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Chemoselective Alkylation of Thiols: A Detailed Investigation of Reactions of Thiols with Halides[1]

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Abstract: Arylthiols, aralkylthiols and alkane thiols can be readily alkylated by alkyl/aralkyl halides in presence of K_2CO_3/DMF to yield unsymmetrical sulphides in nearly quantitative yields. 2-Mercaptoethanol gave the thioether chemoselectively.

Thiolate substitution of alkyl halides is a well known method for the formation of thioethers. The thiolate anions may be generated in solution in the presence of bases such as alkali metal hydroxide or trimethylamine in a suitable solvent[2]. Yields depend on the acidity of thiol, nature of base and solvent. As in Williamson synthesis, yields of thioethers may be improved by phase transfer catalysis[3]. Sodium acetate or potassium hydroxide in ethanol have also been

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employed for thioether formation[4]. K_2CO_3/Acetone has been used extensively for the formation of aryl ethers in natural product chemistry though harsh conditions (refluxing for long periods) are required and invariably low yields of ethers are obtained. Chapman et. al.[5] reported only 4% yield of 4-methoxy-2-methylthiophenol in the reaction of 2-mercapto-4-methoxyphenol with MeI/K_2CO_3/acetone. Recently Bulman Page and coworkers have reported that thiols react with alkyl halides in the presence of sodium carbonate and a catalytic amount of (dppm) $PtCl_2$ [dppm = bis (diphenylphosphinomethane)] to give thioethers[6]. In the absence of complex, sodium carbonate does not mediate any reaction between alkanethiols and alkyl iodides in boiling acetone solution[6]. In view of the above difficulties, we decided to investigate the said reaction in detail with various thiols and halides (including fatty halides).

Results & Discussion

We report herein that sulphides can be readily prepared from arylthiols, aralkylthiols and alkanethiols by treatment with alkyl/benzyl halides in presence of K_2CO_3/DMF at ambient temperature (eq. 1). The reactions are not only slow when DMF is replaced by acetone but significant amounts of the corresponding disulphides

$$RSH + R'X \xrightarrow[\text{Stirring}]{K_2CO_3/DMF,RT} RSR' \qquad ....(1)$$

R = Phenyl, 2-benzothiazolyl, Benzyl, 2-Hydroxyethyl and 1-Butyl.

were also obtained in case of aralkyl and alkanethiols, namely benzyl mercaptan, 2-mercaptoethanol and 1-butanethiol, though faint spots of the disulphides were also seen with arylthiols on TLC. When the reaction mixtures (K_2CO_3/acetone) were exposed to ultrasound, sulphide formation could be accomplished in shorter duration as expected in agreement with other sonochemical reactions[7] but it did not show a dramatic effect on the progress of the reactions as observed with K_2CO_3/DMF as the reagent. Our results are listed in Table 1.

The simultaneous formation of the disulphides is due to competing aerial oxidation since the reactions are slower due to higher pKa of benzyl mercaptan, 2-mercaptoethanol and 1-butanethiol. This is evidenced by the formation of large quantity of benzyl disulphide in the reaction of benzylmercaptan with K_2CO_3/acetone in the absence of any halide and upon exposure to ultrasound (entry 21). The formation of disulphides besides the desired sulphides in the reactions of aralkyl and alkanethiols does not make it a useful

TABLE 1: Reactions of Mercaptans with Halides in Presence of K_2CO_3 Under Different Conditions

Entry	Mercaptan RSH	Halide R'X	Solvent	Mode	Time (hrs)	% Yield[a] Sulphide	Disulphide
1.	Thiophenol	n-Propyl bromide	Acetone	Stirring	2	91	-
2.	Thiophenol	n-Propyl bromide	Acetone	Ultrasound	1	89	-
3.	Thiophenol	n-Propyl bromide	DMF	Stirring	0.25	93	-
4.	Thiophenol	n-Hexadecyl bromide	Acetone	Stirring	3	77	-[b]
5.	Thiophenol	n-Hexadecyl bromide	Acetone	Ultrasound	3	88	-[b]
6.	Thiophenol	n-Hexadecyl bromide	DMF	Stirring	2	94	-
7.	Thiophenol	n-Hexadecyl chloride	Acetone	Stirring	4	28	-[b]
8.	Thiophenol	n-Hexadecyl chloride	Acetone	Ultrasound	4	36	-[b]
9.	Thiophenol	n-Hexadecyl chloride	DMF	Stirring	2	81	-
10.	Thiophenol	n-Dodecyl chloride	DMF	Stirring	1	93	-

11.	Thiophenol	t-Butyl chloride	DMF	Stirring	0.5	-	88
12.	2-Mercapto-benzothiazol	n-Hexadecyl bromide	Acetone	Stirring	4	91	-
13.	2-Mercapto-benzothiazol	n-Hexadecyl bromide	DMF	Stirring	1	94	-
14.	2-Mercapto-benzothiazol	n-Propyl bromide	DMF	Stirring	1	92	-
15.	Benzyl-mercaptan	n-Propyl bromide	Acetone	Stirring	3	70[c]	30[c]
16.	Benzyl-mercaptan	n-Propyl bromide	Acetone/ DMF (1:1)	Stirring	3	90[c]	10[c]
17.	Benzyl-mercaptan	n-Propyl bromide	DMF	Stirring	2	100[c,d]	-
18.	Benzyl-mercaptan	n-Dodecyl bromide	DMF	Stirring	2	96	-
19.	Benzyl-mercaptan	Benzyl chloride	DMF	Stirring	3	88	-
20.	Benzyl-mercaptan	tert-Butyl chloride	DMF	Stirring	2	-	91
21.	Benzyl-mercaptan	-	Acetone	Ultrasound	6	-	68[e]
22.	2-Mercapto-ethanol	n-Propyl bromide	Acetone	Stirring	3	72[c]	28[c]

(contd....)

