **42** in 82% yield (Scheme 16).



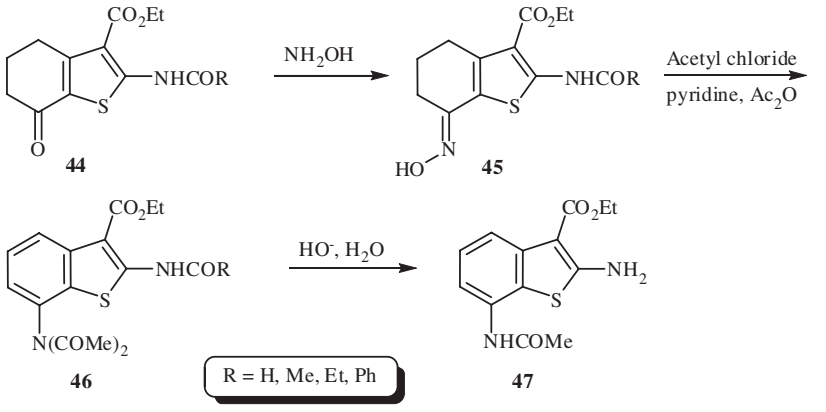
Scheme 16. Synthesis of 4-aminobenzo[*b*]thiophene (**43**).

Ethyl 7-acetamido-2-aminobenzo[*b*]thiophene-3-carboxylate (**47**) was successfully synthesized from ethyl 7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylates **44** according to the reaction shown in Scheme 17 (*34*). Treatment of **44** with hydroxyl amine gave the corresponding oximes **45** in moderate yields. Reaction of **45** with a mixture acetyl chloride and acetic anhydride in pyridine gave the corresponding ethyl 2-acylamino-7-(*N*-acetylacetamido)benzo[*b*]thiophene-3-carboxylates **46** that, on alkaline hydrolysis, afforded **47** (Scheme 17).

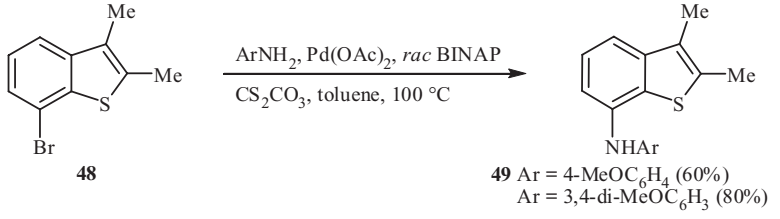
2.10. *From Buchwald–Hartwig coupling*

A series of 7-arylamino-2,3-dimethylbenzo[*b*]thiophenes **49** were synthesized by C–N palladium-catalyzed cross-coupling (*31*, *35–38*) of 7-bromo-2,3-dimethylbenzo[*b*]thiophene (**48**) (*39*) with arylamines (Scheme 18) (*40*). The yields of **49** were 62% and 80% when 4-methoxyaniline and 3,4-dimethoxyaniline were used as the aromatic amines, respectively (*40*). The coupling conditions involves the use of $Pd(OAc)_2$, *rac*. BINAP and Cs_2CO_3 in toluene at 100°C for 22 h under an inert atmosphere (*40*). Similarly, the palladium-catalyzed cross-coupling of **48** and 3-aminopyridine, in the presence of $Pd(OAc)_2$, Xantphos and Cs_2CO_3 in dioxane at 110°C for 5 h, gave 7-pyridylamino-2,3-dimethylbenzo[*b*]thiophene (**49**; Ar = 3-pyridyl) in 76% yield (*40*).

The coupling of substituted 6-bromo-2,3-dimethylbenzo[*b*]thiophenes (**50**) with various aromatic amines containing one or two methoxy group in dry toluene in the presence of a Pd catalytic system, under anhydrous conditions, gave the corresponding 6-arylaminobenzo[*b*]thiophenes in



Scheme 17. Synthesis of ethyl 7-acetamido-2-aminobenzo[*b*]thiophene-3-carboxylate (**47**).



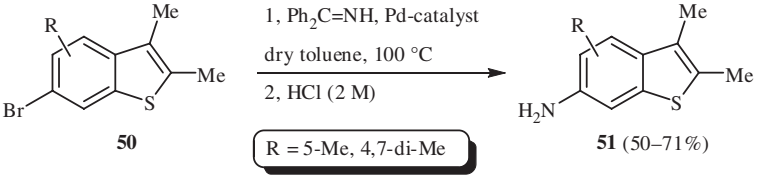
Scheme 18. Synthesis of 7-arylamino-2,3-dimethylbenzo[*b*]thiophenes **49**.

52–80% yields (*41*). Such products could also be obtained in moderate to quantitative yields from the coupling reactions of 6-aminobenzo[*b*]thiophenes with aryl bromide under identical conditions (*41*). However, coupling of 6-bromo-2,3,5-trimethylbenzo[*b*]thiophene (**50**; R = 5-Me) with 2-bromoaniline under similar reaction conditions gave the corresponding arylamino derivative in low yield (20%) even after a 70 h reaction time (*31*). The yield was improved to 40% when 6-amino-2,3,5-trimethylbenzo[*b*]thiophene was coupled with 2-bromoiodobenzene under similar reaction conditions for 21 h (*31*).

6-Bromobenzo[*b*]thiophenes **50** were coupled with benzophenone imine gave the corresponding imino derivatives (*41*). Following hydrolysis with HCl (2 M) 6-aminobenzo[*b*]thiophenes **51** were obtained in 50–71% yields (Scheme 19) (*41*).

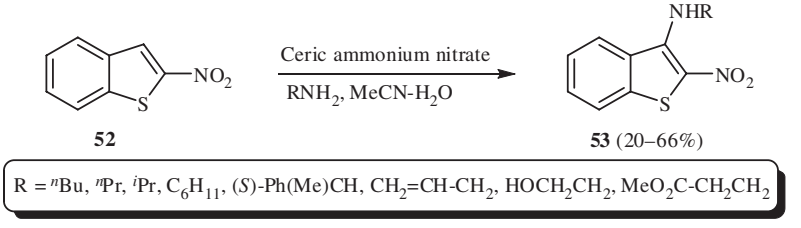
2.11. *By nucleophilic substitution or addition reactions of benzo[b]thiophenes*

Reaction of 3-nitrobenzo[*b*]thiophene with primary or secondary amines in the presence of silver nitrate followed by methylation with iodomethane resulted in a ring opening reaction to give



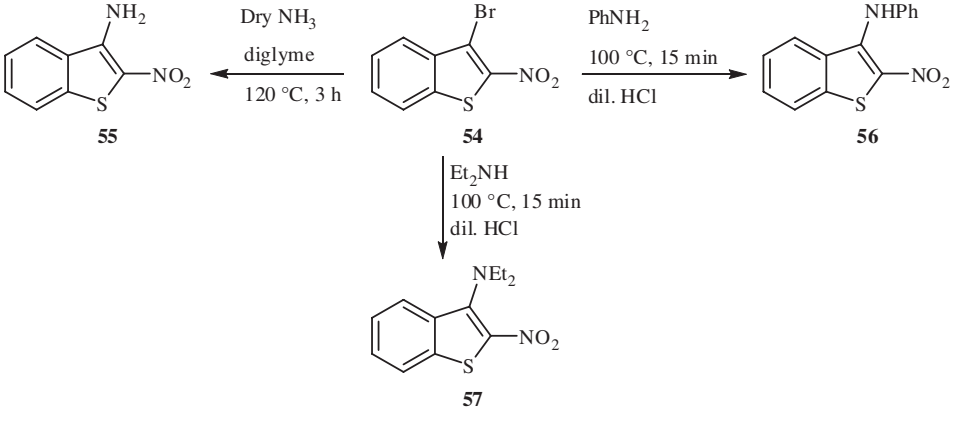
Scheme 19. Synthesis of 6-aminobenzo[*b*]thiophenes **51**.

the corresponding 2-(2-(methylthio)phenyl)nitroethenamines in 10–50% yields (*42*). In contrast, 2-nitrobenzo[*b*]thiophene (**52**) with *n*butylamine under the same reaction conditions gave 3-butylamino-2-nitrobenzo[*b*]thiophene (**53a**) in 5% yield with no ring-opened product being formed. Such product is believed to be formed as a result of oxidative nucleophilic substitution of hydrogen at position 3. The use of a more powerful oxidant, such as ceric ammonium nitrate, could provide a better yield of **53**. Indeed, treatment of 2-itrobenzo[*b*]thiophene (**52**) with primary amines in the presence of ceric ammonium nitrate in aqueous acetonitrile at room temperature gave the corresponding 3-akylamino-2-nitrobenzo[*b*]thiophenes (**53**) in 20–66% yields (Scheme 20) (*42*).



