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Oxidative fragmentation of oxiranes to nitriles with hypervalent iodine(V) reagents in aqueous ammonia

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ABSTRACT

Oxiranes undergo oxidative fragmentation when treated with hypervalent iodine(V) reagents particularly *o*-iodoxybenzoic acid in aqueous ammonia to give nitriles. The reaction goes via the formation of 1, 2-amino alcohols as intermediates followed by C–C bond cleavage.

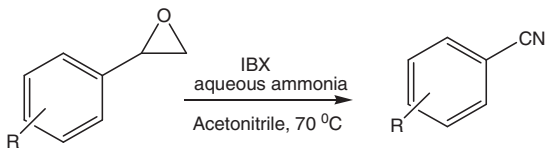
Oxidative fragmentation of oxirane is one of the significant reactions developed in organic chemistry. Oxiranes are easily prepared from olefins[1] or carbonyl compounds[2] and are important intermediates in organic synthesis.[3] The trend of oxiranes to undergo oxidative ring-opening reactions is well-known.[4] Due to their particular polarity and strained three member ring system, a large variety of nucleophiles can be employed for ring opening of these compounds[5] and subsequently transformed into a variety of products.[6] One such a transformation is oxidative C–C bond fragmentation leading to dicarbonyl compounds including diketones, aldehydes, carboxylic acids and their combination depending on the substrate and conditions.[7]

A major advantage of accessing carbonyl compounds through oxiranes via diols rather than olefins is to have additional scope for selective epoxidation of compounds with multiple double bonds.[8] 1,2-Amino alcohols that can be readily obtained from oxiranes undergo photooxidative fragmentation forming carbonyl compounds.[9] Direct oxidative fragmentation of oxiranes using domino reactions such as epoxide opening followed by oxidation is limited. Some examples are the reaction of I,I-bis(trifluoroacetoxy) iodobenzene (BTI) with 2-phenyloxirane undergoing exclusively C–C fragmentation, giving benzaldehyde and formaldehyde. Outcome of the reaction is different if oxirane is alkyl substituted and undergoes C–O fragmentation to give α-hydroxy ketones.[10a]

Other hypervalent based oxidizing agents such as periodic acid[10b] HIO_4 and sodium periodate,[11a,11c] PhIO along with HBF_4 in CH_2Cl_2-hexafluoroisopropanol (HFIP)-H_2O system[11b] have been used with terminal oxiranes leading to formation of aldehydes with one carbon less.

In all these cases formation of vicinal diol is the first step and is followed by oxidative cleavage.[11c] Oxidative fragmentations of terminal oxiranes are well reported with other reagents such as sodium dichromate[12a] in aqueous sulfuric acid as well as CAN[12b] as stoichiometric reagent. A catalytic oxidation of oxiranes has been described using molecular oxygen and DMSO with bismuth(III) mandelate as a catalyst in which terminal oxiranes led to the corresponding carboxylic acids and CO_2.[12c]

IBX chemistry is of current interest as indicated by many latest reviews.[13] Recently we have reported a facile transformation of aldehydes to nitriles[14a] in almost quantitative yield as well as oxidative decarboxylation of α-amino acids to nitriles[14b] using *o*-iodoxybenzoic acid in aqueous ammonia. In continuation of



1a **2a**

R= H

Scheme 1. Oxidative fragmentation of phenyloxirane to benzonitrile.

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Table 1
Optimization of reagent and reaction conditions[a]

Entry	Reagent combination	Temp	Time (h)	Yield[b] (%) **2a**
1	IBX/Water	rt	12	NR[c]
2	IBX/Water	70 °C	8	NR[c]
3	IBX/aqueous ammonia	rt	12	NR[c]
4	IBX/aqueous ammonia	70 °C	4	90
5	DMP/aqueous ammonia	rt	12	NR[c]
6	DMP/aqueous ammonia	70 °C	7	80

[a] Reaction performed on 5 mmol of **1a.**
[b] Isolated yields.
[c] NR = no reaction.

