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Sodium halides as the source of electrophilic halogens in green synthesis of 3-halo- and 3,*n*-dihalobenzo[*b*]thiophenes

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ABSTRACT

A convenient methodology for the synthesis of mono- and di-halogenated benzo[*b*]thiophenes is described herein, which utilizes copper(II) sulfate pentahydrate and various sodium halides in the presence of substituted 2-alkynylthioanisoles. The proposed method is facile, uses ethanol as a green solvent, and results in uniquely substituted benzo[*b*]thiophene structures with isolated yields up to 96%. The most useful component of this methodology is the selective introduction of bromine atoms at every available position (2–7) around the benzo[*b*]thiophene ring, while keeping position 3 occupied by a specific halogen atom such as Cl, Br or I. Aromatic halogens are useful reactive handles; therefore, the selective introduction of halogens at specific positions would be valuable in the targeted synthesis of bioactive molecules and complex organic materials via metal-catalyzed cross coupling reactions. This work is a novel approach towards the synthesis of dihalo substituted benzo[*b*]thiophene core structures, which provides a superior alternative to the current methods discussed herein.

1. Introduction

Substituted benzo[*b*]thiophenes and related chalcogen-containing heterocycles, such as benzofurans and benzoselenophenes, have received much attention in the recent years due to their well-recognized biological[1] and materials-related applications.[2] In particular, the molecules containing the benzo[*b*]thiophene core structure have proven to be promising candidates for biomedical applications, including 5-H7R and 5-HTT receptor modulation, i.e., used in the treatment of depression,[3] estrogen receptor-alpha (ERα) and estrogen receptor-beta (ERβ) modulation,[4] breast cancer prevention,[5] immune system regulation via S1P G-protein coupled receptors,[6] and anti-malarial activity.[7] Additional studies have shown that uniquely substituted benzo[*b*] thiophenes may be useful in the treatment of Staphylococcus infections.[8] Organic materials containing the benzothiophene core structure are showcased in devices including novel phosphorescent organic light emitting diodes (PHOLED's) made possible by the low-lying LUMO and high thermal stability associated with aromatic heterocycles[9]; organic thin-film field effect transistors (OFET's) dependent on the high photostability and ionization potential of core-structure organics[10]; and dye-sensitized solar cells (DSSC's).[11]

Given the significant biological and materials applications associated with benzo[*b*]thiophene derivatives, it is no surprise that many synthetic chemists have worked to develop innovative methods for the synthesis of the substituted core structures.[12] Very recently, Reddy and Valetti developed a [4 + 2] benzannulation between substituted alkenyl thiophenes and various propargyl alcohols to furnish a diverse library of benzo[*b*]thiophene derivatives[13] with the substituents on the 5, 6, and 7 positions. In another report, Yin et al. examined the direct C–H arylation of benzo[*b*]thiophene using catalytic Pd(II) and aryl chlorides to form 2-aryl benzo[*b*]thiophene derivatives.[14] In a similar report, Chen and coworkers utilized a Pd-catalyzed coupling/cyclization reaction of 2-iodothiophenols with terminal alkynes to achieve 2-aryl substituted benzo[*b*]thiophene derivatives in moderate to high yields with fluoro-, chloro- and trifluoromethyl-substituted 5 and 6 positions.[15] Yamauchi and coworkers introduced the multicomponent arylation/cyclization of 2-alkynylthioanisoles to furnish 2,3-diarylated benzo[*b*]thiophene derivatives in a single step using a Pd/phenanthroline catalyst.[16] Cyclization of arylketene dithioacetal monoxides to afford 4, 5, and 6 methoxy-substituted benzo[*b*]

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thiophenes was reported by Yoshida and coworkers.[17] In the recent literature, it is clear that necessity-driven syntheses have been developed for the production of highly-substituted benzo[*b*]thiophene structures and, when considered in combination, the current methods provide a useful network of strategies to afford variously functionalized structures at many positions. However, to our knowledge, no single report has defined a universal strategy for the selective placement of halogens at any desired position on the benzo[*b*]thiophene ring. Furthermore, no work to date has addressed the systematic synthesis of dihalogenated benzo[*b*]thiophenes.

Herein, we report a comprehensive method for the synthesis of mono- and dihalogenated benzo[*b*]thiophenes via electrophilic halocyclization of 2-alkynylthioanisoles. We have determined previously that copper(II) sulfate pentahydrate and sodium halide react in the presence of 2-alkynylthioanisoles **1** to afford mono-halogenated benzo[b]thiophene derivatives **2** in isolated yields up to 98% (Scheme 1).[18] In this all-inclusive study, we have expanded upon this foundation through the implementation of new and varied functional groups to test the flexibility of this reaction as well as to demonstrate a scaffold upon which dihalogenated analogues may be achieved. The reaction of bromo-substituted 2-akynylthioanisoles **3** under the same reaction conditions gives dihalogenated benzo[*b*]thiophenes **4** with isolated yields up to 96% (Scheme 1).

Our approach works at room temperature, tolerates diverse functionalities, and incorporates a green solvent. Additionally, our reaction conditions are not only mild but also tolerant to moisture and air. In addition, this method allows the placement of a bromine reactive handle on positions 2, 4, 5, 6, and 7 around the benzo[*b*]thiophene core ring, while placing chlorine, bromine, or iodine moieties on position 3 depending on which sodium halide (NaCl, NaBr, or NaI) is used for the synthesis. The methods proposed in this report provide an array of easily accessible halogenated compounds with a high potential for functional diversity. The option to install halogens of choice precisely at specific sites opens up many synthetic possibilities due to the well-established halogen selectivity of metal-catalyzed carbon-carbon coupling reactions (I > Br > Cl).

