Selective conversion of aldehydes into nitriles and primary amides in aqueous media

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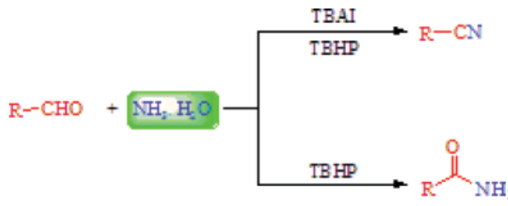
A simple and selective conversion of aldehydes into the corresponding nitriles and primary amides in aqueous ammonia has been developed. The aldehydes were efficiently converted to the corresponding nitriles in moderate to excellent yields using tetrabutylammonium iodide/tert-butyl hydroperoxide system. The primary amides, however, can be selectively synthesised only in the presence of tert-butyl hydroperoxide.

Keywords: selective oxidation, aldehydes, nitriles, primary amides, aqueous ammonia

Nitriles and amides are very important organic compounds not only because of their interesting biological properties, but also their use as versatile starting materials for many other important compounds.[1–3] Generally, the most common procedure for preparation of nitriles is the nucleophilic displacement of substrates bearing suitable leaving groups with inorganic cyanide ions.[4–7] An alternative procedure is the dehydration of aldoximes and aldimines that was formed *in situ* by condensation of aldehydes with hydroxylamine or ammonia.[8–13] On the other hand, conventional methods for the synthesis of amides involve reactions between carboxylic acids or their activated analogues and amines.[14] Other important methods include hydrolysis of nitriles,[15] metal-catalysed aminocarbonylation,[16,17] modified Staudinger reaction,[18] Schmidt reaction,[19] Ritter reaction[20] as well as the Ugi reaction.[21] Recently, the direct oxidative amidation of aldehydes to provide the corresponding amides have received increasing attention due to its high atom-economy and the sole by-product is H_2.[22–24]

While acknowledging the pioneering work in these fields, some drawbacks remain. For example, transition-metal catalysts are used in some cases, which impact cost and metal contamination of the products. The harsh reaction conditions, harmful organic solvents, expensive reagents and formation of toxic by-products also extremely limited their application. Thus, simple and convenient methods for the preparation of nitriles and amides under mild conditions in environmentally benign solvents are highly desirable. We now report an efficient and selective conversion of aldehydes into the corresponding nitriles and primary amides in aqueous ammonia using tetrabutylammonium iodide (TBAI) as catalyst and tert-butyl hydroperoxide (TBHP) as co-oxidant (Scheme 1).

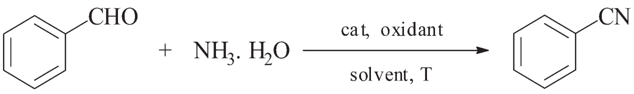
Initial studies were carried out by treating benzaldehyde with aqueous ammonia under different conditions. The results are summarised in Table 1. Interestingly, the blank reaction using TBHP as oxidant without a catalyst provided the benzamide as the sole product in 95% yield (Table 1, entry 1), whereas 92% yield of benzonitrile was obtained in the presence of 20 mol% of TBAI (Table 1, entry 2). Encouraged by the results, we optimised the reaction conditions for the selective synthesis of benzonitrile. It was found that the temperature had a large influence on the reaction. Reaction at room temperature gave the product in only 13% yield. Decreasing the temperature and the amount of the catalyst gave a lower yield of benzonitrile. Furthermore, no reaction was observed in the absence of TBHP. Other commercially available oxidants such as H_2O_2 and NaOCl were tested but no conversion was detected. Finally, various amines including inorganic and organic ammonium salts were checked in the presence of TABI and TBHP, however, these ammonium salts were completely inactive in this reaction.



Scheme 1 Selective synthesis of nitriles and primary amides.

On the basis of the successful synthesis of benzonitrile, the optimised conditions were then applied to a range of other aldehydes. As shown in Table 2, most aldehydes underwent oxidation to afford the corresponding nitriles in good to excellent yields. The electronic properties of the substituents on the benzene ring did not show an obvious influence on the reaction. Both aromatic aldehydes bearing electron-donating groups and electron-withdrawing groups gave the products in high yields within a reasonable time (Table 2, entries 1–9). The heterocyclic aldehyde, 2-furaldehyde, also survived in this oxidation system to afford the 2-furonitrile in 90% yield. In the case of aliphatic aldehydes, the reactions were conducted

Table 1 Optimisation studies for the conversion of benzaldehyde to benzonitrile[a]



