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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® (anti-psychotic drug) and 5-lipoxygenase inhibitors have been recognized (Fig. 1).[2]

The classical methods for preparing aryl nitriles involve the Sandmeyer reaction[3a–d] of aromatic diazonium salts and the Rosenmund-von Braun reaction[3e] 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 arenes,[6] oxidative rearrangement of alkene,[7a] benzyl or allyl halides,[7b] ammoxidation of alcohols[7c] and cyanation of aryl halides[8] 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),[9a] tetrabutylammonium tribromide (TBATB),[9b] ceric ammonium nitrate (CAN),[9c] chloramine-T (CAT),[9d] TEMPO/HMDS/pyridine,[9e] TEMPO/KPF$_6$/NaNO$_2$/HMDS[9f] and SO$_2$F$_2$/Et$_3$N[9g] 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$_3$ [10e,f] 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,

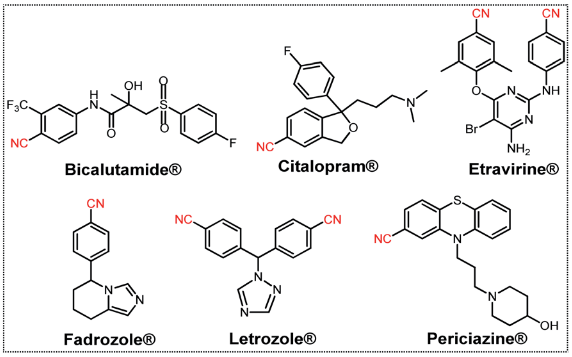

Fig. 1 Some potent biologically active organonitrile drugs.

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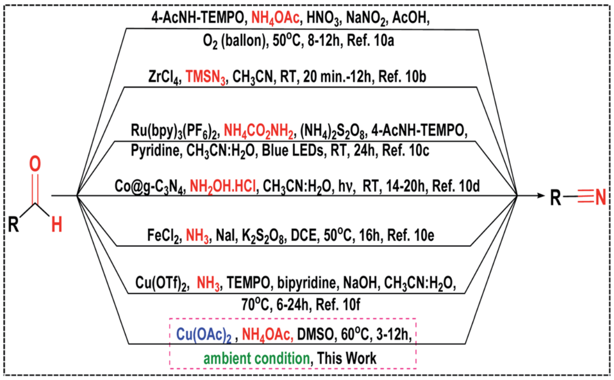
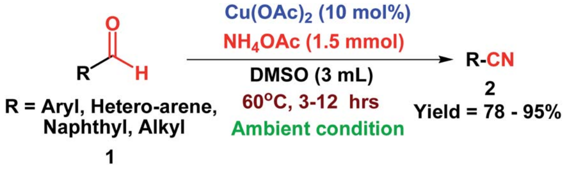


Scheme 1 Different strategies for the direct oxidative transformation of aldehydes to nitriles.

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[11] 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[12] 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[13] 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).

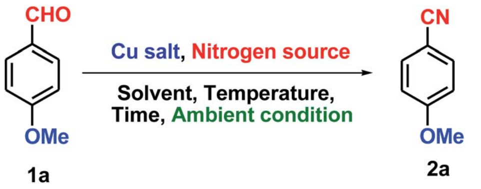


Scheme 2 $Cu(OAc)_2$ catalyzed direct oxidative transformations of aldehydes to nitriles.

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[a]



