IBX/TBAB-Mediated Oxidation of Primary Amines to Nitriles

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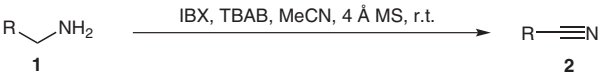
Abstract: The combination of *o*-iodoxybenzoic acid (IBX) and tetrabutylammonium bromide (TBAB) efficiently oxidizes primary amines to the corresponding nitriles in good to excellent yield under mild conditions. The reaction is racemization-free when applied to a chiral lysine derivative.

Key words: *o*-iodoxybenzoic acid (IBX), tetrabutylammonium bromide (TBAB), amines, nitriles, oxidation, dehydrogenation

The nitrile moiety is a ubiquitous functional group found in many natural products, and also serves as an important synthetic handle for the preparation of other functionalities and nitrogen-containing heterocyclic compounds.[1] Accordingly, substantial work has been dedicated to the development of efficient methods for its synthesis. Among these, the direct oxidation of primary amines has been considered as one of the most direct routes. Conventional methods for this oxidative transformation include the use of metal oxidants such as lead tetraacetate,[2] silver oxide,[3] cobalt and nickel peroxide,[4] $K_2S_2O_8$ with metals,[5] OsO_4,[6] Cu(I) or Cu(II) with O_2,[7] and ruthenium reagents.[8] However, these methods suffer from some disadvantages such as the toxicity of the reagents, low yields, limited substrate scope and functional group incompatibility. Therefore, metal-free conditions using, for example, NaOCl,[9] trichloroisocyanuric acid in combination with TEMPO,[10] molecular iodine[11] or 1,3-diiodo-5,5-dimethylhydantoin[12] in aqueous ammonia, and electrochemical methods,[13] have been developed. Surprisingly, hypervalent iodine reagents,[14] which are known to be non-toxic, selective and mild oxidative agents, have rarely been employed for direct oxidative conversion of primary amines into nitriles. Moriarty et al. have developed conditions for the oxidation of amines to nitriles using iodosobenzene, however, only limited examples were given in this report.[15] Nicolaou et al. have shown that Dess–Martin periodinane (DMP) can promote the dehydrogenation of primary amines to give nitriles, although the protocol was applicable only to benzylic amines.[16] On the other hand, oxidation of primary amines to nitriles by *o*-iodoxybenzoic acid (IBX) has not yet been investigated in detail.[17,18]

In a continuation of our ongoing research program dealing with the development of new oxidative multi-component reactions (MCRs),[19] we have recently described an efficient three-component synthesis of α-iminonitrile through a combined use of *o*-iodoxybenzoic acid (IBX)[20] and tetrabutylammonium bromide (TBAB).[21] TBAB was found to play a determinant role in this oxidative transformation.[22] In our initial studies on this reaction, the nitrile resulting from the oxidation of a primary amine was isolated as a minor product. Stimulated by the potential synthetic utility of this transformation, we set out to examine this observation in detail. The recent publication by Kuhakarn et al. on the use of the reagent combination: IBX and I_2, for the oxidation of primary amines to nitriles[23] prompted us to disclose our own findings. We report herein that a range of primary amines can be efficiently oxidized by IBX in the presence of TBAB to afford the corresponding nitriles (Scheme 1).



Scheme 1 IBX/TBAB-mediated oxidation of primary amines to nitriles

Initial studies were carried out using phenethylamine (**1a**) as a model substrate and the results are summarized in Table 1. Since two equivalents of oxidant are required to convert one equivalent of amine into the corresponding nitrile, 2.2 equivalents of IBX was initially used. With IBX in acetonitrile (MeCN), no oxidation was observed (entry 1). Addition of TBAB to the reaction mixture promoted the oxidation to afford the phenylacetonitrile (**2a**) in 35% yield (entry 2). By running the reaction at a substrate concentration of 0.1 M in acetonitrile, the yield increased to 72% (entry 3). Increasing the amount of IBX/TBAB (2.5 equiv) significantly accelerated the reaction, leading to the desired nitrile **2a** in 83% yield (entry 4). A further improvement was obtained by conducting the reaction in the presence of 4 Å molecular sieves (92% yield, entry 5). Attempts to use a catalytic amount of TBAB (0.1 equiv, entry 6) failed to produce the desired transformation. We have also briefly examined the solvent effect and found that use of dichloromethane or tetrahydrofuran gave inferior results (entries 7 and 8). Overall, the optimum conditions consisted of performing the reaction in acetonitrile (~0.1 M) in the presence of IBX, TBAB (2.5 equiv) and 4 Å molecular sieves at room temperature.

