Cu(OAc)$_2$ catalysed aerobic oxidation of aldehydes to nitriles under ligand-free conditions†

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An economically efficient and environmentally benign approach for the direct oxidative transformation of aldehydes to nitriles has been developed using commercially available non-toxic copper acetate as an inexpensive catalyst and ammonium acetate as the source of nitrogen in the presence of aerial oxygen as an eco-friendly oxidant under ligand-free conditions. The reactions were associated with high yield and various sensitive moieties like allyloxy, benzyloxy, t-butyldimethylsilyloxy, hetero-aryl, formyl, keto, chloro, bromo, methylenedioxy and cyano were well tolerated in the aforesaid method. The kinetic studies showed first order dependency on the aldehyde substrate in the reaction rate. The reaction was faster with the electron deficient aldehydes as confirmed by Hammett analysis. Moreover, the present oxidative method was effective on larger scales showing potential for industrial application.

Introduction

Nitrile is an important functional group which has been widely used for different organic transformations towards the synthesis of dyes, pigments, materials, polymers, natural products, agrochemical, and pharmaceuticals.1 Moreover, nitriles also serve as a recurrent pharmacophore in many commercially available drugs, such as Bicalutamide® (prostate cancer and breast cancer therapies), Citalopram® (antidepressant drug), Etravirine® (anti-HIV), Fadrozole® (oncolytic drug), Letrozole® (breast cancer therapy), and Periciazine® (antipsychotic drug) and 5-lipoxygenase inhibitors have been recognized (Fig. 1).2

The classical methods for preparing aryl nitriles involve the Sandmeyer reaction3–d of aromatic diazonium salts and the Rosenmund-von Braun reaction4 of aryl halides, which require stoichiometric amounts of highly toxic CuCN and harsh reaction conditions. Other alternative approaches for nitrile synthesis such as hydrocyanation of alkenes,4 Kolbe nitrile synthesis,5 methyl amines,6 oxidative rearrangement of alkene,7 benzyl or allyl halides,7 ammoxidation of alcohols7 and cyanation of aryl halides8 were reported in the last few years, but most of these methods suffer limitations such as high temperature (>100 °C), use of harmful and expensive metal catalysts as well as toxic and corrosive reagents, requirement of capricious ligands, inert atmosphere, and poor functional group tolerance. Moreover, transition-metal free protocols such as trichloroisocyanuric acid (TCCA),9 tetrabutylammonium tribromide (TBATB),9 ceric ammonium nitrate (CAN),9 chloramine-T (CAT),9d TEMPO/NaNO2/HMDS,9 and SO2F2/Et3N9g have been documented. But still the requirements of highly sensitive and perilous reagents were an inevitable issue. Thus, the development of an alternative protocol for direct oxidative transformation of aldehydes to nitriles associated with some attributes like operational simplicity, ready accessibility of the substrates, cost-effectiveness as well as obviating the isolation of intermediates has received substantial interest in recent times. In this direction, several synthetic strategies using different nitrogen sources viz., NH$_4$OAc,10a TMSN$_3$,10b NH$_4$CO$_2$NH$_2$,10c NH$_2$OH–HCl,10d NH$_3$,10f in the presence of various catalysts have been developed in the last few years (Scheme 1). However, despite the potential utility of the reported protocols listed in Scheme 1, applications of most of them remained limited due to the use of hazardous reagents, expensive ligands,

![Fig. 1](image-url) Some potent biologically active organonitrile drugs.
requirement of additives (such as acids, bases and salts), laborious catalyst preparation and tedious work-up procedures which are less eco-compatible from the sustainable perspective.

Therefore, development of highly efficient strategy avoiding the use of toxic and expensive metal catalysts and utilizing the less hazardous and inexpensive reagents for the synthesis of nitriles is of great demand in the perspective of present environmental scenario. Of late, copper-catalyzed organic transformations has drawn tremendous interest because copper and its compounds are considerably more abundant, less toxic, cheaper in price and environmentally benign compared to other existing precious metal-based catalysts. In this pursuit, we report herein a mild, efficient and eco-compatible protocol for the direct oxidative transformation of aldehydes to nitriles using commercially available non-toxic copper acetate as an inexpensive catalyst and ammonium acetate as the nitrogen source under ambient conditions with a broad substrate scope and tolerance of various sensitive moieties during the reaction (Scheme 1).

