A Convenient Method for the Preparation of Alkyl Aryl Sulfides from Alcohols and (Chloromethylene)dimethylammonium Chloride

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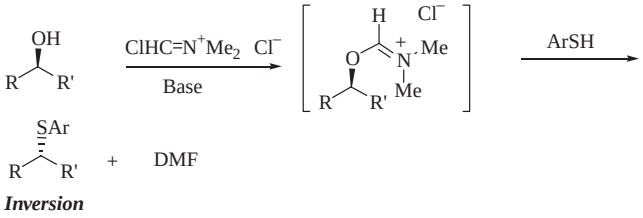
(Chloromethylene)dimethylammonium chloride (Vilsmeier reagent), prepared easily from DMF and oxalyl chloride, works as an efficient condensation reagent for the thioetherification of alcohols in one-pot under mild conditions. Various alcohols are successively converted into the corresponding sulfides with inversion of configurations in moderate to high yields.

Preparation of alkyl aryl sulfides from alcohols is a versatile synthetic method in organic chemistry and several useful preparative methods have been reported. Among them, oxidation–reduction condensation using trivalent phosphorus compounds such as Ph_3P-DEAD-RSH (Mitsunobu reaction) is considered one of the most important and fundamental reaction because it is so useful in constructing chiral centers via the inversion of configuration by S_N2 displacement. Many examples for the preparation of various sulfides from alcohols have accordingly been reported thereafter.[1] However, these conventional methods leave following synthetic problems: (i) isolation of the desired product from co-products such as triphenylphosphine oxide or diethyl hydrazinedicarboxylate is often difficult. (ii) Azodicarboxylate such as diethyl azodicarboxylate is a hazardous compound. Therefore, it is still an important topic to develop more efficient and convenient procedure for the preparation of various sulfides.

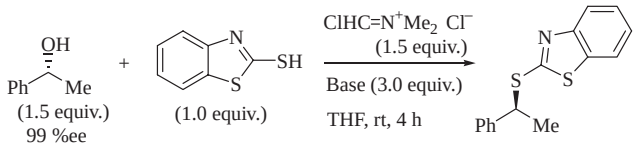
(Chloromethylene)dimethylammonium chloride, prepared easily by the chlorination of an amide, has frequently been used as a formylating reagent or a reagent to activate carboxylic acid for the formation of esters and amides. In spite of their powerful ability to dehydrate carboxylic acids, however, only a few examples have been reported on the methods to dehydrate from an alcoholic moiety.[2] Of few examples, Barrett et al. reported that secondary alcohols could be converted into the corresponding esters by an inverted fashion with Vilsmeier reagents and potassium benzoate.[2a] Also, Fujisawa et al. reported on the synthesis of alkyl chlorides from alcohols by using the iminium salts.[2c]

In this communication, we would like to describe a convenient method for the preparation of alkyl aryl sulfides from various primary, secondary, and tertiary alcohols via (alkoxymethylene)dimethylammonium chloride under mild conditions (Scheme 1).



Scheme 1. Preparation of alkyl aryl sulfides from alcohol.

Table 1. Effect of bases



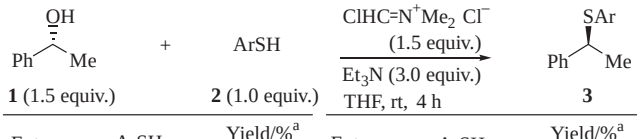
Entry	Base	Yield/%[a] (% ee)[b]	Entry	Base	Yield/%[a] (% ee)[b]
1	NEt_3	87 (99)	4	CsF	N.D.
2	DBU	51 (96)	5	K_2CO_3	57 (11)
3	Pyridine	32 (84)	6	Cs_2CO_3	52 (35)

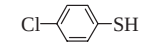
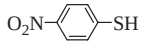
[a]Isolated yields. [b]Determined by HPLC using Daicel CHIRALCEL OD-H (See Ref. 4).