In order to examine the scope of the present reaction, the oxidation of a variety of primary amines were examined under the optimized reaction conditions. The results are summarized in Table 2. In most cases, the reaction went to completion within five minutes to provide the corre-

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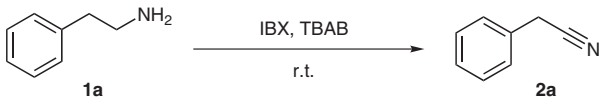
Table 1 Oxidation of Primary Amines to Nitriles; Survey of Reaction Conditions[a]



1a 2a

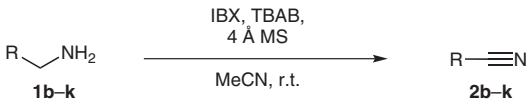
Entry	Solvent	Concn (mol/L)	IBX/TBAB (mole ratio)	Time (min)	Yield (%)[b]
1	MeCN	0.8	2.2/0	60	0
2	MeCN	0.8	2.2/2.2	30	35
3	MeCN	0.1	2.2/2.2	30	72
4	MeCN	0.1	2.5/2.5	5	83
5	MeCN	0.1	2.5/2.5	5	92[c]
6	MeCN	0.1	2.5/0.1	15	0[c]
7	THF	0.1	2.5/2.5	5	20[c]
8	CH_2Cl_2	0.1	2.5/2.5	5	20[c]

[a] Reagents and conditions: amine (0.1 mmol), solvent (1 mL), r.t.
[b] Yields after purification by column chromatography.
[c] The reaction was carried out with 4 Å molecular sieves.

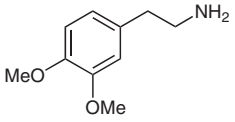
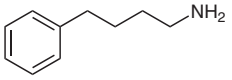
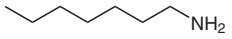
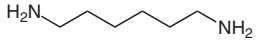
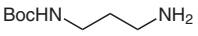
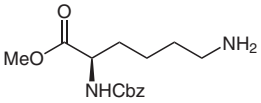
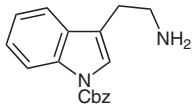
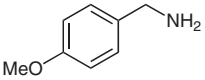
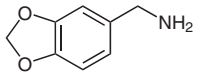
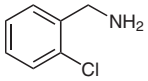
sponding nitriles in good to excellent yields. 1,6-Diaminohexane (**1e**) was successfully oxidized to adiponitrile (**2e**), which is an important precursor for the polymer industry (86%, entry 4). Both *N*-carbamate and indolyl units were tolerated as evidenced by the selective oxidation of **1f**, **1g** and the tryptamine derivative **1h** (entries 5–7).[24] The carboxybenzyl-protected lysine methyl ester (**1g**) was oxidized to nitrile **2g**, without any detectable racemization (confirmed by chiral HPLC analysis). The oxidation of benzyl amines bearing electron-donating or withdrawing groups led to the respective benzonitriles in satisfactory yields (entries 8–10). For the synthesis of aromatic nitriles **2i–k**, the presence of 4 Å molecular sieves was crucial in order to prevent the hydrolysis of the intermediate aldimines to the corresponding aldehydes. With the exception of **2k**, all nitriles were isolated without formation of the aldehyde. It is noteworthy that aliphatic nitriles were obtained more readily and with higher yield than their aromatic counterparts. Therefore, the present procedure is complementary to most of the other conditions used to generate nitriles from primary amines.

