## PAPER

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# Cu-catalyzed aerobic oxidative C–CN bond cleavage of benzyl cyanide for the synthesis of primary amides†

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An efficient method *via* copper-catalyzed aerobic oxidative amidation of benzyl cyanide for primary amides is successfully developed. Using readily available $NH_4Cl$ as a nitrogen source and $Cu/O_2$ as a catalytic oxidation system offers new opportunities for C–CN bond cleavage and primary amide bond formation.

Primary amides are prevalent organic motifs in peptide, protein synthesis, intensifiers of perfume, anti-block reagents, color pigments for inks, detergents, and lubricants.[1] Generally, the synthetic procedures for the preparation of primary amides are rely on the reaction of carboxylic acid,[2] or its derivatives with ammonia or ammonium salt.[3] However, toxic and corrosive, materials, low functional groups tolerance and complex operation are generally required in conventional synthetic procedures. To overcome these problems, alternative methods for primary amide synthesis have been developed. The direct amidation of aldehydes,[4] alcohols,[5] or methylarenes[6] to primary amides represents an interesting topic in this area, however, hazardous peroxides (TBHP), the toxic halogens, or an excess amount of molecular sieves were required. Other attractive approaches include the hydration of nitriles,[7] oxidative amidation of terminal alkynes,[8] transition-metal-catalyzed C–H activation and amidation[9] and catalytic oxidation C–C bond cleavage of ketones into benzamides.[10] Although great progress has been achieved in this field, there still remains significant challenges for synthetic organic chemists in reactivity, efficiencies, and high functional group tolerance.

Recently, C–C bond cleavage has become an attractive topic because of its potential usage in new chemical bond formation *via* inert starting materials.[11] Also molecular oxygen has been considered as an ideal oxidant due to its atom-economical, environmentally benign, and abundance.[12] However, few reactions are compatible with aerobic oxidation[13] and C–C bond cleavage in one transformation.[14] Therefore, the development of an efficient catalytic system towards aerobic oxidative unstrained C–C bonds cleavage is always highly desired. As our

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continued interest in Cu or Fe-catalyzed aerobic oxidative C–C bond cleavage reaction,[15] we developed a Cu-catalyzed aerobic oxidative C–C bond cleavage of benzyl cyanide for the synthesis of primary amides. Using readily available $NH_4Cl$ as a nitrogen source and a $Cu/O_2$ catalytic oxidation system offers new opportunities for primary amide bond formation. The developed methodology tolerated a wide range of functional groups and produced high yields for the synthesis of primary amides.



$$\text{Ar–CH}_2\text{CN} \xrightarrow[\substack{NH_4Cl, NaOH \\ 1\ atm,\ O_2}]{Cu_2O} \text{Ar–C(=O)NH}_2 \qquad (1)$$

We carried out experiments to test the reactivity of benzyl cyanide **1a** with ammonium salts in the presence of a metal catalyst under an oxygen atmosphere and the obtained results are compiled in Table 1. First, our studies started with the reaction between benzyl cyanide **1a** and 5.0 equiv. of ammonia (25% aqueous) in $CH_3CN$ at 120 °C (Table 1, entries 1–5). When 5 mol% of CuCl was used as catalyst, the benzamide **2a** was obtained in 38% yield along with the hydration of nitrile products **2b** (Table 1, entry 1). We then screened the types of catalysts, and discovered that $CuCl_2$ or $Cu_2O$ produces higher yields (Table 1, entries 4–5). However the products **2b** was always by a product. Then, optimization studies were performed to improve the yield of **2a**. To our surprise, when ammonia was replaced with $NH_4Cl$, **2a** was obtained in 50% yield, and only trace amounts **2b** was observed (Table 1, entry 6). Four bases were tested using $Cu_2O$ as the catalyst in $CH_3CN$, and NaOH showed the highest yield (Table 1, entries 6–9). Several copper salts and amine salts were screened (Table 1, entries 10–16), and the best result was obtained under $Cu_2O/NH_4Cl/NaOH$ system (Table 1, entry 9). Noteworthily, NaOH is essential for this reaction. In the absence of NaOH, **2a** could not be obtained at all (Table 1, entry 17). The reaction did not proceed in the

