

Catalyst-free silylation of alcohols and phenols by promoting HMDS in CH_3NO_2 as solvent†

Santosh T. Kadam and Sung Soo Kim*

Received 8th July 2009, Accepted 17th September 2009

First published as an Advance Article on the web 26th October 2009

DOI: 10.1039/b913398d

An uncatalyzed method for the silylation of alcohols and phenols with HMDS in CH_3NO_2 at rt is developed. A diverse range of aromatic and aliphatic alcohols as well as phenols undergo the silylation in very short reaction time with excellent yield. The uncatalyzed reaction requires neither elevated temperature nor high pressure for the silylation.

Introduction

Functional group protection is at the heart of multifunctional and multistep target molecules. Alcohol and phenol moieties represent one of the most ubiquitous functional groups in nature.¹ The formation of a silyl ether from a hydroxyl group is one of the most popular and widely used methods. It is frequently used as a protection method in multistep reactions due to its stability under a variety of conditions, solubility in non-polar solvents and its ease of removal. Silylation of hydroxyl groups is also utilized in analytical chemistry to prepare volatile derivatives of alcohols and phenols for GC and GC-MS analysis.² Many silylating agents, such as chlorotrimethylsilane,³ hexamethyldisiloxane,⁴ and allylsilane⁵ have been used to introduce silyl groups into a variety of alcohols. Hexamethyldisilazane (HMDS) is a stable, commercially available reagent which gives ammonia as the only by-product. Even though the handling of this reagent is convenient, the main drawback is its poor silylating power which demands the use of catalysts and high temperature.⁶ A variety of catalysts have been reported for the activation of HMDS, such as sulfonic acid-functionalized nanoporous silica,⁷ trichloroisocyanuric acid (TCCA),⁸ InBr_3 ,⁹ zirconyl triflate,¹⁰ K-10 montmorillonite,¹¹ H- β zeolite,¹² silica-supported perchloric acid,¹³ barbituric acid,¹⁴ iodine,¹⁵ MgBr_2 ,¹⁶ *N*-bromosuccinimide (NBS)¹⁷ and iron(III) trifluoroacetate.¹⁸

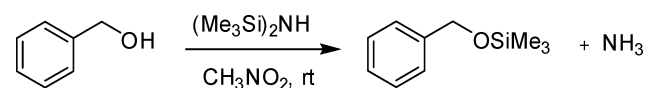
Hence, considering the importance of the silylation reaction, continuous efforts have been made to develop new methodologies involving the application of various catalysts. However, various limitations exist with the reported methodologies, such as long reaction time,¹⁴ high temperature,¹² halogenated solvents,¹⁵ costly catalysts,⁹ toxic metal catalysts¹⁰ and use of excess reagent.²⁵ According to the principle of green chemistry, the synthetic method should be designed to minimize the energy input by running the reaction at ambient temperature and reducing the amount of reagents or catalyst.¹⁹ Thus, with increasing environmental concern, there is a demand for efficient, metal-

or catalyst-free and environmentally benign methods for the silylation of alcohols.

The appropriation of several solvents without intervention of catalyst has been reported for various organic transformations. Watahiki *et al.* have reported DMSO for cyanobenzoylation of aldehydes with benzyl cyanide.²⁰ The combination of DMSO with hexane was employed for the cyanosilylation of aldehyde²¹ as well as synthesis of silyl ether from alcohol and *tert*-butyldimethylsilyl chloride.²² Similarly, Iwanami *et al.* describe the synthesis of cyanohydrin carbonates in DMSO in the presence of molecular sieves.²³ Kumamoto *et al.* show the cyanation of acetal with TMSCN in CH_3NO_2 at 60 °C and high pressure.²⁴ Considering the activity of different silyl reagents in polar solvents, HMDS could be activated in the proper solvent without using catalyst.

