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Research Article

Tetra Butyl Ammonium Bromide Catalyzed Synthesis of Thiols and Thioethers

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ABSTRACT

A simple and commercially feasible route of synthesis of thiols and thioethers was developed using a simple phase transfer catalyst, i.e., Tetra Butyl Ammonium Bromide (TBAB). Sodium hydrogen sulfide (NaSH) is used as a sulfurization agent which is easily available and cost-effective. Thiols are obtained by treating alkyl or benzyl halides with sodium hydrogen sulfide (NaSH) in the presence of a phase transfer catalyst (TBAB) at 10 to 15°C. Thioethers are obtained by benzyl thiols treated with corresponding benzyl halides in the presence of a phase transfer catalyst (TBAB) at 10 to 15°C. Synthesis of thiols and thioethers is achieved by substitution reaction of benzyl or alkyl halides with sulfide in the presence of phase transfer catalyst (TBAB) and monochlorobenzene as a solvent at 10 to 15°C. Milder reaction conditions, excellent yield, shorter reaction time and operational simplicity are the key features of this procedure.

Keywords: Benzyl thiol, Alkyl thiol, C-sulfurization, thioethers, Phase transfer catalyst.

INTRODUCTION

Benzyl or alkyl thiols have important applications in the chemical as well as pharmaceutical industries as they are used as odorants, synthetic flavoring agents, food additives and chemical intermediates. Alkyl thiols are extensively used in chemical and pharmaceutical industries as an intermediate and as a key starting material.

Various organic thiol compounds have been synthesized by reaction with alkyl halide and hydrosulfides. As per available literature, thiols have been synthesized by reaction of benzyl bromide treated with thioacetic acid in methanol,[1] alkyl halides treated with hydrosulphide exchange resin (from Amberlite IRA-400), triethylamine hydrochloride in methanol,[2] benzyl bromide treated with thiourea in water.[3] Alkyl halides are converted into the corresponding thiols by reaction with 1-(2-hydroxyethyl)-4,6-diphenylpyridine-2-thione,[4] benzyl bromide treated with $C_{16}H_{36}N(1+)*Cl_3SSi(1-)$ in dichloromethane,[5] benzyl bromide treated with potassium sulfhydrate, ethanol.[6] Benzyl halides are easily available, but the catalysts used are more expensive.

Also, thiols can be prepared by using another substrate, like benzyl alcohol treated with sodium sulfide, sodium hydrogen carbonate in ethanol,[7] benzyl alcohol treated with N-bromosuccinimide, triphenylphosphine, polymer-supported hydrosulfide resin in acetone,[8] benzyl alcohol treated with Lawessons reagent in toluene.[9] All these routes of synthesis show poor yield, huge effluent, and longer reaction time.

As per available literature, other methods are noticed as benzyl thiocyanate treated with tetra phosphorus decasulfide in toluene,[10] deacetylation of thioacetate using acetyl chloride in methanol,[11] thiols from thioacetates syn Pd catalyzed methanolysis with borohydride exchange resin under mild and neutral conditions,[12] transportation of thiols from thioesters to thioethers has been successfully performed in water using hydrophobic polystyrene-supported sulfonic acid,[13] aliphatic thioacetate was prepared using catalytic tetrabutylammonium cyanide,[14] carbamate converted into thiol using tetraphosphorus decasulfide in toluene.[15] All these reported routes of synthesis also show poor conversion, large effluent, and poor yield.

Benzyl chloride was converted into benzylthiol using hydrosulfide exchange resin in acetonitrile,[16] thiourea in ethanol,[17] hydrosulfide exchange resin (from Amberlite IRA-400), triethylamine hydrochloride in methanol,[18] ethanol and potassium hydrosulfide,[19] sodium hydrogen sulfide and glycerol[20] potassium hydrosulfide,[21] potassium sulfhydrate and ethanol.[22]

Also, disulfide was converted into sulfide using sodium hydrogen telluride in ethanol,[23] using triethyl phosphine in tetrahydrofuran, water,[24] using indium and ammonium chloride in ethanol,[25] using sodium tetrahydroborate, lithium chloride in tetrahydrofuran,[26] cleavage of benzyl disulfide tetrahydrofuran[27] using tetrabutylammonium borohydride in *tert*-butyl alcohol,[28] using magnesium in methanol,[29] using sodium tetrahydroborate and zirconium(IV) chloride in tetrahydrofuran,[30] using triisopropoxyborohydride in tetrahydrofuran,[31] using ammonia, aluminum and iodine,[32] disulfide converted into thiol using 2-hydroxyethanethiol in d(4)-methanol, water-d2, T = 25°C.[33]

Extended to this study, we have developed a simpler, efficient process for the synthesis of thiols and thioethers using phase transfer catalyst. Tetra butyl ammonium bromide (TBAB) was used as a phase transfer catalyst which is easily available. In this process, lower boiling alkyl halide is also efficiently converted into respective alkyl thiol easily with higher yield.

