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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-

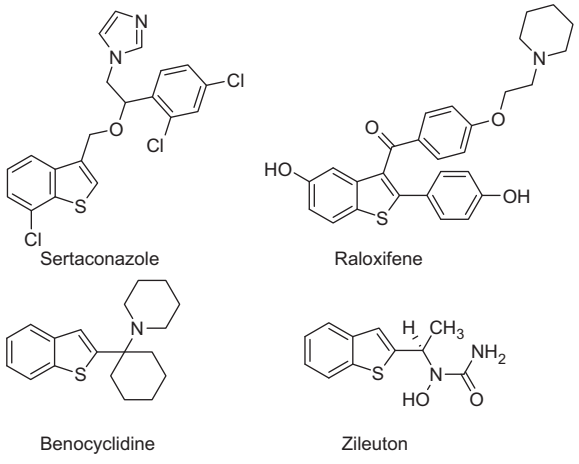

Figure 1. Examples of drugs containing benzo[*b*]thiophene core structure.

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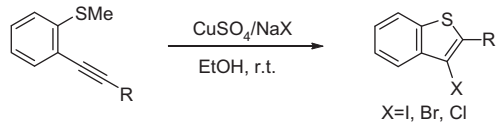
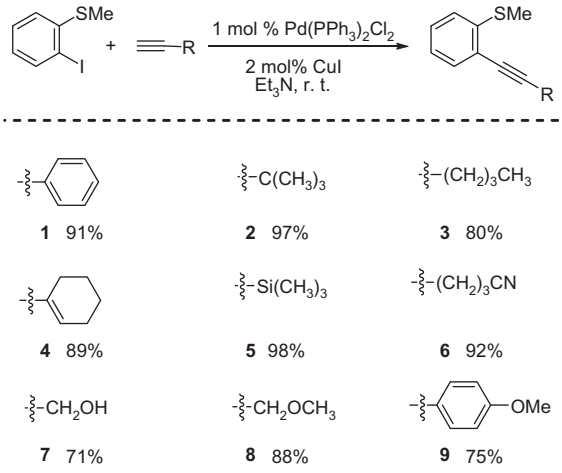


Scheme 1. Synthesis of 2-phenyl-3-iodobenzo[*b*]thiophene framework via modified iodocyclization.



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

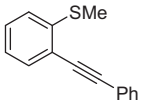
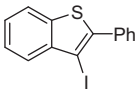
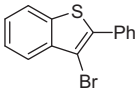
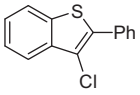
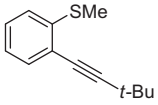
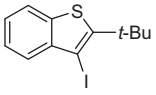
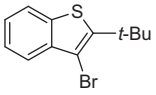
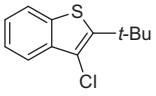
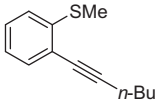
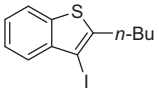
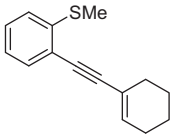
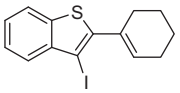
philic cyclization as a key step (Scheme 1).[14] In addition, we have demonstrated high product yields under mild reaction conditions requiring little or no purification. Our method not only employs an environmentally friendly solvent ethanol, but also utilizes safe and inexpensive inorganic salts to 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