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# Preparation of Brominated 2-Alkoxythiophenes via Oxidation and Etherification of 2-Thienyltrifluoroborate Salts

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## ABSTRACT


**The synthesis of ring brominated long-chain 2-alkoxythiophenes is reported, involving mild (Oxone) oxidation of readily prepared 2-thienyltrifluoroborate salts followed by Mitsunobu etherification. Both procedures are operationally straightforward and use inexpensive reagents. Using this approach, several novel mono- and dibrominated octyloxythiophenes with previously elusive substitution patterns were prepared. One such compound was elaborated to a novel 5-alkoxythieno[3,2-*b*]thiophene-2-carboxylate ester, marking the first synthetic entry into this family of compounds.**

Alkoxythiophene subunits have recently attracted attention in a variety of materials applications. The more synthetically accessible 3-alkoxythiophenes have found particular application in conducting polymers[1] for photovoltaic and nonlinear optical applications. Although 2-alkoxythiophenes have been less extensively explored, they have found applications as liquid crystals,[2] photochromic materials,[3] potential nonlinear optical (NLO) materials via organometallic complexes,[4] and bioactive targets.[5]

Traditional approaches for the alkoxylation of heteroaromatic systems include Ullmann-type copper-mediated reactions[6] and nucleophilic aromatic substitution.[7] However, despite several examples of high-yielding alkoxylation to afford 3-alkoxythiophenes[1e,8] (reported yields range from 40 to 90% but are typically above 80%), these approaches are not amenable to functionalization at the C-2 position of the thiophene ring. 2-Methoxylation[9] and 2-ethoxylation[9b,10] of halothiophenes can sometimes be efficient, but yields vary substantially (10−88%) depending on the substrate and are typically modest. Increasing the alkyl tail length results in reduced yields[2c,11] even under

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aggressive conditions. Efficient access to 2-alkoxythiophenes is possible by reaction of $\gamma$-keto esters with Lawesson's reagent; however, this approach requires an aryl substituent at the C-5 position of the resulting 2-alkoxythiophene.[12] Other analogous sulfurization approaches suffer from low yield/reproducibility or problematic mixtures of products.[13] In contrast to phenolic systems, Williamson etherification of hydroxythiophenes (which exist as thienones[14] in the absence of strong hydrogen-bonding groups) gives mixtures of products due to unwanted reaction at the C-3 and C-5 sites.[15] Recently, several palladium-[16] and copper-[8a,e,17] catalyzed coupling approaches to 3-alkoxythiophenes from halothiophenes and alcohols have been reported; however, none of these methods have been extended to 2-alkoxythiophenes. Thus, the preparation of 2-alkoxythiophenes remains a significant synthetic challenge.[18]

We required a series of brominated 2-alkoxythiophenes **3c**–**e** as synthetic intermediates en route to other materials. However, no good literature methods exist for the preparation of C-3 and C-4 brominated 2-alkoxythiophenes, as the previously discussed approaches are generally inefficient and alkoxylation of dibromothiophenes tends to proceed with poor regioselectivity.[9b]

Herein we report the development of a strategically distinct approach to ring brominated 2-alkoxythiophenes that involves the selective metalation of a range of bromothiophene precursors en route to the corresponding

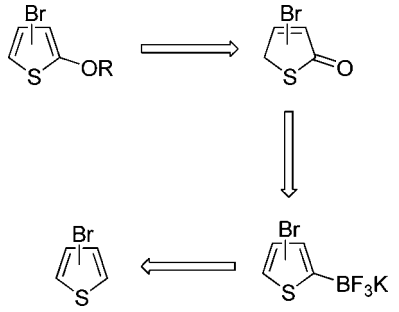


**Figure 1.** Strategic approach to brominated 2-alkoxythiophene targets from bromothiophene precursors.

3-, 4-, or 5-bromo-2-thienyltrifluoroborates. Mild oxidation to the corresponding 2(5*H*)-thienones followed by Mitsunobu etherification then affords the brominated 2-alkoxythiophene target compounds (Figure 1).

Trifluoroborate salts have recently attracted attention as easily handled boronic acid analogs that are stable to a range of reaction conditions, including a variety of oxidants[19] (TPAP/NMO, Swern, Dess-Martin periodinane, and IBX) which leave the trifluoroborate moiety intact. Interestingly, as recently reported by Molander and Cavalcanti,[20] aryl trifluoroborates can be efficiently oxidized to phenols with Oxone in acetone and water at room temperature. The resulting compounds were highly pure after only a silica plug filtration. Although the authors reported the successful oxidation of phenyl, benzo[*b*]furan-2-yl, benzo[*b*]thien-2-yl, and 3-thienyl trifluoroborate salts, 2-thienyltrifluoroborates were not studied. However, we reasoned that these intermediates would offer an attractive approach to novel brominated 2(5*H*)-thienones **2b**–**e**, since it is well-known that hydroxythiophenes instantly tautomerize[14] to 2(5*H*)-thienones.