**Table 1** Optimization of the reaction conditions[a]



| Entry | Cat | [N] source | Base | $2a^b$% | $2b^b$% |
|---|---|---|---|---|---|
| 1 | CuCl | $NH_3 \cdot H_2O$ | — | 35 | 20 |
| 2 | $Cu(OAc)_2$ | $NH_3 \cdot H_2O$ | — | 25 | 30 |
| 3 | CuO | $NH_3 \cdot H_2O$ | — | 40 | 41 |
| 4 | $CuCl_2$ | $NH_3 \cdot H_2O$ | — | 50 | 25 |
| 5 | $Cu_2O$ | $NH_3 \cdot H_2O$ | | 50 | 31 |
| 6 | $Cu_2O$ | $NH_4Cl$ | $Ba(OH)_2$ | 50 | <1 |
| 7 | $Cu_2O$ | $NH_4Cl$ | KOH | 58 | <1 |
| 8 | $Cu_2O$ | $NH_4Cl$ | $Ca(OH)_2$ | 20 | <1 |
| 9 | $Cu_2O$ | $NH_4Cl$ | NaOH | 88 | <1 |
| 10 | CuCl | $NH_4Cl$ | NaOH | 71 | <1 |
| 11 | $CuCl_2$ | $NH_4Cl$ | NaOH | 65 | <1 |
| 12 | $Cu(OAc)_2$ | $NH_4Cl$ | NaOH | 58 | <1 |
| 13 | $Cu_2O$ | $NH_4OAc$ | NaOH | 63 | <1 |
| 14 | $Cu_2O$ | $(NH_4)_2SO_4$ | NaOH | 50 | <1 |
| 15 | $Cu_2O$ | $(NH_4)_2CO_3$ | NaOH | 71 | <1 |
| 16 | $Cu_2O$ | Urea | NaOH | <1 | <1 |
| 17 | $Cu_2O$ | $NH_4Cl$ | — | — | <1 |
| 18 | — | $NH_4Cl$ | NaOH | — | <1 |
| $19^c$ | $Cu_2O$ | $NH_4Cl$ | NaOH | Trace | Trace |
| $20^d$ | $Cu_2O$ | $NH_4Cl$ | NaOH | 20 | <1 |
| $21^e$ | $Cu_2O$ | $NH_4Cl$ | NaOH | 13 | <1 |

[a] Reaction conditions: 2-benzyl cyanide **1a** (0.2 mmol), cat (5 mol%), N source (0.3 mmol), base (0.4 mmol), $CH_3CN$ (2 mL), in 25 mL Schlenk tube, 120 °C, $O_2$ (1 atm), 30 h. [b] Yields were determined by GC using *n*-hexadecane as an internal standard. [c] Air was used as oxidant. [d] Toluene as solvent. [e] DMF as solvent.

absence of copper catalyst (Table 1, entry 18). The reaction was also dependent on dioxygen; when air was used as the oxidant, only trace of **2a** was obtained (Table 1, entry 19). Other solvents such as, toluene and DMF gave lower yields (Table 1, entries 20–21).
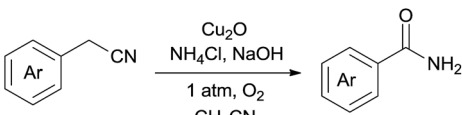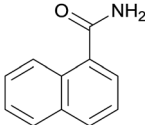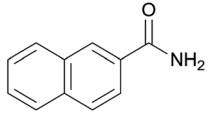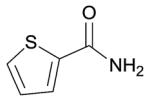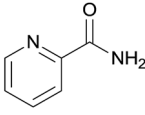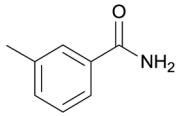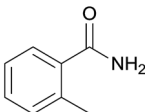
With the optimal conditions in hand, the scope of copper-catalyzed aerobic oxidative amidation of substituted 2-benzyl cyanides with "NH₂" producing primary amides was investigated, the results were compiled in Table 2. A variety of 2-benzyl cyanide with either an electron-donating or an electron-withdrawing group, were all converted readily to the corresponding primary amides efficiently. Thus, in addition to 2-benzyl cyanide, benzyl cyanide with electron-donating substituents methyl (–CH₃), methoxy (–OCH₃) reacted smoothly with NH₄Cl/NaOH to provide the corresponding primary amides **2a–2c** (Table 2, entries 1–3). However, when hydroxyl (–OH) substituted 2-benzyl cyanide was used as a substrate, none of the expected products were detected. This may have been due to the interaction between the hydroxyl and base or oxidizing agent, which would hinder the C–CN bond activation (Table 2, entry 4). Benzyl cyanide with fluoro (–F), chloro (–Cl), bromo (–Br), iodo (–I), trifluoromethyl (–CF₃) or phenyl (–Ph) electron-withdrawing groups served as good substrates to produce the corresponding primary amides **2e–2j** in excellent yields (Table 2,

