Dehydrogenation of Amines to Nitriles in Aqueous Micelles

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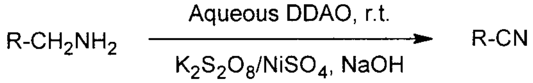
An aqueous reaction medium, based on a surfactant solution of dimethyldodecylamine *N*-oxide (DDAO) has been developed for the oxidative dehydrogenation of primary amines using $NiSO_4$ as catalyst and $K_2S_2O_8$ as oxidant. This reaction medium enhances the rate of the reaction relative to other media previously reported in the literature, which are also toxic. The reactions of various aliphatic and cyclic amines have been investigated and gave nitriles with yields of $>90\,\%$ in mild conditions. The aqueous surfactant solution and reagents were recycled for future use.

Introduction

Oxidative transformations of functional groups are fundamental processes in organic chemistry, being used in both laboratory synthesis and in the manufacturing of bulk chemicals.[1] The search for new, modified, and improved procedures is intensifying, driven mostly by the need for cleaner selectivity and higher efficiency, and by economic and environmental constraints. In the last few years, there has been a strong emphasis on the use of so-called "Green Chemistry" in an effort to protect the environment from pollutants.[2,3]

Stoichiometric oxidation with metal oxidants, such as silver oxide, manganese oxide, nickel peroxide, and chromium and copper compounds, are generally used for the selective transformation of functional groups.[4] These reagents however are corrosive and contain toxic heavy metals in their reduced form. The disposal of these metal oxidants is undesirable from both an economic and environmental point of view. Therefore, research has been directed towards finding ways to use these metals in catalytic amounts. As a result, great effort has been made to develop new and improved catalytic processes. An ideal catalytic oxidation reaction should take place at room temperature in an environmentally friendly solvent system, for example, in water with a green co-oxidant such as oxygen (air) or the extensively studied hydrogen peroxide.[5] In fact, the potassium peroxydisulfate (persulfate) system has been successfully used as a co-oxidant for nickel and can generate reactive nickel peroxide in situ, which is an important oxidant for organic transformations.[6] Yamazaki has successfully converted primary amines into nitriles by using nickel peroxide as a catalyst, generated in situ from nickel and potassium persulfate as co-oxidant, in a biphasic water/dichloromethane reaction media.[7] The use of $K_2S_2O_8$ has several practical advantages: it is a salt, stable, easy to handle, and cheap. This transformation of primary amines into nitriles has been achieved by using several metal oxidants as stoichiometric reagents;[8,9] Nakagawa and Tsuij used nickel peroxide in benzene at 60 °C.[10] This transformation has also been efficiently but not selectively achieved by using ruthenium as the catalyst and O_2, PhIO, or $K_2S_2O_8$ as the co-oxidant.[11,12] When the transformation was carried out in aqueous micellar solutions, using hypochlorite as the oxidant, the yields did not exceed 70–75 %.[13]

In this work we have investigated the use of the same oxidation system as Yamazaki for the transformation of primary amines into nitriles (Scheme 1) in aqueous reaction media without using organic solvents.



$$\text{R-CH}_2\text{NH}_2 \xrightarrow[\text{K}_2\text{S}_2\text{O}_8/\text{NiSO}_4,\ \text{NaOH}]{\text{Aqueous DDAO, r.t.}} \text{R-CN}$$

Scheme 1.

