A Simple Chemoselective Method for the Deprotection of Acetals and Ketals Using Bismuth Nitrate Pentahydrate

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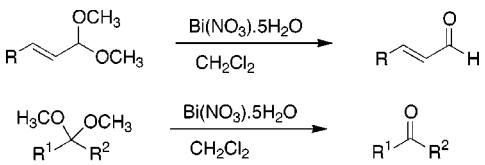
Introduction

Acyclic 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] Some examples include *p*-TsOH/acetone,[2a] Amberlyst-15/acetone/H_2O,[2b] 50% trifluoroacetic acid in $CHCl_3/H_2O$,[2c] aqueous dimethyl sulfoxide,[2d] and $LiBF_4$ in CH_3CN.[2e] However, many of these methods involve the use of corrosive reagents and elevated temperatures. Hence several milder methods that use neutral conditions have also been developed for the deprotection of acetals and ketals.[3a−c] A selective method for cleavage of acetals and ketals in the presence of other acid-labile protective groups such as TBDMS has also been reported.[3d] The identification of a mild and chemoselective bismuth based reagent for the deprotection of acetals formed the basis of this investigation. Bismuth compounds are attractive candidates for use as reagents in organic synthesis for several reasons. Most bismuth compounds are relatively nontoxic, readily available at a low cost and are fairly insensitive to small amounts of water.[4] Bismuth has an electron configuration of $[Xe]4f^{14}5d^{10}6s^26p^3$. Due to the weak shielding of the 4f electrons (Lanthanide contraction), bismuth(III) compounds exhibit Lewis acidity. Bismuth(III) nitrate has been used as a catalyst for the deprotection of *S*,*S*-acetals using air.[5]

Results and Discussion

We wish to report that bismuth nitrate pentahydrate, $Bi(NO_3)_3{\cdot}5H_2O$, is an efficient reagent for the selective deprotection of acyclic acetals derived from ketones and conjugated aldehydes (Scheme 1).

Scheme 1



The experimental procedure is very simple and involves stirring the acetal as a solution in dichloromethane with 25 mol % of bismuth nitrate at room temperature. The reaction is fast and the product is isolated by a simple aqueous workup. Bismuth nitrate is commercially available and requires no special handling. It is insoluble in common organic solvents and is used as a suspension. The best yields were obtained with use of 25 mol % reagent. Dichloromethane was found to be the best solvent for the deprotection. Less satisfactory results were obtained in tetrahydrofuran and diethyl ether. Less than 50% reaction was complete in 2 h in these solvents. The results of this study are summarized in Table 1.

Acetals derived from aromatic aldehydes underwent smooth deprotection at room temperature. Thus, benzaldehyde dimethylacetal (entry 1), piperonal dimethylacetal (entry 2) and the terephthalaldehyde mono(diethyl acetal) (entry 3) were all converted to the corresponding aldehydes in good yields. Similar results were obtained with the conjugated acetals derived from cinnamaldehyde (entry 4) and *trans*-2-hexenal (entry 5). To our surprise, acetals derived from nonconjugated aldehydes were more resistant to the reagent. When the dimethyl acetal of heptanal (entry 6) was subjected to the reaction conditions, no heptanal (<2% based on ^1H NMR) formed and the starting material was recovered unchanged. Even after the reaction mixture was heated at reflux for 24 h in the presence of 25 mol % $Bi(NO_3)_3{\cdot}5H_2O$, over 50% of the starting material remained. Similar results were obtained with phenylacetaldehyde dimethyl acetal (entry 7). Interestingly, the addition of a methyl group alpha to the acetal moiety accelerated the rate of deprotection. Thus, with 2-phenylpropionaldehyde dimethyl acetal (entry 8), deprotection was 50% complete after 2 h at room temperature. Complete deprotection however required another 16 h and the addition of one more equivalent of $Bi(NO_3)_3{\cdot}5H_2O$. The presence of a carbonyl group alpha to the acetal moiety did not seem to accelerate the reaction to any significant extent. No reaction was observed with 2,2-diethoxyacetophenone (entry 9). In contrast, acetals derived from aromatic as well as simple ketones (entries 10−13) underwent smooth deprotection at room temperature. However, reflux conditions were required to deprotect the monacetal derived from benzil (entry 14). Conjugation with a triple bond seemed to accelerate the rate of the deprotection of aldehyde acetals relative to unconjugated aldehyde acetals, but not to the same extent as a double bond. The diethyl acetal of phenylpropargyl aldehyde (entry 15) was only partially converted (40%) to phenylpropargyl aldehyde even after heating at reflux for 24 h.

