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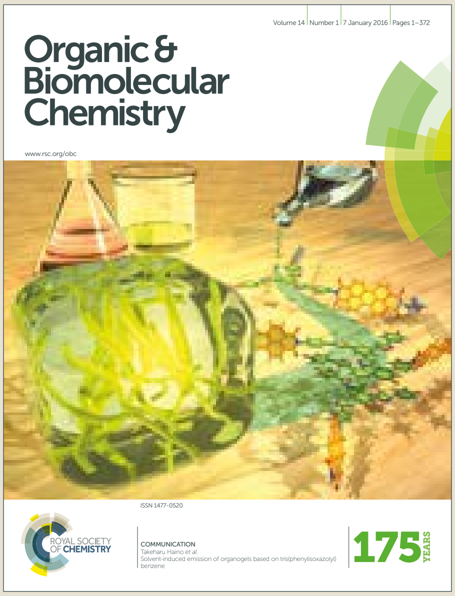

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Copper-Catalyzed Synthesis of Arylcarboxamides from Aldehyde and Isocyanides: Isocyano Group as an N1 Synthon

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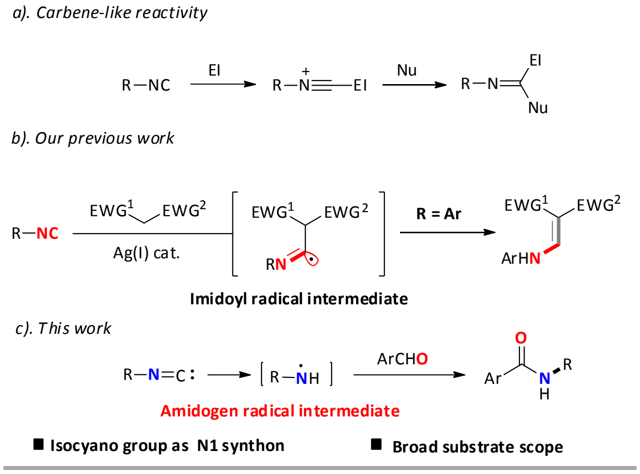
An interesting radical coupling reaction of aromatic aldehydes with isocyanides was disclosed for the synthesis of amides catalyzed by copper. According to the experimental results and mechanistic study, the isocyano group acted as an N1 synthon rather than the carbene-like reactivity, exploiting a new reactivity profile of isocyanide.

C-N bond formation is of utmost importance in organic chemistry, biological molecules, pharmaceutical industries and materials science.[1] In the recent past, substantial advances on C-N bond formation have been dramatically achieved. To the best of our knowledge, three kinds of prominent C-N bond formation reactions have been well-established including Goldberg reaction,[2] Chan-Lam coupling[3] and Buchwald-Hartwig aminations.[4] However, compared to these electrophilic and nucleophilic animation reactions, the development of C–N bonds related to nitrogen-centred radicals is relatively dilatory which is held back by the limited source of nitrogen radicals. Thus, exploring suitable and novel type of nitrogen radicals is still an important and highly attractive research.

Isocyanides are very versatile reagents in organic synthesis, especially in the field of multi-component reactions (IMCRs)[5] and heterocyclic chemistry.[6] However, most of these reported accomplishments are mainly focused on developing them as the carbene-like reactivity; or emerging them as a valuable C1 building block (Figure **1a**).[6c] Additionally, isocyanide insertion reactions, polymerization processes and C-H functionalization reactions have been well-established by using transition metals as the catalysts which are also based on carbene-like reactivity of isocyano groups.[7,8] In contrast, radical isonitrile reaction was less intensively investigated. Very recently, we skilfully avoided the over insertion of isocyanides and used it as a radical coupling/isomerization strategy for the construction of β-aminoenones and tricarbonylmethanes.[9] Nanni and Curran discovered a method for the synthesis of quinoxalines via a radical cascade progress.[10] Surprisingly, these strategies were rapidly developed for the construction of important nitrogen heterocycles, such as phenanthridines and other *N*-containing heterocycles.[6d,6e] Lately, Studer came true the synthesis of iodinated alkyl quinoxalines by using ortho-diisocyanoarenes as radical acceptors via atom transfer and radical addition progress.[11] However, all these transformations were relied on the radicals addition to the isonitrile carbon atom leading to the imidoyl radical intermediate, which indicated that isonitriles was acted as radical acceptors (Figure **1b**). Herein, we reported a novel radical C-N cross-coupling strategy for aromatic aldehyde with isocyanides affording amides. In our current work, C-N bond coupling event immediately occurs via a radical coupling process with the generation of amidogen radical intermediate (Figure **1c**). Remarkably, isocyano group as the source of N1 synthon was less reported formerly.[12]

Figure 1. Reactivity patterns of isonitriles.



