Oxidative Conversion of Amines into Their Corresponding Nitriles Using *o*-Iodoxybenzoic Acid (IBX)/Iodine: Selective Oxidation of Aminoalcohols to Hydroxynitriles

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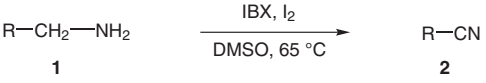
Abstract: *o*-Iodoxybenzoic acid (IBX)/iodine in dimethyl sulfoxide at 65 °C oxidatively and efficiently converted various amines into the corresponding nitriles in good to excellent yields. Under the reaction conditions, amines were selectively oxidized to the nitrile in the presence of a primary hydroxy group within the same molecule.

Key words: selective oxidation, iodine, amines, nitriles, IBX, hydroxynitriles

Nitriles are very important intermediates in synthetic organic chemistry.[1] Consequently, their synthesis under various conditions has been continuously developed. While a wide variety of synthetic approaches to nitriles from diverse chemical sources have been developed,[2] nitrile synthesis from amines has been one of the classical routes. Numerous metal-based oxidants, such as nickel peroxide,[3a] silver reagents,[3b,c] Cu(I) or Cu(II) with O_2,[3d–g] copper reagents,[3h] lead tetraacetate,[3i,j] OsO_4,[3k] $K_2S_2O_8$ with Ni(II),[3l,m] and ruthenium reagents[3n–r] have all been used for carrying out this transformation. Other reagents are PhIO,[4a] NaOCl in ethanol,[4b] trichloroisocyanuric acid with TEMPO,[4c] molecular iodine in aqueous ammonia,[4d] and 1,3-diiodo-5,5-dimethylhydantoin in aqueous ammonia.[4e] In addition, oxidations employing electrochemically generated reagents have also been addressed.[5]

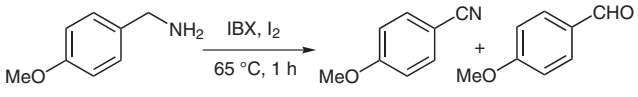
In the past decade, hypervalent iodine reagents have attracted increasing interest because of their selective and mild properties as oxidizing agents in organic synthesis.[6] Of the various hypervalent iodine reagents known, iodine(V) reagents have received substantial attention in recent years, particularly Dess–Martin periodinane (DMP)[7] and *o*-iodoxybenzoic acid (IBX).[8] However, Dess–Martin periodinane is unstable upon prolonged storage and is thus best synthesized immediately prior to use. In contrast, IBX, the DMP precursor, is fairly stable – though it was reported to be explosive upon excessive heating or impact. Some recent applications of IBX in organic transformations include dehydrogenation of ketones and aldehydes to the corresponding α,β-unsaturated analogues,[9a] dehydrogenation of amines to the corresponding imines and N-heterocycles,[9b,c] oxidative cleavage of dithioacetals,[9c] oxidative transformation of primary carboxamides into one-carbon dehomologated nitriles,[9d] and conversion of 1,3-diols into 1,2-diketones.[9e] As part of our interest in finding synthetic applications of IBX and its derivatives,[10] we envisaged the use of an IBX/I_2 combination for the transformation of amines into the corresponding nitriles (Scheme 1). To our knowledge, such a conversion has only been reported using the less stable iodine(V) compound, DMP.[11]



Scheme 1 IBX/I_2 mediated conversion of amines to nitriles

In preliminary studies, *p*-methoxybenzylamine was chosen as a model substrate for investigating reaction conditions. At the outset, the influence of solvents on the yields of the reaction was first examined. The reaction was carried out at 65 °C for one hour in various solvents (DMSO,

Table 1 Solvent Optimization[a]



1a 2a 3a

Entry	Solvent	Product (%)[b]	
		Nitrile **2a**	Aldehyde **3a**
1	DMSO	85	8
2	DMSO/MS (4 Å)	74	10
3	DMSO/$MgSO_4$	81	10
4	MeCN	30	29
5	CH_2Cl_2	40	7
6	EtOAc	41	20
7	THF	33	27
8	Toluene	58	9

[a] All reactions were carried out using IBX (1.25 equiv)/I_2 (2 equiv) at 65 °C for 1 h.
[b] GC yields.

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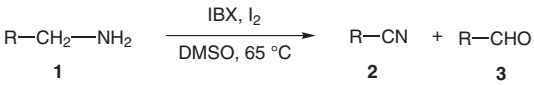
MeCN, CH_2Cl_2, EtOAc, THF and toluene) and the results are summarized in Table 1.

