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Synthesis of benzothiophene derivatives from dilithio reagents, sulfur, and electrophiles via electrophilic cyclization

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Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday

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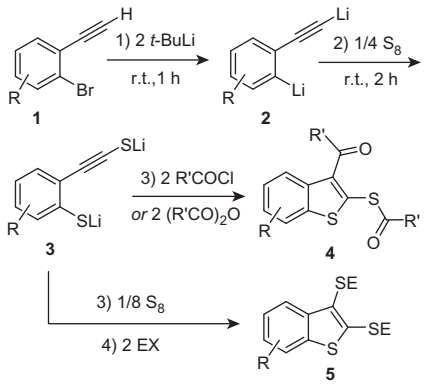
ABSTRACT

Benzothiophene derivatives were synthesized in high yields from readily available *o*-(alkynyllithio)aryllithio compounds, sulfur, and 2 equiv of acid chlorides or other electrophiles. An acid chloride-induced electrophilic cyclization resulted in the formation of the thiophene ring.

Benzothiophene derivatives are a class of important compounds in many aspects.[1] Several synthetic methods have been reported in the literature for the construction of benzothiophene skeletons.[2–6]

Our research group has been working on the synthesis and applications of new types of organolithio reagents, including organo-di-lithio reagents,[7] organo-mono-lithio reagents,[8] and alkynyllithio compounds.[9] As a part of our further interest in the generation and synthetic applications of dilithio compounds, we attempted the in situ generation of *o*-lithiophenylethynyllithiums **2** from their corresponding *o*-bromoethynylbenzenes **1** and *t*-BuLi. Upon successful generation of the dilithio compounds **2**, we carried out their synthetic applications. When this dilithio compound **2** was treated with 0.25 equiv of the element sulfur (S_8), it could be readily transformed to the intermediate **3**. Further treatment of the intermediate **3** with acid chlorides, anhydrides, or additional sulfur triggered the cyclization reaction. In this Letter, we report an alternative synthesis of benzothiophene derivatives **4** and **5** from readily available *o*-lithiophenylethynyllithiums **2**, sulfur, and 2 equiv of acid chlorides or other electrophiles. An acid chloride-induced and a sulfur-induced electrophilic cyclization took place to afford the formation of the thiophene ring (Scheme 1).

o-Bromoethynylbenzene **1** was treated with 2 equiv of *t*-BuLi in Et_2O to afford *o*-lithiophenylethynyllithium **2**, to which was then added 0.25 equiv of S_8. This reaction would afford the intermediate **3**. As given in Table 1, when this intermediate **3a** (R = H) was treated with 2 equiv of MeI or benzylbromide, double methylated product **6a** or the double benzylated product **6b** was obtained in 87% and 89% isolated yields, respectively. This reaction clearly demonstrated the formation of the intermediate **3**. Meanwhile, this



Scheme 1. Synthesis of benzothiophene derivatives via electrophilic cyclization.

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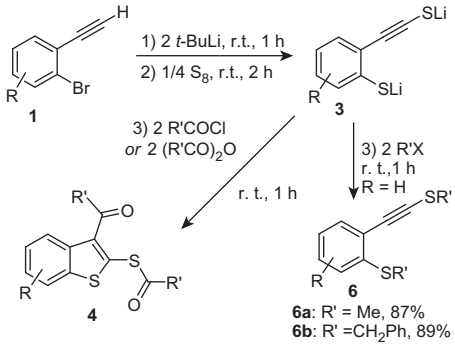
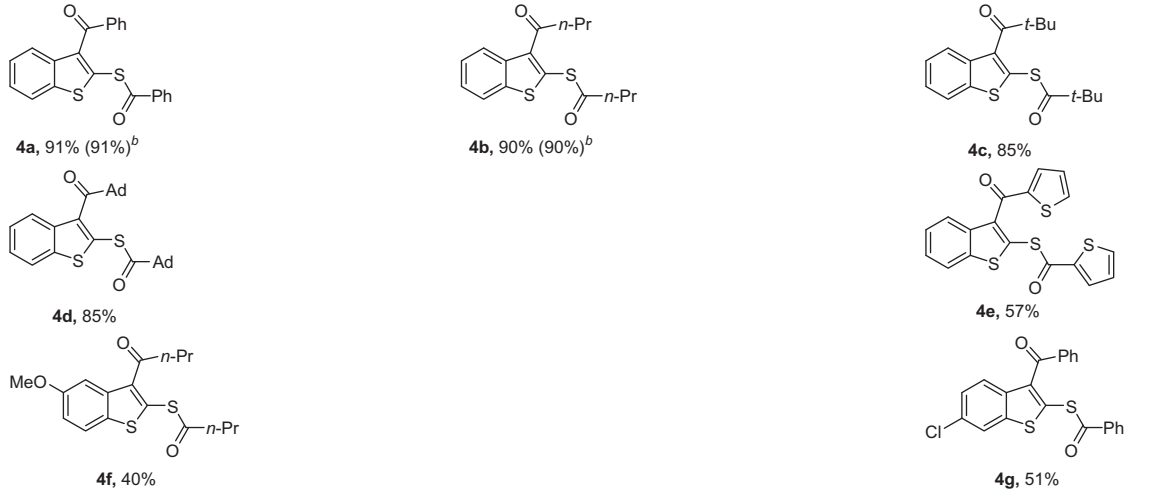
Table 1
Synthesis of benzothiophene derivatives **4** via electrophilic cyclization[a]