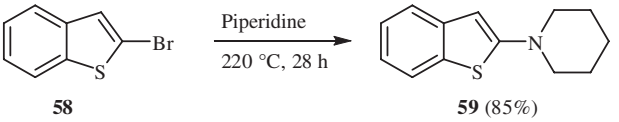
Scheme 20. Synthesis of 3-akylamino-2-nitrobenzo[*b*]thiophenes **53**.

Amination of 3-bromo-2-nitrobenzo[*b*]thiophene (**54**) with dry ammonia in diglyme at 120°C for 3 h gave 3-amino-2-nitrobenzo[*b*]thiophene (**55**; Scheme 21) (*28*). Similarly, reactions of **54** with aniline and diethylamine at 100°C followed by treatment with HCl gave 3-phenylamino-2-nitrobenzo[*b*]thiophene (**56**) and 3-diethylamino-2-nitrobenzo[*b*]thiophene (**57**), respectively (*28*).



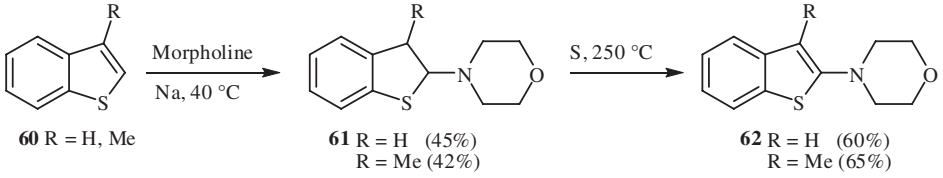
Scheme 21. Synthesis of 2-nitrobenzo[*b*]thiophenes **55**–**57**.

Reaction of 2-bromobenzo[*b*]thiophene (**58**) with piperidine at 220°C in a sealed tube for 28 h gave 2-piperidinobenzo[*b*]thiophene (**59**) in 85% yield (Scheme 22) (*43*). Also, compound **59** was obtained, but in low yield (20%), on heating 3-bromobenzo[*b*]thiophene with piperidine at 250–260°C for 46 h (*43*). It seems likely that the direct substitution reaction of the 3-bromo derivative below 250°C has a high activation reaction compared with that of the 2-bromobenzo[*b*]thiophene (**59**).



Scheme 22. Synthesis of 2-piperidinobenzo[*b*]thiophene (**59**).

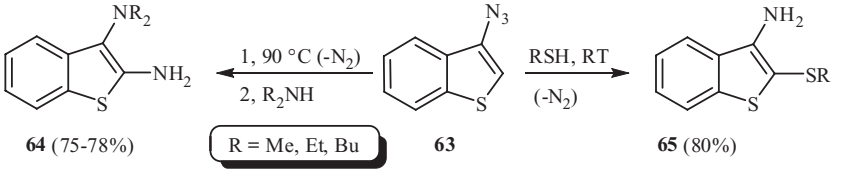
Reactions of benzo[*b*]thiophenes **60** with cyclic secondary amines (pyrrolidine, piperidine and morpholine) in the presence of sodium at 40°C for 18 h gave the corresponding 2-substituted 2,3-dihydrobenzo[*b*]thiophenes in 42–55% yields. Subsequent dehydrogenation gave the corresponding 2-substituted benzo[*b*]thiophenes (*44*). The addition of morpholine at the C2–C3 bond of **60** in the presence of sodium gave the corresponding 2-morpholino-2,3-dihydrobenzo[*b*]thiophenes **61** in 42–45% yields (*44*). Similar additions were observed when sodium hydride or *n*-butyl-lithium was used instead of sodium. 2-Morpholinobenzo[*b*]thiophenes (**62**) were obtained in 60–65% yields by aromatization of **61** with sulfur at 250°C (Scheme 23) (*44*). However, reactions with diethylamine, propylamine and cyclohexylamine were not very successful in which yields of the desired products were 2–5% (*44*). Also, no addition products were obtained for similar reactions using 2,3-dimethylbenzo[*b*]thiophene.



Scheme 23. Synthesis of 2-morpholinobenzo[*b*]thiophenes **62**.

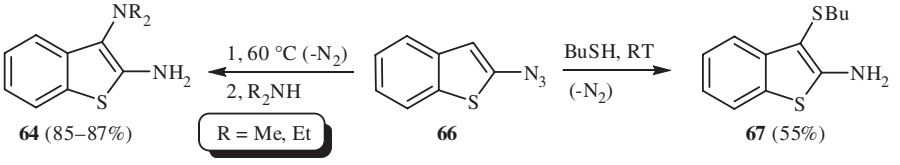
2.12. *From azidobenzo[*b*]thiophenes*

Azidobenzo[*b*]thiophenes were used effectively for the production of aminobenzo[*b*]thiophenes (*45, 46*). Azidobenzo[*b*]thiophenes can be obtained from the reaction of lithium benzo[*b*]thiophenes, obtained via bromine–lithium exchange of the bromo derivatives (*47–49*) on reaction with tosylazide (*46*). Thermolysis of 3-azidobenzo[*b*]thiophene (**63**) at 90°C in the dark in the presence of dialkylamines gave the corresponding 2-amino-3-alkylaminobenzo[*b*]thiophenes **64** (Scheme 24) in 75–78% yields (*45*). A small quantity of 3-aminobenzo[*b*]thiophene (**5**, $R = R^1 = H$) was produced as a by-product in 6–10% yields (*45*). The reaction is believed to involve the formation of azirine ring which undergoes ring opening to give the product. In contrast, treatment of **63** with alkylthiols at room temperature in the dark for a week gave the corresponding 3-amino-2-(alkylthio)benzo[*b*]thiophenes (**65**; Scheme 24) in 80% yields (*45*).



Scheme 24. Synthesis of compounds **64** and **65**.

Compounds **64** were also obtained in even better yields (85–87%) from thermolysis of 2-azidobenzo[*b*]thiophene (**66**) in the presence of dialkylamines at 60°C (Scheme 25). Under such conditions, 3-aminobenzo[*b*]thiophene (**5**, R = R^1 = H) was produced in low yields (3–5%) (*45*). Similarly, treatment of **66** with 1-butanethiol at room temperature gave 2-amino-2-(butylthio)benzo[*b*]thiophene (**67**) in 55% (Scheme 25), along with 3-(6-thioxocyclohexa-2,4-dienylidene)propanenitrile as a side product due to ring cleavage (*45*).

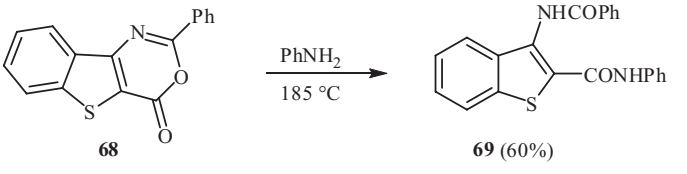


Scheme 25. Synthesis of compounds **64** and **67**.

2.13. *Miscellaneous syntheses*

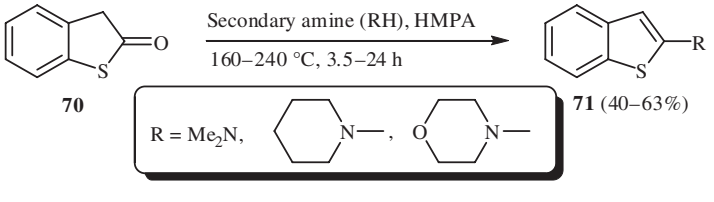
The synthesis of 3-aminobenzo[*b*]thiophene-2-carboxylic acid was first synthesized in 1907 by Friedlander (*50*). However, the procedure involves a number of steps and suffers from the availability of the starting material, 2-aminobenzenethiol (*51, 52*). Carrington has reported the synthesis of ethyl 3-aminobenzo[*b*]thiophene-2-carboxylate via the rearrangement of 3-chloro-1,2-benzoisothiazole. However, the process involves the use of relatively unavailable starting materials that needs to be prepared first (*53*).

3-Benzamido-*N*-phenylbenzo[*b*]thiophene-2-carboxamide (**69**) was prepared in 60% yield from heating 2-phenyl-4*H*-benzothieno[3,2-*d*][1,3]oxazin-4-one (**68**) with aniline at 185°C for 30 min (Scheme 26) (*12*). Hydrolysis of **68** produces the corresponding 3-aminobenzo[*b*]thiophene.



