

# Environment friendly chemoselective deprotection of acetonides and cleavage of acetals and ketals in aqueous medium without using any catalyst or organic solvent

S MUKHERJEE, A SENGUPTA and S C ROY\*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700 032, India  
e-mail: ocsr@iacs.res.in

MS received 2 April 2013; revised 30 July 2013; accepted 12 August 2013

**Abstract.** Highly chemoselective environment friendly deprotection of acetonides and cleavage of acetals and ketones has been achieved by heating in aqueous medium without using any catalyst and organic solvent.

**Keywords.** Environment friendly; acetonides; chemoselective; aqueous medium; deprotection; acetals.

## 1. Introduction

Selective protection and deprotection of sensitive functional groups play a crucial role in multi-step synthesis of complex natural products.<sup>1</sup> Acetonides are actually masked hydroxyl groups in polyhydroxy organic molecules, oligosaccharides and in nucleosides.<sup>2</sup> In carbohydrate chemistry, the synthesis of natural products or their analogues, selective deprotection of acetonides is frequently required leaving the other protecting groups intact.<sup>3</sup> Generally, in organic synthesis, chemoselectively acetonides are deprotected using aqueous acids such as aqueous HCl,<sup>4a</sup> aqueous HBr,<sup>4b</sup> aqueous AcOH,<sup>4c</sup> 0.8% H<sub>2</sub>SO<sub>4</sub> in MeOH,<sup>4d</sup> DOWEX-H<sup>+</sup> in MeOH-H<sub>2</sub>O (9:1),<sup>4e</sup> CF<sub>3</sub>COOH,<sup>4f</sup> CSA,<sup>4g</sup> p-TsOH,<sup>4h</sup> and Lewis acids<sup>5</sup> e.g., aqueous FeCl<sub>3</sub>·6H<sub>2</sub>O/SiO<sub>2</sub>, Zn(NO<sub>3</sub>)<sub>2</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O/(COOH)<sub>2</sub>, BiCl<sub>3</sub>, PMA/SiO<sub>2</sub>, polymeric FeCl<sub>3</sub>, lanthanum (III) nitrate, etc. But under such acidic conditions, other acid-sensitive functionalities may be affected. In our earlier studies,<sup>6a,b</sup> we have achieved the deprotection of OTHP and ketals and acetals using LiCl–DMSO–H<sub>2</sub>O system. We have also established the selective deprotection of acetonides using ceric ammonium nitrate (CAN) as a catalyst.<sup>6c</sup> But the catalysts used (LiCl and CAN) are toxic and strong enough to affect many sensitive functional groups. So, a mild and environment friendly chemoselective deprotection of functional groups is still a challenge in synthetic organic chemistry especially in aqueous medium. We report here an environment friendly efficient method for chemoselective deprotection of

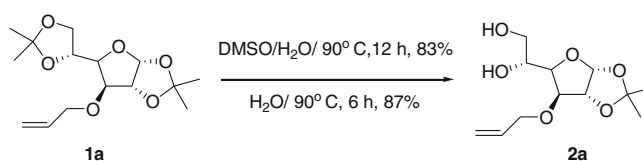
acetonides by simply heating in pure water at 90°C without using any catalyst and any organic solvent.

## 2. Experimental

All melting points were taken on a Gallenkamp melting point apparatus and are uncorrected. The <sup>1</sup>H and <sup>13</sup>C NMR were recorded in CDCl<sub>3</sub> using TMS as an internal standard on 300 and 75 MHz spectrometer (Bruker), respectively and IR were recorded using a Shimadzu FT IR-8300 instrument. High-resolution mass spectra were obtained using a Qtof Micro YA263 instrument. Ethyl acetate was dried over anhydrous calcium chloride. Petroleum ether of boiling range 60–80°C was dried over sodium. Silica gel of 60–120 mesh were used for column chromatography.

