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One-Pot, Regioselective Consecutive Multihalogenation of 2,2′-Bithiophene

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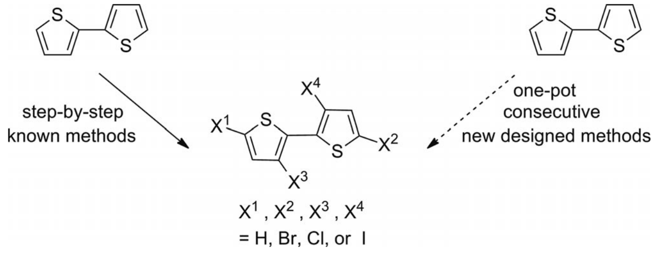
The one-pot regioselective consecutive multihalogenation of 2,2′-bithiophene (**1**) was demonstrated. Compound **1** was consecutively halogenated with lithium halides such as lithium bromide, chloride, and/or iodide in the presence of lead tetraacetate in chloroform at room temperature or under reflux conditions to give 5-bromo(or chloro)-5′-iodo(or chloro)-, 3-bromo(or chloro)-5,5′-dibromo(or dichloro, diiodo)-, 3,3′-dibromo-(or dichloro)-5,5′-diiodo(or dibromo, dichloro)-, and 3,3′,5-tribromo(or trichloro)-5′-iodo(or bromo)-2,2′-bithiophenes. Notably, this process offers a regioselective method for consecutive multihalogenation in one pot, and the yields and selectivity are also higher than those obtained in the step-by-step and concurrent halogenation methods.

Introduction

The regioselective halogenation of electron-rich aromatic compounds is a subject of high interest in various fields of chemistry.[1] Although several electrophilic halogenation reagents and methods have been reported,[1–18] it is hard to control the selectivity and multiplicity in one-pot halogenation reactions. Therefore, significant academic efforts are underway to develop more efficient and selective one-pot consecutive multihalogenation reactions. To the best of our knowledge, the selective multihalogenation of electron-rich aromatic compounds with the use of two or more halogen sources in one pot has not yet been reported.

Motivated by the fact that halo-2,2′-bithiophenes are crucial for the synthesis of various materials used in electrochemistry, polymer science, the semiconductor industry, and nanotechnology,[19] we selected 2,2′-bithiophene (**1**) as a model compound to develop a one-pot, regioselective consecutive multihalogenation system. Specifically, polyhalobithiophenes such as bromochloroiodo-, bromoiodo-, bromochloro-, and dibromodiiodo-2,2′-bithiophenes are key starting materials that allow the synthesis of regioselectively substituted 2,2′-bithiophenes and well-defined oligothiophenes.[19h–19m,20]

A common method used to synthesize halo-2,2′-bithiophenes is the transition-metal-catalyzed coupling of halothiophenes.[19l–19n,20] Several direct halogenations of **1** have been reported by using bromine,[19k] *N*-bromosuccinimide,[21] quaternary ammonium polyhalides,[22] thionyl chloride,[23] and 2-halo-4,5-dichloropyridazin-3(2*H*)-one.[24] However, it is difficult to prepare multihalogenated **1** regioselectively with two or more different halogen atoms in one pot. Inspired by our recent report on the conversion of a nucleophilic halide into an electrophilic one by using a metal halide (MX_n)/lead tetraacetate [$Pb(OAc)_4$] combination,[1a] we attempted the consecutive one-pot multihalogenation of an electron-rich aromatic compound (Scheme 1).



Scheme 1. Known and newly designed halogenation.

According to the literature,[1a,25] treatment of MX_n with $Pb(OAc)_4$ in an organic solvent affords halogen acetate (AcOX), which is an X^+ equivalent and an excellent electrophilic halogenation agent for electron-rich aromatic compounds.

In the reaction of $Pb(OAc)_4$ with MX_n, the concentration of AcOX generated depends on the type and amount of MX_n used (Scheme 2). In turn, the reactivity and regioselec-

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tivity of the halogenation step is controlled by the difference in and order of reactivity of AcOX. Therefore, this system may be very useful for the one-pot consecutive halogenation of electron-rich aromatic compounds. Herein, we report the results of the regioselective consecutive multihalogenation of **1**.