Scheme 26. Synthesis of 3-benzamido-*N*-phenylbenzo[*b*]thiophene-2-carboxamide (**69**).

Reactions of benzo[*b*]thiophene-2(3*H*)one (**70**) with secondary or cyclic amines in the presence of hexamethylphosphoramide (HMPA) at a high temperature (160–240°C) for 3.5–24 h gave the corresponding 2-substituted benzo[*b*]thiophenes **71** (Scheme 27) in moderate to good yields (*54*).



Scheme 27. Synthesis of 2-substituted benzo[*b*]thiophenes **71**.

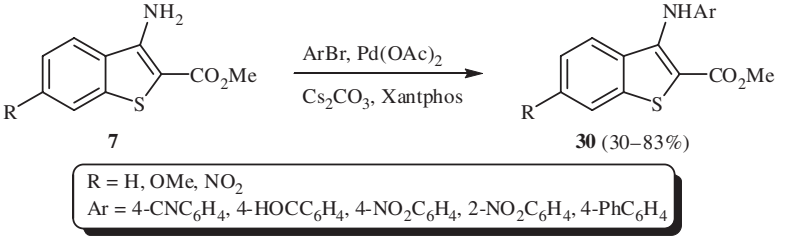
The reaction was successful with dimethylamine, piperidine and morpholine and was found to be dependent on the temperature. Low yields were obtained at lower temperatures. When aniline was used the yield of the desired product was very low (3%) (*54*). The reason for the low yield could be due to reaction of aniline and HMPA to produce 1,3,2,4-diazadiphosphetidines (*55*).

3. Reactions

Reactions of aminobenzo[*b*]thiophenes take place mostly on the amino group. The most common reactions involve arylation, acylation, azo dyes formation, production of ureas, deamination and condensation reactions. The latter reaction has been applied successfully for the production of various condensation products and fused heterocycles containing benzothiophene moiety. Also, acylamino groups can be used as an activator to direct lithiation to the *ortho*-position to produce the corresponding lithium reagents which on reactions with electrophiles would produce the corresponding substituted derivatives.

3.1. *Arylation reactions*

Methyl-3-aminobenzo[*b*]thiophene-2-carboxylates **7** were coupled with a variety of bromoarenes containing electron-deficient withdrawing groups (*e.g.* CN, CHO and NO_2) in the presence of Xantphos (12 mole%), $Pd(OAc)_2$ (10 mole%) and Cs_2CO_3 (2.8 molar equivalents), in dry dioxane at 120°C for 1–5 h under inert atmosphere to give the corresponding *N*-arylamine derivatives **30** (Scheme 28) in 30–83% yields (*56*). Methyl 3-(bis(4-nitrophenyl)amino)benzo[*b*]thiophene-2-carboxylate was obtained as a by-product in 3% yield along with **30** (R = H, 4-$NO_2C_6H_4$). Formation of such triarylamine could be due to the high reactivity of 4-nitrobromobenzene as a Buchwald–Hartwig coupling component, which also reacts with **30** (R = H, 4-$NO_2C_6H_4$). Compounds of the general formula **30** could also be obtained in reasonable to excellent yields from reactions of 3-bromobenzo[*b*]thiophenes with arylamines (*57*).

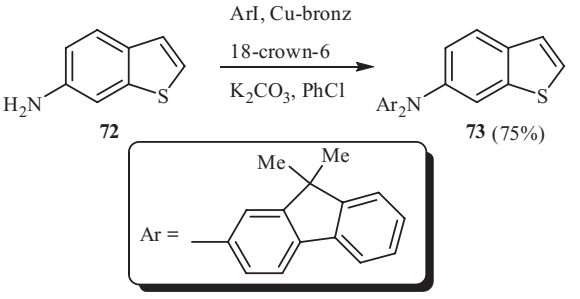


Scheme 28. Synthesis of methyl-3-arylaminobenzo[*b*]thiophene-2-carboxylates **30**.

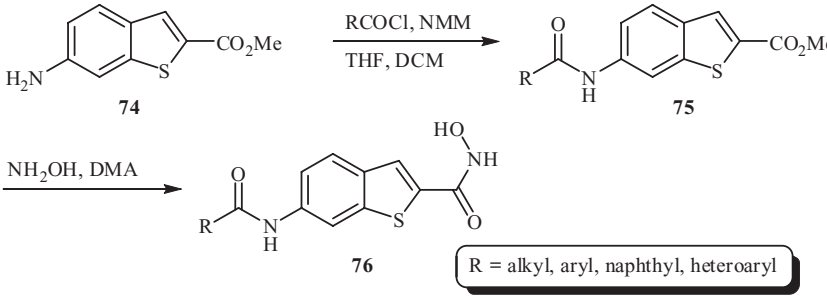
N-Arylation of 6-aminobenzo[*b*]thiophene (**72**) with 2-iodo-9,9-dimethylfluorene under Ullman's condition (*58*) in chlorobenzene as a solvent gave 6-(bis(9,9-dimethylfluorene-2-yl)amino)benzo[*b*]thiophene (**73**) in 75% yield after purification (Scheme 29) (*59*). Compound **72** is also used as a precursor for the production of organic dyes containing bis-dimethylfluorenyl moiety, as dye-sensitized solar cells (*59*).

3.2. *Acylation reactions*

A series of 6-acylaminobenzo[*b*]thiophene-2-hydroxamic acids (**76**) was synthesized from methyl 6-aminobenzo[*b*]thiophene-2-carboxylate (**74**) according to Scheme 30 (*60*). Reaction of **74** with



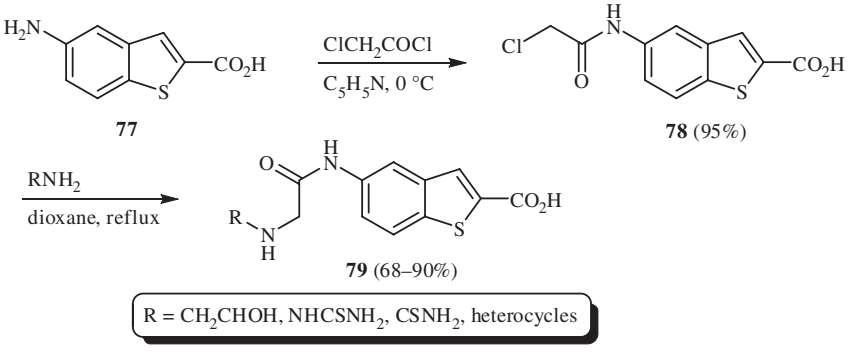
Scheme 29. Synthesis of 6-(bis(9,9-dimethylfluorene-2-yl)amino)benzo[*b*]thiophene (**73**).



Scheme 30. Synthesis of of 6-acylaminobenzo[*b*]thiophene-2-hydroxamic acids (**76**).

various acyl chlorides in a mixture of THF and DCM in the presence of *N*-methylmorpholine for 24 h gave the corresponding 6-acylamino derivatives **75** *in situ* which, on reaction with hydroxylamine in the presence of dimethylamine (DMA), produced the corresponding hydroxamic acid derivatives **76** (*60*).

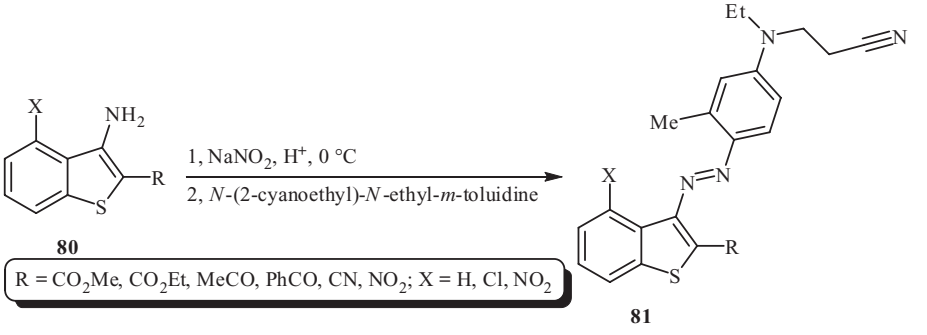
Reaction of 5-aminobenzo[*b*]thiophene-2-caroboxylic acid (**77**) with chloroacetyl chloride in pyridine at 0°C gave the corresponding 5-(2-chloroacetamido)benzo[*b*]thiophene-2-carboxylic acid (**78**; Scheme 31) in 95% yield (*61*). Treatment of **78** with various amines under reflux conditions in dioxane for 8–12 h gave the corresponding 5-acylaminobenzo[*b*]thiophenes **79** in 68–88% yields (Scheme 31). High yields (88–90%) of **79** were also obtained when 1-methylpiperazine and morpholine were used as amines.



