ChemComm
www.rsc.org/chemcomm

A remarkable solvent effect toward the Pd/C-catalyzed cleavage of silyl ethers†

Hironao Sajiki,* Takashi Ikawa, Kazuyuki Hattori and Kosaku Hirota*
Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502-8585, Japan. E-mail: sajiki@gifu-pu.ac.jp; Fax: +81-58-237-5979; Tel: +81-58-237-3931

Received (in Cambridge, UK) 19th November 2002, Accepted 28th January 2003
First published as an Advance Article on the web 11th February 2003

DOI: 10.1039/b211313a

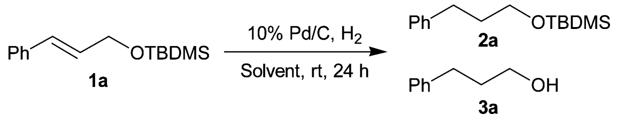
Selective hydrogenation conditions of olefin, benzyl ether and acetylene functionalities in the presence of TBDMS or TES ether have been developed.

The protection of alcohols as their silyl ethers has been recognized as a most useful protective method. Since the introduction of the *tert*-butyldimethylsilyl (TBDMS) protective group in 1972,[1] alcohols and phenols have been quite commonly protected as their TBDMS ethers.[2] TBDMS ethers have the virtue of being very stable to a variety of organic reactions.[2] In general, TBDMS ethers have been believed to be also stable under hydrogenation conditions.[1] Synthesis involving hydrogenation and/or hydrogenolysis processes of reducible functionalities (*e.g.*, olefin and benzyl ether) offer the complete stability of the coexisting silyl ether as a protective group because the unexpected loss of the silyl protective group from a hydroxylic function would greatly impair a synthetic process. However, we have quite recently reported the frequent and unexpected cleavage of TBDMS ethers to form the parent alcohols under mild hydrogenation conditions (ambient H_2 pressure and temperature) using 10% Pd/C in MeOH.[3] In a related reaction, we found that the cleavage of the silyl ether under hydrogenation conditions using 10% Pd/C was strongly affected by the solvent. Encouraged by this interesting observation, we became interested in exploring the stability of silyl ethers under the Pd/C-catalyzed hydrogenation conditions using various solvents to see if perfect stability could be achieved in a specific solvent and to provide an extremely safe and applicable hydrogenation method for reducible functionalities with coexisting silyl ethers. Herein we report the result of our investigation.

Many representative protic and non-protic solvents were chosen for the hydrogenation of 1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (**1a**). Needless to say, the hydrogenation of the olefin function of **1a** was smoothly achieved in all the investigated solvents under the hydrogenation conditions [0.5 mmol of **1a** and 10% Pd/C (10% of the weight of **1a**) in 1 mL of the solvent at ambient H_2 pressure (balloon) and temperature (*ca.* 20 °C) for 24 h]. The significant effect of solvents in the hydrogenation of **1a** is shown in Table 1. Absolute solvents were employed here. Although the unexpected cleavage of the TBDMS protective group of **1a** went essentially to completion in MeOH (entry 1),[4] changing the solvent from MeOH to EtOH, ^{t}BuOH or H_2O markedly decreased the rate of cleavage (66, 8 or 77%, entries 2–4). The TBDMS ether was apparently stable in non-protic solvents (entries 5–11), for example, the cleavage of the TBDMS ether (**1a**) was considerably depressed in hexanes, cyclohexane, DMF and THF as the solvent (entries 5–8). Subsequent screening of reaction conditions revealed that no cleavage of the TBDMS ether was detected even after 24 h by using toluene, EtOAc[5] and MeCN[5] as the solvent (entries 9–11).

To explore the generality of the solvent effect toward the Pd/C-catalyzed cleavage of silyl ethers, such as *tert*-butyldiphenylsilyl (TBDPS), triisopropylsilyl (TIPS) and triethylsilyl (TES) ethers, use of MeOH, THF, EtOAc and MeCN as the typical solvent was investigated (Table 2). As shown in entries 1 and 2, the TBDPS and TIPS protective groups of **1b** and **1c** were stable under hydrogenation conditions using 10% Pd/C even in MeOH.[6] On the other hand, the TES protective group of **1d** could be cleaved easily in MeOH to form the parent alcohol **3a** (entry 3).[4] Although the TBDMS ether **1a** in EtOAc absolutely tolerated the cleavage (Table 1 entry 10), the TES ether **1d** was considerably cleaved (33%) even in EtOAc to give a mixture of **2d** and **3a** (Table 2, entry 5). Gratifyingly, the desilylation of the TES ether was absolutely depressed in

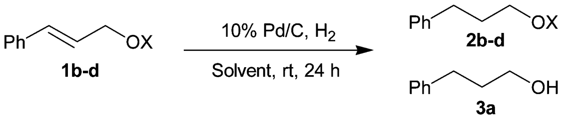
Table 1 Solvent effect toward the TBDMS cleavage of **1a**[a]



