Iodine/aqueous NH_4OAc: an improved reaction system for direct oxidative conversion of aldehydes and alcohols into nitriles

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A convenient method for direct oxidative conversion of aldehydes and alcohols into nitriles has been developed by using the inexpensive and environmentally friendly reagent I_2/aqueous NH_4OAc. The aqueous NH_4OAc as a non-toxic cyanide source is more eco-friendly than aqueous ammonia, because gaseous ammonia evaporates easily from aqueous ammonia but not from aqueous NH_4OAc.

Keywords: molecular iodine, cyanation, aldehydes, primary alcohols, oxidation, ammonium acetate

Nitriles are of considerable interest as the growth is present in dyes, herbicides, natural products and pharmaceuticals.[1,2] In addition, cyanides play a crucial role as they can be easily converted into a variety of functional groups such as acids, amides, ketones, oximes and amines.[3]

Various methods for the synthesis of nitriles have been reported. One of the most convenient methods is based on the transition metal-mediated displacement of halides from aromatic halides by the cyanide ion. Since the discovery of transition metal-catalysed cross-coupling reactions, much interest has been devoted to the development of a practical version of this transformation.[4,5] A number of successful palladium-[6-9] and nickel-catalysed[10-12] protocols have been reported. In addition, dehydration of aldoximes is a useful method for the synthesis of nitriles.[13] However, most of the work has concentrated on the inconvenient traditional sources of cyanide which have some severe drawbacks. Alkali cyanides are highly poisonous, zinc cyanide leads to stoichiometric waste of heavy metal salts and trimethylsilyl cyanide is sensitive to moisture and can easily liberate hydrogen cyanide. This is also true for acetone cyanohydrin. The use of aqueous ammonia or gaseous ammonia is also considered as an expedient method for the transformation of aldehydes and alcohols to their corresponding nitriles. Such as the system of ammonia gas/I_2/MeONa/MeOH,[14] aqueous ammonia /KI/MeONa/MeOH,[15] ammonia gas/H_2O_2/CuCl/*i*-PrOH,[16] aqueous ammonia /I_2,[17,18] etc. However, volatile ammonia has an undesirable smell and is harmful to the environment. In addition, ammonia is a common and undesirable contaminant in waste water and biomass cultivation media and the adverse effects of ammonia have promoted the development of various techniques for its removal.[19] Previously, $NH_2OH{\cdot}HCl$ has also been developed, as a good cyanide source for example under microwave irradiation,[20] in the system $NH_2OH{\cdot}HCl$/HY-zeolite/m.w.,[21] and in the system $NH_2OH{\cdot}HCl/I_2$/DMSO.[22] NH_4OAc has drawn considerable attention as a good reagent for various organic transformations.[23-26] Following our interest in cyanation,[27-29] and as a part of our studies to explore the utility of iodine-catalysed reactions,[30-32] we decided to investigate I_2-mediated synthesis of nitriles by direct oxidative conversion of aldehydes and alcohols using NH_4OAc as the nitrogen cyanide source (Scheme 1).

Firstly, the addition of 1.0 equivalent of molecular iodine to a mixture of benzaldehyde and aq NH_4OAc provided benzonitrile in 37% yield at room temperature (Table 1, entry 1). We found that most of the iodine was not dissolved in the aq. NH_4OAc at room temperature, but the yield was not increased greatly when THF or EtOH was employed (Table 1, entry 1). We then found that iodine was completely dissolved in aq NH_4OAc when the reaction temperature was increased to 50°C. From Table 1, we can see that the appropriate amount of I_2 was 1.0 equivalent to benzaldehyde, and a reaction temperature of 70°C was found to be appropriate (Table 1, entry 4).

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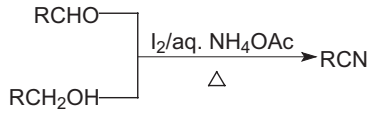
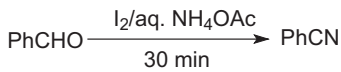


Scheme 1 Iodine-mediated synthesis of nitriles in aq. NH_4OAc.

Table 1 Studies on the conversion of benzaldehyde into benzonitrile by using iodine in aq. NH_4OAc

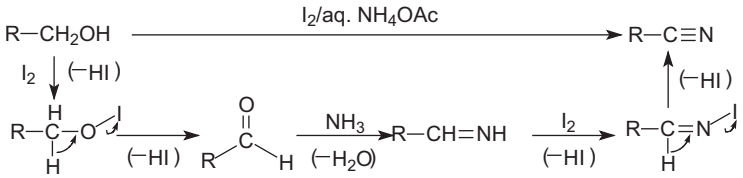


Entry	I_2/aq NH_4Oac(eq/eq)	T/°C	Yield/%[a]
1	1.0/30	25	37 45[b] 54[c]
2	1.0/30	50	55
3	1.0/30	60	78
4	1.0/30	70	94
5	1.0/30	80	95
6	0.9/30	70	87
7	1.1/30	70	93
8	1.0/20	70	73
9	1.0/40	70	94

[a]Isolated yields.
[b]THF (1 ml) was added.
[c]EtOH (1 ml) was added.