Scheme 31. Synthesis of 5-acylaminobenzo[*b*]thiophenes **79**.

3.3. *Azo dyes formation*

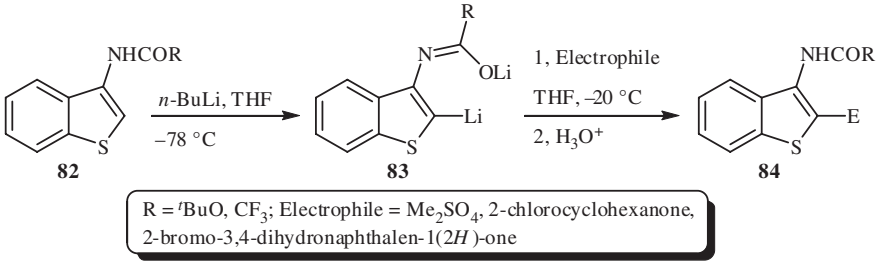
Several monoazo dyes were synthesized from aminobenzo[*b*]thiophenes and have been applied to different types of fibers (*62–69*). For example, diazotization of 3-aminobenzo[*b*]thiophenes **80** with $NaNO_2$ in the presence of an acid at a low temperature (0–5°C) gave the corresponding diazonium salts which on treatment with *N*-(2-cyanoethyl)-*N*-ethyl-*m*-toluidine gave the corresponding azo dyes **81** (Scheme 32) (*62*).



Scheme 32. Synthesis of azo dyes **81**.

3.4. *Directed lithiation*

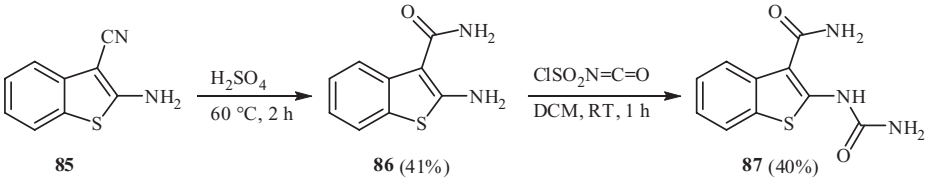
Directed lithiation of 3-(acylamino)benzo[*b*]thiophenes **82** with excess *n*-BuLi (3 mole equivalents) was reported (*70*). It was found that lithiation of **82** with *n*-BuLi in anhydrous THF at -78°C gave the corresponding dilithium intermediates **83** *in situ* which react with various electrophiles at −20°C to give the corresponding 2-substituted derivatives **84** in 24–86% yields (Scheme 33). In the case of reaction of **83** ($R = CF_3$) with 2-chlorocyclohexanone the *cis*-halohydrin 2-(2-chloro-1-hydroxycyclohexy1)-3-(trifluoroacetyl)amino)benzo[*b*]thiophene was obtained in 48% as a result of reaction at the carbonyl group (*70*).



Scheme 33. Synthesis of 2-substituted 3-(acylamino)benzo[*b*]thiophenes **84**.

3.5. *Urea derivatives formation*

Treatment of 2-aminobenzo[*b*]thiophene-3-carbonitrile (**85**) with concentrated H_2SO_4 at 60°C for 2 h gave 2-aminobenzo[*b*]thiophene-3-carboxamide (**86**) in 41% yield (Scheme 34) (*71*).



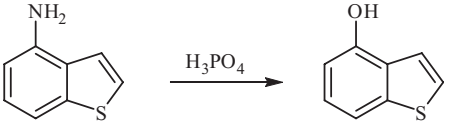
85 **86** (41%) **87** (40%)

Scheme 34. Synthesis of 2-ureidobenzo[*b*]thiophene-3-carboxamide (**87**).

Reaction of **86** with chlorosulfonyl isocyanate in DCM at room temperature for 1 h gave 2-ureidobenzo[*b*]thiophene-3-carboxamide (**87**) in 40% yield (*71*).

3.6. *Formation of hydroxybenzo[b]thiophene*

Hydrolysis of 4-aminobenzo[*b*]thiophene (**43**) in a sealed glass tube which was agitated and heated in an autoclave using highly concentrated phosphoric acid at high temperatures gave 4-hydroxybenzo[*b*]thiophene (**40**; Scheme 35) in 92% yield (*72*). The ratio of H_3PO_4 to **43** was found to be a major factor towards production of a high yield of **40**. The optimum conditions for hydrolysis were found to involve the lowest H_3PO_4 to **43** ratio in which no by-products (*e.g.* benzo[*b*]thiophene) were formed (*72*).

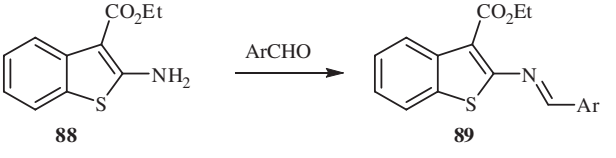


43 **40** (92%)

Scheme 35. Synthesis of 4-hydroxybenzo[*b*]thiophene (**40**).

3.7. *Reactions with aldehydes*

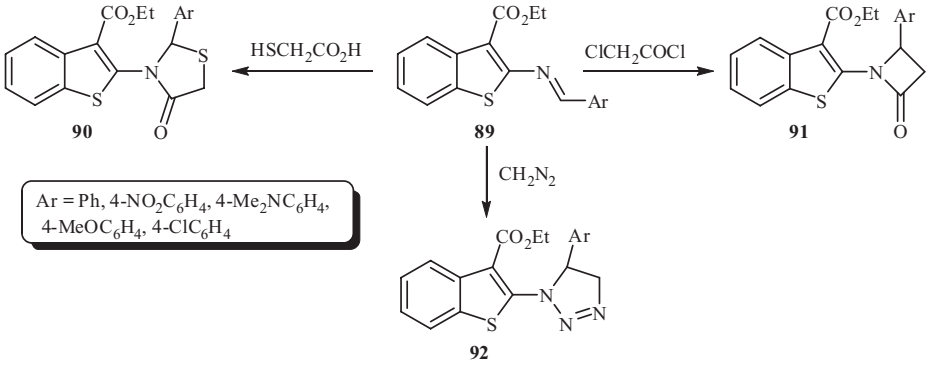
Reaction of ethyl 2-aminobenzo[*b*]thiophene-3-carboxylate (**88**) with various aromatic aldehydes gave the corresponding condensation products **89** (Scheme 36) (*73*).



88 **89**

Scheme 36. Synthesis of condensation products **89**.

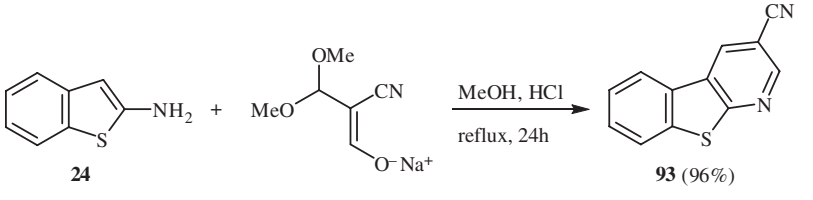
Compounds **89** were used as precursors for the production of various substituted heterocycles (Scheme 37). For example, cyclization reaction of **89** with either 2-mercaptoacetic acid, 2-chloroacetyl chloride or diazomethane gave the corresponding thiazolidinones **90**, β-lactams **91** and triazoles **92**, respectively (*73*).



Scheme 37. Synthesis of compounds **90–92**.

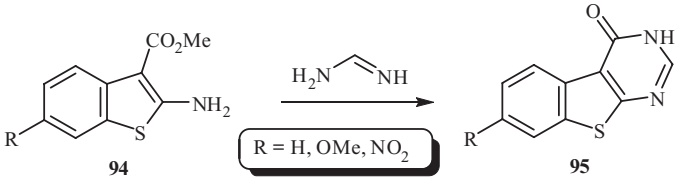
3.8. *Fused heterocycles formation*

Various fused heterocycles have been efficiently synthesized starting from aminobenzo[*b*] thiophenes primarily via cyclocondensation (*74–92*). For example, reaction of 2-aminobenzo[*b*]thiophene (**24**) with an excess of 2-formyl-2,3-dimethoxypropionitrile sodium salt in methanol and in the presence of a catalytic amount of concentrated HCl under reflux conditions for 24 h gave benzo[*b*]thieno[2,3-*b*]pyridine-3-carbonitrile (**93**) in 96% yield (Scheme 38) (*79*).



