Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

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To cite this Article Andrews, Christopher G. , Langler, Richard F. and Branch, Donald R.(2009) 'The rapid decomposition of water-soluble *p*-nitrophenyl disulfides induced by aqueous sodium hydroxide', Journal of Sulfur Chemistry, 30: 1, 22 — 28
To link to this Article: DOI: 10.1080/17415990802422357
URL: http://dx.doi.org/10.1080/17415990802422357

Journal of Sulfur Chemistry
Vol. 30, No. 1, February 2009, 22–28

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The rapid decomposition of water-soluble *p*-nitrophenyl disulfides induced by aqueous sodium hydroxide

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(*Received 12 May 2008; final version received 20 August 2008*)

A pair of *p*-nitrophenyl disulfide carboxylic acids are shown to react rapidly in aqueous base to give *p*-nitrothiophenol-derived anions. Experimental and PM3 computational results support the view that hydroxide ions attack, in a bimolecular fashion, at the appropriate sulfenyl sulfur to produce *p*-nitrophenyl mercaptide anions.

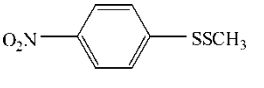
Keywords: disulfide hydrolysis; PM3 computations; nitrophenyl disulfides

1. Introduction

At the present time, we are pursuing a synthetic program aimed at the identification of efficacious organosulfur compounds as agents for the treatment of immune cytopenias. To date, the best of our compounds (*1, 2*) is *p*-nitrophenyl methyl disulfide **1** (Figure 1).

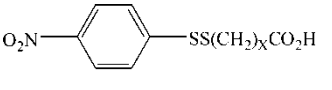
As a part of the current slate of target molecules, we included *p*-nitrophenyl disulfide carboxylic acids **2** and **3** (Figure 2).

The present account details an unexpectedly facile reaction of these acids in an aqueous base.



1

Figure 1. *p*-Nitrophenyl methyl disulfide.



2 X − 1
3 X − 2

Figure 2. Nitrophenyl disulfide acids.

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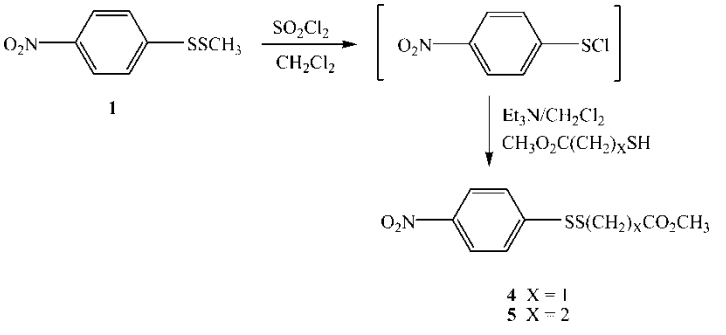
ISSN 1741-5993 print/ISSN 1741-6000 online

DOI: 10.1080/17415990802422357
http://www.informaworld.com

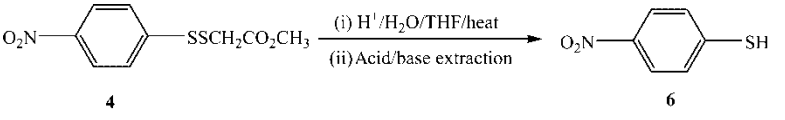
2. Results and discussion

Framework assembly for **2** and **3** was accomplished by the condensation of freshly prepared *p*-nitrobenzenesulfenyl chloride with the appropriate *ω*-mercapto esters. Homogeneous solutions of *p*-nitrobenzenesulfenyl chloride were prepared using our general procedure (Scheme 1) that starts with the appropriate methyl disulfides (*3*, p. 111).



Scheme 1.

Hydrolysis of ester disulfide **4** was undertaken in aqueous tetrahydrofuran with strong-acid catalysis. The workup involved the extraction of the crude product with 1% aqueous sodium hydroxide solution, acidification and back extraction to provide what was expected to be the target disulfide acid **2.** In the event, the base-soluble product proved to be *p*-nitrobenzene thiol **6** (Scheme 2).



