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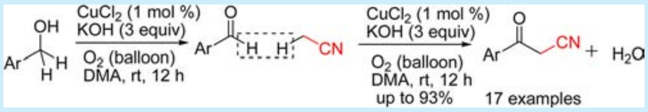
Copper-Catalyzed Aerobic Oxidative Coupling of Aromatic Alcohols and Acetonitrile to β-Ketonitriles

Jiaxuan Shen, Dejun Yang, Yuxiao Liu, Shuangshuang Qin, Jingwu Zhang, Jiangkai Sun, Chunhui Liu, Chaoyang Liu, Xiaomei Zhao, Changhu Chu, and Renhua Liu*

School of Pharmacy, East China University of Science and Technology, Meilong Road 130, Shanghai 200237, China

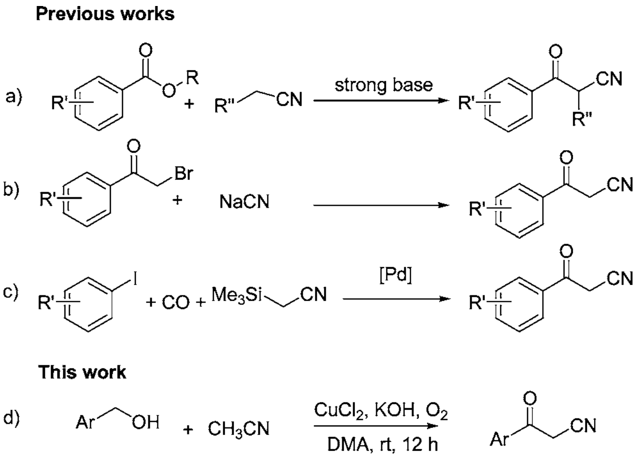
S *Supporting Information*

ABSTRACT: A practical, convenient, and cheap copper-catalyzed aerobic oxidative coupling of aromatic alcohols and acetonitrile to β-ketonitriles has been developed. The green C−C bond formation involving the loss of two hydrogen atoms from the corresponding two carbons, respectively, unlocks opportunities for markedly different synthetic strategies.



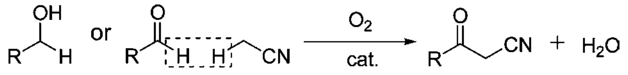
β-Ketonitriles are very useful compounds for the synthesis of a wide variety of heterocyclic structures, including aminopyrazoles,[1] imidazoles,[2] furans,[3] thiophenes,[4] and 2-pyridones.[5] Moreover, they have been used as a precursor for the synthesis of biologically and pharmacologically active compounds,[6] e.g., anti-HCV drugs[6d] and inhibitors against NHE-1.[6a] The frequently used methods for the preparation of β-ketonitriles include the coupling of alkylnitriles and esters in the presence of a strong base[7]or a cyanide displacement reaction with α-bromoketones[8] (Scheme 1a and b). Recently, several new methods have been developed. Ganesan reported a method involving the C-arylation of resin-bound cyanoacetates.[9]Yoo and co-worker developed a method that included the indium-mediated coupling of bromoacetonitriles with cyanides.[10] Lee and co-worker developed a method utilizing the Pd-catalyzed carbonylation of aryl iodides, trimethylsilylacetonitrile, and carbonic oxide (or $Mo(CO)_6$) to produce β-ketonitriles[11] (Scheme 1c). However, these methods suffer from several drawbacks such as the need for a strong base, e.g. KO*t*-Amyl, CH_3ONa, $NaNH_2$ (Scheme 1a), or hypertoxic cyanide, and/or harsh reaction conditions, as well as a multistep preparation process.

Scheme 1. Synthetic Methods of β-Ketonitriles



From a conceptual standpoint, the oxidative cross-coupling of aldehydes/primary alcohols and unactivated simple alkylnitriles with molecular oxygen as the oxidant should be one of the most straightforward and greener approaches to the preparation of β-ketonitriles, as the catalytic methods avoid the use of highly toxic cyanide salts, display high atom economy, and release only innocuous H_2O as the byproducts (see Scheme 2).