Entry	Cu salt (mol%)	Nitrogen source (mmol)	Solvent (mL)	Temp. (°C)	Time (h)	Yield[b] (%)
1	—	NH_4OAc	DMSO	60 °C	12 h	—
2	$CuSO_4$	Aq. NH_3	DMSO	60 °C	12 h	28
3	$CuSO_4$	$(NH_4)_2SO_4$	DMSO	60 °C	12 h	47
4	$CuSO_4$	$(NH_4)_2SO_4$	CH_3CN	60 °C	12 h	35
5	$CuSO_4$	$(NH_4)_2SO_4$	EtOH	60 °C	12 h	—
6	$CuCl_2$	NH_4Cl	DMSO	60 °C	12 h	45
7	$CuCl_2$	NH_4Cl	DMF	60 °C	12 h	49
8	$Cu(NO_3)_2$	NH_4NO_3	DMSO	60 °C	12 h	53
9	$Cu(NO_3)_2$	NH_4NO_3	CH_3CN	60 °C	12 h	42
10	$Cu(OAc)_2$	NH_4OAc	CH_3CN	60 °C	12 h	73
11	$Cu(OAc)_2$	NH_4OAc	DMSO	60 °C	10 h/12 h	90/91
12[c]	$Cu(OAc)_2$	NH_4OAc	DMSO	60 °C	10 h/12 h	—
13	$Cu(OAc)_2$	NH_4OAc	H_2O	60 °C	10 h/12 h	36/38
14	$Cu(OAc)_2$	NH_4OAc	EtOH	Reflux	12 h/14 h	51/54
15	$Cu(OAc)_2$	NH_4OAc	DCM	Reflux	12 h/14 h	48/49
16	$Cu(OAc)_2$	$HCOONH_4$	DMSO	60 °C	8 h/12 h	—
17	$Cu(OAc)_2$	Aq. NH_3	DMSO	60 °C	10 h/12 h	23/24
18	CuO	NH_4OAc	DMSO	60 °C	8 h/12 h	—
19	CuCl	NH_4OAc	DMSO	60 °C	8 h/12 h	—
20	$Cu(OAc)_2 \cdot H_2O$	NH_4OAc	DMSO	60 °C	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]

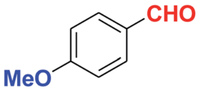
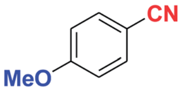
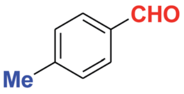
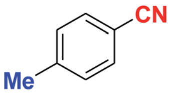
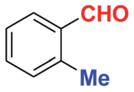
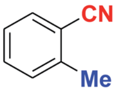
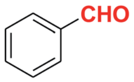
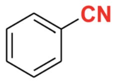
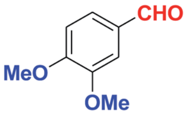
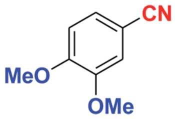
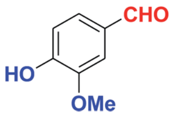
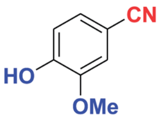
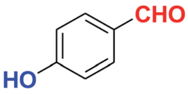
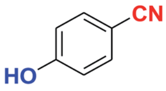
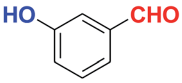
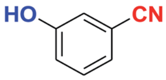
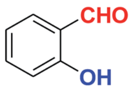
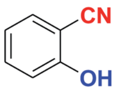
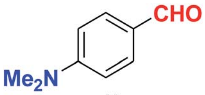
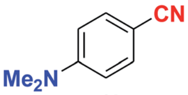
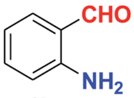
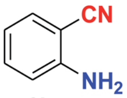
Entry	Substrate	Product	Time (h)	Yield[d] (%)
Synthesis of benzonitriles bearing electron-donating substituents				
1	 **1a**	 **2a**	10	90
2	 **1b**	 **2b**	10	91
3	 **1c**	 **2c**	10	89
4	 **1d**	 **2d**	7.5	90
5	 **1e**	 **2e**	10	90
Synthesis of hydroxy functionalized benzonitriles				
6	 **1f**	 **2f**	10	89
7	 **1g**	 **2g**	10	87
8	 **1h**	 **2h**	10	89
9	 **1i**	 **2i**	10	88
Synthesis of amino functionalized benzonitriles				
10	 **1j**	 **2j**	9.0	88
11	 **1k**	 **2k**	9.0	89

Table 2 (*Contd.*)

