Hexamethylenetetramine–Bromine: A Novel Reagent for Selective Regeneration of Carbonyl Compounds from Oximes and Tosylhydrazones†‡

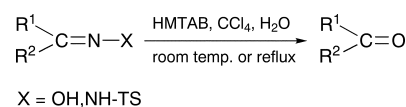## Babasaheb P. Bandgar,[*a] Shivaji B. Admane[b] and Sandip S. Jare[b]

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Hexamethylenetetramine–bromine (HMTAB) has been found to be an efficient and selective reagent for the mild oxidative cleavage of the C=N of oximes and tosylhydrazones to yield their corresponding carbonyl compounds in good to excellent yields under mild conditions.

There has been considerable growth in interest in the development of mild methods for the regeneration of carbonyl compounds from stable and readily prepared oximes and tosylhydrazones.[1] This is because such derivatives of carbonyl compounds serve as effective protecting groups for aldehydes and ketones in organic synthesis.[2] Oximes are also extensively used for the purification and characterization of carbonyl compounds. Since oximes can be prepared from non-carbonyl compounds,[3] the regeneration of carbonyl compounds from oximes provides an alternative method for the preparation of aldehydes and ketones. Most of the known methods of regenerating carbonyl compounds from their nitrogen derivatives have several limitations.[4–11] It is most important to note that most of the reported methods are suitable for the regeneration of ketones but not for aldehydes from their oximes and tosylhydrazones, and that yields are low owing to the over oxidation of regenerated aldehydes to acids. Therefore it is desirable that a method which leads to high recoveries of a wide range aldehydes and ketones should be available. We now report an efficient and general method for the effective and selective cleavage of the C=N of oximes and tosylhydrazones with HMTAB under neutral and mild conditions (Scheme 1).

Hexamethylenetetramine–bromine complex could be readily prepared by adding bromine to a chloroform

$$\underset{R^2}{\overset{R^1}{>}}C=N-X \xrightarrow[\text{room temp. or reflux}]{\text{HMTAB, CCl}_4, \text{H}_2\text{O}} \underset{R^2}{\overset{R^1}{>}}C=O$$

X = OH, NH-TS

Scheme 1

solution of hexamethylenetetramine and it has been used successfully for the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively.[12] This yellow–orange, non-hygroscopic, homogenous solid is very stable at room temperature and is not affected by ordinary exposure to light, air or water and has no offensive odour of bromine or amine. Ease of work-up and the stability of the reagent make it a safe and convenient source of active bromine.[13] The reagent is transformed during reaction into easily removable products and presents a convenient alternative to other *N*-halogenoamines.[14–17]

Table 1 summarizes the results of various oximes which underwent oxidative cleavage with HMTAB to form corresponding carbonyl compounds in good yields under mild conditions. The rate of oxidative cleavage of benzophenone oximes (entries 12–14) was fast. Even the sterically hindered ketone oximes (entries 15, 16) successfully underwent oxidative deoximation with HMTAB to give ketones in good yields.

Table 1 Oxidative cleavage of oximes with HMTAB in CCl$_4$

Entry	Substrate	Reaction conditions		Product[a]	Yield[b] (%)
		Temp. (T/ °C)	Time (t/h)		
1	4-Chlorobenzaldoxime	60	7	4-Chlorobenzandehyde	76
2	4-N,N-Dimethylaminobenzaldoxime	25	3	4-N,N-Dimethylaminobenzaldehyde	77
3	2-Nitrobenzaldoxime	60	5.3	2-Nitrobenzaldehyde	98
4	3-Nitrobenzaldoximes	60	7	3-Nitrobenzaldehyde	87
5	4-Nitrobenzaldoximes	60	6	4-Nitrobenzaldehyde	69
6	Salicylaldehyde oxime	25	4	Salicylaldehyde	40
7	Cyclopentanone oxime	25	4	Cyclopentanone	86
8	Cyclohexanone oxime	25	4	Cyclohexanone	85
9	Acetophenone oxime	25	3	Acetophenone	88
10	4-Chloracetophenone oxime	60	4	4-Chloracetophenone	84
11	4-Methylacetophenone oxime	25	2.5	4-Methylacetophenone	77
12	Benzophenone oxime	25	1.5	Benzophenone	78
13	4-Bromobenzophenone oxime	25	2	4-Bromobenzophenone	90
14	4-Chlorobenzophenone oxime	25	2	4-Chlorobenzophenone	76
15	Camphor oxime	25	2	Camphor	80
16	Menthone oxime	25	2	Menthone	87

[a]Characterized by IR, ^{1}H NMR and comparison with authentic samples. [b]Isolated yields.