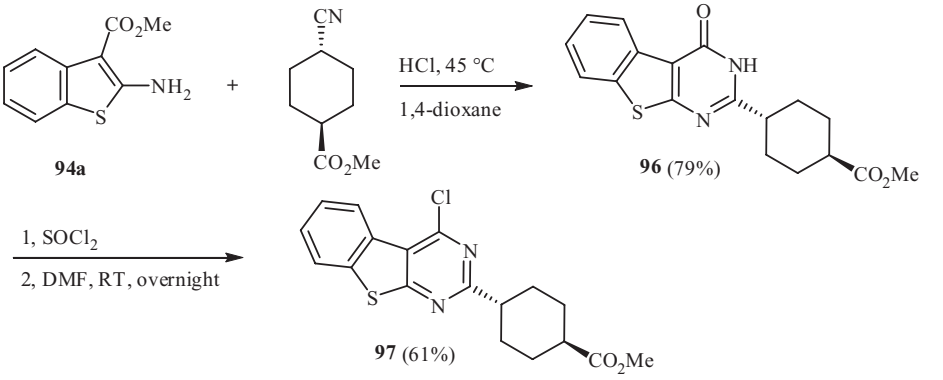
Scheme 38. Synthesis of benzo[*b*]thieno[2,3-*b*]pyridine-3-carbonitrile (**93**).

Various benzothieno[3,2-*d*]pyrimidinones **95** were synthesized from reactions of methyl 3-aminobenzo[*b*]thiophene-2-carboxylates **94** with formamidine (Scheme 39) (*80*).



Scheme 39. Synthesis of benzothieno[3,2-*d*]pyrimidinones **95**.

Reaction of methyl 2-aminobenzo[*b*]thiophene-3-carboylate (**94a**; R = H) with methyl *trans*-4-cyanocyclohexanecarboxylate in 1,4-dioxane in the presence of HCl gas at 45°C for 15 h gave 4-(benzothieno[2,3-*d*]-3*H*-4-oxopyrimidin-2-yl)cyclohexanecarboxylate (**96**) in 79% yield (Scheme 40) (*81*). Treatment of **96** with thionyl chloride at room temperature gave the corresponding chloro derivative **97** in 61% yield (Scheme 40).



Scheme 40. Synthesis of compounds **96** and **97**.

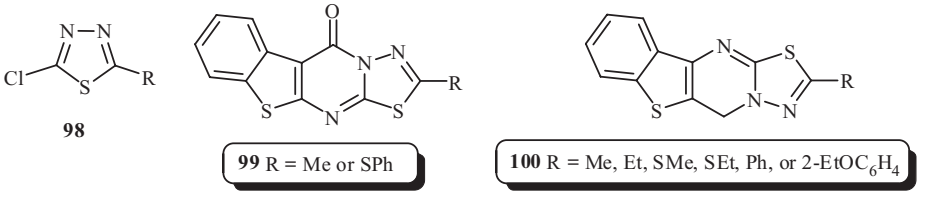
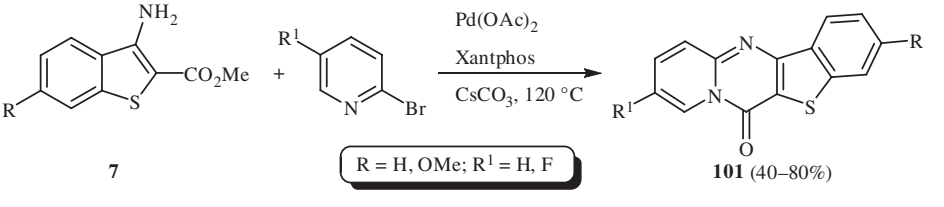


Figure 2. Structures of compounds **98**–**100**.

Cyclocondensation of 5-substituted-2-chloro-1,3,4-thiadiazoles **98** with ethyl 2-aminobenzo[*b*]thiophene-3-carboxylate at 160°C gave the corresponding 10*H*-benzothieno[2,3-*d*][1,3,4]-thiadiazolo[3,2-*a*]pyrimidin-10-ones **99** (Figure 2) (*82*). Similarly, 5*H*-benzothieno[3,2-*d*][1,3,4]-thiadiazolo[3,2-*a*]pyrimidin-5-ones **100** (Figure 2) were obtained from cyclocondensation of 3-aminobenzo[*b*]thiophene-2-carboxylate with **98** (*82*).

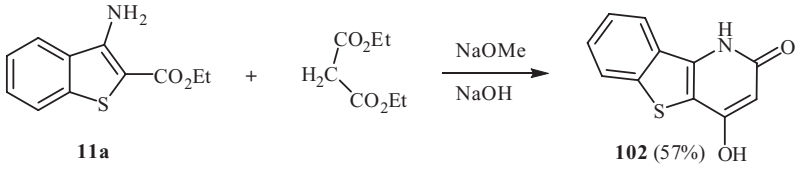
Methyl 3-aminobenzo[*b*]thiophene-2-carboxylates **7** underwent cyclocondensation reactions with 2-bromopyridines, in the presence of palladium acetate, Xantphos and $CsCO_3$ at 120°C for 2–22 h to give the corresponding benzothieno[3,2-*d*]pyrido[1,4-*a*]pyramid-6-ones **101** in 40–80% yields (Scheme 41) (*56*). The reaction involves a C–N coupling and intramolecular cyclization.



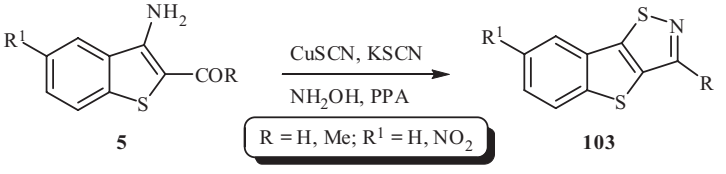
Scheme 41. Synthesis of benzothieno[3,2-*d*]pyrido[1,4-*a*]pyramid-6-ones **101**.

Reaction of ethyl 3-aminobenzo[*b*]thiophene-2-carboxylate (**11a**) with diethyl malonate in an alkaline medium gave benzothienopyridine **102** in 57% (Scheme 42) (*83*).

Treatment of 3-aminobenzo[*b*]thiophenes **5** with a mixture of copper and potassium thiocyanates in the presence of hydroxylamine and PPA gave the corresponding isothiazole derivatives **103** (Scheme 43) (*83*).

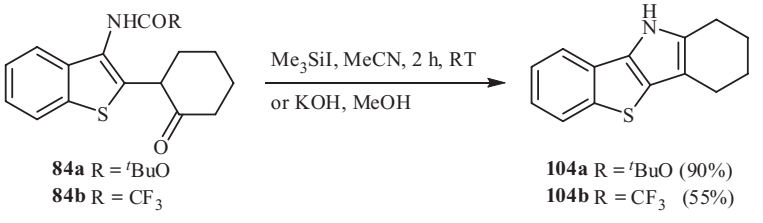


Scheme 42. Synthesis of benzothienopyridine **102**.

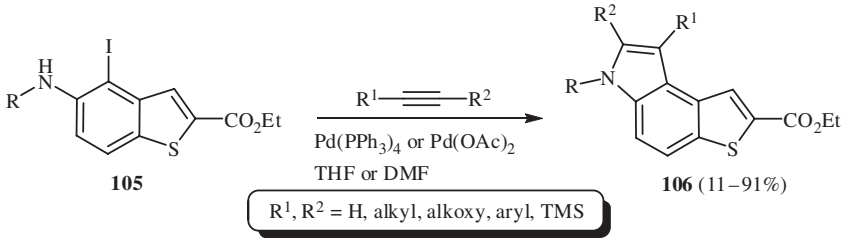


Scheme 43. Synthesis of isothiazole derivatives **103**.

Treatment of **84a**,**b** (see Scheme 33) with iodotrimethylsilane in MeCN or potassium hydroxide in methanol gave the corresponding 1,2,3,4-tetrahydro-10*H*-benzo[*b*]thieno[3,2-*b*]indoles **104a,b** in 90% and 55% yields, respectively (Scheme 44) (*70*).



Scheme 44. Synthesis of 1,2,3,4-tetrahydro-10*H*-benzo[*b*]thieno[3,2-*b*]indoles **104a,b**.