Table 1 (contd....)

23.	2-Mercapto-ethanol	n-Propyl bromide	DMF	Stirring	2	100[c]	-
24.	2-Mercapto-ethanol	Benzyl chloride	DMF	Stirring	3	100[c,f]	-
25.	1-Butanethiol	Benzyl chloride	Acetone	Stirring	7	78[g]	10[g]
26.	1-Butanethiol	Benzyl chloride	DMF	Stirring	2	95	-

a: Isolated yields unless otherwise specified

b: Phenyl disulphide was also observed in the mother liquor besides the n-hexadecyl bromide/chloride by TLC

c: NMR ratios

d: Isolated yield of sulphide, 91%

e: 26% of Benzylmercaptan was also obtained

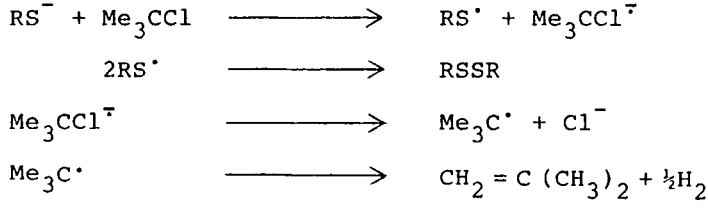
f: Isolated yield of sulphide, 72%

g: Relative ratio by HPLC; 6% of benzyl chloride was also observed by comparison of retention time (ODS-18, reverse phase column with UV detector and methanol as eluent).

synthetic method with K_2CO_3/acetone (see Table 1). On changing the solvent system from acetone to acetone/dimethylformamide (1:1, v/v), we observed a decrease in the amount of disulphide and only sulphides were obtained with K_2CO_3/DMF as the reagent (Table 1).

In an attempt to prepare sulphides with a tertiary halide, we observed that benzenethiol and benzylmercaptan on treatment with tert-butyl chloride in presence of K_2CO_3/DMF yielded the corresponding disulphides exlcusively in a fast reaction (entries 11 & 20). We believe that the rapid formation of disulphide in these reactions and the absence of any tert-butyl chloride could be explained by a change in the reaction pathway (from the conventional thiolate substitution) whereby the mercaptide anion transfers an electron to tert-butyl chloride (Scheme 1).

The formation of disulphides in other reactions by electron transfer from mercaptide anion to oxygen is



Scheme 1

comparatively much slower. The greater reactivity of alkyl bromide compared to the corresponding chloride is in line with the S_N2 reaction[8] for the formation of sulphides. The acceleration in the rate of reaction when exposed to ultrasound augments the list of sonochemical reactions.

The reactions are also chemoselective and no ether formation was observed in the reactions of 2-mercaptoethanol with K_2CO_3/DMF but only the sulphide at ambient temperature. The formation of only sulphides in the reactions of thiols in dimethylformamide could be due to solvation of potassium ions by dimethylformamide thus increasing the nucleophilicity of the mercaptide anions.

Therefore, we conclude that aryl-, aralkyl- and alkanethiols can be readily converted into sulphides on treatment with alkyl halides in presence of K_2CO_3/DMF without the aid of any complex[6]. Exposure to ultrasound, accelerates the reactions. Concurrent formation of disulphides is also observed with K_2CO_3/acetone but dimethylformamide is the solvent of choice for the quantitative formation of sulphides. Chemoselective thioether formation takes place in the reactions of 2-mercaptoethanol.

Experimental

Melting points were recorded on a Tropical Labequip apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer model 621 and Shimadzu model 435 spectrophotometers. NMR spectra were recorded on Perkin Elmer model R-32, 90 MHz and Hitachi FT-NMR 60 MHz with TMS as the internal standard. Thiophenol and 2-mercaptoethanol of commercial grade were used after distillation, 2-mercaptobenzothiazol was used after recrystallization and benzylmercaptan was prepared from benzyl chloride by known method[9]. Anhydrous K_2CO_3, dry acetone and dry DMF were prepared by known methods[9]. Ultrasonic cleaning bath Ralsonics Model R-120 (120 Watts, 3 litre capacity) was used.

General Procedure

In a 50 ml round-bottomed flask mounted over a magnetic stirrer were placed the mercaptan (0.005 mol), the alkyl halide (0.005 mol) and anhydrous K_2CO_3 (0.0075 mol) in 20 mL of dry acetone or dimethylformamide. An air-condenser fitted with a mercury trap was attached to the flask. The contents of the flask were stirred at ambient temperature. The progress of the reaction was monitored by TLC for the disappearance of

mercaptan. After completion of the reaction, the reaction mixture was filtered at water pump and the K_2CO_3 was washed with acetone (3x10 mL). The combined filtrate was concentrated on a Buchi rotary evaporator and ice-cold water (50 mL) was added to the flask. The flask was kept in refrigerator overnight. The product was extracted with dichloromethane, dried (anhyd. $MgSO_4$) and concentrated on a buchi rotavapour to give the product. The products obtained from the reactions of thiophenol with n-hexadecyl bromide and n-hexadecyl chloride were washed with a minimum quantity of methanol to remove the disulphide and any unreacted halide.

The reactions with dimethylformamide were worked up by addition of water ($\sim$ 100 mL) to the reaction mixture followed by extraction with ether (3 x 20 mL). The combined ethereal extract was washed with water (2 x 10 mL), dried (anhyd. $MgSO_4$) and concentrated to give the product. All the compounds were identified by their melting point (wherever available), IR and NMR spectra.

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