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Efficient Access to 2-Aryl-3-Substituted Benzo[*b*]thiophenes

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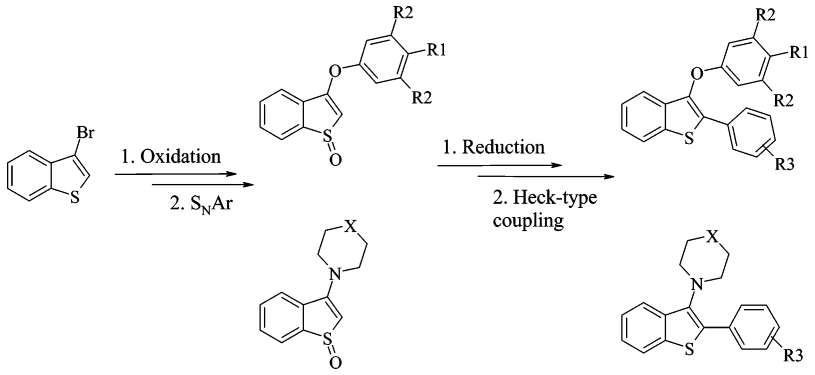
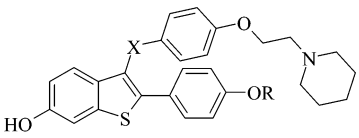


Benzo[*b*]thiophene derivatives are important in part because of their use as selective estrogen receptor modulators. They are usually synthesized by intramolecular cyclization. Here, we propose a method for the synthesis of 2-arylbenzo[*b*]thiophenes with heteroatoms at the 3-positions directly from the benzo[*b*]thiophene core by using an aromatic nucleophilic substitution reaction and Heck-type coupling. This methodology provides 2-aryl-3-amino or phenoxybenzo[*b*]thiophenes in about 35% overall yield in 5 steps.

Introduction

The effect of naturally occurring estrogens, such as 17β-estradiol, on numerous tissues has been recognized for a long time. The declining levels of estrogens during and after menopause have been connected to a large number of post-menopausal pathologies, not only osteoporosis[1] but also cardiovascular diseases, depression and schizophrenia, and Alzheimer's disease.[2] Hormone replacement therapy can restore estrogen levels; therefore, it reduces the risks associated with these pathologies, but it has also been linked to an increased risk of hormone dependent cancers along with numerous side effects. Therefore, researchers have focused on the development of treatment alternatives to better satisfy this medical need.[3] Several synthetic molecules have been described as selective estrogen receptor modulators (SERMs).[4] These molecules antagonize the effects of estrogen on reproductive tissues while mimicking the effects of estrogen on bone and the cardiovascular system.[5] The combination of these effects is thought to provide a uniquely advantageous therapeutic profile for the post-menopausal female population.



X = CO; R = H : Raloxifene
X = O; R = Me : Arzoxifene

FIGURE 1. Structures of Raloxifene and Arzoxifene.

A few years ago, particular interest was given to the synthesis of SERM analogues, such as Raloxifene and Arzoxifene (Figure 1).

In fact, Raloxifene, a 2-arylbenzo[*b*]thiophene, is already commercially available for the prevention of os-

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teoporosis. A structure−activity relationship study showed that the replacement of the carbonyl group with an oxygen resulted in a 10-fold increase in antiestrogen potency both in vivo and in vitro.[6] In addition, the methoxy analogue, Arzoxifene, has improved bioavailability compared with that of Raloxifene.[7] Arzoxifene is currently under investigation as a breast cancer therapy in advanced disease.[8]

