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Synthesis of Benzo[*b*]thiophenes by Cyclization of Arylketene Dithioacetal Monoxides under Pummerer-like Conditions

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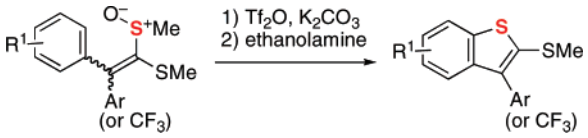
ABSTRACT



Treatment of arylketene bis(methylthio)acetal monoxide with trifluoromethanesulfonic anhydride leads to ring-closure to afford 2-methylthiobenzo[*b*]thiophene in high yield. The reaction is useful for synthesizing multisubstituted benzo[*b*]thiophenes.

The benzo[*b*]thiophene skeleton is a ubiquitous structure found in various compounds ranging from biologically intriguing molecules[1] to advanced organic materials.[2] Construction of the benzo[*b*]thiophene skeleton is hence important. There are several representative methods for the construction, most of which employ benzenethiol derivatives as the starting materials.[3,4] However, methods for synthesis of multisubstituted benzo[*b*]thiophenes are still limited, and hence have to be explored.

We have been interested in ketene dithioacetal monoxides as interesting synthetic intermediates.[5] Here we report a new approach to benzo[*b*]thiophenes starting from ketene dithioacetal monoxides. Our idea is outlined in Scheme 1. Treatment of aryl-substituted ketene dithioacetal monoxide **1** with an oxophilic electrophile would result in cleavage of the oxygen−sulfur bond with concomitant Friedel−Crafts-type electrophilic aromatic substitution to yield **4**. Removal of the methyl group on the cationic sulfur would afford 3-substituted 2-(methylthio)benzo[*b*]thiophene **5**. The synthesis of the starting material **1** was facile and scalable, starting from aryl ketone and formaldehyde dimethyl dithioacetal *S*-oxide (FAMSO) in 3 steps.[6] Thus, our approach to

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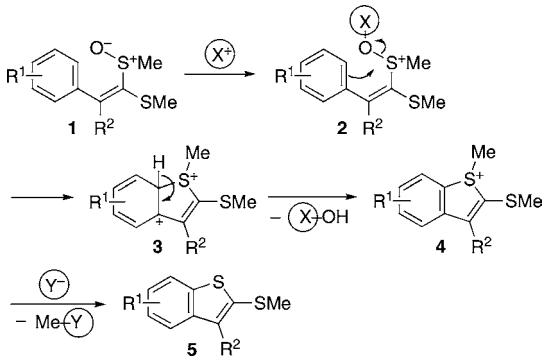
Scheme 1



5 will be useful for the synthesis of multisubstituted benzo[*b*]thiophenes.

The synthesis of the starting material **1** is summarized in Figure 1.[6,7] Although all the results were unoptimized, the

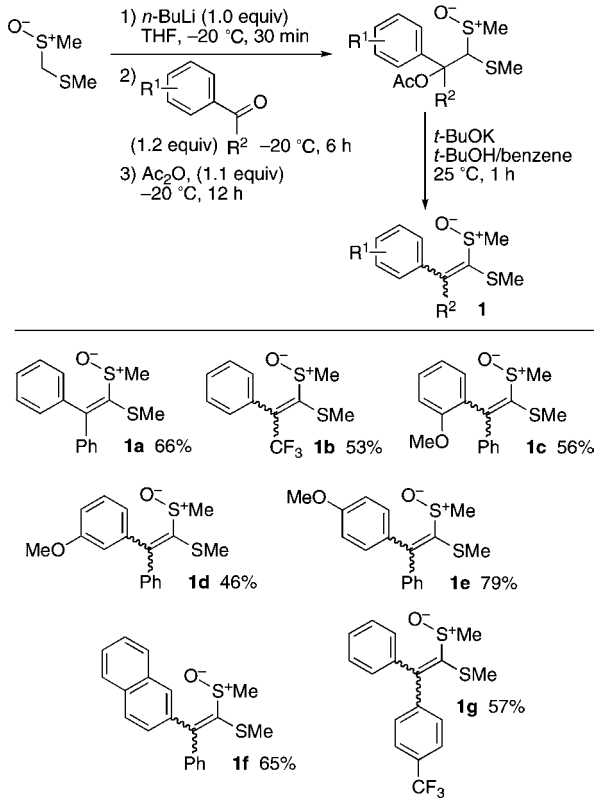
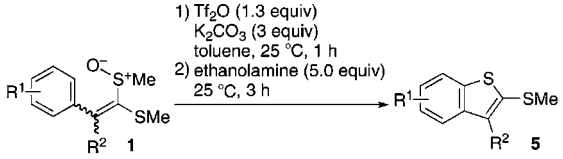