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The most remarkable advantage of this methodology is that it is a general method for oxidative cleavage of a variety of aldoximes and ketone oximes with HMTAB to give the corresponding carbonyl compounds in good yields under neutral, and mild conditions, and no trace of

Table 2 Oxidative cleavage of tosylhydrazones with HMTAB in CCl$_4$ at 25 °C

Entry	Substrate	Reaction time (t/h)	Product^a	Yield^b (%)
1	Butanone tosylhydrazone	0.5	α-Bromobutanone	74
2	4-Chlorobenzaldehyde tosylhydrazone	2	4-Chlorobenzandehyde	69
3	2,4-Dichlorobenzaldehyde tosylhydrazone	1.5	2,4-Dichlorobenzaldehyde	87
4	Furfuraldehyde tosylhydrazone	2	Furfuraldehyde	60
5	2-Nitrobenzaldehyde tosylhydrazone	1.5	2-Nitrobenzaldehyde	88
6	3-Nitrobenzaldehyde tosylhydrazone	5	3-Nitrobenzaldehyde	89
7	4-Nitrobenzaldehyde tosylhydrazone	6	4-Nitrobenzaldehyde	98
8	Salicylaldehyde tosylhydrazone	2	Salicyladehyde	40
9	Cyclopentanone tosylhydrazone	2	Cyclopentanone	50
10	Cyclohexanone tosylhydrazone	2.5	Cyclohexanone	81
11	4-Chloroacetophenone tosylhydrazone	0.5	4-Chloroacetophenone	69
12	Benzophenone tosylhydrazone	0.5	Benzophenone	90

^{a}Characterized by IR, ^{1}H NMR and comparision with authentic samples. ^{b}Isolated product.

acid was formed owing to over oxidation of regenerated aldehyde. This procedure is also useful for chemoselective oxidative deoximation of ketone oximes in preference to aldoximes.

When a mixture of 2,4-dichlorobenzaldoxime and cyclopentanone oxime or 4-nitrobenzaldoxime and acetophenone oxime or 4-chlorobenzaldoxime and 4-bromobenzophenone oxime in CCl$_4$ was allowed to react with HMTAB at room temperature (25 °C) for a period of 4, 3 and 2 h, respectively, the ketoximes cyclopentanone oxime, acetophenone oxime and 4-bromobenzophenone oxime underwent chemoselectively oxidative deoximation giving cyclopentanone (80%), acetophenone (86%) and bromobenzophenone (89%) whereas the aldoximes 2,4-dichlorobenzaldoxime, 4-nitrobenzaldoxime and 4-chlorobenzaldoxime were recovered unchanged.

Table 2 shows the oxidative cleavage of tosylhydrazones with HMTAB in CCl$_4$ to give the corresponding carbonyl compounds in good yields. The aliphatic ketone tosylhydrazone shown in entry 1 underwent oxidative cleavage with HMTAB to give the α-bromoketone due to subsequent bromination of the regenerated ketone. The present procedure is general for the oxidative cleavage of aliphatic, aromatic, heteroaromatic and cyclic tosylhydrazones and no trace of acid was formed owing to over oxidation of regenerated aldehyde. In contrast recently reported methodology, involving the use of 70% TBHP, is suitable only for the deprotection of ketone tosylhydrazones and failed for aliphatic and heteroaromatic tosylhydrazones. In this connection, the present methodology is important and noteworthy.

In conclusion, we hope that the present deprotection methodology of oximes and tosylhydrazones finds wide application in organic systhesis because of the simplicity of work-up and use of readily prepared oxidant (HMTAB) under neutral and mild conditions.

Experimental

Preparation of the Hexamethylenetetramine–Bromine Complex.—A solution of bromine (20.0 g, 125 mmol) in CHCl$_3$ (100 ml) was added dropwise with stirring to a solution of hexamethylenetetramine (8.5 g, 60 mmol) in chloroform (100 ml). A yellow solid separated out as the bromine was taken up. The mixture was stirred for an additional 30 min, then the yellow solid was collected by vacuum filtration. Yield: 25.5 g (92%), mp = 170–175 °C (dec.); ν_{max}/cm^{-1} (KBr) 1460, 1360, 1325, 1045, 840 and 782 (Found: C, 15.9; H, 2.7; N, 12.8. C$_6$H$_{12}$Br$_4$N$_4$ requires C, 15.87; H, 2.63; N, 12.68%). The active bromine content of this complex is 1.5 mol Br$_2$ per mol of the complex, as determined by thiosulfate titrations.

Oximes or tosylhydrazones in CCl$_4$, when stirred at room temperature (25 °C) or boiled under reflux with HMTAB, gave the corresponding carbonyl compounds in good yields.

A Typical Procedure.—A mixture of 4-bromobenzophenone oxime (3 mmol) and HMTAB (3.1 mmol) in CCl$_4$ (10 ml) and 1 ml water was stirred at room temperature (25 °C) for 2 h. After the reaction was complete (TLC), insoluble hexamethylenetetramine was removed by filtration and washed with CCl$_4$ (2 × 10 ml); the CCl$_4$ layer was dried over anhdrous Na$_2$SO$_4$. Removal of the solvent under reduced pressure gave the product in good yield and in almost pure form.

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