Result and discussion

We herein report a novel and simple catalyst-free silylation method of alcohols and phenols under mild conditions (Scheme 1). The effect of various solvents for the silylation of benzyl alcohol is explored (Table 1). The polar aprotic solvents DMF and DMSO produce 20 and 48% of yield, respectively (entries 1 and 2). THF shows a lesser yield (10%) of silylated product (entry 4). Methanol, CH_2Cl_2 , dioxane, CH_3CN and hexane give no product (entries 3 and 5–8). Surprisingly, the reaction in CH_3NO_2 results in the desired product with excellent yield in a very short reaction time (10 min). Accordingly, 1 mL of CH_3NO_2 and 1 mmol of HMDS is sufficient for the completion of silylation reaction with alcohols at rt. This could be the first example of uncatalyzed silylation of alcohols with HMDS in CH_3NO_2 .



Scheme 1 Silylation of alcohols with HMDS in CH_3NO_2 .

A variety of aromatic and aliphatic alcohols have been examined for the silylation in CH_3NO_2 without intervention of any catalyst or promoter (Table 2). Benzyl alcohol and most of its various derivatives undergo the silylation with

Department of Chemistry, Inha University, Incheon, 402-756, South Korea. E-mail: sungsoo@inha.ac.kr

† Electronic supplementary information (ESI) available: Experimental details and ^1H and ^{13}C NMR data. See DOI: 10.1039/b913398d

Table 1 Silylation of benzyl alcohol with HMDS in various solvents

Entry	Solvent	Time	Yield/% ^a
1	DMF	6 h	20
2	DMSO	6 h	48
3	1,4-Dioxane	6 h	NR
4	THF	6 h	10
5	MeOH	6 h	NR
6	CH ₂ Cl ₂	6 h	NR
7	CH ₃ CN	6 h	NR
8	Hexane	6 h	NR
9	CH ₃ NO ₂	10 min	99

Reaction conditions: 1 mmol of benzyl alcohol, 1 mmol of HMDS and 1 mL of solvent at rt.^a Isolated yield.

Table 2 Silylation of primary alcohols with HMDS in CH₃NO₂.^a

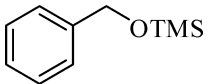
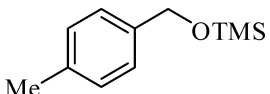
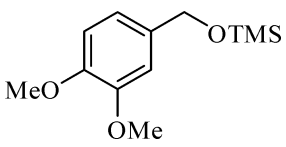
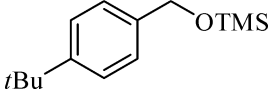
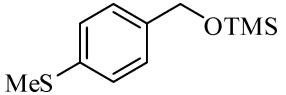
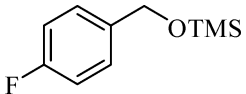
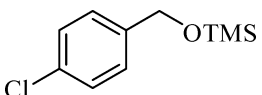
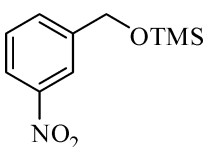
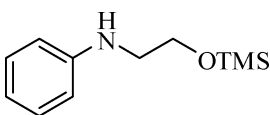
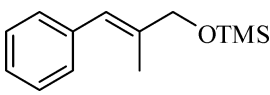
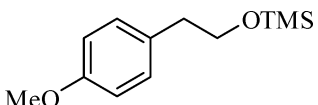
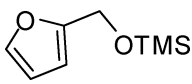
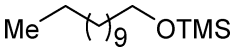
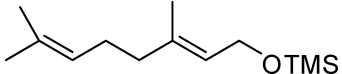
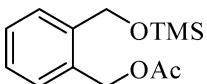
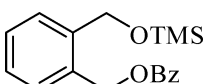
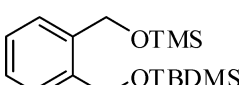
Entry	Products	Yield/% ^b
1		99
2		98
3		99
4		94
5		97
6		96
7		95
8		80 ^c
9		98
10		86 ^c

Table 2 (Contd.)