While no detailed mechanistic studies have been carried out, we assumed that the role of TBAB was to increase the solubility of IBX or intermediates such as **3** (Scheme 2). The high acidity of IBX[25] could indeed favor the formation of tetrabutylammonium salt, which is known to be soluble in acetonitrile.[26,27] The elimination of a molecule of water from **3** would afford the aldimine **4** and IBA (the reduced form of IBX). Further dehydrogenation of imine **4** via the intermediate **5** would then afford the nitrile **2**. Under our reaction conditions, the oxidation of imine **5** to nitrile **2** apparently proceeded faster than its competitive hydrolysis to the aldehyde. Alternatively, TBAB may be oxidized by IBX to tetrabutylammonium tribromide,

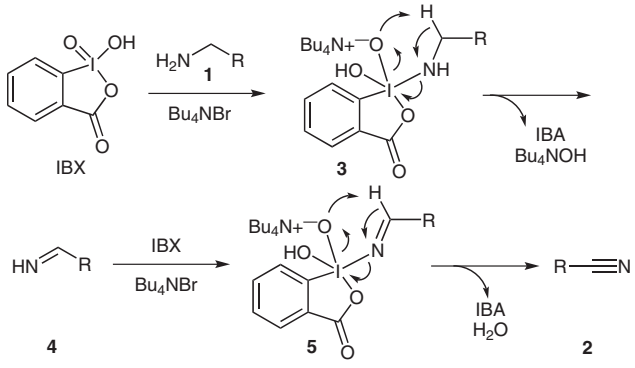
Table 2 Oxidation of Primary Amines to Nitriles with IBX/TBAB[a]



1b–k 2b–k

Entry	RCH_2NH_2	Product	Yield (%)[b]
1		**2b**	72
2		**2c**	84
3		**2d**	89
4		**2e**	86[c]
5		**2f**	75
6		**2g**	76
7		**2h**	65
8		**2i**	72
9		**2j**	77
10		**2k**[d]	50

[a] Reagents and conditions: amine (~0.1 M), MeCN, IBX (2.5 equiv), TBAB (2.5 equiv), r.t.
[b] Yields after purification by column chromatography.
[c] Since nitrile **2e** is water miscible, no extraction was carried out. The mixture was directly filtered through a short pad of Celite, concentrated and purified by column chromatography.
[d] Aldehyde was isolated as a by-product.



Scheme 2 Oxidation of primary amines to nitriles; a mechanistic proposal

which in turn could act as an oxidizing agent to promote the observed transformation.[28] Further work is required in order to fully understand the reaction mechanism.

In summary, we have demonstrated that a combination of IBX and TBAB is highly efficient for the oxidation of primary amines to nitriles. The main attributes of the present protocol are short reaction times, experimental simplicity and good yields. In particular, the easy synthesis of aliphatic nitriles, which are usually less accessible than their aromatic counterparts, make this protocol complementary to other known methodologies.

Reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. All solvents used in the reactions were distilled from appropriate drying agents prior to use. Analytical thin layer chromatography (TLC) was purchased from Merck KGaA (silica gel 60 F254). Flash column chromatography was carried out using Kieselgel 35–70 μm particle sized silica gel (200–400 mesh). Chromatography was performed using silica gel 60 (0.040–0.063 mm) purchased from Merck. ^{1}H NMR spectra were recorded at 500 MHz on a Bruker AC-500 spectrometer and at 300 MHz on a Bruker AC-300 spectrometer. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker AC-300 spectrometer in $CDCl_3$. Proton chemical shifts are reported in ppm (δ) from tetramethylsilane (TMS). Coupling constants (*J*) are reported in Hz. Infrared spectra were recorded on neat samples, using a Perkin–Elmer Spectrum BX FT-IR spectrometer. Optical rotations were performed on a Jasco P-1010 polarimeter (589 nm) using a 700 μL cell with a path length of 1 dm. Mass spectra were determined on an AEI MS-50 instrument using electron-impact ionization (EI), AEI MS-9 using electrospray ionization (ES), and a MALDI-TOF instrument for the high-resolution mass spectra (HRMS).

