Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 49 (2008) 691–694

Tetrahedron Letters

Environmentally friendly organic synthesis using bismuth compounds: bismuth(III) iodide catalyzed deprotection of acetals in water

Aaron D. Bailey, Ashvin R. Baru, Kendall K. Tasche, Ram S. Mohan *

Laboratory for Environmentally Friendly Organic Synthesis, Department of Chemistry, Illinois Wesleyan University, Bloomington, IL 61701, USA

Received 6 September 2007; revised 20 November 2007; accepted 21 November 2007

Abstract

The chemoselective deprotection of a wide range of acetals and ketals in water is catalyzed by bismuth(III) iodide. Bismuth(III) compounds are remarkably nontoxic and hence are attractive as environmentally friendly catalysts.

Keywords: Deprotection; Acetals; Bismuth iodide; Water

The deprotection of acetals is an important step in organic synthesis due to the wide application of acetals, especially in the course of a total synthesis.[1] Hence many reagents have been developed for this purpose.[2] Considerable efforts have also been directed towards developing mild and selective methods for acetal deprotection.[3] However, many of the reagents employed for this purpose are corrosive and often toxic. Our continued interest in bismuth(III) compounds, due largely to their remarkably low toxicity,[4] low cost and ease of handling prompted us to investigate the use of bismuth iodide, BiI_3, as a catalyst for the deprotection of acetals.[5,6] Bismuth iodide is a stable, commercially available solid that has been underutilized in organic synthesis.[7] In spite of the lack of solubility of most organic compounds in water, the low cost, easy availability and non-flammability of water as well as the observation of unexpected rate accelerations have led to an increasing number of organic reactions being carried out in water.[8]

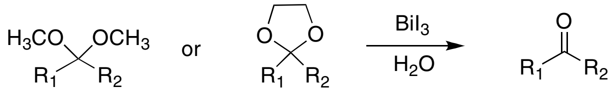
Herein, we report a mild method for the chemoselective deprotection of acetals and ketals in water using bismuth(III) iodide as a catalyst (Table 1). Preliminary studies were conducted in aqueous THF but gratifyingly, subsequent attempts in water proved successful. As can be seen from Table 1, a wide range of acetals and ketals underwent smooth deprotection with as little as 1.0 mol % BiI_3 at room temperature to give the corresponding carbonyl compound in good to excellent yields. Since the substrates shown in Table 1 and BiI_3 are all insoluble in water, the reaction was carried out by stirring a suspension of the substrate and catalyst in water. Under the reaction conditions, TBDMS ethers (entries 6, 16, and 17) and a phenolic ester (entry 7) did not undergo cleavage. Such chemoselectivity is especially useful in the course of a total synthesis where selective deprotection of protecting groups is often necessary. Although a detailed mechanistic study was not carried out, a few observations merit mention. The deprotection reactions were either not successful or incomplete in the absence of the catalyst. The pH of the reaction when carried out at room temperature with 1.0 mol % BiI_3 was found to be ~2.54 suggesting the formation of HI by the hydrolysis of BiI_3. The hydrolysis of bismuth(III) salts has been reported in the literature.[6e] The pH of 1.0 mol % HI in water was found to be ~2.11 and the pH of 3.0 mol % HI in water was found to be 1.66. In an attempt to elucidate the role of HI versus Bi^{3+} as a Lewis acid in the reaction, the deprotection of 2-(3-bromophenyl)-1,3-dioxolane (entry 14a) was carried out under the reaction conditions in the presence of 10 equiv of solid Na_2CO_3. Under

---

* Corresponding author. Tel.: +1 309 556 3829; fax: +1 309 556 3864. *E-mail address:* rmohan@iwu.edu (R. S. Mohan).

