Chlorotrimethylsilane as a Mild and Effective Source of Acid Catalyst in Reductive Benzylation

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New reductive benzylation of hydroxy functions was effected by using the combination of benzaldehyde, TMSCl, and Et_3SiH. TMSCl first reacts with alcohols to form HCl, which is probably the ultimate catalyst for this reaction system. TMSCl can also trap water and thus effectively promote dehydration reactions when more than stoichiometric amount of TMSCl is used. Although excess TMSCl was required for the foregoing reactions, TMSCl could be readily removed by simple evaporation.

Chlorotrimethylsilane (TMSCl) has been used as an acid catalyst for esterification and ketal formation.[1,2] We have also reported the new convenient Fischer glycosidation using TMSCl as acid catalyst.[3] In these reactions, TMSCl first reacts with alcohols or carboxylic acids to form HCl, which is probably the ultimate catalyst for these reaction systems. TMSCl can also trap water and thus effectively promote dehydration reactions when more than stoichiometric amount of TMSCl is used.

We first investigated reductive benzylation of hydroxy function using benzaldehyde, TMSCl, and Et_3SiH. Nishizawa[4a] reported reductive benzylation of hydroxy function, in which the hydroxy group was once trimethylsilylated and then treated with benzaldehyde, TMSOTf, and Et_3SiH.[4,5] However, partial cleavage of O-TMS group prior to benzylation reaction decreased the overall yields in some cases: no benzylation proceeds on a free hydroxy group. We previously described a new one-pot procedure to improve Nishizawa's method for the protection of the hydroxy group of 3-hydroxy fatty acid esters.[6] Direct benzylation was effected in high yields via in situ O-trimethylsilylation by using benzaldehyde, TMS_2O, TMSOTf, and Et_3SiH. This method was, however, not suitable for benzylation of glucose derivatives having many benzyl groups, since some benzyl groups already present were reductively cleaved during the reaction. We, therefore, investigated a combination of TMSCl and Et_3SiH for reductive benzylation via in situ O-trimethylsilylation under milder conditions. A possible reaction mechanism is shown in Figure 1. In this reaction, TMSCl promotes O-trimethylsilylation and then the formation of the oxocarbenium ion intermediate, which is reduced with Et_3SiH to give the desired ether.

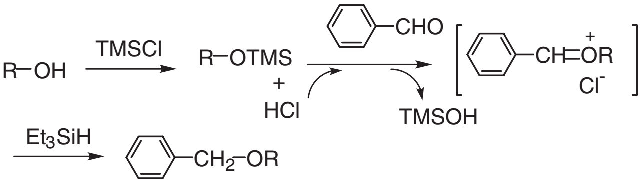


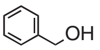
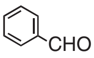
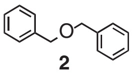
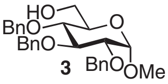
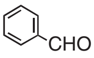
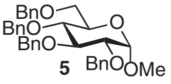
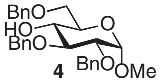
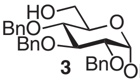
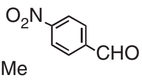
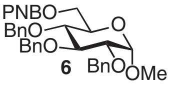
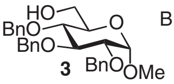
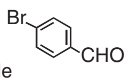
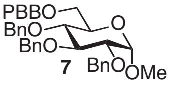
Figure 1. Possible mechanism of the present reductive benzylation.

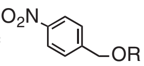
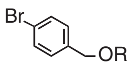
As shown in Table 1, 10 equiv. of TMSCl was required for smooth reductive benzylation of benzyl alcohol (**1**) (Entry 3). The 6-hydroxy group of glucose derivative **3** was benzylated under these conditions in 81% yield (Entry 4).[7] The more hindered 4-hydroxy group of glucose derivative **4** was also smoothly benzylated in 77% yield (Entry 5). Addition of excess benzaldehyde did not improve the yields of the desired benzylated compound but increased the formation of dibenzyl ether **2**.

