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Investigation of the Reaction of Dithiocarbamic Acid Salts with Aromatic Aldehydes

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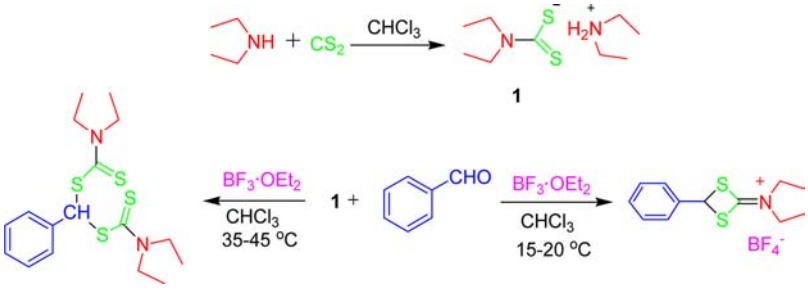
ABSTRACT



A reaction of dithiocarbamic acid salts with carbonyl compounds was investigated for the first time in the presence of $BF_3 \cdot OEt_2$. The reaction is temperature dependent and gives *gem*-bis(dithiocarbamates) at 35−45 °C as a molecule with high equivalents of dithiocarbamate groups. At lower temperatures (15−20 °C), the 2-iminium-1,3-dithietane is obtained as the only product. The structure of a 2-iminium-1,3-dithietane was accomplished by X-ray crystallographic analysis.

Dithiocarbamic acids are the analogue of carbamic acids in which both oxygen atoms are replaced by sulfur atoms. These compounds are good nucleophiles and react with different electrophiles such as alkyl halides,[1] epoxides,[2] α,β-unsaturated carbonyl compounds,[3] etc.[4] Although the dithiocarbamic acids are not stable, their esters or their complexes with metals are stable and have found wide applications as fungicides and pesticides in agriculture,[5] sulfur vulcanization in rubber manufacturing,[6] radical chain transfer agents in the reversible addition−fragmentation chain transfer (RAFT) polymerizations,[7] organic intermediates,[8] and medicinal chemistry.[9] To the best of our knowledge, there is not any report on the

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(1) Azizi, N.; Aryanasab, F.; Saidi, M. R. *Org. Lett.* **2006**, *8*, 5275–5277.
(2) (a) Ziyaei Halimehjani, A.; Saidi, M. R. *Can. J. Chem.* **2006**, *84*, 1515–1519. (b) Azizi, N.; Pourhasan, B.; Aryanasab, F.; Saidi, M. R. *Synlett* **2007**, 2797–2800.
(3) Azizi, N.; Aryanasab, F.; Torkiyan, L.; Ziyaei, A.; Saidi, M. R. *J. Org. Chem.* **2006**, *71*, 3634–3635.
(4) Yavari, I.; Hosseini, N.; Moradi, L.; Mirzaei, A. *Tetrahedron Lett.* **2008**, *49*, 4239–4241.
(5) (a) Marinovich, M.; Viviani, B.; Capra, V.; Corsini, E.; Anselmi, L.; D'Agostino, G.; Nucci, A. D.; Binaglia, M.; Tonini, M.; Galli, C. L. *Chem. Res. Toxicol.* **2002**, *15*, 26–32. (b) Malik, A. K.; Rao, A. L. J. *J. Agric. Food Chem.* **2000**, *48*, 4044–4047. (c) Weissmahr, K. W.; Houghton, C. L.; Sedlak, D. L. *Anal. Chem.* **1998**, *70*, 4800–4804.
(6) (a) Nieuwenhuizen, P. J.; Ehlers, A. W.; Haasnoot, J. G.; Janse, S. R.; Reedijk, J.; Baerends, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 163–168. (b) Messer, W. E. US Patent 1893630, 1930.
(7) (a) Lai, J. T.; Shea, R. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 4298–4316. (b) Duréaault, A.; Gnanou, Y.; Taton, D.; Destarac, M.; Leising, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 2869–2872. (c) Bathfield, M.; D'Agosto, F.; Spitz, R.; Charreyre, M. T.; Delair, T. *J. Am. Chem. Soc.* **2006**, *128*, 2546–2547.
(8) (a) Tsuboi, S.; Takeda, S.; Yamasaki, Y.; Sakai, T.; Utka, M.; Ishida, S.; Yamada, E.; Hirano, J. *Chem. Lett.* **1992**, 1417–1418. (b) Katritzky, A. R.; Singh, S.; Mahapatra, P. P.; Clemense, N.; Kirichenko, K. *ARKIVOC* **2005**, *9*, 63–68. (c) Blanrue, A.; Wilhelm, R. *Synthesis* **2009**, 583–586. (d) Zhang, D.; Chen, J.; Liang, Y.; Zhou, H. *Synth. Commun.* **2005**, *35*, 521–526. (e) Aryanasab, F.; Ziyaei Halimehjani, A.; Saidi, M. R. *Tetrahedron Lett.* **2010**, *51*, 790–792. (f) Ziyaei Halimehjani, A.; Pourshojaei, Y.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 32–34. (g) Rozen, O.; Mishani, E.; Rozen, S. *Tetrahedron* **2010**, *66*, 3579–3582.