As expected, cyclic acetals were much more resistant to the reaction conditions. No reaction was observed at room temperature with the dioxolanes (entries 16 and 17) and the starting material was recovered in quantita-

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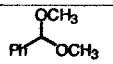
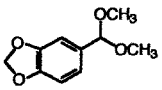
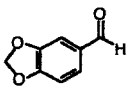
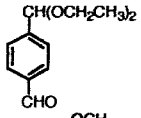
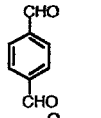
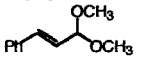
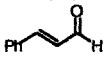
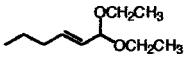
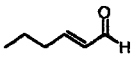
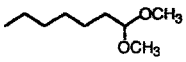
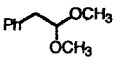
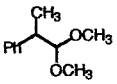
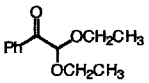
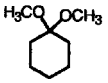
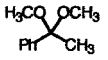
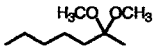
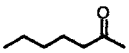
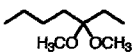
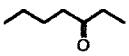
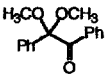
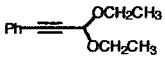
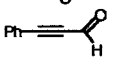
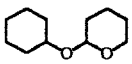
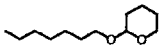
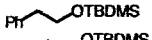
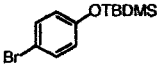
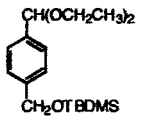
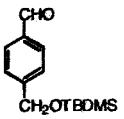
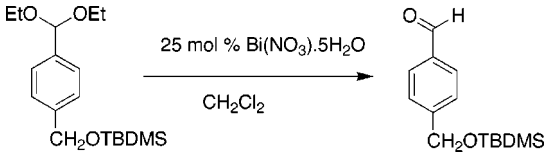
Table 1. Deprotection of Acetals and Ketals in CH_2Cl_2 Using $Bi(NO_3)\cdot 5H_2O$

Entry[a]	Substrate	Time	Product	Yield (%)[b]
1		1 h		80[c]
2[10]		2 h		98[d]
3		1 h		90[e]
4[11]		2 h		76[c]
5		2 h		83[c]
6		2 h	NR	
7		2 h	NR	
8		2 h		foot note f
9		2 h	NR	
10		2 h		86[c]
11		2 h		95[c]
12[12]		2 h		78[c]
13[12]		2 h		86[c]
14		12 h		95[d]
15		2 h		foot note f
16		5 days		88[c]
17		2 h	NR	
18[13]		2 h	NR	
19[14]		2 h	NR	
20[9]		2 h	NR	
21		2 h	NR	
22		45 min		76[g]

[a] Superscripts against entry no. refer to literature reference for substrate. [b] Refers to isolated yield. [c] Purified by Kugelrohr distillation. [d] Crude product was >98% pure (based on ^1H NMR and ^{13}C NMR spectra), and hence, it was not purified further. [e] Purified by trituration with cold hexane. [f] Product was a 1:1 mixture (based on ^1H NMR) of starting material and product. [g] The product has been reported in the literature (see ref 16).

Scheme 2



tive yield. Tetrahydropyranyl ethers derived from cyclohexanol and 2-heptanol (entries 18 and 19) proved resistant to the reaction conditions as well. Similar lack of reactivity was observed with *tert*-butyl dimethylsilyl ethers derived from both phenols and alcohols (entries 20 and 21). To demonstrate the chemoselectivity of this reagent, we prepared (entry 22) the TBDMS ether of 4-(diethoxymethyl)benzenemethanol. We were able to remove the acetal group without affecting the TBDMS group to yield 4-(*tert*-butyldimethylsilyloxy)methylbenzaldehyde in good yield (Scheme 2).

Thus this method can be used to selectively deprotect acyclic acetals in the presence of a THP ether or TBDMS ether in a multifunctional compound.

While detailed mechanistic studies were not carried out, a few points merit comment. No reaction was observed when an acetal was stirred as a solution in dichloromethane saturated with water, suggesting that the presence of bismuth nitrate is necessary to cause deprotection. A suspension of $Bi(NO_3)_3 \cdot 5H_2O$ in water is acidic. The aqueous layer from the workup was also found to be very acidic (pH 2). Thus it appears that the reagent, when suspended in dichloromethane releases small amounts of nitric acid which presumably promotes the deprotection. It is also possible that the coordination of bismuth to the acetal oxygen increases the susceptibility of the acetal carbon to nucleophilic attack by water.