The use of water as solvent is particularly attractive in the development of mild, cheap, and environmentally benign reaction conditions, and therefore there has been considerable interest in the use of water as a reaction medium.[14–16] Furthermore, aqueous association colloids are alternatives to organic solvents as they provide reaction media that are distinct from bulk water in terms of polarity and can accelerate the reaction by binding organic compounds as well as ionic reagents to the micellar surface; they can also enhance the reactivity of associated ions by modifying their solvation shell and provide chemo-, regio-, or stereoselectivity by compartmentalizing the reagents.[17–21]

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Results and Discussion

The conversion of octylamine into octanenitrile by oxidation using a catalytic amount of nickel (1.5 mol-%) and potassium persulfate as co-oxidant (2.5 equiv. with respect to amine) was carried out in different media (see Table 1). Initially only water was used as the solvent and the results were compared with those obtained with the biphasic water/dichloromethane system previously used by Yamazaki. Whilst the use of water did not slow the reaction, it decreased the nitrile yield significantly to 30% and produced a large amount of the by-product, aldimine (entry 1). Various anionic, cationic, and zwitterionic aqueous micellar solutions were screened to study the effect of surfactant structure on the reaction. The following surfactants were used: anionic sodium dodecyl sulfate (SDS), cationic cetyltrialkylammonium salts [$n\mathrm{C}_{16}\mathrm{H}_{33}\mathrm{N}^+\mathrm{R}_3\mathrm{X}^-$: R = Me (CTAX), *n*-Pr (CTPAX); X = Br, OMs (Ms = methanesulfonate), OH], zwitterionic 3-(*N*,*N*-dimethyltetradecylammonio)propanesulfonate [$\mathrm{Me}_2(n\mathrm{C}_{14}\mathrm{H}_{29})\mathrm{N}^+(\mathrm{CH}_2)_3\mathrm{SO}_3^-$ (SB3-14)], and dimethyldodecylamine *N*-oxide [$n\mathrm{C}_{12}\mathrm{H}_{25}\mathrm{Me}_2\mathrm{N}^+\mathrm{O}^-$ (DDAO)]. The use of the anionic surfactant SDS led to a lower conversion than that obtained with water and a low nitrile yield (30%): this was probably due to the fact that both the amine and Ni^{2+} were attracted to the anionic micellar surface, whilst the persulfate anion was repelled (entry 3). The use of cationic surfactants did not improve the outcome of the reaction compared with water: in this case the amine and the anionic persulfate should be attracted by the cationic micellar surface but the Ni^{2+} cation seemed to be repelled. The use of the commercially available CTABr gave only 10% nitrile, much less than that obtained in water alone (entry 4). The use of CTABr derivatives like cetyltrimethylammonium methanesulfonate (CTAOMs) with a weakly bound counterion and cetyltripropylammonium hydroxide (CTPAOH) with a greater degree of steric hindrance at the head group and an even weaker counterion also gave poor results (entries 5 and 6). We concluded that an ionic (both anionic and cationic) micellar interface is not a suitable medium for this reaction, which first requires a reaction between an anion and a cation to form the nickel peroxide, which then reacts with the amine. The investigation, therefore, was extended to zwitterionic surfactants. In spite of the neutral nature of zwitterionic surfactants, electrolytes do bind to zwitterionic micelles, as has been unambiguously established in several experiments.[18,19] We thought that the presence of both cationic and anionic moieties in the zwitterionic surfactant′s polar head group might favour the presence of both the anionic persulfate and the cationic Ni^{2+} at the surface close to the amine. The use of zwitterionic surfactant SB3-14 gave quite good results: in this medium the reaction proceeded with both high reactivity and selectivity, practically the same as obtained in the biphasic systems and much better than obtained in water (entry 7). However aqueous solutions of SB3-14 form an emulsion during the elaboration of the reaction mixture with diethyl ether, which increases the overall time required to obtain the final reaction product. We therefore tried the zwitterionic surfactant DDAO. In this case the product was easily and rapidly extracted from the reaction mixture without the formation of an emulsion and the results were as good as those obtained with SB3-14 (entries 8 and 9). Subsequently, we then shortened the reaction time and found that the conversion of octylamine was completed in 2 hours in DDAO (80% conversion and 75% nitrile in 1 hour). DDAO is therefore a very good reaction medium; it accelerates the reaction and gives the desired product selectively and efficiently in only 2 hours (entry 9).