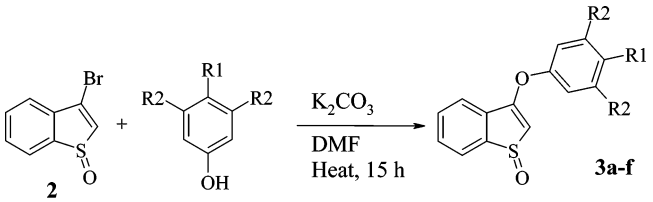
Substituted 2-arylbenzo[*b*]thiophenes are usually synthesized by multistep intramolecular cyclization of thiophenol derivatives, according to the procedures of Kost,[9] De,[10] and Flynn.[11] Nevertheless, these methods often require many steps as well as acidic and/or basic conditions which are not compatible with sensitive functional groups. Surprisingly, little interest has been given to direct access to substituted 2-arylbenzo[*b*]thiophenes from benzo[*b*]thiophene. This paper describes a new and rapid route to Arzoxifene analogues with heteroatoms at the 3-positions. This synthetic approach is based on the nucleophilic aromatic substitution (S_NAr) of 3-bromobenzo[*b*]thiophene followed by a one-step Heck-type coupling of the corresponding 3-substituted benzo[*b*]-thiophenes with aryl halides.[12,13]

Results and Discussion

S_NAr. Few methods are described for the introduction of an heteroatom at the 3-position of the benzo[*b*]-thiophene core. Although Netchitailo[14] synthesized 3-methoxybenzo[*b*]thiophene by reaction of sodium methoxide with 3-bromobenzo[*b*]thiophene, the reaction failed with other substrates, such as phenol derivatives. The synthesis of 3-(*p*-methoxyphenoxy)benzo[*b*]thiophene by the copper iodide-catalyzed reaction of 3-bromobenzo[*b*]-thiophene was reported with a very low yield.[15]

The Buchwald copper iodide-catalyzed amination[16] and etherification[17] of aryl iodides and the Nolan[18] amination reaction of aryl halides were tested on 3-bromobenzo[*b*]-thiophene. Unfortunately, they both failed. Following a method described by our laboratory,[19] we used a copper-catalyzed aromatic nucleophilic substitution of 3-bromobenzo[*b*]thiophene by 2,2,2-trifluoroethanol to produce 3-(2,2,2-trifluoroethoxy)benzo[*b*]thiophene **1** in a 54% yield. Nevertheless, assays with other nonfluorinated alcohols, such as methanol, *n*-butanol, phenol, and benzyl alcohol, failed.

SCHEME 1. Synthesis of 3-Phenoxybenzo[*b*]thiophene 1-Oxides



$R_1 = R_2 = OMe$
or R_1 = H, OMe, F, Cl, CN and R_2 = H

As 3-bromo-2-nitrobenzo[*b*]thiophene reacted, probably by an S_NAr mechanism,[20] with neutral and anionic nucleophiles to give the expected 3-amino-2-nitrobenzo-[*b*]thiophene, the activation of 3-bromobenzo[*b*]thiophene seemed to be necessary. For the synthesis of Arzoxifene and its derivatives, 2-aryl-3-bromobenzo[*b*]thiophene 1-oxides underwent an S_NAr reaction with both phenol and thiophenol derivatives.[6] Recently, De Nanteuil et al.[21] performed the substitution of 2-carboxaldehyde-3-chloro-5,6-disubstituted benzo[*b*]thiophenes with various phenols. Therefore, we assumed that an electron-withdrawing group at the 2-position of 3-bromobenzo[*b*]thiophene as well as its oxidation into the corresponding sulfoxide favors the nucleophilic displacement of bromide by decreasing the charge density at the 3-position and increasing the stabilization of the intermediate (probably a Meisenheimer-like intermediate).

The use of 3-bromobenzo[*b*]thiophene 1-oxide **2** as the starting material for the S_NAr reaction allowed the direct introduction of various phenols and secondary amines. Commercially available 3-bromobenzo[*b*]thiophene[12] was oxidized at room temperature with hydrogen peroxide in a trifluoroacetic acid and dichloromethane mixture to produce 3-bromobenzo[*b*]thiophene 1-oxide **2** in a yield of 85%.[6]

The S_NAr reaction of compound **2** was then completed with various phenolate salts formed in situ with K_2CO_3 as a base (Scheme 1). Reactions were carried out with 2 equiv of both alcohol and K_2CO_3 in DMF to favor nucleophilic attack (Table 1).

