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Ligand-free copper-catalyzed direct amidation of diaryliodonium salts using nitriles as amidation reagents

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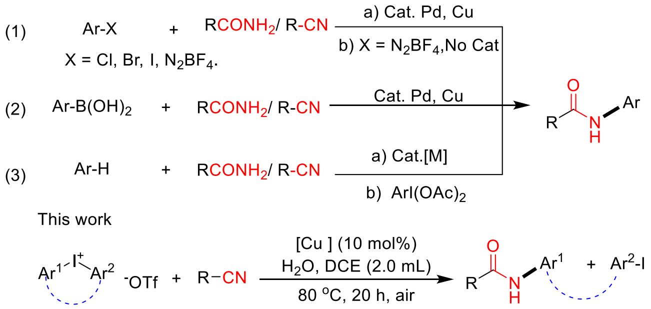
ABSTRACT

An efficient and practical methodology for the synthesis of *N*-arylamides has been developed via copper-catalyzed amidation of diaryliodonium salts with nitriles. Various substituted aryl nitriles and aliphatic nitriles could be applied in the reaction, providing a series of *N*-arylated amides in moderate to good yields. This procedure provides an alternative route for the synthesis of various *N*-arylamides. A proposed mechanism based on control experiments is also presented.

Introduction

Amides are important structure scaffolds existing in natural products, biological compounds, pharmaceuticals and synthetic materials [1,2]. In particular, *N*-arylamides are prevalent in various structurally diverse pharmaceutical products. Therefore, the synthesis of them has aroused great interest from organic chemists and extensive efforts have been devoted to the synthesis of *N*-arylamides. As an early methodology for the construction of C—N bond, Jourdan reaction, Ullmann reaction and Goldberg reaction often suffered from drastic reaction condition, limited substrate tolerance and poor yield [3].

In recent decades, the ligand assisted modifications in these reactions and Buchwald-Hartwig cross-coupling reaction greatly simplified the synthesis of *N*-arylamides and enabled to develop useful synthetic strategies under the mild conditions [Scheme 1, Eq. (1)] [4–6]. Although Buchwald-Hartwig reaction has significant advantages in terms of yield and catalytic performance, palladium catalyst with high price, strong toxicity and dependence on highly toxic phosphorus ligands are severely restricted. The groups of Chan, Evans, and Lam independently reported Cu-mediated oxidative amination of arylboronic acids with amines and other nucleophiles for the formation of C,aryl)-N bonds [7]. Recently, Cu-mediated oxidative amination of arylboronic acids as aryl donors with amides or nitriles was has been widely illustrated by the groups of Yu, Li, Lan and Xiang, independently [Scheme 1, Eq. (2)] [8]. Over the last few years, the direct C—H amination of arenes has been proven to be a powerful tool for the C—N bond formation [Scheme 1, Eq. (3)] [9,10]. Transition metal-catalyzed chelate-assisted C—H amidation provided a valuable alternative for synthesis of *N*-amides [9]. Meanwhile, Xiang groups reported the metal-free oxidative amidation of simple arenes using ArI$(OAc)_2$ as oxidant [10].



Scheme 1. Selected strategies for the synthesis of *N*-arylamides.

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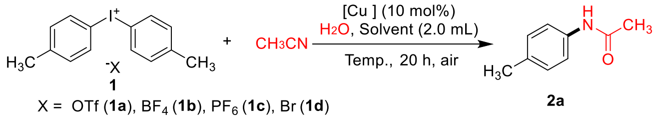
Diaryliodonium salts have recently gained considerable attention and are employed widely as mild, selective, and environmentally benign electrophilic arylating agents in organic synthesis [11]. As reported previously, diaryliodonium salts have been known to transform into aryl radicals via decomposition in acetonitrile, and acetanilide as one of the products has been was observed [12]. Chen group presented an efficient and regioselective synthesis of multiply substituted quinolines from diaryliodoniums, alkynes, and nitriles [13]. Cu-catalyzed ring opening/amination of cyclic diaryliodonum salts by Wen, Gu and Jiang was reported [14].