Results and discussion
Firstly, we conducted a series of experiments to optimize the reaction conditions for the oxidative transformation of 4-

Table 1  Optimization of reaction conditions

| Entry | Cu salt (mol%) | Nitrogen source (mmol) | Solvent (mL) | Temp. (°C) | Time (h) | Yield (%) |
|-------|---------------|------------------------|--------------|------------|---------|-----------|
| 1     | —             | NH₄OAc                 | DMSO         | 60         | 12 h    | —         |
| 2     | CuSO₄        | Aq. NH₃                | DMSO         | 60         | 12 h    | 28        |
| 3     | CuSO₄        | (NH₄)₂SO₄              | DMSO         | 60         | 12 h    | 47        |
| 4     | CuSO₄        | (NH₄)₂SO₄              | CH₃CN       | 60         | 12 h    | 35        |
| 5     | CuCl₂        | NH₄Cl                  | DMF          | 60         | 12 h    | 45        |
| 6     | CuCl₂        | NH₄Cl                  | DMF          | 60         | 12 h    | 49        |
| 7     | Cu(NO₃)₂     | NH₂NO₂                 | DMSO         | 60         | 12 h    | 53        |
| 8     | Cu(NO₃)₂     | NH₂NO₂                 | CH₃CN       | 60         | 12 h    | 42        |
| 9     | Cu(OAc)₂     | NH₄OAc                | CH₃CN       | 60         | 12 h    | 73        |
| 10    | Cu(OAc)₂     | NH₄OAc                | DMSO         | 60         | 10 h/12 h | 90/91 |
| 11    | Cu(OAc)₂     | NH₄OAc                | DMSO         | 60         | 10 h/12 h | —        |
| 12    | Cu(OAc)₂     | NH₄OAc                | DMSO         | 60         | 10 h/12 h | —        |
| 13    | Cu(OAc)₂     | NH₄OAc                | H₂O          | 60         | 10 h/12 h | 36/38 |
| 14    | Cu(OAc)₂     | NH₄OAc                | EtOH         | reflux     | 12 h/14 h | 51/54 |
| 15    | Cu(OAc)₂     | NH₄OAc                | DCM          | reflux     | 12 h/14 h | 48/49 |
| 16    | Cu(OAc)₂     | HCOONH₂               | DMSO         | 60         | 8 h/12 h | —         |
| 17    | Cu(OAc)₂     | Aq. NH₃               | DMSO         | 60         | 10 h/12 h | 23/24 |
| 18    | CuO          | NH₄OAc                | DMSO         | 60         | 8 h/12 h | —         |
| 19    | CuCl         | NH₄OAc                | DMSO         | 60         | 8 h/12 h | —         |
| 20    | Cu(OAc)₂·H₂O | NH₄OAc                | DMSO         | 60         | 12 h    | 78        |

a Reaction conditions: 1a (1.0 mmol), Cu salt (10 mol%), nitrogen source (1.5 mmol), solvent (3 mL), temperature (as indicated), under ambient condition. b Yield of isolated product. c The reaction was carried out under inert (argon) atmosphere.
Table 2  
Cu(OAc)$_2$ catalyzed direct oxidative transformations of aldehydes to nitriles$^a$

| Entry | Substrate | Product | Time (h) | Yield$^d$ (%) |
|-------|-----------|---------|----------|--------------|
| **Synthesis of benzonitriles bearing electron-donating substituents** | | | | |
| 1     | la        | 2a      | 10       | 90           |
| 2     | lb        | 2b      | 10       | 91           |
| 3     | lc        | 2c      | 10       | 89           |
| 4     | ld        | 2d      | 7.5      | 90           |
| 5     | le        | 2e      | 10       | 90           |

| **Synthesis of hydroxy functionalized benzonitriles** | | | | |
| 6     | lf        | 2f      | 10       | 89           |
| 7     | lg        | 2g      | 10       | 87           |
| 8     | lh        | 2h      | 10       | 89           |
| 9     | li        | 2i      | 10       | 88           |

| **Synthesis of amino functionalized benzonitriles** | | | | |
| 10    | lj        | 2j      | 9.0      | 88           |
| 11    | lk        | 2k      | 9.0      | 89           |
Table 2 (Contd.)

