New Synthesis of 1,2,3-Thiadiazole-5-thiol Derivatives

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New syntheses of 1,2,3-thiadiazole-5-thiol derivatives utilizing the thionyl chloride ring-closure of the aldehyde derivatives **5a, b,** and **c** are reported.

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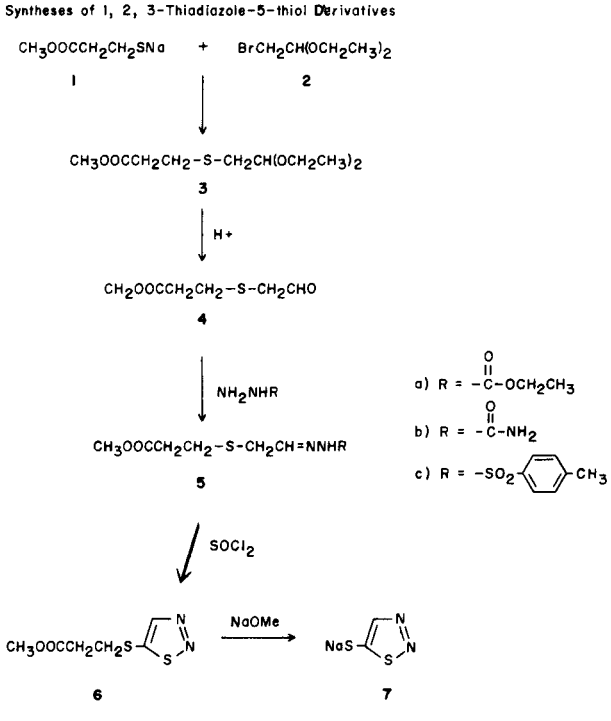
Discussion.

Recently we described a cephalosporin which requires the salt of 5-thiol-1,2,3-thiadiazole as one of the intermediates [1]. The literature preparation of the potassium salt of this compound involved the use of several highly toxic materials, namely thiophosgene and diazomethane and moreover results in a mixture of isomeric thiadiazoles where the desired 1,2,3-thiadiazole is the minor component [2]. The preparation of the 1,2,3-thiadiazole-5-thiol sodium salt has also been reported in a European Patent Application by the reaction of 5-chloro-1,2,3-thiadiazole with sodium sulfide [3]. However, 5-chloro-1,2,3-thiadiazole is known to be thermally unstable and should be avoided as an intermediate [4]. We report here a synthesis of these 1,2,3-thiadiazole derivatives which utilizes the Hurd and Mori type of ring-closure [5].

Chart I



In this approach the thiolate **1** was reacted with bromoacetaldehyde diethylacetal **2** to give compound **3** which was purified by distillation. Treatment of the acetal **3** with dilute acid gave the corresponding aldehyde **4** which was converted to the requisite hydrazine derivatives **5a,b,** and **c**. The semicarbazide **5b** was also synthesized from chloroacetaldehyde semicarbazone by reaction with the thiolate salt **1**. Ring-closure with thionyl chloride and purification by preparative high pressure liquid chromatography produced the thiadiazole derivative **6**. In practice the semicarbazide derivative **5b** gave the best results. Treatment of compound **6** with sodium methoxide afforded the desired sodium salt of 1,2,3-thiadiazole-5-thiolate **7**. These reactions are summarized on Chart I.

EXPERIMENTAL

Methyl 3-(Diethoxyethylthio)propanoate (**3**).

Sodium methoxide (5.4 g, 0.10 mole) was added in portions to a stirred solution of methyl 3-thiopropanoate (12.5 g, 0.10 mole) in 50 ml of methanol. Bromoacetaldehyde diethyl acetal (19.7 g, 0.10 mole) was added dropwise and the mixture was stirred and refluxed for 3 hours. The methanol was evaporated at reduced pressure and the residue was partitioned between 50 ml of water and 50 ml of ethyl acetate. The combined ethyl acetate layers were dried over magnesium sulfate, evaporated and the oily residue was distilled *in vacuo* to afford 12.3 g (52%) of the desired compound, bp 109-112° (0.6-0.7 mm); ir (neat): 1740 cm^{-1} (C=O); nmr 1.20 (t, 6H, J = 7 Hz, C-CH_3), 2.70 (m, 6H, CH_2CH_2-S-CH_2), 3.60 (m, 4H, -OCH_2), 3.70 (S, 3H, -OCH_3), 4.58 (t, 1H, J = 7 Hz, -$CH(OR)_2$).

Anal. Calcd. for $C_{10}H_{20}O_4S$: C, 50.82; H, 8.53; S, 13.57. Found: C, 51.29; H, 8.65; S, 13.65.