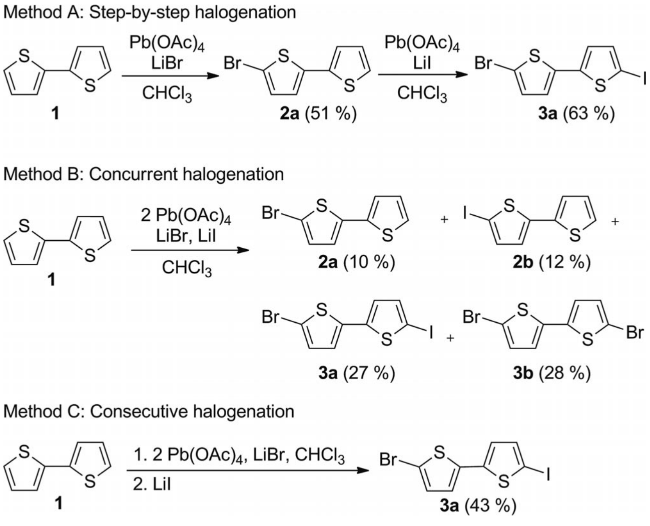
$$\mathrm{Pb(OAc)_4 + MX}_n \longrightarrow \mathrm{Pb(OAc)_2 + MX}_{n-1}\mathrm{(OAc) + AcOX}$$

$$(\mathrm{X = Br, Cl})$$

Scheme 2. Generation of AcOX by the reaction of metal halides (MX_n) with $Pb(OAc)_4$.

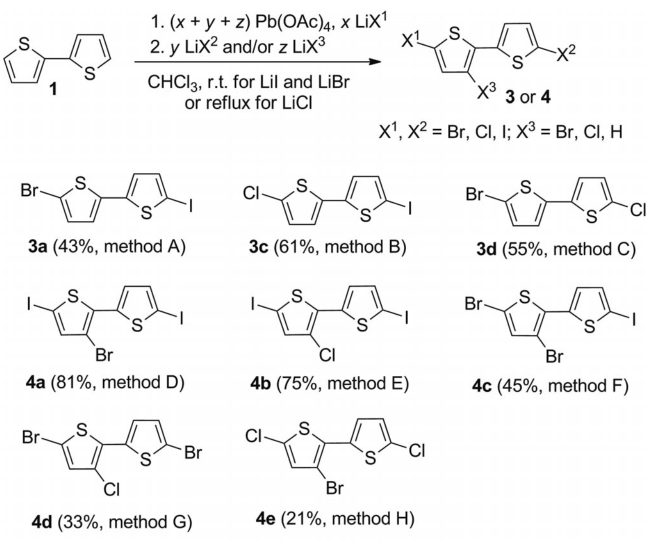
Results and Discussion

To evaluate the above hypothesis, we attempted the consecutive multihalogenation reaction by sequentially adding MX_n to the flask containing an excess amount of $Pb(OAc)_4$. Fortunately, we found that the consecutive reaction of **1** with copper bromide (1 equiv.) followed by copper iodide (1 equiv.) in the presence of $Pb(OAc)_4$ (2 equiv.) in chloroform afforded 30% yield of 5-bromo-5′-iodo-2,2′-bithiophene (**3a**). After screening MX_n and the solvents,[26] we selected the $Pb(OAc)_4$/LiX (X = Br, Cl, I)/$CHCl_3$ system at room temperature as the optimized conditions for the bromination and iodination reactions and the same system at reflux temperature for the chlorination reaction. First, the consecutive reaction of **1** with lithium bromide and then with lithium iodide (each 1 equiv.) under the optimized conditions afforded **3a** in 43% yield (Scheme 3, method C). Bromination, chlorination, and iodination of **1** readily occurred, whereas fluorination was not accomplished under these conditions. To evaluate the efficiency of the consecutive reaction, the yields of the products were compared to those of the step-by-step process and the concurrent process (Scheme 3).



Scheme 3. Comparison of the synthetic processes leading to 5-bromo-5′-iodo-2,2′-bithiophene.