Table 1. Oxidation of octylamine in various media at room temp. using NiSO_4 and $\mathrm{K}_2\mathrm{S}_2\mathrm{O}_8$.[a]

Entry	Medium	Time [h]	Conversion [mol-%]	Nitrile yield [mol-%]
1	$\mathrm{H}_2\mathrm{O}$	24	100	30
2	$\mathrm{H}_2\mathrm{O}/\mathrm{CH}_2\mathrm{Cl}_2$	24	99	96
3	SDS	24	37	31
4	CTABr	24	76	10
5	CTAOMs	24	–	–
6	CTPAOH	24	13	8
7	SB3-14	24	97	97
8	DDAO	24	98	96
9	DDAO	2	95	93

[a] Octylamine = 0.4 mmol; [Surfactant] = 0.1 M, except for CTABr, of which 0.05 M was used owing to its poor solubility; [NiSO_4]/[octylamine] = 0.015, [NaOH]/[octylamine] = 5, [$\mathrm{K}_2\mathrm{S}_2\mathrm{O}_8$]/[octylamine] = 2.5, pH = 12.9. Yields were measured by GC; the difference from 100 in yield is the aldimine *N*-*n*-octylidene-*n*-octylamine.

The metal used, Ni^{2+}, is known to be quite toxic and several oxidation reactions are known to occur in the presence of persulfate and other metal ions, such as Fe^{3+}, Co^{2+}, Mn^{2+}, Cu^{2+}, and Ag^{+}.[22] In fact, powerful radical oxidants are produced in situ by radical processes and the reactions of such oxidants have recently been investigated in an attempt to destroy chlorinated groundwater contaminants.[23] The oxidative reactions of octylamine in DDAO were investigated in the presence of various metal ions (Table 2). The results show that both the persulfate and metal ion are necessary for the reaction to occur. The reaction barely occurred with $\mathrm{Fe}^{\mathrm{III}}$, $\mathrm{Mn}^{\mathrm{II}}$, $\mathrm{Cu}^{\mathrm{II}}$, and $\mathrm{Zn}^{\mathrm{II}}$ salts, whilst the use of $\mathrm{Co}^{\mathrm{II}}$, and especially Ag^{I}, gave significant amounts of aldimine (entries 5 and 6); this is consistent with the silver-catalyzed oxidation of primary amines to aldimine with persulfate as co-oxidant observed by Bacon and Stewart.[24]

Table 2. Oxidation of octylamine at room temp. using $\mathrm{K}_2\mathrm{S}_2\mathrm{O}_8$ and various metal ions in DDAO.[a]

Entry	Metal	Nitrile	Aldimine	Amine
1	$\mathrm{Fe}^{\mathrm{III}}$	–	–	100
2	$\mathrm{Mn}^{\mathrm{II}}$	–	–	100
3	$\mathrm{Cu}^{\mathrm{II}}$	4	20	76
4	$\mathrm{Zn}^{\mathrm{II}}$	1	6	93
5	$\mathrm{Co}^{\mathrm{II}}$	12	37	51
6	Ag^{I}	1	90	9

[a] Octylamine = 0.4 mmol; [DDAO] = 0.1 M; [metal salt]/[octylamine] = 0.015, [NaOH]/[octylamine] = 5, [$\mathrm{K}_2\mathrm{S}_2\mathrm{O}_8$]/[octylamine] = 2.5, pH = 12.9; reaction time = 2 hours. Yields were measured by GC.

Table 3. Oxidation of various amines at room temp. using $NiSO_4$ and $K_2S_2O_8$.[a]

Entry	Amine	Nitrile yield (%) in different media		
		H_2O/CH_2Cl_2	H_2O	DDAO (0.1 M)
1	1-Octylamine	26 (29)	14 (37)	92 (95)
2	1-Dodecylamine	1 (6)	9 (28)	93 (98)
3	1-Tetradecylamine	49 (51)	12 (15)	92 (92)
4	1-Hexadecylamine	63 (65)	11 (12)	95 *94* (95)
5	1-Cyclohexylmethylamine	34 (36)	67 (68)	quant. (quant.)
6	Benzylamine	88 (91)	45 (47)	quant. *82* (quant.)
7	Phenethylamine	39 (41)	62 (74)	97 (99)
8	3-Phenyl-1-propylamine	28 (30)	72 (74)	quant. (quant.)