Scheme 2. An Ideal Approach to β-Ketonitriles



Recently, the catalytic C−C coupling of alcohols has received great attention for both economic and environmental benefits.[12] However, reports on the oxidative C−C cross-coupling of alcohols and alkylnitriles are scarce. The C−C cross-coupling faces two major challenges: deprotonation of unactivated simple alkylnitriles, such as acetonitrile ($pK_a = 31.3$ in DMSO) and the lack of efficient leaving functionalities of the alcohol partner for traditional C−C cross-coupling reactions. To solve the problem of deprotonation of acetonitrile for cyanomethylation of carbonyl substrates, attempts to circumvent the deprotonation of acetonitrile by a functionalized acetonitrile, Me_3SiCH_2CN, have been reported.[13] Another alternative solution to deprotonation of acetonitrile for cyanomethylation of carbonyl substrates is transition-metal catalysis, in which a relatively weak base can be used to deprotonate acetonitrile. These transition metals mainly include copper,[14] nickel,[15] rhodium,[16] or ruthenium.[17] To obtain the solution to the lack of efficient leaving functionalities of an alcohol partner, efforts to activate the C−H bond of aldehydes

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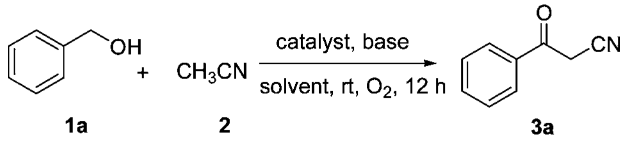
with stoichiometric amounts of oxidants for C−C cross-coupling reactions have been made,[18] but the examples with molecular oxygen as the terminal oxidant under mild conditions are still scarce. A survey of the literature reveals that no such oxidative C−C cross-coupling methods for the synthesis of β-ketonitriles have hitherto been reported. Herein we describe the discovery and development of a cheap and convenient copper catalyst system for the oxidative cross-coupling of aromatic alcohols and acetonitrile to β-ketonitriles with molecular oxygen as the oxidant under mild conditions (Scheme 1d).

The investigation began by attempting the aerobic oxidation of alcohols to the aldehydes using copper as the catalyst. When a benzyl alcohol was used as the substrate with $CuCl_2$ as the catalyst, acetonitrile as the solvent, and KOH as a base, we were surprised to find that $CuCl_2$ could catalytically couple benzyl alcohol with acetonitrile to afford β-ketonitriles in the presence of molecular oxygen. To the best of our knowledge, such an aerobic oxidation has never been reported to date. Thus the unexpected finding promoted us to further investigate the reaction.

We chose benzyl alcohol (**1a**) and acetonitrile (**2**) as representative substrates to systematically screen the reaction conditions. The results were summarized in Table 1. As can be seen, a base additive is required to achieve the oxidation conversion. However, it is not the fact that the stronger bases reach the higher yields of reactions. When strong bases, such as *t*-BuOK and NaH, were used, the yields of **3a** were 60% and 66%, respectively (Table 1, entries 1 and 3). In fact, potassium hydroxide, an easily available and inexpensive modest strong base, resulted in an 86% isolated yield of **3a** (Table 1, entry 8) in the oxidation reactions. The effects of different solvents were also evaluated. Strong polar aprotic solvents are generally effective for the oxidative conversion of benzyl alcohol and acetonitrile to the desired β-ketonitrile. In contrast, weak polar aprotic solvents, e.g. toluene, are unfavorable to the reaction. The observations could be rationalized in terms of the KOH having relatively high solubility in a strong polar aprotic solvent. A variety of metal salts were screened for their ability to promote the oxidative cross-coupling reactions. Copper chloride displayed relatively high catalytic activity in facilitating the oxidative cross-coupling of benzyl alcohols and acetonitrile to the corresponding β-ketonitrile with molecular oxygen. Adversely, $FeCl_3$ and $CoCl_3·6H_2O$ were totally ineffective (Table 1, entries 17 and 18). Considering $CuCl_2$ may react with KOH to generate $Cu(OH)_2$ or CuO in the reaction system, we directly chose $Cu(OH)_2$ and CuO as the catalysts to perform the reaction under the standard reaction conditions, and the results showed no desired products were generated. Thus the optimal reaction conditions were considered to included benzyl alcohols (1 equiv), CH_3CN (10 equiv), $CuCl_2$ (1 mol %), KOH (3 equiv), and DMA as the solvent at room temperature for 12 h.