In the first place, effects of bases were examined by taking a thioetherification of (*R*)-(+)-1-phenylethyl alcohol that used 1.5 equivalents of Vilsmeier reagent in THF at room temperature (Table 1).[3] Then, triethylamine was found to be a suitable base and the corresponding sulfide was obtained in good yields while DBU or pyridine was not effective. Next, insoluble solid bases were tried as the scavenger of hydrogen chloride because they trap the liberated hydrogen chloride. However, neither potassium nor cesium carbonate was effective under these conditions. It is noteworthy to point out that the reaction proceeded with clean inversion of configuration in spite of the easily epimerizable substrate.

Next, the reaction of (*R*)-(+)-1-phenylethyl alcohol with several thiols was tried (Table 2). In the case of sufficiently acidic aryl thiols such as heteroaryl thiols or electron-withdrawing

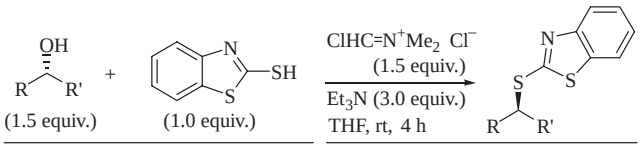
Table 2. Thioetherification of (*R*)-(+)-1-phenylethyl alcohol using various thiols

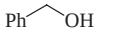
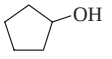
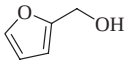
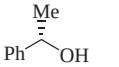
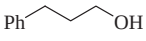
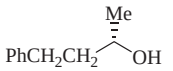
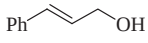
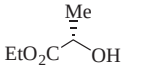
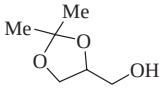
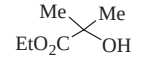
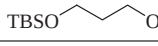
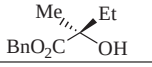


Entry	ArSH		Yield/%[a] (% ee)	Entry	ArSH		Yield/%[a] (% ee)
1		**3a**	51[b] (81)	5		**3e**	87 (99)
2		**3b**	75[b] (98)	6		**3f**	88 (99)
3		**3c**	78 (97)	7		**3g**	81 (99)
4		**3d**	91 (98)	8	AcSH	**3h**	83 (99)

[a]Isolated yields. [b]The reaction time was 20 h.

Table 3. Thioetherification of various alcohols



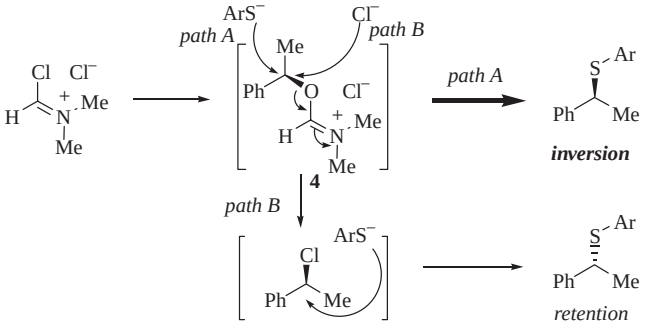
Entry	RR'OH	Yield/%[a] (% ee)	Entry	RR'OH	Yield/%[a] (% ee)
1		91	7		86[b]
2		87	8		87 (99)
3		90[b]	9		81[b] (99)
4		94	10		82 (97)
5		81[c]	11		84[b]
6		70[b]	12		N.D.

[a]Isolated yields. [b]The reaction time was 16 h. [c]Reaction was carried out in toluene at 60 °C.

thiophenols were used, the reaction proceeded to afford the corresponding sulfides at room temperature in good yields with almost complete inversion of stereochemistries (Entries 2–6).[4,5] When benzenethiol was used, however, the desired thioether was obtained in 51% yield with 81% ee (Entry 1). Further, the reactions proceeded smoothly and gave the corresponding thioesters in good yields with complete inversions when thiocarboxylic acids were used as a substrate (Entries 7 and 8).