A series of 2-thienyltrifluoroborate salts **1a**–**e** were readily prepared from commercially available and inexpensive thiophene precursors via the corresponding boronic acids;[21] the syntheses of these materials are described in the Supporting Information.

Oxidation of **1a**–**e** to the corresponding 2(5*H*)-thienones **2a**–**e** was achieved via a modified version of Molander's recent procedure[20] (Table 1). In the operationally straightforward oxidation procedure, 2-thienyltrifluoroborate salt **1** in acetone (0.2 M) was mixed with aqueous Oxone

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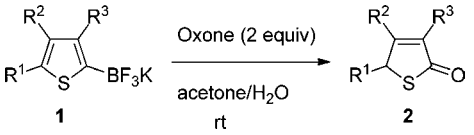
**Table 1.** Oxone-Mediated Oxidation of 2-Thienyltrifluoroborate Salts **1** to 2(5*H*)-Thienones **2**[a]




| entry | product | $R^1$ | $R^2$ | $R^3$ | time (min) | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **2a** | H | H | H | 5 | 71 |
| 2 | **2b** | Br | H | H | 5 | 79[c] |
| 3 | **2c** | H | Br | H | 5 | 79 |
| 4 | **2c** | H | Br | H | 60 | –[d] |
| 5 | **2d** | H | Br | Br | 30 | 63 |
| 6 | **2d** | H | Br | Br | 60 | 77 |
| 7 | **2e** | H | H | Br | 60 | 76 |

[a] Conditions: substrate (0.1 M), Oxone (0.2 M, 2 equiv), in acetone/$H_2O$ (1:1), rt, ambient atmosphere. [b] Isolated yield after silica plug filtration (petroleum ether). [c] Product decomposes upon storage. [d] Significant ( > 10%) presence of a byproduct after silica plug filtration.

(0.4 M in potassium monopersulfate) at room temperature under an ambient atmosphere. Quenching with acid, workup, and elution through a silica plug with dichloromethane furnished the desired 2(5*H*)-thienone **2** in high purity. Although good yields (71−79%) were obtained for **2a**−**c** after only 5 min of reaction (Table 1, entries 1−3), the formation of **2d** was slower, requiring 1 h to reach a comparable yield (entries 5 and 6). Compound **2e** was also prepared using this extended reaction time (entry 7). Interestingly, when the reaction leading to **2c** was allowed to proceed for 1 h (entry 4), a significant amount (*ca.* 10%) of an unidentified byproduct formed, as seen by $^1$H NMR; it was thus important to limit the reaction time to 5 min (entry 3). However, this impurity was easily separable by recrystallization of **2c**. Similar byproduct formation was not seen for **2d**−**e**. Compounds **1a** and **1b** were not exposed to the 1 h reaction conditions due to concerns regarding the stability of **2a** and **2b** and because good yields were achieved after 5 min.

2(5*H*)-Thienones **2a** (liquid)[22] and **2b** (solid, mp = 23 °C)[23] are somewhat air-sensitive and decompose even on storage in the freezer. In contrast, 2(5*H*)-thienones **2c**−**e** are high-melting (*ca.* 80−114 °C) air-stable solids that crystallize easily.

Elaboration of 2(5*H*)-thienones **2a**−**e** to the corresponding 2-alkoxythiophenes **3a**−**e** required a selective *O*-alkylation procedure that avoided the known problems associated with the simple *O*-alkylation of 2(5*H*)-thienones.[15] Our attention was drawn to a recent report by Harris and co-workers,[5b] who achieved the Mitsunobu etherification of the parent 2(5*H*)-thienone **2a** using di-*tert*-butyl azodicarboxylate (DTAD) and polystyrene-supported $PPh_3$ with a variety of alcohols.