Entry	Products	Yield/% ^b
11		94
12		87 ^c
13		79 ^c
14		90
15		99
16		99
17		99

^a Reagents and conditions: alcohols (1 mmol), HMDS (1.0 mmol), CH₃NO₂ (1 mL) at rt with 10 min reaction time, unless otherwise mentioned. ^b Isolated yield. ^c 30 min reaction time.

excellent yields within 10 min of reaction time (entries 1–8). Only *m*-nitrobenzyl alcohol reacts rather slowly (30 min) with reduced yield (80%) (entry 8). This could be due to the electron-withdrawing power of the nitro substituent. Anilinoethanol gives the *o*-silylation product with excellent yield (entry 9). This method is also applicable to *trans*-2-methyl-3-phenyl-2-propen-1-ol with relatively lower yield (86%) and longer reaction time (30 min) (entry 10). Methoxyphenylethanol results in the silylation product with very good yield (entry 11). Silylation of heterocyclic furfuryl alcohol (entry 12) and aliphatic primary lauryl alcohol (entry 13) proceed efficiently with good yield in relatively longer reaction time (30 min). Acid-sensitive geraniol is able to produce the silylation product with considerably good yield (entry 14). This uncatalyzed protocol also tolerates presence of acetyl ester, benzoyl ester and TBDMS ether in order to produce excellent yields (entries 15–17).

The silylation reaction is extended to various secondary alcohols and phenols (Table 3). Benzhydrol and 4,4'-dichlorobenzhydrol react smoothly with HMDS, giving excellent yields (entries 1 and 2). Phenylethanol and *p*-tolylethanol deliver the corresponding silylated products with 84 and 99% yield, respectively (entries 3 and 4). *p*-Bromomethylbenzyl alcohol requires a slightly longer reaction time for the production of silylated product (entry 5). 1-Phenyl-1-propanol requires 10 min for the completion of reaction (entry 6).

Propargyl alcohol and secondary aliphatic alcohol undergo the silylation reaction smoothly with slightly lower yield within

Table 3 Silylation of secondary alcohols and phenols with HMDS in CH_3NO_2 .^a

Entry	Products	Time	Yield/% ^b
1		10 min	99
2		10 min	99
3		30 min	84
4		10 min	99
5		30 min	91
6		10 min	93
7		30 min	87
8		30 min	89
9		6 h	NR
10		30 min	80
11		15 min	95
12		15 min	84
13		15 min	92

Table 3 (Contd.)

Entry	Products	Time	Yield/% ^b
14		6 h	NR
15		6 h	NR

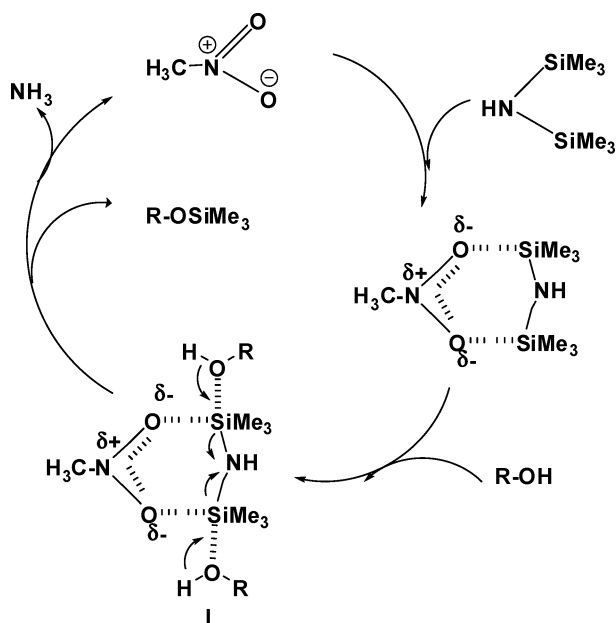
^a Reagents and conditions: alcohols or phenols (1 mmol), HMDS (1.0 mmol), CH_3NO_2 (1 mL) at rt. ^b Isolated yield.