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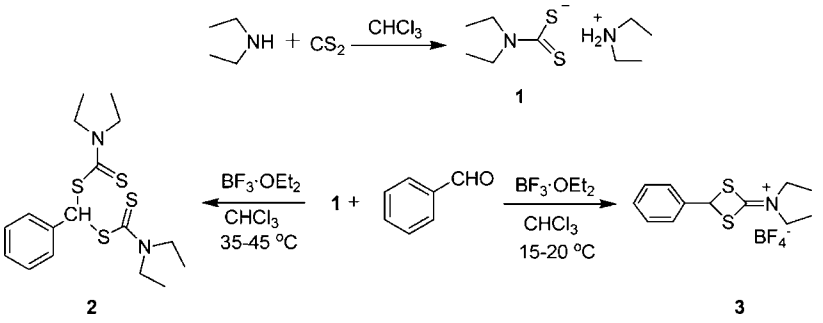
Scheme 1. Synthesis of *gem*-Bis(dithiocarbamte) and 2-Iminium 1,3-Dithietane with Reaction of Benzaldehyde and Dithiocarbamic Acid Salt



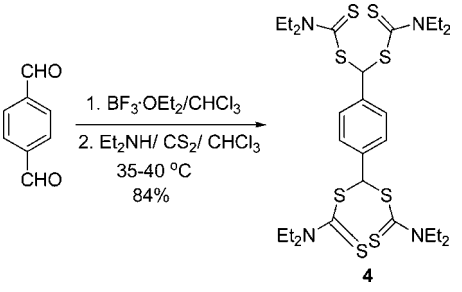
reaction of dithiocarbamic acids with carbonyl compounds. In continuation of our interest toward the synthesis of dithiocarbamates and their applications as intermediates for the synthesis of biologically active compounds,[10] herein we report the reaction of dithiocarbamic acid salts with carbonyl compounds for the first time for the synthesis of *gem*-bis(dithiocarbamates) and 2-iminium-1,3-dithietane salts with the reaction of an aldehyde, CS_2, and an amine in the presence of $BF_3 \cdot OEt_2$ as catalyst.

We began our investigations with a one-pot, three-component reaction of diethylamine, CS_2, and benzaldehyde in the presence of $BF_3 \cdot OEt_2$ in $CHCl_3$ at room temperature. No product was obtained under these conditions. Therefore, an alternative synthetic strategy was pursued. The dithiocarbamic acid salt **1** was prepared in a different vessel and was added to the solution of benzaldehyde and $BF_3 \cdot OEt_2$ in $CHCl_3$ at room temperature. We found that the reaction was completed and the mixture of products **2** and **3** were obtained in 70:30 ratios. By changing the reaction temperature, we found out that the formation of the products is temperature dependent. At 35−45 °C, the *gem*-bis(dithiocarbamate) **2** was obtained as the only product, while at low temperatures (15−20 °C) the 2-(*N,N*-diethyliminium)-4-phenyl-1,3-dithietane tetrafluoroborate **3** was obtained as the only product. It seems that the synthesis of *gem*-bis(dithiocarbamates) passes through the dithietane ring formation (Scheme 1). Attempt to obtain the products using a Bronsted acid such as sulfuric acid, TFA, or PTSA was not successful. We also observed that the transition-metal salts as Lewis acids are not suitable for this reaction because highly stable metal dithiocarbamate complexes are produced.

After optimizing the reaction conditions, we next examined the generality of these conditions to other substrates using several amines and aldehydes. The results are summarized in Tables 1 and 2. A variety of aromatic aldehydes with electron-donating and -withdrawing groups on the benzene ring were used in this reaction with high to excellent yields. In addition, different aliphatic secondary amines such as pyrrolidine, piperidine, diethylamine, and morpholine give high to excellent yields. The reaction does not give the desired products with primary aliphatic amines, aromatic amines, ketones, and aliphatic aldehydes. The dithietane and *gem*-bis(dithiocarbamate) products are white to yellowish solids which are stable for several months.