The best yield of *p*-methoxybenzonitrile (**2a**; 85%) was obtained when the reaction was performed using DMSO as the solvent (Table 1, entry 1). This can be attributed to the enhanced solubilizing power of DMSO, which increases the homogeneity of the reaction. Besides the nitrile, the corresponding aldehyde was also formed as a minor product by the hydrolysis of the intermediate imine. Comparable yields were obtained when the reactions were carried out in the presence of dehydrating additives, i.e. 4 Å molecular sieves and anhydrous magnesium sulfate (Table 1, entries 2–3). It should also be mentioned that the reaction proceeded slower at room temperature and give the nitrile product in lower yield (68%). For the reaction using IBX (1.25 equiv, DMSO, 65 °C) in the absence of iodine, a moderate yield of *p*-methoxybenzonitrile (**2a**) was obtained (50%). A significant increase in the yield was observed by doubling the amount of IBX (2.5 equiv, DMSO, 65 °C) (85%), however, similar results were also obtained when molecular iodine (2 equiv) was employed as an additive, while maintaining the stoichiometry of IBX at 1.25 equivalents. Having established the optimum reaction conditions (Table 1, entry 1), we then investigated the generality and scope of the reaction by varying the amine substrates to include benzylic amines with different substituents, and aliphatic amines. The results are summarized in Table 2.

Table 2 Oxidative Conversion of Amines into Nitriles[a]



Entry	Amine		Time (h)	Product yield (%)[b]	
	1	R		Nitrile **2**	Aldehyde **3**
1	**1a**	4-$MeOC_6H_4$	1	**2a**; 85 (74)	**3a**; 8
2	**1b**	Ph	1.5	**2b**; 71 (57)	**3b**; 8
3	**1c**	3,4-$(MeO)_2C_6H_3$	1	**2c**; 71 (68)	**3c**; 14
4	**1d**	4-MeC_6H_4	1.5	**2d**; 74 (70)	**3d**; 14
5	**1e**	4-BrC_6H_4	1.5	**2e**; 84 (73)	**3e**; 11
6	**1f**	4-ClC_6H_4	1.5	**2f**; 84 (70)	**3f**; 8
7	**1g**	4-FC_6H_4	1.5	**2g**; 72 (44)	**3g**; 9
8	**1h**	2-BrC_6H_4	1.5	**2h**; 71 (68)	**3h**; 6
9	**1i**	4-$O_2NC_6H_4$	1.5	**2i**; 70 (61)	**3i**; 6
10	**1j**	Bn	1.5	**2j**; 70 (56)	**3j**; –
11	**1k**	4-$MeOC_6H_4CH_2$	1.5	**2k**; 71 (58)	**3k**; –
12	**1l**	3,4-$(MeO)_2C_6H_3CH_2$	3	**2l**; 76 (64)	**3l**; –
13	**1m**	C_7H_{15}	3	**2m**; 64 (62)	**3m**; –
14	**1n**	C_9H_{19}	3	**2n**; 68 (62)	**3n**; –

[a] All reactions were carried out using IBX (1.25 equiv)/I_2 (2 equiv) at 65 °C.
[b] GC yield and, in parentheses, isolated yields after purification by column chromatography.

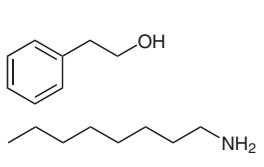
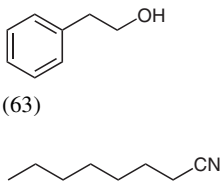
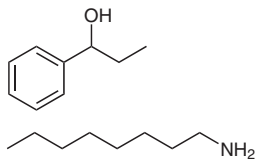
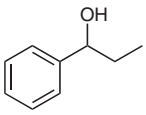
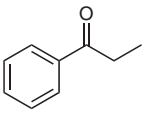
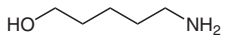
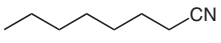
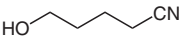
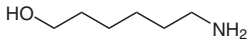
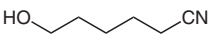
The results illustrated in Table 2 indicate that a range of substituted benzylamine derivatives were converted into the corresponding benzonitrile derivatives in varying yields.[12] Amines containing electron-releasing substituents (entries 1, 3 and 4) as well as amines containing electron-withdrawing substituents (entries 5–9) worked equally well, and the corresponding nitriles were formed in good to excellent yields. In all cases, all of the starting amines were consumed, and the corresponding benzaldehyde derivatives were produced in minor amounts (6–14% by GC) as by-products. Pure nitriles could be isolated by simple column chromatography. It is interesting to note that even though longer reaction times were required, the aliphatic amines were also converted into the corresponding nitriles in moderate to good yields, without any observed aldehyde formation (entries 10–14). Again, in all cases, no starting amine remained.

