A Simple and Efficient Chemoselective Method for the Catalytic Deprotection of Acetals and Ketals Using Bismuth Triflate

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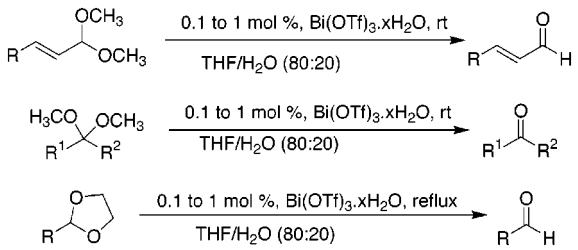
Abstract: Bismuth triflate is a highly efficient catalyst (0.1−1 mol %) for the deprotection of acetals and ketals. The procedure is very facile and selective for acetals derived from ketones and conjugated aldehydes. *tert*-Butyldimethylsilyl ethers are stable to the reaction conditions. The highly catalytic nature of bismuth triflate and the use of a relatively nontoxic solvent system (THF/H_2O) make this procedure particularly attractive for large-scale synthesis.

Acetals are frequently used to protect carbonyl compounds in the course of a total synthesis, and hence several reagents have been developed for their deprotection.[1,2] Considerable effort has also been directed toward developing mild, selective methods for acetal deprotection.[3] Recently, we reported that bismuth(III) nitrate pentahydrate (25 mol %) in CH_2Cl_2 is an efficient reagent for the deprotection of acyclic *O*,*O*-acetals derived from ketones and conjugated aldehydes.[4] Cyclic acetals and TBDMS ethers are not affected by bismuth nitrate. Bismuth compounds are of interest because of their low toxicity and low cost.[5,6] A search for a bismuth-based reagent with greater catalytic activity that also avoided the use of a chlorinated solvent formed the basis of this study and led to the development of bismuth triflate as a catalyst for acetal deprotection. Bismuth triflate has been used as a catalyst for Friedel−Crafts Acylations,[7] sulfonylation of arenes,[8] Diels−Alder reactions,[9] the aza-Diels−Alder reaction,[10] acylation of alcohols,[11] epoxide rearrangements,[12] and acylal synthesis.[13]

Scheme 1



We now wish to report that bismuth triflate in aqueous tetrahydrofuran is a highly efficient catalyst for the selective deprotection of acetals derived from ketones and conjugated aldehydes (Scheme 1).

The experimental procedure is simple and involves stirring the substrate as a solution in THF/H_2O (80:20, v/v) in the presence of bismuth triflate. To test the efficiency of the catalyst, deprotection of several acetals and ketals (entries 1, 6, 11, 16, and 17) was attempted with as little as 0.1 mol % catalyst. In all cases, the corresponding carbonyl compound was obtained in high yield. The highly catalytic nature of this system makes this procedure particularly attractive for large-scale synthesis. The effective large-scale utilization of this system is demonstrated by the successful deprotection of acetophenone dimethyl acetal (entry 11b) and citral dimethyl acetal (entry 6b) on a 10-g scale. Only approximately 30 mg of the catalyst is needed to effect deprotection of acetals on this scale. Bismuth triflate is not commercially available, but can be easily synthesized as the tetrahydrate in the laboratory following a literature method.[14] It is insoluble in common organic solvents and is used as a suspension. It is a noncorrosive solid and has a good shelf life. THF/H_2O was found to be the best solvent system for the deprotection of acetals. Less satisfactory results were obtained in aqueous methanol and CH_2Cl_2 saturated with water. The results of this study are summarized in Table 1.

Dialkyl acetals derived from aromatic aldehydes underwent smooth deprotection at room temperature. Benzaldehyde dimethyl acetal (entry 1), piperonal dimethyl acetal (entry 2), 4-chlorobenzaldehyde dimethyl acetal (entry 3), and terephthalaldehyde *mono*-(diethyl acetal) (entry 4) were all converted to the corresponding aldehyde in good yields. Similar results were obtained with the conjugated acetals derived from cinnamaldehyde

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Table 1. Deprotection of Acetals and Ketals in THF/H_2O Using $Bi(OTf)_3 \cdot xH_2O$