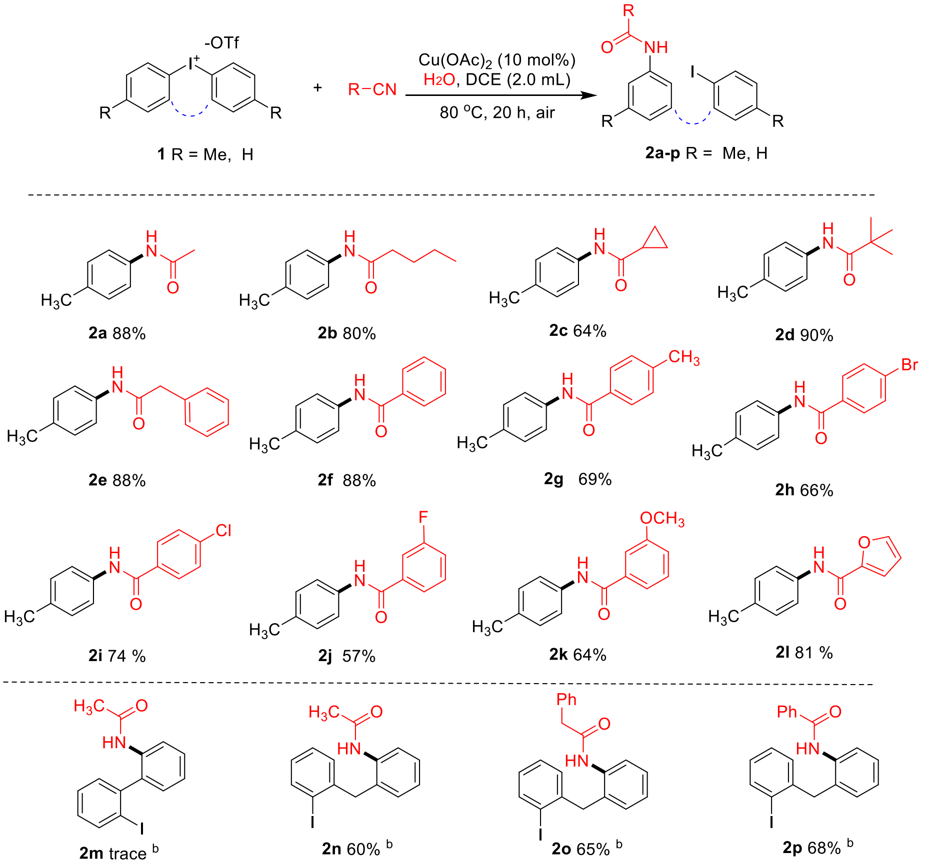
Table 1
Optimization of the reaction conditions.[a]



entry	X	Catalyst	solvent	Yield[b]**2a**, %)
1	OTf	CuCl	$PhCH_3$	9
2	OTf	CuCl	THF	<5
3	OTf	CuCl	DMSO	<5
4	OTf	CuCl	1,4-dioxane	<5
5	OTf	CuCl	DCE	67
6	OTf	CuI	DCE	50
7	OTf	$Cu(OTf)_2$	DCE	88
8	OTf	$CuSO_4{\cdot}5H_2O$	DCE	44
9	OTf	$Cu(OAc)_2$	DCE	88
10	BF_4	$Cu(OAc)_2$	DCE	trace
11	PF_6	$Cu(OAc)_2$	DCE	trace
12	Br	$Cu(OAc)_2$	DCE	trace
13	OTf	–	DCE	0
14[c]	OTf	–	DCE	0

[a] Reaction conditions: **1a** (0.30 mmol), CH_3CN (3.0 equiv), H_2O (1.0 mmol), Cu salts (10 mol %), solvent (2.0 mL), 80 °C, air, 20 h. [b] Isolated yield. [c] 100 °C, N_2, 20 h.

Table 2
Substrate scope of nitriles.[a]