| Entry | Substrate | Product | Time (h) | Yield\(^d\) (%) |
|-------|-----------|---------|----------|-----------------|
| 12    | ![Clover Substrate](image1.png) 11 | ![Clover Product](image2.png) 2l | 6.0    | 93              |
| 13    | ![Bromine Substrate](image3.png) 1m | ![Bromine Product](image4.png) 2m | 6.0    | 91              |
|       | **Synthesis of nitro functionalized benzonitriles** | | | |
| 14    | ![Nitro Substrate](image5.png) 1n | ![Nitro Product](image6.png) 2n | 3.0    | 95              |
| 15    | ![Oxidate Substrate](image7.png) 1o | ![Oxidate Product](image8.png) 2o | 3.0    | 94              |
|       | **Selectivity towards the synthesis of nitriles** | | | |
| 16\(^b\) | ![Selectivity Substrate](image9.png) 1p | ![Selectivity Product](image10.png) 2p | 6.0    | 88              |
| 17\(^c\) | ![Selectivity Substrate](image11.png) 1p | ![Selectivity Product](image12.png) 2q | 6.0    | 87              |
| 18    | ![H3CO Substrate](image13.png) 1q | ![H3CO Product](image14.png) 2r | 6.0    | 88              |
|       | **Synthesis of nitriles bearing naphthyl, methylenedioxy and alkenyl moiety** | | | |
| 19    | ![Naphthyl Substrate](image15.png) 1r | ![Naphthyl Product](image16.png) 2s | 11     | 86              |
| 20    | ![Methylenedioxy Substrate](image17.png) 1s | ![Methylenedioxy Product](image18.png) 2t | 10     | 88              |
| 21    | ![Alkenyl Substrate](image19.png) 1t | ![Alkenyl Product](image20.png) 2u | 10     | 83              |
methoxybenzaldehyde 1a to the corresponding nitrile 2a in the presence of different copper salts as well as various nitrogen sources and solvents. The results are presented in Table 1. The reaction did neither occur at all in the absence of any copper salt (entry 1) nor with CuSO₄ in combination with (NH₄)₂SO₄ in EtOH solvent (entry 5), the unreacted substrates were isolated intact. The conversion was little improved when the reaction was performed in the presence of CuSO₄ with aqueous NH₃ in DMSO medium (entry 2), CuSO₄ with (NH₄)₂SO₄ in DMSO and CH₃CN medium (entries 3 and 4), CuCl₂ with NH₄Cl in DMSO

| Entry | Substrate | Product | Time (h) | Yield (d) (%) |
|-------|-----------|---------|----------|---------------|
| 22    | ![Image](1a.png) | ![Image](2v.png) | 10       | 79            |
| 23    | ![Image](1v.png) | ![Image](2w.png) | 10       | 81            |
| 24    | ![Image](1w.png) | ![Image](2x.png) | 10       | 83            |
| 25    | ![Image](1x.png) | ![Image](2y.png) | 10       | 80            |

| Entry | Substrate | Product | Time (h) | Yield (d) (%) |
|-------|-----------|---------|----------|---------------|
| 26    | ![Image](1y.png) | ![Image](2z.png) | 10       | 86            |
| 27    | ![Image](1z.png) | ![Image](2za.png) | 10       | 84            |
| 28    | ![Image](1za.png) | ![Image](2zb.png) | 10       | 85            |

| Entry | Substrate | Product | Time (h) | Yield (d) (%) |
|-------|-----------|---------|----------|---------------|
| 29    | ![Image](1zb.png) | ![Image](2zc.png) | 12       | 78            |
| 30    | ![Image](1zc.png) | ![Image](2zd.png) | 12       | 79            |
| 31    | ![Image](1zd.png) | ![Image](2ze.png) | 12       | 84            |