Having established the optimal conditions for the $CuCl_2$-based catalysis, we next examined the range of aromatic alcohols to which this catalytic aerobic oxidation could be applied, and the results are summarized in Scheme 3. Several features of this simple inexpensive yet robust system are worth noting. First, the catalytic system is able to be effectively applied to a wide range of aromatic alcohols for the synthesis of β-ketonitriles under mild conditions. The substrates containing a halogen, such as fluorine, chloride, or bromide, on the aromatic ring provided very high isolated yields (**3e**−**3j**), but the oxidative cross-coupling only achieved 45% yields when the aromatic ring was substituted by two bromide atoms (**3k**). However, the compound **3s** was not obtained when an iodide was present on the aromatic ring of benzylic alcohol (**3s**). The benzylic alcohols substituted by electron-donating groups are generally conducive to the oxidation reaction, but substrates that have strong electron-drawing groups on the aromatic ring remained unreactive (**3r**). It is noteworthy that oxygen- and sulfur-containing compounds, which are usually regarded as difficult substrates in most aerobic oxidations involving transition metals due to their strong coordinating ability to transition metals, were also very smoothly converted into the corresponding β-ketonitriles with high isolated yields (**3l**−**3p**). Unfortunately, and despite extensive efforts, primary aliphatic alcohols remained elusive recalcitrant substrates. The use of an aliphatic aldehyde in place of the corresponding alcohol as the substrate still remained unreactive. For the nitrile partner, propionitrile was examined and the results showed they do not lead to the desired products. Curiously, activated malononitrile, ethyl cyanoacetate, and benzyl cyanide that are apt to deprotonate the α-CH protons under basic conditions do not work.

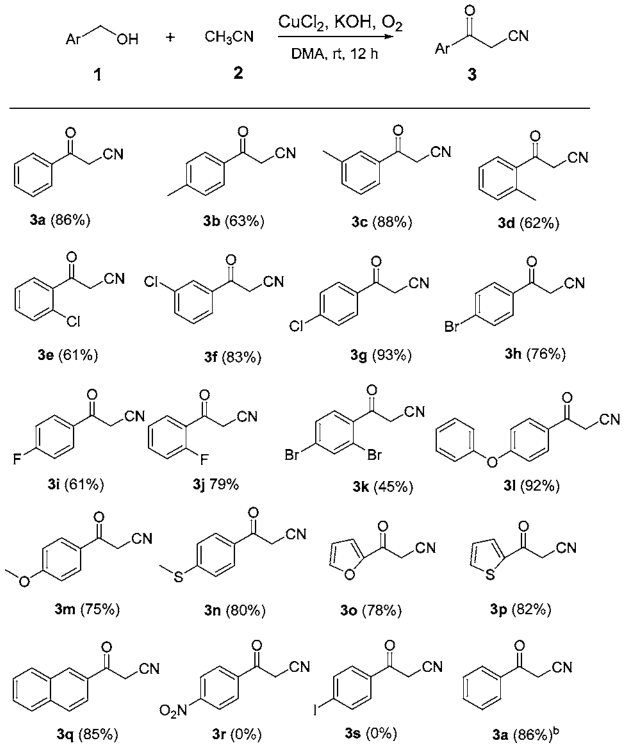
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	base	solvent	yield (%)[b]
1[c]	$CuCl_2$	*t*-BuOK	DMA	60
2[c]	$CuCl_2$	CH_3ONa	DMA	14
3[c]	$CuCl_2$	NaH	DMA	66
4[c]	$CuCl_2$	KOH	DMA	77
5[c]	$CuCl_2$	NaOH	DMA	58
6[c]	$CuCl_2$	Cs_2CO_3	DMA	n.d.[d]
7[c]	$CuCl_2$	LiOH	DMA	n.d.[d]
8	**$CuCl_2$**	**KOH**	**DMA**	**95(86)**
9[e]	$CuCl_2$	KOH	DMA	85
10	–	KOH	DMA	n.d.[d]
11	$CuCl_2$	–	DMA	n.d.[d]
12[f]	$CuCl_2$	KOH	DMA	n.d.[d]
13	$CuCl_2$	KOH	DMF	88
14	$CuCl_2$	KOH	DMSO	10
15	$CuCl_2$	KOH	DCM	n.d.[d]
16	$CuCl_2$	KOH	toluene	n.d.[d]
17	$FeCl_3$	KOH	DMA	n.d.[d]
18	$CoCl_3·6H_2O$	KOH	DMA	n.d.[d]
19	$CuSO_4$	KOH	DMA	20[g]
20	CuI	KOH	DMA	19[g]
21	$Cu(OTf)_2$	KOH	DMA	69[g]
22	$CuBr_2$	KOH	DMA	60[g]
23	CuBr	KOH	DMA	69[g]
24	$Cu(OAc)_2·2H_2O$	KOH	DMA	77[g]
25	$Cu(OH)_2$	KOH	DMA	n.d.[d]
26	CuO	KOH	DMA	n.d.[d]