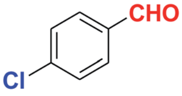
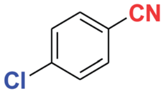
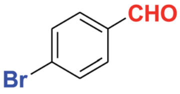
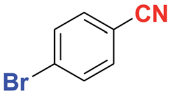
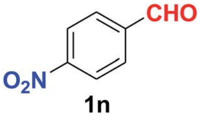
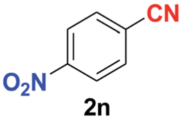
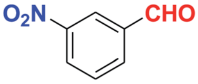
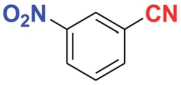
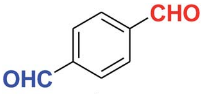
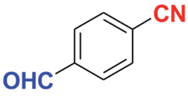
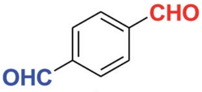
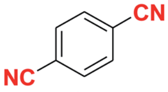
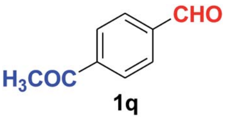
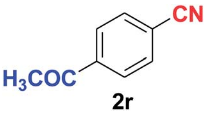
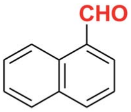
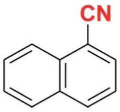
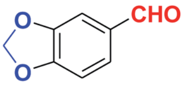
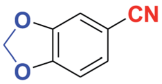
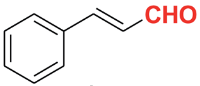
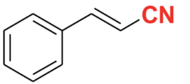
Entry	Substrate	Product	Time (h)	Yield^d (%)
Synthesis of halogenated benzonitriles				
12	 **1l**	 **2l**	6.0	93
13	 **1m**	 **2m**	6.0	91
Synthesis of nitro functionalized benzonitriles				
14	 **1n**	 **2n**	3.0	95
15	 **1o**	 **2o**	3.0	94
Selectivity towards the synthesis of nitriles				
16^b	 **1p**	 **2p**	6.0	88
17^c	 **1p**	 **2q**	6.0	87
18	 **1q**	 **2r**	6.0	88
Synthesis of nitriles bearing naphthyl, methylenedioxy and alkenyl moiety				
19	 **1r**	 **2s**	11	86
20	 **1s**	 **2t**	10	88
21	 **1t**	 **2u**	10	83

Table 2 (*Contd.*)

Entry	Substrate	Product	Time (h)	Yield^d (%)
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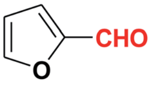
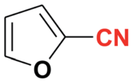
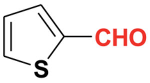
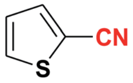
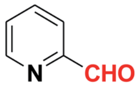
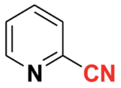
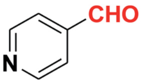
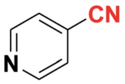
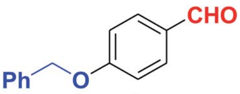
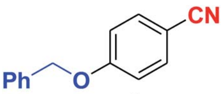
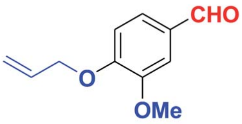
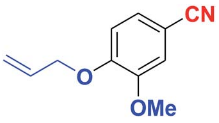
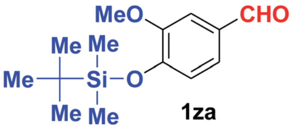
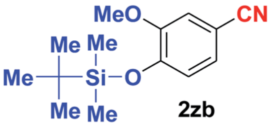
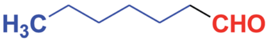
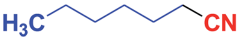
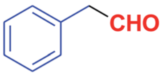
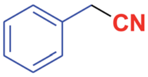
22	 **1u**	 **2v**	10	79
23	 **1v**	 **2w**	10	81
24	 **1w**	 **2x**	10	83
25	 **1x**	 **2y**	10	80
Synthesis of highly vulnerable nitriles				
26	 **1y**	 **2z**	10	86
27	 **1z**	 **2za**	10	84
28	 **1za**	 **2zb**	10	85
Synthesis of aliphatic nitriles				
29	 **1zb**	 **2zc**	12	78
30	 **1zc**	 **2zd**	12	79
31	 **1zd**	 **2ze**	12	84

[a] Reaction conditions: **1a** (1.0 mmol), $Cu(OAc)_2$ (10 mol%), NH_4OAc (1.5 mmol), DMSO (3 mL), 60 °C, under ambient atmosphere. [b] NH_4OAc (1.5 mmol). [c] NH_4OAc (3.0 mmol) were used for 1 mmol of substrate. [d] Yield of isolated and purified product.

