An Efficient Synthesis of Unsymmetrical Sulfides Using Liquid-Liquid Phase-Transfer Catalysis

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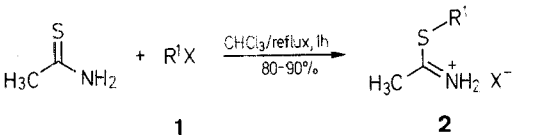
The reaction between alkyl ethaneimidothioate hydrohalides (1-alkylthioethaniminium halides) and organic halides gives unsymmetrical sulfides in good yields under liquid-liquid phase-transfer conditions.

Many methods[1-6] for preparing unsymmetrical sulfides (thioethers) have been reported because functionalised organic sulfides are useful intermediates in preparative organic chemistry. Most of the known methods use unpleasantly smelling alkanethiols.

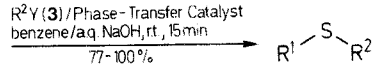
We have earlier reported[7] a one-pot nitrile synthesis via a thioiminium intermediate by use of benzyl chloride and primary thioamides under liquid-liquid phase-transfer conditions at room temperature. In these reactions, benzyl chloride is quantitatively converted into dibenzyl sulfide. In an extension of this work, we report an efficient synthesis of various unsymmetrical sulfides **(4)** by reaction of 1-alkylthioethaniminium halides (**2**, hydrohalides of alkyl ethaneimidothioates), as a source of alkanethiolate ions, and organic halides **(3)** under liquid-liquid phase-transfer conditions. The method does not use unpleasantly smelling alkanethiols; it can be utilized to generate a variety of otherwise unavailable thiolate ions under mild conditions and hence a wide range of functionalised organic sulfides can be obtained.

It is known that the reactions of *S,S*-dialkyl dithiocarbonates with organic halides under liquid-liquid phase-transfer conditions[8] and of 1-alkylthioalkaniminium salts with organic halides under liquid-solid phase-transfer conditions[9] lead to the formation of sulfides. However, the former route requires reaction conditions such as heating a reactant at reflux temperature, and the latter gives only moderate yields due to the formation of by-products such as disulfides.

In present method, 1-alkylthioethaniminium salts **(2)**, freshly prepared (and isolated) from the *S*-alkylation of thioacetamide with organic halides **(1)**, react with alkyl halides **3** to afford sulfides **4** in a liquid-liquid two-phase system consisting of benzene, aqueous sodium hydroxide, and a catalytic amount of tetrabutylammonium bromide (TBAB). The reactions proceed smoothly at room temperature and are complete within 15 min, except for the reactions of **2** with allyl bromide and with ethyl chloroacetate as alkyl halide **3**, the unsymmetrical sulfides **4** being obtained in 77–100% yields. The products **4** are not obtained in the absence of phase-transfer catalyst under otherwise identical conditions.



1 **2**



4 a-r

4	R^1	R^2
a	n-C_4H_9	i-C_4H_9
b	n-C_4H_9	4-$CH_3C_6H_4CH_2$
c	n-C_8H_{17}	C_2H_5
d	n-C_8H_{17}	n-C_4H_9
e	n-C_8H_{17}	$C_6H_5CH_2$
f	n-C_8H_{17}	4-$CH_3C_6H_4CH_2$
g	$H_2C=CH-CH_2$	$C_2H_5OCO-CH_2$
h	$C_6H_5CH_2$	C_2H_5
i	$C_6H_5CH_2$	n-C_4H_9
j	$C_6H_5CH_2$	n-C_8H_{17}
k	$C_6H_5CH_2$	$H_2C=CH-CH_2$
l	$C_6H_5CH_2$	$C_2H_5OCO-CH_2$
m	$C_6H_5CH_2$	4-$CH_3C_6H_4CH_2$
n	$C_6H_5CH_2$	4-$ClC_6H_4CH_2$
o	$C_6H_5CH_2$	4-$NO_2C_6H_4CH_2$
p	4-$CH_3C_6H_4CH_2$	4-$ClC_6H_4CH_2$
q	4-$CH_3C_6H_4CH_2$	4-$NO_2C_6H_4CH_2$
r	4-$CH_3C_6H_4CH_2$	4-$CH_3OC_6H_4CH_2$

Since formation of by-products is rarely observed with this method the unsymmetrical sulfides **4** can be easily be isolated in all cases studied.