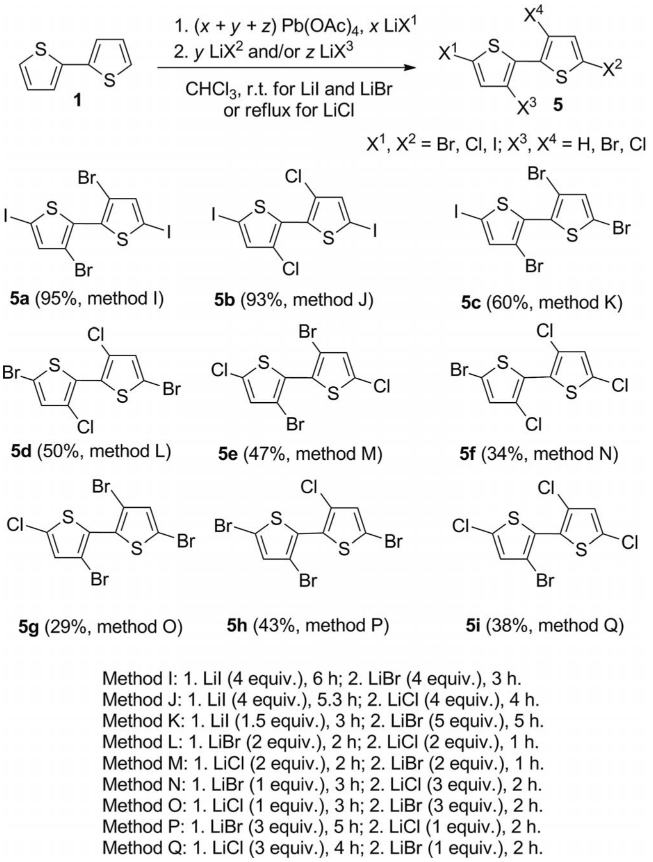
Compound **3a** was also synthesized by a two-step halogenation reaction starting from **1** in 32% overall yield (Scheme 3, method A), whereas the concurrent reaction of **1** with lithium bromide and lithium iodide in the presence of $Pb(OAc)_4$ (2 equiv.) yielded four products: 5-bromo-2,2′-bithiophene (**2a**, 10%), 5-iodo-2,2′-bithiophene (**2b**, 12%), 5-bromo-5′-iodo-2,2′-bithiophene (**3a**, 27%), and 5,5′-dibromo-2,2′-bithiophene (**3b**, 28%; Scheme 3, method B). Thus, the one-pot consecutive halogenation method (Scheme 3, method C) is the most efficient process to generate the desired product. On the basis of these findings, we examined the one-pot consecutive multihalogenation of **1** under the optimized conditions (Schemes 4 and 5). Consecutive dihalogenation of **1** with LiBr, LiCl, and/or LiI under the optimized conditions afforded the corresponding dihalides **3a** (43%), **3c** (61%), and **3d** (55%, Scheme 4). According to our preliminary experiments, the yields of the dihalogenation reactions depend on the order in which the lithium halides are added.[28] The yields of **3a** and **3c** were better if LiI was added last, whereas **3d** was produced in better yields if LiBr was added last. 3,5,5′-Trihalo-2,2′-bithiophenes were prepared by one-pot consecutive halogenation from the corresponding LiX under the optimized conditions to give **4a**–**e** in 21–81% yield (Scheme 4). The yields of 5,5′-diiodo-3-halo-2,2′-bithiophenes **4a** and **4b** were higher than those of the 5,5′-dibromo(dichloro)-3-halo (i.e., **4d** and **4e**) and 5,5′-bromochloro-3-halo (i.e., **4c**) derivatives. Also, 3,3′,5,5′-tetrahalo-2,2′-bithiophenes **5a**–**i** were obtained in 29–95% yield by the one-pot consecutive halo-



method A: 1. LiBr (1 equiv.), 1.5 h; 2. LiI (1 equiv.), 0.5 h.
method B: 1. LiCl (1 equiv.), 5 h; 2. LiI (1 equiv.), 2 h.
method C: 1. LiCl (1 equiv.), 4 h; 2. LiBr (1 equiv.), 2 h.
method D: 1. LiI (4 equiv.), 5 h; 2. LiBr (1.3 equiv.), 1.5 h.
method E: 1. LiI (4 equiv.), 5 h; 2. LiCl (1.5 equiv.), 2 h.
method F: 1. LiI (1 equiv.), 2.5 h; 2. LiBr (2 equiv.), 0.5 h.
method G: 1. LiBr (2 equiv.), 4 h; 2. LiCl (1 equiv.), 1 h.
method H: 1. LiCl (2 equiv.), 5 h; 2. LiBr (1 equiv.), 1 h.

Scheme 4. Consecutive di- and trihalogenation of 2,2′-bithiophene under ambient conditions for LiI and LiBr in $CHCl_3$ and in refluxing $CHCl_3$ for LiCl.

genation system (Scheme 5). The yields of 3,3′-dibromo(or dichloro)-5,5′-diiodo derivatives **5a** and **5b** were higher than those of **5c**–**i**.



