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Green Synthesis of Halogenated Thiophenes, Selenophenes and Benzo[*b*]selenophenes Using Sodium Halides as a Source of Electrophilic Halogens

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Abstract

Herein, we report the first synthesis of chlorinated benzo[*b*]selenophenes via environmentally friendly electrophilic chlorocyclization reaction using “table salt” as a source of “electrophilic chlorine” and ethanol as a solvent. In addition, the synthesis of diverse halogenated heterocycles, including 3-chloro, 3-bromo and 3-iodo thiophenes, selenophenes, and benzo[*b*]selenophenes was successfully accomplished under the same environmentally benign reaction conditions. This methodology has several advantages over other previously reported reactions as it employs simple starting compounds, an environmentally friendly solvent, ethanol, and non-toxic inorganic reagents under mild reaction conditions, resulting in the high product yields.

Graphical Abstract

Keywords

Benzo[*b*]selenophene; Thiophene; Selenophene; Electrophilic halocyclization; Green Chemistry

Sulfur and selenium-containing heterocycles have diverse potential applications in drug discovery, pharmacology, optics, electronics, material science, and so on. Thiophene is a commonly used core structure in pharmaceutical drugs (Figure 1).¹ Thiophene-containing molecules are known to exhibit antimicrobial,² non-steroidal anti-inflammatory,³ platelet inhibitory,⁴ antitumor,⁵ and antiviral activity.⁶ In addition, thiophenes are also used in polymers and materials that have a potential application in the area of organic field-effect

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transistors (OFETs) and organic light-emitting diodes (OLEDs).^{7–13} Selenophenes, a selenium analogue of thiophene, are also known to exhibit biological activities, such as anticancer,¹⁴ antitumor,¹⁵ antidepressant,¹⁶ antioxidant,¹⁷ and antiproliferative activities.¹⁸ Benzo[*b*]selenophenes and selenophenes have a narrow HOMO-LUMO gap when compared with their sulfur analogues and have applications in photonics.¹⁹

The introduction of a halogen atom at specific position(s) on organic molecules not only serves as a reactive handle, but also alters its structural, synthetic, biological, and pharmacological properties, thereby further increasing the demands of halogenated heterocycles.²⁰ Over eighty percent of manufactured drugs are synthesized using or containing halogens due to their versatility and applications.²¹ In the past decade, electrophilic halocyclization has emerged as an effective route of introducing iodine and bromine moiety in the heterocycles.²² However, there are only a few reported examples of introducing chlorine via chlorocyclization reactions.²³ Most of these chlorocyclization reactions lack generality, require harsh reaction conditions, give poor to moderate yields and utilize toxic reagents and solvents.

Herein we describe an environmentally benign process for the synthesis of diverse halogenated thiophenes, selenophenes, and benzo[*b*]selenophenes, which enables further functionalization of these heterocyclic molecules (Scheme 1). Most prominently, rare chlorocyclization was successfully accomplished in diverse heterocyclic systems with this method along with bromo- and iodocyclization. It should be noted that this is the first report on the synthesis of 3-chlorobenzo[*b*]selenophenes via electrophilic chlorocyclization. This is the only reported reaction condition where all three halogens (I, Br, and Cl) can be incorporated in the same heterocyclic compound by only changing the sodium halides as a source of electrophilic halide. Hence, our reaction conditions have a potential to be applied towards the synthesis of diverse heterocycles due to its generality. Our environmentally benign method employs ethanol as a solvent (as opposed to halogenated and toxic solvents used in earlier reported methodologies), along with safe, inexpensive, and readily available inorganic reagents, such as copper (II) sulfate pentahydrate, and sodium halides, notably table salt for chlorocyclization reactions. This method requires mild reaction conditions resulting in very high yields of the products as compared with earlier reports.^{23b,24}

It was determined that the starting alkynes **5–9** and **12** in the presence of a sodium halide, ethanol, and copper (II) sulfate pentahydrate underwent electrophilic cyclization to form thiophene, selenophene, and benzo[*b*]selenophene derivatives with yields as high as 95% (Scheme 1). This methodology utilizes the principles of green chemistry; thus, eliminating the use of harsh solvents and cyclizing agents to create simpler and cleaner electrophilic cyclization reactions. In addition, the multiple electrophilic halocyclizations can be accomplished using the same reactants by simply changing the employed sodium halide. The only shortcoming of our methodology is the use of excess CuSO₄•5H₂O. Our efforts to reduce the quantity of CuSO₄•5H₂O failed and using less than 5 equivalents Cu salt resulted in significantly lower yields of the products.²⁵ Employing solvents such as toluene and DMSO resulted in no reaction, where as DMF, DCM, THF and nitromethane resulted in lower yields of the product.

