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PII: S0040-4039(17)30007-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.01.007
Reference: TETL 48510

To appear in: *Tetrahedron Letters*

Received Date: 6 November 2016
Revised Date: 29 December 2016
Accepted Date: 2 January 2017

Please cite this article as: Kesharwani, T., Giraudy, K.A., Morgan, J.L., Kornman, C., Olaitan, A.D., Green Synthesis of Halogenated Thiophenes, Selenophenes and Benzo[*b*]selenophenes Using Sodium Halides as a Source of Electrophilic Halogens, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.01.007

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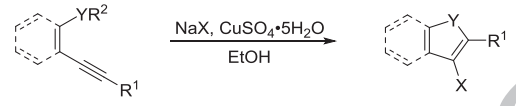

R^1 = aryl, hetroaryl, alkyl, vinyl
R^2 = Me, Bn

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

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

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

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.

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 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.

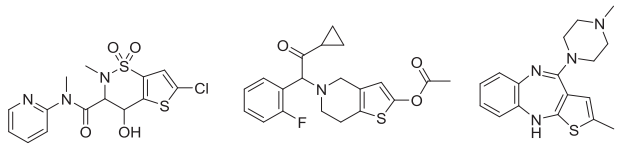
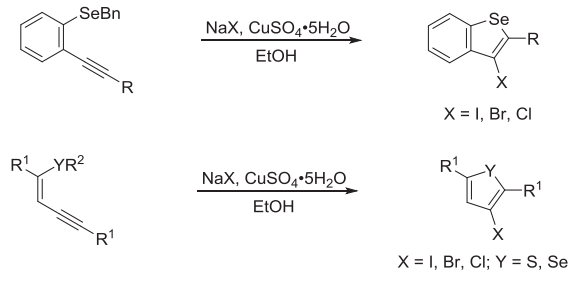


Figure 1. Commercially available drugs containing the thiophene core structure.



- *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.

Herein we describe an environmentally benign process for the synthesis of diverse halogenated thiophenes, selenophenes, and benzo[*b*]selenophenes, which enables further functionalization of

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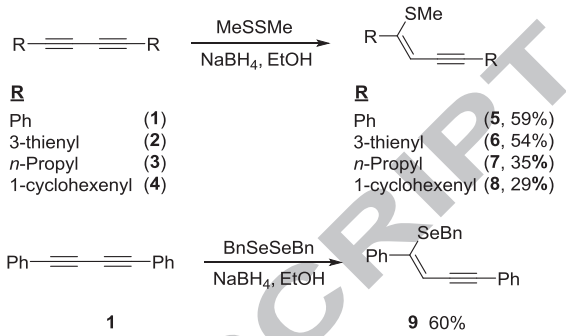
these heterocyclic molecules (Scheme 1). Most prominently, rare chlorocyclization was successfully accomplished in diverse heterocyclic systems with this method along with bromo- and iodocyclization. It should be noted that this is the first report on the synthesis of 3-chlorobenzo[*b*]selenophenes via 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]

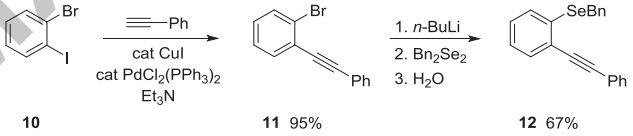
It was determined that the starting alkynes **5-9** and **12** in the presence of a sodium halide, ethanol, and copper (II) sulfate pentahydrate underwent electrophilic cyclization to form thiophene, selenophene, and benzo[*b*]selenophene derivatives with yields as high as 95% (Scheme 1). This methodology 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 $CuSO_4$•$5H_2O$. Our efforts to reduce the quantity of $CuSO_4$•$5H_2O$ 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 $NaBH_4$ 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 Me_2S_2 to Bn_2Se_2, but otherwise the same procedure was followed as described above (Scheme 2, Eq. 2).



Scheme 2. Synthesis of thiophene and selenophene precursors.

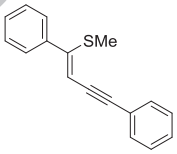
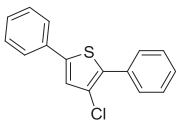
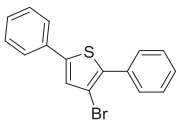
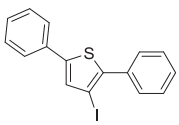
The two-step process for the preparation of alkyne **12**, the starting compound for benzo[*b*]selenophene synthesis, began with Sonogashira coupling of 1-bromo-2-iodobenzene (**10**) with phenylacetylene. The resulting alkyne **11**, when subjected to a lithiation halogen exchange reaction followed by the addition of Bn_2Se_2 resulted in the formation of alkyne **12** with a 63% overall yield for the two steps.