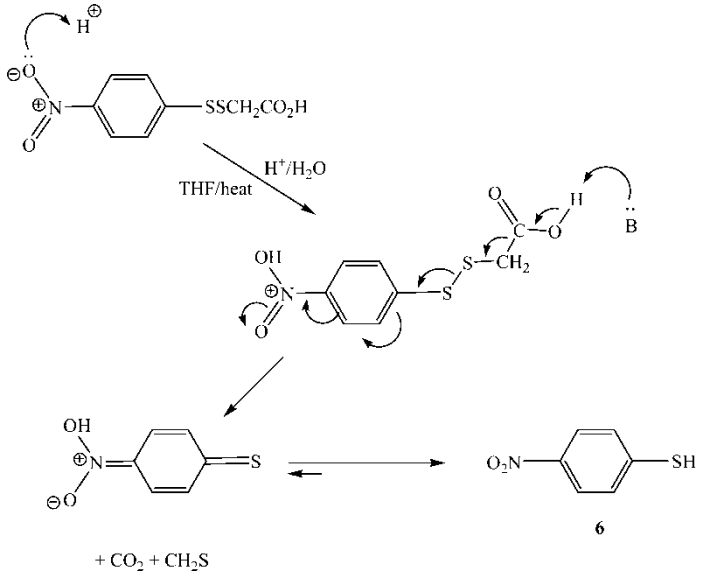
Scheme 2.

At this juncture, it seemed that the loss of the methyl thioglycollate fragment was accomplished during the acid-catalyzed hydrolysis, possibly by the mechanism provided in Scheme 3.

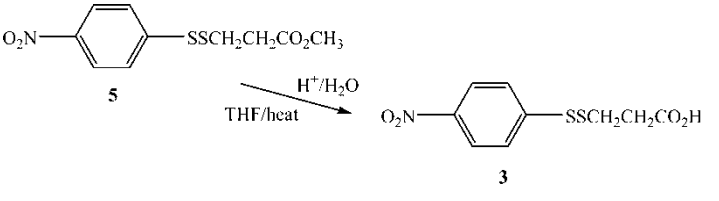
The obvious alternative, base-catalyzed hydrolysis of the acid during the workup, could proceed in a fashion analogous to the acid-catalyzed process shown in Scheme 3 or by direct nucleophilic attack of hydroxide ions at the appropriate sulfenyl sulfur.

To eliminate the ambiguities associated with the thioglycollate systems **2** and **4**, further exploration exploited the simpler structures **3** and **5**. The disulfide ester **5** was prepared as shown in Scheme 1 and hydrolyzed with acid catalysis under the same conditions applied earlier to **4**. In this case, the workup scrupulously avoided a strong base (Scheme 4). Application of the same procedure furnished disulfide acid **2** without complications.

Now, decarboxylation of **3** in aqueous base will not facilitate the direct formation of nitrobenzene thiolate of **6**. Hence, dissolution of **3** in dilute (1%) sodium hydroxide solution, followed by acidification and extraction, should (i) provide unchanged **3** if decarboxylation is key to undoing

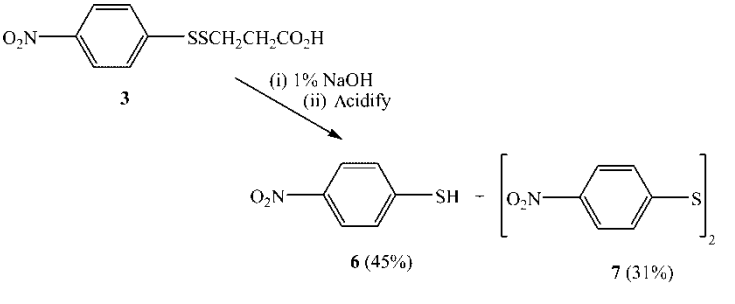


Scheme 3.



Scheme 4.

the SS bond, or (ii) provide thiol **6** if hydroxide ions attack at the appropriate sulfenyl sulfur (S_N2 process). Scheme 5 presents the outcome of the extraction procedure.



Scheme 5.

Nitrodisulfide acid **3** presents nucleophilic hydroxide ions with several electrophilic sites for a possible attack. The most interesting alternatives are (i) the electrophilic sulfenyl sulfur attached to a methylene and (ii) the nitrophenyl ring carbon attached to the disulfide moiety.

