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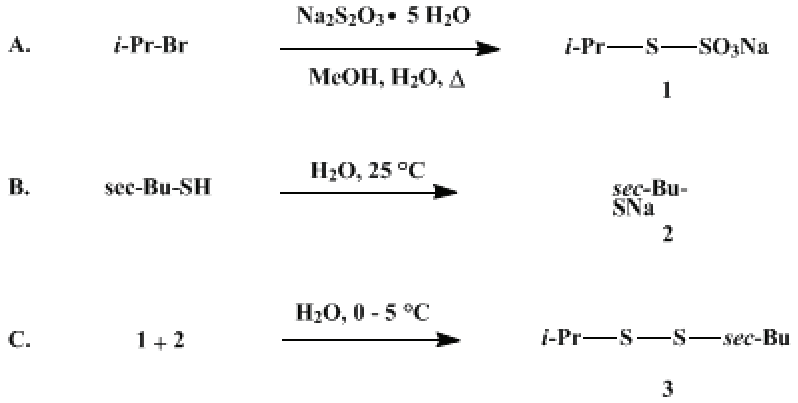
# SULFIDE SYNTHESIS IN PREPARATION OF UNSYMMETRICAL DIALKYL DISULFIDES: *sec*-BUTYL ISOPROPYL DISULFIDE

### [Disulfide, 1-methylethyl 1-methylpropyl]



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## 1. Procedure

*Caution! This procedure should be carried out in an efficient hood to prevent exposure to alkane thiols.*

A. *Sodium isopropyl thiosulfate* **(1).** A 5-l., three-necked, round-bottomed flask equipped with a condenser, a 300-ml. dropping funnel, and a mechanical stirrer is charged with 123 g. (1.00 mole) of freshly distilled 2-bromopropane (Note 1) in 1.2 l. of methanol. Water is added slowly with stirring until a slight turbidity develops (Note 2). The stirred mixture is heated to reflux, and 310 g. (1.25 mole) of sodium thiosulfate pentahydrate (Note 3) in 250 ml. of water is added over a period of 30 minutes. The slightly yellow-tinted solution is heated for an additional 3.5–4.0 hours and allowed to cool to room temperature. The alcohol is removed with a rotary evaporator; the remaining milky solution is diluted with water to a total volume of about 1.2 l and extracted twice with hexane (Note 4). Discarding the organic layers, the aqueous solution of crude thiosulfate is cooled to 0° and stored.

B. *Sodium 2-butanethiolate* **(2).** A 500-ml., three-necked, round-bottomed flask equipped with a dropping funnel, a mechanical stirrer, and a gas-inlet is charged with 40 g. (1.0 mole) of sodium hydroxide in 100 ml. of water. Under an atmosphere of argon (Note 5), 90 g. (1.0 mole) of 2-butanethiol (Note 6) is added dropwise over a 2-hour period, with rapid stirring at room temperature (Note 7). Thiolate solution **2** becomes very viscous toward the end of the addition; it is diluted with 30 ml. of water and cooled to 0°.

C. sec-*Butyl isopropyl disulfide* **(3).** A 3-l., three-necked, round-bottomed flask equipped with a dropping funnel, a thermometer, and a mechanical stirrer is charged with the crude thiosulfate solution **1** and cooled to 0° with the aid of an ice-salt bath. The cold thiolate solution **2** is added rapidly, with vigorous stirring for 3 minutes, followed by 200 ml. of aqueous saturated sodium chloride (Note 8), and the mixture is warmed to 5°. Stirring is stopped after 10 minutes, counted from the start of the addition of the aqueous sodium chloride. The crude disulfide **3**, which separates as an oil, is removed, and the aqueous layer is extracted twice with 250-ml. portions of diethyl ether. The extracts are combined with the oil, washed twice with 150-ml. portions of water, dried briefly over granular calcium sulfate, and filtered through a glass-wool plug. Removal of the solvent leaves 125–133 g. of crude disulfide **3** (Note 9). Distillation of this material at 44.5–45° (1.25 mm.) gives 118–123 g. (73–75%) of pure disulfide **3**

(Note 10).

## 2. Notes

1. The submitters used 2-bromopropane available from Aldrich Chemical Company, Inc. The checkers purchased the reagent from J. T. Baker Chemical Company.
2. The turbidity indicates saturation of alkyl halide. In this way both sodium thiosulfate and 2-bromopropane are nearly in a one-phase system, thus shortening significantly the heating period. Furthermore, competing hydrogen bromide elimination and acid-promoted decomposition of thiosulfate into sulfur and sulfur dioxide are minimized. The checkers added 300 ml. of water over a period of 90 minutes.
3. The submitters used sodium thiosulfate pentahydrate supplied by E. Merck A G, Darmstadt, and the checkers used A.C.S. reagent grade material available from Fisher Scientific Company.
4. This extraction is intended to remove traces of unreacted alkyl halide that might compete for the thiolate in the nucleophilic substitution (Step B).
5. The submitters performed this step in air, but the checkers found that use of an inert atmosphere resulted in a somewhat improved yield.
6. This reagent was purchased from Aldrich Chemical Company, Inc.
7. The submitters observed the separation of a pasty solid at this stage, added four 10-ml. portions of water during the addition of the thiol, and dissolved the entire solid with approximately 240 ml. of water. Sometimes, at this point, as much as 10% of the added thiol separated out as a floating oil. The presence of this thiol affects the course of the reaction, yielding symmetrical disulfides.[2] In this case the organic layer should be separated, added dropwise to an equivalent amount of sodium hydroxide dissolved in a minimum amount of water, and mixed with the original thiolate solution.
8. The submitters found that the addition of sodium chloride facilitated the separation of the insoluble disulfide.
9. This material contained no less than 90% of disulfide **3** according to GC analysis (1.5-m. 5% SE-30 column).
10. The distilled disulfide **3** has the following $^1$H NMR spectrum ($CDCl_3$), δ (multiplicity, coupling constant $J$ in Hz., number of protons, assignment): 1.00 (t, $J = 7.0$, 3H, $CH_3CH_2$), 1.31 (d, $J = 7.0$, 9H, $(CH_3)_2CH$ and $CH_3CH$), 1.62 (m, 2H, $CH_2$), 2.86 (sextuplet, $J = 7.0$, 1H, $CH_3CHCH_2$), 3.02 (septuplet, $J = 7.0$, 1H, $CH_3CHCH_3$).