### 2.1 Representative procedure for deprotection of acetonides, ketals and acetals

A mixture of **1a** (560 mg, 1.9 mmol) and H<sub>2</sub>O (2 ml) was allowed to stir 90°C for 6 h. After completion of the reaction (monitored by TLC), the mixture was allowed to cool to room temperature and was extracted with diethyl ether (3 × 35 mL). The combined organic layer



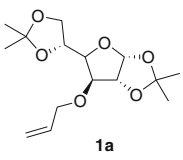
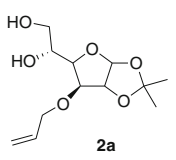
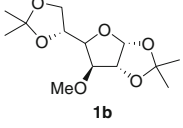
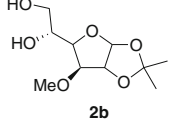
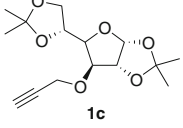
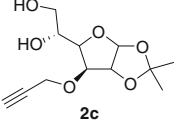
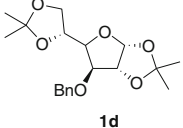
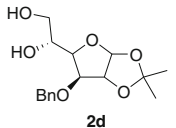
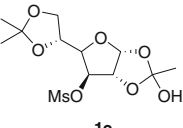
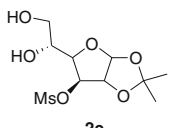
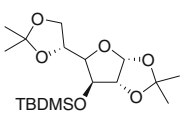
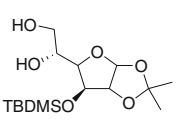
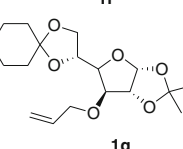
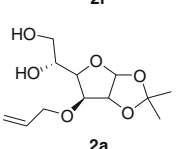
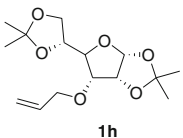
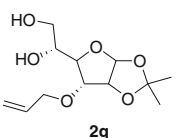
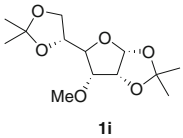
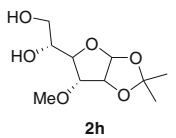
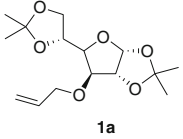
**Scheme 1.** Chemoselective deprotection of acetonide.

\*For correspondence

was dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure yielded the dihydroxy compound **2a** (418 mg, 87%) which was pure

enough for characterization without further purification. IR (neat): 3419, 3413, 3401, 2988, 2936, 1651, 1514, 1456, 1376, 1256, 1218, 1079, 1021  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$

**Table 1.** Chemoselective deprotection of acetonides without using any catalyst and organic solvent.

Entry	Substrate	Product	Reaction time (h)	Yield (%) <sup>a</sup>	Ref.
1			6	87	5 <sup>k</sup>
2			6	85	5 <sup>l</sup>
3			6	91	5 <sup>k</sup>
4			6	90	5 <sup>m</sup>
5			4	95	5 <sup>m</sup>
6			6	86	5 <sup>n,o</sup>
7			6	90	5 <sup>k</sup>
8			6	91	5 <sup>p</sup>
9			4	87	5 <sup>q</sup>
10		No reaction <sup>b</sup>	12	–	

<sup>a</sup>Yields refer to pure products without column chromatography

<sup>b</sup>The reaction was performed in dry toluene at 90°C without water

(500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.30 (s, 3H), 1.47 (s, 3H), 3.09 (brs, OH), 3.70 (dd,  $J = 11.5$ , 5 Hz, 1H), 3.81 (dd,  $J = 11.5$ , 2.5 Hz, 1H), 3.97–4.07 (m, 3H), 4.10 (dd,  $J = 2.5$ , 7.6 Hz, 1H), 4.16 (dd,  $J = 5.0$ , 12.5 Hz, 1H), 4.55 (d,  $J = 4.0$  Hz, 1H), 5.20 (d,  $J = 10.5$  Hz, 1H), 5.29 (d,  $J = 17.5$  Hz, 1H), 5.85–5.93 (m, 1H), 5.89 (d,  $J = 3.5$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ): 26.2, 26.8, 64.4, 64.3, 71.2, 79.9, 82.0, 82.2, 105.1, 111.9, 118.0, 133.9; HRMS calcd for  $\text{C}_{12}\text{H}_{20}\text{O}_6(\text{M}^+ + \text{Na})$ : 283.1158; found 283.1158.

