

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

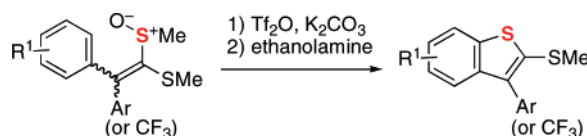
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ABSTRACT



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 molecules¹ 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.

(1) Selected examples: (a) Graham, S. L.; Shepard, K. L.; Anderson, P. S.; Baldwin, J. J.; Best, D. B.; Christy, M. E.; Freedman, M. B.; Gautheron, P.; Habecker, C. N.; Hoffman, J. M.; Lyle, P. A.; Michelson, S. R.; Ponticello, G. S.; Robb, C. M.; Schwam, H.; Smith, A. M.; Smith, R. L.; Sondey, J. M.; Strohmaier, K. M.; Sugrue, M. F.; Varga, S. L. *J. Med. Chem.* **1989**, *32*, 2548–2554. (b) Witter, D. J.; Belvedere, S.; Chen, L.; Secrist, J. P.; Mosley, R. T.; Miller, T. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4562–4567. (c) Grese, T. A.; Cho, S.; Bryant, H. U.; Cole, H. W.; Glasebrook, A. L.; Magee, D. E.; Phillips, D. L.; Rowley, E. R.; Short, L. L. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 201–206.

(2) Selected examples: (a) Kim, M.-S.; Maruyama, H.; Kawai, T.; Irie, M. *Chem. Mater.* **2003**, *15*, 4539–4543. (b) Camaioni, N.; Ridolfi, G.; Fattori, V.; Facaretto, L.; Barbarella, G. *J. Mater. Chem.* **2005**, *15*, 2220–2225. (c) Seed, A. J.; Toyne, K. J.; Goodby, J. W.; Hird, M. J. *Mater. Chem.* **2000**, *10*, 2069–2080. (d) Mazzeo, M.; Vitale, V.; Sala, F. D.; Pisignano, D.; Anni, M.; Barbarella, G.; Favaretto, L.; Zanelli, A.; Cingolani, R.; Gigli, G. *Adv. Mater.* **2003**, *15*, 2060–2063. (e) Yokoyama, Y.; Shiraishi, H.; Tani, Y.; Yokoyama, Y.; Yamaguchi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7194–7195. (f) Irie, M. *Chem. Rev.* **2000**, *100*, 1685–1716.

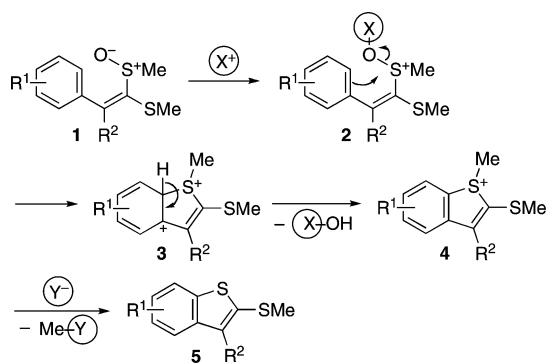
(3) Rayner, C. M.; Graham, M. A. In *Science of Synthesis (Houben-Weyl)*, Category 2; Thomas, E. J., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2000; Vol. 10, Chapter 10.4.

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

(4) Selected recent examples: (a) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473–4475. (b) Larock, R. C.; Yue, D. *Tetrahedron Lett.* **2001**, *42*, 6011–6013. (c) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651–654. (d) Allen, D.; Callaghan, O.; Cordier, F. L.; Dobson, D. R.; Harris, J. R.; Hotten, T. M.; Owton, W. M.; Rathmell, R. E.; Wood, V. A. *Tetrahedron Lett.* **2004**, *45*, 9645–9647. (e) Kobayashi, K.; Nakamura, D.; Miyamoto, K.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1780–1784. (f) Yang, S.-M.; Shie, J.-J.; Fang, J.-M.; Nandy, S. K.; Chang, H.-Y.; Lu, S.-H.; Wang, G. *J. Org. Chem.* **2002**, *67*, 5208–5215. (g) Jeong, H. J.; Yoon, U. Y.; Jang, S. H.; Yoo, U.-A.; Kim, S. N.; Truong, B. T.; Shin, S. C.; Yoon, Y.-J.; Singh, O. M.; Lee, S.-G. *Synlett* **2007**, 1407–1410 and references cited therein.

(5) Yoshida, S.; Yorimitsu, H.; Oshima, K. *Synlett* **2007**, 1622–1624. (6) Ogura, K.; Mitamura, S.; Kishi, K.; Tsuchihashi, G. *Synthesis* **1979**, 880–882.