## 3. Discussion

Unsymmetrical, dialkyl disulfides[3] can be prepared by several methods; three procedures appear to be generally applicable. First, the reaction of an *N*-(alkylthio)- or *N*-(arylthio)phthalimide with thiols[4] gives unsymmetrical disulfides in good yield; however, the synthesis of the thiophthalimide[5,6] requires the corresponding sulfenyl chloride, which is rather unstable and undergoes undesirable side reactions when α-protons are available.[7] Second, the adduct of a thiol and diethyl azodicarboxylate reacts with a thiol, giving unsymmetrical disulfides in high yield.[8] The adduct formation, however, is severely suppressed by steric hindrance in the alkyl portion of the thiol; secondary and tertiary thiols are normally unreactive.[9] Third, the reaction of sodium alkylthiosulfates[10] with thiolates provides unhindered, mixed disulfides in low to moderate yields,[11] and hindered compounds[12] in yields of 6–10%. A general and satisfactory synthetic procedure for hindered, unsymmetrical disulfides was not available at the time the present study was undertaken,[6] the probable reason being that the known methods utilize a sterically sensitive bimolecular attack by a nucleophilic form of sulfur onto a sulfur atom bearing a suitable leaving group. Forcing conditions usually lead to disproportionation[13] and polysulfide formation.[11] The availability and low cost of starting materials and the expeditious process involved in the "Bunte Salt" approach[10] provided a reasonable basis for modifying the existing procedure,[11] extending its applicability to bulky, unsymmetrical disulfides. Table I shows boiling points and distillate composition of a number of mixed disulfides prepared in up to 80% yield by the method presented here;[14] base-catalyzed disproportionation[13] and polymerization[11] appear to be minimized.

TABLE I

UNSYMMETRICAL DIALKYL DISULFIDES PREPARED BY THE THIOSULFATE PROCEDURE. DISTILLATION CONDITIONS AND COMPOSITION[a,b]

| R | R' | bp, °C/torr | yield (%) | RSSR' (%) | RSSR (%) | R'SSR' (%) |
|---|---|---|---|---|---|---|
| $(CH_3)_2CHCH_2$- | $(CH_3)_2CH$- | 33–34/0.15 | 60 | 92 | 6 | 2 |
| $(CH_3)_2CHCH_2$- | $CH_3CH_2$- | 51/3 | 62 | 98 |  | 1 |
| $(CH_3)_2CHCH_2$- | $CH_3$- | 52/8.5 | 65 | 97 |  | 1.5 |
| $(CH_3)_2CHCH_2$- | $CH_2=CHCH_2$ | 57.5/1.5 | 81 | 96 | 2 | 1.5 |
| $(CH_3)_2CH$- | $CH_3CH_2$= | 49/9 | 60 | 98 | <1 | [c] |
| $(CH_3)_2CH$- | $CH_3$- | 37–38/11 | 72 | 98.5 | <1 |  |
| $(CH_3)_2CH$- | $CH_2=CHCH_2$- | 55.5/5 | 69 | 98.5 |  | <1 |
| $C_2H_5CH(CH_3)$- | $(CH_3)_2CH$- | 40–41/0.2 | 73 | 96.5 | 3 | [c] |
| $C_2H_5CH(CH_3)$- | $CH_3CH_2$- | 47/1.5 | 64 | 98.5 | <1 | <1 |
| $C_2H_5CH(CH_3)$- | $CH_3$- | 46.5/6 | 71 | 99 |  |  |
| $C_2H_5CH(CH_3)$- | $CH_2=CHCH_2$- | 51/1 | 71 | 98.5 | <1 |  |
| $(CH_3)_3C$ | $(CH_3)_2CH$ | 30–32/2 | 53 | 96.5 | 1 | <1 |
| $(CH_3)_3C$- | $CH_3CH_2$- | 43–44/5 | 52 | 97 | <1 | 2 |
| $(CH_3)_3C$- | $CH_3$- | 46/12 | 49 | 98.5 | <1 | <1 |
| $(CH_3)_3C$- | $CH_2=CHCH_2$- | 53/2 | 54 | 99 |  |  |

[a] Determined by GC analysis on a 12-ft 5% SE-30 on Chromosorb G column.
[b] Satisfactory analytical data (±0.52% for C, H, S) were obtained for all compounds.
[c] Could not be separated by GC.

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## Appendix
## Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

methanol (67-56-1)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

hydrogen bromide (10035-10-6)

sulfur dioxide (7446-09-5)

2-bromopropane (75-26-3)

sodium thiosulfate (7772-98-7)

sulfur (7704-34-9)

calcium sulfate (7778-18-9)

diethyl azodicarboxylate (1972-28-7)

hexane (110-54-3)

argon (7440-37-1)

thiophthalimide

Disulfide, 1-methylethyl 1-methylpropyl,
sec-Butyl isopropyl disulfide (67421-86-7)

sodium thiosulfate pentahydrate

2-butanethiol (513-53-1)

Sodium 2-butanethiolate

Sodium isopropyl thiosulfate