The attempted use of acyl halides in place of alkylhalides **3** for the synthesis of thiocarboxylic *S*-esters was unsuccessful due to the preferential formation of *N*-acylthioimidates by electrophilic attack of the carbonyl C-atom of the acyl halide on the N-atom of **2**. Likewise, the attempted use of 1,ω-dihaloalkanes in place of **1** and **3** for the preparation of cyclic sulfides was unsuccessful due to the formation of polymeric sulfides.

1-Benzylthioethaniminium Bromide (2, $R^1 = C_6H_5CH_2$, X = Br); Typical Procedure:

A mixture of thioacetamide (3.75 g, 50 mmol) and benzyl bromide (8.55 g, 50 mmol) in $CHCl_3$ (50 mL) is refluxed for 1 h. After cooling, the product is isolated by suction and washed with ether; yield: 11.04 g (90%); m.p. 174–176 °C (Lit.[10] m.p. 174–176 °C).

$C_9H_{12}NSBr$	calc.	C 43.91	H 4.91	N 5.69
(246.2)	found	43.92	4.82	5.75

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.75 (s, 3H, CH_3); 4.80 (s, 2H, SCH_2); 7.31–7.44 (m, 5H_{arom}); 11.78–12.47 (br s, 2H, NH_2).

If with other alkyl halides used instead of benzyl bromide the product does not crystallize from the mixture, some ether is added.

Unsymmetrical Sulfides 4; General Procedure:

A mixture of the freshly prepared 1-alkylthioethaniminium halide **2** (10 mmol), the organic halide **3** (10 mmol), tetrabutylammonium bromide (TBAB; 97 mg, 0.3 mmol), benzene (50 mL), and 30 wt%

Table. [a] Unsymmetrical Sulfides **4** from 1-Alkylthioethaniminium Halides **2** and Alkyl Halides **3**

