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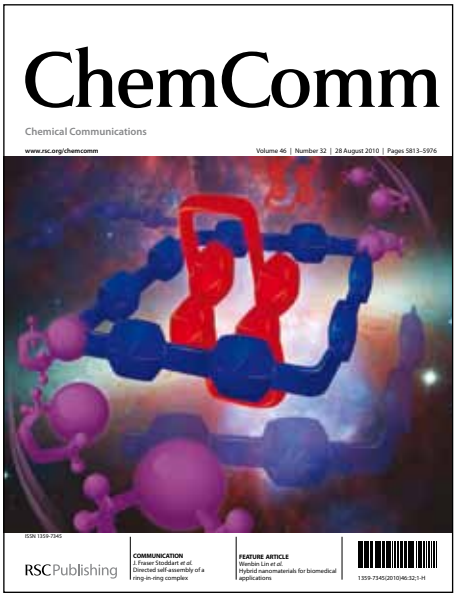

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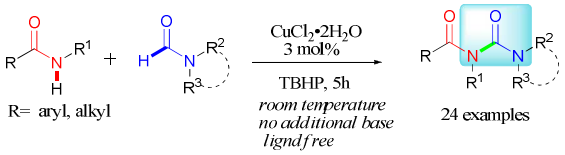
Graphical Abstract



A novel approach for the construction of multisubstituted ureas is reported employing CDC reaction followed by copper catalyzed C–N bond formation.

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ARTICLE TYPE

Copper-Catalyzed C–N Bond Formation through C–H/N–H Activation: A Novel Approach for the Synthesis of Multisubstituted Ureas

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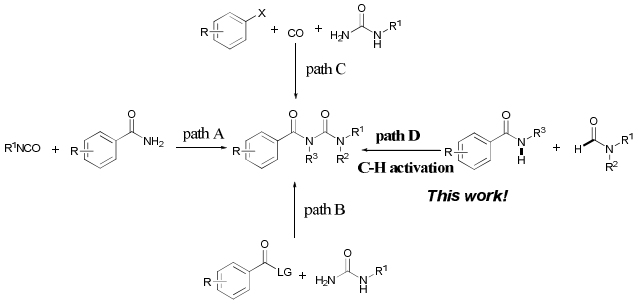
A copper-catalyzed cross-dehydrogenative coupling reaction that involves the activation C–H/N–H bond of formamides and *N*-alkoxy amides has been developed. This protocol affords a novel approach for the synthesis of multisubstituted ureas under mild conditions.

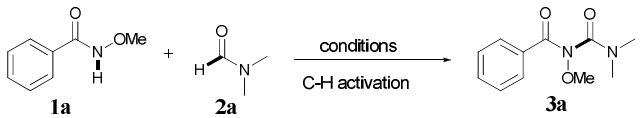
N-acyl ureas are important structural units that are found in various bioactive compounds such as antiinflammatory, hypnotics, analgesic and antitumor.[1,2] Among urea derivatives, the benzoyl ureas were found widespread use within the field of agrochemicals.[2] As a result, the construction of *N*-acyl ureas has intrigued numerous interest and a number of strategies have been developed. Traditionally, *N*-acyl ureas are synthesized by the reaction between an amide and a toxic isocyanate (Scheme 1, path A) or the reaction of suitable activated acid derivatives with ureas (Scheme 1, path B), an unnecessary activated process that often produces large amounts of by-products.[3] A recent progress involves the transition-metal catalyzed cross-coupling reactions of direct carbonylation of aryl halides (Scheme 1, path C). However, the high temperature and high CO pressure (or metal carbonyls as CO precursors) required as well as the presence of halide anions make this reaction environmentally unfavorable.[4] Although some achievements have been accomplished in this area, there still exist significant challenges for chemists in both green and sustainable chemistry to update these old processes.



Scheme 1. The approaches for the synthesis of *N*-acyl ureas.