In conclusion, this paper describes the use of bismuth nitrate pentahydrate for the chemoselective deprotection of acetals derived from ketones and conjugated aldehydes. The advantages of this method are the ease of work up, the observed selectivity and the use of a relatively nontoxic reagent that is easy to handle and is inexpensive.

Experimental Section

NMR spectra were recorded on a JEOL Eclipse NMR spectrometer at 270 MHz (^{1}H) and 67.5 MHz (^{13}C) in $CDCl_3$ as the solvent. Flash chromatography was performed on Merck Silica gel (230−400 Mesh).[6] Thin-layer chromatography was performed on aluminum backed silica gel plates. Spots were visualized under UV light or by spraying the plate with phosphomolybdic acid followed by heating. All products have been reported previously in the literature and were characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. Acetals were either purchased commercially or synthesized as described. Acetals[7] (entry 2 and 4) and THP ethers[8] (entries 18, 19) were made by literature methods. The TBDMS ether from 2-phenethyl alcohol (entry 20)[9] was prepared by treatment of the alcohol with *tert*-butyldimethylsilyl chloride in the presence of DMAP and triethylamine.

General Procedure for Deprotection. A solution of benzaldehyde dimethyl acetal (4.00 g, 26.3 mmol) in dichloromethane (60 mL) was stirred at room temperature as $Bi(NO_3) \cdot 5H_2O$ (3.19 g, 6.58 mmol) was added. After 2 h, the mixture was filtered, and the filtrate was washed with 10% aqueous $NaHCO_3$ (20 mL), saturated NaCl (20 mL) and dried (Na_2SO_4). The solvent was removed on a rotary evaporator to yield a pale yellow liquid that was purified by kugelrohr distillation to give 2.40 g (86%) of a colorless liquid (>98% pure by ^{1}H NMR). The product was identified to be benzaldehyde by ^{1}H NMR, ^{13}C NMR and comparison of the IR spectrum with that of an authentic sample.

General Procedure for Preparation of Acetals (Entries 6, 12, and 13). A solution of the carbonyl compound (1 equiv) in methanol (1 equiv), and trimethyl orthoformate (1.5 equiv) was stirred in a round-bottom flask as *p*-toluenesulfonic acid (0.02 equiv) was added. A short path distillation head was attached, and the flask was heated at 90 °C using an oil bath until no more methanol came off. The process was repeated twice with addition of another equivalent of trimethyl orthoformate each time. The reaction mixture was taken up in diethyl ether, washed with 10% aqueous Na_2CO_3 (25 mL) and H_2O (4 × 20 mL), and dried (Na_2SO_4), and the solvents were removed on a rotary evaporator to give the crude acetal which was further purified by flash chromatography or Kugelrohr distillation.

Preparation of TBDMS Ether of 4-(Diethoxymethyl)-benzenemethanol (22). A solution of 4-(diethoxymethyl)-benzenemethanol[15] (2.00 g, 9.51 mmol), triethylamine (1.23 g, 12.2 mmol), and DMAP (0.678 g, 5.55 mmol) in anhydrous dichloromethane (40 mL) was stirred under N_2 at room temperature as *tert*-butyldimethylsilyl chloride (1.84 g, 12.2 mmol) was added. The mixture was stirred for 4 h, diluted with CH_2Cl_2, washed with water (4 × 25 mL) and saturated NaCl, and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to give a crude product that was purified by flash chromatography (5% ethyl acetate-95% hexanes) to yield 2.17 g of a clear liquid (70%). ^{1}H NMR: δ 0.10 (s, 6 H), 0.95 (s, 9 H), 1.23 (m, 6 H), 3.58 (m, 4 H), 4.75 (s, 2 H), 5.51 (s, 1 H), 7.32 (d, 2 H, J = 8.2 Hz), 7.44 (d, 2 H, J = 8.2 Hz). ^{13}C δ −5.01, 15.14, 18.35, 25.89, 60.80, 64.70, 101.39, 125.73, 126.47, 137.65, 141.43. IR (neat) ν_{max} 1090, 1470, 2940 cm^{-1}. Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H 9.94. Found: C, 66.52; H 10.07.

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