MATERIAL AND METHODS

The chemicals and reagents used in this study were bought from commercial sources and used without purification. Melting points were measured using Electro-thermal IA 9100 apparatus (Shimadzu, Japan), NMR spectra were determined on a Bruker (400 MHz) spectrometer in DMSO-d_6, and the chemical shifts are expressed as ppm against TMS as internal reference. All the compounds synthesized in the present study are novel and were confirmed from spectral data.

General synthetic procedure for compound 2a-k

TBAB (0.1eq), 1.0 mole of compounds 1a-k, 30% NaSH solution (1.0eq), and monochlorobenzene (3V) were taken in round bottom flask and cooled at 10 to 15°C. The reaction mixture was stirred for 5 hours at 10 to 15°C. Layers were separated and the organic layer was extracted with alkali. Alkyl thiol in alkali was acidified and extracted in dichloromethane (2V) at 5 to 10°C. Dichloromethane was removed by distillation and compounds 2a-k were obtained.

General synthesis procedure for compound 4a-j

TBAB (0.1eq), 1.0-mole compound 3a-j, 30% NaSH solution (1.0eq), and monochlorobenzene (3V) were taken in round bottom flask and cooled at 10 to 15°C. The reaction mixture was stirred for 5 hours at 10 to 15°C. Layers were separated and the organic layer was extracted with alkali. Alkyl thiol in alkali was acidified and extracted in dichloromethane (2V) at 5 to 10°C. Dichloromethane was removed by distillation and compounds 4a-j were obtained,

General synthesis procedure for compound 7a-i

TBAB (0.1 eq), 1.0 mole compound 5a-i, compound 6 (1.0eq), and Monochlorobenzene (3V) were taken in round bottom flask and cooled at 10 to 15°C. The reaction mixture was stirred for 5 hours at 10 to 15°C. Layers were separated and the organic layer was extracted with alkali. Alkyl thiol in alkali was acidified and extracted in dichloromethane (2V) at 5 to 10°C. Distillation and compound 7a-i removed dichloromethane were obtained. Complete reaction scheme is shown in Fig. 1.

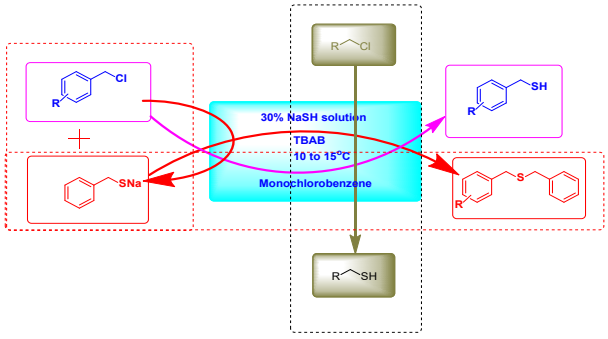


Fig. 1: Complete reaction scheme

RESULTS AND DISCUSSION

Benzyl or alkyl halide has poor solubility in water with good solubility in organic solvents. Sulfurization agent (sodium hydrogen sulfide) is soluble in water and having poor solubility in organic solvents leads to no interaction of reactants for reaction. For such a reaction, the choice of the right solvent becomes a difficult task. To overcome such an issue phase transfer catalyst was selected for reaction.