Although total conversions were observed, partial degradation of 3-bromobenzo[*b*]thiophene 1-oxide **2** occurred at high temperature (during the reaction) producing only 60−80% isolated yields. As shown in Table 1, the effectiveness of the S_NAr reaction is influenced by the electronic effects of the phenol substituents. Electron-donating groups worked better than electron-withdrawing groups in terms of the reaction temperatures and

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TABLE 1. Results for the Synthesis of 3-Phenoxybenzo[*b*]thiophene 1-Oxides

entry	product	R_1	R_2	*T* (°C)	isolated yield (%)
1	**3a**	OMe	H	70	80
2	**3b**	OMe	OMe	90	68
3	**3c**	H	H	70	70
4	**3d**	F	H	70	63
5	**3d**	F	H	110	72
6	**3e**	Cl	H	110	73
7	**3f**	CN	H	110	68
8	**3g**	NO_2	H	120	0

SCHEME 2. Synthesis of 3-Aminobenzo[*b*]thiophene 1-Oxides

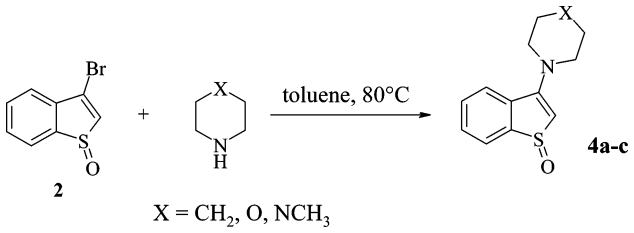

TABLE 2. Results for the Synthesis of 3-Aminobenzo[*b*]thiophene 1-Oxides

entry	product	X	reaction time (h)	isolated yield (%)[a]
1	**4a**	CH_2	2	94[b]
2	**4b**	O	3	85
3	**4b**	O	3	34[c]
4	**4b**	O	3	82[d]
5	**4c**	NCH_3	3	86

[a] At 80 °C in toluene. [b] Obtained after simple extraction. [c] At 100 °C in DMF. [d] At 80 °C in DMF.

yields in accordance with Hammett constants.[22] At an identical temperature (70 °C), the best result was obtained with *p*-methoxyphenol (Table 1, entry 1). Nevertheless, similar yields were obtained with electron deficient phenols in the same reaction time by increasing the temperature (Table 1, entries 5−7). With *p*-nitrophenol (Table 1, entry 8), no conversion was observed at 70 °C in accordance with the strong electron-withdrawing effect of the nitro group (higher Hammett constant, $\sigma_p^+ = 0.78$). At 120 °C, the consumption of 3-bromobenzo[*b*]thiophene 1-oxide **2** was complete, but no expected product was detected. We assumed that a degradation of the sulfoxide **2** occurred at this temperature.

The S_NAr reaction of compound **2** was also carried out with secondary amines and no other base (Scheme 2). With 2 equiv of amine, yields are significantly improved by decreasing the reaction temperature to 80 °C. Indeed, a yield of only 34% was obtained with morpholine at 100 °C in DMF (Table 2, entry 2) versus a yield of about 85% at 80 °C in DMF or toluene (Table 2, entries 3 and 4). At temperatures higher than 80 °C, degradation of 3-aminobenzo[*b*]thiophene 1-oxides **4a**−**c** was observed. Toluene was preferred over DMF because it is easier to remove. In conclusion, lower reaction temperatures associated with shorter reaction times (2−3 h) minimized degradation of 3-bromobenzo[*b*]thiophene 1-oxide **2**. Hence,

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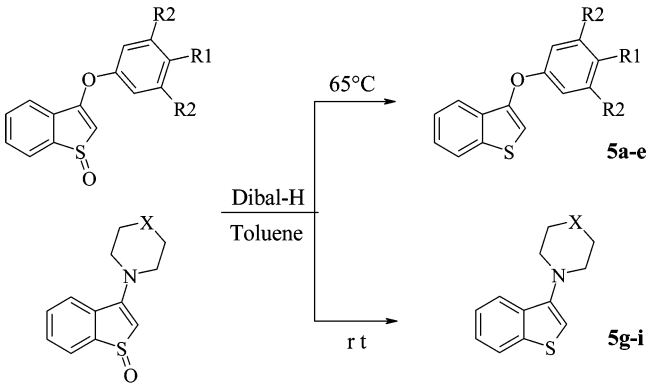
SCHEME 3. Reduction of Sulfoxide Derivatives



