

## Direct Oxidative Conversion of Alkyl Halides into Nitriles with Molecular Iodine in Aqueous Ammonia

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**Abstract:** The direct oxidative conversion of various benzylic alkyl halides and primary alkyl halides into corresponding nitriles was efficiently and simply carried out using molecular iodine in aqueous ammonia. This novel reaction converts alkyl halides into corresponding nitriles without changing the number of carbon atoms.

**Key words:** iodine, ammonia, nitrile, halide

Iodine is one of the essential elements for life. Therefore, molecular iodine, which has moderate oxidizing ability, might be one of the most environmentally benign reagents for organic synthesis. Today, molecular iodine is practically used for various kinds of organic reactions, including oxidation of alcohols or aldehydes to esters, oxidation of sulfides to sulfoxides, oxidation of cyclohexenones to benzene rings, introduction of protecting groups, deprotection of protecting groups, iodocyclization, carbon-carbon bond formation, and formation of heterocycles.<sup>1</sup> On the other hand, nitriles are one of the most important synthetic transformation precursors, particularly into esters, amides, carboxylic acids, amines, and nitrogen-containing heterocycles,<sup>2</sup> and have been used as synthetic intermediates for agricultural chemicals, pharmaceuticals, and functional materials.<sup>3</sup> The most typical method for nitrile synthesis is the reaction of alkyl halides with highly toxic metal cyanide via a nucleophilic pathway. This method, however, increases the number of carbon atoms by one. Consequently, nitriles are generally prepared by the dehydration of amides with  $\text{SOCl}_2$ ,  $\text{TsCl/py}$ ,  $\text{P}_2\text{O}_5$ ,  $\text{POCl}_3$ ,  $\text{COCl}_2$ ,  $(\text{EtO})_3\text{P/I}_2$ , or  $\text{Ph}_3\text{P/CCl}_4$ , by the condensation of carboxylic acids with  $\text{NH}_3/\text{silica gel}$  or  $\text{NH}_3/\text{ethyl polyphosphate}$ , and by the reaction of esters with  $\text{Me}_2\text{AlNH}_2$ .<sup>4</sup> The oxidative conversion of primary amines into corresponding nitriles has been well studied using  $\text{AgO}$ ,  $\text{Pb(OAc)}_4$ , cobalt peroxide,  $\text{Na}_2\text{S}_2\text{O}_8$  or  $(\text{Bu}_4\text{N})_2\text{S}_2\text{O}_8$  with metals;  $\text{NaOCl}$ ,  $\text{K}_3\text{Fe(CN)}_6$ ,  $\text{Cu(I)}$  or  $\text{Cu(II)}$  with oxygen,  $\text{RuCl}_3$  or related Ru reagents,  $\text{PhIO}$ , and trichloroisocyanuric acid with TEMPO.<sup>5</sup> However, to the best of our knowledge, the direct oxidative conversion of alkyl halides into corresponding nitriles without changing the number of carbon atoms has never been reported. As part of our study on the use of molecular iodine for organic synthesis,<sup>6</sup> we would like to report the direct oxidative conversion of benzylic halides and primary alkyl halides

into the corresponding nitriles with molecular iodine in aqueous ammonia. Molecular iodine is an environmentally benign oxidizing reagent that is mild, cheap, and easily available. Moreover, it is useful because it exists as a solid. Previously, we reported a direct, efficient, practical, and less toxic oxidative conversion of various primary alcohols and amines into corresponding nitriles using molecular iodine in aqueous ammonia.<sup>7</sup> When primary alcohols or amines (1 mmol) were treated with molecular iodine (3 mmol) in aqueous ammonia (28–30%, 3 mL) at 60 °C, the corresponding nitriles were obtained in high yields. Based on these results, we planned to perform the direct oxidative conversion of primary alkyl halides into the corresponding nitriles using molecular iodine in aqueous ammonia. Primary alkyl halides should react with ammonia via a  $\text{S}_{\text{N}}2$  nucleophilic pathway to form corresponding amines, and these, in turn, can be oxidatively converted into the corresponding nitriles in a one-pot manner. Practically, the reaction was carried out by treating benzyl chloride (1 mmol) with molecular iodine (2.1 mmol) in aqueous ammonia (28–30%, 3 mL) at 60 °C to provide benzonitrile in good yield, as shown in Table 1 (entry 1).<sup>8</sup> *p*-Chlorobenzyl, *p*-nitrobenzyl, *p*-methylbenzyl, *p*-methoxybenzyl, and 1-naphthylmethyl chlorides could be also converted into corresponding nitriles in good yields under the same conditions (entries 2–6). Benzyl, *p*-chlorobenzyl, *p*-nitrobenzyl, *p*-methylbenzyl, *p*-methoxybenzyl, and 1-naphthylmethyl bromides could be also converted into corresponding nitriles in good yields under the same conditions using 2.4 mmol of molecular iodine (entries 8–13). The same treatment of benzylic iodide such as *p*-chlorobenzyl chloride provided benzonitrile in good yield (entry 15). When the same reaction was carried out with 2-halomethylthiophene as substrate, the yield of 2-cyanothiophene was low. However, after treating 2-halomethylthiophene with aqueous ammonia for two hours at room temperature, adding molecular iodine to the reaction mixture, and warming the obtained mixture at 60 °C, 2-cyanothiophene was obtained in moderate yields (entries 7 and 14).

