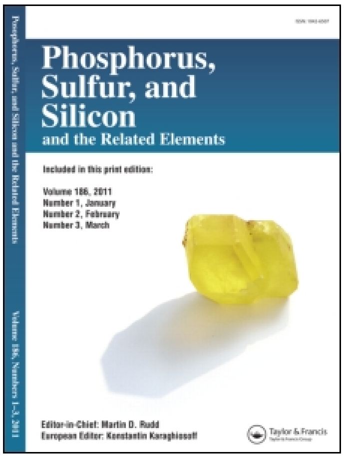


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

p-Toluenesulfonyl Chloride (*p*-TsCl)-Catalyzed Trimethylsilylation of Hydroxyl Groups Using Hexamethyldisilazane and Their Regeneration Under Mild Conditions: The First Example for Catalytic Application of *p*-Toluenesulfonyl Chloride

Ardeshir Khazaei[a]; Amin Rostami[b]; Fatemeh Mantashlo[a]
[a] Faculty of Chemistry, Bu-Ali Sina University, Hamadan, Iran [b] Department of Chemistry, Faculty of Science, University of Kurdistan, Sanandaj, Iran

To cite this Article Khazaei, Ardeshir , Rostami, Amin and Mantashlo, Fatemeh(2009) '*p*-Toluenesulfonyl Chloride (*p*-TsCl)-Catalyzed Trimethylsilylation of Hydroxyl Groups Using Hexamethyldisilazane and Their Regeneration Under Mild Conditions: The First Example for Catalytic Application of *p*-Toluenesulfonyl Chloride', Phosphorus, Sulfur, and Silicon and the Related Elements, 184: 9, 2288 — 2296

To link to this Article: DOI: 10.1080/10426500802453872

URL: http://dx.doi.org/10.1080/10426500802453872

Phosphorus, Sulfur, and Silicon, 184:2288–2296, 2009
Copyright © Taylor & Francis Group, LLC
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802453872

p-Toluenesulfonyl Chloride (*p*-TsCl)-Catalyzed Trimethylsilylation of Hydroxyl Groups Using Hexamethyldisilazane and Their Regeneration Under Mild Conditions: The First Example for Catalytic Application of *p*-Toluenesulfonyl Chloride

Ardeshir Khazaei,[1] Amin Rostami,[2]
and Fatemeh Mantashlo[1]
[1]Faculty of Chemistry, Bu-Ali Sina University, Hamadan, Iran
[2]Department of Chemistry, Faculty of Science, University of Kurdistan, Sanandaj, Iran

The first catalytic application of p-toluenesulfonyl chloride (p-TsCl) for the efficient and selective trimethylsilylation of various types of hydroxyl groups with hexamethyldisilazane (HMDS) in dichloromethane and desilylation of these compounds in water is reported. The reactions were carried out at room temperature and were found to proceed in good to excellent yields.

Keywords Hexamethyldisilazane; hydroxyl group; *p*-toluenesulfonyl chloride; trimethylsilylation

INTRODUCTION

The protection–deprotection sequence is one of the most frequently encountered functional-group transformations in organic synthesis.[1] In particular, the sequence for hydroxyl groups is extremely important because of enormous demands for natural product synthesis and for pharmaceutical agents. The use of a silyl ether function as a protecting group of the hydroxy functionality is well documented in organic synthesis.[2] Several methods have become available for silylation of hydroxy functional groups using a variety of silylating agents, such as trimethylsilyl chloride in the presence of a base,[3] Li_2S,[4] or Mg,[5] ketene methyltrialkylsilyl acetals,[6] allyl silanes,[7] ethyl trimethylsilyl acetate,[8]*N*,

Received 15 August 2008; accepted 5 September 2008.

The authors acknowledge the Bu-Ali Sina University and Kurdistan University Research Councils for partial support of this work.

Address correspondence to Ardeshir Khazaei, Faculty of Chemistry, Bu-Ali Sina University, Hamadan, 65178-38683, Iran. E-mail: khazaei_1326@yahoo.com

N-bis(trimethylsilylurea),[9] methyl 3-(trimethylsilyloxy)crotonate,[10] trimethylsilyl azide,[11] *N*-trimethylsilyl-2-oxazolidinone,[12] *N*, *O*-bis(trimethylsilyl)acetamide,[13] and hexamethyldisilane.[14] However, some of these silylating agents suffer from drawbacks such as lack of reactivity or difficulty in removal of byproducts of the silylation reaction.