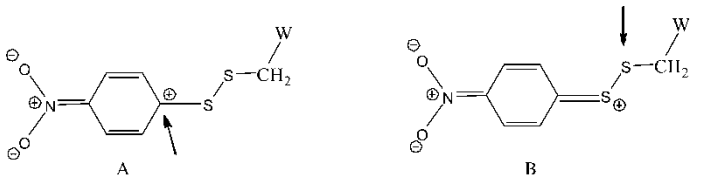
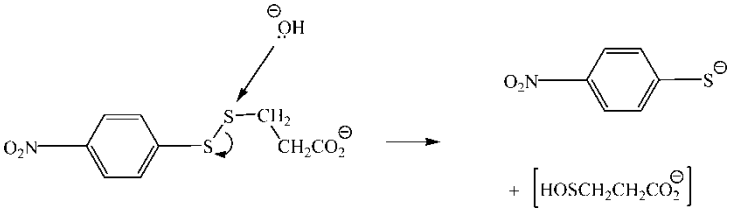


Figure 3. Selected resonance contributors for nitrophenyl disulfides.

A nucleophilic attack at the ring carbon (see arrow, contributor A, Figure 3) would be directly assisted by the nitro group, as indicated by contributor A, whereas a nucleophilic attack at sulfenyl sulfur (see arrow, contributor B, Figure 3) would be indirectly assisted by the nitro group, as indicated by contributor B.

p-Nitrophenyl methyl disulfide **1** was selected as a model system on which to carry out PM3 molecular orbital computations. PM3 results indicate net charges of +0.022 on sulfenyl sulfur (arrow, B, Figure 3) and −0.155 on carbon (arrow, A, Figure 3). On this basis, sulfenyl sulfur ought to be the preferred site for nucleophilic attack. Furthermore, a frontier molecular orbital argument resting on the PM3 LUMO (lowest unoccupied molecular orbital) coefficients for **1** suggest that sulfenyl sulfur (p_y LUMO coefficient, 0.6414) is strongly preferred over carbon (p_y LUMO coefficient, 0.0125) as the electrophilic site. Moreover, the development of a substantial p_y LUMO coefficient at sulfenyl sulfur is entirely consonant with the assumed in-plane, bimolecular substitution. For these reasons, *inter alia*, we propose a mechanism for the decomposition of nitrophenyl disulfide acids **2** and **3** in aqueous base (see Scheme 6).



Scheme 6.

The susceptibility of *p*-nitrophenyl disulfides to nucleophilic attack at sulfenyl sulfur is well documented (*4*). An assortment of nucleophiles has been ranked for thiophilicity (*5*). Triethylphosphite and bisulfide ions were shown to be very good thiophiles, whereas hydroxide ions were found to be much poorer thiophiles in reactions with disulfides. On the other hand, the thiophilicity of hydroxide ions is significantly enhanced for structures such as *p*-nitrophenyl disulfides in which the SS linkage bears a positive charge (*6, 7*). Hence, earlier studies are compatible with the interpretation of our results presented in the current report.

The novelty of our experimental results rests in the unexpectedly facile decomposition of *p*-nitrophenyl disulfide acids **2** and **3** during the brief time the extractive procedure left them in aqueous base. Since base washing of chloroform solutions of simple *p*-nitrophenyl disulfides such as *p*-nitrophenyl methyl disulfide does not lead to significant decomposition, we conclude that the reaction is dramatically facilitated by the complete dissolution of the water-soluble disulfide acids **2** and **3** in the aqueous phase during the extractive procedure.

3. Experimental

3.1. *General*

Infrared spectra were recorded on a Thermo Nicolet 2000 spectrophotometer. ^{1}H NMR (270 MHz) and ^{13}C NMR spectra were obtained on a JEOL JNM-GSX270 Fourier-transform NMR system. Unless otherwise specified, all NMR spectra were obtained in deuterated chloroform using tetramethyl silane as an internal standard. Mass spectra were obtained on a Hewlett-Packard 5988A gas–liquid mass spectrometer system.