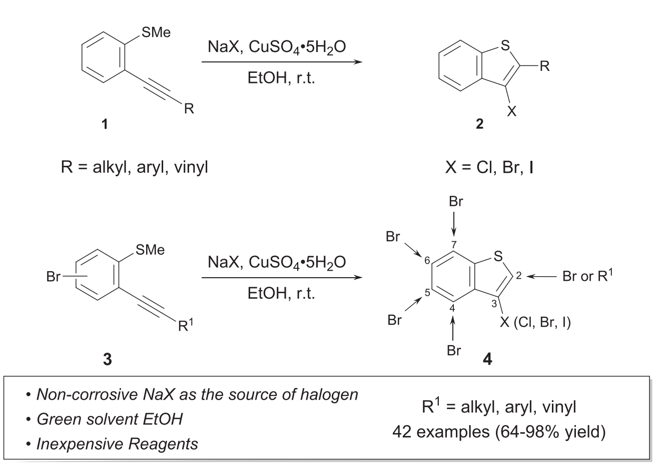
2. Results and discussion

The desired 2-alkynylthioanisoles **6**–**15** used for the synthesis of mono-halogenated benzo[*b*]thiophenes were prepared via the Sonogashira coupling of 2-iodothioanisole **5** (1 equiv.) with substituted terminal alkynes (1.2 equiv.) in the presence of catalytic Pd (2 mol %) and catalytic copper (4 mol %) using trimethylamine as solvent (Scheme 2).[18,19] Using these conditions, a variety of functionalized 2-akynylthioanisoles **6**–**15** were synthesized with isolated yields between 89 and 98% (Scheme 2).

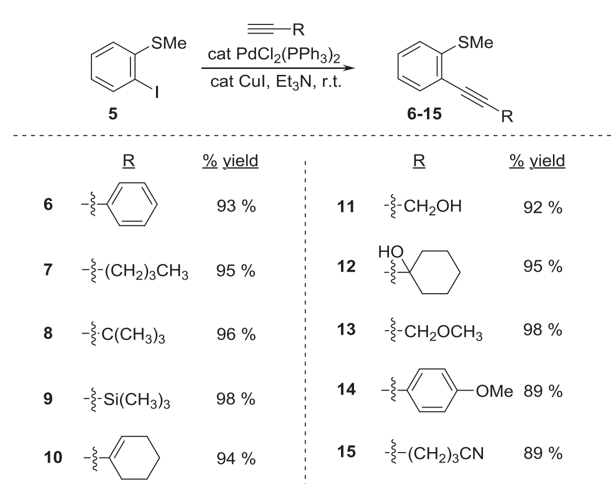
Using variously substituted 2-alkynylthioanisoles **6**–**15** as starting materials, a diverse library of 3-halo benzo[*b*]thiophenes **16**–**45** were synthesized (Table 1). Beginning with a phenyl substituent (entries 1–3), 2-phenyl-3-halogenated benzo[*b*]thiophenes were synthesized. When 2-alkynylthioanisole **6** was subjected to our cyclization conditions using NaCl, 2-phenyl-3-chlorobenzo[*b*]thiophene **16** was formed in excellent 92% yield. When alkyne **6** was subjected to similar reaction conditions, where sodium bromide or iodide was employed instead of sodium chloride, 2-phenyl-3-bromobenzo[*b*]thiophene **17** and 2-phenyl-3-iodobenzo[*b*]thiophene **18** were synthesized in 92% and 83% yields respectively. When an alkyl chain was used instead of a phenyl group on the remote alkyne group the corresponding 2-alkynylthioanisoles, upon chlorocyclization, produced 2-*n*-buyl-3-chlorobenzo[*b*]thiophene **19** in an excellent 86% yield. Once again replacing NaCl with NaBr and NaI, but otherwise using the same reaction conditions, resulted in the bromo- and iodocyclized products **20** and **21** in 83% and 89% yields respectively.

When a sterically hindered *tert*-butyl group was used in place of the linear *n*-butyl group no significant change was observed in reaction yield. The reaction worked equally well furnishing the chloro cyclized product **22** in 82% yield as compared to the 86% yield achieved with the *n*-butyl group (compare entries 22 and 19). Once again NaBr and NaI generated the desired cyclized 2-*tert*-butyl-3-halobenzo[*b*]thiophenes **23** and **24** product in good yields of 89% and 81% respectively. 2-Alkynylthioanisoles with trimethylsilyl substituents (entries 10–12) underwent cyclization to form 3-iodobenzo[*b*]thiophene **27** in excellent 91% yield; however, attempts to synthesize chloro- and bromo-analogues **25** and **26** failed as the reaction yielded a complex, inseparable mixture of products.

Our reaction tolerates vinyl groups as 2-(1-cyclohexen-1-yl) thioanisole (entries 13–15) cyclized to form 3-chlorobenzo[*b*]thiophene **28** in 82% yield, 3-bromobenzo[*b*]thiophene **29** in high yield of 98%, and 3-iodobenzo[*b*]thiophene **30** in a yield of 81%. We also determined that a primary alcohol works well in our cyclization reaction conditions as the propargyl alcohol **11** (entries 16–18) cyclized in the presence of NaCl to form the desired 3-chlorobenzo[*b*]thiophene **31** in excellent 92% yield. Similarly, alcohol **11** resulted



Scheme 1. Synthesis of 3-halobenzo[*b*]thiophenes and systematic synthesis of 3-halo-*n*-bromobenzo[*b*]thiophene.



Scheme 2..