[a] Yields of nitriles were measured by GC; yields by weight are italicized; conversions are given in parentheses; amine = 0.4 mmol, $[NiSO_4]/[amine] = 0.015$, $[NaOH]/[amine] = 5$, $[K_2S_2O_8]/[amine] = 2.5$, pH = 12.9; reaction time = 2 hours.

Ni^{II} is therefore necessary to obtain nitriles from primary amines, whereas silver may be conveniently used to obtain the aldimine *N*-*n*-octylidene-*n*-octylamine selectively and in high yield in 2 hours. This is an improvement on the 15% yield obtained by Bacon and Stewart.

DDAO (0.1 M) is a suitable medium for oxidizing various primary amines with $NiSO_4$ and $K_2S_2O_8$ (Table 3). Cyclic or acyclic amines, including those with a long alkyl chain such as hexadecylamine, and those with an aromatic moiety such as benzylamine, phenethylamine and 3-phenylpropylamine were converted to nitriles, in 2 hours, with high reactivity (conversions > 90%), with a generally high selectivity (> 92%), and a 100 % selectivity for the cyclic amines. Yields by weight, as evaluated for hexadecylamine and benzylamine, were also quite good (Table 3, entries 4 and 6). Reactions were also carried out in water and in the biphasic water/dichloromethane system; the aqueous micellar zwitterionic DDAO reaction medium was more efficient by far than either water alone or the biphasic mixture, which is also highly toxic.

In order to reduce the environmental impact of this reaction system, we tried to reduce the amount of $NiSO_4$ catalyst, as well as that of the surfactant, and to recycle the reaction medium. Although catalytic amounts of $NiSO_4$ were used (1.5 mol-% relative to amine), it should be decreased even further because nickel is a toxic metal. Half the amount (0.75 mol-%) can be conveniently used and the yield of nitrile is still quantitative (if the reaction time is lengthened to 5 hours). The amount of surfactant can also be decreased to 0.05 M and that of NaOH to 2.5 equiv. that of the amine. Therefore the reaction selectively gives the nitrile in 98% yield in 5 hours in 0.05 M DDAO with a $NiSO_4$/amine ratio of 0.75 and a NaOH/amine ratio of 2.5.

Finally attempts were made to recycle the reaction medium so that it can be re-used in subsequent reactions. After extracting the product with diethyl ether in the reaction flask, the aqueous surfactant solution was kept for 30 min under reduced pressure (20 Torr) at room temperature in order to remove any traces of the ether. Afterwards, amine and potassium persulfate were added to the solution for a new reaction. With octylamine, the recycled 0.1 M DDAO solution with $NiSO_4$ (1.5 mol-%) and a NaOH/amine ratio of 5 gave good results: 82% conversion and 71% yield. For solutions containing 0.05 M DDAO, $NiSO_4$ (0.75 mol-%) and a NaOH/amine ratio of 2.5, the second run (recycled) led to quantitative conversion overnight with a yield of 98%.

Conclusions

An aqueous reaction medium, based on a surfactant solution of dimethyldodecylamine *N*-oxide (DDAO), has been developed for the oxidative dehydrogenation of primary amines using $NiSO_4$ as catalyst and $K_2S_2O_8$ as oxidant. Nickel peroxide, the reactive oxidant, was generated in situ; other metal ions did not give significant results. The reaction was accelerated in this medium relative to other media previously reported in the literature, which are also toxic. Most of the investigations were carried out by using octylamine as a model, but other aliphatic and cyclic amines were also studied. In all cases, nitrile yields of >90% were obtained in 2 hours in mild conditions.