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 $CuSO_4$ in combination with $(NH_4)_2SO_4$ 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 $CuSO_4$ with aqueous NH_3 in DMSO medium (entry 2), $CuSO_4$ with $(NH_4)_2SO_4$ in DMSO and CH_3CN medium (entries 3 and 4), $CuCl_2$ with NH_4Cl in DMSO and DMF solvent (entries 6 and 7) and $Cu(NO_3)_2$ with NH_4NO_3 in DMSO and CH_3CN 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_4OAc at 60 °C in CH_3CN medium (entry 10). Surprisingly when the reaction was performed using $Cu(OAc)_2$ along with NH_4OAc 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 yield was much less in the presence of $Cu(OAc)_2$ with NH_4OAc in H_2O medium (entry 13). This reaction was less responsive in ethanol (EtOH) and dichloromethane (DCM) as the solvent even under reflux and a longer period of reaction time (entries 14 and 15). Interestingly, no reaction took place when ammonium formate ($HCOONH_4$) was used as the nitrogen source instead of ammonium acetate (CH_3COONH_4) in the presence of copper acetate (entry 16). Yield was quite low in the presence of aqueous NH_3 (entry 17). The inferior performance was observed in the case of CuO and CuCl (entries 18 and 19). The reaction with $Cu(OAc)_2$ H_2O in the presence of NH_4OAc produces the desired nitrile with 78% yield (entry 20) which is lower than the yield obtained with $Cu(OAc)_2$ (91%, entry 11). Among the screened copper salts and nitrogen sources, $Cu(OAc)_2$ was the most effective catalyst and NH_4OAc was the best option as the nitrogen source. Less toxicity, good stability and cheaper price of ammonium acetate (NH_4OAc) were found to be good attributes to be a better alternative nitrogen source of NH_3. Therefore, the conditions, as delineated in entry 11, have been chosen as the optimized reaction condition for further studies.

To explore the substrate scope and limitation of this oxidative protocol, a systematic investigation on all kinds of aromatic, heterocyclic, naphthyl, and aliphatic aldehydes **1** was carried out under the optimized reaction condition to obtain the corresponding nitriles **2** (Scheme 2). The results are furnished in Table 2.

As evident from Table 2, benzaldehyde as well as other aryl aldehydes bearing electron-donating substituents (**1a–e**) showed excellent reactivity and furnished the products (**2a–e**) in high yields (entries 1–5). Aryl aldehydes bearing phenolic –OH group were equally efficient under the optimized reaction condition to produce the products **2f–i** in good yield (entries 6–9). Deactivated aromatic aldehydes such as 4-*N*,*N*-dimethylaminobenzaldehyde and 2-aminobenzaldehyde afforded the corresponding nitriles **2j** and **2k** under the present reaction condition 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).

Table 3 Experimental details to determine the reaction order

Run	**1a**	NH_4OAc	$Cu(OAc)_2$	DMSO
Run 1	1 mmol	1.5 mmol	10 mol%	3 mL
Run 2	2 mmol	1.5 mmol	10 mol%	3 mL

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 δ 10.10 (due to –C*H*O) along with two doublets at δ 7.98 (due to aromatic protons *ortho* to –CHO) and at δ 7.84 (due to aromatic protons *ortho* to –CN). In the ^{13}C NMR spectrum of **2p**, simultaneous occurrence of two signals at δ 190.6 and δ 117.6 proves the co-existence of –*C*HO and –*C*N 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 δ 7.52 in its ^1H NMR spectrum as well as from the signal (at δ 118.2) specific for –*C*N 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.[9d,f,10b,c,f] We have also investigated the reaction using terephthaldehyde (**1p**) (1 mmol) and ammonium acetate (1.5 mmol) under oxygen atmosphere, the

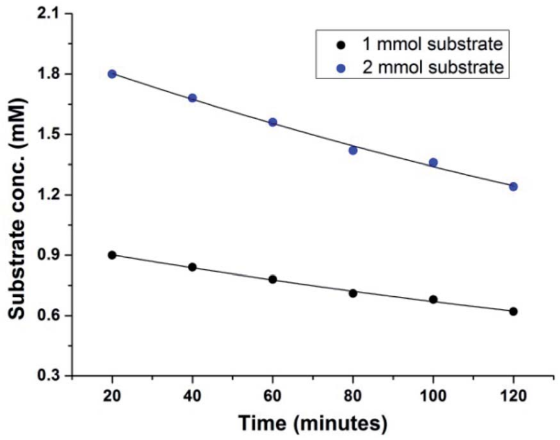


Fig. 2 Dependence of the initial rate of the reaction on [4-methoxybenzaldehyde] using $Cu(OAc)_2$ (10 mol%), NH_4OAc (1.5 mmol), DMSO (3 mL), 60 °C, under ambient atmosphere.