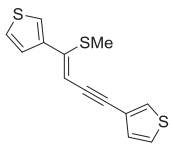
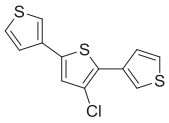
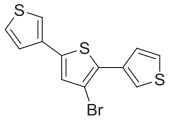
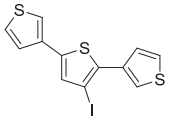
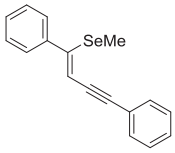
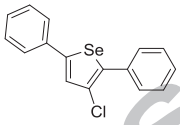
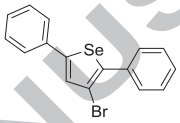
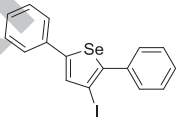
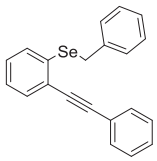
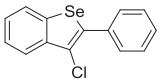
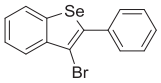
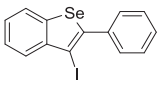


Scheme 3. Synthesis of benzo[*b*]selenophene precursor.

To further study the scope of our methodology, alkynes **5, 6, 9** and **12** were treated with a sodium halide, ethanol, and Cu_2SO_4•$5H_2O$. All cyclizations were monitored by means of thin layer chromatography and the reaction mixtures were purified via column chromatography.

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		**5**	NaCl		**13**	92	65[d]
2		**5**	NaBr		**14**	86	72[d]
3		**5**	NaI		**15**	90	82[e]

4		**6**	NaCl		**16**	91	-
5		**6**	NaBr		**17**	-	-
6		**6**	NaI		**18**	91	-
7		**9**	NaCl		**19**	81	70[d]
8		**9**	NaBr		**20**	92	81[d]
9		**9**	NaI		**21**	95	93[e]
10		**12**	NaCl		**22**	72	-
11		**12**	NaBr		**23**	73	75[f]
12		**12**	NaI		**24**	62	90[f]

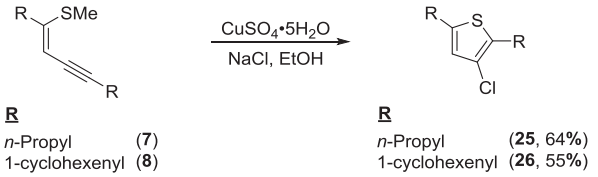
[a] Reaction Condition A: All reactions were performed using 0.30 mmol of the alkyne, 5 equiv of NaX, and 5 equiv of $CuSO_4 \bullet 5H_2O$ in 5 mL of EtOH at room temperature for 24 h. [b] Isolated yields. [c] Literature yield via halocyclization. [d] reference 23b. [e] reference 24. [f] reference 26

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 $Cu_2SO_4 \bullet 5H_2O$ 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 eneyne **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.

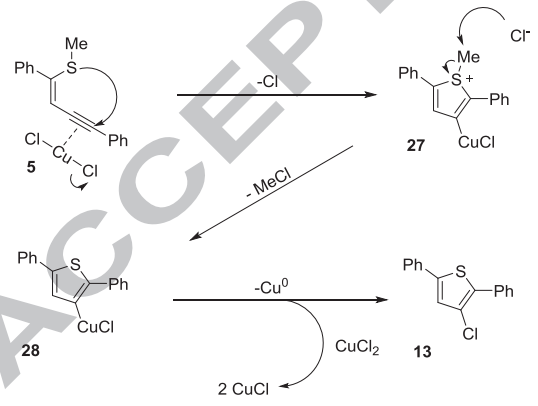
Even though the bromo- and iodocyclization of 2-alkynylmethylselenobenzene has already been reported, there is no reported example of chlorocyclization.[26] Herein we disclose the first ever report of this chlorocyclization reaction starting with 2-alkynylmethylselenobenzene **12** using table salt and 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).



Scheme 4. Synthesis of alkyl and vinyl substituted thiophenes.

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 Cu_2SO_4•$5H_2O$ is mixed with NaCl in ethanol, the resulting $CuCl_2$ 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 $CuCl_2$ to produce CuCl.



Scheme 5. Proposed mechanism for chlorocyclization reaction.

