

# Direct oxidative conversion of alcohols and amines to nitriles with molecular iodine and DIH in aq NH<sub>3</sub>

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**Abstract**—Simple and high-yield procedures for the direct oxidative conversion of various primary alcohols, and primary, secondary, and tertiary amines to the corresponding nitriles were successfully carried out with molecular iodine in aq ammonia and 1,3-diiodo-5,5-dimethylhydantoin in aq NH<sub>3</sub>, respectively.

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## 1. Introduction

Nitriles are one of the most important synthetic transformation precursors, especially into esters, amides, carboxylic acids, amines, and nitrogen-containing heterocycles.<sup>1</sup> Therefore, they have been used as synthetic intermediates for agricultural chemicals, pharmaceutical chemicals, and functional material chemicals.<sup>2</sup> The most typical synthetic method is the reaction of alkyl halides with very toxic metal cyanide via nucleophilic pathway, though one carbon is increased. Consequently, nitriles are generally prepared by the dehydration of amides with SOCl<sub>2</sub>, TsCl/Py, P<sub>2</sub>O<sub>5</sub>, POCl<sub>3</sub>, COCl<sub>2</sub>, (EtO)<sub>3</sub>P/I<sub>2</sub>, Ph<sub>3</sub>P/CCL<sub>4</sub>, etc., by the condensation of carboxylic acids with NH<sub>3</sub>/silica gel, NH<sub>3</sub>/ethyl polyphosphate, etc., and by the reaction of esters with Me<sub>2</sub>AlNH<sub>2</sub>.<sup>3</sup> On the other hand, oxidative conversion of primary amines to the corresponding nitriles has been well studied using AgO,<sup>4a</sup> Pb(OAc)<sub>4</sub>,<sup>4b–4c</sup> cobalt peroxide,<sup>4f</sup> Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> or (Bu<sub>4</sub>N)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> with metals,<sup>4g–4j</sup> NaOCl,<sup>4k–4m</sup> K<sub>3</sub>Fe(CN)<sub>6</sub>,<sup>4n</sup> Cu(I) or Cu(II) with oxygen,<sup>4o–4r</sup> RuCl<sub>3</sub> and related Ru reagents,<sup>4s–4w</sup> PhIO,<sup>4x</sup> and trichloroisocyanuric acid with TEMPO.<sup>4y</sup> Here, as a part of our study for the synthetic use of molecular iodine and related reagents for organic synthesis,<sup>5</sup> we would like to report for the direct oxidative conversion of primary alcohols, and primary, secondary, and tertiary amines to the corresponding nitriles with molecular iodine and related reagents.

## 2. Results and discussion

### 2.1. Conversion of primary alcohols, and primary, secondary, and tertiary amines to nitriles with molecular iodine in aq NH<sub>3</sub>

Molecular iodine is a mild, cheap, and easily available oxidizing reagent, and it is useful because it is solid form and is less toxic than other halogens such as molecular bromine and chlorine. Previously, simple conversion of aldehydes to the corresponding nitriles using molecular iodine in aq NH<sub>3</sub> and CH<sub>3</sub>OH or THF was reported.<sup>6</sup> Today, to the best of our knowledge, direct oxidative conversion of alcohol to the corresponding nitriles in one-pot manner is extremely limited, i.e. using NiSO<sub>4</sub> and K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> in aq NaOH,<sup>7a</sup> NH<sub>4</sub>HCO<sub>3</sub>, (Bu<sub>4</sub>N)<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, and a catalytic amount of Cu(HCO<sub>2</sub>)<sub>2</sub>·Ni(HCO<sub>2</sub>)<sub>2</sub> in aq KOH and <sup>i</sup>PrOH,<sup>7b</sup> and MnO<sub>2</sub>, NH<sub>3</sub>, and MgSO<sub>4</sub> in THF and <sup>i</sup>PrOH for benzylic and cinnamic alcohols.<sup>7c</sup>

