

Rapid and highly efficient trimethylsilylation of alcohols and phenols with hexamethyldisilazane (HMDS) catalysed by *in situ* generated I₂ using Oxone[®]/KI or cerium ammonium nitrate (CAN)/KI systems under mild conditions

ESKANDAR KOLVARI^{a,*}, ARDESHIR KHAZAEI^{b,*}, MOHAMMAD ALI ZOLFIGOL^{b,*}, NADIYA KOUKABI^b, MARYAM GILANDOUST^b and NEDA BAKHIT^b

^aDepartment of Chemistry, Faculty of Science, Semnan University, Semnan, Iran

^bFaculty of Chemistry, Bu-Ali Sina University, Hamedan, Post Box No. 4135, Iran

e-mail: kolvari@semnan.ac.ir; khazaei_1326@yahoo.com; zolfi@basu.ac.ir

MS received 9 February 2010; revised 31 January 2011; accepted 24 June 2011

Abstract. Structurally diverse alcohols and phenols were trimethylsilylated in clean and efficient reactions with hexamethyldisilazane (HMDS) in the presence of a catalytic amount of I₂ generated *in situ* from Oxone[®]/KI or CAN/KI systems. The reactions occur rapidly in good to high yields in wet CH₂Cl₂ at room temperature.

Keywords. Alcohols; phenols; hexamethyldisilazane; Oxone[®]/KI; CAN/KI; *in situ* generated I₂; trimethylsilylation.

1. Introduction

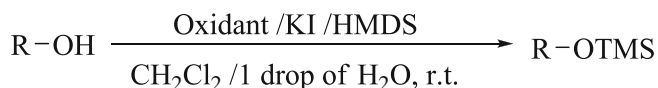
Protection of hydroxy group is a common practice in organic chemistry. Among the protective groups, silyl ethers are extensively utilized in analytical and in preparative organic synthesis.^{1,2} Several methods are available for the silylation of alcohols using a variety of silylating agents.² The use of some silylating agents is limited by their unavailability or the laborious processes of purifying the products. 1,1,1,3,3,3-Hexamethyldisilazane (HMDS) is a stable, inexpensive, and commercially available reagent that can be used for the preparation of trimethylsilyl ethers (TMS ethers) from hydroxy compounds, giving ammonia as the only by-product.^{3,4} Even though the handling of this reagent is easy, its main drawback is its poor silylating ability. Also forceful conditions and long reaction times are required.⁵ Therefore, for the activation of HMDS a variety of catalysts such as Envirocat EPZG[®];⁶ montmorillonite clay;⁷ zirconium sulfophenyl phosphonate;⁸ molecular iodine;⁹ tungstophosphoric acid (H₃PW₁₂O₄₀);¹⁰ lithium perchlorate;¹¹ aluminum triflate;¹² cupric sulfate pentahydrate;¹³ *N*-bromo sulfo-

anamides;¹⁴ sulfamic acid;¹⁵ have been reported. Although these catalysts provide an improvement, usually low selectivity, forceful conditions, and long reaction times have been observed in some of these reports.

Recently, the highly efficient method for trimethylsilylation of alcohols (not phenols) using HMDS catalysed by molecular iodine in CH₂Cl₂ has been reported.⁹ Although molecular iodine is a versatile reagent in organic synthesis,¹⁶ it is highly corrosive, toxic, and sublimable, making its use somewhat unattractive. In order to overcome these disadvantages with molecular iodine, Bailey *et al.* reported a convenient method for *in situ* generation of I₂ using CuSO₄/NaI.¹⁷

Solid acids have many advantages such as simplicity in handling, decreased reactor and plant corrosion problems, and more environmentally safe disposal.^{18–20} Among solid acids, ceric ammonium nitrate, Ce(NH₄)₂(NO₃)₆, (CAN), and Oxone[®] [2KHSO₅·KHSO₄·K₂SO₄] are two commercially available inorganic oxidizing agents. There are several reports in the literature which demonstrate that CAN and Oxone[®] are efficient reagents in organic reactions.^{21–23}

*For correspondence



Oxidant: CAN or Oxone®
R = Aliphatic, aromatic, benzylic

Scheme 1.

2. Experimental

2.1 General

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. Yields refer to isolated pure products. The products were characterized by comparison of their spectral (IR, ¹H-NMR) and physical data with authentic samples.

