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Deprotection of Ketoximes Using Bismuth(III) Nitrate Pentahydrate

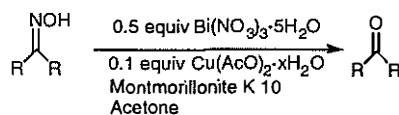
Bryce A. Nattier, Kyle J. Eash, Ram S. Mohan

Abstract: Ketoximes undergo facile deprotection in acetone–H₂O (9:1) in the presence of 0.5 equivalents of Bi(NO₃)₃·5H₂O. Bismuth(III) nitrate is relatively non-toxic, insensitive to air and inexpensive. These features coupled with the use of a relatively non-toxic solvent system make this method an attractive alternative to existing routes for deprotection of ketoximes.

Key words: bismuth and compounds, oximes, deprotection, protecting groups, ketones

Oximes are frequently used to protect carbonyl compounds and hence considerable attention has been given to develop methods for their deprotection.² Oximes can also be synthesized from non-carbonyl compounds and thus their conversion to carbonyl compounds constitutes a useful synthesis of the latter.³ The classical method for deprotection of oximes viz. hydrolytic cleavage requires the use of strong mineral acids and often results in low yields. Hence a number of oxidative methods have been developed for cleavage of oximes. Some examples include Dess–Martin periodinane,⁴ PCC,⁵ TBHP,⁶ I₂/CH₃CN,⁷ manganese acetate/benzene,⁸ and potassium peroxy-monopersulfate.⁹ However, many of these reagents or the solvent systems used are toxic, corrosive or difficult to handle, especially on a large scale. With increasing environmental concerns, it is imperative that new “environment friendly” reagents be developed.¹⁰ One example of such an environment friendly, mild method for deprotection of oximes uses DOWEX®50W.¹¹ Recently, bismuth compounds have become attractive candidates for use as reagents in organic synthesis because most bismuth compounds are relatively non-toxic, readily available at low cost and are fairly insensitive to small amounts of water.¹² Bismuth has an electron configuration of [Xe]4f¹⁴5d¹⁰6s²6p³. Due to the weak shielding of the 4f electrons (Lanthanide contraction), bismuth(III) compounds exhibit Lewis acidity. Bismuth in the +5 state is an oxidizing agent. Recently zinc bismuthate has been reported as a reagent for conversion of allylic and benzylic oximes to the corresponding aldehyde or ketone in high yields.¹³ Zn(BiO₃)₂ is however not commercially available and must be synthesized prior to use. The deprotection of oximes using BiCl₃ under microwave irradiation conditions has also been reported.¹⁴





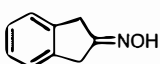
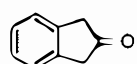


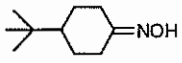
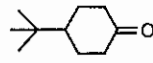
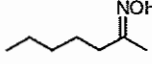
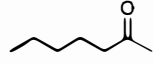
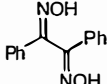
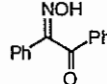
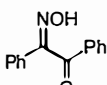
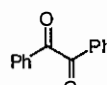

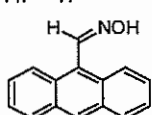

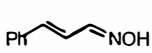
We wish to report that Bi(NO₃)₃·5H₂O is an efficient reagent for the conversion of ketoximes to ketones (Scheme, Table). The reaction is carried out using 0.5 equivalent of Bi(NO₃)₃·5H₂O and 0.1 equivalent of Cu(AcO)₂·xH₂O. The best yields were obtained when bismuth nitrate was mixed with Montmorillonite K 10. Bismuth nitrate pentahydrate is commercially available and requires no special handling. The use of an inert atmosphere is not required for these reactions. Several solvents including acetone–H₂O, acetonitrile, dichloromethane and tetrahydrofuran were investigated during the course of this study. The best results were achieved using acetone–H₂O (9:1, v/v). Deprotection was also observed in good yield in dichloromethane. However, some oximes (acetophenone oxime and cyclohexanone oxime) underwent a very exothermic reaction in dichloromethane. No such exothermic reaction was observed with acetone–H₂O as the solvent system.



