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Efficient Reductive Etherification of Carbonyl Compounds with Alkoxytrimethylsilanes

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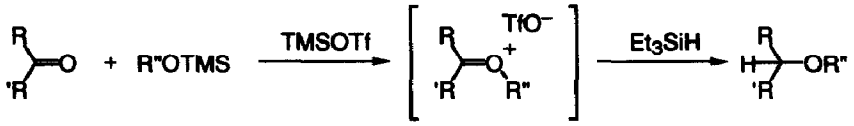
Abstract: An efficient TMSOTf catalyzed ether synthesis from carbonyl compounds and alkoxytrimethylsilanes *via* triethylsilane-reduction is described.

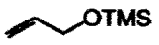
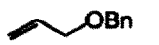
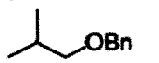
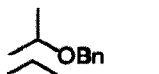
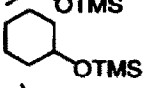
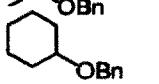
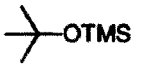
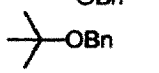
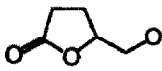
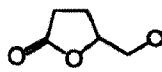
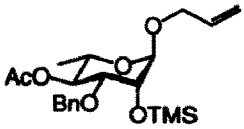
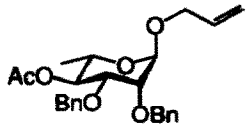
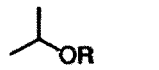
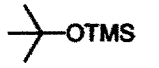
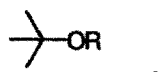
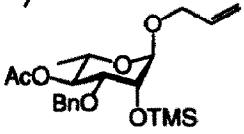
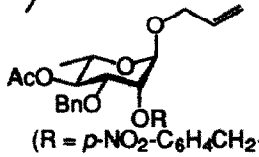
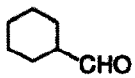
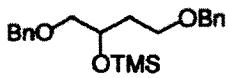
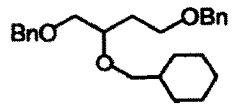
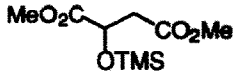
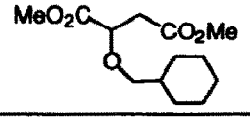
The preparation of ethers is limited in practical sense to Williamson's etherification involving alkylation of an alkoxy anion with an alkyl halide under basic conditions. In connection with a project directed toward natural product synthesis, we required a promising method for the preparation of ethers under non-basic conditions. To this end, we planned to investigate reductive etherification of carbonyl compounds **1** with alkoxytrimethylsilanes **2** giving **4** based upon a combination of Noyori's TMSOTf[1] catalyzed acetalization[2] and trialkylsilane-reduction of acetals.[3] We expected that these two reactions can be successively effected under TMSOTf catalyzed conditions in the same flask, since both reactions proceed through the common oxonium ion intermediate **3**. Although several etherifications of carbonyl compounds or acetals *via* trialkylsilane-reduction have already been developed,[3, 4] there are no widely applicable methods which involves a simple process using readily available reagents. We now wish to report a new convenient and efficient method for the preparation of ethers including benzyl ethers which are the most important protecting groups of alcohols.[5]



1 **2** **3** **4**

Various reactions of aldehydes with alkoxytrimethylsilanes are summarized in Table 1.[6] A typical procedure is described for the synthesis of γ-benzyloxy-γ-butyrolactone (entry 7). TMSOTf (0.1 mmol) was added to an ice-cooled mixture of benzaldehyde (1.2 mmol) and γ-trimethylsilyloxy-γ-butyrolactone (1 mmol) in CH_2Cl_2 (10 ml). After stirring at 0 °C for 1 h, triethylsilane (1 mmol) was added and the mixture was allowed to warm to room temperature. After 12 h, the reaction mixture was diluted with Et_2O, washed with sat. $NaHCO_3$, dried over $MgSO_4$, evaporated, and chromatographed on silica gel to give the benzyl ether in 89% yield. It can be seen that this etherification method worked well in cases of primary and secondary alkoxytrimethylsilanes except one particular example shown in entry 15.[7] In the case of rhamnose derivative, however, the reaction turned out to be verry sluggish under the standard conditions because of its steric hindrance and use of an excess amount of TMSOTf and triethylsilane was neccessary to complete the reaction in reasonable yield (entries 8 and13). Since silyl ethers are easily available from the corresponding alcohols,[8] this