General Procedure

To a stirred suspension of IBX (2.5 mmol) in MeCN under an argon atmosphere, TBAB (2.5 mmol) was added and the mixture was stirred for 5 min. To this yellow suspension was added amine (1.0 mmol) and 4 Å molecular sieves, and the mixture was stirred at r.t. for 5 min. The mixture was quenched with 10% $NaHSO_3$ (2 × 15 mL), and then extracted with EtOAc (3 × 15 mL). The organic phase was washed with sat. $NaHCO_3$ (2 × 15 mL), H_2O (1 × 15 mL), and brine (1 × 15 mL). The combined organic extracts were dried (Na_2SO_2) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2) afforded the pure nitrile.

2-Phenylacetonitrile (2a)

IR (neat): 3120, 3033, 2920, 2850, 2251 (C≡N), 1602, 1580, 1496, 1454 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.75 (s, 2 H), 7.33–7.40 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6 (CH_2), 117.9 (CN), 127.9 (2 × CH_{Ar}), 128.0 (CH_{Ar}), 129.1 (2 × CH_{Ar}), 130.0 (CH_{Ar}).

MS (ESI$^+$): *m*/*z* = 118.6 [M + H$^+$].

2-(3,4-Dimethoxyphenyl)acetonitrile (2b)

IR (neat): 3065, 2970, 2834, 2242 (C≡N), 1608, 1593, 1514, 1466, 1256, 1234 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.70 (s, 2 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 6.81 (s, 1 H, ArH), 6.84–6.87 (m, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2 (CH_2), 56.0 (2 × CH_3), 111.0 (CH_{Ar}), 111.5 (CH_{Ar}), 118.1 (CN), 120.2 (CH_{Ar}), 122.2 (C_q), 148.8(C_q), 149.4 (C_q).

4-Phenylbutyronitrile (2c)

IR (neat): 3140, 2926, 2858, 2246 (C≡N), 1602, 1580, 1496, 1454 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85–1.95 (m, 2 H), 2.23 (t, *J* = 7.0 Hz, 2 H), 2.70 (t, *J* = 7.0 Hz, 2 H), 7.09–7.28 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4 (CH_2), 26.9 (CH_2), 34.4 (CH_2), 119.5 (CN), 126.5 (CH_{Ar}), 128.5 (2 × CH_{Ar}), 128.7 (2 × CH_{Ar}), 139.7 (C_q).

MS (IE): *m*/*z* = 145.0 [M]$^{+\cdot}$.

Heptanenitrile (2d)

IR (neat): 3120, 2930, 2857, 2248 (C≡N), 1643, 1471, 1427, 823 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.28–1.33 (m, 4 H), 1.40–1.49 (m, 2 H), 1.60–1.70 (m, 2 H), 2.31 (t, *J* = 7.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 17.1 (CH_2), 22.4 (CH_2), 25.3 (CH_2), 28.3 (CH_2), 30.93 (CH_2), 119.9 (CN).

MS (IE): *m*/*z* = 111.0 [M]$^{+\cdot}$.

Adiponitrile (2e)

IR (neat): 2944, 2876, 2246 (C≡N), 1460, 1425 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.80–1.84 (m, 4 H), 2.40–2.44 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.7 (2 × CH_2), 24.3 (2 × CH_2), 118.8 (2 × CN).

***tert*-Butyl-2-cyanoethylcarbamate (2f)**

IR (neat): 3356, 3000–2850, 2246 (C≡N), 1687, 1526, 1365, 1394, 1275 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 2.60 (t, *J* = 6.3 Hz, 2 H, CH_2), 3.40 (t, *J* = 6.3 Hz, 2 H, CH_3), 4.94 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9 (CH_2), 28.3 (CH_3), 36.9 (CH_2), 80.1 (C_q), 118.2 (CN), 155.6 (C_q).

MS (ESI$^+$): *m*/*z* 193.1 [M + Na$^+$].

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{14}N_2O_2Na$: 193.0957; found: 193.0959.