It is well known that Cu_2SO_4•$5H_2O$ in the presence of NaI or NaBr results in the formation of CuI_2 or $CuBr_2$, respectively, which easily gets converted to I_2 and Br_2 in situ.[28] The mechanism of the cyclization reaction involving an I_2 and Br_2 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.

Acknowledgments

We are grateful to Research Corporation for Science Advancement for a Cottrell College Science Award (ID 23248), the University of West Florida (UWF), and UWF's Office of Research and Sponsored Programs for supporting this research. Research is also supported by the National Institute of General Medical Sciences of the National Institutes of Health under grant number 1T34GM110517-01. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Authors are also grateful to Dr. Tim Royappa for his help and support throughout the project.

References and Notes

(1) Gramec, D.; Mašič, L. P.; Dolenc, M. S. *Chem. Res. Toxicol.* **2014**, *27*, 1344–1358.
(2) Bondock, S.; Fadaly, W.; Metwally, M. A. *Eur. J. Med. Chem.* **2010**, *45*, 3692–3701.
(3) Przybilla, B.; Schwab-Przybilla, U.; Ruzicka, T.; Ring, J. *Photodermatol.* **1987**, *4*, 73–78.
(4) John, J.; Koshy, S. K. G. *J. Am. Board Fam. Med.* **2012**, *25*, 343–349.
(5) Forsch, R. A.; Wright, J. E.; Rosowsky, A. *Bioorg. Med. Chem.* **2002**, *10*, 2067–2076.
(6) Hudson, J. B.; Graham, E. A.; Micki, N.; Hudson, L.; Towers, G. H. N. *Photochem. Photobiol.* **1986**, *44*, 477–482.
(7) Mishra, A.; Ma, C.-Q.; Segura, J. L.; Bäuerle, P. *Handbook of Thiophene-Based Materials*; John Wiley & Sons, Ltd, 2009.
(8) Chou, Y.-H.; Takasugi, S.; Goseki, R.; Ishizone, T.; Chen, W.-C. *Polym. Chem.* **2014**, *5*, 1063–1071.
(9) Osken, I.; Gundogan, A. S.; Tekin, E.; Eroglu, M. S.; Ozturk, T. *Macromolecules* **2013**, *46*, 9202–9210.
(10) Mushrush, M.; Facchetti, A.; Lefenfeld, M.; Katz, H. E.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 9414–9423.
(11) Roncali, J. *Chem. Rev.* **1992**, *92*, 711–738.
(12) Roncali, J. *Chem. Rev.* **1997**, *97*, 173–206.
(13) Mehmood, U.; Al-Ahmed, A.; Hussein, I. A. *Renew. Sust. Energ. Rev.* **2016**, *57*, 550–561.
(14) Shiah, H.-S.; Lee, W.-S.; Juang, S.-H.; Hong, P.-C.; Lung, C.-C.; Chang, C.-J.; Chou, K.-M.; Chang, J.-Y. *Biochem. Pharmacol.* **2007**, *73*, 610–619.
(15) Juang, S.-H.; Lung, C.-C.; Hsu, P.-C.; Hsu, K.-S.; Li, Y.-C.; Hong, P.-C.; Shiah, H.-S.; Kuo, C.-C.; Huang, C.-W.; Wang, Y.-C.; Huang, L.; Chen, T. S.; Chen, S.-F.; Fu, K.-C.; Hsu, C.-L.; Lin, M.-J.; Chang, C.; Ashendel, C. L.; Chan, T. C. K.; Chou, K.-M.; Chang, J.-Y. *Mol. Cancer Ther.* **2007**, *6*, 193–202.
(16) Gai, B. M.; Stein, A. L.; Roehrs, J. A.; Bilheri, F. N.; Nogueira, C. W.; Zeni, G. *Org. Biomol. Chem.* **2012**, *10*, 798–807.
(17) Schumacher, R. F.; Rosário, A. R.; Souza, A. C. G.; Acker, C. I.; Nogueira, C. W.; Zeni, G. *Bioorg. Med. Chem.* **2011**, *19*, 1418–1425.
(18) Franchetti, P.; Cappellacci, L.; Sheikha, G. A.; Jayaram, H. N.; Gurudutt, V. V.; Sint, T.; Schneider, B. P.; Jones, W. D.; Goldstein, B. M.; Perra, G.; De Montis, A.; Loi, A. G.; La Colla, P.; Grifantini, M. *J. Med. Chem.* **1997**, *40*, 1731–1737.
(19) (a) Chang, W.-H.; Meng, L.; Dou, L.; You, J.; Chen, C.-C.; Yang, Y.; Young, E. P.; Li, G.; Yang, Y. *Macromolecules* **2015**, *48*, 562–568. (b) Shahid, M.; Ashraf, R. S.; Huang, Z.; Kronemeijer, A. J.; McCarthy-Ward, T.; McCulloch, I.; Durrant, J. R.; Sirringhaus, H.; Heeney, M. *J. Mater. Chem.* **2012**, *22*, 12817–12823. (c) Alghamdi, A. A. B.; Watters, D. C.; Yi, H.; Al-Faifi, S.; Almeataq, M. S.; Coles,

