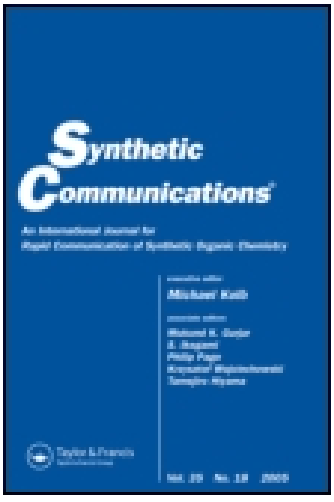

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A Versatile One-Pot Synthesis of Dialkyl Disulfides and Sulfides

David W. Emerson [a] , Byron L. Bennett [a] & Spencer M. Steinberg [a]
[a] Department of Chemistry , The University of Nevada , Las Vegas, NV, USA
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A Versatile One-Pot Synthesis of Dialkyl Disulfides and Sulfides

David W. Emerson, Byron L. Bennett, and Spencer M. Steinberg
Department of Chemistry, The University of Nevada,
Las Vegas, NV, USA

Abstract: Conversions of monofluoroalkyl and alkyl bromides to the corresponding dialkyl disulfides in a one-pot synthesis using thiourea followed by basic hydrogen peroxide are described. Modified methods afford access to unsymmetrical disulfides and sulfides.

Keywords: Disulfides, fluorine and fluorine compounds, sulfides

INTRODUCTION

The study of self-assembled monolayers (SAMs) from organosulfur compounds is currently an active area of research. Dialkyl disulfides can be used to produce monomolecular layers on certain metal surfaces, e.g., Au and Ag,[1–4] underscoring the importance of synthesizing disulfides useful for forming SAMs. Interest continues in this field and extensive reviews have appeared.[5,6] Insights have been gained about mechanisms by which disulfides evolve into monomolecular layers on Au and/or Ag surfaces.[7–9] Thiols, disulfides, and sulfides too are of interest.[10,11] This continuing activity suggests that simple synthetic methods for making disulfides and sulfides will be useful. Heretofore disulfides containing fluorine have incorporated perfluorinated sections of the carbon chain, but terminal monofluorinated chain-ends may prove interesting.

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Address correspondence to David W. Emerson, Department of Chemistry, The University of Nevada, Box 454003, Las Vegas, NV 89154-4003, USA. E-mail: emerson@unlv.nevada.edu

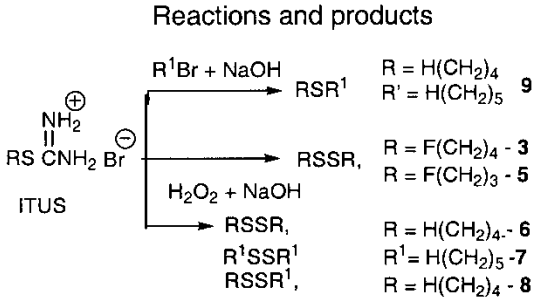
Attempts to synthesize 4-fluoro-1-butanethiol, **1**) from 1-bromo-4-fluorobutane, **2**) by forming the intermediate isothiuronium salt (ITUS) followed by an alkaline workup[1],[12] resulted mainly in tetrahydrothiophene,[13] possibly by an intramolecular displacement reaction despite fluoride being a poor leaving group.

Work by others showed varying degrees of complexity in the reagents employed and the steps needed to get the final product. Basic hydrogen peroxide oxidized an arenethiol to disulfide, sulfinate, and sulfonate but the disulfide was not the precursor of the other two products.[14] Fluorine-containing alkanethiols were produced by action of base on ITUs and were oxidized by atmospheric oxygen.[15,16] Aqueous in situ-generated alkali metaldisulfides and alkyl halides produced symmetrical disulfides.[17–19] Piperidinium tetrathiotungstate or tetrathiomolybdate[20] and benzyltriethylammonium tetracosathioheptamolybdate[21] produce disulfides. An aralkanethiol of some complexity made from an ITUS was oxidized to the disulfide by iodine.[4] Conversion of alkyl thiocyanates to disulfides by aqueous ammonia was reported.[22]

