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Environmentally benign process for the synthesis of 2,3-disubstituted benzo[*b*]thiophenes using electrophilic cyclization

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ABSTRACT

We have developed a greener process for the synthesis of 2,3-disubstituted benzo[*b*]thiophenes using electrophilic cyclization as a key step. Our method not only employs an environmentally friendly solvent ethanol, but also utilizes safe and inexpensive inorganic reagents to furnish the desired products in high yields under mild reaction conditions. In addition to iodo- and bromocyclization, chlorocylization was also successfully accomplished.

Benzo[*b*]thiophenes are naturally occurring[1] heterocyclic compounds with diverse applications in medicinal chemistry and material science, resulting in high interest in industry as well as academia. They display a wide range of biological and physiological functions such as anti-inflammatory,[2] anti-fungal,[3] anti-depressants,[4] estrogen receptor modulator,[5] FimH antagonists,[6] anti-mitotic,[7] kinases inhibitor,[8] and anti-tumor activities.[9] Several commercially available drugs also contain the benzo[*b*]thiophene core structure such as sertaconazole nitrate, zileuton, raloxifene, and benocyclidine (Fig. 1). Along with various medicinal properties, these sulfur-containing molecules have found their interest in organic materials.[10] Benzothiophenes have superior durability and solubility compared to their hydrocarbon analogues, which make them better materials for organic semiconductors.

In recent years, halogen- and transition metal-mediated 5-*endo*-dig cyclization of alkynes possessing a sulfur nucleophile in close proximity has emerged as the most promising way to synthesize 2,3-disubstituted benzo[*b*]thiophenes derivatives.[11] The heteroaromatic carbon–halogen bonds obtained in 5-*endo*-dig cyclization reactions using halonium ions further allow the derivatization of core structures by palladium-catalyzed cross coupling reactions.[12] These reactions proceed in high yields and tolerate a variety of functional groups, but they do require toxic solvents such as DCM and corrosive halogens. However, the chlorocyclization are rarely reported. Only one chlorocyclization of 2-alkynylthioanisoles has been reported by Wu and Lu, with disadvantages of requiring high temperature and toxic acetonitrile as a solvent.[13]

Herein, we report an environmentally benign process for the synthesis of 2,3-disubstituted benzo[*b*]thiophenes using electro-

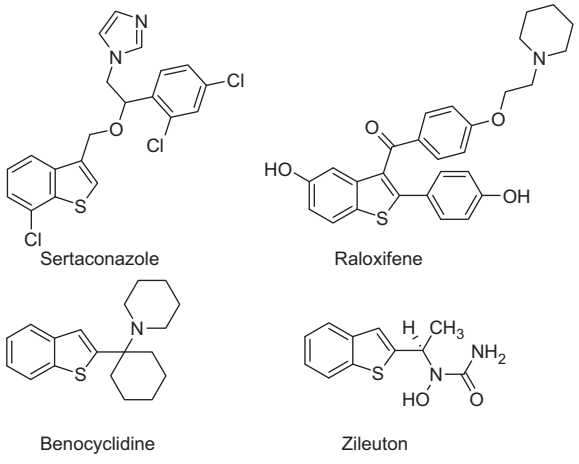

Figure 1. Examples of drugs containing benzo[*b*]thiophene core structure.

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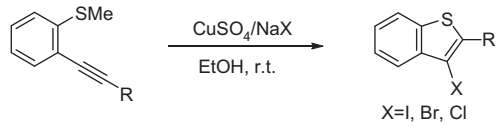
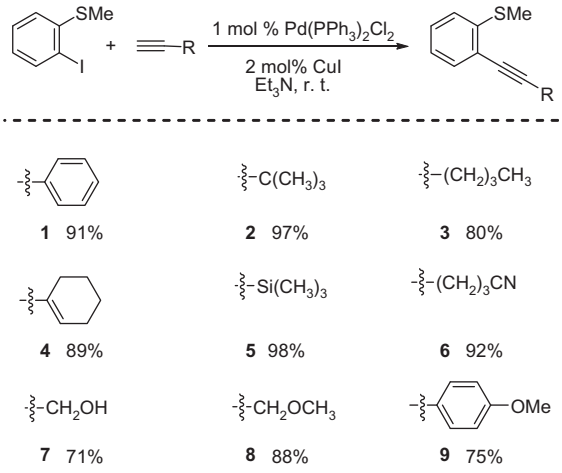


Scheme 1. Synthesis of 2-phenyl-3-iodobenzo[*b*]thiophene framework via modified iodocyclization.