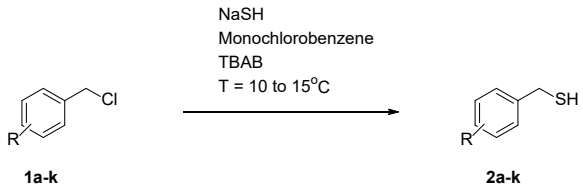
The reaction of benzyl or alkyl halide with aqueous sodium hydrogen sulfide was performed by, with and without phase transfer catalyst and without phase transfer catalyst, no reaction was noticed. Due to the poor solubility of benzyl or alkyl halide in the aqueous phase, there is no interaction with sodium hydrogen sulfide, which leads to no reaction. To make an effective interaction, we increased the agitation rate and observed no reaction conversion. Phase transfer catalyst helps to make the interaction between alkyl halide and sodium hydrogen sulfide and leads to reaction conversion at lower temperatures. The reaction was conducted below room temperature as well as at higher temperatures. We noticed the best conversion and best yield at lower temperatures, whereas at higher temperatures formation of dialkyl disulfide was noticed, which leads lower yield. Synthesis of alkyl thiols using a phase transfer catalyst is a simple and efficient method. The major advantage of this method is high reaction yield and can be used for commercial production. Lower aliphatic alkyl halide (As shown in Scheme 1) like ethyl chloride, propyl chloride, and butyl chloride also react with sodium hydrogen sulfide in the presence of a phase transfer catalyst. Further, sodium salt of benzyl or alkyl thiol treated with an alkyl halide in presence of a phase transfer catalyst (Scheme 2) obtained thioether.

Compounds 1a-k were treated with 30% NaSH solution in the presence of TBAB as a catalyst and monochlorobenzene as a solvent (Scheme 3) as per the procedure stated above. The percentage yield of obtained products 2a-k is summarized in Table 1.

Benzyl thiol (2a)

Yield = 98%, colorless liquid, boiling point is 195°C, LC purity 99%, ^{1}H-NMR 400 MHz, DMSO D6): δ ppm 2.917(s 6H), 7.491–7.435 (m, 2H), 7.853–7.848 (d, 1H, J= 2Hz), 8.553(S,1H). ^{13}C-NMR 400 MHz, DMSO (D6): δ ppm 27.73, 126.63, 128.13, 128.38, 141.52.

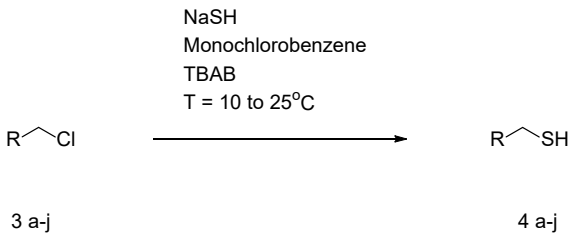
Alkyl halides are converted to corresponding alkyl thiol. Compounds 3a-j were treated with aqueous NaSH solution in the presence of TBAB and Monochlorobenzene as a solvent as per the procedure stated in the relevant section. Percentage yield of obtained products 4a-j and reaction time data is summarized in (Table 2). The



Scheme 3: Synthesis of substituted benzyl thiol (2a-k)

Table 1: Synthesis of substituted benzyl thiol (2a-k)

Entry	*(R)*	*Product*	*Time (Hours)*	*%Yield.*
1	H	(2a)	5	98
2	4-OCH_3	(2b)	5	95
3	2-Cl	(2c)	5	95
4	4-Cl	(2d)	5	95
5	4-CH_3	(2e)	5	94
6	4-C_2H_5	(2f)	5	94
7	4-C_3H_7	(2g)	5	94
8	4-C_6H_5	(2h)	5	90
9	4-Nitro	(2i)	5	88
10	2-Br	(2j)	5	88
11	4-Br	(2k)	5	88



Scheme 1: Synthesis of akylthiol (4a-j)

Table 2: Synthesis of alkylthiol (4a-j)

Entry	*(R)*	*Product*	*Time (Hours.)*	*%Yield.*
1	H	(4a)	5	95
2	CH_3	(4b)	5	95
3	C_2H_5	(4c)	5	95
4	C_3H_7	(4d)	5	95
5	n-C_4H_9	(4e)	5	94
6	C_5H_{11}	(4f)	5	94
7	C_6H_{13}	(4g)	5	94
8	C_7H_{15}	(4h)	5	90
9	C_8H_{17}	(4i)	5	88
10	$C_{11}H_{23}$	(4j)	5	88

formation of derivatives was justified by ^{1}H-NMR and ^{13}C NMR analysis.

Dodecanethiol(4j)

Yield = 88%, Colorless liquid, Boiling Point is 266–283°C, GC purity 98%, ^{1}H NMR 400 MHz, DMSO D6): δ ppm 1.372(s 10H), 2.662 (m, 1H). ^{13}C NMR 400 MHz, DMSO (D6): δ ppm 34.57, 39.10, 39.31, 39.52, 39.72, 39.93, 40.72.