RESULTS AND DISCUSSION

Our strategy was to prepare the ITUSs from alkyl halides by inverse addition of the soft, nonbasic nucleophile, thiourea. We added a mixture of sodium hydroxide and hydrogen peroxide to the reaction mixture expecting that the liberated thiol would be oxidized promptly to the disulfide[23] and that fewer unwanted side reactions would result. Extraction and cleanup of the product followed. Three methods are described in the Experimental section. Starting with 4-fluoro-1-bromobutane (**2**) we synthesized the hitherto unknown 4-fluoro-1-butyl disulfide (**3**) that is presumably a more stable compound than the thiol (**1**). We also report synthesis of the unknown 3-fluoro-1-propyl disulfide (**5**) from 1-bromo-3-fluoropropane (**4**). We prepared solutions of the ITUSs from (**2**) and (**4**) by inverse addition of thiourea followed by addition of sodium hydroxide and hydrogen peroxide to liberate the thiols and oxidize them rapidly. Solvent extraction and evaporation followed by distillation afforded the desired products in acceptable yield and high purity. No effort was made to optimize yields. The identities of (**3**) and (**5**) were confirmed by nuclear magnetic resonance (NMR), Fourier transform infrared (FTIR), and mass[24] spectroscopy and elemental analysis. We also made simple symmetrical and unsymmetrical dialkyl disulfides and a sulfide in acceptable yields, Table 1 & Scheme 1, and found that

[1]This paper was apparently not abstracted by *Chemical Abstracts.* It is a convincingly documented example of the synthesis of a volatile alkanethiol via the ITUS route.



Scheme 1.

components of the extract of a reaction mixture containing dialkyl disulfides, separated on a thin layer chromatography (TLC) plate, can be identified by flash heating gas chromatography-mass spectrometry (GC-MS) of coating scraped from the plate and heated by a Pt filament pyrolyzer. Compound **3** in addition to the parent compound, produced tetrahydrothiophene as the major conmponent and **5** yielded mostly the parent compound and small amounts of diallyldisulfide and 1,2-dithiolane.

A mixture of unsymmetrical disulfides can be made by making different ITUSs in the same vessel, followed by oxidation with basic hydrogen peroxide. With equimolar amounts of two different ITUSs there is approximately twice as much unsymmetrical disulfide compared to the two symmetrical products. Symmetrical sulfides may be prepared by adding the same alkyl halide to the solution in which the ITUS was prepared, and then adding base without an oxidant. An unsymmetrical sulfide was made by adding an alkyl halide different from the one used to make the ITUS and then adding base.

Table 1. Isolated yields and parent ions[24]

Compound, No.	Method	Yield[a] %	Notes, Refs.
$[F\text{-}(CH_2)_4\text{-}S]_2$, **3**	A	40	M/z = 214
	C	52[b]	
$[F\text{-}(CH_2)_3\text{-}S]_2$ **5**	A	58	M/z = 186
$[H\text{-}(CH_2)_4\text{-}S]_2$ **6**	B	69.9	M/z = 178
$[H\text{-}(CH_2)_5\text{-}S]_2$ **7**	B	69	M/z = 206
$[H\text{-}(CH_2)_5\text{-}S\text{-}S\text{-}(CH_2)_4\text{-}H]$ **8**	B		M/z = 192[24,28]
6, 7, 8	B	50	M/z = 178, 192, 206
$[H\text{-}(CH_2)_5\text{-}S\text{-}(CH_2)_4\text{-}H]$ **9**	B	59	m/z = 160[28]

[a]Isolated yield based on alkyl halide.
[b]Yield on basis of the ITUS was 63%.

EXPERIMENTAL

Bromofluoroalkanes were obtained from Aldrich Chemical Co. and were used without further purification. The tetrahydrofuran (THF), ethyl ether, mixed hexanes, and pentane used evaporated without leaving a residue. Hydrogen peroxide was supplied by VWR. The TLC plates, 5 × 20 cm, 250 μ silica gel GF coated were supplied by Analtech. Useful directions for syntheses of ITUSs exist.[25] Temperatures are uncorrected and reported distillation temperatures are the oven temperatures of the Kugelrohr apparatus. Distillation pressures were measured with a simple mercury manometer. House vacuum varied between 380 and 200 torr. The GC-MS analyses were performed on a Varian 3400 GC/Saturn 3 system equipped with a J & W Scientific DB-5-MS column (30 m × 0.25 mm, 0.25 μ film). The samples were injected in dichloromethane. The temperature of the GC oven was held for 6 min at 40°C and then ramped to 280°C at 12°C/min. Flash heating GC/MS employed a CDS pyroprobe 2000 connected to a Varian Model 3400 GC and a Varian Saturn 3 mass spectrometer. Samples were heated at 300–500°C for 20 sec. Volatilized products were separated on a Supelco EC-5 capillary column (30 m × 0.25 mm, 0.25 μ film) and analyzed by electron impact mass spectrometry. The GC oven was programmed as shown previously.