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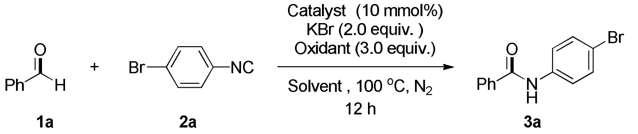
We initiated the exploratory reaction between benzaldehyde (1a) and p-bromophenyl isonitrile (2a) as a model reaction by varying the metal salts, solvents and oxidant to optimize the protocol (Table 1). Delightfully, the reaction catalysed by CuI in the presence of 2 equiv of KBr and tert-butyl hydroperoxide (TBHP) afforded 3a in 81% yield (entry 1) under nitrogen atmosphere. Compared to CuI, other metal catalysts ($FeCl_2$, $CuBr_2$, $AgNO_3$, CuBr, CuCl, and Ag_2CO_3) presented lower catalytic activity or even failed in this transformation (entries 2-7). Subsequently, a series of solvents including 1,4-dioxane, DCE, CH_3CN, benzene (entries 8-11) were tested to further improve the result, and toluene was more adequate for the reaction than other solvents. Encouraged by these finding, we also explored the influence of the oxidants, including $K_2S_2O_8$ and DTBP, regrettably, no desired product 3a was formed (entries 12–14). It is worth mentioning that no reaction was observed in the absence of catalyst (entry 15). Additionally, no desired product was obtained under the O_2 atmosphere (entry 16). There was no doubt that entry 1 was as the optimal reaction conditions.

Table 1. Optimization of the Reaction Conditions[a]

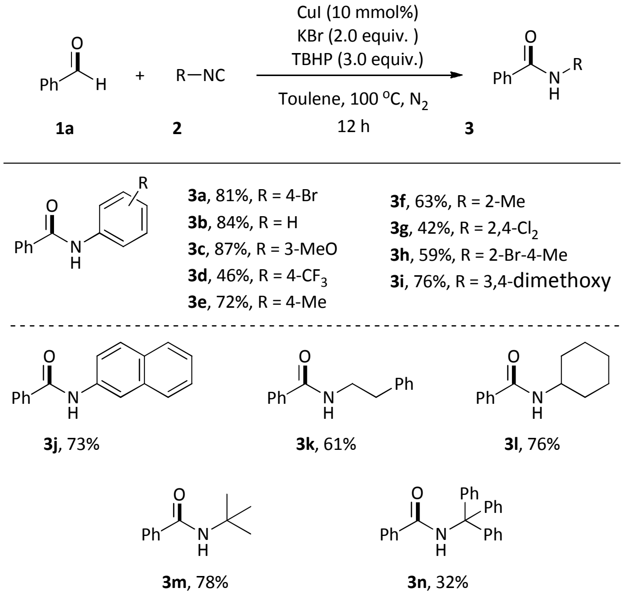


entry	catalyst	solvent	oxidant	3a (%)[b]
1	CuI	toluene	TBHP	81
2	$FeCl_2$	toluene	TBHP	0
3	$CuBr_2$	toluene	TBHP	23
4	$AgNO_3$	toluene	TBHP	0
5	CuBr	toluene	TBHP	43
6	CuCl	toluene	TBHP	32
7	Ag_2CO_3	toluene	TBHP	0
8	CuI	dioxane	TBHP	48
9	CuI	DCE	TBHP	57
10	CuI	CH_3CN	TBHP	0
11	CuI	benzene	TBHP	65
12	CuI	toluene	$K_2S_2O_8$	0
13	CuI	toluene	DTBP	0
14	CuI	toluene	Selectfluor	0
15	--	toluene	TBHP	0
16[c]	CuI	toluene	TBHP	0

[a] All reactions were carried out with **1a** (1.0 mmol), **2a** (0.5 mmol), oxidant (1.5 mmol), KBr (1.0 mmol) and catalyst (10 mol%) in solvent (2.0 mL) at 100 °C under N_2 atmosphere for 12 h. [b] Isolated yields. [c] under O_2 atmosphere for 12 h.