### 3. Results and discussion

Initially, a solution of the diacetonide **1a** (60 mg, 0.2 mmol) in DMSO (2 mL) and water (10 mmol) without any catalyst was heated with stirring at  $90^\circ\text{C}$  for 12 h and it was found that the deprotected **2a** was formed in 83% yield. During modification of the reaction conditions to reduce the reaction time and for better yield of the product, the mixture of diacetonide **1a** (560 mg, 1.9 mmol) and pure  $\text{H}_2\text{O}$  (2 mL) without any organic solvent was stirred at  $90^\circ\text{C}$  for 6 h and surprisingly it

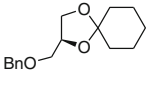
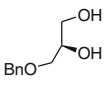
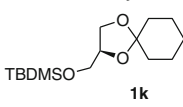
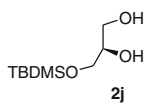
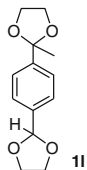
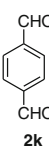
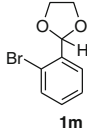
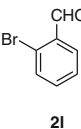
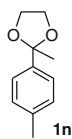
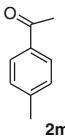
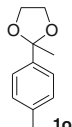
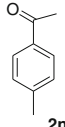
was observed that the mono deprotected compound **2a** was isolated in 87% yield (scheme 1). Then, a series of acetonides **1a–i** were chemoselectively deprotected to furnish **2a–h** under the reaction conditions and the results are summarized in table 1.

It was revealed that various functionalities like double bond, triple bond, benzyloxy, mesyloxy, methoxy and TBDMS ethers remain unaffected under the reaction conditions. It was also observed that reaction did not proceed at all when heated at  $90^\circ\text{C}$  for 12 h in dry toluene without the presence of water (entry 10, table 1). All the compounds were characterized by IR, NMR and HRMS analysis and by comparing the data with authentic samples.<sup>5,6</sup>

Not only acetonides but also the ketals and acetals could easily be deprotected<sup>7</sup> under the reaction conditions (table 2). The deprotection of acetals is much faster compared to ketals.

In a controlled experiment, a mixture of **1m** (64 mg, 0.28 mmol) and **1n** (50 mg, 0.28 mmol) was stirred in water (2 mL) at  $90^\circ\text{C}$  for 2 h. It was observed that the acetal **1m** was completely deprotected to give **2m** remaining the ketal **1n** unaffected ( $^1\text{H}$  NMR study).

**Table 2.** Deprotection of acetals and ketals in water.

Entry	Substrate	Product	Time (h)	Yield (%) <sup>a</sup>	Ref.
1			8	96	6 <sup>c</sup>
2			6	83	5 <sup>r</sup>
3			4	93	6 <sup>b</sup>
4			2	98	7 <sup>a</sup>
5			6	76	7 <sup>b</sup>
6			6	88	7 <sup>c</sup>

<sup>a</sup>Yields refer to pure isolated product

#### 4. Conclusions

We have developed an efficient, environment friendly selective deprotection of acetonides and cleavage of acetals and ketals in aqueous media under heating at 90°C without using any catalyst and any organic solvent.

#### Acknowledgements

We thank the Department of Science and Technology (DST), New Delhi for financial support (SR/S-1/OC-12/2011). SM thanks the Council of Scientific and Industrial Research (CSIR), New Delhi for the award of Fellowship.