Terephthaldehyde was used in this reaction and the desired product with four dithiocarbamate groups **4** was obtained in high yields (Scheme 2).

Scheme 2. Reaction of Dithiocarbamic Acid Salt with Terephthaldehyde



Deprotection of the *gem*-bis(dithiocarbamates) was investigated in the presence of different acids such as HCl, $HClO_4$, HNO_3, and H_2SO_4 in water. Although it is well documented that the *gem*-bis (dithiocarbamates) converted to 2-iminium-1,3-dithietane rings with concentrated H_2SO_4 and 70% $HClO_4$,[11] but these compounds are stable in aqueous solution of HCl, $HClO_4$ and H_2SO_4 for several

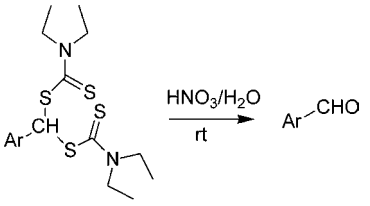
(9) (a) Aboul-Fadl, T.; El-Shorbagi, A. *Eur. J. Med. Chem.* **1996**, *31*, 165–169. (b) Cascio, G.; Lorenzi, L.; Caglio, D.; Manghisi, E.; Arcamone, F.; Guanti, G.; Satta, G.; Morandotti, G.; Sperning, R. *Farmaco* **1996**, *51*, 189–196. (c) Imamura, H.; Ohtake, N.; Jona, H.; Shimizu, A.; Moriya, M.; Sato, H.; Sugimoto, Y.; Ikeura, C.; Kiyonaga, H.; Nakano, M.; Hagano, R.; Abe, S.; Yamada, K.; Hashizume, T.; Morishima, H. *Bioorg. Med. Chem. Lett.* **2001**, *9*, 1571–1578. (d) Gerhauser, C.; You, M.; Liu, J.; Moriarty, R. T.; Hawthorne, M.; Mehta, R. G.; Moon, R. C.; Pezzuto, J. M. *Cancer Res.* **1997**, *57*, 272–278. (e) Scozzafava, A.; Mastorlorenzo, A.; Supuran, C. T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1887–1891. (f) Hou, X. L.; Ge, Z. M.; Wang, T. M.; Guo, W.; Cui, J. R.; Cheng, T. M.; Lai, C. S.; Li, R. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4214–4219.

(10) (a) Ziyaei Halimehjani, A.; Maleki, H.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 2747–2749. (b) Ziyaei Halimehjani, A.; Marjani, K.; Ashouri, A. *Green Chem.* **2010**, *12*, 1306–1310.

(11) Ueno, Y.; Okawara, M. *Chem. Lett.* **1973**, 863–866.

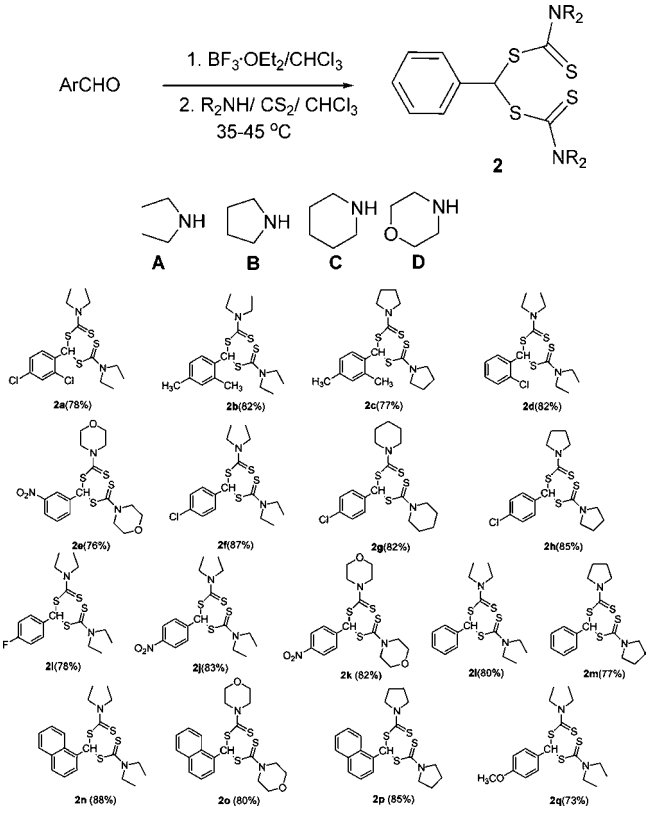
hours except in the presence of nitric acid, the aldehyde was recovered after few minutes with evolution of NO_2 gas with excellent yields (Scheme 3). This procedure is also effective for acid-sensitive compounds such as **2q** without affecting the methoxy group. The mechanism of deprotection is not yet known. The *gem*-bis(dithiocarbamates) are also stable in aqueous basic medium for several hours.