Scheme

While detailed mechanistic studies were not carried out, a few points merit comment. The use of Montmorillonite K 10 gave a better yield of product though deprotection was also observed in its absence. Presumably, Montmorillonite K 10 acts as a carrier to increase the surface area in this heterogeneous reaction. In the absence of copper(II) acetate, the crude product was found to contain up to 10% acetone oxime. The formation of acetone oxime is not surprising in light of the fact that oximes have been synthesized from aldehydes and ketones using acid catalyzed transoximations by acetone oxime.¹⁵ No deprotection was observed when cyclohexanone oxime or acetophenone oxime was heated in acetone–H₂O in the absence of bismuth nitrate, suggesting that the presence of this reagent is necessary for deprotection. A suspension of Bi(NO₃)₃·5H₂O in water is acidic. The aqueous layer from the work up was also found to be very acidic (pH 2). Thus it appears that the reagent, when suspended in the solvent, releases small amounts of nitric acid which presumably promotes the deprotection. It is also possible that the coordination of bismuth to the oxime nitrogen increases the susceptibility of the oxime carbon to nucleophilic attack by water.

Table Deprotection of Ketoximes using $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ in Acetone– H_2O

Entry	Oxime	Time (h)	Product	Yield (%) ^a
1		2		88 ^b
2		3		80 ^c
3		3		76 ^c
4		2		80 ^d
5 ¹²		2		90 ^d
6 ^{2,d}		5		80 ^d
7		12		68 ^c
8		21		65 ^c
9		4	NR ^f	
10		4	NR ^f	
11		12		^e
12		12		^e

^a Refers to yield of isolated product.^b Purified by Kugelrohr distillation.^c Purified by flash chromatography.^d Crude product was found to be >98% pure by ¹H and ¹³C NMR spectroscopy and hence further purification was deemed unnecessary.^e NMR analysis of the crude product showed that only partial deprotection (25%) had occurred after 12 h.^f NR = No reaction.

The results of this study are summarized in the Table. The deprotection works well with a variety of ketoximes. In contrast to monooximes, benzil dioxime (entry 7) underwent hydrolysis at a much slower rate and hence it was possible to isolate benzil monooxime from this reaction. Benzil monooxime was also synthesized from benzil¹⁶ and subjected to the reaction conditions. Deprotection to benzil was observed but as expected, the rate of the reaction was much slower. This suggests that the deprotection occurs in a sequential manner and that the rate of deprotection of the dioxime is faster than that of the intermediate monooxime. Aldoximes on the other hand proved

much more resistant to the deprotection conditions. Benzaldehyde oxime (entry 9) and anthraldehyde oxime (entry 10) were recovered unchanged when subjected to the reaction conditions for 4 hours. Only partial deprotection (approx. 25%) was observed when heptanal oxime (entry 11) or cinnamaldehyde oxime (entry 12) was heated for 12 hours under the same conditions. This is in contrast to results obtained with zinc bismuthate, which works well for deprotection of aldoximes but fails to give good yields of ketone with aliphatic ketoximes or dioximes.¹³

A representative procedure is given here: A solution of 2-heptanone oxime (2.00 g, 15.5 mmol) in acetone– H_2O (9:1, v/v) (50 mL) was stirred as $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (3.75 g, 7.74 mmol), $\text{Cu}(\text{AcO})_2 \cdot x\text{H}_2\text{O}$ (0.28 g, 1.55 mmol) and Montmorillonite K 10 (3.0 g) were added. The mixture was stirred and heated at reflux. After 5 h, the mixture was suction filtered and the solids were rinsed with acetone. The combined filtrates were concentrated on a rotary evaporator to remove most of the acetone. The residue was partitioned between sat. NaCl and Et_2O . The organic layer was washed with sat. NaHCO_3 , sat. NaCl, dried (Na_2SO_4), and the solvents were removed on a rotary evaporator to yield 1.42 g (80%) of 2-heptanone that was determined to be > 98% pure by ¹H and ¹³C NMR spectroscopy.

In summary, this work demonstrates a new and useful method for deprotection of ketoximes. The advantages include (1) the use of a relatively non-toxic reagent that is insensitive to air and moisture and (2) the use of a relatively non-toxic solvent system.

Acknowledgement

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