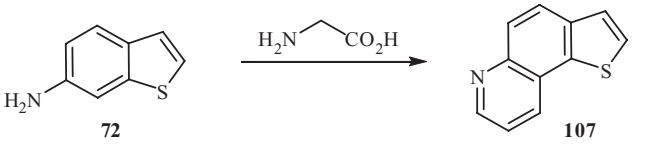


Scheme 45. Synthesis of substituted thieno[3,2-*e*]indoles **106**.

Cyclization reactions of 5-aminobenzothiophenes **105** with internal and terminal acetylenes gave the corresponding substituted thieno[3,2-*e*]indoles **106** (Scheme 45) (*84, 85*). 7-Substituted thieno[3,2-*e*]indoles **106** (Scheme 45) were efficiently synthesized in a one-pot procedure from 4-iodo-5-(methylsulfonamido)benzothiophene (**105**; R = Ms) and terminal alkynes using $Pd(PPh_3)_4$ as a catalyst in THF and in the presence of CuI and *iso*-propylamine (*84, 85*). The indole ring formation requires coupling of terminal alkynes onto the benzo[*b*]thiophene ring system via Sonogashira coupling (*86, 87*) followed by cyclization reaction to give **106**. Reaction of 5-amino-4-iodobenzo[*b*]thiophene (**105**; R = H) with internal alkynes, using $Pd(OAc)_2$

as a catalyst in DMF at 100°C and in the presence of tetrabutylammonium fluoride and a base under Larock's heterocyclization reaction conditions (*89–92*) gave 7,8-disubstituted thieno[3,2-*e*]indoles **106** (*84*).

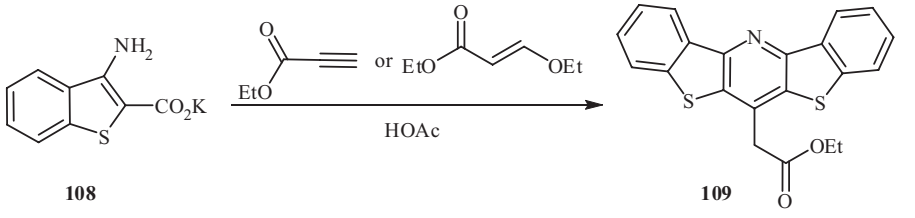
Reaction of 6-aminobenzo[*b*]thiophene (**72**) with glycine under Skraup reaction conditions gave thieno[2,3-*f*]quinoline (**107**; Scheme 46) (*91*).



72 **107**

Scheme 46. Synthesis of thieno[2,3-*f*]quinoline (**107**).

Ethyl 2-(6,12dihydro-bis[1]benzothieno[3,2-*b*:2',3'-*e*]pyridine-6-yl)acetate (**109**; Scheme 47) was obtained as the main product from heating the potassium salt of 3-aminobenzo[*b*]thiophene-2-carboxylate (**108**) with ethyl propiolate or ethyl 3-ethoxyacrylate in acetic acid as a solvent (*92*).



108 **109**

Scheme 47. Synthesis of ethyl 2-(6,12dihydro-bis[1]benzothieno[3,2-*b*:2′,3′-*e*]pyridine-6-yl) acetate (**109**).

4. Biological activities

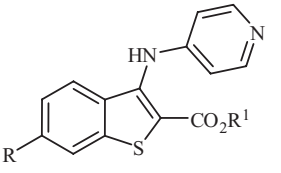
2-Dimethylamino-6-hydroxybenzo[*b*]thiophene derivatives are important intermediates in the synthesis of the selective estrogen receptor modulator, raloxifene, and its analogues (*93–96*). Compounds **4** (Scheme 1) inhibit cancer cell growth at the subnanomolar concentration and potently inhibited the binding of [^{3}H]colchicine to tubulin (*7*). Compounds **79** (Scheme 31) were found to have potent anti-inflammatory activity (*61*).

Hydroxamic acids **76** (Scheme 30) could be used to treat cancer (*60*). They are useful in treating patients having a tumor characterized by proliferation of neoplastic cells. They are useful in the prevention and treatment of RTX-mediated diseases, such as autoimmune, allergic and inflammatory diseases (*60*). Also, they are used to prevent and/or treat diseases of the central nervous system such as neurodegenerative diseases (*60*).

Compounds of the general formula **109** (Scheme 47) are useful as inhibitors of IKK-β phosphorylation of Ikβ. Such compounds block pathological activation of transcription factor NF-Kβ in which diseases excessive activation of NF-Kβ is implicated (*71*).

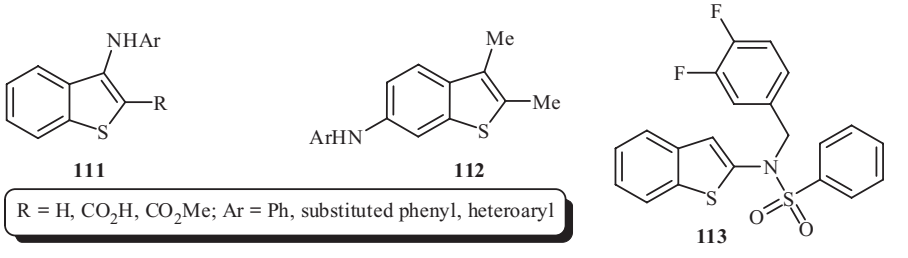
Compounds **110** (Figure 3) are used to treat allergy, asthma, rhinitis, dermatitis, β-cell lymphomas, tumors and diseases associated with bacterial, rhinovirius or respiratory syncytial virus infections (*97*).

Compounds **111** and **112** (Figure 4) were found to show antioxidant activities (*98*). The sulfonamide (**113**; Figure 4) acts as a modulator of the TRPM8 receptor (*99*). It is used to treat various



110 R = H, F, CF_3; R^1 = H, Et

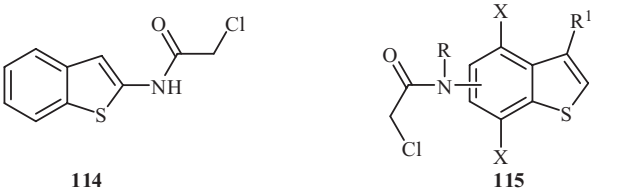
Figure 3. Structures of compounds **110**.



111 **112** **113**

R = H, CO_2H, CO_2Me; Ar = Ph, substituted phenyl, heteroaryl

Figure 4. Structures of compounds **111–113**.



114 **115**

R = H, Me, Et, ^{i}Pr, CH_2=CH-, cyclopropyl; R^1 = Ph, NO_2; X = Br, I

Figure 5. Structures of compounds **114** and **115**.

diseases, syndromes and disorders, including those that cause inflammatory or neuropathic pain (*99*) The inflammatory pain could be, for example, due to inflammatory bowel disease, visceral pain, osteoarthritis, rheumatoid arthritis, back pain, joint pain, abdominal pain, labor, musculoskeletal diseases, skin diseases, toothache, eczema, irritable bowel syndrome, chronic pain syndrome, chronic fatigue syndrome or post-mastectomy pain syndrome.

N-Benzothienylchloroacetamides **114** and **115** (Figure 5) are used as herbicides, particularly as pre-emergent herbicides (*100*).

5. Conclusions

The chemistry of aminobenzo[*b*]thiophenes has exhibited promise on a number of fronts; the full evaluation of its utility in heterocycles synthesis was not sufficiently investigated. The aim of this review was to demonstrate the wide applications of such compounds in organic synthesis and in medicinal chemistry.

Aminobenzo[*b*]thiophenes could be synthesized efficiently via Buchwald–Hartwig coupling using a palladium catalytic system and Willgerodt–Kindler routes using primary and secondary

amines, nucleophilic reaction followed by Thorpe–Ziegler cyclization and arylation reactions with electron-deficient aryl halides. Other syntheses involve a nitro group displacement of benzonitriles by a thiol anion followed by cyclization. Reactions of aminobenzo[*b*]thiophenes take place mostly on the amino group such as arylation, acylation, azo dyes formation, production of ureas, deamination and condensation reactions. Also, acylamino moieties can be used as directing metallating groups and/or activators to direct lithiation to the *ortho*-position to produce the corresponding lithium reagents which on reactions with electrophiles would produce the corresponding substituted derivatives. Several heterocycles containing a benzothiophene moiety show various useful biological activities.