The FTIR spectra of neat samples between NaCl disks were obtained on a Nicollet 200 instrument. The high-field NMR spectra were obtained on a Bruker AMX400 spectrometer in 5 mm sample tubes (Wilmad). ^{1}H and ^{13}C chemical shifts are quoted relative to solvent resonance(s) as internal standard. ^{19}F chemical shifts are externally referenced to $CFCl_3$ (convention: upfield shifts are negative). H-H COSY spectra were acquired to confirm signal assignments for the ^{1}H spectra of **3** and **5**.

Compounds and CAS Registry numbers are: thiourea [62-56-6], 1-bromo-4-fluorobutane, **2**, [462-72-6], 1-bromo-3-fluoropropane, **4** [352-91-0], n-butyl disulfide, **6** [629-45-8], n-pentyl disulfide, **7**, [112-51-6], n-butyl n-pentyl disulfide, **8** [72437-52-6], and n-butyl n-pentyl sulfide, **9** [24768-42-1].[29]

Method A

Preparation of 4-fluoro-1-butyl Disulfide, **3**

A solution of 0.380 g, 5 mmol, of thiourea in 2 mL of THF and 1 mL of water was added with vigorous stirring to 0.775 g, (4.9 mmol) of **2**, in 2 mL of THF in a round-bottomed flask. Thiourea was added in eight portions, five minutes apart with heating. The heat was then turned off and the mixture was stirred overnight. The reaction mixture was transferred to a 25 mL Erlenmeyer flask; 5 mL of ethyl ether and 2 mL of hexanes were added. Three mL of 2 N sodium hydroxide, (6 mmol), and 0.306 mL of 25% hydrogen peroxide,

(2.3 mmol), were mixed and added dropwise with vigorous stirring over a 20-minute period. The mixture was stirred for 1 h and allowed to stand for one day. The mixture was separated and the top layer was extracted with saturated brine. The bottom layer was extracted with 5 mL of ethyl ether. The combined organic layer was dried over anhydrous sodium sulfate. A small portion of this solution was spotted across a TLC plate, developed with dichloromethane; $R_f = 0.70$. This band was scraped off, eluted with dichloromethane and the eluate was analyzed by GC-MS. The parent ion and base peak was at m/z 214 with fragments of intensities $\geq 8\%$ at 140, 120, 87, and 55. The product layer was rotary evaporated at house vacuum. The cloudy residue was filtered through cotton in a Pasteur pipette and chased with 0.5 mL of ethyl ether. The clear solution was again rotary evaporated and a drop of the residue was applied to a TLC plate and developed. Some of the coating was analyzed by flash heating GC-MS giving the same result as before. A Kugelrohr distillation yielded a first fraction at 25–100°C at <2 torr that was discarded. A second fraction boiling at 107–109°C at <1 torr was collected; 0.209 g.; 39.9%. The liquid tended to bead up in the receiver suggesting a high surface tension. The viscous residue weighed 0.008 g and was not further investigated. Calculated for $C_8H_{16}F_2S_2$: C 44.83% H 7.52%; Found C 45.16 % H 7.32%. EI MS (70 eV) m/z M^+ Calculated: 214.066, observed 214. ^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K) δ 4.43 (d,t, $^2J_{FH} = 47$ Hz, $^3J_{HH} = 7$ Hz, 4H, $FCH_2CH_2CH_2CH_2S$) 2.72 (t, $^3J_{HH} = 7$ Hz, 4H, $FCH_2CH_2CH_2CH_2S$) 1.83 (br, 4H, $FCH_2CH_2CH_2$-CH_2S) 1.78 (m, 4H, $FCH_2CH_2CH_2CH_2S$). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 295 K) δ 83.67 (d, $^1J_{FC} = 165$ Hz, 2C, FCH_2CH_2 CH_2CH_2S), 38.5 (s, 2C, $FCH_2CH_2CH_2CH_2S$), 29.3 (d, $^3J_{FC} = 20$ Hz, 2C, $FCH_2CH_2CH_2CH_2S$) 25.1 (d, $^3J_{FC} = 4$ Hz, 2C, $FCH_2CH_2CH_2CH_2S$). ^{19}F NMR (376.5 MHz, $CDCl_3$, 295K) δ −223.6 (t,t, $^2J_{HF} = 47$ Hz, $^3J_{HF} = 26$ Hz, 2F, FCH_2) FTIR (neat, NaCl disks, cm^{-1} ν 2961, 2906, 2866, 1475, 1449, 1416, 1390, 1298, 1267, 1248, 1209, 1158, 1064, 1037, 982, 947, 924, 893, 799.