When the same reaction was carried out under the same conditions with 1-iodododecane (1 mmol) as substrate, the corresponding lauritrile was not formed at all, and the starting material was quantitatively recovered, as shown in Table 2 (entry 1). Thus, we examined the effect of additives as cosolvent, such as THF, dioxane, DMSO, or DMF, in promoting the nucleophilic reaction of ammonia to 1-iodododecane, and found that lauritrile could

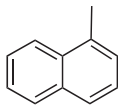

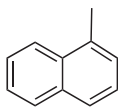

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**Table 1** Conversion of Benzylic Halides to Nitriles

ArCH <sub>2</sub> X		$\xrightarrow[60\text{ }^\circ\text{C}]{\text{I}_2, \text{aq NH}_3 (3.0\text{ mL})}$				ArCN
Entry	X	Ar	I <sub>2</sub> (equiv)	Time (h)	Yield (%)	
1	Cl	Ph	2.1	4	73	
2	Cl	4-ClC <sub>6</sub> H <sub>4</sub>	2.1	10	73	
3	Cl	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	2.1	4	92	
4	Cl	4-MeC <sub>6</sub> H <sub>4</sub>	2.1	2	82	
5	Cl	4-MeOC <sub>6</sub> H <sub>4</sub>	2.1	4	88	
6	Cl		2.1	4	83	
7	Cl		2.1	4 <sup>a</sup>	60	
8	Br	Ph	2.4	8	78	
9	Br	4-ClC <sub>6</sub> H <sub>4</sub>	2.4	4	78	
10	Br	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	2.4	4	88	
11	Br	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	2.4	4	88	
12	Br	4-MeOC <sub>6</sub> H <sub>4</sub>	2.4	4	84	
13	Br		2.4	4	87	
14	Br		2.4	4 <sup>a</sup>	49	
15	I	4-ClC <sub>6</sub> H <sub>4</sub>	2.4	8	78	

<sup>a</sup> Iodine was added after 2 h.

be obtained in moderate yields (entries 2–11). After several trials, we found that the addition of a small amount of DMF in a screw-capped glass vial (10 mL), instead of a standard reactor under balloon, improved the yield of lau-

**Table 2** Conversion of 1-Iodododecane to Lauronitrile

Entry	1. aq NH <sub>3</sub> , cosolvent, 60 °C			2. I <sub>2</sub> (3.0 equiv), aq NH <sub>3</sub> , 60 °C, 4 h		
	aq NH <sub>3</sub> (mL)	Cosolvent (mL)	Time (h)	aq NH <sub>3</sub> (mL)	C <sub>11</sub> H <sub>23</sub> I	C <sub>11</sub> H <sub>23</sub> CN
1	3.0	None	24	3.0	99	0
2	3.0	THF (1.0)	24	3.0	99	0
3	3.0	THF (3.0)	24	3.0	18	36
4	3.0	Dioxane (1.0)	24	3.0	87	11
5	3.0	DMSO (1.0)	24	3.0	96	3

ronitrile (entries 12 and 13).<sup>9</sup> We believe that the escape of ammonia gas from the reaction mixture under the present conditions is restrained by using a screw-capped glass vial. Thus, the optimal conditions are as follows: 1-iodododecane (1 mmol) was treated with aqueous ammonia (1 mL) and a small amount of DMF (0.01 mL) for 72 hours at 60 °C in a screw-capped glass vial at the first stage to form the corresponding amine, and then molecular iodine (3 mmol) and aqueous ammonia (6 mL) were added and the mixture was warmed at 60 °C again for four hours (entry 12). Based on these results, various primary alkyl halides were reacted with molecular iodine in aqueous ammonia and a small amount of DMF to form the corresponding nitriles, as shown in Table 3. The reactivity depends on the alkyl halides used: primary alkyl chlorides are less reactive than primary alkyl bromides and iodides. Moreover, primary alkyl-chained halides, such as 1-dodecyl halides, 3-phenylpropyl halides, 4-phenylbutyl halides, 5-phenylpentyl halides, and 11-halo-undecanoic acids, were efficiently converted into corresponding nitriles in good yields (entries 1–3, and 9–17). In contrast, cyclohexylmethyl halides were less reactive and adamantylmethyl halides did not react at all due to steric hindrance of the initial conversion into corresponding amines via a nucleophilic manner with ammonia (entries 4–6).