Reductive alkylation of **3** with 1-naphthaldehyde and 9-anthracenecarboldehyde gave trace amount of the alkylated product but most of the starting aldehydes were transformed to symmetrical ethers via reduction of the aldehydes and subsequent reductive alkylation of the resulting alcohols. These results suggest more reactive aldehydes than benzaldehyde cannot be used, since they might be consumed prior to alkylation. By contrast, less reactive *p*-nitrobenzaldehyde can be used for the present reductive alkylation. We previously reported the use of *p*-nitrobenzyl group for temporary protection of hydroxy functions.[8]

Table 1. Reductive benzylation using TMSCl and Et_3SiH

$$\mathrm{R{\cdot}OH} \xrightarrow[\mathrm{CH_2Cl_2,\ r.t.,\ 3\ h}]{\mathrm{PhCHO\ (1\ equiv.),\ TMSCl,\ Et_3SiH\ (2\ equiv.)}} \mathrm{R{\cdot}OBn}$$

Entry	R·OH	PhCHO	TMSCl	R·OBn	Yield/%
1	 **1**		1 eq	 **2**	8
2			5 eq		83
3			10 eq		quant
4	 **3**		10 eq	 **5**	81%
5	 **4**		10 eq		77%
6	 **3**		10 eq	 **6**	70%
7	 **3**		10 eq	 **7**	52%

PNB-OR =  PBB-OR = 

The *p*-nitrobenzyl group has been so far introduced to hydroxy functions by using *p*-nitrobenzylbromide-Ag_2O, *p*-nitrobenzylbromide-AgOTf-2,4,6-collidine, or *p*-nitobenzyl triflate or by Nishizawa's method. The hydroxy group of **3** was conveniently *p*-nitrobenzylated by the present method in a comparable yield (Entry 6). *p*-Bromobenzylation of **3** by the present method did not give good yield, because of debromination under the reducing condition of Et_3SiH (Entry 7). This PBB (*p*-bromobenzyl) ethers of **7** should be converted to the more labile, substituted *p*-arylbenzyl ethers via a Pd-catalyzed Suzuki–Miyaura coupling without using phosphine ligands and be subsequently removed by acids or oxidants.[9]

p-Methoxybenzyl group was completely cleaved under the present reaction conditions. We previously reported that *p*-acylaminobenzyl group was much more stable to Lewis acids than *p*-methoxybenzyl group but was cleaved by DDQ in a comparable rate.[4d,10] *p*-Acylaminobenzyl group, however, also smoothly cleaved with TMSCl–Et_3SiH. In other words, a combination of TMSCl–Et_3SiH is useful for selective cleavage of *p*-methoxybenzyl and *p*-acylaminobenzyl groups.[11]

In conclusion, we have developed a new convenient method for the preparation of ethers from carbonyl compounds and non-protected alcohols under non-basic and non-metal conditions. TMSCl works as both an acid catalyst and dehydrating agent. Although excess TMSCl was required for the foregoing reactions, TMSCl could be readily removed by simple evaporation.

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References and Notes

1 M. A. Brook and T.-H. Chan, *Synthesis*, **1983**, 201.

2 T.-H. Chan, M. A. Brook, and T. Chaly, *Synthesis*, **1983**, 203. Esterification was basically effected by using 2.2 equiv. of TMSCl and alcohols as solvents at room temperature or under reflux in THF. We found that esterification of *N*-fluorenylmethyloxycarbonyl (Fmoc) amino acids also proceeded smoothly in CH_2Cl_2 at room temperature by using 2 equiv. of alcohols and 5 equiv. of TMSCl against carboxylic acids to give the desired esters quantitatively.

3 M. Izumi, K. Fukase, and S. Kusumoto, *Biosci. Biotechnol. Biochem.*, **66**, 211 (2002).

4 a) S. Hatakeyama, H. Mori, K. Kitano, H. Yamada, and M. Nishizawa, *Tetrahedron Lett.*, **35**, 4367 (1994). b) Trityl perchlorate promoted reduction of carbonyl compounds with triethylsilane: J. Kato, N. Iwasawa, and T. Mukaiyama, *Chem. Lett.*, **1985**, 743. c) Trimethylsilyl iodide catalyzed reductive coupling of carbonyl compounds with trialkylsilanes: M. B. Sassaman, K. Kotian, G. K. S. Prakash, and G. A. Olah, *J. Org. Chem.*, **52**, 4314 (1987). d) Reductive benzylation via *O*-tetrahydropyranyl ether: T. Suzuki, K. Ohashi, and T. Oriyama, *Synthesis*, **1999**, 1561. e) Bismuth trichloride catalyzed efficient reductive etherification of carbonyl compounds with alcohols: M. Wada, S. Nagayama, K. Mizutani, R. Hiroi, and N. Miyoshi, *Chem. Lett.*, **2002**, 248.

5 Reductive *N*-benzylation has also reported. a) S.-C. Shim, K.-T. Huh, S.-S. Oh, and D.-H. Oh, *Bull. Korean Chem. Soc.*, **7**, 484 (1986). b) R. B. C. Pillai, *Indian J. Chem. Sect. B*, **35B**, 487 (1996).