D.; Kingsley, J.; Lidzey, D. G.; Iraqi, A. *J. Mater. Chem. A* **2013**, *1*, 5165–5171. (d) Hollinger, J.; Seferos, D. S. *Macromolecules* **2014**, *47*, 5002–5009. (e) Hollinger, J.; Gao, D.; Seferos, D. S. *Isr. J. Chem.* **2014**, *54*, 440–453. (f) Lee, W.-H.; Son, S. K.; Kim, K.; Lee, S. K.; Shin, W. S.; Moon, S.-J.; Kang, I.-N. *Macromolecules* **2012**, *45*, 1303–1312.

(20) (a) Hernandes, M. Z.; Cavalcanti, S. M. T.; Moreira, D. R. M.; Leite, W. F. de; Junior, A.; Lima, A. C. *Curr. Drug Targets* **2010**, *11*, 303–314. (b) Zimmermann, M. O.; Lange, A.; Boeckler, F. M. *J. Chem. Inf. Model.* **2015**, *55*, 687–699.

(21) Wishart, D. S.; Knox, C.; Guo, A. C.; Shrivastava, S.; Hassanali, M.; Stothard, P.; Chang, Z.; Woolsey, J. *Nucleic Acids Res.* **2006**, *34*, D668–D672.

(22) (a) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937–2980. (b) Ali, S.; Zhu, H.; Xia, X.; Ji, K.; Yang, Y. *Org. Lett.* **2011**, *13*, 2598–2601. (c) Zhu, H.; Ji, K.; Yang, F.; Wang, L.; Zhao, S.; Ali, S. *Org. Lett.* **2011**, *13*, 684–687. (d) Mothe, S. R.; Kothandaraman, P.; Rao, W.; Chan, P. W. H. *J. Org. Chem.* **2011**, *76*, 2521–2531. (e) Chen, C. C.; Yang, S. C.; Wu, M. J. *J. Org. Chem.* **2011**, *76*, 10269–10274. (f) Mancuso, R.; Gabriele, B. *Molecules* **2014**, *19*, 15687–15719. (g) Gabriele, B.; Mancuso, R.; Larock, R. C. *Curr. Org. Chem.* **2014**, 341–358.

(23) (a) Kim, S.; Dahal, N.; Kesharwani, T. *Tetrahedron Lett.* **2013**, *54*, 4373–4376. (b) Barancelli, D. A.; Schumacher, R. F.; Leite, M. R.; Zeni, G. *Eur. J. Org. Chem.* **2011**, *2011*, 6713–6718. (c) Huang, H.; He, G.; Zhu, G.; Zhu, X.; Qiu, S.; Zhu, H. *J. Org. Chem.* **2015**, *80*, 3480–3487. (d) Shen, Z.; Lu, X. *Adv. Synth. Catal.* **2009**, *351*, 3107–3112. (e) Fu, W.-J.; Xu, F.-J.; Guo, W.-B.; Zhu, M.; Xu, C. *Bull. Korean Chem. Soc. 2013,* **2013**, *34*, 887–891.

(24) Santana, A. S.; Carvalho, D. B.; Cassemiro, N. S.; Viana, L. H.; Hurtado, G. R.; Amaral, M. S.; Kassab, N. M.; Guerrero, P. G.; Barbosa, S. L.; Dabdoub, M. J.; Baroni, A. C. M. *Tetrahedron Lett.* **2014**, *55*, 52–55.

(25) Please see supporting information for the reaction optimization

(26) Kesharwani, T.; Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 2307–2312.

(27) Shen, Z.; Lu, X. *Adv. Synth. Catal.* **2009**, *351*, 3107–3112.

(28) Lu, W.-D.; Wu, M.-J. *Tetrahedron* **2007**, *63*, 356–362.

(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; ^{1}H 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