3.2. *Preparation of* 3*-mercapto methyl propionate*

Methanol (54 mL) and concentrated sulfuric acid (5.2 mL) were added to a solution of 3-mercapto propionic acid (20 g, 0.19 mol). A Soxhlet extractor was loaded with a thimble containing anhydrous magnesium sulfate (12 g) and the extractor fitted to the reaction flask. The reaction mixture was refluxed for 25 h.

The reaction mixture was cooled to ambient temperature and washed with water (two 50 mL aliquots). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. The residue was rectified at reduced pressure affording 3-mercapto methyl propionate (18.3 g, bp 68–73 °C/17.5 Torr, 0.15 mol, 81%). The mercapto ester had IR 2570, 1734 cm^{-1}. ^{1}H NMR (270 MHz) δ 1.57 (t, $J = 8.1$ Hz, 1H), 2.58 (t, $J = 6$ Hz, 2H), 2.68 (q, 2H), 3.62 (s, 3H). ^{13}C NMR δ 19.7, 38.2, 51.7, 172.0. MS: 120 (M^+, 100%), 88 (71%), 61(55%).

3.3. *Preparation of disulfide esters* 4 *and* 5

The disulfide esters **4** and **5** were prepared as outlined below for **5**.

Sulfuryl chloride (0.68 g, 5.0 mmol) in dry methylene chloride (1 mL) was added dropwise to a solution of *p*-nitrophenyl methyl disulfide **1** (1.02 g, 5.0 mmol) in dry methylene chloride (6 mL). The reaction mixture was refluxed for 0.5 h. The solvent was evaporated and fresh, dry methylene chloride (3 mL) added. A solution of 3-mercapto methyl propionate (0.60 g, 5.0 mmol) in dry methylene chloride (3 mL) was added, followed by dry pyridine (0.8 mL). The reaction mixture was stirred at ambient temperature for 18 h.

Methylene chloride (200 mL) was added and the resultant solution washed with 2.5% hydrochloric acid (100 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. The crude product was chromatographed on silica gel (100 g) employing 1:1 chloroform/petroleum ether (100 mL fractions) for elution. Fractions 16–20 were combined and concentrated affording disulfide ester **5** (0.73 g, 2.7 mmol, 53%). Disulfide ester **5** had IR 1730, 1515 and 1340 cm^{-1}. ^{1}H NMR (270 MHz) δ 2.69 (t, $J = 7.0$ Hz, 2H), 2.98 (t, $J = 7.0$ Hz, 2H), 3.65 (s, 3H), 7.62 (d, $J = 8.9$ Hz, 2H), 8.15 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR δ 33.5, 52.0, 124.1, 126.0, 146.4, 171.6. MS: 273 ($M^{+\cdot}$, 38%), 242 (10%), 186 (11%), 119 (100%), 87 (83%).

Chromatographed disulfide ester **4** was obtained in 71% yield. Nitrophenyl ester **4** had IR 1730, 1500 and 1340 cm^{-1}. ^{1}H NMR (270 MHz) δ 3.55 (s, 2H), 3.62 (s, 3H), 7.68 (d, $J = 8.5$ Hz, 2H), 8.20 (d, $J = 8.5$ Hz, 2H). ^{13}C NMR δ 40.6, 52.6, 124.2, 126.4, 145.4, 168.8. MS: 259 ($M^{+\cdot}$, 100%), 200 (21%), 140 (32%).

3.4. *Preparation of disulfide acids* 2 *and* 3

Disulfide acids **2** and **3** were prepared as outlined below for **3**.

Water (26 mL) and concentrated sulfuric acid (1.2 mL) were added to a solution of ester disulfide **5** (1.19 g, 4.34 mmol) in tetrahydrofuran (100 mL). The reaction mixture was refluxed for 24 h. Chloroform (200 mL) was added and the resultant mixture extracted with water (two, 100 mL aliquots). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated.

