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A New Synthesis of Benzo[*b*]thiophene-2-thiolates and Their Derivatives *via* Base-Promoted Transformation of 4-(2-Mercaptophenyl)-1,2,3-thiadiazoles

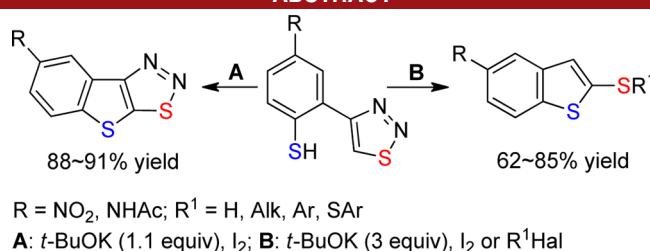
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ABSTRACT



A reaction of 4-(2-mercaptophenyl)-1,2,3-thiadiazoles with an oxidant in the presence of 1.1 equiv of base afforded good yields of benzo[4,5]thieno[3,2-*d*][1,2,3]thiadiazoles *via* the intramolecular oxidative nucleophilic substitution of a hydrogen (ONHS) pathway. The reaction of 4-(2-mercaptophenyl)-1,2,3-thiadiazoles in the presence of ≥ 2 equiv of base gave 2-mercaptobenzo[*b*]thiophenes *via* an anionic ring-opening/ring-closure pathway.

5-Unsubstituted-1,2,3-thiadiazoles are reactive compounds which find use in organic chemistry as a convenient and easily available source of acetylenic thiolates.¹ These highly reactive thiolates may undergo further transformations affording various acyclic, alicyclic, and heterocyclic compounds containing sulfur.²

(1) (a) Raap, R.; Micetich, R. G. *Can. J. Chem.* **1968**, *46*, 1057–1063. (b) Rodionova, L. S.; Petrov, M. L.; Petrov, A. A. *Zh. Org. Khim.* **1978**, *14*, 2050–2054.

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As a continuation of our previous studies³ dealing with the synthesis of 2-mercaptobenzo[*b*]furans and -indoles *via* intramolecular cyclization of *ortho*-hydroxy- and -aminothioketenes, in this work, we present a method for the synthesis of 2-mercaptobenzo[*b*]thiophenes from 4-(2-mercaptophenyl)-1,2,3-thiadiazoles. Some aspects of 4-(2-mercaptophenyl)-1,2,3-thiadiazoles peculiar to reactivity as compared with those of 4-(2-hydroxyphenyl)-1,2,3-thiadiazoles and 4-(2-aminophenyl)-1,2,3-thiadiazoles will be discussed in this paper (Scheme 1).

Benzo[*b*]thiophen-2-thiol and its 5- and 7-chloro derivatives were prepared by treatment of the appropriate 2-benzo[*b*]thienyl-lithium derivative with sulfur in 55–68% yield.⁴

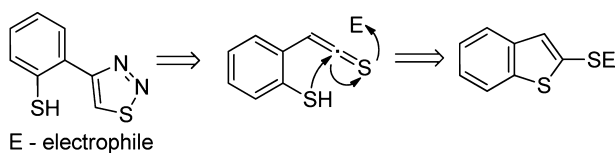
A high-temperature reaction of H₂S with 2-chlorobenzo[*b*]thiophene gave mainly the corresponding thiol in 23% yield.⁵

Benzo[*b*]thiophen-2-thiol was used for the synthesis of novel 1,4-dithiins, as pentacene analogs, which consisted of

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Scheme 1. 5-*exo-dig* Cyclization of *ortho*-Mercaptophenylthio-ketene



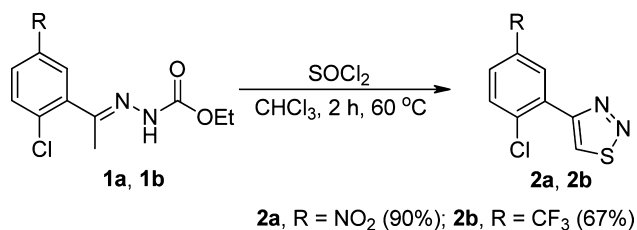
the parent 1,4-dithiin with two benzo[*b*]thiophenes on both sides. These compounds may find application in organic field-effect transistor (OFET) manufacture.^{4a}