Methyl 3-(Formylmethylthio)propanoate (**4**).

A mixture of methyl 3-(diethoxyethylthio)propanoate (**3**) (13.2 g, 0.056 mole) and 200 ml of 1% aqueous hydrochloric acid was stirred, under nitrogen for 4 hours. The solution was decanted from a small amount of insoluble oil and adjusted to *p*H 4.5 with sodium acetate. The solution was extracted with four 100 ml portions of ethyl acetate which were combined and dried over magnesium sulfate. Evaporation of the solvent at reduced pressure gave 8.2 g (90%) of the desired compound as a colorless oil; ir (neat): 1740 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.70 (m, 4H, -CH_2CH_2-S), 3.25 (d, 2H, J = 4 Hz, -CH_2-CHO), 3.75 (S, 3H, -OCH_3), 9.53 (t, 1H, J = 4 Hz, -CHO).

Anal. Calcd. for $C_6H_{10}O_3S$: C, 44.43; H, 6.29; S, 19.77. Found: C, 44.04; H, 6.32; S, 19.97.

Methyl 3-(Formylmethylthio)propanoate Ethoxycarbonyl Hydrazone (**5a**).

Methyl 3-(diethoxyethylthio)propanoate (**3**) (4.73 g, 0.02 mole) was converted to the aldehyde as described above using 100 ml of 1% hydro-

chloric acid. After the *p*H was adjusted to 4.2, ethyl carbazate (2.08 g, 0.02 mole) was added and the solution was stirred under nitrogen for 2 hours. The resulting solution was extracted with three 100 ml portions of ethyl acetate and the combined extracts were dried over magnesium sulfate and evaporated to an oil. The oil was chromatographed on silica gel (200 g) using ethyl acetate:hexane (1:1) as the eluant and 100 ml fractions were collected. Fractions 8-13 were combined and evaporated to afford 1.8 g of the desired compound as an oil which crystallized on standing; ir (potassium bromide): 1710 and 1740 cm^{-1} (C=O); nmr (deuteriochloroform) δ 1.27 (t, 3H, J = 7 Hz, CH_3-C), 2.65 (m, 4H, -CH_2-CH_2-), 3.30 (d, 2H, J = 7 Hz, -SCH_2CHO), 3.70 (S, 3H, -OCH_3), 4.25 (q, 2H, J = 7 Hz, -OCH_2-C), 7.15 (t, 1H, J = 7 Hz, -CH=), 8.30 (1H, S, NH).

Anal. Calcd. for $C_9H_{16}N_2O_4S$: C, 43.54; H, 6.49; N, 11.28; S, 12.91. Found: C, 44.16; H, 6.62; N, 11.52; S, 12.63.

Methyl 3-(Formylmethylthio)propanoate Semicarbazone (**5b**). Method A.

A mixture of sodium methoxide (1.08 g, 20 mmoles), methyl 3-thiopropanoate (2.4 g, 20 mmoles) and chloroacetaldehyde semicarbazone (2.72 g, 20 mmoles) in 40 ml of methanol was stirred and refluxed for 5 hours. On cooling the reaction mixture was filtered and the filtrate evaporated to a syrup which was chromatographed on 500 ml of silica gel using chloroform:methanol (85:15) as the eluant to give 3.48 g (79%) of product; ir (neat): 1690 and 1740 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.60 (m, 4H, -CH_2-CH_2-), 3.17 (d, 2H, J = 7 Hz, -CH_2-CH=), 3.65 (S, 3H, -OCH_3), 5.95 (S, 2H, NH_2), 7.04 (t, 1H, J = 7 Hz, -CH=N), 10.1 (S, 1H, NH).

Anal. Calcd. for $C_7H_{13}N_3O_3S$: C, 38.35; H, 5.98; N, 19.16; S, 14.62. Found: C, 38.65; H, 6.24; N, 19.25; S, 15.01.

Method B.

A mixture of semicarbazide hydrochloride (6.7 g, 0.06 mole) and sodium acetate (6.7 g, 0.08 mole) in 50 ml of ethanol was refluxed for 10 minutes, then filtered while hot and methyl 3-(formylmethylthio)propanoate (**4**) (10.6 g, 0.065 mole) was added to the filtrate. The solution was refluxed for 1 hour, cooled, diluted with water (200 ml), and extracted with three 100 ml portions of ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate and evaporated to give 11.8 g of an amber oil. The infrared spectrum of this material was virtually identical to the material prepared by Method A.

Methyl 3-(Formylmethylthio)propanoate *p*-Toluenesulfonylhydrazone (**5c**).