**Table 2** Cu-catalysed aerobic oxidative amidation of benzyl cyanide with $NH_4Cl$ producing primary amides[a]



| Entry | Benzonitriles | Products | Yield[b] |
|---|---|---|---|
| 1 | **1a** | | **2a**, 82% |
| 2 | **1b** | | **2b**, 81% |
| 3 | **1c** | | **2c**, 79% |
| 4 | **1d** | | **2d**, trace |
| 5 | **1e** | | **2e**, 81% |
| 6 | **1f** | | **2f**, 78% |
| 7 | **1g** | | **2g**, 83% |
| 8 | **1h** | | **2h**, 69% |
| 9 | **1i** | | **2i**, 78% |
| 10 | **1j** | | **2j**, 73% |
| $11^c$ | **1k** | | **2k**, 92% |

**Table 2** (*Contd.*)



| Entry | Benzonitriles | Products | Yield[b] |
|---|---|---|---|
| 12 | **1l** | | **2l**, 57% |
| 13 | **1m** | | **2m**, 71% |
| 14 | **1n** | | **2n**, 63% |
| 15 | **1o** | | **2o**, 72% |
| 16 | **1p** | | **2p**, 71% |
| 17[d] | **1q** | | **2q**, 35% |

[a] Reaction conditions: substrate **1a–1q** (0.2 mmol), Cu$_2$O (5 mol%), NH$_4$Cl (0.3 mmol), NaOH (0.4 mmol), CH$_3$CN (2 mL), O$_2$ in 25 mL Schlenk tube, 120 °C, 24 h. [b] Isolated yield. [c] 16 h. [d] 48 h.

entries 5–10), and there is no sharp difference. Interestingly, when nitro (–NO$_2$) substituted 2-benzyl cyanide were used, the corresponding 4-nitrobenzamide was obtained in high yield and with short time (Table 2, entry 11).

Even the 1-(naphthalen-2-yl)acetonitrile and 2-(naphthalen-2-yl)acetonitrile furnished the corresponding primary amide **2l** and **2m** in 57% and 71% yield respectively. The heteroaryl-substituted primary amide **2n** and **2o** were obtained from the corresponding 2-(thiophen-2-yl)acetonitrile or 2-(pyridin-2-yl)acetonitrile under the present Cu$_2$O/NH$_4$Cl/NaOH system. While, the reaction was influenced by the substituent steric effects. For example, the yield of **2q** was decreased for *ortho*-substituted 2-benzyl cyanide contrast to *para*-substituted and *meta*-substituted 2-benzyl cyanide (Table 2, entry 2, entries 16–17).