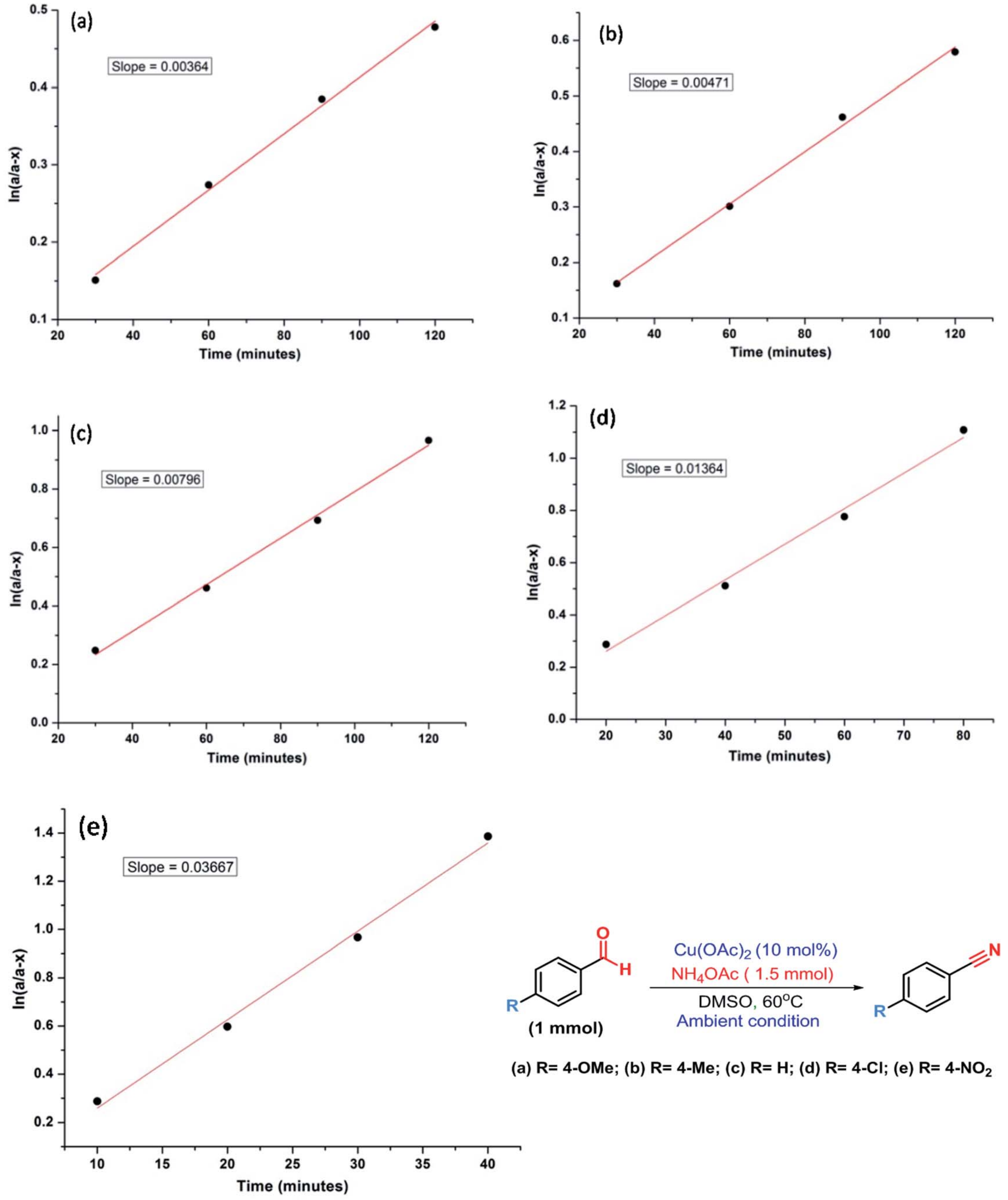


Fig. 3 Determination of rate constant for the electronically disparate aldehydes during the synthesis of nitriles (a–e).