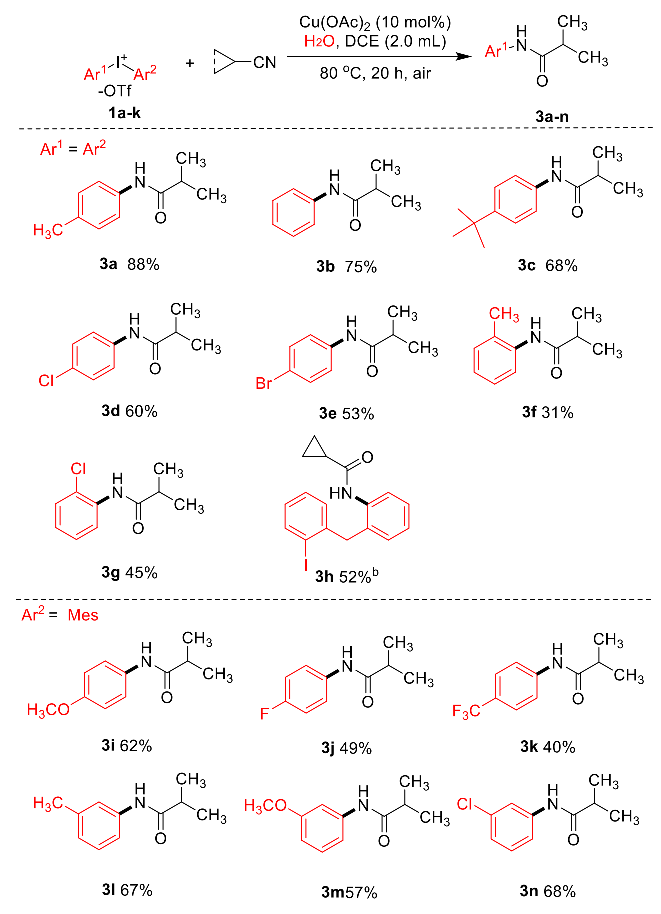


1 R = Me, H
2a-p R = Me, H

2a 88%
2b 80%
2c 64%
2d 90%
2e 88%
2f 88%
2g 69%
2h 66%
2i 74 %
2j 57%
2k 64%
2l 81 %
2m trace [b]
2n 60% [b]
2o 65% [b]
2p 68% [b]

Reaction conditions: [a] **1a** (0.30 mmol), RCN (3.0 equiv), H_2O (1.0 mmol), $Cu(OAc)_2$ (10 mol %), DCE (2.0 mL), air, 20 h. Isolated yield. [b] CuCl (10 mol %).

Table 3
Substrate scope of diaryliodonium salts.[a]



[a] Reaction conditions: **1a** (0.30 mmol), RCN (3.0 equiv), H_2O (1.0 mmol), $Cu(OAc)_2$ (10 mol %), DCE (2.0 mL), air, 20 h. Isolated yield. [b] CuCl (10 mol %).

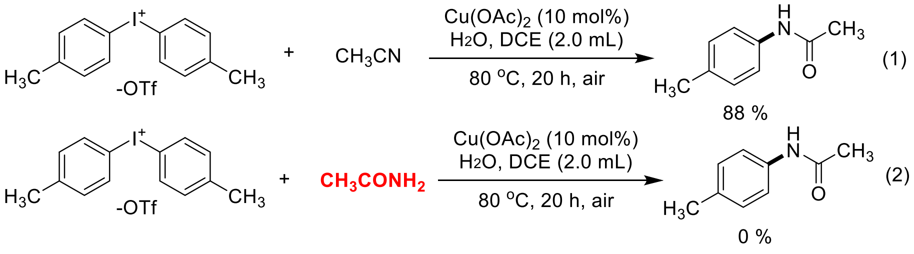
Moreover, nitriles are utilized widely in organic reactions as versatile synthons in organic synthesis [15,16]. Nitriles as nitrogen nucleophilic reagents instead of amides can make the synthesis of *N*-arylamides more accessible [15]. It is reported recently that copper-catalyzed acylation of cyclic diaryliodoniums with nitrile species has been developed for the preparation of iodo-functionalized diarylmethane amides [16a]. Recently, we developed a general and practical method for the synthesis of tertiary amides via the copper-catalyzed aerobic oxidative amidation of tertiary amines [17]. Base on such results, we report a direct copper-catalyzed amidation of diaryliodonium salts with nitriles for the synthesis of *N*-arylamides [Scheme 1, Eq. (4)].

Results and discussion

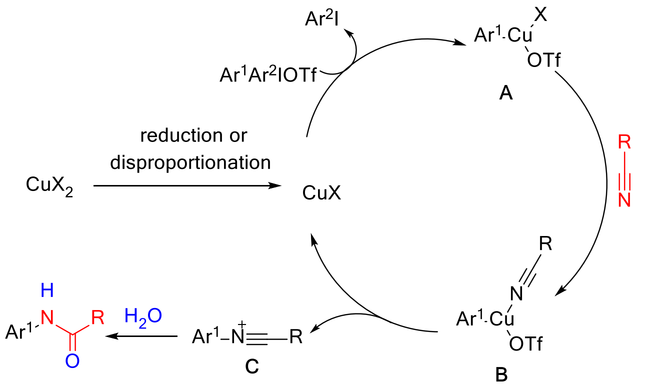
We started our investigations with di(*p*-toly)liodonium trifluoromethanesulfonate **1a** with acetonitrile as the model substrate, and the effect of solvents and metal catalysts were systematically examined (Table 1). A screening of solvents revealed that DCE proved to be the most effective solvent in the reaction, affording the *N*-(p-tolyl)acetamide **2a** in 67% yield. Other solvents such as CH_3CN, DMSO, 1, 4-dioxane and THF gave a lower yield (Table 1, entries 1–5). In a set of copper sources screened, $Cu(OTf)_2$ and $Cu(OAc)_2$ exhibited superior results compared to $CuSO_4{\cdot}5H_2O$, CuI and CuCl (entries 5–9). (*p*-toly)liodonium salts (**1a-1d**), bearing different counter anions were studied (Table 1, entries 9–12). Among all the tested reagents, (*p*-toly)liodonium triflate furnished the desired product **2a** in 88% yield (Table 1, entry 9), whereas tetrafluoroborate, Hexafluorophosphate and bromide gave lower yields (Table 1, entries 10–12). Finally, control experiments confirmed that without the Cu source no product was observed (entry 13). We performed this reaction only at elevated temperature as an additional control (entry 14). After 20 h at 100 °C, no product **2a** was observed (determined by GC–MS and ^1H NMR spectroscopy).