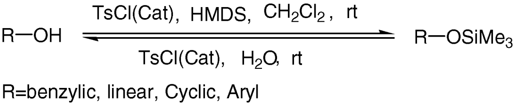
1,1,1,3,3,3-Hexamethyldisilazane (HMDS), one of the most common silylating agents, readily silylates alcohols, acids, amines, thiols, phenols, amides, thioamides, sulfonamides, enolizable ketones, etc. The byproduct of this reaction is ammonia, which is readily removed from the reaction medium. However, the low silylation power of HMDS is the main drawback to its use,[15] and thus various catalysts for the activation of this reagent have been reported.[16–21] Although these methods produce good results in many instances, few of these catalysts can perform both protection and deprotection of hydroxyl groups as trimethylsilyl ethers do. Therefore, there is still a demand to develop new mild methods for the trimethylsilylation of hydroxyl compounds and their regeneration in the presence of inexpensive, selective, and bench-top catalysts.

Similar to protection, deprotection of the trimethylsilyl ethers constitutes an important process in the synthetic chemistry of polyfunctional molecules including the total synthesis of natural products. Although several methods have been reported for the deprotection of trimethylsilyl ethers,[22–26] the development of a mild, efficient, and ecofriendly method for the deprotection of trimethylsilyl ethers continues to be desirable.

RESULTS AND DISCUSSION

p-Toluenesulfonyl chloride is a cheap, commercially available reagent that has been widely used as a sulfonyl transfer reagent[27] and as an initiator in a wide range of polymerization reactions,[28] but there is only one report of its use as a chlorinating agent for α-chlorination of ketones.[29] However, to the best of our knowledge, there is no report on the catalytic application of *p*-toluenesulfonyl chloride in organic transformations.

In a result of our investigations on preparation and catalytic applications of *N*-halogen compounds (as source of positive halogen) in organic synthesis,[30–34] herein for the first time we disclose the use of a catalytic amount of *p*-toluenesulfonyl chloride as a source of "Cl^+" for efficient O-trimethylsilylation of a wide variety of hydroxyl groups (alcohols and phenols) using readily available HMDS and the desilylation of the corresponding TMS ethers in water (Scheme 1).



SCHEME 1

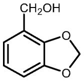
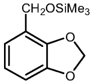
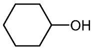
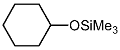
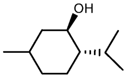
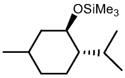
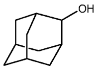
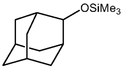
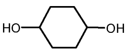
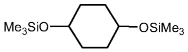
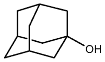
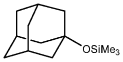
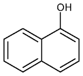
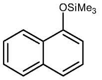
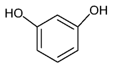
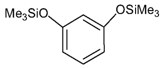
We first examined the effect of different ratios of ROH:HMDS: catalyst. The 1.0:0.7:0.06 ratio hydroxyl groups gave the best results and produced trimethylsilyl ethers in quantitative yields. The results of the reactions of a diverse range of hydroxyl compounds are collected in Table I.

The reported data show that *p*-TsCl can affect the O-trimethylsilylation of primary, secondary, and tertiary alcohols in good to excellent yields. Primary benzylic alcohols with electron-donating and electron-withdrawing groups were terimethylsilylated in the presence of 0.03–0.06 mmol of catalyst, and the corresponding trimethylsilyl ethers were obtained in good to excellent yields (Table I, Entries 1–6). Benzhydrol and 1-phenylethanol as two model compounds for secondary benzylic alcohols were satisfactorily subjected to trimethylsilylation as well (Table I, Entries 9,7). Trimethylsilylation of linear and cyclic saturated primary and secondary alcohols was achieved in the presence of a catalyst (0.1–0.2 mmol) at room temperature (Table I, Entries 7–8 and 11–15). Interestingly, 1-adamantanol as a model for the hindered tertiary alcohols was converted to the corresponding trimethylsilyl ethers (Table I, Entry 16). These results indicate that primary and secondary hydroxyl groups react faster than the tertiary ones. The reaction conditions are mild and are not sufficiently acidic to cause side reactions.