Product	X in **1** and **2**	Y in **3**	Yield[b] (%)	m.p. (°C) (solvent)[c] or b.p. (°C/torr)	Molecular Formula[d] or Lit. Data	HRMS (70 ev)[e] *m/e* (M^+)	^{1}H-NMR ($CDCl_3$/TMS)[f] δ, *J*(Hz)
4a	Br	Br	88	42–43/20	$C_8H_{18}S$ (146.2)	146.1125	0.92 [t, 3H, J = 7.4, $S(CH_2)_3C\underline{H}_3$]; 0.99 [d, 6H, J = 6.6, $SCH_2CH(C\underline{H}_3)_2$]; 1.40 [sext, 2H, J = 7.4, $S(CH_2)_2C\underline{H}_2-CH_3$]; 1.56 (quin, 2H, J = 7.4, $SCH_2C\underline{H}_2CH_2CH_3$); 1.79 [sept, 1H, J = 6.6, $SCH_2C\underline{H}(CH_3)_2$]; 2.39 [d, 2H, J = 6.6, $SC\underline{H}_2CH(CH_3)_2$]; 2.49 [t, 2H, J = 7.4, $SC\underline{H}_2(CH_2)_2CH_3$]
4b	Br	Cl	82	90–91/4	$C_{12}H_{18}S$ (194.3)	194.1151	0.88 [t, 3H, J = 7.4, $S(CH_2)_3C\underline{H}_3$]; 1.36 [sext, 2H, J = 7.4, $S(CH_2)_2C\underline{H}_2CH_3$]; 1.53 (quin, 2H, J = 7.4, $SCH_2C\underline{H}_2CH_2CH_3$); 2.31 (s, 3H, $SCH_2C_6H_4C\underline{H}_3$); 2.40 [t, 2H, J = 7.4, $SC\underline{H}_2(CH_2)_2CH_3$]; 3.65 (s, 2H, $SC\underline{H}_2C_6H_5CH_3$); 7.09 (d, $2H_{arom}$, J = 7.7); 7.18 (d, $2H_{arom}$, J = 7.7)
4c	Br	Br	90	100–103/10	102–103/11[11]	174.1469	
4d	Br	Br	91	120–122/10	125/14[12]	202.1771	
4e	Br	Br	91	171–173/10	175–176/12[13]	236.1592	
4f	Br	Cl	95	150–151/4	$C_{16}H_{26}S$ (250.4)	250.1726	0.88 [t, 3H, J = 7.4, $S(CH_2)_7C\underline{H}_3$]; 1.25 [s, 8H, $SCH_2(C\underline{H}_2)_4CH_2CH_2CH_3$]; 1.31 [sext, 2H, J = 7.4, $S(CH_2)_6C\underline{H}_2CH_3$]; 1.54 [quin, 2H, J = 7.4, $S(CH_2)_5C\underline{H}_2CH_2CH_3$]; 2.32 (s, 3H, $SCH_2C_6H_4C\underline{H}_3$); 2.40 [t, 2H, J = 7.4, $SC\underline{H}_2(CH_2)_6CH_3$]; 3.66 (s, 2H, $SC\underline{H}_2C_6H_4CH_3$); 7.10 (d, $2H_{arom}$, J = 7.7); 7.18 (d, $2H_{arom}$, J = 7.7)
4g	Br	Cl	77[g]	66–67/6	$C_7H_{12}O_2S$ (160.2)	160.0574	1.29 (t, 3H, J = 7.1, $COOCH_2C\underline{H}_3$); 3.16 (s, 2H, $SC\underline{H}_2CO$); 3.24 (d, 2H, J = 7.1, $SC\underline{H}_2CH=CH_2$); 4.18 (q, 2H, J = 7.1, $COOC\underline{H}_2CH_3$); 5.15 (m, 2H, $SCH_2CH=C\underline{H}_2$); 5.76 (m, 1H, $SCH_2C\underline{H}=CH_2$)
4h	Br	Br	80	80–82/6	98–99/13[14]	152.0650	
4i	Br	Br	97	110–112/10	110–113/10[15]	180.0961	
4j	Br	Br	92	see **4e**			
4k	Br	Br	80[g]	112–113/10	115–116/14[14]	164.0673	
4l	Br	Cl	86[g]	117–118/5.5	$C_{11}H_{14}O_2S$ (210.2)	210.0722	1.28 (t, 3H, J = 7.1, $COOCH_2C\underline{H}_3$); 3.05 (s, 2H, $SC\underline{H}_2CO$); 3.82 (s, 2H, $SC\underline{H}_2C_6H_5$); 4.16 (q, 2H, J = 7.1, $COOC\underline{H}_2CH_3$); 7.22–7.35 (m, $5H_{arom}$)
4m	Br	Cl	96	142–143/3	150/6[16]	228.0998	
4n	Br	Cl	95	164–165/5	$C_{14}H_{13}ClS$ (248.7)	248.0427	3.51 (s, 2H, $SC\underline{H}_2$); 3.56 (s, 2H, $SC\underline{H}_2$); 7.16–7.45 (m, $9H_{arom}$)
4o	Br	Cl	~100	53–54 (C_6H_6/PE)	57[17]	259.0660	
4p	Cl	Cl	~100	53–54 (C_6H_6/PE)	$C_{15}H_{15}ClS$ (262.7)	262.0560	2.33 (s, 3H, $CH_2C_6H_4C\underline{H}_3$); 3.54 (s, 2H, $SC\underline{H}_2$); 3.55 (s, 2H, $SC\underline{H}_2$); 7.10–7.29 (m, $8H_{arom}$)
4q	Cl	Br	~100	89–90 (C_6H_6/PE)	$C_{15}H_{15}NO_2S$ (273.3)	273.0821	2.33 (s, 3H, $CH_2C_6H_4C\underline{H}_3$); 3.58 (s, 2H, $SC\underline{H}_2$); 3.64 (s, 2H, $SC\underline{H}_2$); 7.11–8.15 (m, $8H_{arom}$)
4r	Cl	Cl	92	175–176/4	$C_{16}H_{18}OS$ (258.3)	258.1082	2.33 (s, 3H, $CH_2C_6H_4C\underline{H}_3$); 3.55 (s, 4H, $C\underline{H}_2SC\underline{H}_2$); 3.78 (s, 3H, $CH_2C_6H_4OC\underline{H}_3$); 6.83–7.21 (m, $8H_{arom}$)

[a] Reactions were carried out at room temperature for 15 min at the mol ratio 1 : 1 : 0.03 for iminium salt, halide, and TBAB.
[b] Yield of pure isolated product based on **1**.
[c] Uncorrected, measured with a Yanagimoto apparatus.
[d] Satisfactory microanalyses obtained: C ± 0.2, H ± 0.02, S ± 0.2.
[e] Recorded on a Hitachi M-80B spectrometer.
[f] Obtained on a JEOL GX-400 spectrometer.
[g] Reaction time: 1.5 h.

aqueous NaOH (50 g) is vigorously stirred at room temperature for 15 min (1.5 h in the cases of **4q**, **4k**, and **4l**) under nitrogen. The organic layer is separated, washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and evaporated. The residual product is distilled under reduced pressure to afford the pure unsymmetrical sulfide **4**.

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