#### References

- (a) Schkeryantz J M and Danishefsky S J 1995 *J. Am. Chem. Soc.* **117** 4722; (b) Masters J J, Link J T, Snyder L B, Young W B and Danishefsky S J 1995 *Angew. Chem., Int. Ed. Engl.* **34** 1723; (c) Boyce R J and Pattenden G 1996 *Tetrahedron Lett.* **37** 3501
- (a) Clode D M 1979 *Chem. Rev.* **79** 491; (b) Nicolaou K C, Daines R A, Uenishi J, Li W S, Papahatjis D P and Chakraborty T K 1988 *J. Am. Chem. Soc.* **110** 4672
- (a) Banerjee S and Ghosh S J 2003 *Org. Chem.* **68** 3981; (b) Krishna P R, Kannan V and Sharma G V M 2004 *J. Org. Chem.* **69** 6467; (c) Hanessian S, Huang G, Chenel C, Machaalani R and Loiseleur O 2005 *J. Org. Chem.* **70** 6721; (d) Sharma G V M and Gopinath T 2005 *Tetrahedron Lett.* **46** 1307
- (a) Fleet G W J and Smith P W 1985 *Tetrahedron Lett.* **26** 1469; (b) Gerspacher M and Rapoport H 1991 *J. Org. Chem.* **56** 3700; (c) Yadav J S, Chander M C and Reddy K K 1992 *Tetrahedron Lett.* **33** 135; (d) Manna S, Viala J, Yadagiri P and Falck J R 1986 *Tetrahedron Lett.* **27** 2679; (e) Park K H, Yoon Y J and Lee S G 1994 *Tetrahedron Lett.* **35** 9737; (f) Leblanc Y, Fitzsimmons B J, Adams J, Perez F and Rokach J 1986 *J. Org. Chem.* **51** 789; (g) Baurle S, Hoppen S and Koert U 1999 *Angew. Chem., Int. Ed.* **38** 1263; (h) Ichihara A, Ubukata M and Sakamura S 1997 *Tetrahedron Lett.* **38** 3473
- (a) Barbot F and Miginiac P 1983 *Synthesis* 651; (b) Sterzycki R 1979 *Synthesis* 724; (c) Kantam M L, Swapna V and Santhi P L 1995 *Synth. Commun.* **25** 2529; (d) Xiao X and Bai D 2001 *Synlett* **4**, 535; (e) Vijayasaraadhi S, Singh J and Aidhen I S 2000 *Synlett* **1** 110; (f) Kim K S, Song Y H, Lee B H and Hahn C S 1986 *J. Org. Chem.* **51** 404; (g) Yadav J S, Raghavendra S, Satyanarayana M and Balanarsaiah E 2005 *Synlett* **16** 2461; (h) Swamy N R and Venkateswarlu Y 2002 *Tetrahedron Lett.* **43** 7549; (i) Chari M A and Syamasundar K 2005 *Synthesis* 708; (j) Reddy S M, Reddy Y V and Venkateswarlu Y 2005 *Tetrahedron Lett.* **46** 7439; (k) Maddani M R and Prabhu K R 2011 *Synlett* **6** 821; (l) Yadav J S, Satyanarayana M, Raghavendra S and Balanarsaiah E 2005 *Tetrahedron Lett.* **46** 8745; (m) Fleet G W J and Witty D R 1990 *Tetrahedron: Asymmetry* **1** 119; (n) Rajput V K, Roy B and Mukhopadhyay B 2006 *Tetrahedron Lett.* **47** 6987; (o) Barrades J S, Errea M I and Accorso N B D 2012 *Carbohydr. Res.* **355** 79; (p) Shing T K M and Leung G Y C 2002 *Tetrahedron* **58** 7545; (q) Sharma G V M, Yadav T A, Choudhury M and Kunwar A C 2012 *J. Org. Chem.* **77** 6834; (r) Christiane M and Carreira E M 2005 *J. Am. Chem. Soc.* **127** 11505
- (a) Maiti G and Roy S C 1996 *J. Org. Chem.* **61** 6038; (b) Mandal P K, Dutta P and Roy S C 1997 *Tetrahedron Lett.* **38** 7271; (c) Jana S and Roy S C 2007 *Indian J. Chem.* **46B** 707
- (a) Habibi M, Tangestaninejad S, Baltork I, Mirkhani V and Yadollahi B 2001 *Tetrahedron Lett.* **42** 6771; (b) Li J, Wu Y, Fuller N, Markus M and Li W J 2010 *Org. Chem.* **75** 1077; (c) Yuan C, Yang Li, Yue G, Yu T, Zhong W and Liu B 2012 *Tetrahedron Lett.* **53** 6972