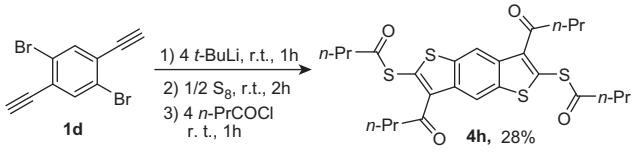




[a] Isolated yields.
[b] The yields in parenthesis were obtained with anhydride.

reaction also demonstrated that no cyclization was induced. When 2 equiv of acyl chlorides was added, an electrophilic cyclization occurred to afford the corresponding di-substituted benzo[*b*]thiophenes **4a–e** under this condition.[1f,i,10] Acyl chlorides with either alkyl or aromatic substituents could all afford their corresponding benzo[*b*]thiophenes **4a–d** in high isolated yields.[11] Heteroaromatic acyl chloride, such as thiophene-2-carbonyl chloride was also applicable, yielding **4e** in a moderate yield. Benzoic anhydride and butyric anhydride could also induce this electrophilic cyclization, leading to the cyclized products **4a** and **4b** in 91% and 90% isolated yields, respectively (Table 1). To check functional group tolerance in this reaction, we applied 1-bromo-2-ethynyl-4-methoxybenzene and 2-bromo-4-chloro-1-ethynylbenzene and found **4f** and **4g** were also obtained, but in relatively lower yields.

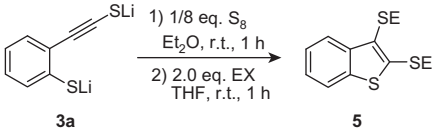
Since ladder π-conjugated compounds of fully ring-fused polycyclic skeletons are an important class of materials possessing significant potential for application in organic electronics,[1f,i] we applied the above synthetic protocol starting with **1d** (Scheme 2). As expected, the ladder-type ring-fused polycyclic product **4h** was synthesized. Although the yield is not good, the synthesis of such a functionalized ladder π-conjugated compound is unprecedented.

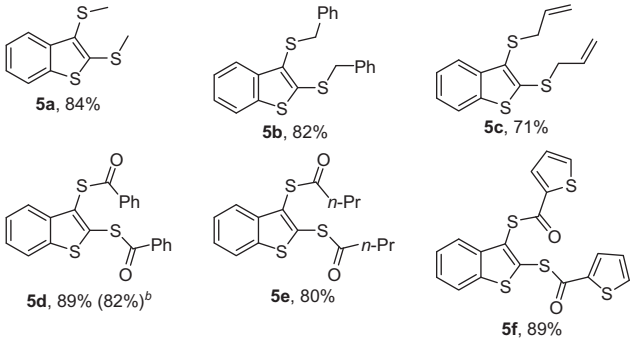


Scheme 2. Synthesis of a ladder-type π-conjugated compound **4h** via the above synthetic protocol.

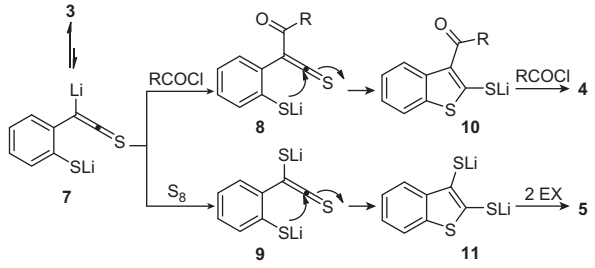
Addition of another equivalent of element sulfur to *o*-lithiophenylethynyllithium **3a** could induce cyclization to give a benzothiophene bearing two S–Li bonds.[1f,i,10] Further reaction of this

Table 2
Synthesis of benzothiophene derivatives **5** via electrophilic cyclization[a]





[a] Isolated yields.
[b] The yields in parenthesis were obtained with anhydride.