Entry	Amine	Catalyst /mmol	Oxidant /mmol	T/°C	Yield /%[b]
1	$NH_3.H_2O$	–	TBHP (3)	80	95[c]
2	$NH_3.H_2O$	TBAI (0.2)	TBHP (3)	80	92
3	$NH_3.H_2O$	TBAI (0.2)	TBHP (1.2)	80	90
4	$NH_3.H_2O$	TBAI (0.2)	TBHP (1.2)	60	74
5	$NH_3.H_2O$	TBAI (0.2)	TBHP (1.2)	rt	13
6	$NH_3.H_2O$	TBAI (0.1)	TBHP (1.2)	80	85
7	$NH_3.H_2O$	TBAI (0.05)	TBHP (1.2)	80	71
8	$NH_3.H_2O$	TBAI (0.2)	H_2O_2 (1.2)	80	NR[d]
9	$NH_3.H_2O$	TBAI (0.2)	NaOCl (1.2)	80	NR[d]
10	$NH_3.H_2O$	TBAI (0.2)	–	80	NR[d]
11	$NH_3.H_2O$	KI (0.2)	TBHP (1.2)	80	81
12	NH_4Cl	TBAI (0.2)	TBHP (1.2)	80	NR[d]
13	$HCOONH_4$	TBAI (0.2)	TBHP (1.2)	80	NR[d]
14	CH_3COONH_4	TBAI (0.2)	TBHP (1.2)	80	NR[d]
15	$(NH_4)_2CO_3$	TBAI (0.2)	TBHP (1.2)	80	NR[d]

[a] Reaction conditions: benzaldehyde (1 mmol), $NH_3.H_2O$ (3 mL), 12 h.
[b] Isolated yields.
[c] Benzamide was the product.
[d] No reaction.

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Table 2 Oxidation of aldehydes into nitriles with TBAI and TBHP in aqueous ammonia[a]

$$\mathrm{R{-}CHO} + \mathrm{NH_3.\,H_2O} \xrightarrow[80\ ℃]{\mathrm{TBAI,\ TBHP}} \mathrm{R{-}CN}$$

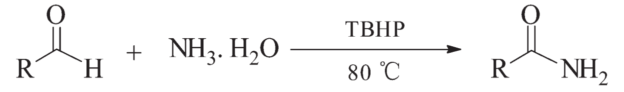
Entry	R	t (h)	Yield/%[b]	Mp/°C[lit.]
1	C_6H_5-	12	92	Oil[6]
2	4-MeC_6H_4-	12	90	Oil[25]
3	4-$MeOC_6H_4$-	16	85	58–60(58–59)[26]
4	4-ClC_6H_4-	12	95	90–92(91–92)[26]
5	3-ClC_6H_4-	12	90	38–40(39–40)[25]
6	2-ClC_6H_4-	12	82	43–45(42–44)[25]
7	4-BrC_6H_4-	12	93	110–112(110–115)[27]
8	4-FC_6H_4-	12	87	32–34(32–34)[27]
9	4-$CF_3C_6H_4$-	12	89	38–40(37–38)[25]
10	2-Furyl-	12	90	Oil[28]
11	$C_6H_5CH_2$-	16	82	Oil[28]
12	$CH_3(CH_2)_3$-	24	65	Oil[25]
13	$CH_3(CH_2)_5$-	24	60	Oil[25]

[a] Reaction conditions: aldehyde (1 mmol), $NH_3.H_2O$ (3 mL), TBAI (0.2 mmol), TBHP (1.2 mmol), 80 °C.
[b] Isolated yields.

sluggishly and the required nitriles were obtained in moderate yields by prolonging the reaction time (Table 2, entries 12 and 13). Moreover, trace amides as by-products were detected in all cases.

Since benzamide could be selectively obtained in the presence of TBHP (Table 1, entry 1), we next investigated the optimal conditions for the synthesis of benzamide. It was found that a 93% yield of product was obtained with 1.2 equiv. of TBHP at 80 °C within 12 h. To explore the generality and scope of the reaction, the oxidative amidation reaction was carried out with various aldehydes under the optimised conditions. The results are shown in Table 3. All the aromatic aldehydes exhibited good reactivity for the reaction, affording the corresponding amides in 83–97% yield. The reactivity of pentanal, however, was relatively lower and a moderate yield was obtained.