Scheme 2. Synthesis of 2-alkynylthioanisoles via Sonogashira coupling.

philic cyclization as a key step (Scheme 1).[14] In addition, we have demonstrated high product yields under mild reaction conditions requiring little or no purification. Our method not only employs an environmentally friendly solvent ethanol, but also utilizes safe and inexpensive inorganic salts to furnish the desired products at room temperature. Along with iodo- and bromocyclization, this method accomplishes the rare chlorocyclization using table salt (NaCl) as a reagent and tolerates several functional groups leading to a diverse library of benzo[*b*]thiophenes derivatives.

To further assess the applicability of our reaction the desired starting reactants, 2-alkynylthioanisoles **1**–**9**, were synthesized using the Sonogashira coupling reaction (Scheme 2).

We found that 2-phenylethynylthioanisole (**1**), when reacted with equimolar $CuSO_4$ and NaI mixture in ethanol at room temperature for 24 h, resulted in the formation of 3-iodo substituted benzo[*b*]thiophene **1a** in a high yield of 83% (Table 1, entry 1). To further study the scope of this green strategy, NaBr and NaCl were employed along with $CuSO_4$. Cyclization attempts using NaBr/$CuSO_4$ resulted in the formation of bromocyclized product **1b** in 92% yield (entry 2). Chlorocyclization of **1** was also successful, resulting in the formation of **1c** in 92% yield, which is higher than previously reported chlorocyclization (entry 3).[13]

Our reaction conditions work well with alkyl substituted thioanisoles. Both bulky *tert*-butyl (**2**) and linear *n*-butyl (**3**) substituted alkynes resulted in higher yields of iodocyclized benzo[*b*]thiophenes **2a** and **3a** respectively (entries 4 and 7). Earlier studies showed that bromocyclization of **2** was unsuccessful in giving synthetically useful yield of **2b** (10%) and resulted in high-

Table 1
5-*endo*-dig Cyclization of 2-alkynylthioanisoles to corresponding 3-halosubstituted benzo[*b*]thiophenes[a]

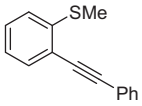
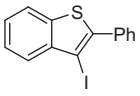
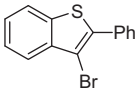
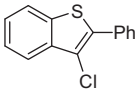
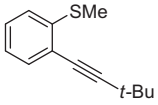
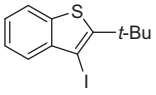
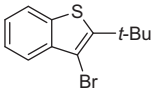
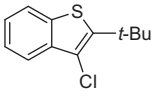
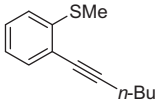
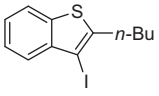
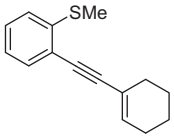
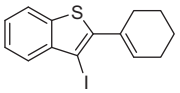
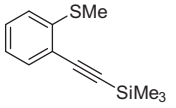
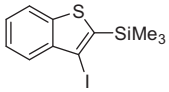
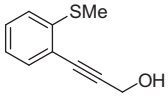
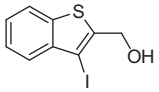
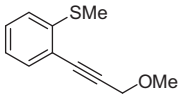
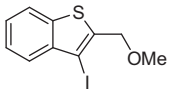
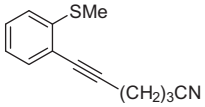
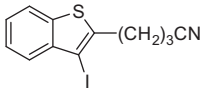
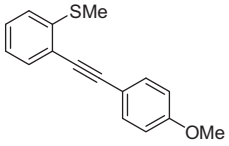
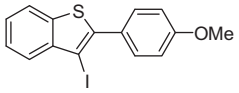
Entry	Substrate		Reaction condition	Product		Yield[b] (%)
1		**1**	A		**1a**	83
2			B		**1b**	92
3			C		**1c**	92
4		**2**	A		**2a**	81
5			B		**2b**	89
6			C		**2c**	82
7		**3**	A		**3a**	89
8		**4**	A		**4a**	81