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

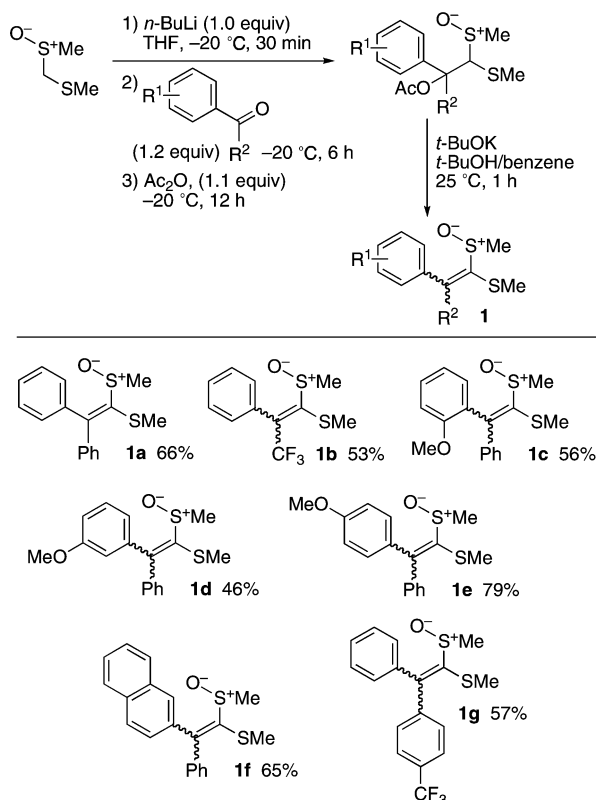
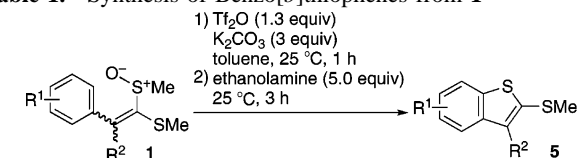


Figure 1. Synthesis of ketene dithioacetal monoxides, precursors of benzo-*[b]*thiophenes.

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 (Tf₂O) 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.

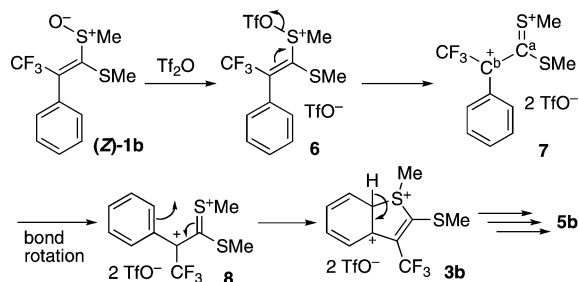
mixture provided benzo-*[b]*thiophene **5a** in 86% yield (Table 1, entry 1).⁸ It is worth noting that no addition of a nucleophile at the diphenyl-substituted olefinic carbon was

(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 NH₄Cl was poured into the mixture, and the product was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over anhydrous Na₂SO₄ 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 NH₄Cl was poured into the mixture and the product was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by chromatography on silica gel provided methyl 1-methylsulfinyl-2,2-diphenylethenyl sulfide (**1a**, 1.84 g, 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 Tf₂O.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 Tf₂O 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

(8) **Experimental procedure:** Methyl 1-methylsulfinyl-2,2-diphenylethyl sulfide (**1a**, 54.9 mg, 0.19 mmol), K₂CO₃ (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 NaHCO₃ was poured into the mixture and the product was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ 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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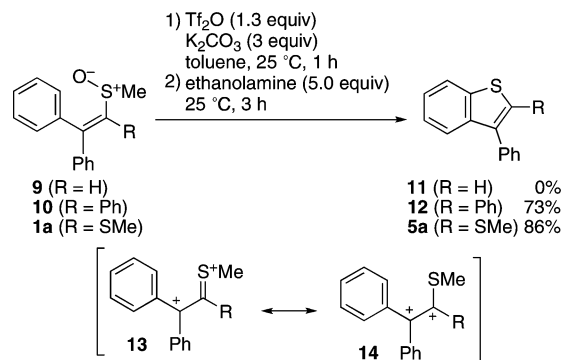
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(12) Synthesis of 3-trifluoromethylbenzo[*b*]thiophenes is not easy. (a) Sawada, H.; Nakayama, M.; Yoshida, M.; Yoshida, T.; Kamigata, N. *J. Fluorine Chem.* **1990**, *46*, 423–431. (b) Akiyama, T.; Kato, K.; Kajitani, M.; Sakaguchi, Y.; Nakamura, J.; Hayashi, H.; Sugimori, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3531–3537. (c) Owton, W. M. *Tetrahedron Lett.* **2003**, *44*, 7147–7149.

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 R² 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

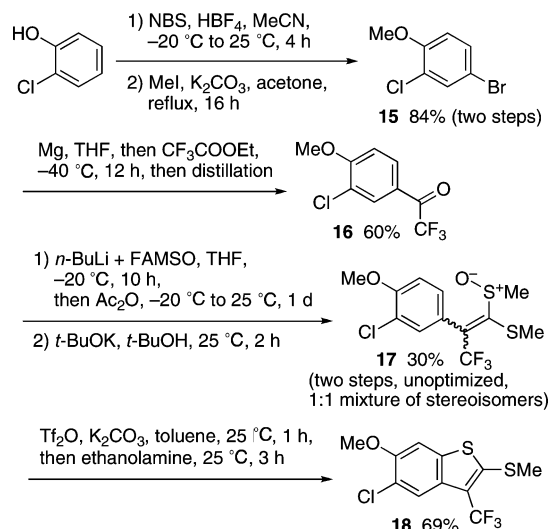
Scheme 3



group under the same conditions afforded a complex mixture. On the other hand, methyl 1,2,2-triphenylethyl 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



4). Bromination of *o*-chlorophenol¹³ 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 conjugation⁶ yielded **17**. The ring-closure of **17** by Tf₂O 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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