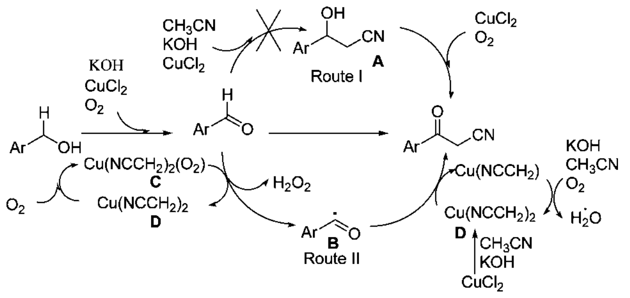
[a] Conditions: **1a** (1 mmol), **2** (10 mmol), catalyst (1 mol %), base (3 mmol), solvent (10 mL), O_2 balloon, rt, 12 h. [b] GC yield based on **1a** used; the number in parentheses shows isolated yield. [c] Base (2 mmol) was used. [d] No product was detected by GC. [e] Base (4 mmol) was used. [f] Nitrogen balloon. [g] Isolated yield.

Scheme 3. Generalization to Substituted Aromatic Alcohols with Acetonitrile[a]



[a] Conditions: **1** (1 mmol), **2** (10 mmol), catalyst (1 mol %), base (3 mmol), DMA (10 mL), O_2 balloon, rt, 12 h. [b] Benzaldehyde as substrate. Yield refers to isolated yields.

Scheme 4. Probable Reaction Mechanism



In the present case, a detailed mechanism for the overall catalytic process cannot yet be described, but an outline of a potential mechanism may be deduced (see Scheme 4) based on the existing experiment results. At first, the benzyl alcohols were oxidized to the benzaldehydes by the catalytic system; indeed, we detected the generation of benzaldehydes during the reaction. Moreover, when benzaldehydes were used to replace the corresponding benzyl alcohols to perform the oxidation reactions, we obtained the same β-ketonitrile products with the same high yields (Scheme 3, condition b). Thus cyanomethylation of aldehydes with acetonitrile is the key to understanding the reaction mechanism. Route I was first considered; however, the experimental results did not support this thinking. We have carried out the reaction with benzaldehydes and acetonitrile under standard reaction conditions with the only variance being the use of N_2 in place of O_2, and the results showed that both compound intermediate A and target compound β-ketonitriles were not generated. The base-catalyzed aldol condensation of acetonitrile and benzaldehydes to compound A, a reaction without dioxygen, did not occur. Moreover, intermediate A was not detected during all the aerobic oxidations either. Thus route I should be unreasonable. The negative results toward the aldol condensation of acetonitrile and benzaldehydes may be attributed to the alkalinity of KOH being not strong enough to effectively deprotonate acetonitrile to result in the aldol condensation reactions. Recognizing that the incorporation of molecular oxygen into the reaction system has been the keystone for the aerobic oxidations, we proposed route II as the mechanism of the oxidative cross-coupling reaction. In route II, the reactions may proceed via an oxidation of the benzaldehydes to intermediate B with active oxidant C, and then the intermediate B was further oxidized by Cu(II) compound D to generate target β-ketonitrile compounds. Molecular oxygen was activated by compound D to generate active oxidant C, and the latter could oxidize benzaldehydes to B and H_2O_2. Compound D, derived from $CuCl_2$, KOH, and CH_3CN, fulfilled the oxidation of B to target β-ketonitriles. The formation of compound D from $CuCl_2$, KOH, and CH_3CN is reasonable as the Lewis acidic copper center would lower the pK_a value of acetonitrile substantially once it is coordinated. Although no direct evidence was obtained to verify the oxidation of B with compound D, several reports on copper(II) salts oxidizing a benzyl free redical have provided useful insights for understanding the current reaction mechanism.[19]

In conclusion, we have developed an efficient method for the synthesis of β-ketonitriles from aromatic alcohols and acetonitrile using easily available $CuCl_2$ as the catalyst and O_2 as the oxidant without any ligands under mild reaction conditions. A plausible overall mechanism described here is expected to help tailor other catalysts and substrates, so as to develop more efficient catalytic processes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liurh@ecust.edu.cn.

Notes

The authors declare no competing financial interest.

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