A possible reaction pathway for the conversion of benzylic and primary alkyl halides into the corresponding nitriles with molecular iodine in aqueous ammonia is shown in Scheme 1. The initial nucleophilic reaction of ammonia with halides occurs to generate the corresponding amines (**a**). N-Iodination of the amines with molecular iodine takes place to form N-iodo compounds (**b**), and this is followed by β-elimination of HI with ammonia to provide aldemines (**c**). Then, aldemines (**c**) react with molecular iodine to generate N-iodo compound (**d**), and this is followed by β-elimination of HI with ammonia to give corresponding nitriles.

**Table 2** Conversion of 1-Iodododecane to Lauronitrile (continued)

1. aq NH<sub>3</sub>, cosolvent, 60 °C  
2. I<sub>2</sub> (3.0 equiv), aq NH<sub>3</sub>,  
60 °C, 4 h

$$n\text{-C}_{11}\text{H}_{23}\text{CH}_2\text{I} \longrightarrow n\text{-C}_{11}\text{H}_{23}\text{CN}$$


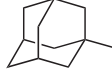
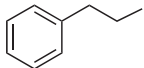
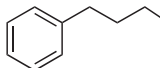
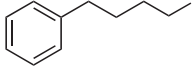
Entry	First step			Second step		Yield (%)	
	aq NH <sub>3</sub> (mL)	Cosolvent (mL)	Time (h)	aq NH <sub>3</sub> (mL)	C <sub>11</sub> H <sub>23</sub> I	C <sub>11</sub> H <sub>23</sub> CN	
6	3.0	DMF (1.0)	24	3.0	0	38	
7	3.0	DMF (0.1)	48	3.0	0	45	
8	3.0	DMF (0.1)	48	6.0	0	52	
9	3.0	DMF (0.03)	72	6.0	0	63	
10	3.0	DMF (0.01)	72	6.0	27	49	
11	1.0	DMF (0.01)	72	6.0	45	37	
12 <sup>a</sup>	1.0	DMF (0.01)	72	6.0	0	75	
13 <sup>a</sup>	0.5	DMF (0.005)	72	6.0	2	71	

<sup>a</sup> A screw-capped glass vial (10 mL) was used.

**Table 3** Conversion of Primary Alkyl Halides to Nitriles

1. aq NH<sub>3</sub>, cosolvent  
2. I<sub>2</sub> (3.0 equiv), aq NH<sub>3</sub>, 60 °C

$$\text{RCH}_2\text{X} \longrightarrow \text{RCN}$$

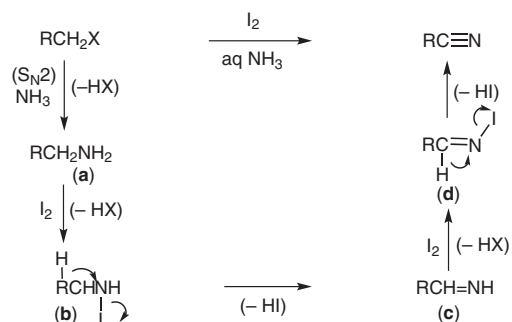
Entry	R	X	First step				Second step		Yield (%)
			Cosolvent (mL)	aq NH <sub>3</sub> (mL)	Temp (°C)	Time (h)	aq NH <sub>3</sub> (mL)	Time (h)	
1 <sup>a</sup>		I	DMF (0.01)	1.0	60	72	6.0	4	75
2 <sup>a</sup>	<i>n</i> -C <sub>11</sub> H <sub>23</sub>	Br	DMF (0.03)	1.0	60	72	6.0	4	69
3 <sup>a</sup>		Cl	DMF (0.03)	1.0	100	72	6.0	4	49 (19 <sup>b</sup> )
4 <sup>a</sup>		I	DMF (0.01)	1.0	100	24	6.0	4	48
5 <sup>a</sup>		Br	DMF (0.01)	1.0	100	24	6.0	4	39 (7 <sup>b</sup> )
6 <sup>a</sup>		I	DMF (0.01)	1.0	100	24	6.0	4	0 (99 <sup>b</sup> )
7 <sup>a,c</sup>	-(CH <sub>2</sub> ) <sub>8</sub> -	I	None	3.0	60	4	6.0	6	54
8 <sup>a,c</sup>		Br	None	3.0	60	24	6.0	6	58
9 <sup>d</sup>		I	None	3.0	60	12	3.0	4	70
10		Br	None	5.0	60	24	3.0	4	73
11 <sup>a</sup>		Cl	None	3.0	100	24	3.0	4	65
12 <sup>a,d</sup>		I	None	3.0	60	4	3.0	4	56
13		Br	None	5.0	60	48	3.0	4	68
14 <sup>a,d</sup>		I	None	3.0	60	4	3.0	4	63
15 <sup>a</sup>		Br	None	5.0	60	24	3.0	4	76
16	-(CH <sub>2</sub> ) <sub>9</sub> CO <sub>2</sub> H	I	None	3.0	60	4	3.0	4	53
17		Br	None	5.0	60	4	3.0	12	56