3a R_1 = OMe, R_2 = H
3b R_1 = OMe, R_2 = OMe
3c R_1 = H, R_2 = H
3d R_1 = F, R_2 = H
3e R_1 = Cl, R_2 = H

4a X = CH_2
4b X = O
4c X = NCH_3

3-aminobenzo[*b*]thiophene 1-oxides **4a**−**c** were obtained in better yields (85−95%).

After total conversion, **4a** was easily isolated with a 94% yield after extraction and aqueous washing. When flash chromatographies were required (**4b,c**), the use of a neutral silica gel gave the desired products, whereas partial hydrolysis of 3-aminobenzo[*b*]thiophene 1-oxide into benzo[*b*]thiophen-3-one 1-oxide occurred with acidic silica gel. Indeed, it is known that tertiary enamines can be hydrolyzed in acidic medium to give the corresponding ketones.[23] For instance, the acidic hydrolysis of 2-(dimethylamino)-6-methoxybenzo[*b*]thiophene into 6-methoxybenzo[*b*]thiophen-2-one has been reported by Grese et al.[24]

Reduction. When tested with sulfoxide derivatives, no reaction was observed for the catalytic Heck-type coupling. The reduction of sulfoxides using different reducing agents, such as $LiAlH_4$[6] or Dibal-H,[25] has been described. Benzo[*b*]thiophene 1-oxide derivatives **3a**−**e** and **4a**−**c** were generally reduced with total conversion when a slight excess of Dibal-H (1.3 equiv) in anhydrous toluene was added (Scheme 3). Reduced products were obtained in a 60−80% yield (Table 3). 3-Amino derivatives **4a**−**c** were reduced in short times at room temperature (Table 3, entries 9−11), whereas heating at 65 °C for about 5 h was necessary for the reduction of 3-phenoxy derivatives **3a**−**e** (Table 3, entries 1−6). At room temperature, the reduction time of the 3-phenoxy derivatives was greatly increased and conversion was not complete (Table 3, entries 3 and 4).

The reduction of 3-(*p*-cyanophenoxy)benzo[*b*]thiophene 1-oxide **3f** with Dibal-H produced an imine derivative characterized by ^1H and ^{13}C NMR analyses. Purification of this crude product by flash chromatography produced aldehyde **6** and amine **7** in 39% and 33% yields, respec-

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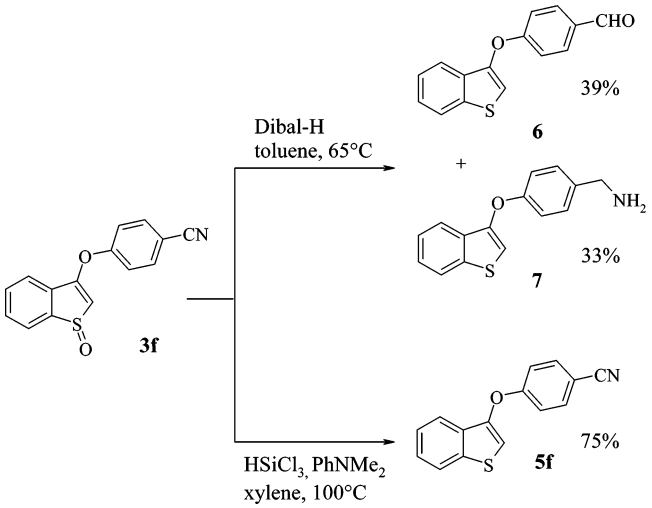
TABLE 3. Reduction of Sulfoxide Derivatives

entry	substrate	product	reaction time (h)	isolated yield (%)[a]
1	**3a**	**5a**	5	81
2	**3b**	**5b**	5	63
3	**3c**	**5c**	5	85
4	**3c**	**5c**	24[b]	–
5	**3d**	**5d**	5	72
6	**3e**	**5e**	5	80
7	**3f**	**6**	5	39[c]
8	**3f**	**7**	5	33[c]
9	**4a**	**5g**	2[b]	72
10	**4b**	**5h**	0.5[b]	75
11	**4c**	**5i**	3[b]	68