With the optimized reaction in hand, we next investigated the scopes and limitations of this transformation (Scheme 1). A variety of alkyl and aryl isonitriles underwent the coupling with benzaldehyde (1a) smoothly. There was little electronic effect on this conversion, which could tolerate compatibly with various groups at the position of aromatic ring (such as Br, MeO, Me, CF_3 and H, etc.) affording the desired products (3a-3f) in moderate to good yields. To our delight, the bis-substituted substrates were also well tolerated to give products (3g-3i) in 42~76% yields. Additionally, it is worth to be noted that the 2-isocyanonaphthalene could react with benzaldehyde smoothly, leading to the corresponding product 3j in 73% yield. Furthermore, a series of alkyl isonitriles was also tested, and found in delight that they were all suitable for this transform (3k-3n) in appropriate yields, even if the substrates with strong steric effect, such as 2-isocyano-2-methylpropane and (isocyanomethanetriyl)tribenzene, also could efficiently react with 1a, affording the corresponding products 3m and 3n.

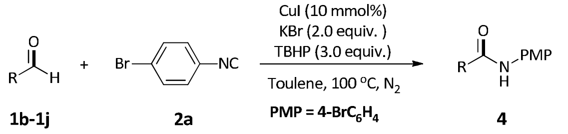
Scheme 1. The scope of isonitriles[a,b]



[a] All reactions were carried out with **1a** (1.0 mmol), **2** (0.5 mmol), TBHP (1.5 mmol), KBr (1.0 mmol) and CuI (10 mmol%) in toluene (2.0 mL) at 100 °C under N_2 atmosphere for 12 h. [b] Isolated yields.

Subsequently, to further expand the scope of substrates, we focused our concentration on investigating the influence on aldehydes under the standard conditions (Scheme 2). Delightfully, a range of aromatic aldehydes reacted with 2a stably, furnishing the expected products (4a-4g) in 37~89% yields. Among these, the aromatic rings with electron-donating (R = OMe or Me) or withdrawing groups (R = Br, NO_2 and CN) presented high reactivity along with little electronic effect. Unfortunately, when 4-pyridinecarboxaldehyde was used as a substrate, there was no expected product in a mixture system. Besides, as an example of alkyl aldehydes, n-pentanal was also tested for this reaction. Regretfully, the experimental results showed that it was ineffective substrate, and no reaction took place as we expected.

Scheme 2. The scope of aldehydes [a,b]



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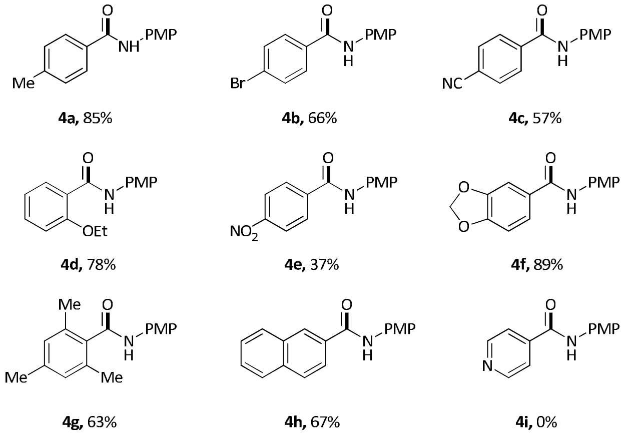