Entry	Solvent	Relative yield (%)[b]	
		2a	**3a**
1	MeOH[c]	0	100
2	EtOH	34	66
3	^{t}BuOH	92	8
4	H_2O	23	77
5	Hexanes	86	14
6	Cyclohexane	89	11
7	DMF	87	13
8	THF	98	2
9	**Toluene**	**100**	**0**
10	**EtOAc**	**100**	**0**
11	**MeCN**	**100**	**0**

[a] 10% Pd/C was purchased from Aldrich. [b] Determined by ^{1}H NMR. [c] No reaction was observed under Ar atmosphere.

Table 2 Solvent effect toward the silyl ether cleavage of **1d**[a]



Entry	Substrate	X	Solvent	Relative yield (%)[b]	
				2b–d	**3a**
1	**1b**[c]	TBDPS	MeOH	100	0
2	**1c**[c]	TIPS	MeOH	100	0
3	**1d**	TES	MeOH[d]	0	100
4	**1d**	TES	THF	63	37
5	**1d**	TES	EtOAc	67	33
6	**1d**	**TES**	**MeCN**	**100**	**0**

[a] 10% Pd/C was purchased from Aldrich. [b] Determined by ^{1}H NMR. [c] TBDPS and TIPS ethers of **1b** and **1c** were also completely tolerated in THF, EtOAc and MeCN. [d] No reaction was observed under Ar atmosphere.

---

† Electronic supplementary information (ESI) available: characterization data and references and supplementary Tables 4 and 5. See http://www.rsc.org/suppdata/cc/b2/b211313a/

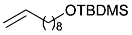
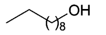
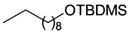
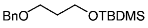
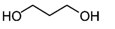
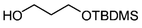
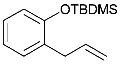
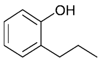
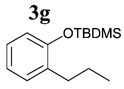
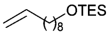
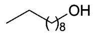
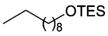
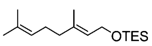
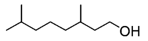
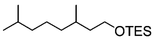
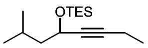
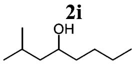
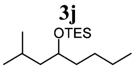
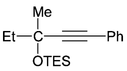
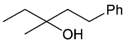
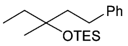
MeCN[5] and chemoselective hydrogenation of the olefin was achieved to give **2d** as the sole product (entry 6).

To elucidate the solvent effect and establish the viability of a safe hydrogenation process for TBDMS and TES ethers possessing other reducible functionalities, competition experiments were performed by using a variety of TBDMS and TES ethers under the same hydrogenation conditions in absolute MeOH and EtOAc or MeCN, and the results were particularly informative (Table 3). While consumption of the benzyl ether of **1f** in EtOAc required somewhat longer reaction time (36 h),[7] acetylene, olefin and benzyl ether functionalities were easily hydrogenated in each solvent. The extent of undesirable cleavage of the alkyl or aryl TBDMS ether in MeOH was significantly dependent on the structure of the substrate (entries 1–3) while appreciable cleavage of the TBDMS ether under the conditions was observed in all cases in Table 3.[8] By contrast, the cleavage entirely tolerates the TBDMS ethers upon employment of EtOAc or MeCN as a solvent and the product was obtained in quantitative isolated yield. In the cases of TES ethers, even including a sterically hindered TES group on the tertiary alcohol (**1k**), complete loss of the TES protective group was observed in MeOH (entries 4–7). It is interesting to note that the perfect and ready cleavage of TES ethers proceeds in MeOH, suggesting that the process will be applicable to a novel and selective deprotection method of the TES protective group under neutral and mild conditions.[9] The complete suppression procedure for the desilylation of the TES protective group was achieved by making use of MeCN as a solvent (entries 4–7). In all cases, the hydrogenation gave a single product without any TES cleavage. These results in EtOAc and/or MeCN provide a perfectly chemoselective and safe hydrogenation method of other reducible functionalities leaving intact the TBDMS and TES ether as a widely applicable protective group.