[a] At 65 °C with 1.3 equiv of Dibal-H. [b] At room temperature with 1.3 equiv of Dibal-H, no total conversion. [c] With 4 equivs of Dibal-H.

SCHEME 4. Reduction of 3-(*p*-Cyanophenoxy)benzo[*b*]thiophene 1-Oxide



tively (Scheme 4) (Table 3, entries 7 and 8). According to a recent procedure described by Carretero et al.[26] for the reduction of a *tert*-butylsulfoxide group into a *tert*-butylsulfinyl group, a chemoselective sulfoxide reduction of the cyano derivative **3f** was undertaken with a mixture of $HSiCl_3$ and *N,N*-dimethylaniline in xylene[27] to produce 3-(*p*-cyanophenoxy)benzo[*b*]thiophene **5f** in a yield of 75% (Scheme 4).

Coupling. Miura[28] and Ohta[29] were the first to report the synthesis of 2-arylbenzo[*b*]thiophenes in moderate yields using palladium salts and triphenylphosphine. Recently, Sall[15] and Samat[30] described the synthesis of 2-arylbenzo[*b*]thiophene derivatives by Suzuki coupling in better yields. On the basis of the improvements of a catalytic Heck-type reaction previously developed on thiophene derivatives,[31] we succeeded in the direct arylation of 3-substituted benzo[*b*]thiophenes.[12,13] This method allowed us to synthesize 2-arylbenzo[*b*]thiophenes in one step, whereas usual arylation reactions,[32] such as Stille-,[33] Kumada-,[34] or Suzuki-type[35] coupling, require a prior regioselective halogenation of the substrate and the use of organometallic reagents. On the basis of this efficient one-step catalytic benzo[*b*]thiophene arylation (Scheme 5), 3-substituted benzo[*b*]thiophenes **5a**–**i** were arylated at the 2-position.

TABLE 4. Arylation of Benzo[*b*]thiophene Derivatives

entry	substrate	product	reaction time (h)	conversion[a] (isolated yield)[b] (%)
1	**5a**	**8a**	7	94 (67)
2	**5b**	**8b**	7	92 (61)
3	**5c**	**8c**	6	91 (69)
4	**5c**	**9c**	8	97 (73)
5	**5c**	**10c**	9	91 (70)
6	**5d**	**8d**	8	96 (60)
7	**5e**	**8e**	9	95 (60)
8	**5f**	**8f**	5	90 (73)
9	**5g**	**8g**	3	95 (80)
10	**5g**	**9g**	7	91 (63)
11	**5g**	**10g**	4	98 (75)
12	**5h**	**8h**	9	100 (65)
13	**5i**	**8i**	9	94 (52)

[a] Determined by GC. [b] Performed with 5% $Pd(OAc)_2$, 3 equiv of K_2CO_3, 1.1 equiv of aryl bromide, and 1 equiv of DCH-18-C-6 in DMF at 110 °C.

The activation of the 2,3-double bond by a functional group at the 3-position is necessary to obtain acceptable yields without any phosphine. This reaction was performed with electron-donating and electron-withdrawing substituents at the 3-position. To avoid the symmetrical Ullmann-type coupling side reaction of the aryl halide, aryl bromides were preferred to their iodide analogues.[36] Heck-type couplings were carried out using a slight excess of aryl bromide, an excess of potassium carbonate as a base, and a crown ether, DCH-18-C-6, in DMF at 110 °C (Table 4).