Experimental Section

General Remarks: The preparation and purification of the surfactants have been described previously.[20,21] Amines and nitriles (apart from tetradecanenitrile and hexadecanenitrile which were prepared) were from Aldrich and used without further purification. Anisole, from Aldrich, was used as the internal standard and was used without further purification. ^1H NMR spectra were recorded with a 200 MHz FT Bruker instrument in $CDCl_3$ and the chemical shifts were measured relative to internal TMS.

Reactions in Aqueous Solution: Reactions were carried out in 50-mL round-bottomed flasks. Potassium persulfate (0.96 mmol) was dissolved in a NaOH (20 mL) or aqueous basic surfactant solution (20 mL). Amine (0.38 mmol) was then added and dissolved by warming. A solution of $NiSO_4$ (0.0057 mmol) was then added under magnetic stirring and a suspension of fine black particles of nickel peroxide was produced. The resulting mixture was stirred at room temperature. At the end of the reaction, a known amount of the internal standard anisole was added and then the mixture was extracted with Et_2O (3 × 30 mL). Vigorous shaking of the reaction mixtures should be avoided with all the surfactants, apart from DDAO, to prevent the formation of emulsions. The combined extracts were dried with anhydrous Na_2SO_4 and analyzed by GC. When the yield by weight was evaluated, no internal standard was added; the mixture was extracted with Et_2O, the combined extracts were washed with 10% HCl to remove any unreacted amine, and then with brine until a neutral solution was obtained. The extracts were then dried, and the solvent removed by evaporation under reduced pressure to give the crude product, which was pure by GC, which was then weighed.

Reactions in Biphasic Water/Dichloromethane Solution: Reactions were carried out in 50-mL round-bottomed flasks. Potassium persulfate (0.96 mmol) was dissolved in NaOH solution (8 mL). Amine (0.38 mmol) was then dissolved in CH_2Cl_2 (3 mL) and this solution was added to the aqueous persulfate solution. A solution of $NiSO_4$ (0.0057 mmol) was then added under magnetic stirring and a suspension of fine black particles of nickel peroxide was produced. The resulting mixture was stirred at room temperature. At the end of the reaction, the reaction work-up was carried out as described for the reactions in aqueous solutions.

Product Analysis: Reaction products were analyzed quantitatively by GLC on an HP 35 MS instrument (FID) with a column injection, equipped with a 15 m × 0.53 mm HP 5 capillary column, 1 µm film thickness. Response factors were determined by using known mixtures of the products. All analyses were made in duplicate and errors of <5 mol-% were obtained.

Preparation and Characterization of the Products: Tetradecanenitrile and hexadecanenitrile were prepared from tetradecylamine and hexadecylamine, respectively, and oxidized in DDAO as described above: the corresponding nitriles were obtained with yields by weight of 92 and 94%, respectively, and characterized by ^1H NMR spectrum (200 MHz, $CDCl_3$, room temp.): $\delta = 0.88$ (t, 3 H, CH_3), 1.26–1.47 (m, 16 H, chain), 1.66 (m, 2 H, CH_2CH_2CN), 2.33 (t, 2 H, CH_2CN) ppm.

N-*n*-Octylidene-*n*-octylamine was prepared by the condensation of octane and *n*-octylamine in Et_2O: the reaction was completed within a few minutes. It was also prepared from the reaction of octylamine in $AgNO_3$ and the product was characterized from its ^1H NMR spectrum (200 MHz, $CDCl_3$, room temp.): $\delta = 0.89$ (t, 6 H, CH_3), 1.24–1.61 (m, 22 H, chain), 2.21 (m, 2 H, $CH_2C{=}N$), 3.37 (t, 2 H, CH_2N), 7.61 (t, 1 H, $CH{=}N$) ppm.

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