Thioetherification of various alcohols under the optimized conditions are summarized in Table 3. The reactions of primary and secondary alcohols proceeded smoothly and afforded the desired sulfides even when ethyl ester and *tert*-butyldimethylsilyl groups coexisted in the same molecule (Entries 1–10). Next, the stereo-course of the present reaction was studied by using chiral secondary alcohols and the desired 2-benzothiazolyl sulfides were then obtained with virtually complete inversion of configurations (Entries 8–10). Further, an alcohol having an ester group at the quaternary centers was smoothly transformed into the sulfide in good yield (Entry 11). On the other hand, no similar reaction proceeded when a more hindered chiral tertiary alcohol was used as a substrate (Entry 12).

A proposed reaction mechanism is illustrated in Scheme 2. In the first place, (chloromethylene)dimethylammonium chloride reacts with (*R*)-(+)-1-phenylethyl alcohol to form the adducts **4** through addition and elimination processes. In the next step, two different pathways may possibly be considered: that is, i) when sufficiently acidic aryl thiols were used as substrates, the nucleophilic attack of the thiolate anions takes place at the benzylic carbon of the salt **4** and forms the corresponding sulfides with inversion of configurations via path **A**, or ii) when the nucleophilicity of the thiol was not sufficient, rate of the reaction is slow. Therefore, the salt **4** competitively reacts with the chloride ion and the following thioetherification with thiol via



Scheme 2.

path **B** gives the corresponding sulfide with partial inversion of configuration.

Thus, a convenient method for the preparation of inverted alkyl aryl sulfides from various chiral alcohols was established by using readily available Vilsmeier reagent under mild conditions. Further investigations on the preparation of the iminium salts and their application to various dehydration reactions are now in progress.

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References and Notes

1 a) K. Ikegai, W. Pluempanupat, and T. Mukaiyama, *Chem. Lett.*, **34**, 638 (2005). b) T. Mukaiyama and K. Ikegai, *Chem. Lett.*, **33**, 1522 (2004). c) J. R. Falck, J.-Y. Lai, S.-D. Cho, and J. Yu, *Tetrahedron Lett.*, **40**, 2903 (1999). d) D. L. Hughes, *Org. Prep. Proced. Int.*, **28**, 127 (1996). e) H. Kotsuki, K. Matsumoto, and H. Nishizawa, *Tetrahedron Lett.*, **32**, 4155 (1991). f) I. Nakagawa, K. Aki, and T. Hata, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1315. g) T. Mukaiyama, S. Ikeda, and S. Kobayashi, *Chem. Lett.*, **1975**, 1159.

2 For the reactions using iminium salts: a) A. G. M. Barrett, N. Koike, and P. A. Procopiou, *J. Chem. Soc., Chem. Commun.*, **1995**, 1403. b) P. A. Procopiou, A. C. Brodie, M. J. Deal, and D. F. Hayman, *Tetrahedron Lett.*, **1993**, 7483. c) T. Fujisawa, T. Mori, K. Fukumoto, and T. Sato, *Chem. Lett.*, **1982**, 1891.

3 Typical experimental procedure is as follows (Table 1, Entry 1): to a stirred solution of DMF (117 µL, 1.37 mmol) in dry CH_2Cl_2 (3.0 mL) were added dropwise oxalyl chloride (108 µL, 1.24 mmol) at 0 °C under argon atmosphere. The mixture was stirred for 5 min at the same temperature and solvent was evaporated. The obtained white solid was cooled down to 0 °C and suspended in dry THF. (*R*)-(+)-Phenylethyl alcohol (151.2 mg, 1.24 mmol) and triethylamine (346.7 µL, 2.49 mmol) and 2-mercaptobenzothiazole (138.7 mg, 0.83 mmol) were added sequentially. The reaction mixture was stirred for 4 h at room temperature. After completion of the reaction, it was quenched with water. The mixture was extracted with AcOEt and the organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtrated and concentrated. The crude product was purified by preparative TLC to afford the desired product (196.2 mg, 87%) as colorless prisms.

4 Enantiomeric purity for thioether **3e** was determined by HPLC (CHIRALCEL OD-H, hexane/^{i}PrOH = 50:1, flow rate = 1.0 mL/min): ^{t}R = 7.7 min.

5 The absolute configurations of **3b**–**3g** were determined by comparing with configuration of products, which were prepared via our procedure.[1a,1b]

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