At first, a direct, efficient, practical, and less toxic oxidative conversion of primary alcohols to the corresponding nitriles, using molecular iodine in aq NH<sub>3</sub> was studied.<sup>8</sup> Thus, when 3-phenylpropanol (1 mmol) was treated with molecular iodine in aq NH<sub>3</sub>, changing the amounts of molecular iodine and aq NH<sub>3</sub> under empty balloon, 3-phenylpropionitrile was formed as shown in Table 1. When the reaction was carried out in a sealed tube, the amount of aq NH<sub>3</sub> could be reduced (entries 7–10). However, it is not so practical. The results indicate that the reaction with 3.0 equiv of molecular iodine and 45 equiv of aq NH<sub>3</sub> (3 mL, 28–30%) under empty balloon at 60 °C gave 3-phenylpropionitrile in the best yield (entry 5).

**Keywords:** Primary alcohol; Primary amine; Secondary amine; Tertiary amine; Iodine; 1,3-Diiodo-5,5-dimethylhydantoin; Nitrile; Aq NH<sub>3</sub>.

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**Table 1.** Oxidative conversion of 3-phenylpropanol to 3-phenylpropionitrile with I<sub>2</sub>/aq NH<sub>3</sub>

$$\text{Ph}(\text{CH}_2)_2\text{CH}_2\text{OH} \xrightarrow[24\text{h}]{\text{I}_2, \text{aq. NH}_3} \text{Ph}(\text{CH}_2)_2\text{CN}$$

Entry	I <sub>2</sub> /aq NH <sub>3</sub> (equiv)	Temp. (°C)	Yield (%)
1	2.5/10	rt	14 (86 <sup>a</sup> )
2	2.5/10	50	62 (28 <sup>a</sup> )
3	2.5/20	50	74 (20 <sup>a</sup> )
4	2.5/45	50	67 (29 <sup>a</sup> )
5	3.0/45	60	91
6 <sup>b</sup>	3.0/10	60	51 (34 <sup>a</sup> )
7 <sup>c</sup>	3.0/5	60	31 (53 <sup>a</sup> )
8 <sup>c</sup>	3.0/10	60	48 (31 <sup>a</sup> )
9 <sup>c</sup>	3.0/15	60	81 (12 <sup>a</sup> )
10 <sup>c</sup>	3.0/20	60	85 (12 <sup>a</sup> )

<sup>a</sup> Yield of the starting material.<sup>b</sup> K<sub>2</sub>CO<sub>3</sub> (2.0 equiv) was added.<sup>c</sup> Reaction was carried out in a sealed tube.

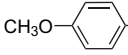
When the reactivity of molecular iodine was compared with those of *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), *N*-iodosuccinimide (NIS), ICl, and Ca(OCl)<sub>2</sub> in aq NH<sub>3</sub> using *p*-methoxybenzyl alcohol and 1-dodecanol, NBS and NCS did not work, and NIS and ICl gave the corresponding nitriles in good to moderate yields as shown in Table 2. However, the yields with molecular iodine were better than those with NIS and ICl, and practically NIS is expensive and ICl is not so easy to operate. Based on these results, various primary alcohols such as benzylic alcohols, straight-chained alcohols, adamantylmethanol were treated with molecular iodine in aq NH<sub>3</sub> to provide the corresponding nitriles in good yields, except for cinnamyl alcohol, which induced further addition reaction to the formed cinnamionitrile by ammonia in aq NH<sub>3</sub> under the warming temperature as shown in Table 3. The reaction could be also carried out in preparative scale without any problem to give the corresponding nitrile in good yield (entry 15). Diols could be also transformed to the corresponding dinitriles using twice the amount of molecular iodine and aq NH<sub>3</sub> (entries 13 and 20).