Table 1 (*continued*)

Entry	Substrate		Reaction condition	Product		Yield[b] (%)
9		**5**	A		**5a**	91
10		**6**	A		**6a**	90
11		**7**	A		**7a**	97
12		**8**	A		**8a**	82
13		**9**	A		**9a**	86

[a] Reaction condition A: all reactions were performed using 0.30 mmol of thioether, 5.0 equiv of $CuSO_4$, and 5.0 equiv NaI in 5 mL of EtOH at room temperature for 24 h. Reaction condition B: reaction was performed using 5.0 equiv of NaBr instead of NaI for condition A. Reaction condition C: reaction was performed using 5.0 equiv of NaCl instead of NaI for condition A.

[b] Isolated yields.

er amounts of addition product.[13] On the other hand, our reaction condition furnished only desired product **2b** in high yield of 89% when thioanisole **2** was subjected to cyclization using NaBr (entry 5), making our method superior. Chlorocyclization of **2** resulted in the formation of **2c** in a high yield of 82% (entry 6).

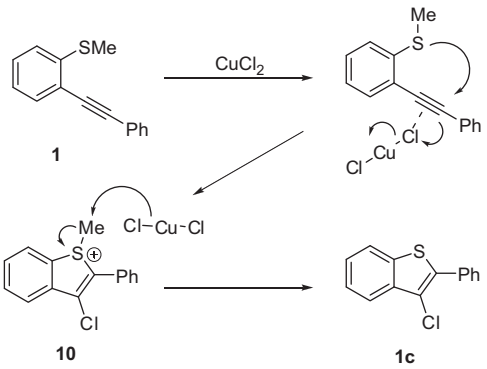
To explore the tolerance of several functional groups in our reaction condition, thioanisole-containing functional groups were employed. Our reaction conditions seem wide-ranging as vinyl, TMS, alcohol, ether, and nitrile functionality were successfully employed (entries 8–13). Iodocyclization of cyclohexene holding alkyne **4** resulted in the formation of **4a** in 81% yield (entry 8), and alkyne **5** bearing TMS functionality furnished product **5a** in 91% yield (entry 9). Thioanisole bearing propargyl alcohol or propargyl ether was also successfully employed for cyclization reactions and the resulting products **6a** and **7a** were obtained in good yields of 90% and 97%, respectively (entries 10 and 11). Benzothiophene **8a** tethered with nitrile functionality was prepared from alkyne **8** in 82% yield (entry 12). Using the strong electron-rich group, *p*-methoxyphenyl, resulted in a slightly higher yield of cyclized product **9a** when compared with phenyl group (compare entries 1 and 13).

$$CuSO_4 + 2\,NaX \longrightarrow Na_2SO_4 + CuX_2 \quad (X = I, Br, Cl) \qquad (1)$$

$$2\,CuX_2 \longrightarrow 2\,CuX + X_2 \quad (X = I, Br) \qquad (2)$$

It is well established that $CuSO_4$ when mixed with NaCl in situ generated cupric chloride[15] (Eq. 1) that could lead to the chlorocyclization by the mechanism given in Scheme 3. The proposed mechanism involves the co-ordination of cupric chloride with the alkyne followed by an anti-attack from sulfur to give cationic intermediate **10**. The methyl group can subsequently be removed by S_N2 displacement with the help of $CuCl_2$.