After establishing these conditions, we selected di(*p*-tolyl)iodonium trifluoromethanesulfonate **1a** as the partner to react with different nitriles to evaluate the substrate scope of the nitriles. The results in Table 2 show that both aryl nitriles and aliphatic nitriles could undergo this transformation to generate the desired products in moderate to excellent yields (57–88%). The desired products in excellent yields were obtained when aliphatic nitriles were selected as the substrates (**2a-2e,** Table 2). Pleasingly, substituted benzonitriles bearing electron-donating and electron-withdrawing groups smoothly underwent this reaction generating the desired products in good yield (**2f-2l**, Table 2). Halogenated benzonitriles with F or Cl smoothly led to the corresponding amides with the halogen substituents intact (**2h-2j**, Table 2). The heterocyclic aromatic nitriles also successfully underwent the reaction to afford the desired products in 81% yield (**2l**, Table 2). However, the reaction did not occur for five-membered cyclic diaryliodonium salts to provide the desired product (**2m**, Table 2). Importantly, six-membered cyclic diaryliodonium salts with a range of nitriles (e.g. acetonitrile, benzonitrile and phenylacetonitrile) delivered the desired amide products in good yields (**2n-2p**, Table 2).

Subsequently, the reactivity of different diaryliodonium salts with isobutyronitrile was investigated in this amidation. As shown in Table 3, the diaryliodonium salts containing substituents in the *para*, *meta* and *ortho* positions of the aryl moiety were efficiently coupled with the isobutyronitrile, producing the corresponding desired products with 31–88% yields (Table 3, 3a–3n). However, the steric hindrance of diaryliodonium salts affected this reaction significantly (Table 3, 3a–3e vs **3f-3g**). When unsymmetrical iodonium salts were used in the amidation, the desired products were obtained in moderate yield (Table 3, 3i–3n). When a methyl was



Scheme 2. Control experiments.



Scheme 3. Proposed mechanism.

present in the *ortho* position of the phenyl group of the iodonium salt, the desired product was isolated in 31% yield (Table 3, 3f). In contrast, the methyl group was *para* or *meta* to the iodonium salt, and the desired compounds were obtained in 88% and 67% yields, respectively (Table 3, 3a and 3l). To our delight, the desired amide product was obtained by reacting the six-membered cyclic diaryliodonium salts with cyclopropylcarbonitrile as the cyclic counterpart in 52% yield (Table 3, 3h).

Some control experiments were performed to probe the mechanism of the amidation reaction. The observations were listed in Scheme 2.The diaryliodonium salt **1a** was employed to react with acetonitrile to get the corresponding product **2a** in a yield of 88% [Eq. (1), Scheme 2]. It was found that no product **2a** was detected when using acetamide to react with di(*p*-tolyl)iodonium trifluoromethanesulfonate **1a** instead of acetonitrile under the standard condition [Eq. (2), Scheme 2]. These results indicate that the possibility of amide from the hydrolysis of nitriles being involved in the reaction might be ruled out.

On the basis of the control experiments and previous reports [15], a proposed mechanism is illustrated in Scheme 3. Initially, CuX_2 through the disproportionation or reduction formed the active catalyst CuX. Next, diaryliodonium salts generate highly electrophilic arylcopper(III) species **A** in the presence of the Cu(I) catalyst, This copper(III)-intermediate interacts with nitriles, which then produce a cationic species **C** through a reductive elimination of intermediates **B** and releases the active catalyst CuOTf to complete the catalytic cycle. The resulting arylcationic species can undergo further hydrolysis reactions, providing the final products. The proposed reaction mechanism is similar to previous reports [8b,10,16].

Conclusion

In conclusion, we have developed an efficient and alternative protocol for the synthesis of *N*-arylamides via copper-catalyzed amidation of diaryliodonium salts with nitriles. This reaction demonstrates excellent reactivity, good functional group compatibility and provides an alternative route for the synthesis of various *N*-arylamides. Accordingly, this reaction is expected to have great potential as a practical approach for the amidation of natural products, medicine and organic functional materials. Efforts to explore the applications of the amidation are underway in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office. Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153048.

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