To get more information of the reaction mechanism, a few potential intermediates were subjected to the reaction under standard conditions. As shown below, phenylacetic acid **1r** was

used as a substrate under the standard reaction conditions, while **2a** was not detected at all (eqn (2)). Benzaldehyde **1s** was treated under the optimized conditions, **2a** was obtained in 15% yield (eqn (3)), indicating that an aldehyde or acid was not the efficient intermediate. The reaction of benzonitrile **1t** with NH$_4$Cl/NaOH under standard conditions was also explored, and the desired benzamide **2a** was not detected at all, showing that benzyl cyanide was not converted to benzonitrile via hydration of nitriles to primary amides (eqn (4)). The reaction of benzoyl cyanide **1u** and NH$_4$Cl/NaOH was performed in the absence of Cu$_2$O, the corresponding primary amide **2a** was obtained in 89% yield (eqn (5)). The results indicated that benzoyl cyanide **1u** was the efficient intermediate for this transformation, at first benzyl cyanide was converted to benzoyl cyanide via sp$^3$ C–H bond oxygenation. Under dry conditions and in the absence of air, the desired product **2a** was also generated in 82% yield under the optimal conditions, thus the oxygen atoms of the product amides should originate from molecular dioxygen (eqn (6)).
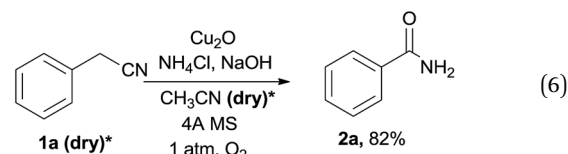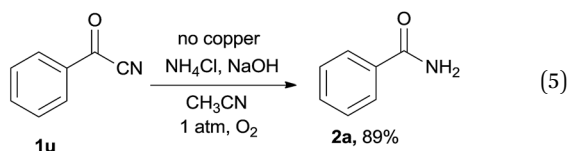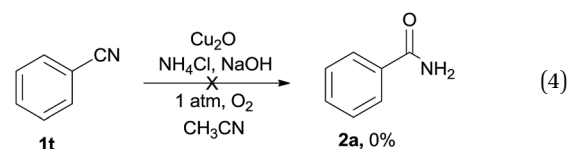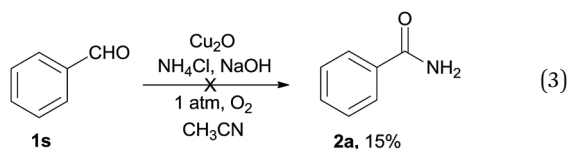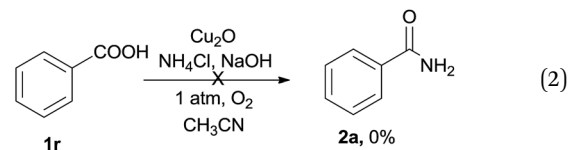


*The solvent CH$_3$CN and **1a** were dried, degassed by standard methods before use, and stored under nitrogen using standard Schlenk techniques.
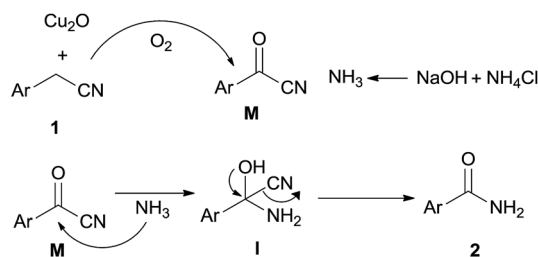
**Scheme 1** Plausible reaction pathway for the synthesis of primary amides **2**.

Based on the above results and the reported literature,[15a] a possible mechanism for the copper-catalyzed aerobic oxidative amidation of benzyl cyanide to the synthesis of primary amides is suggested in Scheme 1. The catalytic cycle reaction involved sp$^3$ C–H bond oxygenation of benzyl cyanide to the intermediate benzoyl cyanide **M** and with the Cu catalyst being regenerated, NH$_3$ was generated from the heating of NH$_4$Cl and NaOH. Then intermediate benzoyl cyanide **M** was attacked by NH$_3$ to generate **I**, followed by C–CN bond cleavage affording the desired primary amide **2**.

## Conclusions

In summary, we have developed a simple and highly efficient method for the synthesis of primary amides *via* C–CN bond cleavage under copper-catalyzed aerobic oxidative conditions. Using readily available NH$_4$Cl as a nitrogen source, conversion of benzyl cyanides to primary amides provides an opportunity to utilize inert starting materials to construct amides bond. The present method is practical and economical, and the starting materials are readily available.

## Acknowledgements

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