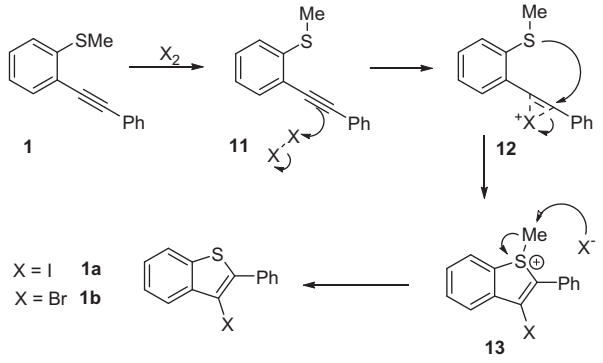
Copper sulfate when mixed with NaI and NaBr also produces CuI_2 and $CuBr_2$, respectively (Eq. 1). However, CuI_2 and $CuBr_2$ are known to quickly decompose into CuI and CuBr along with I_2 and Br_2, respectively (Eq. 2).[15] This could lead to plausible halocyclization mechanism via initial co-ordination of electrophilic halogen with the alkyne to form **12**, followed by an attack from nearby sulfur atom to give sulfonium salt **13** (Scheme 4). The iodine or bromine anion generated from the above process could displace the methyl group attached to cationic sulfur via an S_N2 reaction resulting in the formation of benzo[*b*]thiophene **1a** or **1b**.



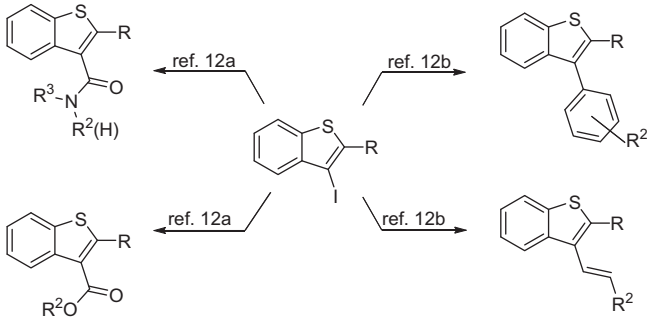
Scheme 3. Proposed mechanism of cholorocyclization involving in situ generated $CuCl_2$ electrophile.

Heteroaromatic carbon–iodine bond generated after halocyclization is a very useful intermediate for the synthesis of a wide variety of 2,3-disubstituted benzo[*b*]thiophenes. Larock and co-workers have utilized palladium-catalyzed cross-coupling reactions to generate a diverse library of benzo[*b*]thiophenes using 3-iodobenzo[*b*]thiophenes (Scheme 5).[12]

In summary, we have developed a green method for the synthesis of benzo[*b*]thiophenes by employing an environmentally friendly solvent ethanol, and inexpensive inorganic salts. Our method is mild and tolerates a variety of functional groups. This



Scheme 4. Proposed mechanism of cyclization involving in situ generated I_2 and Br_2 electrophile.



Scheme 5. Synthesis of 2-alkynylthioanisoles via Sonogashira coupling.

method not only can be used to produce well established iodo- and bromocyclized products, but also to produce relatively scarce chlorocyclized products in high yields. Alkynes bearing aryl, alkyl, vinyl, and TMS groups were also successfully cyclized. Therefore, this facile and green method can be successfully utilized to synthesize wide-ranging benzo[*b*]thiophene derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.139.

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14. Method A: to a 6 dram vial containing 2-alkynylthioanisole (0.30 mmol), $CuSO_4{\cdot}5H_2O$ (374 g, 1.5 mmol), NaI (224 mg, 1.5 mmol) and 3 mL of EtOH were added. The solution was allowed to stir overnight. This mixture was concentrated under vacuum, absorbed in silica gel and was purified by column chromatography using hexanes as the eluent. 3-Iodo-2-phenylbenzo[*b*]thiophene (**1a**) was isolated as a yellow oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34–7.40 (td, J = 7.5, 1.5 Hz, 1H), 7.42–7.50 (m, 4H), 7.66–7.69 (m, 2H), 7.75–7.78 (m, 1H), 7.81–7.84 (m, 1H). Other characterization data are in good agreement with the previous reported data.[11d]
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