doi:10.1246/cl.2013.162

Published on the web February 2, 2013

Molecular Iodine in Aqueous Ammonia: Oxidative Fragmentation of Oxiranes to Nitriles

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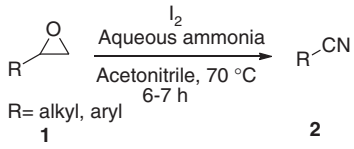
Oxiranes undergo oxidative fragmentation, when treated with iodine in aqueous ammonia, to give nitriles. The reaction goes via formation of 1,2-amino alcohols as intermediates followed by C–C bond cleavage. Advantages of the method are use of off-the-shelf nonexplosive, unlike previously used potentially explosive *o*-iodoxybenzoic acid, reagents, mild reaction conditions, and easy work-up procedure.

Iodine, a readily available, versatile, and mild oxidizing agent, is a good alternative for toxic heavy metal reagents in many oxidative transformations, and transformations using it are of current interest.[1] Iodine promotes many transformations, which include oxidative cyclizations, oxidative rearrangements, ring expansion and contraction, and C–N bond formation among others.[2] Iodine–aqueous ammonia combination has been used in oxidative transformation of 1-arylethanols and arylmethyl halides, giving arylamides[3a] and arylnitriles[3b] respectively. Nitriles formed by the oxidation of primary alcohols and aldehydes using this reagent system under microwave irradiation, have been converted, in situ, into triazines and tetrazoles, through [2 + 3] cycloaddition with dicyanamide and sodium azide respectively.[3c]

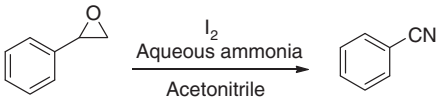
Oxidative fragmentation of double bond and oxiranes is a significant transformation useful in synthetic organic chemistry. Oxiranes, showing particular polarity and a strained three-membered ring system,[4] are an important class of organic compounds[5] and are amenable for a variety of useful transformations.[6] Literature reports a variety of methods for oxidative C–C bond fragmentation of oxiranes. Reagents used for oxidative C–C bond fragmentation of terminal oxiranes are sodium dichromate in aqueous sulfuric acid[7] and CAN.[8] A catalytic method, using molecular oxygen and DMSO with bismuth(III) mandelate as catalyst, is also known leading to formation of corresponding carboxylic acids and CO_2.[9] Extensively investigated reagents, for this transformation, are hypervalent iodine-based oxidizing agents. Reaction of *I*,*I*-bis(trifluoroacetoxy)iodobenzene (BTI) with 2-aryloxiranes brings about exclusively C–C fragmentation giving benzaldehydes, whereas with alkyl-substituted oxiranes there was no fragmentation, instead oxidative ring opening occurs leading to formation of α-hydroxy ketones.[10] Similarly, other hypervalent iodine reagents used are, HIO_4 or combination of HIO_4 and sodium periodate,[11,12] PhIO along with HBF_4 in a CH_2Cl_2–hexafluoroisopropyl alcohol–H_2O system.[13] Mechanistically, in all these cases, formation of vicinal diol is the first step and is followed by oxidative cleavage.

Recently, we have reported oxidative fragmentation of oxiranes to nitriles with hypervalent iodine(V) reagents, particularly *o*-iodoxybenzoic acid (IBX) in aqueous ammonia.[14] In continuation of our studies, we found that hypervalency of iodine is not really essential for the oxidative fragmentation and molecular iodine in aqueous ammonia would be equally effective. These findings, using off-the-shelf reagents, molecular iodine and aqueous ammonia, leading to a new, more convenient, and cost effective method for oxidative C–C fragmentation of oxiranes is reported in this letter (Scheme 1). The present method is an improved version of our ealier method with respect to use of nonexplosive molecular iodine over potentially explosive IBX.



Scheme 1. Oxidative C–C fragmentation of oxiranes to nitriles.

