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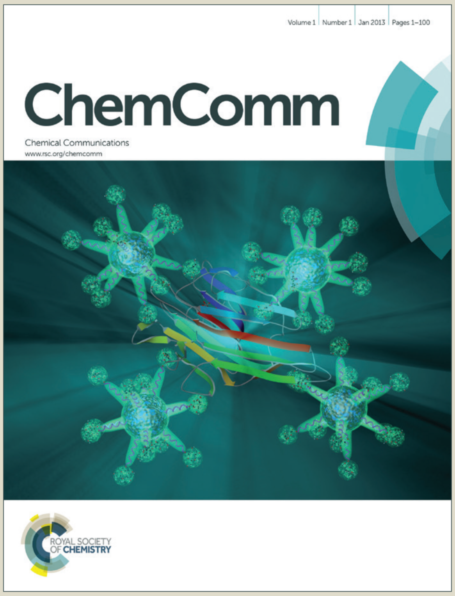

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Copper-catalyzed aerobic conversion of C=O bond of ketones to C≡N bond using ammonium salt as nitrogen source

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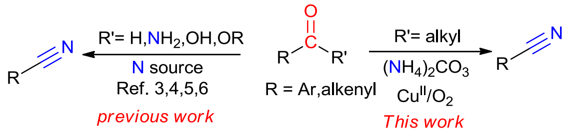
Bin Xu, Qing Jiang, An Zhao, Jing Jia, Qiang Liu, Weiping Luo and Cancheng Guo*

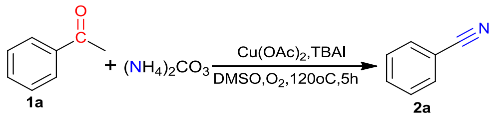
A conversion of C=O bond of ketones to C≡N bond is described. This conversion is catalyzed by copper salts with ammonium salts as the nitrogen source in the present of molecular oxygen. A wide variety of ketones can be converted into the corresponding compounds containing C≡N bond. Based on the preliminary experiments, a plausible mechanism of this transformation is disclosed.

The conversion of C=O bond to C≡N bond has been widely used in organic synthesis[1] and attracted continuous attention of chemists because the compounds contained C≡N bond are versatile intermediates in the synthesis of useful medicines and functional materials.[2] Generally, the fundamental methodology for this conversion of C=O bond to C≡N bond is the transformation from aldehydes through the Schmidt reaction with azide or the catalytic oxidation condensation with ammonia.[3] Alternatively, the transformation from primary amides[4] or carbonyl acids[5] is another attractive method for this conversion (Scheme 1). Recently, a few elegant examples for the conversion of C=O bond to C≡N bond have been reported. Muldoon reported an efficient protocol using the Cu-TEMPO-air catalytic system to achieve the conversion of C=O bond of aldehydes to C≡N bond.[3d] Beller's group represented the conversion of C=O bond of amides to C≡N bond with hydrosilanes as the dehydrating agents.[4b, 4c] Kappe developed a continues-flow protocol for this conversion from carboxylic acid in one-step without any catalyst or additives under high-temperature/pressure (350 °C, 65 bar).[5c] Togo and co-workers reported a facile conversion of C=O bond of esters to C≡N bond by the treatment of SDBBA-H and I_2 in aq ammonia.[6] Despite impressive progress on the conversion of C=O bond to C≡N bond. Besides, the oxidative cleavage of C-C bond of ketones under Cu-catalyzed conditions has been known.[7] To the best of our knowledge, the conversion of C=O bond of ketones to C≡N bond has not been established to date. Herein, we present the copper-catalyzed conversion of C=O bond of ketones to C≡N bond using ammonium salt as nitrogen source in the present of molecular oxygen.



Scheme 1 The methodologies for the conversion of C=O to C≡N

The initial survey of the reaction conditions was performed with acetophenone **(1a)** as the model substrate, and the results were summarized in Table S1 of SI (Supporting Information). To our delight, acetophenone (**1a**) could be converted into benzonitrile (**2a**) in 80% yield with 1.0 equiv of $(NH_4)_2CO_3$, 0.3 equiv of $Cu(OAc)_2$ and 0.3 equiv of TBAI in DMSO under 1 atm O_2 at 120 °C (Scheme 2). Comparing the reactant with the product, this reaction achieved the conversion of C=O bond of ketones to C≡N bond. The results in Table S1 also showed that other copper salts, such as CuI, CuBr, $CuBr_2$ and so on, proved to be less effective than $Cu(OAc)_2$. On the other hand, other metal catalysts like $FeCl_2$, $FeCl_3$, $Ni(OAc)_2$ and $AgNO_3$ could not accomplish this conversion which suggested the copper salts showed the unique ability in this transformation (Table S1, entries 1-12). Subsequently, the investigation on the influence of solvents represented other solvents exhibited inferior reactivity in this transformation (Table S1, entries 13-17). When other nitrogen sources were used instead of $(NH_4)_2CO_3$, none showed the higher efficiency than $(NH_4)_2CO_3$ (Table S1, entries 18-22). Furthermore, an evaluation of additives revealed that TBAI provided a significant improvement in yield (Table S1, entries 23-29). In addition, varying the loading of $(NH_4)_2CO_3$ and the temperature had little effect on the yield (Table S1, entries 30-33). Control experiments highlighted the essential roles of Cu catalysts and oxygen in this transformation (Table S1, entries 34-37).