References

(1) Bastrakov, M.A.; Starosotnikov, A.M.; Shevelev, S.A. *Arkivoc* **2009,** (*iv*), 88–114.
(2) Kirsch, G.; Hesse S.; Comel, A. *Curr. Org. Synth*. **2004,** *1*, 47–63.
(3) Grinev, A.N.; Kharizomenova, I.A.; Kapustina, M.V.; Sheinker, Yu.N.; Alekseeva, Rubtsov, N.M.; Kuleshova, E.F. *Khim. Geterotsiklich. Soedin*. **1986,** *9*, 1178–1180; *Chem. Abstr*. **1986,** *107*, 39544.
(4) Beck, J.R. *Tetrahedron* **1978,** *34*, 2057–2068.
(5) Nakayama, J. In *Comprehensive Heterocyclic Chemistry II: Thiophenes and Their Benzo Derivatives*; Bird, C.W., Ed.; Elsevier Science: Oxford, 1996; Vol. 2.
(6) Beck, J.R. *J. Heterocycl. Chem.* **1978,** *15*, 513–514.
(7) Romagnoli, R.; Baraldi, P.G.; Carrion, M.D.; Cara, C.L.; Preti, D.; Fruttarolo, F.; Pavani, M.G.; Tabrizi, M.A.; Tolomeo, M.; Grimaudo, S.; Di Cristina, A.; Balzarini, J.; Hadfield, J.A.; Brancale, A.; Hamel, E. *J. Med. Chem.* **2007,** *50*, 2273–2277.
(8) Romagnoli, R.; Baraldi, P.G.; Jung, M.K.; Iaconinoto, M.A.; Carrion, M.D.; Preti, D.; Tabrizi, M.A.; Fruttarlo, F.; De Clercq, E.; Balzarini, J.; Hamel, E. *Bioorg. Med. Chem. Lett*. **2005,** *15*, 4048–4052.
(9) Offer, J.; Boddy, C.N.C.; Dawson, P.E. *J. Am. Chem. Soc*. **2002,** *124*, 4642–4646.
(10) Beck, J.R.; Yahner, A. *J. Org. Chem*. **1974,** *39*, 3440–3441.
(11) Bauer, L.; Welsh, T.L. *J. Org. Chem*. **1961,** *26*, 1443–1445.
(12) Beck, J.R.; Yahner, J.A. *J. Org. Chem.* **1973,** *38*, 2450–2452.
(13) Beck, J.R. *J. Org. Chem*. **1972,** *37*, 3224–3226.
(14) Dalinger, I.L.; Cherkasova, T.I.; Khutoretskii, V.M.; Shevelev, S.A. *Mendeleev Commun.* **2000,** 72–73.
(15) Zlotin, S.G.; Kislitsin, P.G.; Kucherov, F.A.; Gakh, A.A. *Heterocycles* **2006,** *68*, 1109–1119.
(16) Bridges, A.J.; Zhou, H. *J. Heterocycl. Chem*. **1997,** *34*, 1163–1172.
(17) Roos, E.; Wagner, K. Ger. Offen. DE, 1901291, 1970; *Chem. Abstr*. **1970,** *73*, 89236.
(18) Conrad, P.C.; Gardner, J.P. PCT Int. Appl. WO, 018364, 2002; *Chem. Abstr.* **2002,** *136*, 216640.
(19) Zbryev, O.I.; Stiasni, N.; Kappe, C.O. *J. Comb. Chem.* **2003,** *5*, 145–148.
(20) Solovyev, A.Y.; Androsov, D.A.; Neckers, D.C. *J. Org. Chem*. **2007,** *72*, 3122–3124.
(21) Gewald, K.; Schinke, E.; Böettcher, H. *Chem. Ber*. **1966,** *99*, 94–100.
(22) Stacy, G.W.; Villaescusa, F.W.; Wollner, T.E. *J. Org. Chem*. **1965,** *30*, 4074–4078.
(23) Harnish, D.P.; Tarbell, D.S. *J. Am. Chem. Soc*. **1948,** *70*, 4123–4127.
(24) Takeuchi, K.; Kohn, T.J.; Sall, D.J.; Denney, M.L.; McCowan, J.R.; Smith, G.F.; Gifford-Moore, D.S. *Bioorg. Med. Chem. Lett.* **1999,** *9*, 759–764.
(25) Ablenas, F.J.; George, B.E.; Maleki, M.; Jain, R.; Hopkinson, A.C.; Lee-Ruff, E. *Can. J. Chem.* **1987,** *65*, 1800–1803.
(26) Gulevskaya, V.I.; Kuvshinov, A.M.; Shevelev, S.A. *Heterocycl. Commun.* **2001,** *7*, 283–287.
(27) Benincori, T.; Sannicolò, F. *J. Org. Chem*. **1988,** *53*, 1309–1312.
(28) Van Zyl, G.; Bredeweg, C.J.; Rynbrandt, R.H.; Neckers, D.C. *Can. J. Chem*. **1966,** *44*, 2283–2289.
(29) Fieser, L.F.; Kennelly, R.G. *J. Am. Chem. Soc*. **1935,** *57*, 1611–1616.
(30) Martin-Smith, M.; Gates, M.J. *J. Am. Chem. Soc*. **1956,** *78*, 5351–5357.
(31) Ferreira, I.C.F.R.; Queiroz, M.-J.R.P.; Kirsch, G. *Tetrahedron* **2002,** *58*, 7943–7949.
(32) Bordwell, F.G.; Stange, H. *J. Am. Chem. Soc*. **1955,** *77*, 5939–5944.
(33) Bonini, C.; Funicello, M.; Scialpi, R.; Spagnolo, P. *Tetrahedron* **2003,** *59*, 7515–7520.
(34) Grinev, A.N.; Kharizomenova, I.A.; Kapustina, M.V.; Sheinker, Yu.N.; Alekseeva, L.M.; Rubtsov, N.M.; Kuleshova, E.F. *Khim. Geterotsikl. Soedin*. **1986,** 1178–1180; *Chem. Abstr*. **1987,** *107*, 39544.
(35) Hartwig, J.F. *Synlett* **1997,** 329–340.
(36) Yang, B.H.; Buchwald, S.L. *J. Organomet. Chem*. **1999,** *576*, 125–146.
(37) Muci, A.R.; Buchwald, S.L. *Top. Curr. Chem*. **2002,** *219*, 131–209.
(38) Buchwald, S.L., Mauger, C.; Mignani, G.; Scholz, U.I. *Adv. Synth. Catal.* **2006,** *348*, 23–39.
(39) Silva, N.O.; Abreu, A.S.; Ferreira, P.M.T.; Monteiro, L.S.; Queiroz, M.-J.R.P. *Eur. J. Org. Chem*. **2002,** 2524–2528.
(40) Queiroz, M.-J.R.P.; Ferreira, I.C.F.R.; Calhelha, R.C.; Estevinho, L.M. *Bioorg. Med. Chem*. **2007,** *15*, 1788–1794.
(41) Ferreira, I.C.F.R.; Queiroza, M.-J.R.P.; Kirsch, G. *Tetrahedron* **2003,** *59*, 975–981.
(42) Surange, S.S.; Rajappa, S. *Tetrahedron Lett*. **1998,** *39*, 7169–7172.