Today, some outline work on the reaction of benzylamine with molecular iodine in acetonitrile to form imine, *N*-benzylidenebenzylamine, benzonitrile, etc., was reported.<sup>9</sup>

However, detailed study for the reaction of amines with molecular iodine in aq NH<sub>3</sub> has not been carried out. Thus,


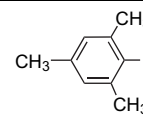
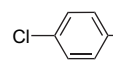
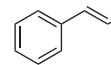
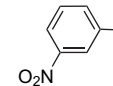


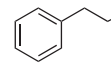
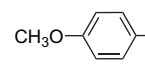
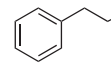
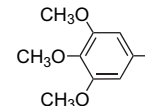
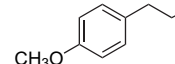

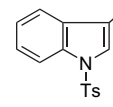

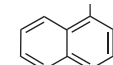

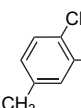
**Table 2.** Oxidative conversion of alcohols to nitriles with halogen reagents in aq NH<sub>3</sub>

$$\text{R-CH}_2\text{OH} \xrightarrow[60\text{ }^\circ\text{C}]{\text{Reagent, aq. NH}_3 (3.0\text{ mL})} \text{R-CN}$$

Entry	R-	Reagent	Time (h)	Yield (%)
1		I <sub>2</sub> (3.0 equiv)	2	99
2		NBS (3.0 equiv)	2	2 (88 <sup>a</sup> )
3		NCS (3.0 equiv)	2	0 (99 <sup>a</sup> )
4		NIS (3.0 equiv)	2	92 (8 <sup>b</sup> )
5		ICI (3–6 equiv)	2	97
6		Ca(OCl) <sub>2</sub> (1.5 equiv)	2	0 (94 <sup>a</sup> )
7	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> -	I <sub>2</sub> (3.0 equiv)	8	91
8		NIS (3.0 equiv)	8	60 (40 <sup>a</sup> )
9		ICI (3–6 equiv)	8	67 (31 <sup>a</sup> )

<sup>a</sup> Yield of the starting material.**Table 3.** Oxidative conversion of alcohol to nitriles with I<sub>2</sub>/aq NH<sub>3</sub>

$$\text{R-CH}_2\text{OH} \xrightarrow[60\text{ }^\circ\text{C}]{\text{I}_2 (3.0\text{ eq.})} \text{R-CN}$$

Entry	R-	Time (h)	Yield (%)	Entry	R-	Time (h)	Yield (%)
1		2	86	11 <sup>a</sup>		30	68
2		2	95	12		4	42
3		3	92	13 <sup>b</sup>		2	99
4		3	77	14		24	91
5		2	99	15 <sup>c</sup>		42	90
6		2	97	16		21	63
7		3	67	17	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> -	8	91
8		4	66	18		8	68
9		4	80	19		6	90
10		6	80	20 <sup>b</sup>	-(CH <sub>2</sub> ) <sub>8</sub> -	24	99

<sup>a</sup> Reaction was carried out at 80 °C and I<sub>2</sub> (1.5 equiv) was added again after 24 h.<sup>b</sup> I<sub>2</sub> (6.0 equiv) and aq NH<sub>3</sub> (6.0 mL) were used.<sup>c</sup> Reaction was carried out using 10 mmol (1.36 g) of alcohol.

the reaction was very simply carried out by treatment of benzylic and aliphatic primary amines (1 mmol) with molecular iodine (2.1–3.0 mmol) in aq NH<sub>3</sub> (28–30%, 3 mL) at 60 °C to provide the corresponding nitriles in good yields as shown in Table 4.<sup>10</sup> When the same reaction was carried out in water or <sup>t</sup>BuOH in the presence of K<sub>2</sub>CO<sub>3</sub>, instead of aq ammonia, the yield of nitrile was decreased as shown in entries 5 and 6. Diamines were also converted to the corresponding dinitriles in good yields (entries 14–17). DL-2-phenylglycine was converted to benzonitrile through oxidative decarboxylation (entries 18 and 19).

When *N*-methyl secondary amines and *N,N*-dimethyl tertiary amines were treated with molecular iodine under the same conditions, the corresponding nitriles could be again obtained in good yields as shown in Table 5. Moreover, bis(dodecyl)amine (1 mmol), bis(4-methylbenzyl)amine (1 mmol), tris(dodecyl)amine (1 mmol), and tris(4-methylbenzyl)amine (1 mmol) were treated with 4.5 equiv, 4.5 equiv, 6.5 equiv, and 6.5 equiv of molecular iodine, in

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