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Bismuth Compounds in Organic Synthesis. Deprotection of Ketoximes Using Bismuth Bromide-Bismuth Triflate

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Abstract—Ketoximes undergo deprotection in CH_3CN/acetone/H_2O (3:6:1) in the presence of 20–40 mol% $BiBr_3$/5 mol% $Bi(OTf)_3$. Bismuth(III) salts are 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.

Keywords: bismuth and compounds; oximes; deprotection; environment-friendly chemistry.

Oximes are frequently used to protect carbonyl compounds and hence considerable attention has been given to develop methods for their deprotection.[1] Oximes can also be synthesized from non-carbonyl compounds and thus their conversion to carbonyl compounds constitutes a useful synthesis of the latter.[2] The classical method for deprotection of oximes viz. hydrolytic cleavage requires the use of strong mineral acids and often results in low yields due to the formation of polymeric by-products. Hence a number of oxidative methods have been developed for the cleavage of oximes. Some examples include Dess–Martin periodinane,[3] PCC,[4] TBHP,[5] I_2/CH_3CN,[6] manganese acetate/benzene,[7] and potassium peroxymonopersulfate.[8] However, many of these reagents or the solvents 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.[9] One example of a mild method for deprotection of oximes uses DOWEX-50 resin.[10] 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.[11] 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. $BiCl_3$/microwave,[12] $BiCl_3$ in the presence of benzyltriphenylphosphonium peroxymonosulfate[13] and $Bi(NO_3)_3\cdot5H_2O$[14] have been used for the deprotection of oximes. We now report the use of a new bismuth-based catalyst system (bismuth bromide/bismuth triflate) for the deprotection of ketoximes.

Our continued work with bismuth(III) reagents has led to the development of bismuth bromide/bismuth triflate as an efficient reagent for the conversion of ketoximes to ketones (Scheme 1, Table 1).
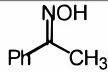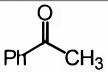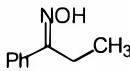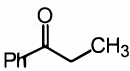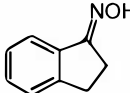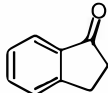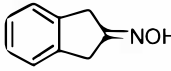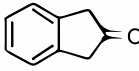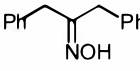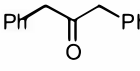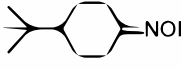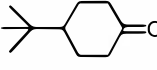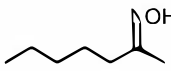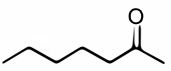
The reaction is carried out using 20–40 mol% $BiBr_3$ and 5 mol% $Bi(OTf)_3\cdot4H_2O$ as a co-catalyst. The use of an inert atmosphere is not required for these reactions. Several solvents were investigated during the course of this study. The best results were achieved using CH_3CN/acetone/H_2O (3:6:1, v/v/v). The results of this study are summarized in Table 1.

While detailed mechanistic studies were not carried out, a few points merit comment. While $BiBr_3$ alone was effective in catalyzing the deprotection, the addition of $Bi(OTf)_3$ accelerated the reaction considerably. The use of 5 mol% $Bi(OTf)_3$ alone (no $BiBr_3$) was almost ineffective in catalyzing the deprotection. However, when 40 mol% $Bi(OTf)_3$ was used alone, the deprotection did
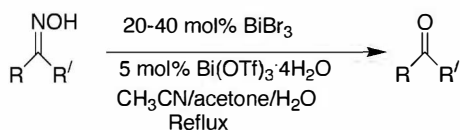
Scheme 1.

Table 1. Deprotection of ketoximes using $BiBr_3$-$Bi(OTf)_3 \cdot 4H_2O$ in CH_3CN/acetone/H_2O

Entry	Oxime	Time, h	Product	Yield (%) [a,b]
1		2.5		68 (94)
2		2		77 (98)
3		22		76 (98)[c]
4		3		79 (96)
5		0.7 h		65 (95)
6		4		85 (96)[c]
7		1		79 (93)
8		1		64 (92)

[a]Yields are not optimized. Refers to yield of isolated product. .
[b]Numbers in parentheses refer to percent purity of crude product as estimated by ^{1}H & ^{13}C NMR spectroscopy and GC analysis. The remainder was oxime in all cases.
[c]Product was purified by recrystallization from hexane.

proceed smoothly. Since $BiBr_3$ is commercially available, we found it more practical to use $BiBr_3$ with $Bi(OTf)_3$ as a co-catalyst.[15] A suspension of the catalyst system in water is acidic (pH 2). Hence it is possible that the true catalyst is HBr and/or TfOH, released from hydrolysis of $BiBr_3$ and $Bi(OTf)_3$. Indeed, the deprotection of 1-indanone oxime using 1.2 equivalents of HBr and 15 mol% TfOH proceeded smoothly, but the highly corrosive nature of HBr and TfOH detract from their use. The attempted deprotection of 1-indanone oxime using $BiBr_3$ and $Bi(OTf)_3$ in the presence of proton-sponge®(N,N,N',N'-tetramethyl-1,8-naphthalenediamine)[16] was unsuccessful suggesting that the main role of the catalysts is to provide an acidic reaction medium.

The choice of solvents also merits comments. Acetone/H_2O was found to be effective but the rate of deprotection was considerably slower in this solvent system. For example, the deprotection of 1-indanone oxime in acetone/H_2O took over 12 h, while the addition of the polar coordinating solvent CH_3CN accelerated the reaction considerably (reaction time = 3 h). Acetone oxime was found to be a product of the reaction. This is not surprising in light of the fact that oximes have

been synthesized from aldehydes and ketones by acid catalyzed transoximations using acetone oxime.[17] This suggests that the role of acetone is to drive the equilibrium towards product formation. The deprotection of 1-indanone oxime in acetonitrile/water (6:4) was only 78% complete after 5 h, suggesting that acetone plays a crucial role in driving the reaction. Water is also necessary for the deprotection since the reaction was significantly slower in CH_3CN/acetone as the solvent.

The deprotection works well with a variety of ketoximes. Aldoximes on the other hand proved much more resistant to the deprotection conditions. With benzaldehyde oxime, the reaction reached a 1:1 equilibrium mixture of benzaldehyde and the starting oxime within an hour. When the reaction was carried out with 40 mol% $BiBr_3$/20 mol% $Bi(OTf)_3$, the reaction reached a 3.5:1 equilibrium mixture of benzaldehyde and the starting oxime in 1 h.

A representative procedure is given here: A solution 1-indanone oxime (0.500 g, 3.40 mmol) in CH_3CN/acetone/H_2O (3:6:1, v/v/v) (5.00 mL) was stirred as $BiBr_3$ (0.609 g, 1.36 mmol), and $Bi(OTf)_3 \cdot 4H_2O$ (0.111 g,

0.170 mmol) were added. The mixture was stirred and heated at reflux. Reaction progress was followed by GC analysis. After 3 h, 10% aqueous acetic acid was added and the mixture was suction filtered and the solids were rinsed with ether (20 mL). The combined filtrates were concentrated on a rotary evaporator to remove the organic solvents. The residue was extracted with ether (2×40 mL). The organic layer was washed successively with 2 M NaOH (15 mL), H_2O (3×15 mL), saturated aqueous NaCl (20 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to yield 0.356 g (79%) of 1-indanone that was determined to be at least 96% pure by ^1H and ^{13}C NMR spectroscopy and GC analysis.

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

Acknowledgements

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