Table 2
Oxidative fragmentation of oxiranes to nitriles[a]

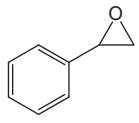
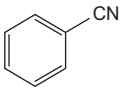
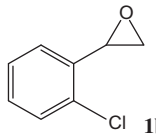
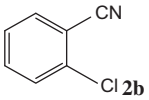
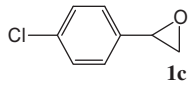
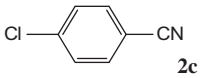
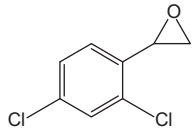
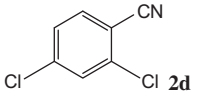
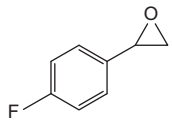
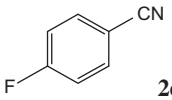
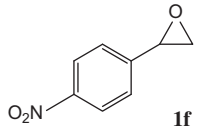
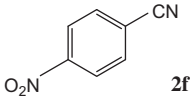
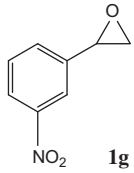
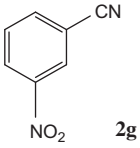
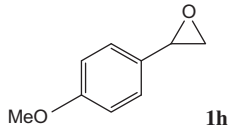
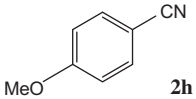
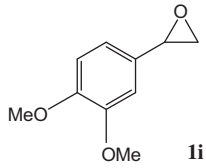
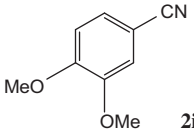
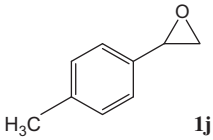
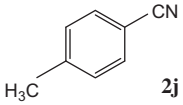
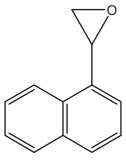
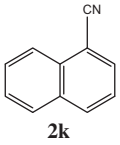
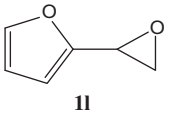
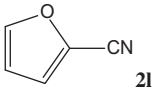
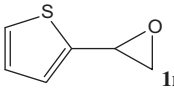
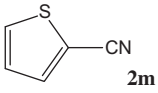
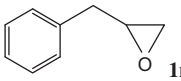
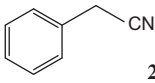
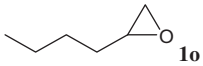
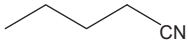
Entry	Substrate (**1**)	Product (**2**)	Yield (%)[b]
1	 **1a**	 **2a**	90
2	 **1b**	 **2b**	91
3	 **1c**	 **2c**	82
4	 **1d**	 **2d**	85
5	 **1e**	 **2e**	83
6	 **1f**	 **2f**	86
7	 **1g**	 **2g**	85
8	 **1h**	 **2h**	84
9	 **1i**	 **2i**	83

Table 2 (*continued*)

Entry	Substrate (**1**)	Product (**2**)	Yield (%)[b]
10	 **1j**	 **2j**	86
11	 **1k**	 **2k**	85
12	 **1l**	 **2l**	82
13	 **1m**	 **2m**	84
14	 **1n**	 **2n**	90
15	 **1o**	 **2o**	76

[a] Reactions were carried out on 5 mmol scale in aqueous ammonia at 70 °C with IBX. (2.0 equiv) up to 3.5–4 h.
[b] Isolated yields.

our investigations with hypervalent iodine reagents in aqueous ammonia, we reacted phenyloxirane with IBX in aqueous ammonia at 70 °C and observed oxidative fragmentation forming benzonitrile (Scheme 1). In the follow up investigations it was found that oxiranes undergo nucleophilic ring opening on reaction with ammonia forming 1,2-amino alcohol as intermediates which subsequently undergo oxidative fragmentation. To the best of our knowledge, this is the first report on the oxidative fragmentation of oxiranes (aryl/alkyl) forming nitriles.