Recently, the increasing upsurge in attention to the transition-metal catalyzed reactions via the cleavage of a unique C–H bond has presented one of the most attractive and powerful strategies for C–C and C–X bond formation.[5] The two most prevalent methods are C–H bond functionalization[6] and the cross-dehydrogenative coupling (CDC).[7] However, the CDC method is more fascinating because the substrate prefunctionalization is unnecessary and it is in accord with the concept of green chemistry.[8] More recently, copper-catalyzed oxidative coupling reactions have been widely investigated, and much more attention has been paid to highly selective oxidations for activating the C–H bonds.[7b, 9] Although the dehydrogenative coupling of benzaldehydes with amides to form imides has been reported,[10] the direct conversions of two different amides into *N*-acyl ureas are rarely developed. Herein, we wish to report a novel, operationally simple copper-catalyzed CDC reaction for the synthesis of *N*-acyl ureas via C–H/N–H bond activation from *N*-alkoxyaryl amides[11] and formamides.[12]

Table 1. The oxidative amidation of *N*-methoxybenzamide with *N*, *N* dimethylformamide via C–H/N–H bond activation [a]



1a **2a** **3a**

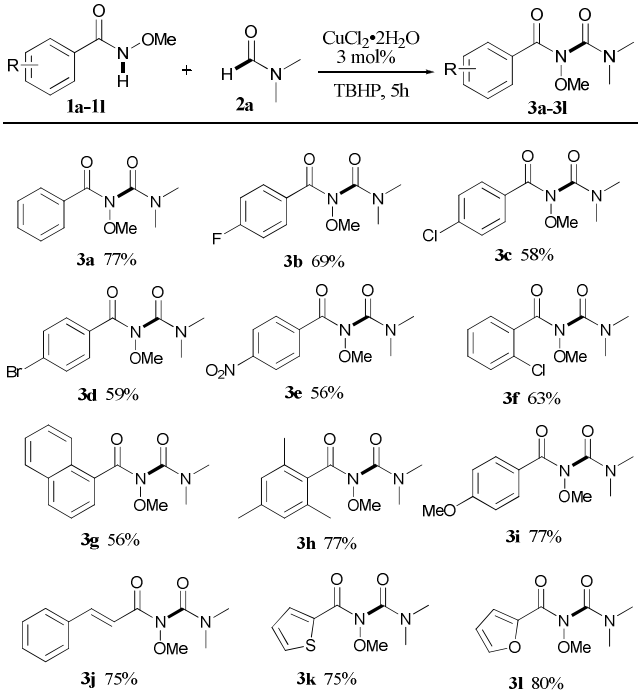
Entry	Catalyst	Ligand	Solvent	Yield(%)[b]
1	$CuCl_2{\cdot}2H_2O$	none	DMF	77
2	CuBr	none	DMF	72
3	$Cu(OTf)_2$	none	DMF	0
4	$Cu(OAc)_2{\cdot}H_2O$	none	DMF	0
5	$CuCl_2{\cdot}2H_2O$	phen	DMF	63
6	$CuCl_2{\cdot}2H_2O$	bpy	DMF	77
7	$CuCl_2{\cdot}2H_2O$	TMEDA	DMF	71
8	$CuCl_2{\cdot}2H_2O$	DMEDA	DMF	75
9[c]	$CuCl_2{\cdot}2H_2O$	none	hexane	38
10[c]	$CuCl_2{\cdot}2H_2O$	none	DMSO	60
11[c]	$CuCl_2{\cdot}2H_2O$	none	Dioxane	25
12[c]	$CuCl_2{\cdot}2H_2O$	none	CH_3CN	trace

[a] Reaction conditions: 0.5 mmol *N*-methoxybenzamide **1a**, 3 mol% Cu catalyst, 5 mol% ligand, 52 equiv *N*, *N*-dimethylformamide **2a**, room temperature, TBHP (3.0 equiv), 5h. [b] Isolated yield. [c] 6 equiv *N*, *N*-dimethylformamide.