*Reaction conditions: 1a (1.0 mmol), Cu(OAc)₂ (10 mol%), NH₄OAc (1.5 mmol), DMSO (3 mL), 60 °C, under ambient atmosphere. *b* NH₄OAc (1.5 mmol). *c* NH₄OAc (3.0 mmol) were used for 1 mmol of substrate. *d* Yield of isolated and purified product.
and DMF solvent (entries 6 and 7) and Cu(NO$_3$)$_2$ with NH$_4$NO$_3$ in DMSO and CH$_3$CN medium (entries 8 and 9). Interestingly the extent of conversion was increased to 73% when the reaction was studied in the presence of Cu(OAc)$_2$ along with NH$_4$OAc at 60 °C in CH$_3$CN medium (entry 10). Surprisingly when the reaction was performed using Cu(OAc)$_2$ along with NH$_4$OAc in DMSO medium under ambient atmosphere, the extent of conversion was increased to 90% within a shorter reaction time (entry 11).

But, when the reaction was performed under an inert (Ar) atmosphere in the absence of aerial oxygen, no trace of nitrile 2a was detected in the reaction mixture, the substrate 1a remained intact (entry 12). This observation indicated the importance of atmospheric oxygen as the eco-friendly oxidant during the aforementioned transformation. Moreover, this observation also indicated that DMSO does not have any role as an oxidant towards this oxidative transformation. It is simply used as the solvent in the aforementioned protocol. The effective role of DMSO towards this reaction might be speculated to originate from the better solubilization of the organic substrate as well as ionic reagent and catalyst along with rendering some stabilization towards the polar intermediates through solvation. The ionic reagent and catalyst along with rendering some stabilization and a longer period of reaction time (entries 14 and 11). This protocol was also effective transformation to the corresponding nitriles with 88% and 89% yield respectively (entries 10 and 11). This protocol was also effective for the substrates bearing halogen which produced the nitriles 2l and 2m in good yield within a shorter reaction time without any dehalogenated product (entries 12 and 13). Aldehydes with electron-withdrawing groups (–NO$_2$) at m- and p-positions underwent efficient transformation to the corresponding nitriles 2n and 2o with 95% and 94% yields within 3 hours (entries 14 and 15).

Quite interestingly, terephthaldehyde (1p) was converted to the 4-formylbenzonitrile (2p) and terephthalonitrile (2q) in 88% and 87% yield using 1.5 mmol and 3.0 mmol of ammonium acetate respectively (entries 16 and 17) as the source of nitrogen with respect to 1 mmol of substrate. The structure of 2p was substantiated by the singlet at $\delta$ 10.10 (due to –CHO) along with two doublets at $\delta$ 7.98 (due to aromatic protons ortho to –CHO) and at $\delta$ 7.84 (due to aromatic protons ortho to –CN). In the $^{13}$C NMR spectrum of 2p, simultaneous occurrence of two signals at $\delta$ 190.6 and $\delta$ 117.6 proves the co-existence of –CHO and –CN groups respectively. 4-Formylbenzonitrile (2p) furnished terephthalonitrile (2q) in 85% yield using 1.5 mmol of ammonium acetate. The formation of 2q was confirmed by the presence of only one singlet due to chemically equivalent aromatic hydrogens at $\delta$ 7.52 in its $^1$H NMR spectrum as well as from the signal (at $\delta$ 118.2) specific for –CN in the $^{13}$C NMR spectrum. This regioselectivity is an extremely important attribute of the present protocol in contrast to many reported methods where no such selectivity was observed. We have also investigated the reaction using terephthaldehyde (1p) (1 mmol) and ammonium acetate (1.5 mmol) under oxygen atmosphere, the condition with 88% and 89% yield respectively (entries 10 and 11).