Scheme 2 Conversion of acetophenone under the optimal conditions

College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, P.R. China .Fax: +86-731-88821488; Tel: +86-731-88821488.
E-mail: ccguo@hnu.edu.cn.

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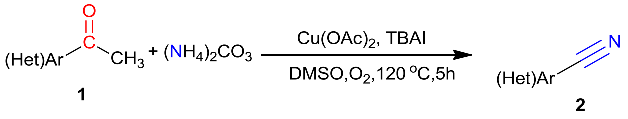
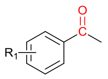
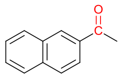
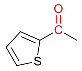
Subsequently, the scope of the (hetero)aryl methyl ketones was investigated under the standard reaction conditions (Scheme 2). It was found that the C=O bond of the (hetero)aryl methyl ketones could be converted into C≡N bond in 49-90% yield (Table 1). As shown in Table 1, acetophenone derivatives bearing electron-donating substituents (MeO, EtO, *t*-Bu, Me) could achieve this conversion in 71-90% yield (Table 1, entries 1-9). Nevertheless, the C=O bond of the acetophenone derivatives with electron-withdrawing substituents (F, Cl, Br, I, NO_2, CN) could be converted into C≡N bond in yields ranging from 49 to 85% (Table 1, entries 10-17). Furthermore, acetophenone bearing the same substituents at different positions had influence on the efficiency of this transformation. For example, 2-methyl-acetophenone (**1f**) gave lower yield than 4-/3-methyl-acetophenone (**1e**/**1g**) (Table1, entries 5-7). Importantly, halogen substituents on the phenyl ring were well tolerated with this conversion, which enable a potential application in further functionalization (Table 1, entries 10-15). Furthermore, 2-acetonaphthone (**1r**) and 2-acetylthiophene (**1s**) could also realize the conversion of C=O bond to C≡N bond in moderate yield (Table 1, entries 18 and 19).

Table 1 Substrate Scope of (Het)Aryl Methyl Ketones **1**[a]



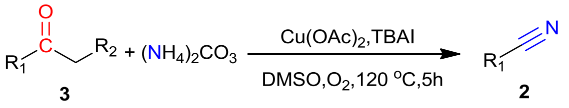
Entry	1		yield of **2**[b]
1		R_1 = H (**1a**)	80% (**2a**)[c]
2		4-OMe (**1b**)	90% (**2b**)
3		4-OEt (**1c**)	88% (**2c**)
4		4-tBu (**1d**)	80% (**2d**)
5		4-Me (**1e**)	86% (**2e**)
6		2-Me (**1f**)	68% (**2f**)
7		3-Me (**1g**)	79% (**2g**)
8		3,4-dou-OMe (**1h**)	89% (**2h**)
9		1,3,5-tri-Me (**1i**)	71% (**2i**)
10		4-F (**1j**)	65% (**2j**)
11		4-Cl (**1k**)	85% (**2k**)
12		4-Br (**1l**)	77% (**2l**)
13		2-Br (**1m**)	70% (**2m**)
14		3-Br (**1n**)	78% (**2n**)
15		4-I (**1o**)	82% (**2o**)
16		4-NO_2 (**1p**)	75% (**2p**)
17		4-CN (**1q**)	49% (**2q**)
18		(**1r**)	63% (**2r**)
19		(**1s**)	51% (**2s**)

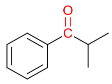
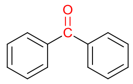
[a] Standard conditions: ketones (1.0mmol), $(NH_4)_2CO_3$ (1.0equiv), $Cu(OAc)_2$ (0.3mmol), TBAI (0.3mmol), DMSO (3.0 mL), 120°C for 5 h. [b] Isolated yield after column chromatography. [c] GC yield.