Different phase transfer catalysts were used for reactions. Reactions are done as per the procedure provided in 2.1.1. It is seen that tetra butyl ammonium bromide (TBAB) is working nicely and is easily commercially available. The yield of compound 2a and reaction time data are summarized in Table 3.

Table 3: Effect of phase transfer catalyst (PTC) on synthesis of compound 2a

Entry	*Product*	*Phase transfer catalyst*	*Reaction time*	*%Yield.*
1	2a	Tetra butyl ammonium bromide	5h	98
2	2a	Benzyl tributyl ammonium bromide	8h	78
3	2a	Tetra butyl ammonium chloride	10h	75
4	2a	Tetra butyl ammonium iodide	12h	75
5	2a	Trimethyl phenyl ammonium chloride	12h	74

Table 4: Effect of different solvent for synthesis of compound 2a

Entry	*Solvent*	*Time (Hours.)*	*%Yield.*
1	Monochlorobenzene	5	95
2	Di-dichloromethane	5	90
3	Dichloroethane	5	90
4	Toluene	5	85
5	O-Xylene	5	80

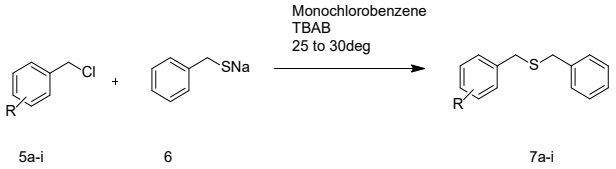
Different solvents were used for the reaction as per the procedure. As the reaction is biphasic, the role of solvent is especially important for reaction conversion and product isolation. It is seen that monochlorobenzene gives the highest conversion and yield. The yield of compound 2a and reaction time data is summarized in Table 4.

Reaction at lower temperatures gives best yield. It was observed that 10 to 15°C temperature is suitable for reaction. We conducted the reaction using compound 2a at different temperatures as mentioned in table 5 as per procedure, a yield of compound 2a and reaction time are summarized in Table 5.

We have extended the scope of synthesis for the preparation of diphenyl sulfide. Sodium salt of benzyl thiol was treated with corresponding benzyl chloride in the presence of TBAB as a catalyst and monochlorobenzene as a solvent. The reaction was performed as per the procedure given in 2.1.3 (Scheme 2).

Table 5: Effect of reaction temperature on synthesis of compound 2a

Entry	*Temperature (°C)*	*Time (Hours.)*	*%Yield*
1	0–5	5	88
2	5–10	5	90
3	10–15	5	95
4	15–20	5	92
5	20–25	5	90
6	25–30	5	88
7	30–35	5	75
8	35–40	5	75
9	40–45	5	60



5a-i 6 7a-i

Scheme 2: Synthesis of substituted diphenyl sulfide (7a-i)

Table 6: Synthesis of substituted diphenyl sulfide (7a-i)

Entry	*(R)*	*Product*	*Time (Hours)*	*%Yield.*
1	H	(7a)	5	95
2	4-OCH_3	(7b)	5	95
3	2-Cl	(7c)	5	95
4	4-Cl	(7d)	5	94
5	4-CH_3	(7e)	5	94
6	4-C_2H_5	(7f)	5	94
7	4-C_3H_7	(7g)	5	94
8	4-C_6H_5	(7h)	5	92
9	4-Br	(7i)	5	92

Compound 5a-i was treated with compound 6 in the presence of TBAB as a phase transfer catalyst and monochlorobenzene as a solvent (Scheme 2). The yield and reaction time data of the obtained product (7a-i) is summarized in Table 6.

Dibenzylsulfide (7a)

Yield = 95%, Pale beige solid, Melting point is 47 to 50°C, ^{1}H-NMR 400 MHz, DMSO (D6): δ ppm 3.642 (s 2H), 7.225 to 7.340(m, 5H) ^{13}C-NMR 400 MHz, DMSO (D6): δ ppm 35.14, 126.83, 128.40, 128.84, 138.28.

CONCLUSION

In conclusion, we have developed a convenient synthetic procedure for thiols and sulfides by substitution reaction of benzyl or alkyl halides with sodium salt of sulfide in the presence of phase transfer catalyst (TBAB) and monochlorobenzene as a solvent. TBAB is commercially available and inexpensive. The time needed for the completion of the reaction is reduced and yields of the products are increased. The method is suitable for commercial-scale production.

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