2.2 Typical procedure for trimethylsilylation of alcohols and phenols

The alcohol or phenol (1 mmol) was added to a mixture of CAN or Oxone® (0.2 mmol) and KI (0.2 mmol) in CH₂Cl₂ (1 mL) and 0.05 mL of H₂O. Then HMDS (1 mmol in 1 mL CH₂Cl₂) was added drop-wise to this mixture within 5 min. The mixture was stirred vigorously at room temperature for the specified time (tables 4, 5). After completion of the reaction (TLC),

Table 1. Comparison between various oxidizing agents/KI systems for the trimethylsilylation of benzyl alcohol.^a

Entry	Oxidant	Time (h)	Yield (%) ^b
1	Na ₂ S ₂ O ₈	2	-
2	K ₂ S ₂ O ₈	2	-
3	Sodium perborate	3	-
4	(NH ₄) ₂ S ₂ O ₈	1	-
5	Oxone®	immediate ^c	100
6	Oxone®	6 ^d	100
7	UHP ^e	2	-
8	DABCO-DNODP ^f	2	-
9	PVP-H ₂ O ₂ ^g	2	-
10	Sodium percarbonate	3	-
11	CAN	immediate ^c	100
12	CAN	1 ^b	100

^aReaction condition: Benzyl alcohol (1.0 mmol); oxidant (0.2 mmol); KI (0.2 mmol); 1 mL moistened CH₂Cl₂; ^bGC yield; ^cThe completion of the reaction was confirmed by TLC and GC; ^dWithout KI; ^eUrea Hydrogen Peroxide (UHP); ^f1,4-Diazabicyclo[2.2.2]octane 1,4-bis(oxide)-bis(hydrogen peroxide) (DABCO-DNODP); ^gPolyvinylpyrrolidone- H₂O₂ (PVP-H₂O₂)

Table 2. Comparison of various types of MX for the trimethylsilylation of benzyl alcohol.^a

Entry	Oxidizer acid	MX	Time (h)	Yield (%) ^b
1	Oxone®	KI	immediate ^b	100
2	Oxone®	KI ^c	1	-
3	Oxone®	KCl	1	-
4	Oxone®	KBr ^c	1	58
5	CAN	KI	immediate	100
6	CAN	KI ^d	1	-
7	CAN	KCl	1	-
8	CAN	KBr ^c	1	60

^a Reaction condition: Benzyl alcohol (1.0 mmol); oxidant (0.2 mmol); MX (0.2 mmol); 1 mL moistened CH₂Cl₂. ^bThe completion of the reaction was confirmed by TLC and GC. ^cGC yield. ^d Solvent-free

the mixture was filtered and the solids were washed with CH₂Cl₂ (5 mL). Powdered Na₂S₂O₃ (2 g) was added to the reaction mixture, then the mixture was stirred for additional 5 min, and the resulting mixture was filtered. Finally, H₂O (10 mL) was added to destroy the extra amount of HMDS, the organic layer was separated and the filtrate was dried (Na₂SO₄). Evaporation of the solvent under reduced pressure gave almost pure product.

3. Results and discussion

In continuation of our studies using CAN²⁴ and Oxone®²⁵⁻²⁷ in organic transformations, we have been interested in finding out a catalytic system for trimethylsilylation of alcohols and phenols. In this

Table 3. Comparison of various solvents for the trimethylsilylation of benzyl alcohol using I₂ generated *in situ* from Oxone® (0.2 mmol) in the presence of a catalytic amount of KI (0.2 mmol).

Entry	Solvent	The amount of solvent (ml)	Time (h)	Yield (%) ^a
1	CH ₃ CN	2	2	60
2	CH ₃ CN/H ₂ O	2/0.05	2	75
3	CH ₂ Cl ₂	2	2	-
4	CH ₂ Cl ₂ /H ₂ O	5/0.05	2	80
5	CH ₂ Cl ₂ /H ₂ O	2/0.05	immediate ^b	100
6	THF/H ₂ O	2/0.05	2	60
7	CHCl ₃ /H ₂ O	2/0.05	2	85
8	<i>n</i> -Hexane	2	2	-

^aGC yield. ^bThe completion of the reaction was confirmed by TLC and GC

Table 4. Trimethylsilylation of alcohols (1 mmol) using HMDS (1 mmol) catalysed with I_2 generated *in situ* from Oxone[®] (**I**) (0.2 mmol) or CAN (**II**) (0.2 mmol) in the presence of a catalytic amount of KI (0.2) in dichloromethane and 0.05 mL of H_2O at room temperature.