A compound having a 2-mercaptobenzo[*b*]thiophene moiety at the C(2) position of 1 β -methylcarbapenem was found to be the potent inhibitor of class B metallo- β -lactamases, also having antimicrobial activity against β -lactamase-producing bacteria, synergistically enhancing the effect of imipenem and ceftazidime.⁶

Herein, we would like to report a convenient one-pot synthesis of 2-mercaptobenzo[*b*]thiophenes having electron-donating and -withdrawing substituents on the phenyl ring, as well as its various *S*-derivatives. The reaction involves a base-promoted transformation of the new readily available 4-(2-mercaptophenyl)-1,2,3-thiadiazoles *via* an anionic ring-opening/ring-closure pathway. In the course of our study we also observed an unexpected formation of benzo[4,5]thieno[3,2-*d*]-[1,2,3]thiadiazoles, representing a rare case of the oxidative nucleophilic substitution of hydrogen (ONHS) reaction with the participation of the sulfur nucleophile.

In order to obtain entry to 4-(2-mercaptophenyl)-1,2,3-thiadiazoles, we first prepared 4-(2-chlorophenyl)-1,2,3-thiadiazoles **2a** and **2b** by treating ethoxycarbonylhydrazones of 2-chloroacetophenones **1a** and **1b** with thionyl chloride in accordance with the Hurd–Mori procedure (Scheme 2).^{1a,7}

Scheme 2. Synthesis of 4-(2-Chlorophenyl)-1,2,3-thiadiazoles

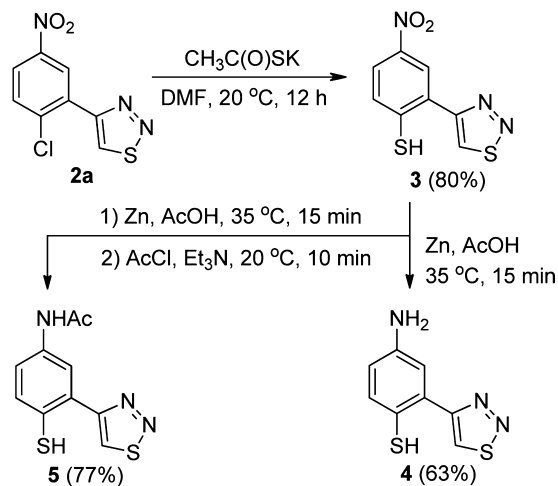


The reaction of 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole **2a** with potassium thioacetate in DMF at 20 °C afforded the corresponding thiophenol **3** in 80% yield. The reduction of the nitro group in compound **3** with zinc powder in acetic acid gave unstable *para*-aminothiophenol **4** (63%) that could be stabilized as its *N*-acetyl derivative

5 (77%) on addition of acetyl chloride directly to the reaction mixture, thus avoiding isolation of the intermediate product **4** (Scheme 3).

A similar reaction of the 4-(2-chloro-5-(trifluoromethyl)-phenyl)-1,2,3-thiadiazole **2b** with potassium thioacetate in DMF at 50 °C failed to give the desired product. An attempt to promote the reaction by applying a higher temperature resulted in accumulation of decomposition products.

Scheme 3. Synthesis of 2-(1,2,3-Thiadiazol-4-yl)thiophenols



We next studied base-catalyzed anionic ring opening of thiadiazoles **3** and **5** (Scheme 4). The reaction of **3** with 1.1 equiv of KOH in THF in the presence of MeI gave methyl sulfide **6**, while the heterocyclic ring remained intact. The treatment of the thiadiazole **3** with 3 equiv of *t*-BuOK in THF in the presence of MeI resulted in the formation of ethynyl sulfide **7**. The treatment of thiadiazole **3** or **5** with 3 equiv of *t*-BuOK in THF followed by the addition of (a) dilute hydrochloric acid to weakly acidic pH giving a 76% yield of benzo[*b*]thiophene-2-thiol **8**; (b) water and an alkylating agent affording benzo[*b*]thiophene-2-sulfides **9a–9f** (Table 1); and (c) water and an arylating agent (2,4-dinitrochlorobenzene) giving a mixture of monoarylation **10** and diarylation **11** products evidenced the contribution of an anion-radical mechanism of the aromatic nucleophilic substitution.