Table 1. Reductive Etherifications of Aldehydes[a]

entry	aldehyde	alkoxytrimethylsilane	temp. (°C)[b]	product	yield (%)[c]
1	PhCHO	BnOTMS	−78 → −30	BnOBn	96
2			−30 → 0		99
3			0 → r. t.		81
4			0 → r. t.		92
5			−78 → −30		99
6			0 → r. t.		16
				(BnOBn)	(32)
7			0 → r. t.		89
8			−78 → −30		54[d] (82)[e] 96[f]
9		PhOTMS	0 → r. t.	PhOBn (BnOBn)	0 (11)
10	*p*-NO_2-C_6H_4CHO	*n*-C_6H_{13}OTMS	0 → r. t.	*n*-C_6H_{13}OR	88
11			0 → r. t.		73
12			0 → r. t.		63
13			−78 → −30	 (R = *p*-NO_2-$C_6H_4CH_2$-)	52[f] (89)[e]
14			−30		84
15			−30		36

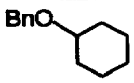
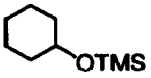
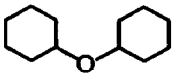
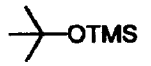
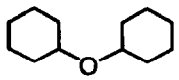
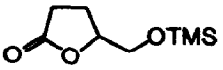
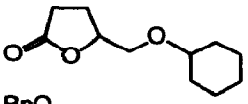
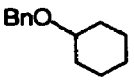
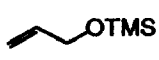
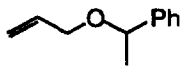
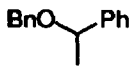
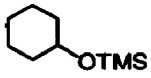
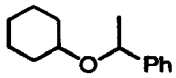
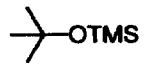
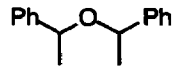
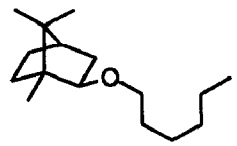
a) The reaction was carried out using aldehyde (1.2 equiv.), alkoxytrimethylsilane (1 equiv.), Et_3SiH (1.2 equiv.) and TMSOTf (0.1 equiv.) in CH_2Cl_2 (0.1 M) unless otherwise noted. b) The reaction temperature was warmed up after addition of Et_3SiH. c) Isolated yield. d) The reaction was carried out using TMSOTf (0.2 equiv.) in toluene. The benzyl ether was obtained in somewhat lower yield under the standard conditions. e) Yield based on consumed starting TMS ether. f) The reaction was carried out using TMSOTf (2 equiv.) and Et_3SiH (2 equiv.) in toluene.

method can be effectively employed for the protection of alcohols as a benzyl or *p*-nitrobenzyl ether.[9] Entries 7, 8, and 13 show the marked advantage of this protection method in which ester, lactone, and glycosidic acetal

functionalities are unaffected. The following are limitations of the present etherification method. The reactions of silyl ethers of *tert*-butyl alcohol and phenol with benzaldehyde led to poor yields of the corresponding ethers and gave mostly dibenzyl ether through reductive self-etherification of benzaldehyde (entries 6 and 9), although a better result was obtained with *p*-nitrobenzaldehyde (entry 12). This method can not be applicable to the preparation of *p*-methoxybenzyl ethers[10] because of extreme instability of *p*-methoxybenzaldehyde under etherification conditions.

Table 2 shows that reactions of ketones with primary and secondary alkoxytrimethylsilanes again gave the ethers in good to excellent yields. However, in the case of less reactive silyl ether such as *tert*-butoxytrimetylsilane, symmetrical ethers were formed through reductive self-etherification of ketones (entries 3 and 9). It is important to note that, upon reaction of cyclohexenone with benzyloxytrimethylsilane, reduction of the olefinic double bond concomitantly took place to give benzyl cyclohexyl ether (entry 5).

Table 2. Reductive Etherifications of Ketones[a]

entry	ketone	alkoxytrimethylsilane	temp. (°C)[b]	product	yield (%)[c]
1		BnOTMS	–78 → –30		100
2			–78 → –30		95
3			–78 → –30		35
4			0 → r. t.		93
5		BnOTMS	–78 → –30		50
6			–30 → 0		85
7		BnOTMS	–78 → –30		100
8			0 → r. t.		96
9			0 → r. t.		28
10		n-$C_6H_{13}OTMS$	0 → r. t.		88[d]

a) The reaction was carried out using ketone (1 equiv.), alkoxytrimethylsilane (1.2 equiv.), Et_3SiH (1.2 equiv.) and TMSOTf (0.1 equiv.) in CH_2Cl_2 (0.1 M) unless otherwise noted. b) The reaction temperature was warmed up after addition of Et_3SiH. c) Isolated yield. d) TMSOTf (1 equiv.) was used.

In conclusion, we have developed a new convenient method with broad applicability for the preparation of ethers, in particular, benzyl ethers under non-basic conditions which is complementary to the conventional Williamson's etherification.

Acknowledgement. We thank Professor T. Tsunoda of Tokushima Bunri University for helpful discussions.

References and Notes

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6. All new compounds exhibited satisfactory spectral (^{1}H NMR, IR) and analytical (high-resolution mass) data.

7. The low yield observed can be attributed to competitive β-elimination reaction.

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