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.127

Table 1
Deprotection of acetals and ketals in water catalyzed by BiI_3



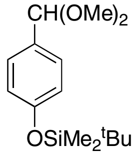
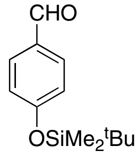
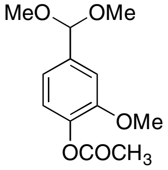
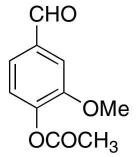
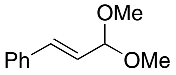
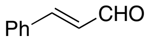
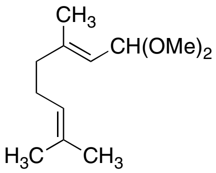
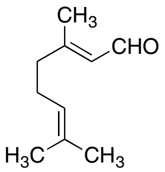
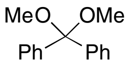
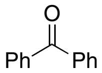
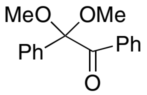
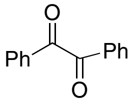
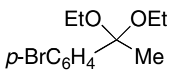
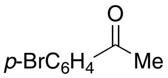
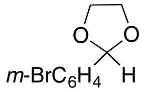
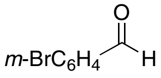
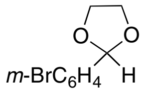
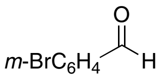
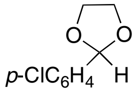
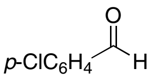
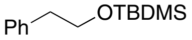
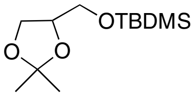
Entry	Substrate[a]	Product[b]	mol % BiI_3	Time[c] and temp	Yield[d] (%)
1a	*m*-$BrC_6H_4CH(OEt)_2$	*m*-BrC_6H_4CHO	1.0	45 min, 100 °C	85
1b	*m*-$BrC_6H_4CH(OEt)_2$	*m*-BrC_6H_4CHO	1.0	20 h, rt	89
2	*p*-$ClC_6H_4CH(OMe)_2$	*p*-ClC_6H_4CHO	1.0	1 h 10 min, 100 °C	84
3	*p*-$CH_3OC_6H_4CH(OMe)_2$	*p*-$CH_3OC_6H_4CHO$	1.0	1 h 15 min, rt	85
4	*p*-$Me_2NC_6H_4CH(OMe)_2$	*p*-$Me_2NC_6H_4CHO$	1.0	2 h, rt	85
5	*p*-$CH_3C_6H_4CH(OMe)_2$	*p*-$CH_3C_6H_4CHO$	1.0	1 h, rt	85
6			5.0	15 h, rt	91
7			1.0	1 h, 100 °C	83
8	$CH_3(CH_2)_{10}CH(OMe)_2$	$CH_3(CH_2)_{10}CHO$	5.0	1 h 20 min 100 °C	80
9			1.0	1 h 40 min, rt	91
10			1.0	50 min, rt	95
11			1.0	1 h 35 min, 100 °C	91
12			15.0	28 h 25 min, 100 °C	93
13			1.0	2 h, 100 °C	99
14a			1.0	45 min, 100 °C	91
14b			1.0	22 h, rt	82[e]
15			1.0	1 h 25 min, 100 °C	85

Table 1 (*continued*)

Entry	Substrate[a]	Product[b]	mol % BiI_3	Time[c] and temp	Yield[d] (%)
16		NR[f]	10.0	3 h, rt	
17		NR[f]	1.0	1 h 30 min, rt	

[a] Acetals were either purchased commercially or synthesized by a previously reported method.[10]

[b] All products have been previously reported and were characterized by ^1H and ^{13}C NMR spectroscopy.

[c] Reaction progress was followed by GC, TLC, or ^1H NMR.

[d] Refers to yield of the isolated product. The crude product was found to be >98% pure unless mentioned otherwise and hence further purification was deemed unnecessary.

[e] GC analysis indicated that the crude product is 96% pure.