Preparation of 3-fluoro-1-propyl Disulfide, **5**

The preparation was performed essentially the same way as the preparation of **3**. Thiourea, 0.83 g, (11 mmol), and 1.38 g, (9.6 mmol), **4**, in 2:1 THF/water reacted overnight. A 5 : 2 ether/hexanes mixture and a solution of 7.5 mL, 20 mmol, of 2 N sodium hydroxide and 1.02 mL of 25% hydrogen peroxide, 7.5 mmol, were added. After separation and solvent evaporation a Kugerohr distillation at <1 torr yielded two fractions <93°C and 93–97°C that proved to be identical by proton NMR. Elemental analysis, calculated for $C_6H_{12}F_2S_2$: C 38.69%, H 6.49%; Found C 38.58% H 6.29%. EI MS (70 eV) m/z M^+ Calculated: 186.034 observed 186. ^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K) δ 4.53 (d,t, $^2J_{FH} = 47$ Hz, $^3J_{HH} = 6$ Hz, 4H, $FCH_2CH_2CH_2S-$) 2.78 (t, $^3J_{HH} = 7$ Hz, 4H, $FCH_2CH_2CH_2S-$) 2.08 (d -t,t (overlapping),

$^{3}J_{FH} = 26\,Hz$, $^{3}J_{HH} = 6.5\,Hz$ (average), 4H, $FCH_2CH_2CH_2S-$). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, 295 K) δ 82.1 (d, $^{1}J_{FC} = 165\,Hz$, 2C, $FCH_2CH_2CH_2S$), 34.1 (d, $^{2}J_{FC} = 4\,Hz$, 2C, $FCH_2CH_2CH_2S$), 30.0 (d, $^{3}J_{FC} = 20\,Hz$, 2C, $FCH_2CH_2CH_2S$). ^{19}F NMR (376.5 MHz, $CDCl_3$, 295K)δ -225.8 (t,t, $^{2}J_{HF} = 47\,Hz$, $^{3}J_{HF} = 26\,Hz$, 2F, FCH_2). FTIR (neat, NaCl disk, cm^{-1}, ν 2966, 2904, 1472, 1434, 1388, 1347, 1286, 1261, 1211, 1168, 1076, 1057, 1016, 893.

Method B

Dimethyl sulfoxide (DMSO) was used as a solvent. The alkyl halide and thiourea were added to a flask on a stirrer/hot plate without a reflux condenser. After completion of the reaction, the solution of sodium hydroxide and hydrogen peroxide[2][26] was added gradually with stirring followed by heating to 60°C for 0.5 h or more. Water and pentane were added to the cooled mixture with vigorous stirring and the workup was completed in the usual manner. The hydrocarbon extraction solvent extracts nonpolar components from a polar reaction mixture with vanishingly small quantities of other components.[27] Mixtures of unsymmetrical and symmetrical disulfides were made by using two different alkyl halides and proceeding as one would in making a disulfide. About twice as much unsymmetrical disulfide (statistical mixtures can also be made by photolyzing mixtures of disulfides)[28] is made compared to the two symmetrical disulfides that also result. To make an unsymmetrical sulfide, the ITUS of one halide was prepared in DMSO, a different alkyl halide was then added followed by two equivalents of base. The remainder of the procedure was the same.

Method C

The alkyl halide **2** (10.1 mmol) and acetonitrile were combined and (12.9 mmol) of thiourea was added in seven portions. The mixture was heated to 55–65°C for 15 minutes. Pentane was added and the solid was filtered off. The filtrate was evaporated via an air stream and the solid was triturated with pentane to remove any unreacted **2**. The solid ITUS fractions were combined and dissolved in methanol. A mixture of 7 mL of 2 N sodium hydroxide and 0.7 mL (5.1 mmol) hydrogen peroxide was added gradually with pentane, as the extraction solvent. Passing the dried extract through 1.2 cm of alumina topped with 1 cm of activated carbon pellets in a

[2]Solvation of peroxyanions ROO^- inhibits reactions with sulfoxides. We found that HOO^- evidently reacts with the thiolate ion in preference to DMSO.

Pasteur pipette and rotary evaporation led to 0.555 g of **3** in high purity without distillation. Yield, 52% basis alkyl halide, 63% basis ITUS.

Supplementary Data

NMR, FTIR, and GC-MS spectra of **3** & **5** are available by request addressed to any co-author.