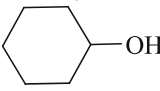
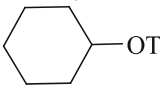
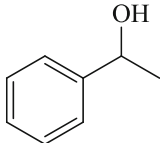
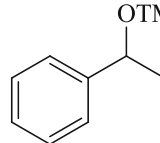
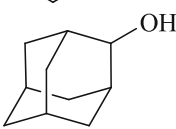
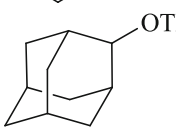
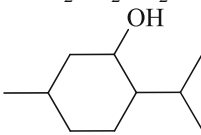
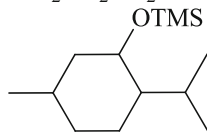
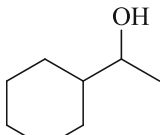
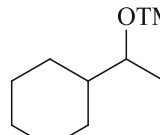
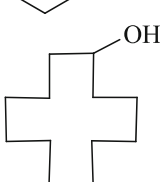
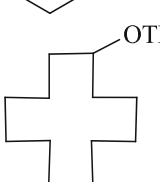
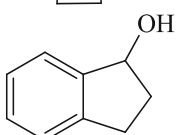
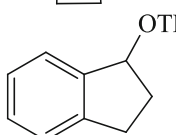
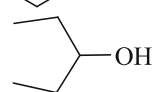
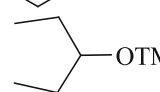
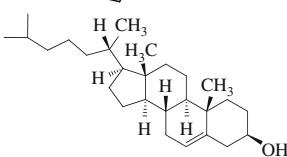
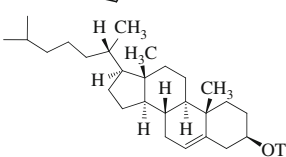
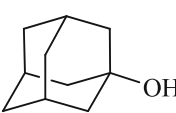
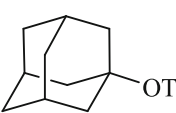
Entry	Substrate	Time (min)		Product ^a		Yield (%) ^b	
		I	II			I	II
1	<chem>PhCH2OH</chem>	immediate ^c	immediate ^c	<chem>PhCH2OTMS</chem>	28	92	90
2	<chem>4-MeO-C6H4CH2OH</chem>	immediate	immediate	<chem>4-MeO-C6H4CH2OTMS</chem>	28	94	95
3		immediate	immediate		28	87	90
4		immediate	immediate		28	83	82
5		11	9		28	93	95
6	<chem>4-Cl-C6H4CH2OH</chem>	immediate	immediate	<chem>4-Cl-C6H4CH2OTMS</chem>	29	95	95
7	<chem>PhCH(OH)Ph</chem>	immediate	immediate	<chem>PhCH(OTMS)Ph</chem>	29	90	93
8	<chem>CH3(CH2)6CH2OH</chem>	immediate	immediate	<chem>CH3(CH2)6CH2OTMS</chem>	29	92	91
9	<chem>2,4-(Cl)2C6H4CH2OH</chem>	immediate	immediate	<chem>2,4-(Cl)2C6H4CH2OTMS</chem>	30	94	96
10	<chem>PhCH2CH2OH</chem>	immediate	immediate	<chem>PhCH2CH2OTMS</chem>	31	92	93
11	<chem>PhCH2CH2CH2OH</chem>	immediate	immediate	<chem>PhCH2CH2CH2OTMS</chem>	31	90	90
12		immediate	immediate		31	95	97
13		immediate	immediate		32	85	87
14		20	15		33	93	93
15		30	25		33	90	92
16		immediate	immediate		33	97	99
17		immediate	2		34	97	97
18		10	15		35	90	92

Table 4. (continued)

Entry	Substrate	Time (min)		Product ^a		Yield (%) ^b	
		I	II			I	II
19		30	45		36	83	85
20		40	35		36	87	90

^aAll products were characterized by comparison of their spectral data (¹H-NMR; IR) and with those of authentic samples.

^bIsolated yield. ^cThe completion of the reactions were confirmed by TLC and GC

context, we have found that a combination of CAN or Oxone[®] and a catalytic amount of KI in the presence of HMDS generate *in situ* I₂ as an efficient catalyst for the trimethylsilylation of alcohols and phenols (scheme 1).