The desired precursors for the synthesis of 3-halothiophenes were obtained via a stereoselective method, previously reported in the literature for producing alkylthio-1,4-diaryl-1-buten-3-yne. 1,3-Phenyl and 3-thienyl diynes **1–2** when reacted with methyl disulfide and NaBH₄ formed enynes **5** and **6** in moderate yields of 59% and 54%, respectively (Scheme 2, Eq. 1). Similarly, alkyl and vinyl enyne substrates **7** and **8** were obtained in 35% and 29% yields, respectively. Enyne **9**, the precursor to the synthesis of 3-haloselenophene, was obtained by changing Me₂S₂ to Bn₂Se₂, but otherwise the same procedure was followed as described above (Scheme 2, Eq. 2).

The two-step process for the preparation of alkyne **12**, the starting compound for benzo[*b*]selenophene synthesis, began with Sonogashira coupling of 1-bromo-2-iodobenzene (**10**) with phenylacetylene. The resulting alkyne **11**, when subjected to a lithiation halogen exchange reaction followed by the addition of Bn₂Se₂ resulted in the formation of alkyne **12** with a 63% overall yield for the two steps.

To further study the scope of our methodology, alkynes **5**, **6**, **9** and **12** were treated with a sodium halide, ethanol, and Cu₂SO₄•5H₂O. All cyclizations were monitored by means of thin layer chromatography and the reaction mixtures were purified via column chromatography.

Cyclization of the starting phenyl-substituted vinyl methyl thiol **5** resulted in the desired 3-halothiophene products **13–15** with excellent yields of 92%, 86%, and 90%, respectively (Table 1, entries 1–3). Our greener and milder reaction conditions resulted in the higher yields of chloro-, bromo-, and iodocyclized products compared to an earlier reported methodology.^{23b,24} Replacing the phenyl group with a 3-thienyl moiety in the starting vinyl methyl thiol resulted in the cyclized chlorothiophene product **16** with an excellent yield of 91% (Table 1, entry 4). Our efforts to synthesize bromothiophene **17** failed, as cyclization of enyne **6** with NaBr and Cu₂SO₄•5H₂O resulted in a complex reaction mixture. When NaBr was replaced with NaI, the resulting iodocyclized product **18** was obtained in an excellent yield of 91% (Table 1, entry 6). This is the first report of the synthesis of chloro- and iodo-substituted oligothiophenes **16** and **18**, which are difficult to synthesize and may have potential application in OLEDs and OFETs.

The enyne **9**, a selenium analogue of alkyne **5**, when subjected to the same cyclization conditions furnished the desired chloro-, bromo-, and iodoselenophene products **19–21**, in high yields of 81%, 92%, and 95%, respectively (Table 1, entries 7–9). Once again chloro- and bromocyclized products were obtained by our method in higher yields compared to the methodology reported by others^{23b,24} indicating the superiority of our reaction conditions.

Even though the bromo- and iodocyclization of 2-alkynylmethylselenobenzene has already been reported, there is no reported example of chlorocyclization.²⁶ Herein we disclose the first ever report of this chlorocyclization reaction starting with 2-alkynylmethylselenobenzene **12** using table salt and the green solvent ethanol (Table 1, entry 10). The resulting 3-chlorobenzo[*b*]selenophene **22** was obtained in a good yield of 72%. Replacing NaCl with NaBr and NaI resulted in the formation of bromobenzo[*b*]selenophene **23** and iodobenzo[*b*]selenophene **24** in the respective yields of 73% and 62%.

We also extended the scope of our chlorocyclization reaction beyond aryl- and heteroaryl-containing enynes. The chlorocyclization reaction of *n*-propyl enyne **7** and 1-cyclohexenyl enyne **8** resulted in the formation of corresponding 3-chlorothiophenes **25** and **26** in the moderate yield of 64% and 55%, respectively (Scheme 4).

The proposed mechanism for our chlorocyclization reaction is outlined in scheme 4, which is based on a 3-haloindole synthesis reported by Lu and coworkers.²⁷ When Cu₂SO₄•5H₂O is mixed with NaCl in ethanol, the resulting CuCl₂ can weakly coordinate with alkyne **5**, followed by an anti-attack from a nearby S nucleophile to give the intermediate **27**. The methyl group can be removed subsequently by S_N2 displacement with the help of chloride anion to form intermediate **28**. Finally, a reductive elimination will lead to the desired product **13**. The resulting Cu(0) can easily be oxidized by CuCl₂ to produce CuCl.