4a, 85% **4b,** 66% **4c,** 57%

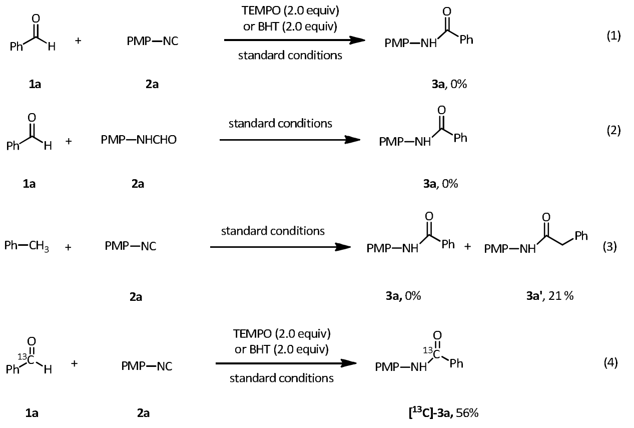
4d, 78% **4e,** 37% **4f,** 89%

4g, 63% **4h,** 67% **4i,** 0%

[a] All reactions were carried out with **1** (1.0 mmol), **2a** (0.5 mmol), TBHP (1.5 mmol), KBr (1.0 mmol) and CuI (10 mmol%) in toluene (2.0 mL) at 100 °C under N_2 atmosphere for 12 h. [b] Isolated yields.

To probe a plausible mechanistic route for this reaction, several experimental investigations were conducted and performed under the standard conditions (Scheme 3). Once the radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butylhydroxytoluene (BHT) was added to the solution of **1a** and **2a**, the reaction was completely suppressed. Despite the adducts were failed to be captured, the result predicted that the reaction should go through a free radical intermediate [Eq. (1)].[13] Meanwhile, *N*-(4-bromophenyl)formamide was tested the plausible mechanistic progress, and there was no desired products [Eq. (2)].[14] Further, the possibility of the solvent as the acyl source via oxidation process was excluded as no **3a** could be isolated from the reaction [Eq. (3)]. However, we detected the product **3a'** in 21% yield, suggesting the mechanism route is different from that of ref.12. Finally, using [^{13}C]-**1a** as a reactant, isotope-labelling study unambiguously confirmed the aromatic aldehyde compounds as the source of acyl affording [^{13}C]-**3a** in 56% yield [Eq. (4)].

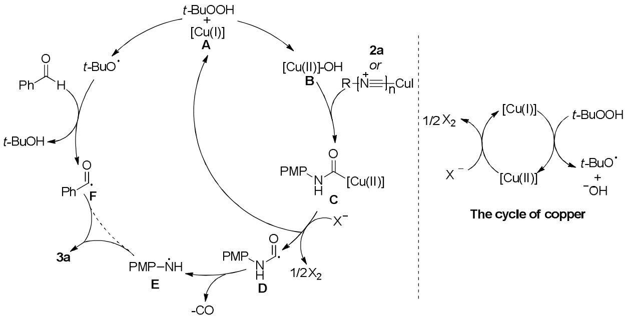
Scheme 3. Control reactions for Mechanistic Investigations[a]



[a] Isolated yields. PMP = 4-BrC_6H_4.

On the basis of the above experimental results and related literature precedents,[9,12,15] a plausible mechanism was tentatively outlined by using **1a** and **2a** as model substrates in Scheme 4. In the radical initiation stage, the low-valent copper catalyst transfers an electron to TBHP affording copper species **B**[17] and *tert*-butoxyl radical. Then, the complex CuI(RNC)$_n$ may be formed and reacts with **B** to give the intermediate **C**. Afterwards, the fate of **C**, is to donate an electron to X^- (X = Br or I), generating **A**, radical **D** and simple substance X_2, thereby leading to the regeneration of **A** catalyst and completing the catalytic cycle. Subsequently, the intermediate **D** then eliminates carbon monoxide to form radical **E**. Meanwhile, *tert*-butoxyl radical abstracts a hydrogen atom from aldehyde **1a** leading to acyl radical **F** and tertiary butanol. Finally, two radicals **E** and **F** couple directly to release the product **3a**.

Scheme 4. Plausible Mechanism



In conclusions, we have developed an intriguing and novel copper-catalyzed radical coupling reaction of aromatic aldehyde with isocyanides, providing a very convenient and modular approach to the synthesis of amides. This report presented a new fundamental C-N bond forming reaction between two basic chemicals with broad range of substrates. Importantly, this approach is mechanistically different from the classical transition-metal-catalyzed isocyanides chemistry, which isocyano group as an N1 synthon rather than the carbene-like reactivity was disclosed.

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