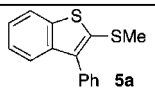
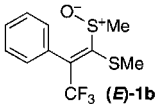
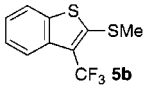
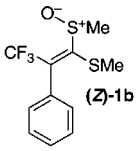
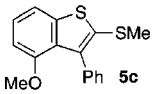
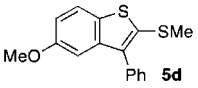
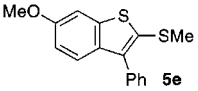
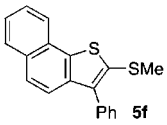
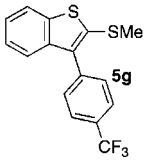
Figure 1. Synthesis of ketene dithioacetal monoxides, precursors of benzo[*b*]thiophenes.

overall transformations were facile to give **1a**−**g** in satisfactory yields. The products except for **1a** were obtained as 1:1 stereoisomeric mixtures. The stereoisomers of **1b** were separable from each other on silica gel.

Treatment of **1a** with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of potassium carbonate in toluene at 25 °C followed by addition of ethanolamine to the reaction

Table 1. Synthesis of Benzo[*b*]thiophenes from **1**



entry	**1**[a]	**5**	yield /%
1	**1a**	 **5a**	86
2	 **(*E*)-1b**	 **5b**	90
3	 **(*Z*)-1b**	**5b**	78
4	**1c**	 **5c**	66
5	**1d**	 **5d**	87
6	**1e**	 **5e**	87
7	**1f**	 **5f**	88
8	**1g**	 **5g**	78

[a] In the reactions of **1c**−**f**, ca. 1:1 mixtures of stereoisomers were used. In the reaction of **1g**, a 7:1 mixture of the stereoisomers was used, although the stereochemistry of each isomer could not be assigned.

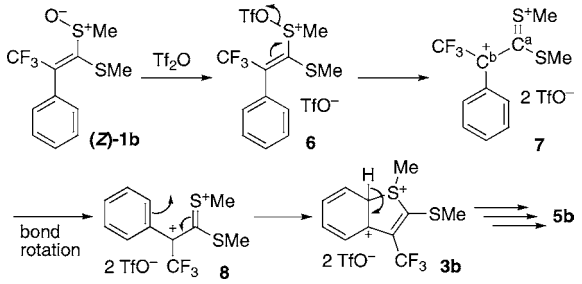
mixture provided benzo[*b*]thiophene **5a** in 86% yield (Table 1, entry 1).[8] It is worth noting that no addition of a nucleophile at the diphenyl-substituted olefinic carbon was

(7) **Experimental procedure:** Formaldehyde dimethyl dithioacetal *S*-oxide (1.0 mL, 10 mmol) and THF (10 mL) were placed in a flask under an atmosphere of argon. *n*-Butyllithium in hexane (1.62 M, 6.0 mL, 10 mmol) was added to the solution at −20 °C, and the mixture was stirred at the same temperature for 30 min. Benzophenone (2.2 g, 12 mmol) was added to the reaction mixture, and the mixture was stirred at −20 °C for 6 h. Acetic anhydride (1.0 mL, 11 mmol) was added to the reaction mixture, and the mixture was stirred at −20 °C for 12 h. Saturated aqueous NH_4Cl was poured into the mixture, and the product was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude mixture, benzene (10 mL), and *tert*-butyl alcohol (10 mL) were placed in a flask under an atmosphere of argon. Potassium *tert*-butoxide was added to the solution at 25 °C, and the mixture was stirred for 1 h. Saturated aqueous NH_4Cl was poured into the mixture and the product was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by chromatography on silica gel provided methyl 1-methylsulfinyl-2,2-diphenylethenyl sulfide (**1a**, 1.84g, 66%).

observed under the Pummerer-like conditions.[9] None of **5a** was obtained when trifluoroacetic anhydride, *p*-toluenesulfonyl chloride, or trifluoromethanesulfonic acid was used instead of Tf_2O.[10]

Trifluoromethyl-substituted (*E*)-**1b** was subjected to the cyclization reaction to yield benzo[*b*]thiophene **5b**[11,12] having a trifluoromethyl group at the 3 position in high yield (entry 2). Interestingly, its stereoisomer (*Z*)-**1b** also underwent the cyclization to afford **5b** in good yield (entry 3). The participation of (*Z*)-**1b** in the cyclization suggests a detailed reaction mechanism (Scheme 2). The sulfur−oxygen bond

Scheme 2

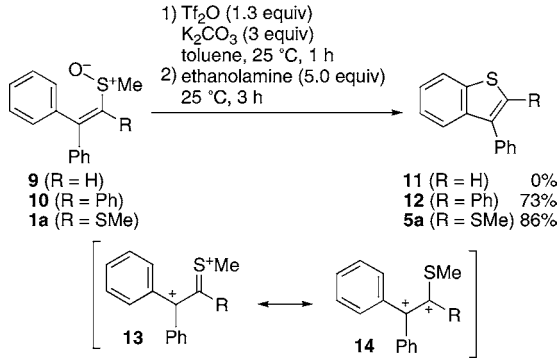


cleavage by Tf_2O would produce a highly stabilized dication **7**. The C^a-C^b single bond of **7** would rotate to form **8**. The dication **8** has a suitable conformation for the cyclization to yield **3b**.