Method I: 1. LiI (4 equiv.), 6 h; 2. LiBr (4 equiv.), 3 h.
Method J: 1. LiI (4 equiv.), 5.3 h; 2. LiCl (4 equiv.), 4 h.
Method K: 1. LiI (1.5 equiv.), 3 h; 2. LiBr (5 equiv.), 5 h.
Method L: 1. LiBr (2 equiv.), 2 h; 2. LiCl (2 equiv.), 1 h.
Method M: 1. LiCl (2 equiv.), 2 h; 2. LiBr (2 equiv.), 1 h.
Method N: 1. LiBr (1 equiv.), 3 h; 2. LiCl (3 equiv.), 2 h.
Method O: 1. LiCl (1 equiv.), 3 h; 2. LiBr (3 equiv.), 2 h.
Method P: 1. LiBr (3 equiv.), 5 h; 2. LiCl (1 equiv.), 2 h.
Method Q: 1. LiCl (3 equiv.), 4 h; 2. LiBr (1 equiv.), 2 h.

Scheme 5. Consecutive tetrahalogenation of 2,2′-bithiophene under ambient conditions for LiI and LiBr in $CHCl_3$ and in refluxing $CHCl_3$ for LiCl.

Regioselectivity in the electrophilic halogenation of **1** is well explained by the Wheland intermediates.[24,27,29] Because of the delocalization of the intermediate cation, electrophilic attack from the 2-position is more favorable than from the 3-position in the thiophene ring. The cationic intermediates resulting from attack at both the 3(or 3′)-position and the 5(or 5′)-position in the bithiophenes is also resonance stabilized. The structures of all the products were characterized by HRMS and FTIR, ^{1}H NMR, and ^{13}C NMR spectroscopy. All analytical samples were also compared with the reference samples, which were prepared by the step-by-step halogenation.

Conclusions

In summary, we have accomplished the one-pot, regioselective consecutive multihalogenation of **1** by using LiX (X = Cl, Br, and I)/$Pb(OAc)_4$ in chloroform. By controlling the order in which MX_n is added, the selectivity could be adjusted. The multiplicity of the halogen atoms was also controlled by adjusting the amount of lithium halides. Iodination is more favorable than bromination and chlorination in our system. Ultimately, our consecutive halogenation provides an alternative to the step-by-step multihalogenation of electron-rich aromatic compounds. The scope of the applications of this new methodology is currently being investigated in our laboratory.

Experimental Section

General Procedure for Dihalogenation: Lead tetraacetate (2.80 g, 6.014 mmol, 2 equiv., 95% reagent) was dissolved in chloroform (15–50 mL). After adding the first lithium halide (1 equiv.), the mixture was stirred at room temperature or heated at reflux until 2,2′-bithiophene (0.5 g, 3.007 mmol) disappeared from the TLC plate. The second lithium halide (1 equiv.) was then added to the reaction mixture under the same conditions. The resulting mixture was stirred at room temperature or heated at reflux until monohalo-2,2′-bithiophene disappeared from the TLC plate. After filtering the reaction mixture, the solvent was evaporated under reduced pressure. The crude product was applied on top of an open-bed silica gel column. The column was eluted with *n*-hexane. Fractions containing the product were combined and evaporated under reduced pressure to give the corresponding dihalo-2,2′-bithiophenes **3**.

General Procedure for Tri- or Tetrahalogenation: Lead tetraacetate (3 or 4 equiv., 95% reagent) was dissolved in chloroform (15–50 mL). After adding the first lithium halide (1, 2 or 3 equiv.), the mixture was stirred at room temperature or heated at reflux until 2,2′-bithiophene (0.5 g, 3.007 mmol) disappeared from the TLC plate. The second lithium halide (1, 2, or 3 equiv.) was then added to the reaction mixture under the same conditions. The resulting mixture was stirred at room temperature or heated at reflux until halo-2,2′-bithiophene disappeared from the TLC plate. After filtering the reaction mixture, the solvent was evaporated under reduced pressure. The crude product was applied on top of an open-bed silica gel column (2.5 × 25 cm). The column was eluted with *n*-hexane. Fractions containing the product were combined and evaporated under reduced pressure to give the corresponding tri- or tetrahalo-2,2′-bithiophenes **4** or **5**.

Supporting Information (see footnote on the first page of this article): Metal halide and solvent screening, full experimental and spectroscopic data.

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