It is well known that Cu₂SO₄•5H₂O in the presence of NaI or NaBr results in the formation of CuI₂ or CuBr₂, respectively, which easily gets converted to I₂ and Br₂ in situ.²⁸ The mechanism of the cyclization reaction involving an I₂ and Br₂ electrophile is well established.²⁶ Our method generates these corrosive reagents in situ; thus, eliminating the potentially harmful effects associated with the handling of these reagents.

In summary, we reported the first synthesis of 3-chlorobenzo[*b*]selenophene via electrophilic chlorocyclization reaction in good yields. In addition, this environmentally benign high-yielding method was further used for the synthesis of biologically and materially useful halogenated thiophenes and selenophenes. This methodology has several advantages over other previously reported reactions as it employs simple starting compounds, an environmentally friendly solvent, ethanol and non-toxic inorganic reagents under mild reaction conditions, resulting in high product yields.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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28. **General procedure for the synthesis of compounds 9–20:** To a 6-dram vial containing starting alkyne (0.30 mmol), 5 mL 95% ethanol was added. To the mixture, sodium halide (5 equiv) and copper (II) sulfate pentahydrate (5 equiv) were added. The reaction mixture was allowed to stir at room temperature for 24 hours. All reaction mixtures were purified via column chromatography using varying concentrations of hexanes as eluent. **3-Iodo-2,5-diphenylthiophene (11).** The product was isolated as a yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.33 (t, $J = 7.2$ Hz, 2H), 7.39–7.47 (m, 5H), 7.59 (d, $J = 7.2$ Hz, 2H), 7.66 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 79.0, 126.0, 128.5, 128.8, 128.9, 129.4, 129.6, 132.7, 133.5, 134.6, 141.9, 145.5. Other characterization data are in good agreement with the previous reported data.²⁴

Highlights

First report on the synthesis of benzo[*b*]selenophene via chlorocyclization

“Table salt” is employed as the source of electrophilic chlorine

Green reaction using EtOH as solvent and non-corrosive sodium halides

Respective halogens (Cl, Br and I) can be incorporated by only changing sodium halide

Synthesis of halogenated oligothiophenes that are difficult to obtained otherwise

Figure 1.
Commercially available drugs containing the thiophene core structure.

X = I, Br, Cl

X = I, Br, Cl; Y = S, Se

- First report on the synthesis of benzo[*b*]selenophene via chlorocyclization
- Higher reaction yields
- Green solvent EtOH
- Room temperature
- Inexpensive and non-corrosive sodium halides as the source of halogen

Scheme 1.

Halogenated thiophenes, selenophenes and benzo[*b*]selenophenes via copper-mediated halocyclization.

Scheme 2.
Synthesis of thiophene and selenophene precursors.

Scheme 3.
Synthesis of benzo[*b*]selenophene precursor.

Scheme 4.
Synthesis of alkyl and vinyl substituted thiophenes.

Scheme 5.
Proposed mechanism for chlorocyclization reaction.

Table 1
 Synthesis of halogenated thiophenes, selenophenes and benzo[*b*]selenophenes via green electrophilic cyclization ^a

Entry	Alkyne	Sodium Halide	Product	% yield ^b	% lit yield ^c
1		NaCl		92	65 ^d
2		NaBr		86	72 ^d
3		NaI		90	82 ^e

Entry	Alkyne	Sodium Halide	Product	% yield ^b	% lit yield ^c
4		NaCl		91	-
5		NaBr		-	-
6		NaI		91	-

Entry	Alkyne	Sodium Halide	Product	% yield ^d	% lit yield ^c
7		NaCl		81	70 ^d
8	9	NaBr		92	81 ^d
9	9	NaI		95	93 ^e

Entry	Alkyne	Sodium Halide	Product	% yield ^b	% lit yield ^c
10		NaCl		72	-
11	12	NaBr		73	75 ^f
12	12	NaI		62	90 ^f

^aReaction Condition A: All reactions were performed using 0.30 mmol of the alkyne, 5 equiv of NaX, and 5 equiv of CuSO₄•5H₂O in 5 mL of EtOH at room temperature for 24 h.

^bIsolated yields.

^cLiterature yield via halocyclization.

^dreference 23b.

^ereference 24.

^freference 26