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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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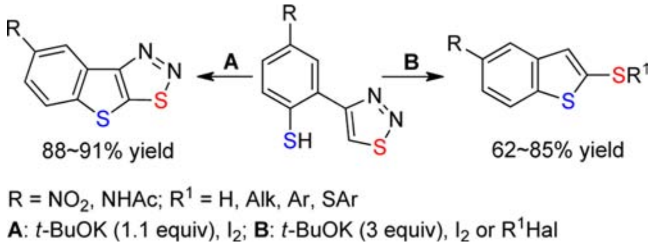
ABSTRACT



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]

As a continuation of our previous studies[3] 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 approriate 2-benzo[*b*]thienyl-lithium derivative with sulfur in 55–68% yield.[4]

A high-temperature reaction of H$_2$S 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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(4) (a) Yamamoto, T.; Ogawa, S.; Sato, R. *Tetrahedron Lett.* **2004**, *45*, 7943–7946. (b) Chapman, N. B.; Hughes, C. G.; Scrowston, R. M. *J. Chem. Soc. C* **1970**, *18*, 2431–2455.

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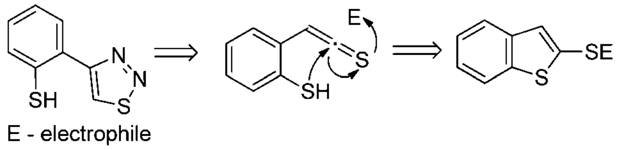
Scheme 1. 5-*exo-dig* Cyclization of *ortho*-Mercaptophenylthioketene



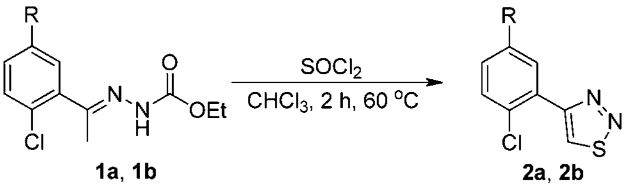
the parent 1,4-dithiin with two benzo[*b*]thiophenes on both sides. These compounds may find application in organic field-effect transistor (OFET) manufacture.[4a]

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

Herein, we would like to report a convenient one-pot synthesis of 2-mertcaptobenzo[*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-chlophenyl)-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

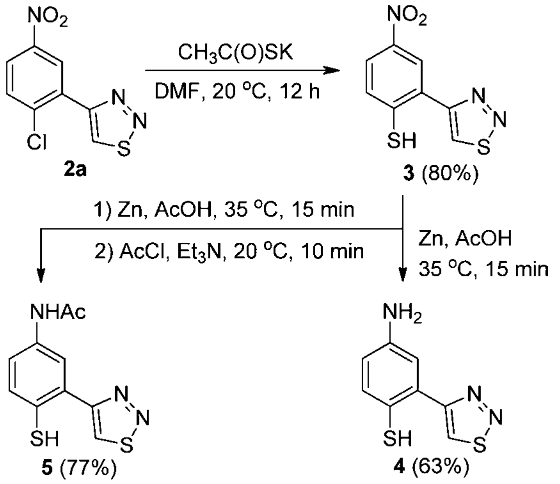


2a, R = NO_2 (90%); **2b**, R = CF_3 (67%)