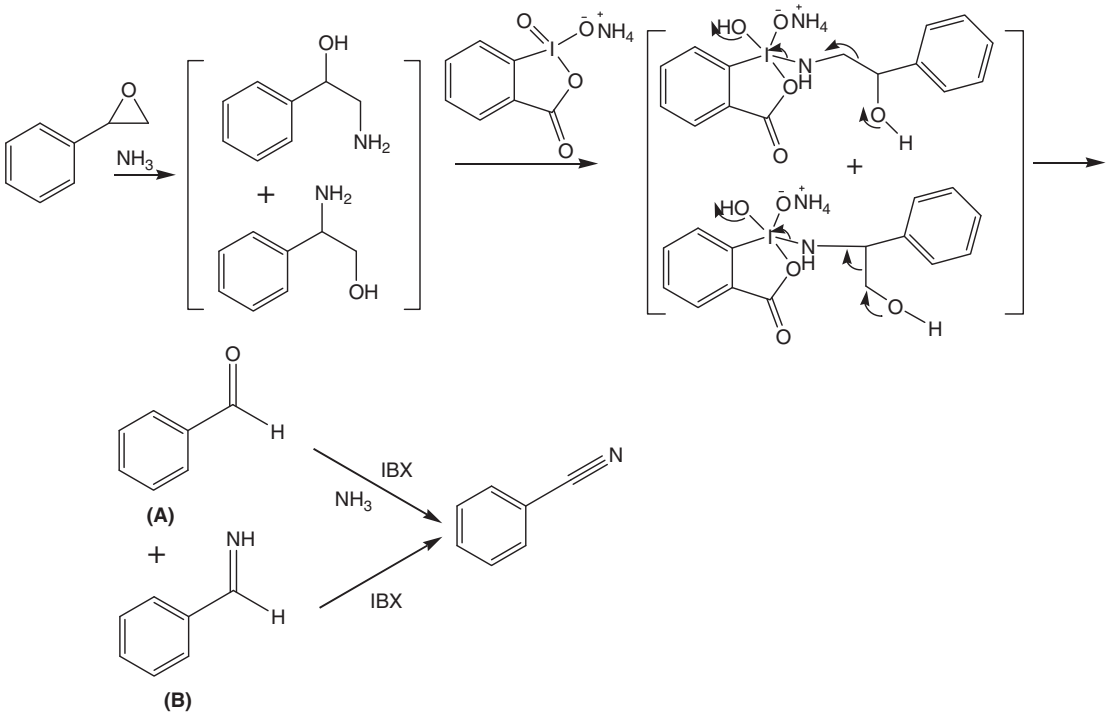
In our preliminary experiments, 1.0 equiv of phenyloxirane **1a** was treated with 2.0 equiv of IBX in aqueous ammonia in acetonitrile as a co-solvent at 70 °C. As expected benzonitrile, **2a** was obtained in excellent yields in 4 h, whereas the reaction did not occur at room temperature even after 12 h (Table 1).

It is to be noted that when only water is the solvent, there was no reaction (Table 1, entries 1 and 2). Another hypervalent iodine reagent Dess–Martin periodinane (DMP) was also found to be viable for this reaction (Table 1, entry 6).

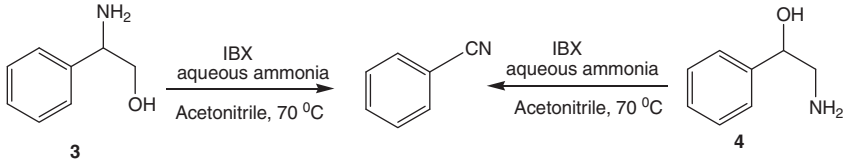
To explore the generality of the reaction, a variety of substrates were reacted with optimized reaction conditions[15], that is, 2.0 equiv of IBX in aqueous ammonia in acetonitrile as a co-solvent at 70 °C. The results are summarized in Table 2. A variety of oxiranes including substituted aromatic, hetero-aromatic and aliphatic were transformed into nitriles smoothly via this protocol in moderate to good yields. Aromatic substrate carrying electron withdrawing or donating groups reacted equally facile (Table 2, entries 2–10). Thiophene and furan rings were stable under the present reaction conditions (Table 2, entries 12 and 13). Equally facile reaction was observed with aliphatic oxiranes (Table 2, entries 14 and 15).