30 min reaction time (entries 7 and 8). The present method is not applicable to tertiary alcohol, even after 6 h reaction time (entry 9). This may indicate that the steric effect is serious enough to prevent the reaction taking place. Interestingly, phenols also undergo the silylation to produce silyl ether in considerably high yields (entries 10–13). Unsubstituted phenol requires a longer reaction time (30 min) relative to electron-donating *p*- and *o*-methoxy and *p*-isopropyl phenol (15 min) (entries 11–13). However, *p*-nitro phenol fails to produce silylation product (entry 14). This result may indicate that the electron-withdrawing ability of the nitro group could reduce the electron density on the oxygen atom that prohibits the silylation. It is very interesting to note that *m*-nitrobenzyl alcohol (entry 8, Table 2) gives a pretty good yield, because no such conjugation could occur here. The reaction of benzyl amine did not produce the corresponding silyl ether, even after 6 h reaction time (entry 15). This may be due to the high affinity of silicon for oxygen atoms compared to the nitrogen of benzyl amine.³⁰ These data demonstrate that HMDS does not interact with amines under the present conditions.

A possible mechanism and the role of CH_3NO_2 are shown in Scheme 2. Several reports have indicated that the oxygen atom of heteroatom oxide can activate the silylating reagent through coordination with the silicon atom.²⁴ Alcohols react with the activated HMDS– CH_3NO_2 (I) complex to produce the O-silyl ether with the liberation of ammonia. The evolution of ammonia is confirmed by its strong and pungent odor and red litmus paper, which turns from red to blue. The cyanation of acetal in CH_3NO_2 as solvent demands high pressure and elevated temperature,²⁴ but the present silylation reaction involves quite mild reaction conditions.

Conclusion

A novel and efficient uncatalyzed method for the silylation of alcohols and phenols is developed. Alcohols (phenols) and HMDS react to give silylated products in CH_3NO_2 as solvent without the aid of a catalyst. The major advantages of the method are mild reaction conditions, easy work up and the absence of catalyst. This could be the most economically convenient method for the silylation of alcohol, compared to other reported catalytic methods. Under the non-metallic and catalyst-free conditions, the reaction becomes “environmentally friendly”.



Scheme 2 Plausible mechanism for the silylation of alcohols with HMDS in CH_3NO_2 .

Experimental section

General

In all cases, the ^1H NMR (400/200 MHz) spectra were recorded with a Varian Gemini 2000 spectrometer. Chemical shifts are reported in ppm in CDCl_3 with tetramethylsilane as an internal standard. ^{13}C NMR data were collected on a Varian Gemini 2000 spectrometer (50 MHz). GC-MS data were recorded with 1200 L Single Quadrupole GC/MS System with 3800GC/Varian.

General procedure for the silylation of alcohols or phenols

To a mixture of alcohol (phenol) (1 mmol) and CH_3NO_2 (1 mL), HMDS (1 mmol) was added at rt. The completion of the reaction was monitored with TLC. After the completion of the reaction, the reaction mixture was concentrated *in vacuo*. The viscous mass was subjected to silica gel flash column chromatography to obtain the pure compound.

^1H , ^{13}C NMR and GC-MS data for new products are given below (Table 2, entries 9, 15, 16, 17 and Table 3, entries 7 and 8). ^1H , ^{13}C NMR and HRMS data for known products are the same as literature values.^{10,13,26–29}

***N*-(2-Trimethylsilyloxy)ethyl)aniline (Table 2, entry 9).** δ_{H} (200 MHz; CDCl_3 ; Me_4Si): 0.00 (s, 9H), 3.09 (t, $J = 7.6$ Hz, 2H), 3.64 (t, $J = 7.6$ Hz, 2H), 3.88 (s, 1H), 6.48–6.61 (m, 3H), 7.00–7.08 (m, 2H). δ_{C} (50 MHz; CDCl_3 , Me_4Si): 0.5, 45.9, 61.0, 113.2, 117.5, 129.2, 148.3. GCMS: $m/z = 209$ [M^+].