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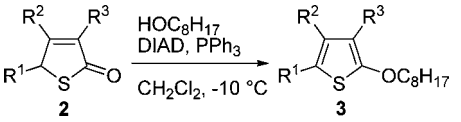
**Table 2.** Synthesis of Substituted 2-Alkoxythiophenes by Mitsunobu Etherification[a]



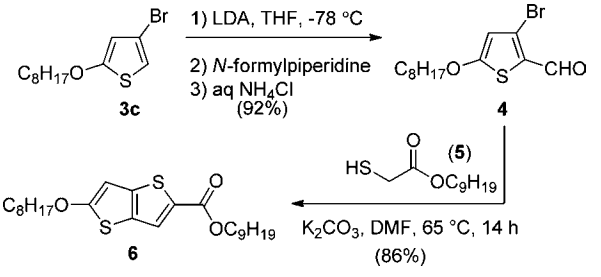

| entry | product | $R^1$ | $R^2$ | $R^3$ | time (h) | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **3a** | H | H | H | 1 | 83 |
| 2 | **3b** | Br | H | H | 24 | –[c] |
| 3 | **3c** | H | Br | H | 1 | 86 |
| 4 | **3d** | H | Br | Br | 1 | 87 |
| 5 | **3e** | H | H | Br | 1 | 80 |

[a] Conditions: (i) $PPh_3$ (3 equiv), $CH_2Cl_2$, −10 °C, (ii) DIAD (3 equiv), −10 °C, 10 min, (iii) 1-octanol (3 equiv), −10 °C, 30 min, (iv) substrate **2** (1 equiv), −10 °C → rt, 1 h, unless otherwise stated. [b] Isolated yield after column chromatography (petroleum ether). [c] Only trace amounts of product detected by $^1$H NMR.

We modified Harris' conditions for experimental convenience and lowered expense. 2(5*H*)-Thienones **2** were treated with 3 equiv each of diisopropyl azodicarboxylate (DIAD), $PPh_3$, and 1-octanol in anhydrous dichloromethane at *ca.* −10 °C under an argon atmosphere (Table 2). After 1 h at room temperature, the reaction mixture was concentrated and filtered through a short silica plug with petroleum ether to remove the polar byproduct. The resulting crude products **3** could easily be further purified by column chromatography to afford air-stable, colorless liquids. Using this method, we prepared **3a** (entry 1) and **3c**−**e** (entries 3−5) in excellent yields (80−87%). This reaction was amenable to scale-up (~2 g quantities of **3c** and **3d** were prepared) with no change in yield.

Interestingly, despite the efficiency of this chemistry when using other substrates, 5-bromo-2(5*H*)-thienone **2b** could not be transformed in this way to desired product **3b** (Table 2, entry 2). After 24 h under these conditions, only a trace of the desired product was seen by $^1$H NMR. Additionally, a larger proportion of the protodebrominated adduct **3a** was noticed, indicative of a competing side reaction with substrate **2b**.

**Scheme 1.** Elaboration of 2-Alkoxythiophene **3c** to Novel 5-Alkoxythienothiophene **6**



In order to preliminarily demonstrate the usefulness of these 2-alkoxythiophenes as synthetic building blocks, we have prepared the first long-chain alkoxythienothiophene from 2-alkoxythiophene **3c** (Scheme 1). Previously, only a handful of simple short-chain (OR = OMe, OEt, O*t*-Bu) 5-alkoxythieno[3,2-*b*]thiophenes have been reported.[24] Importantly, the methods used were harsh as well as inefficient and could not be extended to other alkyl chains. Indeed, in our hands, an analogous nucleophilic substitution approach to **6** from a 2-chlorothieno[3,2-*b*]-thiophene-2-carboxylate ester gave no traces of the desired product.

Formylation of **3c** with LDA and *N*-formylpiperidine afforded **4** in excellent yield (92%). Exploiting our recently reported method for thienothiophene synthesis,[25] we treated aldehyde **4** with nonyl mercaptoacetate **5** in the presence of base at 65 °C, affording thienothiophene **6** in good yield (86%) via a tandem nucleophilic aromatic substitution and aldol condensation reaction (we saw no difference in the two-step yield whether or not intermediate **4** was purified).

In summary, we have developed the first efficient synthetic approach to long-chain ring brominated 2-alkoxythiophenes. This oxidation and etherification sequence, starting from readily prepared potassium 2-thienyltrifluoroborate salts, is operationally straightforward and employs inexpensive reagents. Moreover, it allows access to 2-alkoxythiophenes bearing halogens as functional handles in previously elusive substitution patterns. Efforts are ongoing in our laboratory to expand the scope of this transformation and to explore the use of these ring brominated 2-alkoxythiophenes as synthetic building blocks en route to electron-rich organic materials.

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**Supporting Information Available.** Experimental procedures, characterization data, and $^{1}H$ and $^{13}C$ NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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