Scheme 3. Proposed mechanisms for the formation of benzothiophene **4** and **5**.

species with 2 equiv of electrophilic reagents (EX) such as acyl chlorides or alkyl halides afforded a new type of di-S-substituted benzo[*b*]thiophenes **5a–f** as the sole products in good to excellent isolated yields (Table 2).[12] Until now, the synthesis of benzothiophenes bearing carbonyl groups was seldom reported.

With the results in hands, we supposed the reaction mechanism below (Scheme 3). The lithioalkynolate **3** should be isomerized to the intermediate **7** which bears a thioketene part.[13] In the presence of acyl chloride or elemental sulfur, intermediates **8** and **9** bearing the thioketene part might be formed. These intermediates **8** and **9** would then undergo intramolecular 5-*exo*-dig cyclization to construct the thiophene rings **10** and **11**. Further reaction of compounds **10** and **11** with electrophiles generated the final products **4** and **5**, respectively.

In summary, we reported a convenient synthesis of multi-substituted benzothiophene derivatives from readily available dilithio reagents, elemental sulfur, and 2 equiv of acid chlorides. By carefully controlling the amount of sulfur, the thiophene ring could be conveniently constructed bearing different substituted groups by an acid chloride-induced or S-induced cyclization.

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Supplementary data

Supplementary data (experimental procedures and characterization data for all new compounds and copies of NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.098.

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11. *Typical procedure for the preparation of products* **4**: In a 25 mL of flask, *t*-BuLi (2 mmol, 1.6 M in pentane) was added dropwise at −78 °C to a stirred solution of *o*-bromoethynyl-benzene (1 mmol, 181 mg) or its derivative (1 mmol) in Et_2O (5 mL) and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 1 h, S_8 (0.25 mmol, 64 mg) was added and the reaction was stirred at room temperature for 2 h. The solvent of the reaction mixture was evaporated under vacuum and THF (5 mL) was added. After that, acid chloride (2 mmol) or anhydride (2 mmol) was added dropwise at room temperature. After stirring at room temperature for 1 h, the solvent of the reaction mixture was evaporated under vacuum. The residue was purified by chromatography to give products **4**.
Compound **4a**, Yellow oil, isolated yield 91% (340 mg); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si, 25 °C): δ = 7.30–7.90 (m, 14H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si, 25 °C): δ = 121.90 (1 CH), 123.90 (1 CH), 124.96 (1 CH), 125.79 (1 CH), 127.64 (2 CH), 128.53 (2 CH), 128.77 (2 CH), 129.75 (1 quat. C), 129.87 (2 CH), 133.64 (1 CH), 134.15 (1 CH), 135.48 (1 quat. C), 137.59 (1 quat. C), 137.79 (1 quat. C), 141.10 (1 quat. C), 142.23 (1 quat. C), 187.73 (1 quat. C), 192.29 (1 quat. C). HRMS calcd for $C_{22}H_{14}O_2S_2$ $[M+H]^+$: 375.0514, found 375.0514.
12. *Typical procedure for the preparation of products* **5**: In a 25 mL of flask, **3** was dissolved in 5 mL Et_2O. Another S_8 (0.125 mmol, 32 mg) was added and the reaction was stirred at room temperature for 1 h. The solvent of the reaction mixture was evaporated under vacuum and THF (5 mL) was added. After that, electrophilic reagents (2 mmol) were added dropwise at room temperature. After being stirred at room temperature for 1 h, the solvent of the reaction mixture was evaporated under vacuum. The residue was purified by chromatography to give products **5**.
Compound **5a**, Yellow oil, isolated yield 84% (162 mg); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si, 25 °C): δ = 2.34 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 7.23–7.42 (m, 2H, CH), 7.71–7.87 (m, 2H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si, 25 °C): δ = 18.10 (1 CH_3), 18.26 (1 CH_3), 121.85 (1 CH), 121.96 (1 CH), 123.89 (1 CH), 124.34 (1 quat. C), 124.84 (1 CH), 138.44 (1 quat. C), 140.65 (1 quat. C), 145.11 (1 quat. C). HRMS calcd for $C_{10}H_{10}S_3$ $[M+H]^+$: 227.0023, found 227.0018.
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