To explore the generality and scope of the reaction, 2-naphthol and resorcinol as two model compounds for phenols were subjected to trimethylsilylation catalyzed by *p*-TsCl in good yields (Table I, Entries 17–18).

As shown in Table I, the amounts of HMDS and catalyst depend on the nature of the alcohol used as substrate. Therefore, we explored the ability of this method to discriminate between different kinds of hydroxyl groups (primary, secondary, and tertiary). In a binary mixture of 2,4-dichlorobenzyl alcohol (as a model for primary alcohol) and 1-phenylethanol (as a model for secondary alcohol), the primary alcohol was completely converted to the corresponding trimethylsilyl ether,

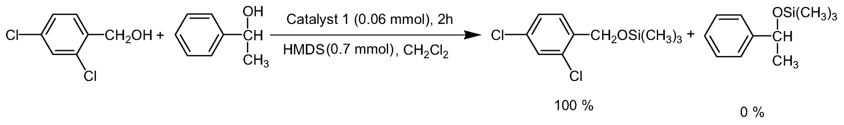
TABLE I Trimethylsilylation of the Alcohols or Phenols Using HMDS Catalyzed with *p*-TsCl in CH_2Cl_2 at Room Temperature

Entry	Substrate	HMDS: Cat (mmol)	Time (min)	Product	Yields[a] (%)
1	4-OMe-$C_6H_4CH_2OH$	0.7:0.03	7	4-OMe-$C_6H_4CH_2OSiMe_3$	81
2	4-Cl-$C_6H_4CH_2OH$	0.7:0.06	9	4-Cl-$C_6H_4CH_2OSiMe_3$	97
3	2,4-$(Cl)_2C_6H_3CH_2OH$	0.7:0.06	12	2,4-$(Cl)C_6H_3CH_2OSiMe_3$	95
4	4-F-$C_6H_4CH_2OH$	0.7:0.06	20	4-F-$C_6H_4CH_2OSiMe_3$	96
5	4-NO_2-$C_6H_4CH_2OH$	0.7:0.06	20	4-NO_2-$C_6H_4CH_2OSiMe_3$	92
6		0.1: 0.7	11		75
7	$PhCH_2CH_2OH$	0.7:0.1	8	$PhCH_2CH_2OSiMe_3$	83
8	$CH_3(CH_2)_{14}CH_2OH$	0.7:0.1	9	$CH_3(CH_2)_{14}CH_2OSiMe_3$	78
9	$PhCH(OH)CH_3$	0.7:0.1	17	$PhCH(OSiMe_3)CH_3$	95
10	$PhCH(OH)Ph$	0.7:0.1	17	$PhCH(OSiMe_3)Ph$	80
11		0.7:0.1	14		91
12		0.7:0.1	30		86
13		0.7:0.2	150		82
14	$CH_3(CH_2)_4CH(OH)CH_3$	0.7:0.1	10	$CH_3(CH_2)_4CH(OSiMe_3)CH_3$	73
15		1.4:0.2	30		85
16		0.7:0.2	h17		78
17		0.06: 0.7	16		90
18		1.4:0.12	19		83

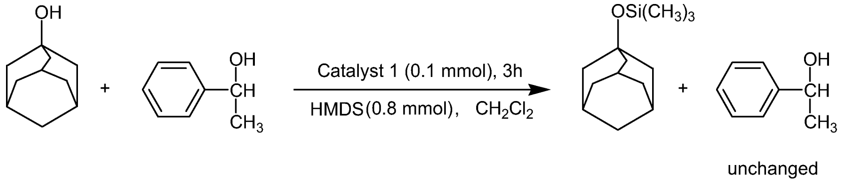
[a] All products were characterized by comparison of their spectral data (^1H-NMR, IR) with those of authentic samples.

while 0% conversion was observed for the secondary alcohol (Scheme 2).

