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A Facile One-pot Synthesis of Sulfides from Alkyl Halides and Alcohols Using Tetramethylthiourea

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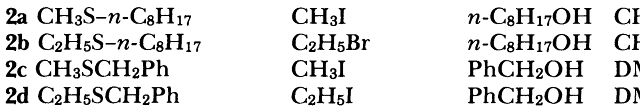
Synopsis. Sulfides can be readily prepared under mild conditions by a reaction of tetramethylthiourea with alkyl halides and alcohols in the presence of sodium hydride in satisfactory yields. The scope and limitation of this method are also presented.

The reaction of alkyl halides with Na_2S, leading to symmetrical sulfides, is well known. And, unsymmetrical sulfides are widely synthesized by neucleophilic substitution reaction of alkyl and aryl halides with thiols under basic conditions.1) Recently, some convenient methods for the preparation of sulfides by the reaction of 2-alkylthio-1,3-benzoxazoles with sodium alkoxide,2) and 2-alkoxy-1-methylpyridinium salt with thiol in the presence of triethylamine,3) have been reported.

In the course of our investigation of the reaction of thiocarbamoyl derivatives, we have now found a convenient one-pot preparative method of sulfides (**2**) under mild conditions from alkyl halides and alcohols using tetramethylthiourea (**1**) as starting material which is easily available.



1 **2**

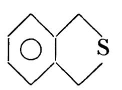
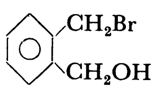
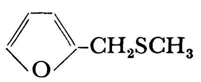
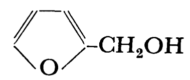
Results and Discussion

The reaction of **1** with alkyl halides in *N,N*-dimethylformamide (or acetonitrile) for 1 h followed by treatment of alcohols in the presence of sodium hydride for 10 min at room temperature gave readily dialkyl sulfides (**2**) in satisfactory yields.

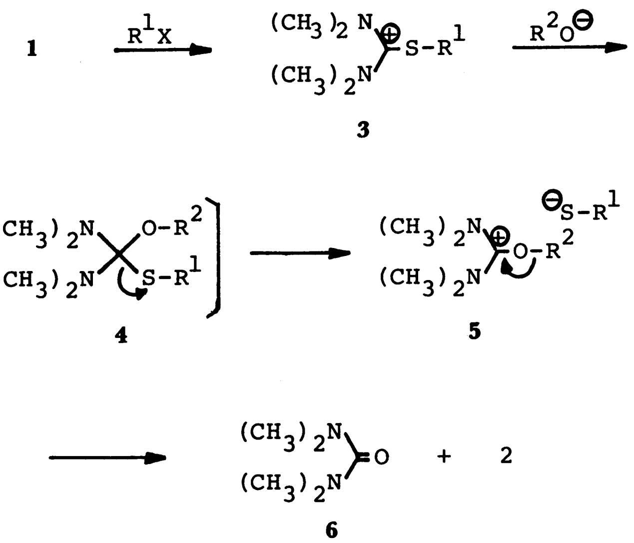
In the case of synthesis of methyl or ethyl sulfide (R^1SCH_3 or $R^2SC_2H_5$), the reagent methanol or ethanol was employed also as a solvent instead of *N,N*-dimethylformamide or acetonitrile, and sodium metal was used instead of sodium hydride. The results are summarized in the Table 1.

The postulated reaction mechanism is shown in the Scheme. Actually, intermediate *S*-alkyltetramethylthiouronium salt (**3**) was obtained as a crystals by the treatment of **1** with alkyl halide in acetone at room temperature for several days in good yield, and then the reaction of **3** with alcohol using sodium hydride in *N,N*-dimethylformamide gave the sulfide **2**. In this reaction, unstable *O*-alkyltetramethyluronium salt (**5**), derived from **3** *via* intermediate **4**, may be undergone nucleophilic attack by alkanethiolate ion to give sulfide **2** and tetramethylurea (**6**).

TABLE 1. SULFIDES (**2**) FROM TETRAMETHYLTHIOUREA, ALKYL HALIDES AND ALCOHOLS USING BASE

R^1-S-R^2	R^1X	R^2OH	Solvent	Base	Yield a) %	Bp θ_b/°C(Torr) or Mp θ_m/°C	Lit Bp θ_b/°C(Torr) or Mp θ_m/°C
2a CH_3S-*n*-C_8H_{17}	CH_3I	*n*-$C_8H_{17}OH$	CH_3CN	NaH	45	219—221(760)	104—105(20)4)
2b C_2H_5S-*n*-C_8H_{17}	C_2H_5Br	*n*-$C_8H_{17}OH$	CH_3CN	NaH	40	228—230(760)	108(16)4)
2c CH_3SCH_2Ph	CH_3I	$PhCH_2OH$	DMF	NaH	65	199—201(760)	195—198(760)6)
2d $C_2H_5SCH_2Ph$	C_2H_5I	$PhCH_2OH$	DMF	NaH	76	223—224(760)	103(16)4)
2e $(PhCH_2)_2S$	$PhCH_2Br$	$PhCH_2OH$	CH_3CN	NaH	90	44—45	472)
2f 			DMF	NaH	65	233—234(760)	94(7)2)
2g $PhCH_2CH_2SC_2H_5$	$PhCH_2CH_2Br$	C_2H_5OH	DMF	NaH	60	258—260(760)	93—94(5)2)
2h $PhCH_2SCH_2CH{=}CH_2$	$CH_2{=}CH$-CH_2Br	$PhCH_2OH$	DMF	NaH	76	79—80(6)	—
2i $(CH_2{=}CHCH_2)_2S$	$CH_2{=}CH$-CH_2Br	$CH_2{=}CHCH_2OH$	DMF	NaH	50	27—28(4)	35(6)5)
2j 	CH_3I		DMF	NaH	56	41—42(7)	—
2c CH_3SCH_2Ph	$PhCH_2Cl$	CH_3OH	CH_3OH	$NaOCH_3$	65	199—201(760)	195—198(760)6)
2d $C_2H_5SCH_2Ph$	$PhCH_2Cl$	C_2H_5OH	C_2H_5OH	$NaOC_2H_5$	63	223—224(760)	103(16)4)

a) Yield of isolated product.