We further studied oxidation reactions of thiadiazoles **3** and **5**, as well as oxidation reactions of their deprotonation and decompositions products (Scheme 5). It was established that the oxidation of the neutral form of the thiadiazole **3** by iodine in THF at 20 °C gave dimerization product **12** in 92% yield. The oxidation of thiadiazoles **3** and **5** by iodine, after treatment of the reaction mixture with 1.1 equiv of sodium hydride, in THF at 20 °C, unexpectedly led to the formation of the benzo[4,5]thieno[3,2-*d*][1,2,3]thiadiazoles **13a** and **13b**. Finally, the decomposition of thiadiazole **3** with 3 equiv of *t*-BuOK in THF at 20 °C followed by the addition of iodine gave 2,2-dithiobisbenzo[*b*]thiophene **14** in 79% yield. In the case

(6) Nagano, R.; Adachi, Y.; Imamura, H.; Yamada, K.; Hashizume, T.; Morishima, A. *Antimicrob. Agents Chemother.* **1999**, 43, 2497–2503.

(7) Hurd, C. D.; Mori, R. I. *J. Am. Chem. Soc.* **1955**, 77, 5359–5364.

Scheme 4. Reactions of 2-(1,2,3-Thiadiazol-4-yl)thiophenols in the Presence of Base

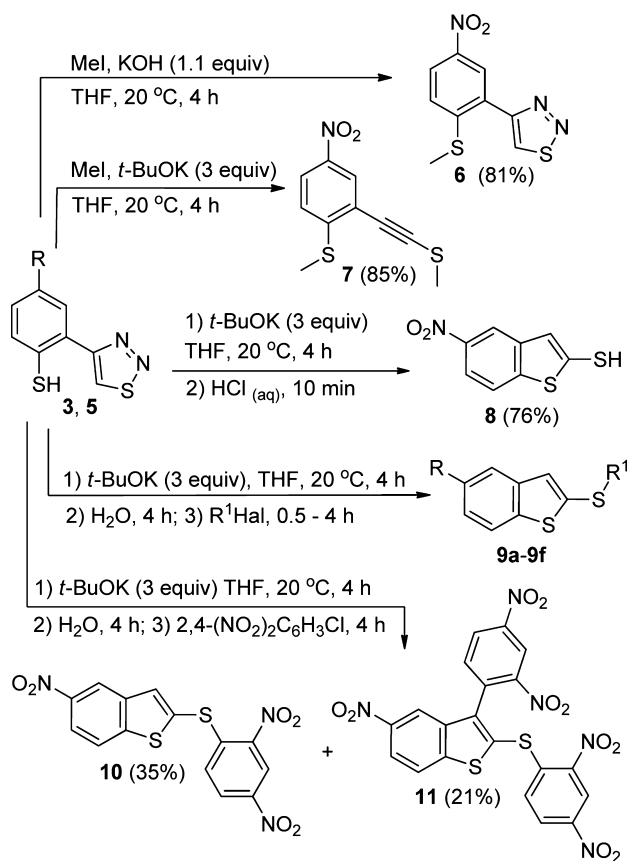


Table 1. Synthesis of Benzo[*b*]thiophenes-2-sulfides

entry	compd	R	R ¹	yield, %
1	9a	NO ₂	CH ₃	78
2	9b	NO ₂	CH ₂ C ₆ H ₅	62
3	9c	NO ₂	CH ₂ C(O)NH(4-MeOC ₆ H ₄)	75
4	9d	NHAc	CH ₃	73
5	9e	NHAc	CH ₂ C ₆ H ₅	71
6	9f	NHAc	CH ₂ C(O)NH(4-MeOC ₆ H ₄)	85

of thiadiazole **5**, having the electron-donating acetamido group on the benzene ring, the oxidation resulted in the formation of the complex mixture of oligomeric materials.