Benzyl (*R*)-1-(Methoxycarbonyl)-4-cyanobutylcarbamate (2g)

$[\alpha]_D^{25}$ –8.13 (*c* 0.98, $CHCl_3$).

IR (neat): 3421, 3089, 2950, 2247 (C≡N), 1744 and 1710 (C=O), 755 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.67–1.83 (m, 4 H), 2.39 (t, *J* = 6.5 Hz, 2 H), 3.77 (s, 3 H), 4.38–4.44 (m, 1 H), 5.11 (s, 2 H), 5.34 (br s, 1 H, NH), 7.31–7.38 (m, 5 H, 5 × ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.8 (CH_2), 21.5 (CH_2), 31.9 (CH_2), 52.7 (CH_3), 53.0 (CH), 67.3 (CH_2), 119.0 (CN), 128.2 (2 × CH_{Ar}), 128.3 (CH_{Ar}), 128.6 (2 × CH_{Ar}), 136.0 (C_q), 155.9 (C_q), 172.1 (C_q).

MS (ESI$^+$): *m*/*z* = 313.1 [M + Na$^+$].

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{18}N_2O_4Na$: 313.1164; found: 313.1160.

***N*-Carboxybenzyl-3-cyanomethylindole (2h)**

IR (neat): 3140, 3000, 2960, 2860, 2252 (C≡N), 1721 (C=O), 1614, 1574, 1498, 1470, 738 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.76 (s, 2 H), 5.46 (s, 2 H), 7.29–7.34 (m, 2 H, 2 × ArH), 7.34–7.45 (m, 3 H, 3 × ArH), 7.45–7.54 (m, 3 H, 3 × ArH), 7.68–7.70 (m, 1 H, ArH), 8.21 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_2), 69.1 (CH_2), 110.5 (C_q), 115.6 (CH_{Ar}), 117.0 (CN), 118.4 (CH_{Ar}), 123.5 (CH_{Ar}), 123.9 (C_q), 125.6 (CH_{Ar}), 128.5 (C_q), 128.6 (2 × CH_{Ar}), 128.9 (2 × CH_{Ar}), 128.9 (CH_{Ar}), 134.8 (C_q), 135.6 (C_q), 150.5 (C_q).

MS (ESI$^+$): *m*/*z* = 313.1 [M + Na^+].

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{14}N_2O_2Na$: 313.0953; found: 313.0953.

4-Methoxybenzonitrile (2i)
IR (neat): 3100, 3025, 2840 (CH_3), 2216 (C≡N), 1604, 1576, 1508, 1458, 1256 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 6.85 (d, *J* = 9.0 Hz, 2 H, ArH), 7.59 (d, *J* = 9.0 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.6 (CH_3), 104.0 (C_q), 114.7 (2 × CH_{Ar}), 119.2 (CN), 134.0 (2 × CH_{Ar}), 162.8 (C_q).

MS (ESI$^+$): *m*/*z* = 134.1 [M + H^+].

Piperonylnitrile (2j)
IR (neat): 3100, 2921, 2850, 2221 (C≡N), 1618, 1603, 1499, 1442, 1256 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.07 (s, 2 H), 6.86 (d, *J* = 8.1 Hz, 1 H, ArH), 7.03 (d, *J* = 1.6 Hz, 1 H, ArH), 7.21 (dd, *J* = 8.1, 1.6 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 102.2 (CH_2), 105.0 (C_q), 109.1 (CH_{Ar}), 111.4 (CH_{Ar}), 118.9 (CN), 128.2 (CH_{Ar}), 148.0 (C_q), 151.5 (C_q).

2-Chlorobenzonitrile (2k)
IR (neat): 3093, 3067, 2229 (C≡N), 1591, 1566, 1471, 1439, 756 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (t, *J* = 7.9 Hz, 1 H, ArH), 7.51–7.56 (m, 2 H, ArH), 7.68 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.4 (C_q), 116.0 (CN), 127.2 (CH_{Ar}), 130.1 (CH_{Ar}), 133.9 (CH_{Ar}), 134.0 (CH_{Ar}), 136.9 (C_q).

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