The crude product was chromatographed on silica gel (100 g) employing chloroform (100 mL fractions) for elution. Fractions 10–16 were combined and concentrated affording disulfide acid **3** (0.59 g, 2.28 mmol, 53%, mp 113–114 °C). The product was recrystallized from ethyl acetate. $C_9H_9NO_4S_2$ requires C, 41.7; H, 3.5. Found: C, 41.9; H, 3.6. Compound **3** had IR 3350, 1705, 1515 and 1335 cm^{-1}. ^1H NMR (270 MHz) δ 2.77 (t, $J = 6.6$ Hz, 2H), 2.99 (t, $J = 6.6$ Hz, 2H), 7.65 (d, $J = 8.9$ Hz, 2H), 8.16 (d, $J = 8.9$ Hz, 2H), 10.68 (broad s, 1H). ^{13}C NMR δ 33.0, 33.4, 124.2, 126.1, 146.2, 146.5, 177.1. MS: 259 ($M^{+\cdot}$, 56%), 155 (100%).

Chromatographed disulfide acid **2** was obtained in 20% yield (mp 94–96 °C). $C_8H_7NO_4S_2$ requires C, 39.2; H, 2.9. Found: C, 39.1; H, 3.0. Compound **2** had IR 3420, 2940, 1705, 1510 and 1335 cm^{-1}. ^1H NMR (270 MHz) δ 3.51 (s, 2H), 7.67 (d, $J = 8.9$ Hz, 2H), 8.15 (d, $J = 8.9$ Hz, 2H), 10.65 (broad s, 1H). ^{13}C NMR δ 40.5, 124.1, 126.8, 145.0, 146.7, 174.7. MS: 245 ($M^{+\cdot}$, 100%), 186 (31%), 155 (39%), 140 (39%).

3.5. *Acid-catalyzed hydrolysis of* **4** *with base extractive workup*

Water (34 mL) and concentrated sulfuric acid (1.1 mL) were added to a solution of ester disulfide **4** (1.06 g, 4.1 mmol) in tetrahydrofuran (100 mL). The reaction mixture was refluxed for 21 h. Chloroform (200 mL) was added and the resultant mixture washed with water (two, 100 mL portions). The organic layer was concentrated.

The crude product was dissolved in chloroform (100 mL) and the resultant solution extracted with 1% W/V sodium hydroxide (two, 50 mL aliquots). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated to give unchanged **4** (0.30 g, 29%).

The combined aqueous layers were acidified with concentrated hydrochloric acid (3.5 mL) and the resultant mixture extracted with chloroform (three, 75 mL aliquots). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated to afford *p*-nitrothiophenol **6** (0.32 g, 2.1 mmol, 51%). Compound **6** has been prepared earlier (*8*) but no spectroscopic data were provided. Compound **6** had IR 2550, 1500 and 1340 cm^{-1}. ^1H NMR (270 MHz) δ 3.81 (s, 1H), 7.30 (d, $J = 8.9$ Hz, 2H), 8.05 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR δ 124.3, 128.4, 141.9, 145.6. MS: 155 ($M^{+\cdot}$, 100%), 109 (48%).

3.6. *Reaction of disulfide acid* **3** *in aqueous base*

Disulfide acid **3** (33 mg, 130 μmol) was dissolved in chloroform (10 mL) and the resultant solution extracted with 1% W/V sodium hydroxide (two, 5 mL portions). The combined aqueous extracts were acidified with concentrated hydrochloric acid (25 drops).

The aqueous mixture was extracted with chloroform (three, 10 mL aliquots). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated, affording the crude product (16 mg).

The crude product was chromatographed on silica gel (2 g) employing 3:1 chloroform/petroleum ether (2 mL fractions) for elution. Fractions 3–6 were combined and concentrated giving a mixture of *p*-nitrothiophenol **6** and di(*p*-nitrophenyl) disulfide **7**. The mixture was dissolved in chloroform (15 mL) and the resultant solution extracted with 5% W/V sodium hydroxide (three, 10 mL portions). The combined aqueous layers were set aside. The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated, furnishing disulfide **7** (5 mg, 20 μmol, 31%). The combined aqueous layers were acidified with concentrated hydrochloric acid and the resultant

mixture washed with chloroform (three, 10 mL aliquots). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated to give *p*-nitrothiophenol (9 mg, 58 μmol, 45%).

Acknowledgements

The authors thank Canadian Blood Services for financial support. Mass spectra were obtained by R. Smith. K.D. Guckert provided some technical assistance.

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