Under the optimised reaction conditions, we investigated the direct oxidative conversion of aldehydes into nitriles with I_2/aq NH_4OAc. The results are summarised in Table 2. Table 2 showed that the aromatic aldehydes, having different substituents such as chloro, nitro, methoxy, and methyl, were converted into the corresponding nitriles in high yields in a short time, and the reaction of aliphatic aldehydes also gave the corresponding nitriles in high yields. However, a low yield of *p*-hydroxybenzonitrile was obtained after 2 h (Table 2, entry 8), perhaps because *p*-hydroxybenzaldehyde has a high melting point and it remains in the solid state during the reaction.

We next examined the direct oxidative conversion of various primary alcohols into nitriles with I_2/aq NH_4OAc (Table 3). In each instance, the reaction was carried out at 100°C with the given reaction time. As shown in Table 3, the primary aromatic alcohols, having different substituents such as chloro, nitro, methoxy, and methyl were converted into the corresponding benzonitrile derivatives in high yields within 3 h. However, the reaction of aliphatic alcohols under the same conditions only gave the corresponding nitriles in moderate yields after 10 h. A higher yield of cyclohexanecarbonitrile was obtained when more I_2 was employed (Table 3, entry 7).



Scheme 2 Plausible reaction pathway for nitrile

Table 2 Conversion of aldehydes into nitriles by using iodine in aq. NH_4OAc

Entry	RCHO	Reaction time/min	Yield/%[a]
1	C_6H_5CHO	25	94
2	4-$NO_2C_6H_4CHO$	20	96
3	3-$NO_2C_6H_4CHO$	25	95
4	2-$NO_2C_6H_4CHO$	30	92
5	4-ClC_6H_4CHO	20	97
6	3-ClC_6H_4CHO	25	90
7	2-ClC_6H_4CHO	30	91
8	4-HOC_6H_4CHO	120	54
9	2-HOC_6H_4CHO	30	92
10	4-$MeOC_6H_4CHO$	25	92
11	4-MeC_6H_4CHO	25	95
12	2-Furaldehyde	15	86
13	3-Pyridinecarboxaldehyde	20	87
14	CH_3CH_2CHO	30	90
15	$CH_3(CH_2)_2CHO$	30	87
16	Cinnamaldehyde	15	90

[a]Isolated yields.

A plausible reaction pathway for the conversion of primary alcohols into the corresponding nitriles with molecular iodine has been suggested by H. Togo (Scheme 2).[18]

In conclusion, the present synthetic method is a simple, inexpensive, effective and green synthesis of nitriles using iodine in aq. NH_4OAc. The advantages of the present reaction are the elimination of metals, organic solvents and toxic reagents, operational simplicity and the high yields of products.

Experimental

CAUTION: Iodine reacts with ammonia water under certain conditions to give a black powder of nitrogen triiodide monoamine ($NI_3{\cdot}NH_3$).[19] The dry powder explodes readily by mechanical shock, heat, or irradiation. Use of excess reagent should therefore be avoided.

Reagents were obtained from commercial sources. All products were known compounds and were identified by comparing their physical data GC–MS details and ^1H NMR data with those reported in the literature.[33-35]

Typical procedure for transformation of aldehydes into nitriles: To a solution of aldehyde (1 mmol) and aq. NH_4OAc (3 ml, 30 mmol) was added I_2 (1 mmol) at room temperature. The mixture was stirred at 70°C for an appropriate time (see Table 2) as required for completion of the reaction. After the completion of the reaction, the mixture obtained was treated with $Na_2S_2O_3$ solution (5%). Then the solution was extracted with Et_2O (3 × 10 ml). The organic layer was dried and concentrated to provide the corresponding product in an almost pure state. If necessary, the crude product was purified by column chromatography on silica gel (EtOAc:petroleum ether = 2:9) to afford the corresponding pure product.

Typical procedure for transformation of primary alcohols to nitriles: To a solution of primary alcohol (1 mmol) and aq. NH_4OAc (3 ml, 30 mmol) was added I_2 (3 mmol) at room temperature. The mixture was stirred at 100°C for an appropriate time (see Table 3) as required for completion of the reaction. After the completion of the reaction, the mixture obtained was treated as above to afford the corresponding pure product.

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Table 3 Conversion of primary alcohols into nitriles by using iodine in aq. NH_4OAc

Entry	RCH_2OH	Reaction time/h	Yield/%[a]
1	$C_6H_5CH_2OH$	2	83
2	4-$NO_2C_6H_4CH_2OH$	2	95
3	4-$ClC_6H_4CH_2OH$	2	93
4	3-$ClC_6H_4CH_2OH$	3	90
5	4-$MeOC_6H_4CH_2OH$	2	92
6	4-$MeC_6H_4CH_2OH$	2	90
7	*c*-$C_6H_{11}CH_2OH$	10	59
		10	75[b]
8	*n*-$C_7H_{15}CH_2OH$	10	64
9	*n*-$C_5H_{11}CH_2OH$	10	65
10	*n*-$C_3H_7CH_2OH$	10	56

[a]Isolated yields.
[b]I_2 (4.0 eq) was used.

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