Table 3 Oxidative amidation of aldehydes with TBHP[a]



Entry	R	t/h	Yield/%[b]	M.p. /°C[lit.]
1	C_6H_5-	12	93	125–126(125–127)[29]
2	4-MeC_6H_4-	12	88	159–160(161–163)[29]
3	4-$MeOC_6H_4$-	12	91	164–167(166–167)[30]
4	4-ClC_6H_4-	12	95	177–179(178–180)[31]
5	3-ClC_6H_4-	12	92	135–136(135–137)[31]
6	2-ClC_6H_4-	12	83	139–140(140–141)[31]
7	4-BrC_6H_4-	12	93	190–193(190–192)[32]
8	4-FC_6H_4-	12	84	154–156(153–154)[32]
9	4-$NO_2C_6H_4$-	12	97[c]	198–200(199–201)[30]
10	4-$CF_3C_6H_4$-	12	90	182–184(182–183)[32]
11	$CH_3(CH_2)_3$-	24	67	104–106(102–104)[30]

[a] Reaction conditions: aldehyde (1 mmol), $NH_3.H_2O$ (3 mL), TBHP (1.2 mmol), 80 °C.
[b] Isolated yields.
[c] CH_3CN was the solvent.

According to the above results, the mechanism in Scheme 2 was proposed. For the preparation of amide, the reaction between aldehyde and aqueous ammonia may proceed by a hemiaminal intermediate **c**, which subsequently oxidised to amides by TBHP.[24] While in the presence of TBAI, the colour of the reaction mixture was changed to brown, which means the I^- was oxidised to the iodine. The iodine then accelerated the reaction between aldehyde and aqueous ammonia to form imine. The imine intermediate further reacted with iodine to give N-iodo aldimine **b**, which was finally converted into nitrile by β-elimination of HI with ammonia.[33]

In summary, a simple and efficient method for conversion of aldehydes into the corresponding nitriles and amides in aqueous ammonia has been developed using the combination of TBAI and TBHP. The present method avoids the use of expensive metal catalysts, harmful solvents and harsh conditions. The excellent yield, high selectivity and atom economy make our methods more environmentally benign and acceptable.

Experimental

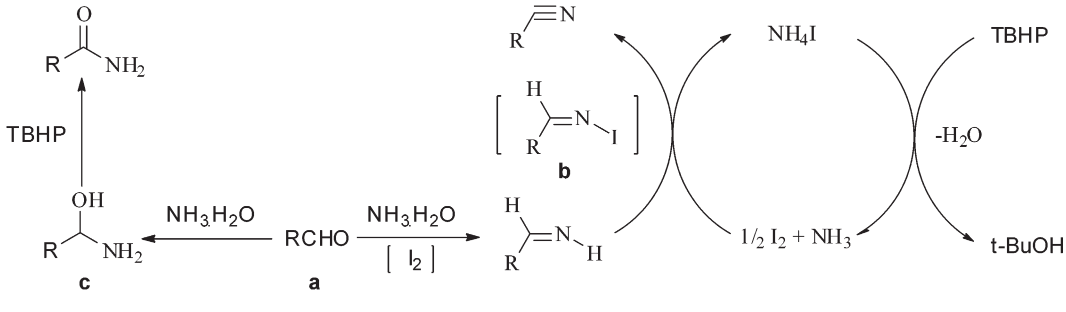
All reagents were obtained from local commercial suppliers and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance III 500 analyser. GC and MS analyses were performed on a HP5890-GCQ instrument. All the products are known compounds and were identified by comparing of their physical and spectra data with those reported in the literature.

Conversion of aldehydes into nitriles; general procedure

Aldehyde (1 mmol), ammonia water (3 mL, 25–28% aqueous solution), TBAI (74 mg, 0.2 mmol) and TBHP (1.2 mmol, 70% aqueous solution) were added to a test tube under air. Then the reaction mixture was stirred in an oil bath at 80 °C for an appropriate time as indicated by TLC. After the reaction was complete, the mixture was cooled to room temperature, and the solid products were collected by simple filtration, whereas liquid products were extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with H_2O (3 × 10 mL). Then the organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. If necessary, the product was purified by column chromatography on silica gel with EtOAc–petroleum ether as the eluent.

Conversion of aldehydes into amides; general procedure

Aldehyde (1 mmol), ammonia water (3 mL, 25–28% aqueous solution) and TBHP (1.2 mmol, 70% aqueous solution) were added to a test tube in air. Then the reaction mixture was stirred in an oil bath at 80 °C for an appropriate time as indicated by TLC. After the reaction was complete, the mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The amide products were isolated and purified by column chromatography on silica gel.



Scheme 2

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