(43) Brower, K.R.; Amstutz, E.D. *J. Org. Chem.* **1954,** *19*, 411–414.
(44) Grandclaudon, P.; Lablache-Combier, A. *J. Org. Chem*. **1978,** *43*, 4379–4381.
(45) Toselli, M.; Spagnolo, P.; Zanirato, P. *Gazz. Chim. Ital*. **1989,** *119*, 411–413.
(46) Zanirato, P. *Arkivoc* **2009,** *(i)*, 97–128.
(47) Chinchilla, R.; Najera, C.; Yus, M. *Arkivoc* **2007,** *(x)*, 152–231.
(48) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Amsterdam, 2002.
(49) Wakefield, B.J. *Organolithium Methods in Best Synthetic Methods*; Katritzky, A.R., Meth-Cohn, O., Rees, C.W., Eds.; Academic: Orlando, **1988**.
(50) Friedlander, P. *Justus Liebigs Ann. Chem*. **1907,** *351*, 390–420.
(51) Hartough, H.D.; Meisel, S.L. *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Ed.; Interscience: New York, 1954.
(52) Iddon, B.; Scrowston, R.M. *Adv. Heterocycl. Chem*. **1970,** *11*, 177–381.
(53) Carrington, D.E.L.; Clarke, K.; Scrowston, R.M. *Tetrahedron Lett*. **1971,** *12*, 1075–1078.
(54) Vesterager, N.O.; Pedersen, E.B.; Lawesson, S.-O. *Tetrahedron* **1973,** *29*, 321–329.
(55) Vesterager, N.O.; Dyrnesli, R.; Pedersen, E.B.; Lawesson, S.-O. *Synthesis* **1972,** 548.
(56) Queiroz, Maria-Joao R.P.; Calhelha, R.C.; Kirsch, G. *Tetrahedron* **2007,** *63*, 13000–13005.
(57) Queiroz, M.-J.R.P.; Begouin, A.; Ferreira, I.C.F.R.; Kirsch, G.; Calhelha, R.C.; Barbosa, S.; Estevinho, L.M. *Eur. J. Org. Chem.* **2004,** 3679–3685.
(58) Bushby, R.J.; McGill, D.R.; Ng, K.M.; Taylor, N. *J. Mater. Chem*. **1997,** *7*, 2343–2354.
(59) Choi, H.; Lee, J.K.; Song, K.; Kanga, S.O.; Ko, J. *Tetrahedron* **2007,** *63*, 3115–3121.
(60) Miller, T.A.; Witter, D.J.; Belvedene, S. PCT Inl. Appl. WO, 034880, 2005; *Chem. Abstr*. **2005,** *142*, 392278.
(61) Radwan, M.A.A.; Shehab, M.A.; El-Shenawy, S.M. *Monatsch. Chem.* **2009,** *140*, 445–450.
(62) Hallas, G.; Towns, A.D. *Dyes Pigm.* **1997,** *35*, 219–237.
(63) Hallas, G.; Towns, A.D. *Dyes Pigm.* **1996,** *31*, 273–289.
(64) Maradiya, H.R.; Patel, V.S. *Int. J. Polym. Mater*. **2001,** *49*, 295–309.
(65) Maradiya, H.R.; Patel, V.S. *Adv. Col. Sci. Technol*. **2001,** *4*, 54–58.
(66) Maradiya, H.R.; Patel, V.S. *Khim. Geterotsikli. Soedin.* **2002,** *38*, 281–286; *Chem. Abstr*. **2003,** *138*, 14683.
(67) Maradiya, H.R.; Patel, V.S. *Khim. Geterotsikli. Soedin.* **2003,** *39*, 357–363; *Chem. Abstr*. **2003,** *39*, 351751.
(68) Rangnekar, D.W.; Jhaveri, P.V. *Indian J. Fibre Text. Res*. **1990,** *15*, 26–29.
(69) Kamel, M.; Allam, M.A.; Al-Aref, S.; Al-Aref, A.T. *Egypt. J. Chem*. **1973,** *16*, 49–68; *Chem. Abstr*. **1974**, *80*, 97319.
(70) Prats, M.; Gálves, C.; Gasanz, Y.; Rodriguez, A. *J. Org. Chem*. **1992,** *57*, 2184–2188.
(71) Callahan, J.F.; Wan, Z. PCT Int. Appl. WO, 104219, 2003; *Chem. Abstr*. **2004,** *140*, 27756.
(72) Boswell, D.E.; Brennan, J.A.; Landis, P.S. *Tetrahedron Lett.* **1970,** *11*, 5265–5266.
(73) Bayoumy, B.E.-S. *Polish J. Chem*. **1991,** *65*, 1403–1407.
(74) Rajasekharan, K.N.; Thomas, L. *Indian J. Chem*. **1983,** *22B*, 76–77.
(75) Gravier, D.; Hou, G.; Casadebaig, F.; Dupin, J.P.; Bernard, H.; Boisseau, M. *Pharmazie* **1992,** *47*, 754–757.
(76) Ammar, Y.A.; Ismail, M.M.F.; El-Gaby, M.S.A.; Zahran, M.A. *Indian J. Chem*. **2002,** *41B*, 1486–1491.
(77) Muchiri, D.R.; Midgley, J.M. *J. Kenya Chem. Soc*. **1999,** *1*, 5–9; *Chem. Abstr*. **2007,** *147*, 301012.
(78) Schneller, S.W.; Clough, F.W. *Heterocycles* **1975,** *3*, 135–138.
(79) Levacher, V.; Boussad, N.; Dupas, G.; Bourguignon, J.; Quéguiner, G. *Tetrahedron* **1992,** *48*, 831–840.
(80) Bridges, A.J.; Zhou, H. *J. Heterocycl. Chem*. **1997,** *34*, 1163–1172.
(81) Juraszyk, H.; Wendel, P.; Woissyk, M. Ger. Offen. De, 19958926, 2001; *Chem. Abstr*. **2001,** *135*, 19661.
(82) Russo, F.; Santagati, A.; Santagati, M.; Caruso, A.; Trombadore, S.; Amico-Roxas, M. *Farmaco* **1987,** *42*, 437–447; *Chem. Abstr*. **1987,** *107*, 146825.
(83) Clark, K.; Fox, W.R.; Scrowston, R.M. *J. Chem. Res. (S)* **1980,** 33.
(84) Van Snick, W.; Dehaen, W. *Tetrahedron* **2009,** *65*, 8497–8501.
(85) Van Snick, W.; Nulens, W.; Jambon, S.; Dehaen, W. *Synthesis* **2009,** 767–774.
(86) Chinchilla, R.; Nájera, C. *Chem. Rev*. **2007,** *107*, 874–922.
(87) Alonso, F.; Beletskaya, I.P.; Yus, M. *Chem. Rev*. **2004,** *104*, 3079–3160.
(88) Müller, T.E.; Hultzsch, K.C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev*. **2008,** *108*, 3795–3892.
(89) Larock, R.C.; Yum, E.K. *J. Am. Chem. Soc*. **1991,** *113*, 6689–6690.
(90) Larock, R.C.; Yum, E.K.; Refvik, M.D. *J. Org. Chem*. **1998,** *63*, 7652–7662.
(91) Sauter, F.; Jordis, U.; Tanyolac, S. *Sci. Pharm.* **1988,** *56*, 73–80; *Chem. Abstr*. **1989,** *110*, 75358.
(92) Goerlitzer, K.; Meyer, H. *Pharmazie* **2004,** *59*, 673–675.
(93) Grese, T.A.; Pennington, L.D.; Sluka, J.P.; Adrian, M.D.; Cole, H.W.; Fuson, T.R.; Magee, D.E.; Phillips, D.L.; Rowley, E.R.; Shetler, P.K.; Short, L.L.; Venugopalan, M.; Yang, N.N.; Sato, M.; Glasebrook, A.L.; Bryant, H.U. *J. Med. Chem.* **1998,** *41*, 1272–1283.
(94) Grese, T.A.; Cho, S.; Finley, D.R.; Godfrey, A.G.; Jones, C.D.; Lugar, C.; Martin, M.; Matsumoto, K.; Pennington, L.; Winter, M.A.; Adrian, M.D.; Cole, H.W.; Magee, D.E.; Phillips, D.L.; Rowley, E.R.; Short, L.L.; Glasebrook, A.L.; Bryant, H.U. *J. Med. Chem.* **1997,** *40*, 146–167.
(95) Lee, K.C.; Moon, B.C.; Lee, J.H.; Chung, K.-H.; Katzenellenbogen, J.A.; Chi, D.Y. *Bioorg. Med. Chem.* **2003,** *11*, 3649–3658.
(96) Takeuchi, K.; Kohn, T.J.; Sall, D.J.; Denney, M.L.; McCowan, J.R.; Smith, G.F.; Gifford-Moore, D.S. *Bioorg. Med. Chem.* **1999,** *9*, 759–764.

(97) Merriman, G.H.; Weintraub, P.M.; Sabol, J.S.; Dharanipragada, R.; Hrib, N.J.; Jurcak, J.G.; Gross, A.; Whiteley, B.; Musick, K.Y.; Klein, J.T. PCT Int. Appl. WO, 091215; 2003; *Chem. Abstr*. **2003,** *139*, 364826.
(98) Abreu, R.M.V.; Ferreira, I.C.F.R.; Queiroz, M.J.R.P. *Eur. J. Med. Chem*. **2009,** *44*, 1952–1958.
(99) Branum, S.T.; Colburn, R.W.; Dax, S.L.; Flores, C.M.; Jetter, M.C.; Liu, Yi; Ludovici, D.; Macielag, M.J.; Matthews, J.M.; Mcnally, J.J.; Reaney, L.M.; Russell, R.K.; Qin, N.; Wells, K.M.; Youells, S.C.; Youngman, M.A. PCT Int. Appl. WO, 012430, 2009; *Chem. Abstr*. **2009,** *150*, 168153.
(100) Driscoll, P.R.; Kaufman, H.A. US Patent, 3495967, 1970; *Chem. Abstr*. **1970,** *72*, 90268.