X-ray crystallographic analysis of the compound **9b** evidenced that the benzo[*b*]thiophene fragment and the nitro group are coplanar, whereas the benzo[*b*]thiophene and the benzylsulfenyl fragments adopt an orthogonal configuration (Figure 1).

A plausible mechanism of the benzo[*b*]thiophene-2-thiolate formation is shown in Scheme 6. Addition of the first equivalent of *t*-BuOK to a solution of the thiadiazole in THF resulted in the formation thiophenolate **15**. Unlike the related phenolates,^{3a,b} we did not observe the subsequent decomposition of the thiadiazole ring as a result

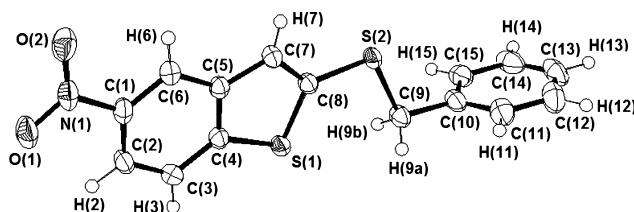
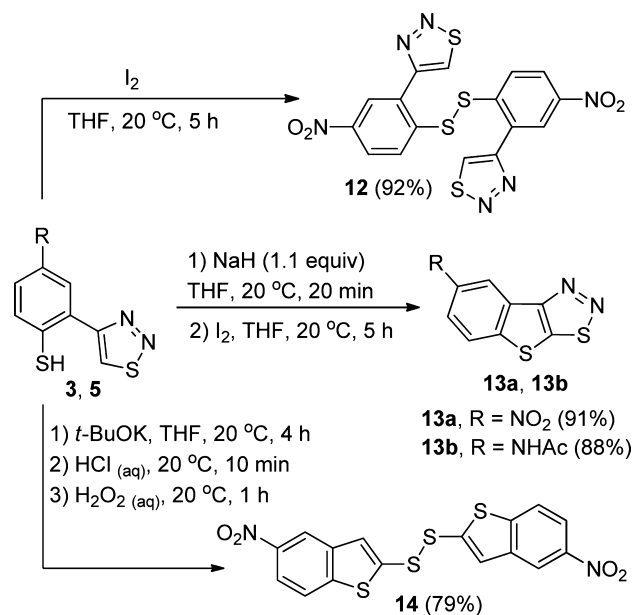


Figure 1. Single crystal X-ray structure of compound **9b**.

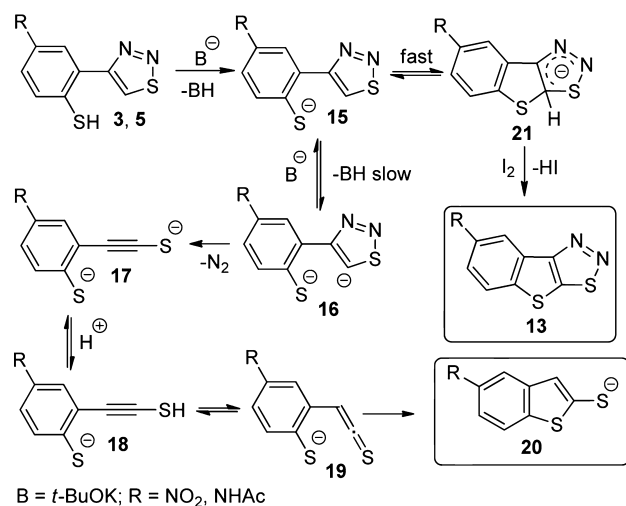
Scheme 5. Reactions of 2-(1,2,3-Thiadiazol-4-yl)thiophenols in the Presence of Base and Oxidizing Agent