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REFERENCES

1. (a) Nuzzo, R. G.; Allara, D. L. *J. Am. Chem. Soc.* **1983**, *105* (13), 4481–4483; (b) Nuzzo, R. G.; Zegarski, B. R.; Dubois, L. H. *J. Am. Chem. Soc.* **1987**, *109* (3), 733–740.
2. Porter, M. D.; Bright, T. B.; Allara, D. L.; Chidsey, C. E.D. *J. Am. Chem. Soc.* **1987**, *109* (12), 3559–3568.
3. Troughton, E. B.; Bain, C. D.; Whitesides, G. M.; Nuzzo, R. G.; Allara, D. L.; Porter, M. D. *Langmuir* **1988**, *4* (2), 365–385.
4. Haas, U.; Thalacker, C.; Adams, J.; Fuhrmann, J.; Riethmüller, S.; Beginn, U.; Ziener, U.; Möller, M.; Dobrawa, R.; Würthner, F. *J. Mater. Chem.* **2003**, *13* (4), 767–772.
5. Whitesides, G. M.; Laibinis, P. E. *Langmuir* **1990**, *6* (1), 87–96.
6. Ulman, A. *Chem. Rev.* **1996**, *96* (4), 1533–1554.
7. Eu, S.; Paik, W.-K. *Mol. Cryst. Liq. Cryst.* **1999**, *337*, 49–52.
8. Paik, W.-K.; Eu, S.; Lee, K.; Chon; Kim, M. *Langmuir* **2000**, *16* (26), 10198–10205.
9. Hayashi, T.; Kodama, C.; Nozoye, H. *Appl. Surf. Sci.* **2001**, *169–170*, 100–103.
10. Bain, C. D.; Troughton, E. B.; Tao, Y.-T.; Evall, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111* (1), 321–335.
11. Trevor, J. L.; Lukke, K. R.; Pellin, M. J.; Hanley, L. *Langmuir* **1998**, *14* (7), 1664–1673.
12. Arndt, F. *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 2236.
13. Johnson, A. L.; Stiever, J. J. Synthesis of Materials for Nanotechnology. 46th Ann. Mtg, Apr. 6, 2002AZ-NV Acad. Sci.
14. Evans, B. J.; Doi, J. T.; Musker, W. K. *J. Org. Chem.* **1990**, *55* (8), 2337–2344.
15. Hobo, T.; Ishikawa, K.; Suzuki, S.; Watabe, K. *J. Chromatogr.* **1985**, *330* (1), 131–140.
16. Mureau, N.; Guittard, F.; Géribaldi, S. *Tetrahedron Lett.* **2000**, *41* (16), 2885–2889.
17. Hase, T. A.; Perakyla, H. *Synth. Commun.* **1982**, *12* (12), 947–950.

18. Gladysz, J. A.; Wong, V. K.; Jick, B. S. *Tetrahedron* **1979**, *35* (20), 2329–2335.
19. (a) Wang, J.-X.; Cui, W.; Hu, Y. *Synth. Commun.* **1995**, *25* (22), 3573–3581; (b) Wang, J.-X.; Gao, L.; Huang, D. *Synth. Commun.* **2002**, *32* (7), 963–969.
20. Dhar, P.; Chandrasekaran, S. *J. Org. Chem.* **1989**, *54* (13), 2998–3000.
21. Polshettiwar, V.; Nivsarkar, M.; Acharya, J.; Kaushik, M. P. *Tetrahedron Lett.* **2003**, *44* (5), 887–889.
22. Rybin, A. G.; Zil'berman, E. N.; Zhivoderov, A. V. *Zh. Obshch. Khim.* **1983**, *53* (8), 1863–1867*Chem.* Abstr. **1984**, *100*, 5970.
23. Boeseken, J. *Recl. Trav. Chim. Pays-Bas* **1948**, *67*, 603–621.
24. Gupta, D.; Knight, A. R.; Smith, P. J. *Can. J. Chem.* **1981**, *59* (3), 543–548.
25. *Vogel's Textbook of Organic Chemistry*, 4th Ed.; Furniss, B. S., Hannaford, A. J., Rogers, V., Smith, P. W. G., Tatchell, A. R., Eds.; Longman, Harlow & Wiley: New York, 1978; pp. 581–584, 1118–1119, 1200–1203.
26. Ogata, Y.; Suyama, S. *J. Chem. Soc. Perkin Trans. 2* **1973** (6), 755–758.
27. Emerson, D. W.; Craig, A. P.; Potts, I. W., Jr. *J. Org. Chem.* **1967**, *32* (1), 102–105.
28. Gupta, D.; Knight, A. R. *Can. J. Chem.* **1980**, *58* (13), 1350–1354.
29. Laurent, R. *Geochim. Cosmochim. Acta* **2001**, *65* (1), 3827–3877.