Excellent selectivity was also observed for 1-phenylethanol in the presence of 1-adamantanol (as a model for tertiary alcohol). The only observed product was 1-phenylethyl trimethylsilyl ether in 100% conversion (Scheme 3).



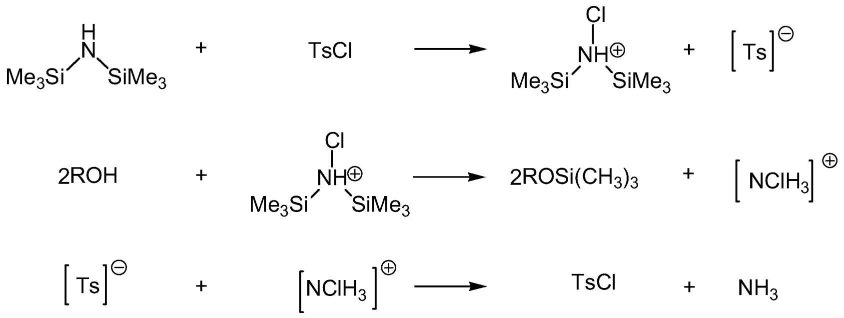
SCHEME 2



SCHEME 3

Organic reactions in water have received much attention because water is a cheap, safe, and environmentally benign solvent.[35] However, we investigated the possibility of deprotection of trimethylsilyl ethers using *p*-TsCl as catalyst in water. It was found that the TMS group could be removed efficiently in the presence catalytic amount of *p*-TsCl in water at room temperature in good to excellent yields. Various types of structurally diverse TMS ethers were deprotected using this procedure, and the results are summarized in Table II.

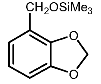
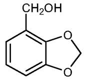
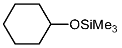
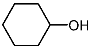
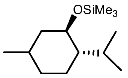
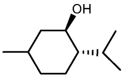
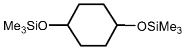
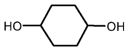
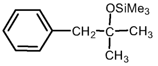
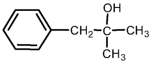
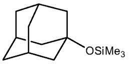
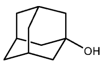
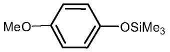
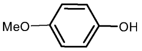
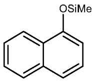
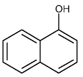
The actual role of *p*-toluenesulfonyl chloride is not clear. On the basis of the previously reported mechanisms for applying of *p*-TsCl for α -chlorination of ketones,[29] one explanation for these processes is that *p*-TsCl might act as a source for the formation of Cl^+ , which polarizes the Si–N bond in HMDS to produce the reactive silylating agent (as a Lewis acid). Therefore the mechanism shown in Scheme 4 is proposed.



SCHEME 4

However, at this time we have obtained no experimental evidence for these two features of *p*-TsCl, and the actual role of this reagent should

TABLE II Deprotection of Trimethylsilyl Ethers in the Presence of a Catalytic Amount of *p*-TsCl (0.07 mmol) in Water (3 mL) at Room Temperature

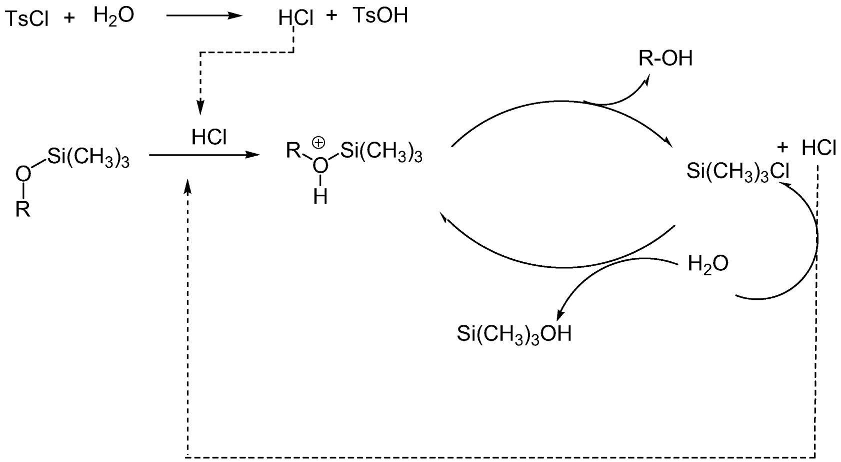
Entry	Substrate	Time(min)	Product	Yields[a](%)
1	4-MeO-$C_6H_4CH_2OSiMe_3$	Immediate	4-MeO-$C_6H_4CH_2OH$	85
2	4-Cl-$C_6H_4CH_2OSiMe_3$	Immediate	4-Cl-$C_6H_4CH_2OH$	90
3		20		86
4	$CH_3(CH_2)_{14}CH_2OSiMe_3$	12	$CH_3(CH_2)_{14}CH_2OH$	83
5	$PhCH_2CH_2OSiMe_3$	Immediate	$PhCH_2CH_2OH$	87
6		6		95
7		10		80
8	$CH_3(CH_2)_4CH(OSiMe_3)CH_3$	5	$CH_3(CH_2)_4CH(OH)CH_3$	91
9		5		95
10		25		60
11		22		72
12		Immediate		78
13		9		73