Table 1. Optimization of reagent and reaction conditions[a]



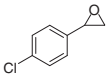
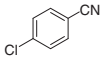
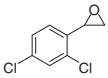
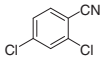
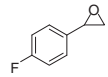
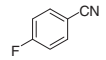
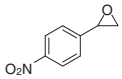
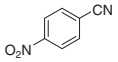
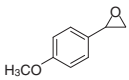
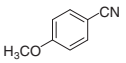
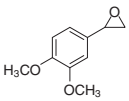
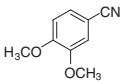
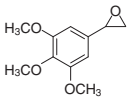
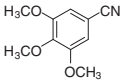
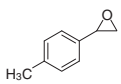
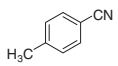
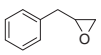
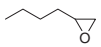
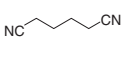
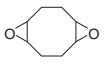
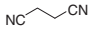
Entry	Temperature	Time/h	Yield[b]/%, **2a**
1	rt	18	10
2	70 °C	6	86

[a]Reactions were carried out on 5 mmol scale using I_2 (2.5 equiv) in aqueous ammonia and acetonitrile as a cosolvent. [b]Isolated yields.

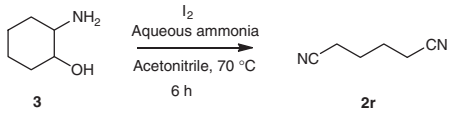
In our preliminary experiments, 1.0 equiv of phenyloxirane (**1a**) was treated with 2.5 equiv of I_2 in aqueous ammonia, using acetonitrile as a cosolvent at 70 °C. Oxidative fragmentation occurred giving benzonitrile (**2a**) in good yields in 6 h, the same reaction performed at room temperature was slow, and the reaction remained incomplete even after stirring for 18 h and gave **2a** in just 10% yields (Table 1, Entries 1and 2).

To explore the generality of the reaction, a variety of oxiranes including substituted aromatic, heteroaromatic, aliphatic, and alicyclic were transformed into nitriles smoothly via this protocol, i.e., oxirane was treated with 2.5 equiv of I_2 in aqueous ammonia and acetonitrile as a cosolvent at 70 °C,[15] the results are summarized in Table 2. Aromatic substrates, carrying electron-withdrawing or -donating groups, reacted equally facile (Table 2, Entries 2–12). Thiophene- and furan-containing substrates also underwent reaction smoothly (Table 2, Entries 13 and 14). Equally facile reaction was observed with aliphatic

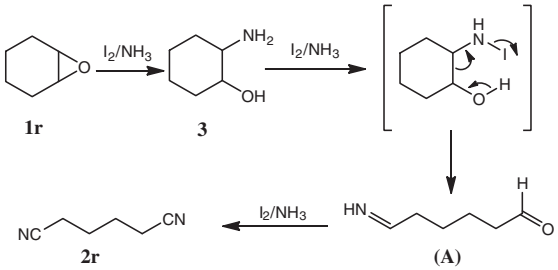
Table 2. Oxidative fragmentation of oxiranes to nitriles[a]

Entry	Substrate		Product		Yield/%[b]
1		**1a**		**2a**	86
2		**1b**		**2b**	83
3		**1c**		**2c**	81
4		**1d**		**2d**	86
5		**1e**		**2e**	81
6		**1f**		**2f**	85
7		**1g**		**2g**	82
8		**1h**		**2h**	82
9		**1i**		**2i**	83
10		**1j**		**2j**	85
11		**1k**		**2k**	83
12		**1l**		**2l**	81
13		**1m**		**2m**	80
14		**1n**		**2n**	83
15		**1o**		**2o**	85
16		**1p**		**2p**	71
17		**1q**		**2q**	70
18		**1r**		**2r**	70[c]
19		**1s**		**2s**	71[d]

[a]Reactions were carried out on 5 mmol scale with I_2 (2.5 equiv) in aqueous ammonia and acetonitrile as a cosolvent at 70 °C for 6–7 h. [b]Isolated yields. [c]With I_2 (3.5 equiv). [d]With I_2 (7 equiv).



Scheme 2. Reaction of 2-amino-1-cyclohexanol (**3**) with I_2/aqueous ammonia.



Scheme 3. Plausible mechanism for the oxidative fragmentation of oxirane to nitrile.

and alicyclic oxiranes, but isolated yields were slightly on the lower side (Table 2, Entries 15–19). It is noteworthy that methoxy group, furan and thiophene rings were stable under the reaction system. All the oxiranes were synthesized by literature methods.[16]

An attempt has been to formulate a reasonable mechanism for the transformation. During the reaction it was observed that oxiranes react faster, indicated by faster disappearance of oxiranes, to form intermediates which react further to form nitriles. This indicates that oxiranes undergo iodine-catalyzed nucleophilic ring opening by ammonia to form intermediate amino alcohols, as the first step, followed by fragmentation. To support this presumption, in case of reaction with cyclohexene epoxide **1r** intermediate 2-amino-1-cyclohexanol (**3**) was isolated in 60% yield, by quenching the reaction, after 1 h, as soon as cyclohexene epoxide disappeared and characterized by IR and ^{1}H NMR.[17] Compound **3** on treatment with I_2 in aqueous ammonia at 70 °C smoothly underwent fragmentation to give adiponitrile (**2r**) in 70% yield in 6 h (Scheme 2).