Table 3 Experimental details to determine the reaction order

| Run | 1a | NH$_4$OAc | Cu(OAc)$_2$ | DMSO |
|-----|----|----------|-------------|------|
| Run 1 | 1 mmol | 1.5 mmol | 10 mol% | 3 mL |
| Run 2 | 2 mmol | 1.5 mmol | 10 mol% | 3 mL |

Fig. 2 Dependence of the initial rate of the reaction on [4-methoxybenzaldehyde] using Cu(OAc)$_2$ (10 mol%), NH$_4$OAc (1.5 mmol), DMSO (3 mL), 60 °C, under ambient atmosphere.
product 2p was obtained exclusively with 86% yield within 4 h without formation of any terephthalonitrile (2q) product. This observation further suggested the importance of oxygen as the eco-friendly oxidant as well as the selective formation of nitrile product during the aforementioned transformation. However, we restricted ourselves to the use of aerial oxygen for the entire study due to procedural simplicity involving the ambient atmosphere albeit longer reaction time for comparable conversion. 4-Acetylbenzaldehyde reacted smoothly to furnish 4-acetylbenzonitrile 2r with 88% yield within 6 hours (entry 18). Therefore, it can be concluded that the reaction was highly selective for aldehyde. The method was also successful for 2s containing naphthyl moiety with satisfactory yield within 11 hours (entry 19). Hydrolyzable groups like methylenedioxy in 2t also survived under the aforesaid protocol (entry 20). This is not commonly observed in some literature reports.9d,e,10b–f The present method was extended towards the efficient synthesis of α,β-unsaturated nitrile 2u (entry 21). Acid-sensitive electron-rich as well as electron-deficient heteroaromatic moieties also survived during this reaction (2v–y) which paved the way towards the construction of important molecular skeletons densely loaded with heterocycles in satisfactory yields (entries

![Fig. 3 Determination of rate constant for the electronically disparate aldehydes during the synthesis of nitriles (a–e).](image-url)
It is extremely important to note the fact that highly vulnerable groups like O-benzyl, O-allyl, and O-\(t\)-butylsilyl were also tolerated under the optimized reaction condition to furnish 2z, 2za, and 2zb respectively with good yields (entries 26–28). This is not commonly observed in some literature reports.9d–g,10a–f Furthermore, aliphatic nitriles 2zc, 2zd, and 2ze were also produced quite efficiently during a longer period under the aforesaid protocol (entries 29–31) from the corresponding aliphatic aldehydes (1zb–zd).

We next performed the kinetic experiments with the aforesaid protocol in order to determine the order of the reaction. Therefore, two identical experiments were carried out following the general procedure varying only the concentration of 4-methoxybenzaldehyde 1a (Table 3). The initial rate of the reaction for different run was calculated to determine the order with respect to aldehyde 1a. The kinetic studies showed that the reaction rate depends on the concentration of 4-methoxybenzaldehyde 1a only (Fig. 2). Therefore, the aforesaid oxidative protocol follows first order kinetics (see ESI†).

Table 2 demonstrated that both electron donating as well as electron withdrawing substituents showed an excellent reactivity and produced the desired products in excellent yield with different time intervals. Electronic effect was noted in this direct oxidative transformation of aldehydes to nitriles.

Therefore, kinetic experiments were carried out using several electronically disparate benzaldehydes following the general procedure (Fig. 3). It was evident from Fig. 3 that the reactions with electron withdrawing substituent were faster than with electron donating substituent and better conversion was achieved within shorter reaction time in the former case. It was also evident that the rate of the reaction with 4-nitrobenzaldehyde was nine times faster than with 4-methoxybenzaldehyde. Therefore, Hammett analysis (Table 4) was carried out using various substituted benzaldehydes under the optimized reaction conditions. A very good linear relationship was observed when relative rates \([\log (k_X/k_H)]\) with these substituted benzaldehydes were plotted against the substituent constant (\(\sigma_p\)) (Fig. 4). It was also observed that a positive p value of +0.95 and the reactivity sequence: \(p-\text{NO}_2 > p-\text{Cl} > p-\text{H} > p-\text{Me} > p-\text{OMe}\) for this oxidative protocol. This observation further suggested that the electron-withdrawing substituent should enhance the reaction and the results were consistent with the reactivity of the substrates reported in Table 2.

Based on the aforesaid investigations and literature precedence,10a,14a–c a plausible mechanistic pathway for this oxidative transformation is depicted in Scheme 3. At the outset, \text{Cu(OAc)}_2
activates the carbonyl carbon to react with NH₄OAc to form aldimine intermediate (A). Then the unstable aldimine intermediate (A) reacts with Cu(OAc)₂ to form the iminylcuprate intermediate (B), which on subsequent oxidation forms the corresponding nitrile 2 with the liberation of CuOAc which further oxidized to Cu(OAc)₂ in the presence of aerial oxygen. Here, Cu(OAc)₂ serving as a Lewis acid and aerial oxygen acts as an eco-friendly oxidant towards this oxidative transformation.