Scheme

These our methods do not use ill-smelling thiols and are applicable to the syntheses of various dialkyl sulfides under mild conditions. Dialkyl sulfides containing heterocyclic moiety, *e.g.*, furfuryl methyl sulfide (**2j**), was also obtained. However, our methods were unsuitable for the syntheses of aryl sulfides and dialkyl sulfides having branched-chain alkyl moiety such as *t*-butyl or isopropyl group because of instability of crowded intermediate **4**. Thiourea could not be used as the reagent instead of tetramethylthiourea since inert imines (HN=C(NH_2)-SR) was only obtained from thiourea with alkyl halides.

Experimental

*Typical Procedure for the Syntheses of Sulfides (**2a**—**2j**) by Use of Sodium Hydride in* N,N-*Dimethylformamide or Acetonitrile. Benzyl Methyl Sulfide (**2c**):* A solution of **1** (1.0 g, 7.6 mmol) and methyl iodide (1.4 g, 10 mmol) in *N,N*-dimethylformamide (10 ml) was stirred at room temperature for 1 h, and then benzyl alcohol (0.84 g, 7.8 mmol) was added. To the solution was added dropwise sodium hydride (0.5 g, 21 mmol) dispersed in hexane (5 ml) under stirring at room temperature, then the reaction mixture was further stirred for 10 min, and quenched with water. The organic layer was extracted with hexane (3×15 ml), dried with magnesium sulfate, concentrated in a rotatory evaporator and distilled to give benzyl methyl sulfide (**2c**) as colorless oil. Yield 0.68 g (65%); bp 199—201 °C/760 Torr[†] (lit,[6]) 195—198 °C/760 Torr).

*Allyl Benzyl Sulfide (**2h**).* Compound **2h** was prepared similarly. ^{1}H NMR (CCl_4) δ=2.92 (2H, d, J=8 Hz, S$\underline{CH_2}$-CH=), 3.56 (2H, s, Ph-CH_2S), 5.00, 5.05 (two br. d, J=18 $\underline{H}$z, J=9 Hz, CH=C$\underline{H_2}$), 5.50—6.00 (1H, m, C$\underline{H}$=CH_2), and 7.22 (5H, br. s, $\underline{C_6H_5}$). Found: C, 72.86; H, 7.44%. Calcd for $C_{10}H_{12}S$: C, 73.12; H, 7.36%.

*2-Furfuryl Methyl Sulfide (**2j**).* Compound **2j** was prepared similarly. ^{1}H NMR (CCl_4) δ=2.01 (3H, s, CH_3), 3.55 (2H, s, CH_2), 6.02 (1H, d, J=3 Hz, CH=C-O), 6.16 (1H, dd, J=3 and 2 Hz, C$\underline{H}$=CH-O), 7.20 (1H, d, J=2 Hz, =CH-O). Found: C, 56.02; $\underline{H}$, 6.39%. Calcd for C_6H_8OS: C, 56.22; H, 6.29%.

*Typical Procedure for the Syntheses of Sulfides (**2c** and **2d**) by Use of Sodium Alkoxide in Alcohol. Benzyl Ethyl Sulfide (**2d**).* A solution of **1** (1.5 g, 11 mmol) and benzyl chloride (1.4 g, 11.1 mmol) in ethanol (10 ml) was refluxed for 4 h. After cooling the solution to room temperature, sodium metal (0.3 g, 13 mmol) was added and the reaction mixture was stirred for 10 min, and then quenched with water. The mixture obtained was worked up as described above **2c** to give **2d** as colorless oil. Yield 1.1 g (63%); bp 223—224 °C/760 Torr (lit,[4]) bp 103 °C/16 Torr).

*S-Methyl Tetramethylthiouronium Iodide (**3a**).* Preparation of **3a** was described below as an example of synthetic procedure of **3**. A solution of **1** (4.0 g, 30 mmol) and methyl iodide (4.6 g, 32 mmol) in acetone (50 ml) was allowed to stand for 1 d at room temperature, and then the precipitate deposited was filtered off, washed with acetone (2×5 ml) and dried *in vacuo* to give **3a** as colorless crystals. Yield 7.9 g (96%); mp 177—180 °C (Mp was not given in the literature[7]) because of its hygroscopicity).

*Benzyl Methyl Sulfide (**2c**) from **3a** and Benzyl Alcohol.* Preparation of **2c** was described below as an example of synthetic procedure of **2** from **3** and alcohol. To a solution of **3a** (1.0 g, 3.7 mmol) and benzyl alcohol (0.34 g, 3.7 mmol) in *N,N*-dimethylformamide (10 ml) was added dropwise sodium hydride (0.5 g, 21 mmol) dispersed in hexane (5 ml), and then the reaction mixture was stirred at room temperature for 10 min, and quenched with water. The organic layer was extracted with hexane (3×15 ml), dried with magnesium sulfate, concentrated in a rotatory evaporator and distilled to give **2c** as colorless oil. Yield 0.3 g (60%); bp 199—201 °C/760 Torr.

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[†] 1 Torr=133.322 Pa.