To find the best system for *in situ* generation of I₂, first we studied a number of oxidizing agents in combination of KI for the trimethylsilylation of alcohols and phenols. As it can be seen in table 1, the best results are obtained from CAN/KI and Oxone[®]/KI systems.

Table 5. Trimethylsilylation of phenols (1 mmol) using HMDS (1 mmol) catalysed with I₂ generated *in situ* from Oxone[®] (I) (0.2 mmol) or CAN (II) (0.2 mmol) in the presence of a catalytic amount of KI (0.2) in CH₂Cl₂ and 0.05 mL of H₂O at room temperature.

Entry	Substrate	Time (min)		Product ^a		Yield (%) ^b	
		I	II			I	II
1		immediate ^c	immediate		28	95	94
2		4	2		29	97	98
3		immediate	immediate		37	90	91
4		immediate	immediate		38	93	95
5		NR	NR	-		-	-
6		NR	NR	-		-	-

^aAll products were characterized by comparison of their spectral data (¹H-NMR; IR) with those of authentic samples.

^bIsolated yields. ^cThe completion of the reactions were confirmed by TLC and GC

Apart from KI, we also used a catalytic amount of KCl and KBr for the described system and the obtained results are depicted in table 2. From these results, it is clear that KI is more efficient than KCl or KBr. Also as a model we studied the trimethylsilylation of benzyl alcohol in different solvents (table 3).

Thus, in this article we wish to report the trimethylsilylation of alcohols and phenols under mild and homogeneous conditions. A variety of alcohols and phenols were subjected to silylation reaction with a combination of CAN or Oxone[®] and a catalytic amount of KI in the presence of HMDS. All protection reactions were performed under mild and homogeneous conditions, at room temperature with good to high yields. These reactions were carried out in CH₂Cl₂ wetted by 0.05 mL of H₂O (table 4).

As shown in table 4, in the cases of primary and secondary alcohols the reactions were completed rapidly. Interestingly, different types of highly hindered tertiary alcohols were successfully converted to the corresponding trimethylsilyl ethers in almost quantitative yields at room temperature (table 4, entries 18–20). Moreover no side products were observed in these reactions.

The data in table 5 clearly show that different types of phenols were successfully converted to the corresponding silyl ethers in short reaction times and in almost quantitative yields. We observed that amines and thiols were not silylated under these reaction conditions even after prolonged times (table 5, entries 5, 6).

We measured the amount of *in situ* generated I₂ in wet CH₂Cl₂ by UV-Visible spectrophotometric method. It was found that 0.42 and 0.38 mmoles of I₂ are produced for every mmol of KI using Oxone and CAN as oxidant respectively.

To prove that molecular iodine is the actual catalyst, we conducted trimethylsilylation of benzyl alcohol with hexamethyldisilazane in the presence of catalytic amounts of CAN or Oxone[®] (0.2 mmol) instead of the system of CAN/KI or Oxone[®]/KI. The reaction was completed after 1 h and 6 h, respectively, while benzyl alcohol was trimethylsilylated with hexamethyldisilazane in the presence of CAN/KI or Oxone/KI, in very short reaction times (table 4, entry 1).

We have found that cerium residue generated through the reaction with CAN and KI has some positive effects on the silylation of alcohols with hexamethyldisilazane (as Lewis acid). We also compared trimethylsilylation of benzyl alcohol between I₂ and CeCl₃/I₂ at –15°C. The reactions were completed after 15 min and 10 min, respectively, indicating some cooperative catalysis between a Ce(III) complex and molecular iodine is operative.

4. Conclusion

In summary, a mild method for the *in situ* generation of I₂ from inexpensive materials, CAN/KI or Oxone[®]/KI, has been developed. The *in situ* generated I₂ has been shown to be an effective promoter for trimethylsilylation of variety alcohols and phenols using HMDS under mild conditions.

Acknowledgements

We thank Semnan University Research Council, Bu-Ali Sina University Research Council, and Center of Excellence in Development of Chemical Methods (CEDCM), national foundation of elites (BMN) for supporting this work. Also, we thank Mr. Mehdi Damali Amiri for his help in editing the manuscript.