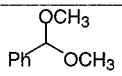
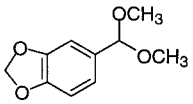
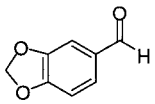
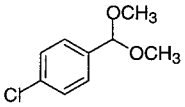
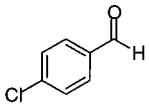
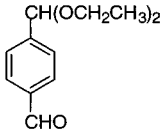
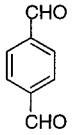
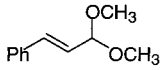
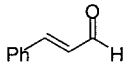
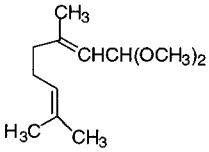
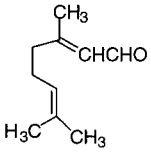
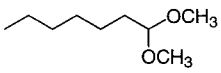
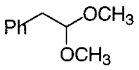
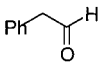
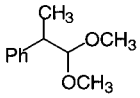
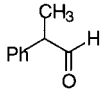
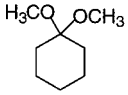
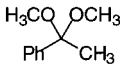
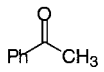
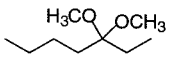
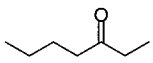
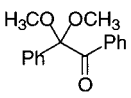
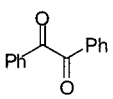
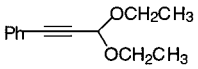
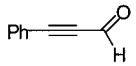
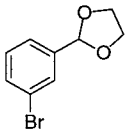
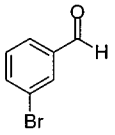
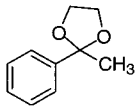
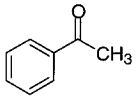
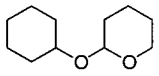
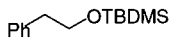
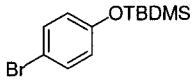
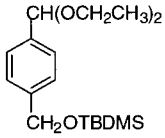
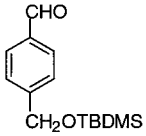
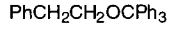
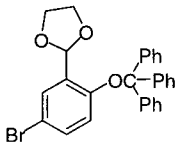
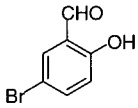
Entry	Substrate	Time, conditions	Product[a]	Yield (%)[b]
1		1 h, rt		84[c]
2		2 h, rt		98[c]
3		12 h, rt		81[c]
4		3 h, reflux		87[d]
5		1 h, rt		90[c]
6a		2h, rt		93[c]
6b	10-g scale	2.25 h, rt		86[c]
7		24 h, reflux	NR	
8		3 h, reflux		55[e]
9		12 h, reflux		72[c]
10		1 h, rt		65[c]
11a		45 min, rt		87[c]
11b	10-g scale	40 min, rt		94[c]
12		4 h, rt		88[c]
13		12 h, reflux		See foot note f
14		12 h, reflux		87[c]
15		3 h, reflux		85[e]

Table 1. (Continued)

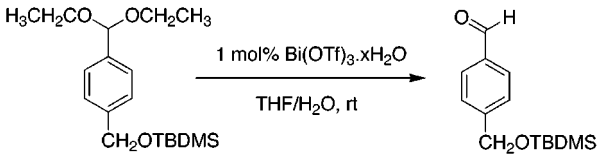
Entry	Substrate	Time, conditions	Product[a]	Yield (%)[b]
16		6 h, reflux		89[e]
17		6 h, reflux		86[c]
18		2 h, rt	NR	
19		2 h, rt	NR	
20		2 h, rt	NR	
21		45 min, rt		89[e]
22		12 h, reflux	NR	
23		12 h, reflux		98[g]

[a] All the products have been reported previously in the literature.[4] [b] Refers to yield of isolated product. [c] Crude product was >98% pure (based on ^{1}H NMR and ^{13}C NMR spectra) and hence it was not purified further. [d] Purified by trituration with cold hexanes. [e] Purified by flash column chromatography. [f] Product was a mixture of SM (67%) and benzil (33%). [g] Work up was modified as follows: After removal of THF, the residue was extracted with ether. Product was then isolated by extraction of the ether solution with 2 M aqueous NaOH followed by acidification.

(entry 5) and citral (entry 6). Acetals derived from nonconjugated aldehydes were more resistant to the reagent. When the dimethyl acetal of heptanal (entry 7) was subjected to the reaction conditions, almost no heptanal (<2% based on ^{1}H NMR) formed and the starting material was recovered unchanged. Even after the reaction mixture was heated at reflux for 24 h, >95% of the starting material remained. However, both phenylacetaldehyde dimethyl acetal (entry 8) and 2-phenylpropionaldehyde dimethyl acetal (entry 9) underwent deprotection when heated at reflux. Acetals derived from aromatic as well as aliphatic ketones (entries 10−12) underwent smooth deprotection at room temperature. The presence of a carbonyl group α to the acetal moiety slowed the rate of deprotection. Thus the monacetal derived from benzil underwent only partial deprotection, even when heated at reflux (entry 13). Conjugation with a triple bond accelerated the rate of the deprotection of aldehyde acetals relative to unconjugated aldehyde acetals, but not to the same degree as a double bond. The diethyl acetal of phenylpropargyl aldehyde (entry 14) was converted to phenylpropargyl aldehyde in good yield when heated at reflux for 12 h.