We further demonstrated the synthetic utility of the combination of IBX/I_2 for selective oxidation of amines in the presence of a hydroxy group. The results are summarized in Table 3. Under similar reaction conditions [IBX (1.25 equiv), I_2 (2 equiv), DMSO, 65 °C, 3 h], when equimolar amounts of 2-phenylethanol and 1-octanamine were employed in the reaction, only the 1-octanamine was converted into the corresponding octanenitrile in 62% isolated yield (Table 3, entry 1). ^{1}H NMR analysis of the crude product did not reveal any aldehyde signal, and the starting 2-phenylethanol was recovered in 63% yield. When 1-phenyl-1-propanol was employed in place of 2-phenylethanol, we again observed quantitative conversion of 1-octanamine into the corresponding nitrile, however, in this case, the alcohol was also transformed into the corresponding ketone in 34% yield (Table 3, entry 2). We believe that oxidation of the secondary hydroxy group to the ketone was effected by iodine. The experimental results implied that the primary aliphatic hydroxy group was resistant to the reaction conditions employed. Further examples of selective oxidation of an aminoalcohol to the corresponding hydroxynitrile are shown in entries 3 and 4. 5-Amino-1-pentanol and 6-amino-1-hexanol were both converted into the corresponding 5-hydroxypentanenitrile and 6-hydroxyhexanenitrile in moderate to good yields.

Comparative studies of our method (Method **A**) with the method developed by Iida and Togo, using molecular iodine in aqueous ammonia (Method **B**)[4d] were conducted. The selectivity and efficiency of our method was clearly demonstrated using the aminoalcohol **1p**, as shown in Table 4. Under our reaction conditions, formation of the dinitrile **4p** was not observed (Table 4, entry 1). Oxidation of **1p** employing iodine in aqueous ammonia resulted in equimolar amounts of hydroxynitrile **2p** and dinitrile **4p** (Table 4, entries 2–3).

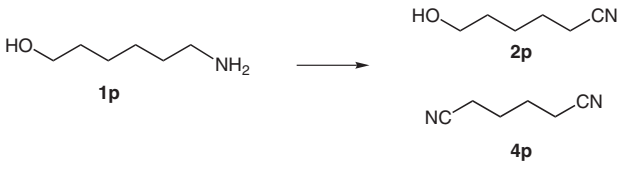
A plausible reaction pathway for the conversion of amines into nitriles in the presence of an IBX/I_2 combination is shown in Scheme 2. According to work by Nicolaou,[9c] in the first step the amine is proposed to undergo oxidation by IBX to produce an intermediate aldimine. Subsequently, this aldimine is further oxidized by molecular iodine to

Table 3 Selective Oxidation of Amines[a]

Entry	Substrate	Product conversion (%)[b]
1	 **1m**	 (63) **2m**; (62)
2	 **1m**	 66  34
3	 **1o**	 **2m**; Quantitative  **2o**; (37)
4	 **1p**	 **2p**; (67)

[a] All reactions were carried out using IBX (1.25 equiv)/I_2 (2 equiv), DMSO, 65 °C, 3 h.
[b] Calculated from ^{1}H NMR (300 MHz) integration. Yields given in parentheses are isolated yields after purification by column chromatography.

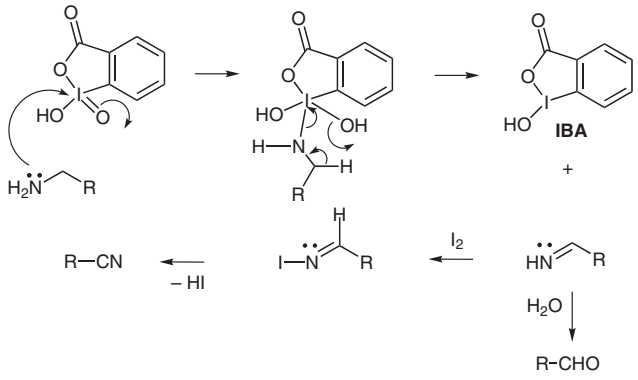
Table 4 Oxidation of 6-Amino-1-hexanol to 6-Hydroxyhexanenitrile