To ensure the synthetic scalability and practical applicability of our newly developed oxidative protocol, a gram scale reaction of 4-methoxybenzaldehyde 1a was performed (Scheme 4) the outcome of which was almost similar as that in the small scale reaction. The reaction mixture was extracted with EtOAc and the crude was further purified by column chromatography on a short column of silica gel using 1–5% ethyl acetate–hexane as eluent to obtain 2a. Therefore, Cu(OAc)₂/NH₄OAc catalyzed oxidative protocol can be readily scaled up to gram-scale, which bears a significant prospect for industrial application.

Conclusions

We have developed a mild, operationally simple, cost-effective and eco-friendly protocol for the direct oxidative conversion of aldehydes to nitriles using commercially available relatively less toxic copper acetate as an inexpensive catalyst and ammonium acetate as the source of nitrogen in the presence of environmentally benign aerial oxygen as an eco-friendly oxidant under ligand-free and base-free condition. The kinetic experiments showed the first-order dependence of the substrate aldehyde towards the reaction rate. Moreover, Hammett analysis confirmed that the reaction was faster with the electron-deficient aldehydes. The synthetic utility and practical applicability of this newly developed protocol were demonstrated through a scale-up experiment. The salient features of the present protocol are procedural simplicity, ready accessibility and lower toxicity of the copper catalyst as well as the nitrogen source, sustainability in terms of using aerial oxygen as an eco-friendly oxidant, and tolerance of various sensitive moieties during the reaction.

Experimental section

Materials and methods

All reactants were purchased from SRL, AVRA Chemicals, Alfa-aesar, Spectrochem, and Sigma Aldrich and used as received without further purification. ¹H and ¹³C NMR spectra were obtained on a Bruker spectrometer (300 MHz and 400 MHz) and JEOL Spectrometer (500 MHz) in CDCl₃ and DMSO-d₆, solutions with TMS as an internal reference. Melting points were determined in open capillary on electrical bath which is uncorrected. Column chromatography was performed on silica gel (60–120 mesh) from SRL, India. Thin layer chromatographic separations were performed on pre-coated silica gel plates using silica gel G for TLC (E. Merck).

General experimental procedure for the Cu(OAc)₂ catalyzed oxidative transformation of aldehydes to nitriles

To a stirred suspension of aldehyde 1 (1.0 mmol) and ammonium acetate (1.5 mmol) in DMSO (3 mL), Cu(OAc)₂ (10 mol%) was added. The reaction mixture was stirred for an appropriate time at 60 ºC under ambient atmosphere. The progress of the reaction was monitored with TLC. Then the reaction mixture was cooled to room temperature, ethyl acetate (15 mL) was added to dissolve the product. The reaction mixture was repeatedly extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with water (3 × 5 mL) and dried over anhydrous Na₂SO₄. The crude product 2 was obtained by removal of the solvent under reduced pressure which was further purified by column chromatography on a short column of silica gel using 1–10% ethyl acetate–hexane as eluent.

Procedure for the Cu(OAc)₂ catalyzed gram-scale synthesis of nitrile (2a)

To a stirred suspension of 4-methoxybenzaldehyde 1a (20.0 mmol, 2.723 g) and ammonium acetate (30.0 mmol, 2.310 g) in DMSO (60 mL), Cu(OAc)₂ (0.336 g, 10 mol%) was added and the reaction mixture was stirred for the appropriate time at 60 ºC under ambient atmosphere. The progress of the reaction was monitored with TLC. Then the reaction mixture was cooled to room temperature, ethyl acetate (300 mL) was added to dissolve the product. The reaction mixture was repeatedly extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with water (3 × 100 mL). After drying with anhydrous sodium sulfate, the solvent was removed under reduced pressure to furnish the crude product 2a, which was further purified by column chromatography of silica gel using ethyl acetate–hexane as eluent. (Yield: 89%, 2.370 g).

Conflict of interest

The authors declare that there is no conflict of interest in this study.

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