[f] Starting material was recovered unchanged.

these conditions no deprotection was observed and the starting dioxolane was recovered. The deprotection of citral dimethyl acetal (entry 10) using 1.0 mol % BiI_3 in the presence of proton sponge™ [1,8-(dimethylamino)naphthalene][9] was also unsuccessful. These results suggest that it is unlikely that the hydrolysis is catalyzed primarily by coordination of Bi^{3+} to the acetal oxygen and rather point to the role of HI in the deprotection. The deprotection of both 2-(3-bromophenyl)-1,3-dioxolane (entry 14) and citral dimethyl acetal (entry 10) was carried out successfully at room temperature using 3.0 mol % HI in water. Although the available evidence suggests that HI plays an active role in the reaction, the use of bismuth iodide remains a more attractive option than HI because it is non-corrosive and easier to dispense in contrast to hydriodic acid.

A representative procedure is given here: A mixture of *trans*-cinnamaldehyde dimethyl acetal (0.5064 g, 2.84 mmol) in H_2O (5.0 mL) was stirred as BiI_3 (0.0168 g, 0.0284 mmol, 1.0 mol %) was added. The reaction was monitored by TLC (EtOAc/hexanes, 20/80, v/v). After 1 h 40 min, EtOAc (40.0 mL) was added to the reaction mixture and the biphasic mixture was filtered through a bed of Celite. The aqueous layer from the filtrate was extracted with EtOAc (20 mL) and the combined organic layers were washed with 5% aqueous $Na_2S_2O_3$ (10 mL), 10% aqueous Na_2CO_3 (10 mL), saturated aqueous NaCl (10 mL), and dried (Na_2SO_4). The solvent was removed on a rotary evaporator to yield 0.3403 g (91%) of a clear liquid that was identified to be *trans*-cinnamaldehyde by ^1H and ^{13}C NMR spectroscopy. The purity of the crude product was determined to be >98% by ^1H and ^{13}C NMR as well as GC analysis.

In summary, a chemoselective method for the deprotection of acetals and ketals catalyzed by bismuth(III) iodide in H_2O has been developed.

Acknowledgments

The authors gratefully acknowledge funding from the National Science Foundation for a RUI (Research in Undergraduate Institutions) Grant (# 0650682) awarded to R.S.M.