To expand the substrate scope of this transformation, aryl ketones with long chain alkyl and aliphatic ketones were investigated. From the experimental results shown in Table 2, the important conclusions could be drawn as follows: (1) The conversion of C=O bond of ketones to C≡N bond could be applied in the aryl ketones with a long-chain alky group but in lower efficiency (Table 2, entries 1-5). (2) Aliphatic ketones could also achieve this conversion in moderate yield (Table 2, entries 6-8). Thereinto, when 1,2-diphenylethanone **(3i)** was chosen as the substrate, not only 62% yield of benzonitrile was obtained, but also benzamide was produced as the other product in 40% yield. (3) The methylene at the α-position of the carbonyl group is essential in this conversion (Table 2, entries 9 and 10).

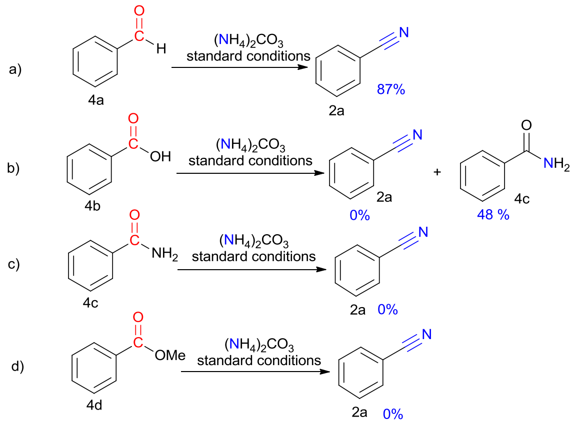
For further investigation, other compounds contained C=O bond, such as benzaldehyde (**4a**), benzoic acid (**4b**), benzamide (**4c**) and methyl benzoate (**4d**), were employed as the substrate (Scheme 3). Disappointingly, only the C=O bond of benzaldehyde (**4a**) could be converted into C≡N bond in 87% yield (Scheme 3a).

Table 2 Substrate Scope of Alkyl Ketones **3**[a]



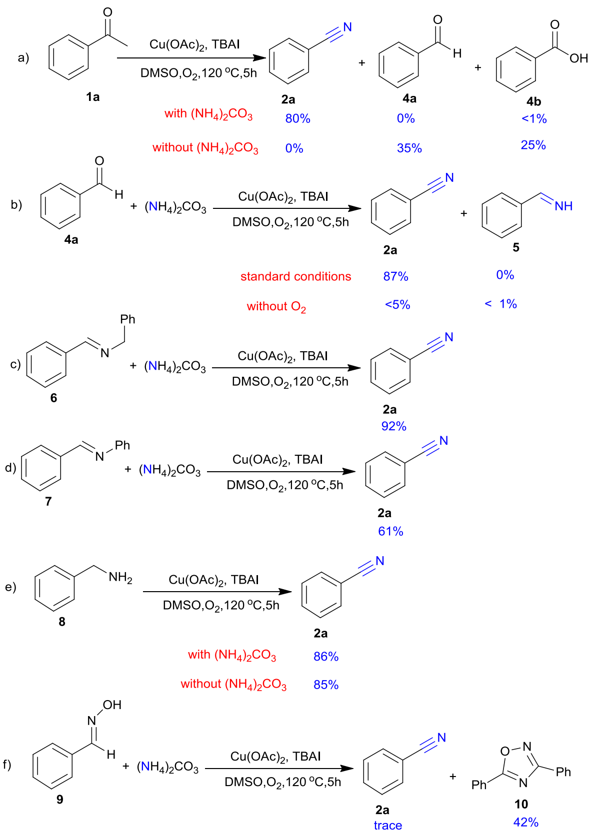
Entry	R_1 =	R_2 =	3	yield of **2**[b]
1	Ph	Me	**3a**	46% (**2a**)[c]
2	4-MeOC_6H_4	Me	**3b**	48% (**2b**)
3	4-MeC_6H_4	Me	**3c**	49% (**2e**)
4	4-ClC_6H_4	Me	**3d**	45% (**2k**)
5	Ph	*n*-Pr	**3e**	49% (**2a**)[c]
6	4-MeO$C_6H_4CH_2$	H	**3f**	59% (**2b**)
7	4-F$C_6H_4CH_2$	H	**3g**	47% (**2j**)
8	$C_6H_4CH{=}CH_2$	H	**3h**	35% (**2t**)
9	Ph	Ph	**3i**	62%(**2a**)[c,d]
10			**3j**	0
11			**3k**	0

[a] Standard conditions: ketones (1.0mmol), $(NH_4)_2CO_3$ (1.0equiv), $Cu(OAc)_2$ (0.3mmol,30mol%), TBAI (0.3mmol,30mol%), DMSO (3.0 mL) ,120°C for 5 h. [b] Isolated yield after column chromatography. [c] GC yield. [d] benzamide(**4c**) was isolated in 40% yield.