of intramolecular proton transfer from the heterocyclic ring to the sulfur anion. Direct deprotonation of the heterocyclic ring was achieved by addition of the second equivalent of *t*-BuOK and resulted in the formation of dianion **16** (the formation of an 1,2,3-thiadiazol-5-yl intermediate dianion **16** was not observed in our experiment, but was supported by data reported in the literature^{3a,8}). The subsequent thiadiazole ring opening accompanied by liberation of nitrogen gave dithiolate **17**, which could be trapped as its dimethyl derivative **7** (Scheme 4). Addition of a proton donor, such as water, to the reaction mixture resulted in partial protonation of dithiolate **17** affording alkynethiol **18**, which existed in equilibrium with its highly reactive thioketene tautomer **19**. An intramolecular addition of nucleophilic thiophenolate to the electrophilic thioketene moiety of **19** led to the formation of benzo[*b*]thiophene-2-thiolate **20**, which could participate in further protonation, alkylation, arylation, and oxidation reactions (Schemes 4, 5).

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Scheme 6. Mechanism of the Base-Promoted Transformation of 2-(1,2,3-Thiadiazol-4-yl)thiophenols



It is worthy of note that even under the influence of excess *t*-BuOK (≥ 3 equiv), decomposition of the thiadiazole ring of the thiophenolate **15** occurs relatively slowly (few hours), which is nontypical for the related phenolates.^{3a,b} Rapid and almost quantitative formation of benzo[4,5]thieno[3,2-*d*][1,2,3]thiadiazoles **13** (Scheme 6) on addition of such a relatively mild oxidant as iodine may explain the slow rate of heterocyclic ring decomposition in compound **15**. Apparently, thiophenolate anion **15** having higher nucleophilicity compared to the related phenolate tends to form stable tricyclic intramolecular anionic adduct **21**. For this reason, the concentration of the thiophenolate **15** in the reaction mixture is relatively low, thus preventing its rapid conversion to the deprotonated intermediate **16** and, after a series of transformations, to the final cyclization product **20**. Formation of the benzo[4,5]thieno[3,2-*d*][1,2,3]thiadiazoles **13a** and **13b** by oxidative aromatization of the adduct **21** represents

(9) Małosza, M.; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631–2666.

(10) Meier, H.; Trickes, G.; Laping, E.; Merkle, U. *Chem. Ber.* **1980**, *113*, 183–192.

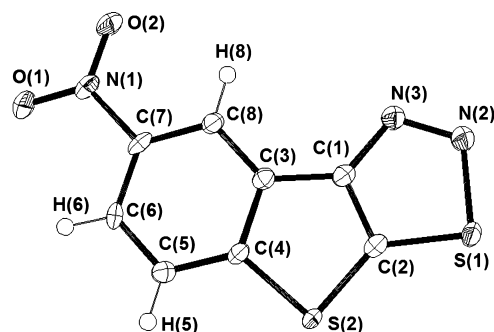


Figure 2. Single crystal X-ray structure of compound **13a**.

a rare example of the oxidative nucleophilic substitution of hydrogen (ONHS) reaction with the participation of a sulfur nucleophile.⁹ Another, conventional Hurd–Mori approach⁷ was employed for the synthesis of 6-chloro-8-methylbenzothieno[3,2-*d*][1,2,3]thiadiazole from a semicarbazone of 6-chloro-4-methylbenzo[*b*]thiophene-3(2*H*)one.¹⁰

X-ray crystallographic analysis of compound **13a** evidenced the planar molecular geometry. A comparison of X-ray data for compound **13a** with those of 1,2,3-benzo[4,5]thiadiazole¹¹ indicated that the bond lengths and the bond angles were insignificantly varied in the range of 0.008–0.018 Å and 0.36°–1.00° correspondingly (Figure 2).

In summary, we have developed a new convenient approach to 2-mercaptobenzo[*b*]thiophenes and benzo[4,5]thieno[3,2-*d*][1,2,3]thiadiazoles from the readily available 4-(2-mercaptophenyl)-1,2,3-thiadiazoles.

Supporting Information Available. Experimental details and characterization data of new compounds along with copies of ¹H, ¹³C NMR, mass spectra, and X-ray data (for compounds **9b** and **13a**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

(11) Mayr, A. J.; Carrasco-Flores, B.; Cervantes-Lee, F.; Pannell, K. H.; Párkányi, L.; Raghuveer, K. *J. Organomet. Chem.* **1991**, *405*, 309–322.

The authors declare no competing financial interest.