Based on these finding, a plausible mechanism is formulated as shown in Scheme 3. Intermediate **3** formed by iodine-catalyzed ammonolysis of epoxide, otherwise a slow reaction requiring 5 h to completion, undergoes oxidative fragmentation to form imino aldehyde (**A**), which on subsequent oxidations forms **2r**.

In conclusion, we have developed a general, economical, and convenient method for oxidative C–C fragmentation of oxiranes to nitriles using off-the-shelf, readily available reagents, molecular iodine and aqueous ammonia.

We sincerely thank the University Grants Commission (UGC), India for financial support.

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15 **General procedure for oxidative fragmentation of oxiranes**: In a 100-mL round bottom flask, I_2 (12.5 mmol) in aqueous ammonia (25 mL of a 28–30% solution) was mixed with oxirane (5.0 mmol) in 5 mL of acetonitrile. The reaction mixture was heated at 70 °C and maintained at this temperature till complete consumption of oxiranes and intermediates amino alcohol as analyzed by TLC (reaction time 6–7 h). The mixture was cooled to room temperature and extracted with chloroform (2 × 15 mL). The organic layer was washed with 10% aqueous sodium thiosulfate solution (2 × 15 mL), evaporated and chromatographed to afford the pure product.
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17 **Isolation of 2-amino-1-cyclohexanol (3)**: Reaction was conducted according to general procedure and proceeded for 1 h till cyclohexene epoxide disappeared (by TLC), and extracted with chloroform (2 × 15 mL). The organic layer was dried over sodium sulfate, evaporated and chromatographed to afford pure product (Yield 60%) as white solid. Mp 66–68 °C (lit.[18] 68 °C) IR (KBr): 3351, 3331, 3280, 3100, 2929, 2856, 1587, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.18–3.08 (1H, m), 2.75–2.5 (3H, br s), 2.49–2.4 (1H, m), 2.2–1.91 (1H, m), 1.89–1.81 (1H, m), 1.77–1.62 (2H, m), 1.34–1.18 (3H, m), 1.17–1.05 (1H, m); GCMS *m*/*z*: 115 (M^+), 72, 56, 43, 30.
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19 a) S. Iida, R. Ohmura, H. Togo, *Tetrahedron* **2009**, *65*, 6257. b) *Dictionary of Organic Compounds*, 6th ed., Chapman and Hall Electronic Publishing House, London, **1996**. **Spectral data of selected nitriles**. **Benzonitrile (2a)**: Oil (lit.[19a] Oil); IR (neat): 2229 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.81–7.53 (5H, m). **4-Nitrobenzonitrile (2f)**: Solid, mp 140–142 °C (lit.[19a] 142 °C); IR (KBr): 2233 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.38 (2H, d, $J = 8.8$ Hz), 8.18 (2H, d, $J = 8.8$ Hz). **4-Methoxybenzonitrile (2h)**: Solid, mp 55–56 °C (lit.[19a] 55–57 °C); IR (neat): 2215 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.76 (2H, d, $J = 8.8$ Hz), 7.1 (2H, d, $J = 8.8$ Hz), 3.83 (3H, s). **Phenylacetonitrile (2o)**: Oil (lit.[19b] Oil); IR (neat): 2252 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.41–7.31 (5H, m), 4.03 (2H, s). **Pentanenitrile (2p)**: Oil (lit.[19b] Oil); IR (neat): 2246 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.45 (2H, t, $J = 6.5$ Hz), 1.50 (2H, m), 1.36 (2H, m), 0.87 (3H, t, $J = 6.5$ Hz). **Adiponitrile (2r)**: Oil (lit.[19b] Oil); IR (neat): 2250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (4H, m), 1.77 (4H, m). **Succinonitrile (2s)**: Solid, mp 50–52 °C (lit.[19b] 50–54 °C); IR (neat): 2247 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.88 (4H, s).