[a] All products were characterized by comparison of their spectral data (^{1}H-NMR, IR) with those of authentic samples.

be further studied in detail. We also suggest the mechanisms shown in Scheme 5 for desilylation of trimethylsilyl ethers using *p*-TsCl in water.

CONCLUSION

In summary, in this article the first catalytic application of *p*-TsCl for protection of a variety of hydroxyl groups as TMS ethers using HMDS and deportation of them under very mild conditions has been shown. The main advantages of our protocol are fast reaction, selectivity, inexpensive reagent, easy work-up conditions, mild conditions, and good to high yields. Therefore this procedure could be utilized in transformations that need mild reaction conditions. Further research on catalytic



SCHEME 5

applications of *P*-TsCl for other functional group transformations is currently ongoing.

EXPERIMENTAL

General Procedure for Trimethylsilylation of Alcohols and Phenols Using HMDS Catalyzed with *p*-TsCl in CH_2Cl_2

Alcohols or phenols (1 mmol) were added to a mixture of HMDS (0.7 mmol) and *p*-TsCl (0.06 mmol) in CH_2Cl_2 (5 mL), and then the mixture was stirred at room temperature for the specified time (Table I). The progress was monitored by TLC. After completion of the reaction, 2.5% aqueous NaOH (10 mL) was added, then the trimethylsilyl ethers were extracted with CH_2Cl_2 (3 × 10 mL), and the organic layer was dried over anhydrous Na_2SO_4. CH_2Cl_2 was removed under reduced pressure, and the product was purified through a short column of silica gel to obtain pure trimethylsilyl ethers.

General Procedure for Deprotection of Trimethylsilyl Ethers Catalyzed with *p*-TsCl

p-TsCl (0.08 mmol) was added to a mixture of TMS ethers (1 mmol) in H_2O (3 mL), then the mixture was stirred at room temperature for the specified time (Table II). The progress of the reaction was monitored by TLC. After completion of the reaction, the alcohols or phenols were extracted with CH_2Cl_2 (3 × 10 mL), and the organic layer was dried over anhydrous Na_2SO_4. Dichloromethane was removed under reduced pressure, and the product was purified through a short column of silica gel to obtain pure alcohol or phenol.

REFERENCES

[1] T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed. (John Wiley, New York, 1999).

[2] K. Jarowicki and P. Kocienski, *J. Chem. Soc. Perkin. Trans.***1,** 2109 (2001).

[3] R. G. Visser, H. J. T. Boos, and L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, **99,** 70 (1980).

[4] G. A. Olah, G. B. Gupta, S. Snaring, and R. Malhotra, *J. Org. Chem.*, **44,** 4272 (1979).

[5] I. Nishiguchi, Y. Kita, M. Watanabe, Y. Ishino, T. Ohno, and H. Maekawa, *Synlett*, 1025 (2000).

[6] Y. Kita, J. Haruta, J. Segawa, and Y. Tamura, *Tetrahedron Lett.*, **20,** 4311 (1979).