2-((Trimethylsilyloxy)methyl)benzyl acetate (Table 2, entry 15). δ_{H} (400 MHz; CDCl_3 ; Me_4Si): 0.15 (s, 9H), 2.09 (s, 3H), 4.75 (s, 2H), 5.18 (s, 2H), 7.25–7.37 (m, 3H), 7.4 (d, $J = 6.8$ Hz, 1H). δ_{C} (CDCl_3 , 400 MHz): –0.4, 20.9, 62.3, 63.8, 127.5, 127.7, 128.47, 129.2, 133.3, 139.2. GCMS: $m/z = 252$ [M^+].

2-((Trimethylsilyloxy)methyl)benzyl benzoate (Table 2, entry 16). δ_{H} (400 MHz; CDCl_3 ; Me_4Si): 0.13 (s, 9H), 4.83 (s, 2H),

5.45 (s, 2H), 7.30–7.35 (m, 5H), 7.43–7.56 (m, 2H), 8.06–8.08 (m, 2H); δ_{C} (50 MHz; CDCl_3 , Me_4Si): –0.41, 62.49, 64.35, 127.57, 128.43, 128.53, 129.17, 129.71, 130.15, 133.07, 133.44, 139.33, 166.33. GCMS: $m/z = 314$ [M^+].

***tert*-Butyldimethyl(2((trimethylsilyloxy)methyl)benzyloxy)-silane (Table 2, entry 17).** δ_{H} (400 MHz; CDCl_3 ; Me_4Si): 0.13 (s, 9H), 0.92 (s, 9H), 4.70 (s, 2H), 4.75 (s, 2H), 7.22–7.24 (m, 2H), 7.36–7.42 (m, 2H); δ_{C} (50 MHz; CDCl_3 , Me_4Si): –5.25, –0.41, 18.40, 25.98, 62.35, 62.77, 126.64, 126.91, 127.03, 127.20, 137.78, 138.46. GCMS: $m/z = 324$ [M^+].

Trimethyl(4-phenylbut-3-yn-2-yloxy)silane (Table 3, entry 7). δ_{H} (200 MHz; CDCl_3 ; Me_4Si): 0.02 (s, 3H), 1.59 (d, $J = 8.2$ Hz, 3H), 4.84 (q, $J = 6.4$ Hz, 1H), 7.33–7.45 (m, 3H), 7.48–7.53 (m, 2H). δ_{C} (50 MHz; CDCl_3 , Me_4Si): 0.1, 25.4, 59.1, 83.6, 91.5, 123.0, 128.8, 128.3, 128.6, 131.7, 131.7. GCMS: $m/z = 218$ [M^+].

(Hexan-3-yloxy)trimethylsilane (Table 3, entry 8). δ_{H} (400 MHz; CDCl_3 ; Me_4Si): 0.14 (s, 9H), 0.79–0.94 (m, 6H), 1.25–1.51 (m, 8H), 3.52 (qt, $J = 12$ Hz, 1H). δ_{C} (50 MHz; CDCl_3 , Me_4Si): 0.34, 9.93, 13.99, 22.63, 25.35, 30.02, 31.99, 36.89, 73.88. GCMS: $m/z = 174$ [M^+].

Acknowledgements

The authors thank the Centre for Biological Modulators of the KRICT for financial support. Thanks are also due to BK 21 administrated by the Korea Research Council.