Moderate to good yields (60–80%) were obtained with 3-phenoxybenzo[*b*]thiophenes (Table 4, entries 1–8) as well as with 3-aminobenzo[*b*]thiophenes (Table 4, entries 9–13). No influence from the electron-rich or electron-poor nature of the aryl bromide was noticed (Table 4, entries 3–5 and 9–11). Generally, conversions are above 90% with short to moderate reaction times. However, isolated yields rarely exceeded 70%. In fact, without an external reducing agent, such as phosphine, small quantities of benzo[*b*]thiophene dimer were formed during the Heck-like coupling along with the reduction of Pd(II) into Pd(0), hence the gap between the conversion and the isolated yield. Moreover, this dimerization and the byproduct resulting from the symmetrical Ullmann-type coupling of the aryl halide complicated further purifications leading to moderate isolated yields of the pure desired product.

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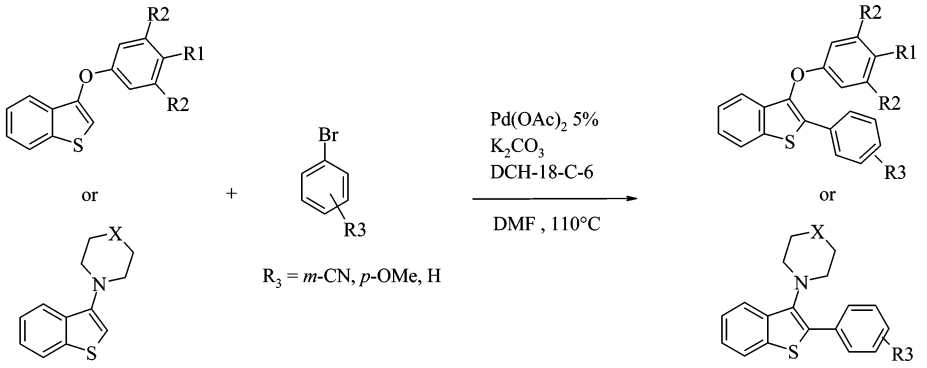
SCHEME 5. Heck-Type Coupling of Benzo[*b*]thiophene Derivatives



5a R_1 = OMe, R_2 = H
5b R_1 = OMe, R_2 = OMe
5c R_1 = H, R_2 = H
5d R_1 = F, R_2 = H
5e R_1 = Cl, R_2 = H
5f R_1 = CN, R_2 = H

5g X = CH_2
5h X = O
5i X =NCH_3

8a R_1 = OMe, R_2 = H, R_3 = *m*-CN
8b R_1 = OMe, R_2 = OMe, R_3 = *m*-CN
8c R_1 = H, R_2 = H, R_3 = *m*-CN
9c R_1 = H, R_2 = H, R_3 = H
10c R_1 = H, R_2 = H, R_3 = *p*-OMe
8d R_1 = F, R_2 = H, R_3 = *m*-CN
8e R_1 = Cl, R_2 = H, R_3 = *m*-CN
8f R_1 = CN, R_2 = H, R_3 = *m*-CN

8g X = CH_2, R_3 = *m*-CN
9g X = CH_2, R_3 = H
10g X = CH_2, R_3 = *p*-OMe
8h X = O, R_3 = *m*-CN
8i X =NCH_3, R_3 = *m*-CN

Conclusion

The use of the sulfoxide form of 3-bromobenzo[*b*]-thiophene allowed its nucleophilic substitution with various phenolates and secondary amines in good yields. 3-Phenoxy and 3-aminobenzo[*b*]thiophene 1-oxide derivatives were reduced and then coupled with various aryl halides according to a Heck-type reaction to produce a series of 3-phenoxy and 3-amino-2-arylbenzo[*b*]thiophenes. This new methodology allows direct access to a large number of 2,3-disubstituted benzo[*b*]thiophenes of great potential biological properties.

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Supporting Information Available: Experimental procedures and characterization data for all compounds, ^{1}H NMR and ^{13}C NMR spectra of compounds **2**, **3c**, **4a**, **5c**, **5g**, **6**, **7**, **8c**, **9c**, **10c**, **8g**, **9g**, and **10g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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