References

1. Van-Look G, Simchen G and Heberle J (eds.) 1995 *Silylation Agents* (Switzerland: Fluka, Buchs)
2. Greene T W and Wuts P G M 3rd ed. 1999 *Protective groups in organic synthesis* (New York: Wiley)
3. Tarkelson S and Anisworth C 1976 *Synthesis* 722
4. Cossy J and Pale P 1978 *Tetrahedron Lett.* **28** 6039
5. Bruynes C A and Jurriens T K 1982 *J. Org. Chem.* **47** 3966
6. Bandgar B P and Wadgaonkar P P 1997 *Synth. Commun.* **27** 2069
7. Zhang Z-H, Li T-S, Yang F and Fu C-G 1998 *Synth. Commun.* **28** 3105
8. Curini M, Epifano F, Marcotullio M C, Rosati O and Costantino U 1999 *Synth. Commun.* **29** 541
9. Karimi B and Golshani B 2000 *J. Org. Chem.* **65** 7228
10. Firouzabadi H, Iranpoor N, Amani K and Nowrouzi F 2002 *J. Chem. Soc. Perkin. Trans.* 2601
11. Azizi N and Saidi M R 2003 *Organometallics* **23** 1457
12. Firouzabadi H, Iranpoor N, Sobhani S and Ghassamipour S 2005 *Synthesis* 595
13. Akhlaghinia B and Tavakoli S 2005 *Synthesis* 1775
14. Ghorbani-Vaghei R and Malaekhpour S M 2010 *Phosphorus, Sulfur Silicon Relat. Elem.* **185** 582
15. Rostami A, Ahmad-Jangi F, Zarebin M R and Akradi J 2010 *Synth. Commun.* **40** 1500
16. Togo H and Iida S 2006 *Synlett.* 2159
17. Bailey A D, Cherney S M, Anzalone P W, Anderson E D, Ernat J J and Mohan R S 2006 *Synlett.* 215
18. Corma A and Garcia H 1997 *Catal. Today* **38** 257
19. Firouzabadi H and Jafari A A 2005 *J. Iran. Chem. Soc.* **2** 85
20. Salehi P, Zolfigol M A and Baghbanzadeh M 2006 *Curr. Org. Chem.* **10** 2171
21. Molander G A 1992 *Chem. Rev.* **92** 29
22. Nair V and Deepthi A 2007 *Chem. Rev.* **107** 1862
23. Narsaiah A V 2002 *Synlett.* **2002** 1178
24. Zolfigol M A, Borazjani M K, Mallakpour S E and Nasr-Isfahani H 2000 *Synth. Commun.* **30** 2573

25. Zolfigol M A, Bagherzadeh M, Chehardoli G and Mallakpour S E 2001 *Synth. Commun.* **31** 1149
26. Zolfigol M A, Bagherzadeh M, Mallakpour S E, Chehardoli G, Kolvari E, Choghamrani A G and Koukabi N 2007 *Catal. Commun.* **8** 256
27. Zolfigol M A, Bagherzadeh M, Mallakpour S, Chehardoli G, Ghorbani-Choghamarani A, Koukabi N, Dehghanian M and Doroudgar M 2007 *J. Mol. Catal. A: Chem.* **270** 219
28. Kadam S T and Kim S S 2009 *J. Organomet. Chem.* **694** 2562
29. Azizi N, Yousefi R and Saidi M R 2006 *J. Organomet. Chem.* **691** 817
30. Ghorbani-Vaghei R, Zolfigol M A, Chegeny M and Veisi H 2006 *Tetrahedron Lett.* **47** 4505
31. Narsaiah A V 2007 *J. Organomet. Chem.* **692** 3614
32. Zolfigol M A, Mohammadpoor-Baltork I and Shiri M 2008 *J. Iran. Chem. Soc.* **5** 90
33. Khazaei A, Zolfigol M A, Rostami A and Choghamarani A G 2007 *Catal. Commun.* **8** 543
34. Firouzabadi H, Iranpoor N and Farahi S 2009 *Catal. Commun.* **10** 1547
35. Shirini F, Zolfigol M A and Abedini M 2005 *Phosphorus, Sulfur Silicon Relat. Elem.* **180** 2299
36. Niknam K, Zolfigol M A, Chehardoli G and Dehghanian M 2008 *Chin. J. Catal.* **29** 901
37. Khazaei A, Rahmati S and Rostami A 2009 *Helv. Chem. Acta* **92** 1434
38. Shirini F, Marjani K, Nahzomi H T and Zolfigol M A 2008 *Phosphorus, Sulfur Silicon Relat. Elem.* **183** 168