Entry	Method[a]	Product (%)	
		2p	**4p**
1	**A** (3 h)	67	–
2	**B** (4 h)	21	22
3	**B** (24 h)	17	24

[a] Method **A**: IBX (1.25 equiv), I_2 (2 equiv), DMSO, 65 °C; Method **B**: I_2 (3 equiv), aq NH_3 (45 equiv), 60 °C.

give the nitrile product.[4d] The unreacted aldimine, upon hydrolysis, gives the aldehyde by-product.



Scheme 2 Suggested reaction mechanism

In conclusion, the *o*-iodoxybenzoic acid (IBX)/iodine combination provides an alternative to the existing methods for the transformation of amines into nitriles. The synthetic utility of the method for selective oxidation of aminoalcohols possessing a primary aliphatic hydroxy group to the hydroxynitriles was demonstrated. To the best of our knowledge, this transformation has not been reported in the literature. The reaction is simple and proceeds under mild reaction conditions. Advantages of this method are the use of a thermally stable reagent, IBX and inexpensive molecular iodine.

Melting points (uncorrected) were determined on an Electrothermal 9100 Apparatus. Reagents were obtained from commercial sources and used as received. Column chromatography was performed using silica gel 60 (70–230 mesh). Analytical TLC was performed with silica gel 60 PF_{254} aluminium sheets with 0.2 mm layers of silica gel. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ solution with TMS as an internal standard. IR spectra were recorded on a GX FT-IR system Perkin–Elmer infrared spectrometer. HRMS spectra were recorded on a Bruker Esquire apparatus. GC was performed on an Agilent 6890 Series Gas Chromatograph and analyzed with HP Chemstation software.

Conversion of Amines into Nitriles; General Procedure

IBX (1.25 equiv) was dissolved in DMSO (2 mL) and the mixture was stirred at r.t. until the mixture became clear. To this solution was added I_2 (2 equiv) and amine (1 equiv), and the reaction mixture was stirred at 65 °C until the starting amine had been completely consumed (TLC monitoring). The mixture was quenched by addition of sat. aq sodium thiosulfate (5 mL) and then basified with sat. aq $NaHCO_3$ (5 mL) followed by stirring. After removal by filtration of the solid formed, the liquid phase was extracted with Et_2O (3 × 5 mL) and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried (anhydrous $MgSO_4$) and filtered. The solvent was removed under reduced pressure (water aspirator) at r.t. to give the crude material, which was examined by gas chromatography in order to determine product conversion. Purification of the crude product by column chromatography (SiO_2) provided the pure nitrile.[12]

5-Hydroxypentanenitrile (2o)

The general procedure was followed using 5-amino-1-pentanol (93 mg, 0.9 mmol). Column chromatography on silica gel (18 × 3 cm; hexanes, 100% to hexanes–EtOAc, 3:2) gave the title compound.

Yield: 33 mg (37%); pale-yellow liquid; R_f = 0.15 (hexanes–EtOAc, 3:2).[13]

IR (neat): 3418 (O–H), 2249 (C≡N) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.70 (t, *J* = 5.8 Hz, 2 H), 2.42 (t, *J* = 5.8 Hz, 2 H), 1.88–1.68 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 119.6, 61.5, 31.2, 22.0, 16.9.

HRMS (ESI-TOF): *m*/*z* [M + Na^+] calcd for C_5H_9NONa: 122.0582; found: 122.0619.

6-Hydroxyhexanenitrile (2p)

The general procedure was followed using 6-amino-1-hexanol (105 mg, 0.9 mmol). Column chromatography on silica gel (18 × 3 cm; hexanes, 100% to hexanes–EtOAc, 3:2) gave the title compound.

Yield: 67 mg (67%); pale-yellow liquid; R_f = 0.15 (hexanes–EtOAc, 3:2).

IR (neat): 3391 (O–H), 2246 (C≡N) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.55 (t, *J* = 6.9 Hz, 2 H), 2.30 (t, *J* = 6.9 Hz, 2 H), 1.70–1.40 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 119.6, 62.3, 31.7, 25.2, 25.0, 17.1.

HRMS (ESI-TOF): *m*/*z* [M + Na^+] calcd for $C_6H_{11}NONa$: 136.0739; found: 136.0769.

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