Scheme 3. Deprotection of *gem*-Bis(dithiocarbamates) **2l**, **2n**, and **2q**



2l	98%
2n	95%
2q	98%

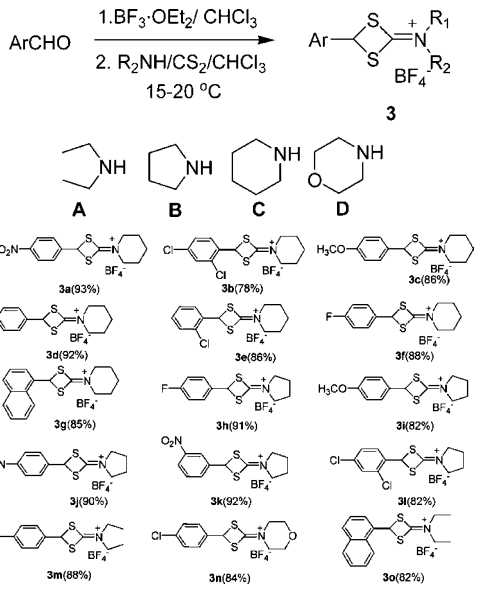
Table 1. Synthesis of *gem*-Bis(dithiocarbamates) with Various Amines and Aldehydes



[a] Isolated yield.

The structures of products were confirmed by ^1H and ^{13}C NMR spectroscopy and CHN analysis.The ^1H NMR spectra of the *gem*-bis(dithiocarbamates) show a singlet

Table 2. Diversity in the Synthesis of 2-Iminium 1,3-Dithietane Tetrafluoroborate



[a] Isolated yield.

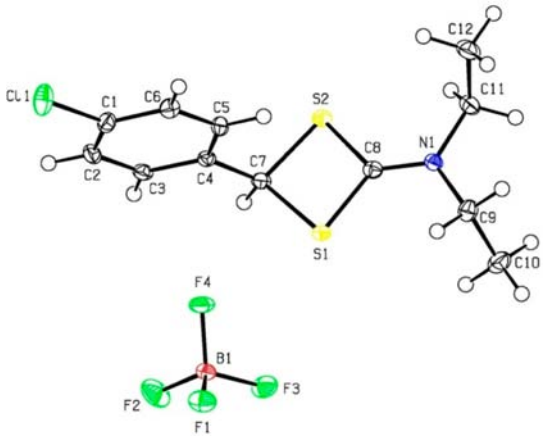
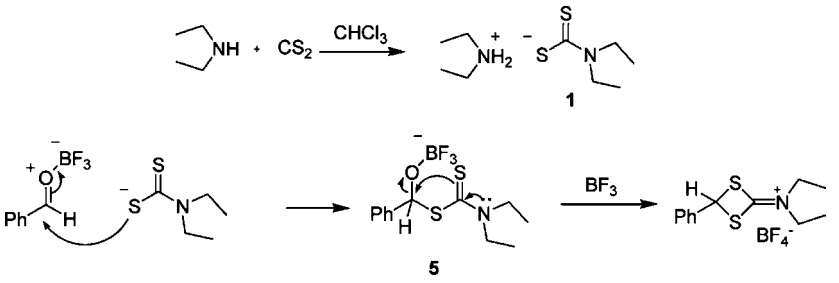


Figure 1. ORTEP representations of the structure of **3m**. Thermal ellipsoids have been drawn at the 50% probability level. Selected bond lengths (Å) and angles (deg): C(8)−S(1), 1.729(3); C(8)−S(2), 1.727(3); C(8)−N(1), 1.290(3); C(7)−S(1), 1.847(2); C(7)−S(2), 1.847(3); S(2)−C(8)−N(1), 128.53(19)°; S(1)−C(8)−N(1), 129.57(19)°; S(2)−C(8)−S(1), 101.90(13)°; S(2)−C(7)−S(1), 93.23(11)°; S(2)−C(7)−C(4), 115.28(16)°; S(1)−C(7)−C(4), 114.25(16)°.