References

- (a) T. W. Green and P. G. M. Wuts, in *protective Groups in Organic Synthesis*, 3rd edn, John Wiley & Sons, New York, 1999, p150; (b) S. Otera, *Chem. Rev.*, 1993, **93**, 1449; (c) S. A. Fraklin, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2451.
- G. V. Look, G. Smchen and J. Heberle, *Silylation agents*, Fluka, Buchs, Switzerland, 1195.
- B. P. Bandgar, S. N. Chavare and S. S. Pandit, *J. Chin. Chem. Soc.*, 2005, **52**, 125.
- B. E. Cooper, *Chem. Ind.*, 1978, **107**, 794.
- T. Morita, Y. Okamoto and H. Sakurai, *Tetrahedron Lett.*, 1980, **21**, 835.
- C. A. Bruynes and T. K. Jurriens, *J. Org. Chem.*, 1982, **47**, 3966.
- D. Zareyeea and B. Karimi, *Tetrahedron Lett.*, 2007, **48**, 1277.
- A. Khazaei, M. A. Zolfigol, A. Rostami and A. G. Choghamarani, *Catal. Commun.*, 2007, **8**, 543.
- J. S. Yadav, B. V. S. Reddy, A. K. Basak, G. Baishya and A. V. Narsaiah, *Synthesis*, 2006, 3831.
- M. Moghadam, S. Tangestaninejad, V. Mirkhani, I. Mohammadpoor-Baltork, S. Chahardahcheric and Z. Tavakoli, *J. Organomet. Chem.*, 2008, **693**, 2041.
- Z. H. Zang, T. S. Li, F. Yang and C. G. Fu, *Synth. Commun.*, 1998, **28**, 3105.
- V. H. Tillu, V. H. Jadhav, H. B. Borate and R. D. Wakharkar, *Arkivoc*, 2004, 83.
- H. R. Shaterian, F. Shahrekipoor and M. Ghashang, *J. Mol. Catal. A: Chem.*, 2007, **272**, 142 and references cited therein.
- K. Khazaei, M. A. Zolfigol, Z. Tanbakouchian, M. Shiri, K. Niknam and J. Saïen, *Catal. Commun.*, 2007, **8**, 917.
- B. Karimi and B. Golshani, *J. Org. Chem.*, 2000, **65**, 7228.
- M. M. Mojtahedi, H. Abbasi and M. S. Abaee, *J. Mol. Catal. A: Chem.*, 2006, **250**, 6.
- H. R. Shaterian, R. Doostmohammadi and M. Ghashang, *Chin. J. Chem.*, 2008, **26**, 1709.
- H. Firouzabadi, N. Iranpoor, A. A. Jafari and M. R. Jafari, *J. Organomet. Chem.*, 2008, **693**, 2711.
- P. Anastas and J. C. Warner, in *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998.

- 20 T. Watahiki, S. Ohba and T. Oriyama, *Org. Lett.*, 2003, **5**, 2679.
- 21 F. L. Cabirol, A. E. C. Lim, U. Hanefeld, R. A. Sheldon and I. M. Lyapkalo, *J. Org. Chem.*, 2008, **73**, 2446.
- 22 T. Watahiki, M. Matsuzaki and T. Oriyama, *Green Chem.*, 2003, **5**, 82.
- 23 T. Watahiki, Y. Hinakubo and T. Oriyama, *Tetrahedron Lett.*, 2005, **46**, 5881.
- 24 K. Kumamoto, K. Nakano, Y. Ichikawa and H. Kotsuki, *Synlett*, 2006, **12**, 1968 and references cited therein.
- 25 A. V. Narsaiah, *J. Organomet. Chem.*, 2007, **692**, 3614.
- 26 M. R. Saidi and N. Azizi, *Organometallics*, 2004, **23**, 1457.
- 27 S. T. Kadam and S. S. Kim, *J. Organomet. Chem.*, 2009, **694**, 2562.
- 28 G. Rajagopal, Hanbin Lee and S. S. Kim, *Tetrahedron*, 2009, **65**, 4735.
- 29 J. M. Midgley, S. J. Millership and B. W. Whalley, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1384.
- 30 (a) H. Vorbruggen and K. Krolukiewicz, *Justus Liebigs Ann. Chem.*, 1976, 746; (b) H. Vorbruggen, K. Krolukiewicz and U. Niedballa, *Justus Liebigs Ann. Chem.*, 1975, 988; (c) M. J. Cook, A. R. Katritzky and P. Linda, *Adv. Heterocycl. Chem.*, 1974, **17**, 255; (d) R. A. Singer and M. Dore, *Org. Process Res. Dev.*, 2008, **12**, 1261.