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A New Synthetic Route to β-Hydroxythioethers from Carbonyl Compounds Using Samarium(II) Diiodide (SmI_2)

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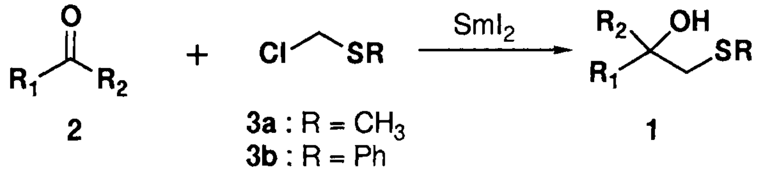
In the presence of samarium diiodide (SmI_2) in THF, chloromethyl sulfides reacted with carbonyl compounds to give β-hydroxythioethers under mild and neutral conditions in moderate to good yields.

Because of possible conversion into various useful compounds such as vinyl[1)] or allyl sulfide,[2)] oxirane,[3)] alkene,[4)] and α-hydroxyaldehyde,[5)] β-hydroxythioethers (**1**) are useful compounds in synthetic organic chemistry. Recently, Utimoto,[6a)] Hosomi,[6b)] and Mitchell[6c)] reported mild preparation methods for **1**. These methods avoid use of the severe reaction conditions (*e.g.* strong base, $LiAlH_4$).[6d-f)] We have been interested in the development of another useful preparation method for **1** under mild and neutral conditions.

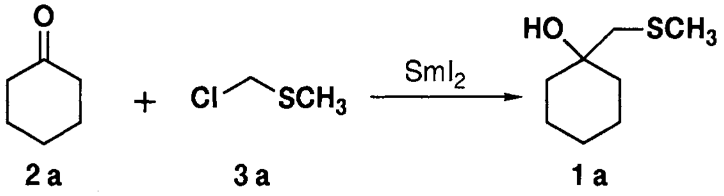
Since Kagan *et al.* reported the first work on SmI_2 in synthetic organic chemistry,[7)] many applications with SmI_2 have been developed.[8)] In this paper, we describe a convenient procedure for preparation of **1** by the reaction of carbonyl compounds (**2**) with chloromethyl sulfides (**3**) in the presence of SmI_2.[9)]



Scheme 1.

First, we examined the reaction of cyclohexanone (**2a**) with chloromethyl methyl sulfide (**3a**) under various conditions. The results are summarized in Table 1. In Runs 1 and 5, 1-methylthiomethyl-1-cyclohexanol (**1a**)[10)] was given in high yields. Addition of hexamethylphosphoric triamide (HMPA) in the reaction mixture shortened the reaction time.[11)] However, addition of two or more equivalents of HMPA or

Table 1. Reaction of **2a** with **3a** in the Presence of SmI_2



Run[a)]	HMPA (equiv.)	Proton source (equiv.)	Reaction time /h[b)]	Yield /%[c)]
1	none	none	1	96 (71)
2	none	MeOH (1.1)	1	67 (51)
3	none	*i*-PrOH (1.1)	1	39
4	none	*t*-BuOH (1.1)	1	35
5	1	none	0.5	96
6	2	none	0.5	79
7	5	none	0.5	21
8	10	none	0.5	35
9	1	MeOH (1.1)	0.5	53

a) To a suspension of SmI_2 (2.2 mmol) in THF(10 ml), a solution of **2a** (98 mg, 1.0 mmol) and **3a** (97 mg, 1.0 mmol) , if any, HMPA and/or proton source, in THF (2.0 ml) was added dropwise at room temperature under N_2 atmosphere.

b) The time when the initial characteristic blue color turned to yellowish green.

c) Determined by GLC analysis with an internal standard. Isolated yields are given in parentheses.

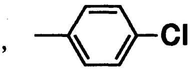
proton sources such as MeOH, *i*-PrOH, or *t*-BuOH gave rise to decrease of the yield of **1a**.

Under the same conditions as Run 1, the reactions of various carbonyl compounds (**2**) and chloromethyl methyl sulfide (**3a**) or α-chlorothioanisole (**3b**) were examined, and the results are summarized in Table 2. Ketones (Runs 1-6) afforded alcohols (**1**) in moderate to good yields. In the reactions with aldehydes (Runs 7-11), though the reaction time was very short, the yield of **1** were lower to a certain extent except the case of pivalaldehyde (Runs 9 and 10). In the case of Run 7, addition of butyraldehyde (**2b**) and **3a** to SmI_2 solution is critical. Simultaneous addition of **2b** and **3a** gave only trace of 1-methylthio-2-pentanol (**1b**). However, addition of **3a** followed by treatment with **2b** afforded **1b** in 43% yield.

For a representative example (Run 4), to a SmI_2 (1.1 mmol) solution in THF (11 ml) was added dropwise a solution of 2-octanone (64 mg, 0.50 mmol) and chloromethyl methyl sulfide (48 mg, 0.50 mmol) in THF (2.0 ml) at room temperature under N_2 atmosphere. After 3 h, the typical blue color of SmI_2 turned to yellowish green. 10% HCl was added and the mixture was extracted with ether. The extract was washed with water, sodium thiosulfate solution, and brine, dried (Na_2SO_4), and evaporated. The oily residue was chromatographed on silica gel with ether/*n*-hexane (1 : 4) to afford 2-methylthiomethyl-2-octanol (86 mg, 90%)[10] as colorless oil.

In conclusion, a mild and neutral preparation method for β-hydroxythioether (**1**) was achieved by the reaction of chloromethyl sulfides with carbonyl compounds in the presence of SmI_2. Applications of this reaction are under investigation.

Table 2. Reactions of Carbonyl Compounds(**2**) with Sulfides(**3**)

Run	Carbonyl compound (**2**)	Chloromethyl sulfide (**3**) R	Reaction time[a]	Product (**1**)[10] R_1, R_2	Yield/%[b]
1	Cyclohexanone	Ph	3 h	$-(CH_2)_5-$	73
2	Cyclooctanone	Me	1 h	$-(CH_2)_7-$	82
3	Cyclooctanone	Ph	5 h	$-(CH_2)_7-$	78
4	2-Octanone	Me	3 h	CH_3-, $-(CH_2)_5CH_3$	90
5	2-Octanone	Ph	10 h	CH_3-, $-(CH_2)_5CH_3$	86
6	Benzophenone	Ph	12 h[c]	Ph-, -Ph	71
7	Butyraldehyde	Me	<5 min	H-, $-(CH_2)_2CH_3$	43[d]
8	Isobutyraldehyde	Me	<5 min	H-, $-CH(CH_3)_2$	36
9	Pivalaldehyde	Me	<5 min	H-, $-C(CH_3)_3$	72
10	Pivalaldehyde	Ph	<5 min	H-, $-C(CH_3)_3$	53
11	*p*-Chlorobenzaldehyde	Me	<5 min	H-, 	46

a) The time when the characteristic blue color turned to yellowish green.

b) Isolated yield. All products obtained are oily.

c) Four equivalents of SmI_2 was used.

d) This yield was obtained by addition of **3a** followed by treatment with **2b**.

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