peak at 7−8 ppm for the benzylic hydrogen. Also the ^{13}C of dithiocarbamate moiety was assigned at 185−195 ppm in ^{13}C NMR spectra.The benzylic hydrogen in the dithietane ring was observed at 5.5−6.5 ppm as singlet in ^1H NMR spectra. In addition, the peak at 175−185 ppm in ^{13}C NMR was assigned to the carbon of the iminium moiety in the dithietane products. The peak near −152 ppm in the

Scheme 4. Proposed Mechanism for Preparation of the Dithietane Ring



^{19}F NMR spectra was assigned to the tetrafluoroborate anion. In addition, the boron was observed around −20 ppm in ^{11}B NMR. A single crystal of **3m** (see Table 2, entry 13) was prepared in $CHCl_3$, and X-ray crystallographic analysis established the structure of the 1,3-dithietane ring. ORTEP representations are shown in Figure 1 (CCDC no. 870959; for details of the crystal structure data and refinement of **3m** see the Supporting Information. The formation of the dithietane ring results a highly distorted tetrahedron structure around the central C(7) atom. As shown in Figure 1, the observed bond distances of C(8)−S(1), 1.729(3) Å and C(8)−S(2), 1.727(3) Å, are virtually equal and very similar and which are shorter than C(7)−S(1), 1.847(2) Å and C(7)−S(2), 1.847(3) Å because of incorporation of sulfur atoms in resonance with iminium group.

A proposed mechanism for the preparation of 1,3-dithietane ring is given in Scheme 4. Reaction of an amine with carbon disulfide gave the dithiocarbamic acid salt **1** which then added to an activated aldehyde with BF_3 to prepare the intermediate **5**. Intramolecular addition of the sulfur atom gave the dithietane ring with removal of the oxygen group at low temperature. At higher temperatures, intermolecular of another dithiocarbamic acid salt with intermediate **5** gave the *gem*-bis (dithiocarbamate).

In conclusion, for the first time, we have shown that the reaction of dithiocarbamic acid salts with carbonyl compounds can be used for the preparation of *gem*-bis(dithiocarbamates) and substituted 2-iminium-1,3-dithietane rings using an aldehyde, CS_2, and an amine catalyzed by $BF_3 \cdot OEt_2$ in chloroform. The *gem*-bis(dithiocarbamates) may be used as new fungicides, especially *gem*-bis(dithiocarbamate) prepared with terephthaldehyde with high equivalents of dithiocarbamate in its structure.[12] In addition, we believe this procedure for the synthesis of *gem*-bis(dithiocarbamates) as a new protective methodology can be utilized widely in modern organic synthesis for the protection of carbonyl group in aldehydes.[13] In addition, deprotection of *gem*-bis(dithiocarbamates) is simple and can be carried out in aqueous nitric acid. We have shown a novel and efficient procedure for the synthesis of substituted 2-iminium-1,3-dithietane rings[14] in one step. The key advantages of this protocol are its operational simplicity, high to excellent yields of products, and its ability to directly access the substituted 2-iminium-1,3-dithietane salts in one step.

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Supporting Information Available. Full experimental details, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all compounds, mass spectra for **2a** and **3f**, and X-ray data for **3m** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Len, C.; Boulogne-Merlot, A. S.; Postel, D.; Ronco, G.; Villa, P.; Goubert, C.; Jeufrault, E.; Mathon, B.; Simon, H. *J. Agric. Food Chem.* **1996**, *44*, 2856–2858.

(13) Recent references for the protection of carbonyl compounds: (a) Carmeli, M.; Rozen, O. *Tetrahedron Lett*. **2006**, *47*, 763–766. (b) Ren, Y.-M.; Cai, C. *Tetrahedron Lett*. **2008**, *49*, 7110–7112. (c) Srivastava, P.; Srivastava, R. *Catal. Commun*. **2008**, *9*, 645–649.

(14) (a) Bollinger, F. G. U.S. Patent 4,311,572, 1982; *Chem. Abstr*. **1982**, *96*, 142833e. (b) Bollinger, F. G. U.S. Patent 4,231,783, 1980; *Chem. Abstr*. **1979**, *92*, 76492g. (c) Teach, E. G. U.S. Patent 4,451,280, 1984; *Chem. Abstr*. **1983**, *98*, 6348z. (d) Bollinger, F. G. U.S. Patent 4,411,688, 1983; *Chem. Abstr*. **1983**, *98*, 16668h. (e) Gutman, A. D. U.S. Patent 4,414,019, 1983; *Chem. Abstr*. **1984**, *98*, 48681y.

The authors declare no competing financial interest.