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 furnished 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,g,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

Table 4 Hammett Analysis with the *para*-substitution constant (σ_P)

Substrate	$k \times 10^{-4}$ (min^{-1})	k_X/k_H	log (k_X/k_H)	σ_P	ρ
4-Methoxybenzaldehyde	36.4	0.457	−0.340	−0.268	+0.95
4-Methylbenzaldehyde	47.1	0.591	−0.228	−0.170	
Benzaldehyde	79.6	1	0	0	
4-Chlorobenzaldehyde	136.4	1.713	0.234	0.230	
4-Nitrobenzaldehyde	366.7	4.606	0.663	0.780	

22–25). 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 to **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.

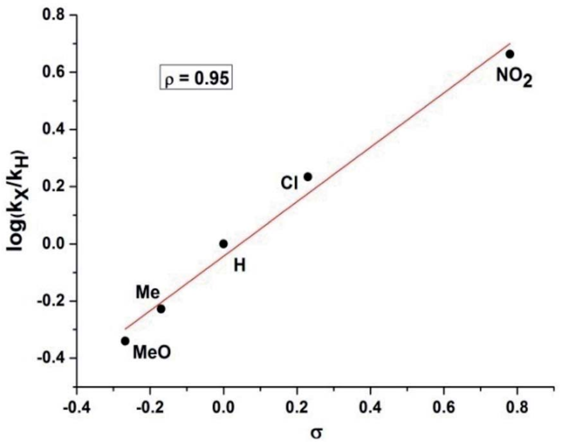
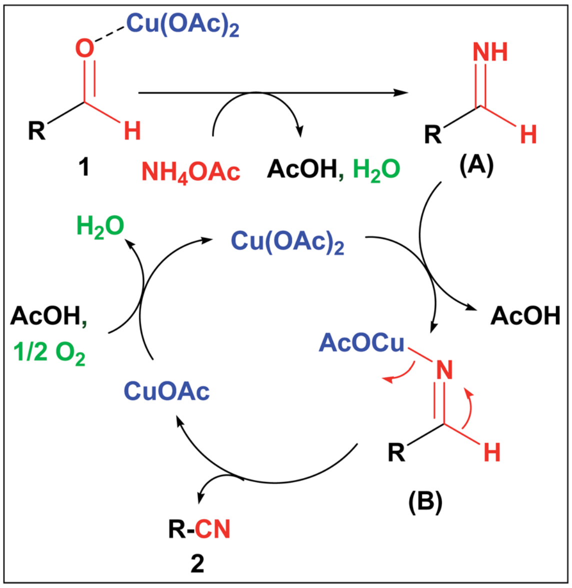


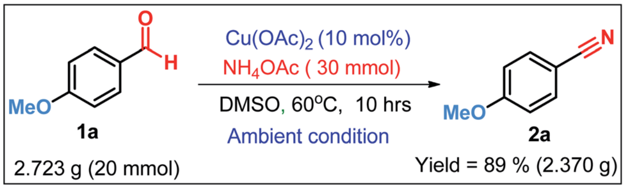
Fig. 4 Hammett analysis of electronically disparate aldehydes for the direct synthesis of nitriles from aldehydes using standard reaction conditions.

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 (σ) (Fig. 4). It was also observed that a positive ρ value of +0.95 and the reactivity sequence: *p*-NO_2 > *p*-Cl > *p*-H > *p*-Me > *p*-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, $Cu(OAc)_2$



Scheme 3 Plausible mechanism for the oxidative transformation of aldehydes to nitriles.



Scheme 4 Gram scale applicability of $Cu(OAc)_2/NH_4OAc$ catalyzed oxidative protocol.

activates the carbonyl carbon to react with NH_4OAc 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, $Cu(OAc)_2/NH_4OAc$ 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 ^{13}C NMR spectra were obtained on a Bruker spectrometer (300 MHz and 400 MHz) and JEOL Spectrometer (500 MHz) in $CDCl_3$ and DMSO-d_6 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 °C 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 Na_2SO_4. 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 °C 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.

Acknowledgements

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