A mixture of methyl 3-(formylmethylthio)propanoate (**4**) (8.2 g, 50.6 mmoles) and *p*-toluenesulfonylhydrazide (9.4 g, 50.6 mmoles) in 75 ml of ethanol was refluxed for 2 hours. On cooling the white crystalline product was collected and dried to afford 5.4 g (32%), mp 94-96°; ir (potassium bromide): 1740 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.45 (S, 3H, CH_3-C), 2.50 (m, 6H, -CH_2-CH_2-), 3.20 (d, 2H, J = 7 Hz, CH_2S), 3.70 (S, 3H, -OCH_3), 3.70 (S, 3H, -OCH_3), 7.15 (t, 1H, J = 7 Hz, -CH=N), 7.35 (d, 2H, aromatic H, J = 9 Hz), 7.82 (d, 2H, aromatic H, J = 9 Hz), 8.50 (S, 1H, NH).

Anal. Calcd. for $C_{13}H_{18}N_2O_4S_2$: C, 47.27; H, 5.49; N, 8.49; S, 19.38. Found: C, 47.04; H, 5.37; N, 8.42; S, 19.53.

5-Methoxycarbonylethylthio-1,2,3-thiadiazole (**6**). Method A.

A 177.5 g (0.81 mole) portion of methyl 3-(formylmethylthio)propanoate semicarbazone (**5b**) was diluted with 100 ml of dry methylene chloride and this was added, fairly rapidly, using a dropping funnel, to 175 ml of thionyl chloride with rapid stirring which was continued for 2 hours after addition is complete. The reaction mixture was then evaporated under reduced pressure and two portions of methylene chloride were added and removed under reduced pressure. The residue was dissolved in ethyl acetate, filtered and the filtrate washed first with saturated aqueous sodium bicarbonate and then with brine. The solution was dried over magnesium sulfate, an equal volume of hexane is added and the solution was filtered through a silica gel pad topped with diatomaceous earth. The pad was washed with a 1:1 solution of ethyl acetate and hexane and this wash was concentrated under reduced pressure to an oil. The oil was dissolved in 100 ml of a 20% ethyl acetate in hexane solution. One half of this solution was injected onto a Waters Prep 500 hplc, using two prepacked columns and eluted with a solution of 12.5% ethyl acetate in hexane containing 1% methanol. After 2.5 liters of solvent has been eluted (one liter being the void volume), fractions 3-7 (containing approximately 3 liters of eluent) are combined and concentrated under reduced pressure. This procedure was repeated with the other half of the solution of the product, total yield is 57.8 g (34%) of the desired compound. This material was identical (ir, nmr and tlc) to material prepared by the method of Demaree *et al.* [2].

Method B.

A solution of 2.40 ml of thionyl chloride in 3 ml of methylene chloride was added dropwise rapidly to a stirred solution of 8.23 g of methyl (3-formylmethylthio)propanoate ethoxycarbonylhydrazone (**5a**) and 9.25 ml of triethylamine in 25 ml of methylene chloride. After 30 minutes, 2.4 ml of thionyl chloride was added rapidly, dropwise. After 60 minutes, 2.4 ml of thionyl chloride was again added as above. After a total reaction time of 2 hours, the mixture was evaporated at reduced pressure with mild heat. Ether was added to the residue which was then filtered. The filtrate was evaporated to a residue which was chromatographed on 500 g of silica gel using hexane:ethyl acetate (4:1) and collecting fractions of 50 ml each. Fractions 10-21 were collected, pooled and evaporated, giving 3.13 g of the desired compound as an oil.

Method C.

A 0.5 g portion of methyl 3-(formylmethylthio)propanoate *p*-toluenesulfonyl hydrazone (**5c**) was added to 4 ml of thionyl chloride and allowed to react for 30 minutes. The mixture was evaporated to dryness, the residue dissolved in methylene chloride and again evaporated. This crude product was purified by thick layer chromatography giving 184 mg of the desired compound.

Sodium 1,2,3-Thiadiazole-5-thiolate (**7**).

A solution of sodium methoxide (75.6 mg, 14 mmoles) in 20 ml of methanol was added to a solution of 5-methoxycarbonylethylthio-1,2,3-thiadiazole (3.13 g 15.3 mmoles) in 30 ml of methanol. After 45 minutes, the reaction solution was evaporated *in vacuo* to about 5 ml. A 3 ml portion of methanol was added and then about 15 ml of ether causing precipitation of a solid. This solid was collected, washed with ether, dried and recrystallized from methanol-ether, giving 1.94 g (79%) of the desired product.

Anal. Calcd. for $C_2HN_2S_2Na{\cdot}2H_2O$: C, 13.64; H, 2.84; N, 15.91. Found: C, 13.57; H, 2.62; N, 15.64.

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