Towards understanding the transformation an explanation is given in Scheme 2.

Oxirane on nucleophilc ring opening with ammonia forms 1, 2-amino alcohol which on reaction with IBX undergoes fragmentation to form aldehyde (**A**) and aldimine **(B)** intermediates



Scheme 2. Plausible mechanism for the oxidative fragmentation of oxirane to nitrile.



Scheme 3. Reaction of 1, 2-amino alcohols with IBX/aqueous ammonia.

respectively. These undergo subsequent oxidations to form nitriles.[14] This mechanism was supported by carrying out reaction of 2-amino-2-phenylethanol **3** and 2-amino-1-phenylethanol **4** with IBX in aqueous ammonia at 70 °C, where expected benzonitrile was obtained in very high yields and as the sole product (Scheme 3). It is pertinent to note that reaction carried out in IBX/water the substrate failed to react pointing to ammonolysis of oxirane as the first step (Table 1, entries 1 and 2).

This is the first report of oxidative fragmentation of oxiranes by hypervalent iodine(V) reagents including DMP and IBX in aqueous ammonia giving nitriles with ammonolysis being the first step. Further explorations on this transformation are under way.

Acknowledgements

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15. *General procedure for oxidative fragmentation of oxiranes.* To a stirred solution of IBX (10.0 mmol) in aqueous ammonia (25 mL of a 28–30% solution) was added oxirane (5.0 mmol) in 5 mL of acetonitrile in one portion. The reaction mixture was stirred at 70 °C until complete consumption of starting material as observed on TLC (up to 4 h). After completion of reaction, the reaction mixture was extracted with chloroform (2 × 15 mL). The organic layer was washed with water (2 × 10 mL); bisulfate solution (15 mL) followed by water (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure

to give crude product. Pure product was obtained after column chromatography (silica gel, mesh size 60–120, eluent ethyl acetate/hexane 05:95).

Spectral data of selected nitriles. *4-Nitrobenzonitrile (2f):* solid, mp 140–142 °C (lit.[16a]142 °C). IR (KBr): 2230 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.36 (2H, d, *J* = 8.9 Hz), 7.91 (2H, d, *J* = 8.9 Hz).

4-Methoxybenzonitrile (2h): solid, mp 55–56 °C (lit.[16a] 55−57 °C). IR (neat): 2216 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (2H, d, *J* = 8.9 Hz), 6.91 (2H, d, *J* = 8.9 Hz), 3.83 (3H, s).

2-Cyanofuran (2l). Oil (Lit.[16b] Oil). IR (Neat): 2229 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ = 8.02 (1H, d, *J* = 1.6 Hz), 7.16 (1H, d, *J* = 3.62), 6.71 (1H, dd, *J* = 3.6 and 1.6 Hz).

2-Cyanothiopene (2m). Oil (lit.[16a] Oil). IR (Neat): 2227 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.98 (1H, dd, *J* = 5.0 and 3.8 Hz) 7.65(1H, d, *J* = 3.8 Hz), 7.61 (1H, d, *J* = 5.0 Hz).

Phenylacetonitrile (2n). Oil (lit.[16b] Oil). IR (neat): 2221 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ = 7.61–7.55(5H, m), 3.24 (2H, s).

Pentanenitrile (2o). Oil (lit.[16b] oil). IR (neat): 2245 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.86 (2H, t), 1.67 (2H, m), 1.32(2H, m), 0.87 (3H, t).

16. (a) Iida, S.; Ohmura, R.; Togo, H. *Tetrahedron* **2009**, *65*, 6257; (b) Dictionary of Organic Compounds, Sixth Ed.; Chapman and Hall electronic Publishing House, London 1996.