Cyclic acetals did not undergo deprotection at room temperature (entries 15−17), and the starting material was recovered in quantitative yield in all cases. However, they underwent smooth deprotection under reflux conditions. This is in contrast to results obtained using bismuth(III) nitrate pentahydrate as a reagent for deprotection of acetals which proved to be ineffective for deprotection of dioxolanes. Tetrahydropyranyl ether (entry 18) as well as *tert*-butyldimethylsilyl ethers derived from both alcohols and phenols (entries 19 and 20) were resistant to the reaction conditions. To demonstrate the chemoselectivity of this reagent, the TBDMS ether (entry 21) of 4-(diethoxymethyl)benzenemethanol was prepared.[4] We were able to remove the acetal group without affecting the TBDMS group to yield 4-(*tert*-butyldimethylsilyloxy)methylbenzaldehyde in a good yield (Scheme 2).

Scheme 2



Thus this method can be used to selectively deprotect an acetal in the presence of a TBDMS group in a multifunctional compound. While the trityl ether derived

from an alcohol proved resistant to the reagent (entry 22), deprotection of a trityl ether derived from a phenol was observed. The bifunctional compound containing a dioxolane and trityl-protected phenol moiety (entry 23) was converted to the corresponding bromosalicyladehyde in an excellent yield.

Several control experiments were carried out in order to gain some mechanistic insights. No reaction was observed when the substrate was stirred as a solution in THF/H_2O in the absence of the catalyst, indicating that the presence of bismuth triflate is necessary to cause deprotection. A suspension of $Bi(OTf)_3 \cdot xH_2O$ in water is acidic, and the aqueous layer from the workup was also found to be acidic (pH 2). Deprotection of several acetals (entries 1, 3, 4, 11, and 15) was attempted in THF/H_2O containing a few drops of triflic acid (approximately 2 mol %) instead of bismuth triflate. In all cases the corresponding carbonyl compound was formed in comparable yields. However, unlike bismuth(III) triflate which is a noncorrosive solid, triflic acid is a corrosive liquid that is difficult to handle even on a small scale. Deprotection was also studied in a buffered medium to see if there remained any Lewis acid catalytic effect.[15] The deprotection of benzaldehyde dimethyl acetal (entry 1) and acetophenone dimethyl acetal (entry 11) was carried out with 1 mol % bismuth triflate in the presence of (a) 2 mol % Proton-Sponge ([1,8-bis-dimethylamino]-naphthalene)[16] and (b) 5 mol % solid potassium carbonate. Significant deprotection (>10%) did not occur in any case, and the starting material was recovered in good yields. If the deprotection was accelerated primarily by complexation of the Lewis acid to the carbonyl group, one would expect the added potassium carbonate to have little effect on the rate of deprotection. However, since signifcant deprotection does not occur in the presence of potassium carbonate, it appears that triflic acid is the active catalyst in this system.

In conclusion, this paper describes the use of bismuth triflate for the chemoselective deprotection of acetals derived from ketones and conjugated aldehydes. The advantages of this method are (1) the highly catalytic nature of the reagent, (2) the observed selectivity, and (3) the use of a relatively nontoxic solvent system.

Experimental Section[17]

Typical Procedure. A solution of (1,1-dimethoxyethyl)-benzene (1.00 g, 6.02 mmol) (entry 11) in THF/H_2O (8 mL of THF, 2 mL of H_2O) was stirred at room temperature as $Bi(OTf)_3 \cdot xH_2O$ (4.0 mg, 6×10^{-3} mmol) was added. After 45 min, THF was removed on a rotary evaporator, and the residue was extracted with diethyl ether. The organic layer was washed with 10% aqueous $NaHCO_3$ and saturated NaCl and dried (Na_2SO_4). The solvent was removed on a rotary evaporator to yield 0.630 g (87%) of acetophenone that was determined to be >98% pure by ^1H and ^{13}C NMR spectroscopy.

Large Scale Deprotection. A solution of citral dimethyl acetal (10.0 g, 0.050 mol) (entry 6) in THF/H_2O (80 mL of THF, 20 mL of H_2O) was stirred at room temperature as $Bi(OTf)_3 \cdot xH_2O$ (33.1 mg, 0.0504 mmol) was added. After 2 h, THF was removed on a rotary evaporator, and the residue was extracted with diethyl ether (2×40 mL). The organic layer was washed with 10% aqueous $NaHCO_3$ and saturated NaCl and dried (Na_2SO_4). The solvent was removed on a rotary evaporator to yield 7.17 g (93%) of citral that was determined to be >98% pure by ^1H and ^{13}C NMR spectroscopy. Based on GC and NMR analysis of the product, it was concluded that no isomerization of the double bond in citral acetal occurred during the deprotection.

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(16) Brezinski, B.; Grech, E.; Malarski, Z.; Sobczyk, L. *J. Chem. Soc., Perkin Trans. 2* **1991**, *2*, 857.

(17) For details of the general Experimental Section, see ref 4.