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

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

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

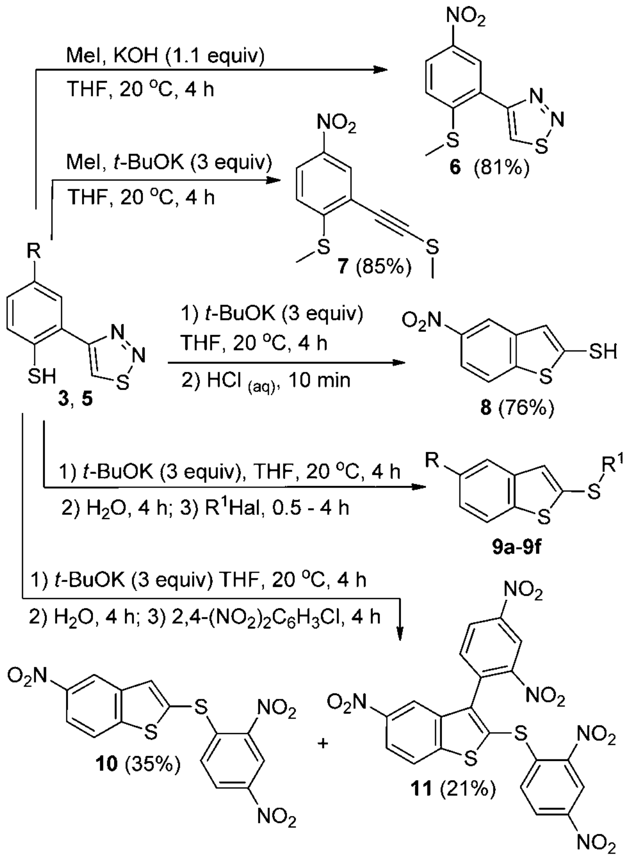


Table 1. Synthesis of Benzo[*b*]thiophenes-2-sulfides

entry	compd	R	R^1	yield, %
1	**9a**	NO_2	CH_3	78
2	**9b**	NO_2	$CH_2C_6H_5$	62
3	**9c**	NO_2	$CH_2C(O)NH(4\text{-}MeOC_6H_4)$	75
4	**9d**	NHAc	CH_3	73
5	**9e**	NHAc	$CH_2C_6H_5$	71
6	**9f**	NHAc	$CH_2C(O)NH(4\text{-}MeOC_6H_4)$	85

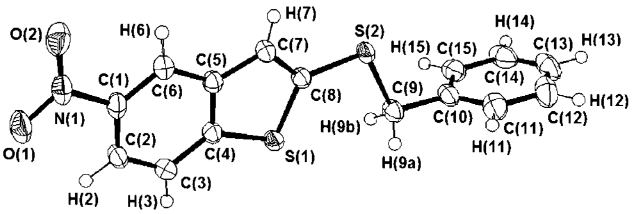
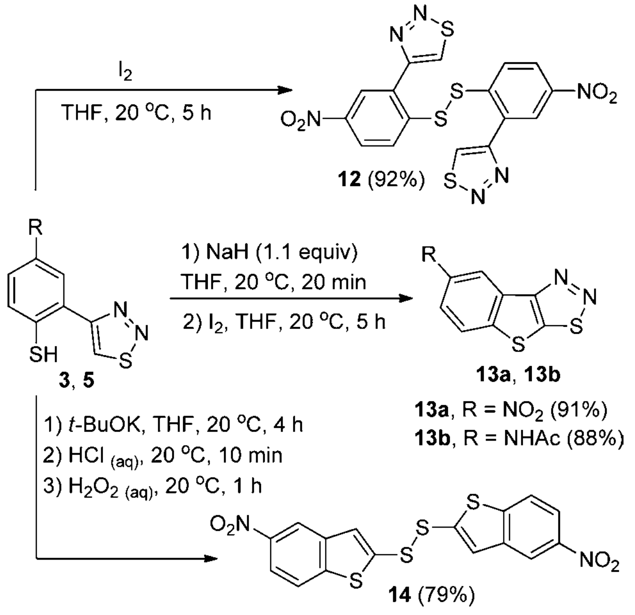


Figure 1. Single crystal X-ray structure of compound **9b**.

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



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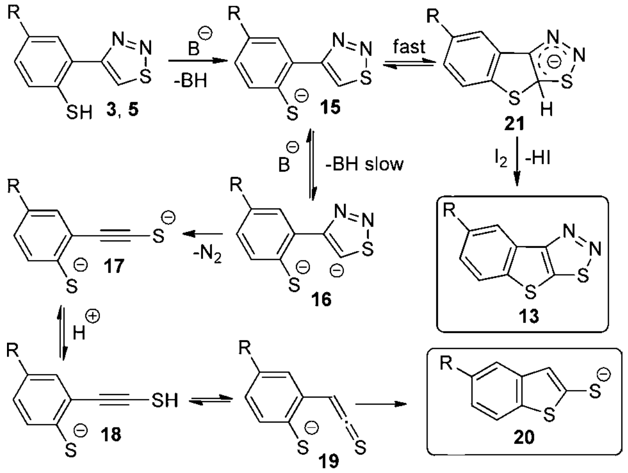
Scheme 6. Mechanism of the Base-Promoted Transformation of 2-(1,2,3-Thiadiazol-4-yl)thiophenols



B = t-BuOK; R = NO_2, NHAc

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 quantative 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 relativly 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 a rare example of the oxidative nucleophilic substitution of hydrogen (ONHS) reaction with the participation of a sulfur nucleophile.[9] Another, conventional Hurd−Mori approach[7] 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]

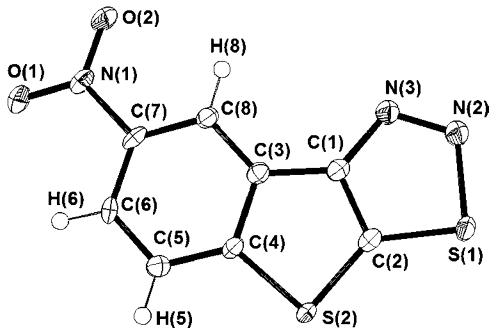


Figure 2. Single crystal X-ray structure of compound **13a**.

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]thiadiazole[11] 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 ^{1}H, ^{13}C 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.

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The authors declare no competing financial interest.