<sup>a</sup> A screw-capped glass vial (10 mL) was used.

<sup>b</sup> Yield of the starting material.

<sup>c</sup> Iodine (6.0 equiv) was used.

<sup>d</sup> First step was carried out under dark condition.



Scheme 1

In conclusion, benzylic halides and primary alkyl halides could be easily and directly converted into the corresponding nitriles without changing the number of carbon atoms in good yields, using molecular iodine in aqueous ammonia. As is well known, the advantages of molecular iodine are operational simplicity, low cost, and low toxicity, and therefore, the present reaction should be a useful and environmentally benign method for the preparation of nitriles from halides.

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### (8) Typical Procedure for Oxidative Conversion of Benzyl Halides into Nitriles with I<sub>2</sub>

To a mixture of 4-methylbenzyl chloride (140.6 mg, 1 mmol) and aq NH<sub>3</sub> (3.0 mL, 45 mmol) was added I<sub>2</sub> (533.0 mg, 2.1 mmol) at r.t. under an empty balloon. The obtained mixture was stirred at 60 °C. After 4 h at the same temperature, the reaction mixture was quenched with H<sub>2</sub>O (10 mL) and sat. aq Na<sub>2</sub>SO<sub>3</sub> (2 mL) at 0 °C and was extracted with Et<sub>2</sub>O (3 × 15 mL). The organic layer was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub> to provide *p*-tolunitrile in 82% yield in an almost pure state. If necessary, the product was purified by a column chromatography (SiO<sub>2</sub>; hexane–EtOAc, 4:1) to give pure *p*-tolunitrile as a colorless solid; mp 25 °C. IR (NaCl): 2230 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.55 (2 H, d, *J* = 7.9 Hz), 7.27 (2 H, d, *J* = 7.9 Hz), 2.42 (3 H, s).

### (9) Typical Procedure for Oxidative Conversion of Alkyl Halides into Nitriles with I<sub>2</sub>

A mixture of 3-phenylpropyl bromide (199.1 mg, 1 mmol) and aq NH<sub>3</sub> (5.0 mL, 75 mmol) in a screw-capped glass vial (10 mL) was stirred at 60 °C for 24 h. Then, aq NH<sub>3</sub> (3.0 mL, 45 mmol) and I<sub>2</sub> (761.4 mg, 3.0 mmol) were added. After 4 h at the same temperature, the reaction mixture was quenched with H<sub>2</sub>O (10 mL) and sat. aq Na<sub>2</sub>SO<sub>3</sub> (2 mL) at 0 °C and was extracted with Et<sub>2</sub>O (3 × 15 mL). The organic layer was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub> to provide 3-phenylpropionitrile in 73% yield in an almost pure state. If necessary, the product was purified by column chromatography (SiO<sub>2</sub>; hexane–EtOAc, 4:1) to give pure 3-phenylpropionitrile as a colorless oil. IR (NaCl): 2250 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.34 (2 H, t, *J* = 8.2 Hz), 7.28 (1 H, t, *J* = 8.2 Hz), 7.23 (2 H, d, *J* = 8.2 Hz), 2.96 (2 H, d, *J* = 7.9 Hz), 2.62 (2 H, d, *J* = 7.9 Hz).

All nitrile products mentioned in this work, except 10-cyanodecanoic acid, were identified with commercially available authentic samples.

### 10-Cyanodecanoic Acid

Mp 42–44 °C. IR (neat): 2243, 1690 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.35 (t, *J* = 7.4 Hz, 2 H), 7.34 (t, *J* = 7.2 Hz, 1 H), 1.64 (m, 4 H), 1.44 (br, 2 H) 1.32 (br, 9 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 179.7, 119.9, 34.0, 29.1, 29.0, 28.72, 28.66, 25.4, 24.7, 17.2. HRMS: *m/z* calcd for C<sub>11</sub>H<sub>19</sub>O<sub>2</sub>N: 198.1494; found: 198.1484.