6 K. Fukase, Y. Fukase, M. Oikawa, W.-C. Liu, Y. Suda, and S. Kusumoto, *Tetrahedron*, **54**, 4033 (1998).

7 A typical procedure for reductive benzylation was as follows: To a solution of methyl 2,3,4-*O*-tribenzyl-α–D-glucopyranoside (**3**, 232 mg, 0.5 mmol) in CH_2Cl_2 (2.0 mL) was added chlorotrimethylsilane (0.63 mL, 5.0 mmol) and benzaldehyde (0.05 mL, 0.5 mmol) and triethylsilane (0.16 mL, 1.0 mmol). The mixture stirred at room temperature for 3 h, and evaporated under reduced pressure. The residue was submitted to flash chromatography (silica gel, eluent: $CHCl_3/MeOH$, 10:1, v/v), to give a pure colorless product **5**. Yield 224 mg (81%). **5**: ^1H NMR ($CDCl_3$) δ 3.37 (3H, s, $OC\underline{H}_3$), 3.55 (1H, dd, $J = 9.5$, 3.6 Hz, H-2), 3.59–3.65 (2H, m, H-4 and H-5), 3.69–3.75 (2H, m, H-6), 3.97 (1H, dd, $J = 9.5$, 9.2 Hz, H-3), 4.45–4.98 (8H, m, $PhC\underline{H}_2$- x4), 4.61 (1H, d, $J = 3.6$ Hz, H-1), 7.11–7.37 (20H, m, $\underline{Ph}CH_2$- x4). **6**: ^1H NMR ($CDCl_3$) δ 3.37 (3H, s, $OC\underline{H}_3$), 3.55 (1H, dd, $J = 9.5$, 3.6 Hz, H-2), 3.60–3.64 (2H, m, H-4 and H-5), 3.69–3.75 (2H, m, H-6), 3.97 (1H, dd, $J = 9.5$, 9.2 Hz, H-3), 4.45–4.98 (8H, m, $PhC\underline{H}_2$- x4), 4.62 (1H, d, $J = 3.6$ Hz, H-1), 7.12–7.37 (20H, m, $\underline{Ph}CH_2$- x3), 7.63 (2H, d, $J = 9.0$ Hz, $NO_2\underline{Ph}CH_2$–), 8.27 (2H, d, $J = 9.0$ Hz, $NO_2\underline{Ph}CH_2$–). **7**: ^1H NMR ($CDCl_3$) δ 3.35 (3H, s, $OC\underline{H}_3$), 3.54 (1H, dd, $J = 9.5$, 3.6 Hz, H-2), 3.59–3.64 (2H, m, H-4 and H-5), 3.69–3.74 (2H, m, H-6), 3.97 (1H, dd, $J = 9.5$, 9.2 Hz, H-3), 4.44–4.98 (8H, m, $PhC\underline{H}_2$- x4), 4.61 (1H, d, $J = 3.6$ Hz, H-1), 7.12–7.37 (20H, m, $\underline{Ph}CH_2$- x3), 7.25 (2H, d, $J = 9.0$ Hz, $Br\underline{Ph}CH_2$–), 7.51 (2H, d, $J = 9.0$ Hz, $Br\underline{Ph}CH_2$–).

8 a) K. Fukase, H. Tanaka, S. Torii, and S. Kusumoto, *Tetrahedron Lett.*, **31**, 389 (1990). b) K. Fukase, T. Matsumoto, N. Ito, T. Yoshimura, S. Kotani, and S. Kusumoto, *Bull. Chem. Soc. Jpn.*, **65**, 2643 (1992). c) K. Fukase, T. Yoshimura, S. Kotani, and S. Kusumoto, *Bull. Chem. Soc. Jpn.*, **67**, 473 (1994).

9 X.-Y. Liu and P. H. Seeberger, *Chem. Commun.*, **2004**, 1708.

10 K. Fukase, T. Yoshimura, M. Hashida, and S. Kusumoto, *Tetrahedron Lett.*, **32**, 4019 (1991).

11 Reductive cleavage of 4-methoxybenzyl group with $Et_3SiH\text{-}BF_3 \cdot Et_2O$: Y. Morimoto, M. Iwahashi, K. Nishida, Y. Hayashi, and H. Shirahama, *Angew. Chem., Int. Ed. Engl.*, **35**, 904 (1996).