References and notes

1. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999; (b) Hanson, J. R. *Protecting Groups in Organic Synthesis*, 1st ed.; Blackwell Science: Malden, MA, 1999; (c) Kocienski, P. J. *Protecting Groups*, 1st ed.; Georg Thieme: Stuttgart, 1994.
2. *p*-TsOH/acetone: (a) Colvin, E. W.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Chem. Commun.* **1971**, 858; 50% Trifluoroacetic acid in $CHCl_3$–H_2O: (b) Ellison, R. A.; Lukenbach, E. R.; Chiu, C.-W. *Tetrahedron Lett.* **1975**, *16*, 499; $LiBF_4$: (c) Lipshutz, B. H.; Harvey, D. F. *Synth. Commun.* **1982**, *12*, 267; Amberlyst-15/aqueous acetone: (d) Coppola, G. M. *Synthesis* **1984**, 1021; aqueous DMSO: (e) Kametani, T.; Kondoh, H.; Honda, T.; Ishizone, H.; Suzuki, Y.; Mori, W. *Chem. Lett.* **1989**, *18*, 901; $Bi(NO_3)_3\cdot5H_2O$: (f) Eash, K. J.; Pulia, M. S.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2000**, *65*, 8399; (g) Sabitha, G.; Babu, R. S.; Reddy, E. V.; Yadav, J. S. *Chem. Lett.* **2000**, *29*, 1074.
3. $TiCl_4$: (a) Balme, G.; Goré, J. *J. Org. Chem.* **1983**, *48*, 3336; $FeCl_3\cdot6H_2O$ on silica gel: (b) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404; Ph_3P/CBr_4: (c) Johnstone, C.; Kerr, W. J.; Scott, J. S. *J. Chem. Soc., Chem. Commun.* **1996**, 341; $CeCl_3$: (d) Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183; $FeCl_3\cdot6H_2O$: (e) Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684; $TMSN(SO_2F)_2$: (f) Kaur, G.; Trehan, A.; Trehan, S. *J. Org. Chem.* **1998**, *63*, 2365; Ceric ammonium nitrate: (g) Markó, I. E.; Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C. *Angew. Chem., Int. Ed.* **1999**, *38*, 3207; $Bi(OTf)_3\cdot4H_2O$: (h) Carrigan, M. D.; Sarapa, D.; Smith, R. C.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2002**, *67*, 1027; (i) Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Tagarelli, A.; Sindona, G.; Bartoli, G. *J. Org. Chem.* **2002**, *67*, 9093; β-Cyclodextrin: (j) Krishnaveni, N. S.; Surendra, K.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 2018; $HClO_4$/silica gel: (k) Agarwal, A.; Vankar, Y. D. *Carbohydr. Res.* **2005**, *340*, 1661; I_2 (l) Sun, J.; Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932; $CuSO_4$/NaI: (m) Bailey, A. D.; Cherney, S. M.; Anzalone, P. W.; Anderson, E. D.; Ernat, J. J.; Mohan, R. S. *Synlett* **2006**, 215.
4. Most bismuth(III) compounds have an LD_{50} value that is comparable to or even less than that of NaCl (see Ref. 6c).
5. (a) Irwing-Sax, N.; Bewis, R. J. *Dangerous Properties of Industrial Materials*; Van Nostrand Reinhold: New York, 1989; pp 283–284, 522–523; (b) *The Chemistry of Organic Arsenic, Antimony and Bismuth Compounds*; Dill, K., McGown, E. L., Patai, S., Eds.; J. Wiley: New York, 1994; pp 695–713; (c) *The Chemistry of Organic Arsenic, Antimony and Bismuth Compounds*; Worsmer, U., Nir, I., Patai, S., Eds.; J. Wiley: New York, 1994; pp 715–723; (d) *Chemistry of Arsenic, Antimony and Bismuth*; Reglinski, J., Norman, N. C., Eds.; Blackie Academic and Professional: New York, 1998; pp 403–440.

6. For reviews, see: (a) Marshall, J. A. *Chemtracts* **1997**, 1064; (b) Suzuki, H.; Ikegami, T.; Matano, Y. *Synthesis* **1997**, 249; (c) *Organobismuth Chemistry*; Suzuki, H., Matano, Y., Eds.; Elsevier: Amsterdam, 2001; (d) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373; (e) Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517.
7. (a) Le Roux, C.; Gaspard-Iloughmane, H.; Dubac, J.; Jaud, J.; Vignaux, P. *J. Org. Chem.* **1993**, *58*, 1835; (b) Komatsu, N.; Uda, M.; Suzuki, H. *Synlett* **1995**, 984; (c) Keramane, E. M.; Boyer, B.; Roque, J.-P. *Tetrahedron* **2001**, *57*, 1909; (d) Donnelly, S.; Thomas, E. J.; Fielding, M. *Tetrahedron Lett.* **2004**, *45*, 6779; (e) Cunha, S.; Rodrigues, M. T. *Tetrahedron Lett.* **2006**, *47*, 6955.
8. (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley-Interscience: New York, 1997. For a review on organic chemistry in water, see: (b) Li, C.- J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68.
9. Brzezinski, B.; Grech, E.; Malarski, Z.; Sobczyk, L. *J. Chem. Soc., Perkin. Trans. 2* **1991**, 857.
10. Leonard, N. M.; Oswald, M. C.; Freiberg, D. A.; Nattier, B. A.; Smith, R. C.; Mohan, R. S. *J. Org. Chem.* **2002**, *67*, 5202.