Table 3 Cleavage of the TBDMS or TES ethers under 10% Pd/C-catalyzed hydrogenation conditions[a]

$$\underset{\mathbf{1}}{\text{R-OX}} \xrightarrow[\text{Solvent, rt, 24 h}]{\text{10\% Pd/C, H}_2} \underset{\mathbf{2}}{\text{R'-OX}} + \underset{\mathbf{3}}{\text{R'-OH}}$$

X = TBDMS or TES

Entry	Substrate	Solvent	**2**:**3**[b]	Product	Yield (%)[c]
1	 **1e**	MeOH	0:100	 **3e**	80
		EtOAc	100:0	 **2e**	98
2	 **1f**	MeOH	82:18	 **3f**	[d]
		EtOAc[e]	100:0	 **2f**	95
3	 **1g**	MeOH	92:8	 + **2g** **3g**	[d]
		EtOAc	100:0	 **2g**	100
4	 **1h**	MeOH	0:100	 **3e**	94[f](67)[g]
		MeCN	100:0	 **2h**	99
5	 **1i**	MeOH	0:100	 **3i**	92[f](45)[g]
		MeCN	100:0	 **2i**	88
6	 **1j**	MeOH	0:100	 **3j**	90[f](21)[g]
		MeCN	100:0	 **2j**	93
7	 **1k**	MeOH	0:100	 **3k**	96
		MeCN	100:0	 **2k**	98

[a] Unless otherwise specified, the reaction was carried out using 0.5 mmol of the substrate (**1**) with 10% Pd/C (10% of the weight of the substrate **1**) in MeOH (2 mL) or EtOAc (2 mL) under hydrogen atmosphere (1 atm) at rt for 24 h. [b] Determined by ^{1}H NMR. [c] Isolated yield. [d] The ratio of the product was estimated by ^{1}H NMR. [e] The benzyl ether of **1f** was completely hydrogenolyzed in EtOAc for 36 h. [f] Product contaminated with small amount of TESOH. [g] The yield of isolated and analytically pure product is indicated in parentheses. The low isolated yield is due to the volatile nature of the product and difficulty of purification using silica gel column chromatography.

Evidently, the desilylation of **1a** and **1d** never occurred in the absence of hydrogen or 10% Pd/C and no suppression was observed in the presence of a basic gel-type resin (Amberlite® IRA-40 or IRA-410) as an acid scavenger to eliminate the possibility of a contaminated acid-catalyzed methanolysis. However, the mechanism for the remarkable solvent effect (suppression of the silyl ether cleavage) is not clear yet (see Supplementary Information†).[4]

In conclusion, we have discovered a remarkable solvent effect toward the Pd/C-catalyzed cleavage of TBDMS and TES ethers and it was applied to the development of a chemoselective hydrogenation method for olefin, benzyl ether and acetylene functionalities distinguishing from the TBDMS and TES protective groups of a hydroxy group by the employment of EtOAc or MeCN as a solvent. The ready availability of the catalyst (commercially available), the high yields, simplicity of the procedure, and selective nature of the hydrogenation, render this new and simple methodology advantageous for work involving TBDMS and TES ether manipulation.

Notes and references

1 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190.

2 Selected reviews: (*a*) T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edn., Wiley-Interscience, New York, 1999; (*b*) P. J. Kocienski, *Protecting Groups*, Thieme-Verlag, Stuttgart, 1994, p. 28.

3 (*a*) K. Hattori, H. Sajiki and K. Hirota, *Tetrahedron Lett.*, 2000, **41**, 5711; (*b*) K. Hattori, H. Sajiki and K. Hirota, *Tetrahedron*, 2001, **57**, 2109.

4 To eliminate the possibility of a contaminated acid in 10% Pd/C-catalyzed cleavage of the silyl protective groups, the reactions of **1a** and **1d** were performed without hydrogen. As a consequence of the reaction, no cleavage occurred, even after 24 h (see Supplementary Information, Table 4†) (ref. 3).

5 The addition of a small amount of MeOH or H_2O into the reaction mixture (0.1 mL per 1.0 mL of EtOAc or MeCN) caused no cleavage of the TBDMS (**1a**) or TES (**1d**) ether for 24 h (see Supplementary Information, Table 5†).

6 The TBDPS and TIPS protective groups are considerably more stable to a variety of organic reaction conditions than the TBDMS group because of the greater bulkiness (ref. 2*a*).

7 Several removal methods of OBn in the presence of silyl ethers were previously reported. See: (*a*) H. Toshima, S. Yoshida, T. Suzuki, S. Nishiyama and S. Yamamura, *Tetrahedron Lett.*, 1989, **48**, 6721; (*b*) F. Yokokawa, Y. Hamada and T. Shioiri, *Chem. Commun.*, 1996, 871; (*c*) B. Sas, P. De Clercq and M. Vandewalle, *Synlett*, 1997, 1167.

8 In the cases of highly hindered TBDMS ethers, such as (1*R*, 2*S*, 5*R*)-1-*tert*-butyldimethylsilyloxy-2-isopropyl-5-methylcyclohexane, no cleavage of the TBDMS protective group was observed even in MeOH.

9 The development of mild and effective deprotection methods of silyl ethers with excellent chemoselectivity are still highly desirable because of practical benefits for synthetic chemistry. For example, see: S. V. Ankala and G. Fenteany, *Tetrahedron Lett.*, 2002, **42**, 4729.