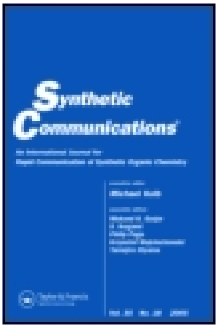

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A SIMPLE AND CONVENIENT METHOD FOR PREPARATION OF SULFIDES

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Abstract: Tetraethylammonium hydrogen carbonate (TEAHC) and tetraethylammonium carbonate (TEAC) obtained respectively by chemical and electrochemical way, react with thiols in acetonitrile affording, after addition of a suitable alkylating reagent, the corresponding sulfides in high to excellent yields.

Here we present a simple, mild and easy method for the synthesis of symmetrical and unsymmetrical sulfides by addition of alkyl halides and bromoesters to solutions of tetraethylammonium carbonate[1] or hydrogen carbonate[2] and thiols. This method affords both very high yields of sulfides at room temperature, avoiding hard reaction conditions and elaborate reagents and work-up procedures.

TEAHC was simply obtained by saturating a methanol solution of commercially available tetraethylammonium hydroxide (TEAOH) with carbon

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Table 1. Ethylation of Benzylthiol with Different Solvents and Alkylating Reagents.

$$PhCH_2SH \xrightarrow[2.\ CH_3CH_2X]{1.\ TEAHC^{a}} PhCH_2SCH_2CH_3$$

Entry	Solvent	X	Yield (%)[b]
1	CH_2Cl_2	I	41
2	Et_2O	I	72
3	DMF	I	91
4	MeCN	I	91
5	MeCN	Br	93
6	MeCN	OTs	90

[a] A molar ratio RSH:TEAHC 1:1.5 was used; an excess of alkylating reagent was added after 90 min. [b] Yields refer to isolated sulfide.

dioxide.[2,3] Benzyl thiol was used as model compound to evaluate the effect of different solvents and alkylating reagents on the reaction yields. The results are reported in Table 1.

As shown in Table 1, very high yields of ethyl benzyl sulfide were obtained when using polar aprotic solvents, whereas the nature of the leaving group of the electrophile did not seem to affect the reaction yield.[4]

Using MeCN as solvent the reaction was carried out with different thiols and alkylating reagents; results are reported in Table 2 (entries 1-8). Comparable results were obtained when the reaction was carried out using TEAC obtained by electrochemical procedure (entries 9-12). Under no circumstances the respective carboxylation products were obtained. α-Bromoesters reacted readily to afford a convenient synthesis of α-(alkylthio) or α-(phenylthio)esters (entries 2-4, 8).

Table 2. Reaction of Sulfides with TEAHC or TEAC and Alkylating Reagents.

$$\underset{\mathbf{1}}{\mathrm{RSH}} \xrightarrow[2.\ \mathrm{R'X}]{1.\ \mathrm{Base}} \underset{\mathbf{2}}{\mathrm{RSR'}}$$

Entry	Substr.	R	R'	Base	X	Products Yield (%)[a]
1	**1a**	Ph	Et	TEAHC	I	**2a** (93)
2	**1a**	Ph	CH(Me)CO_2Et	TEAHC	Br	**2b** (97)
3	**1a**	Ph	CH(Et)CO_2Et	TEAHC	Br	**2c** (89)
4	**1b**	$PhCH_2$	CH_2CO_2Me	TEAHC	Br	**2d** (98)
5	**1b**	$PhCH_2$	$PhCH_2$	TEAHC	Br	**2e** (95)
6	**1c**	*n*-Octyl	$PhCH_2$	TEAHC	Br	**2f** (92)
7	**1c**	*n*-Octyl	Et	TEAHC	I	**2g** (92)
8	**1d**	Cyclohexyl	CH(Et)CO_2Et	TEAHC	Br	**2h** (96)
9	**1b**	$PhCH_2$	Et	TEAC	I	**2j** (90)
10	**1a**	Ph	Et	TEAC	I	**2a** (87)
11	**1a**	Ph	CH(Et)CO_2Et	TEAC	Br	**2c** (90)
12	**1c**	*n*-Octyl	Et	TEAC	I	**2g** (91)

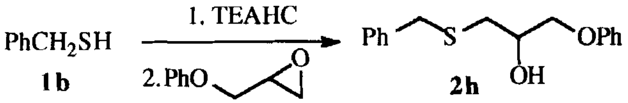
[a] Yield referto isolated sulfides.

A symmetrical sulfide was also obtained starting from benzylthiol and benzyl bromide (entry 5). Using benzyl halide as alkylating reagent, protected S-benzyl thioether were obtained (entries 5,6).

The reaction with 1,2-epoxy-3-phenoxy propane was also tested; the corresponding β-hydroxy sulfide (less-hindered side attack product) was obtained only in moderate yield (51% isolated). (Fig. 1)

EXPERIMENTAL

GENERAL: TLC analyses were performed on Merck kiesegel 60 F254 plates. Flash chromatography was carried out on ICN silica gel (230-400 mesh). ^{1}H and



51% Isolated yield

FIG. 1: Reaction of Benzylthiol with TEAHC and 1,2-Epoxy-3-phenoxypropane.

^{13}C-NMR were determinated at 200 and 50.3 MHz respectively using $CDCl_3$ as internal standard. GC-MS measurements (EI, 70 eV) were carried out on a Supelco SP2250 30m × 0.32mm capillary column using a Varian Saturn 2000 gaschromatography-mass detector equipped with a ion trap mass selective detector. Dry acetonitrile (Lab-scan, anhydroscan) was used as received. TEAHC was prepared as reported by Venturello[3] starting from a methanol solution (25% w/w) of TEAOH (Fluka). The reagent was dried under vacuum for 24 hours and then was stored under argon.

Thiols **1a-d** and all the alkylating reagents are commercially available and were used as received.

Reaction of thiols with TEAHC. General procedure: Thiol (1.0 mmol) was added, at room temperature, to a solution of TEAHC (1.5 mmol) in MeCN (15 mL). After 90 min an excess (2.0 ÷ 2.5 mmol) of alkylating reagent was added and the reaction was stirred overnight. After removal of the solvent, simple filtration or flash chromatography afforded the desired sulfide (see also ref. 2).

Reaction of thiols with TEAC. General procedure: a solution of MeCN-Et_4NClO_4 (0.1 mol dm^{-3}), with continuous CO_2 bubbling, was electrolysed (divided cell, Pt anode, 0°C) over a Cu cathode at a potential (-2.1 V *vs.* SCE). At the end of electrolysis (1.5 F · mol^{-1}) the thiol was added. After 90 min an excess

(2.0 ÷ 2.5 mmol) of alkylating reagent was added and the reaction was stirred overnight. After removal of the solvent, simple filtration or flash chromatography afforded the desired sulfide (see also ref. 1).

Compounds **2a-h** are commercial or well known compounds; product assignment was determinated by ^{1}H-NMR, ^{13}C-NMR and elemental analysis compared to authentic materials or literature assignments.

All new compounds gave satisfactory elemental analyses (C ± 0.3 %; H ± 0.2 %;).

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4. When the reaction was carried out using the system TEAOH - MeOH and EtI in MeCN, the corresponding ethyl benzyl sulfide was isolated in 68% yield.

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