[7] G. A. Olah, A. Husain, B. G. B. Gupta, G. F. Salem, and S. C. Narang, *J. Org. Chem.*, **46,** 5212 (1981).

[8] E. Nakamura, K. Hashimoto, and I. Kuwajima, *Bull. Chem. Soc. Jpn.*, **54,** 805 (1981).

[9] W. Verboom, G. W. Visser, and D. N. Reinhoudt, *Synthesis*, 807 (1981).

[10] T. Veysoglu and L. A. Mitscher, *Tetrahedron Lett.*, **22,** 1303 (1981).

[11] D. Amantini, F. Fringuelli, F. Pizzo, and L. Vaccaro*, J. Org. Chem.*, **66,** 6734 (2001).

[12] J. M. Aizpurua and C. Palomo, *Bull. Soc. Chim. Fr Mem II*, 265 (1982).

[13] Y. Tanabe, M. Murakami, K. Kitaichi, and Y. Yoshida, *Tetrahedron Lett.*, **45,** 8409 (1994).

[14] E. Hirakawa, K. Hironaka, H. Otsuka, and T. Hayashi, *Chem. Commun.*, 3927 (2006).

[15] C. A. Bruynes and T. K. Jurriens, *J. Org. Chem.*, **47,** 3966 (1982).

[16] D. Zareyee and B. Karimi, *Tetrahedron Lett.*, **48,** 1277 (2007).

[17] F. Shirini, M. A. Zolfigol, and M. Abedini, *Bull. Chem. Soc. Jpn.*, **78,** 1982 (2005).

[18] J. S. Yadav, B. V. S. Reddy, A. K. Basak, G. Baishya, and A. V. Narsaiah, *Synthesis*, 3831 (2006).

[19] R. Ghorbani-Vaghei, M. A. Zolfigol, M. Chegeny, and H. Veisi, *Tetrahedron Lett.*, **47,** 4505 (2006).

[20] H. Firouzabadi, N. Iranpoor, S. Sobhani, and S. Ghassamipour, *Synthesis*, 295 (2005).

[21] B. Akhlaghinia and S. Tavakoli, *Synthesis*, 1775 (2005).

[22] A. Vakalopoulos and H. M. R. Hoffmann, *Org. Lett.*, **2,** 1447 (2000).

[23] Z. Yu and J. G. Vercade, *J. Org. Chem.*, **65,** 2065 (2000).

[24] M. H. Habibi, S. Tangestaninejad, I. Mohammadpoor-baltork, V. Mirkhani, and B. Yadollahi, *Tetrahedron Lett.*, **42,** 6771 (2001).

[25] Y. G. Wang, X. X. Wu, and Z. Y. Jiang, *Tetrahedron Lett.*, **45,** 2973 (2004).

[26] R. D. Crouch and A. Williams, *Synth. Commun.*, **36,** 959 (2006).

[27] A. Khalafi-Nezhad, A. Parhami, M. V. Soltani-Rad, and A. Zarea, *Tetrahedron Lett.*, **46**, 6879 (2005) and references therein.

[28] S. Mallakpour and E. Kowsari, *J. Appl. Polym. Sci.*, **101,** 455 (2006) and references therein.

[29] K. M. Brummond and K. D. Gesenberg, *Tetrahedron Lett.*, **40,** 2231 (1999).

[30] A. Khazaei, A. Rostami, Z. Tanbakouchian, and Z. Zinati, *J. Braz. Chem. Soc.*, **17,** 206 (2006).

[31] A. Khazaei, M. A. Zolfigol, A. Rostami, and A. Ghorbani-Choghamarani, *Catal. Commun.*, **8,** 543 (2007).

[32] A. Khazaei, A. Rostami, S. Rahmati, and M. Mahboubifar, *Phosphorus, Sulfur, and Silicon*, **182,** 537 (2007).

[33] A. Khazaei, A. Rostami, and M. Mahboubifar, *Catal. Commun.*, **8,** 383 (2007).

[34] A. Khazaei, A. Rostami, A. Raiatzadeh, and M. Mahboubifar, *Can. J. Chem.*, **85,** 336 (2007).

[35] P. A. Grieco, *Organic Synthesis in Water* (Blackie Academic Professional, London, 1998).