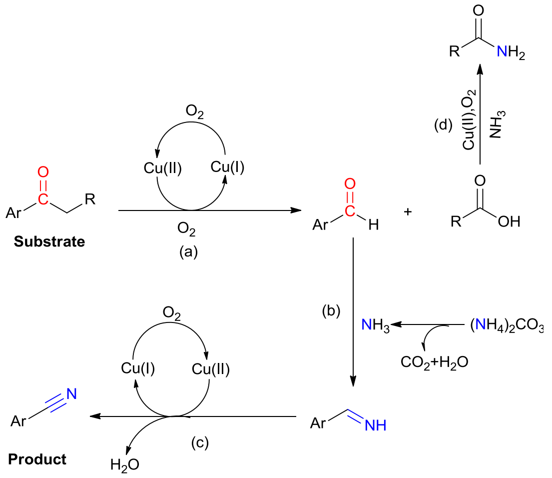
Scheme 3 the application of this conversion in other carbonyl compounds

To explore the mechanism of this transformation, some control experiments were carried out. When acetophenone (**1a**) reacted under the standard conditions without $(NH_4)_2CO_3$, 35% yield of benzaldehyde (**4a**) and 25% yield of benzoic acid (**4b**) were detected by GC with using bromobenzene as an internal standard (Scheme 4a). It implied that benzaldehyde may be further oxidized under the present conditions which is in accord with the literature.[8] And benzaldehyde (**4a**) can afford benzonitrile (**2a**) in 87% yield under the standard conditions (Scheme 3a). Even though benzaldehyde (**4a**) was formed in low yield under this catalyst system, combining the above results, we can hypothesize that once benzaldehyde is formed, it will convert to benzonitrile, thus decreasing the overoxidation of the benzaldehyde. Interestingly, when benzaldehyde reacted with $(NH_4)_2CO_3$ under N_2 atmosphere, not only trace (<5%) of benzonitrile was obtained, but also trace amount (<1%) of the corresponding benzaldimine (**5**) could be detected by GC-MS (Scheme 4b, details see Supporting Information). These results implied that the condensation of benzaldehyde with ammonia could occur without oxygen. However, the benzaldimine (**5**) cannot be obtained in higher yield or isolated because of their chemically labile nature. Notably, when imines (**6**) and (**7**) were chosen as the substrate, benzonitrile could be obtained in 92% and 61% yields, respectively. Furthermore, when benzylamine (**8**) reacted with or without $(NH_4)_2CO_3$, nitriles could be obtained in 85% or 86% yield. The above preliminary results revealed that imines can be oxidized to nitriles under the standard conditions. On the other hand, when benzaldoxime (**9**) reacted with $(NH_4)_2CO_3$ under the standard conditions, only trace amount of benzonitrile was obtained, but 42% of 3,5-diphenyl-1,2,4-oxadiazole (**10**) was produced, which suggested that Beckmann rearrangement was not the major reaction path.



Scheme 4 Investigations into the reaction mechanism.

In order to identify the fragment of the ketones, substrate acetophenone (**1a**), propiophenone (**3a**) and 1-phenylpentan-1-one (**3e**) were tested under the standard conditions. As expected, apart from the generation of benzonitrile (**2a**), trace amount of formamide (**7a**), acetamide (**7b**) and *n*-butyramide (**7c**) could be detected by GC-MS, respectively (see Supporting Information).



Scheme 5 The proposed reaction mechanism.

On the basis of the above preliminary results and related reports,[8-9] a plausible mechanism of this copper-catalyzed conversion of C=O bond from ketones to C≡N bond was proposed (Scheme 3). Initially, the substrate is oxidized to give the corresponding aldehyde and carboxylic acid through the oxidation cleavage of C-C bond in the present of Cu slats and molecular oxygen (step a). Subsequently, aldehyde reacts with ammonia to produce the corresponding imine (step b). Finally, the imine is readily transformed to product catalyzed by the Cu/O_2 system (step c). Meanwhile, carboxylic acid reacted with the ammonia to produce the corresponding amide under the present conditions (step d).

In summary, we have described a copper-catalyzed conversion of C=O bond of ketones to C≡N bond. A wide range of ketones can be subjected to this transformation. Moreover, the usage of the oxygen as the sole oxidation and ammonium salt as nitrogen source makes this transformation very practical. Preliminary mechanistic research showed the aldehyde might be an intermediate in the conversion through the oxidation C-C bond cleavage of ketones. Based on the above results, this protocol represents a novel approach to realize the conversion of C=O bond to C≡N bond, which should be of importance in organic chemistry and medicinal chemistry.

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