When a 1:1 stereoisomeric mixture of **1c** was treated under the cyclization conditions, the cyclization onto the more electron-rich methoxyphenyl group took place exclusively (entry 4). The reaction of *m*-methoxyphenyl-substituted **1d** led to the C−S bond formation at the para position to the methoxy group selectively (entry 5). Neither C−S bond formation at the ortho position to the methoxy group nor on the other phenyl group was observed. The cyclization reaction of a stereoisomeric mixture of **1e** also took place absolutely onto the methoxyphenyl group (entry 6). In the reaction of **1f**, the cyclization onto the naphthalene is highly preferable to that onto the phenyl ring (entry 7). The reaction of **1g** bearing a trifluoromethylphenyl group and a phenyl group yielded **5g** selectively (entry 8). In cases where R^2 are alkyl groups such as methyl and ethyl, the reactions afforded complex mixtures.

The methylthio group of **1** plays an important role for the synthesis (Scheme 3). Treatment of **9** bearing no methylthio

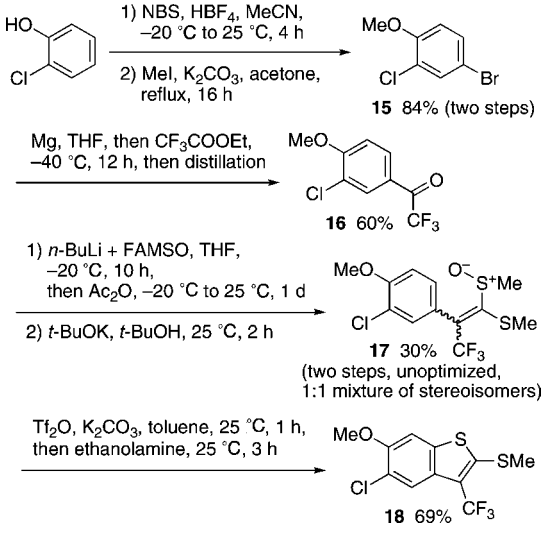
Scheme 3



group under the same conditions afforded a complex mixture. On the other hand, methyl 1,2,2-triphenylethenyl sulfoxide (**10**) reacted to provide 2,3-diphenylbenzo[*b*]thiophene (**12**) in good yield. These results suggest that sufficient stability of the dicationic intermediate **13**/**14** would be quite important for the success of the ring-closure.

The synthesis of **18**, a highly substituted benzo[*b*]thiophene, underscores the utility of the present method (Scheme

Scheme 4



(8) **Experimental procedure:** Methyl 1-methylsulfinyl-2,2-diphenylethenyl sulfide (**1a**, 54.9 mg, 0.19 mmol), K_2CO_3 (90.4 mg, 0.66 mmol), and toluene (4.0 mL) were placed in a flask under an atmosphere of argon. Trifluoromethanesulfonic anhydride (0.045 mL, 0.27 mmol) was added, and the mixture was stirred at 25 °C for 1 h. Ethanolamine (0.060 mL, 1.0 mmol) was added to the reaction mixture, and the mixture was stirred at 25 °C for 3 h. Saturated aqueous $NaHCO_3$ was poured into the mixture and the product was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by chromatography on silica gel provided 2-methylthio-3-phenylbenzo[*b*]thiophene (**5a**, 42.2 mg, 0.16 mmol, 86%).

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(10) High oxophilicity of Tf_2O and its applications were summarized: Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 3077−3119.

(11) The biological activity of 3-trifluoromethylbenzo[*b*]thiophene has been attracting attention. (a) Nussbaumer, P.; Petranyi, G.; Stütz, A. *J. Med. Chem.* **1991**, *34*, 65−73. (b) Gokhale, V. M.; Kulkarni, V. M. *Bioorg. Med. Chem.* **2000**, *8*, 2487−2499. (c) Gokhale, V. M.; Kulkarni, V. M. *J. Med. Chem.* **1999**, *42*, 5348−5358.

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4). Bromination of *o*-chlorophenol[13] followed by methylation yielded **15**. Trifluoroacetylation of magnesiated **15** yielded trifluoromethyl ketone **16** on a large scale.[14] Nucleophilic addition of lithiated FAMSO to **16** followed by elongating conjugation[6] yielded **17**. The ring-closure of **17** by Tf_2O afforded **18**.

Multisubstituted benzo[*b*]thiophenes can find many applications in various fields of chemistry. The present protocol provides a conceptually new and useful approach to the benzo[*b*]thiophene skeleton.

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Supporting Information Available: Characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Konno, T.; Takehana, T.; Mishima, M.; Ishihara, T. *J. Org. Chem.* **2006**, *71*, 3545−3550.