To optimize the direct cross-dehydrogenative coupling reaction conditions for *N*-acyl urea synthesis, *N*-methoxybenzamide **1a** and *N*, *N*-dimethylformamide (DMF) **2a** were used in the model reaction and TBHP was employed as the oxidant (Table 1). To our delight, the reaction could occur under the catalysis of $CuCl_2{\cdot}2H_2O$ (3 mol%) at room

temperature, affording the product **3a** in 77% yield. Then, different copper catalysts were tested. Among the copper catalysts screened, $CuCl_2·2H_2O$ showed the best catalytic activity (Table 1, entries 1-4). Meanwhile, the addition of ligands such as TMEDA, DMEDA, bpy and phen were ineffective to improve the yield of *N*-acyl ureas (Table 1, entries 5-8). In addition, solvent effects were also examined. However, the reaction proceeded roughly (Table 1, entries 9-12). Hence, the optimal reaction conditions were involved in formamides (26.0 mmol), *N*-methoxybenzamide (0.5 mmol), TBHP (3.0 equiv) at room temperature for 5 h with $CuCl_2·2H_2O$ (3 mol%) as catalyst and no ligands (more details see Table S1 in ESI).

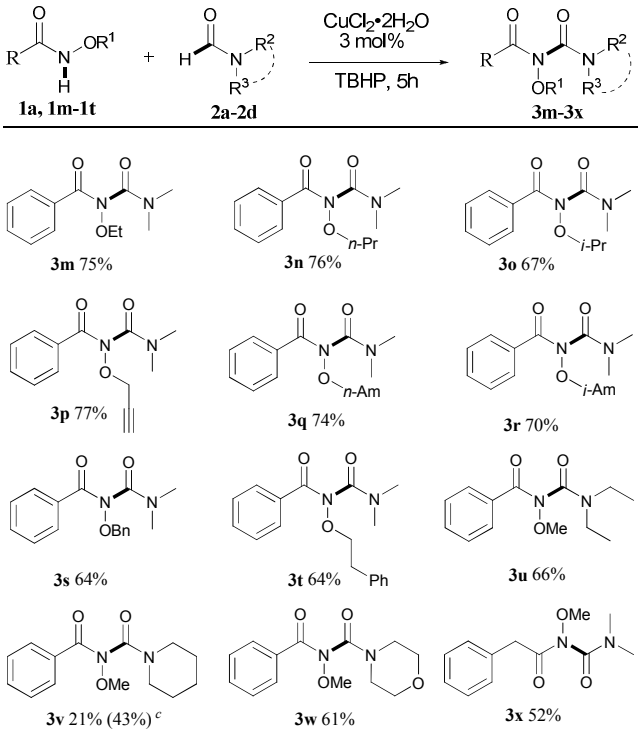
Table 2. Oxidative amidation of different *N*-methoxylamides with DMF *via* C–H/N–H bond activation [a, b]



[a] Reaction conditions: **1** (0.5 mmol), 52 equiv DMF, room temperature, TBHP (3.0 equiv), 5 h. [b] Yield of isolated product.

Under the optimized reaction conditions, the scope of the *N*-methoxyarylamides in the direct cross-dehydrogenative coupling reaction of DMF was investigated. The results can be seen from Table 2, the electron-withdrawing groups as well as the electron-donating groups were well tolerated. The reaction proceeded very well and provided the desired product in moderate to high yields. In general, *N*-methoxyarylamides bearing electron-withdrawing substituents on the aromatic ring made the yields decreased (**3b-3f**). For example, when *N*-methoxy-4-nitrobenzamide was applied in the reaction, the negative effect of the electron-withdrawing group was observed, and the substrate was tansformed into the product **3e** in moderate yield. It should be noted that halide substituted *N*-methoxybenzamides were well tolerated, and provided the corresponding products, which could be further applied in traditional cross-coupling reactions (**3c**, **3d** and **3f**). Moreover, the double bond which is sensitive to oxidation was not destroyed during the reaction (**3j**). Furthermore, the heteroaryl *N*-methoxyamides were also effective substrates for the cross-dehydrogenative coupling reaction (**3k** and **3l**).

Table 3. Scope of the reaction with *N*-alkoxyarylamides and *N*, *N*-disubstituted formamides via C–H/N–H bond activation [a, b]

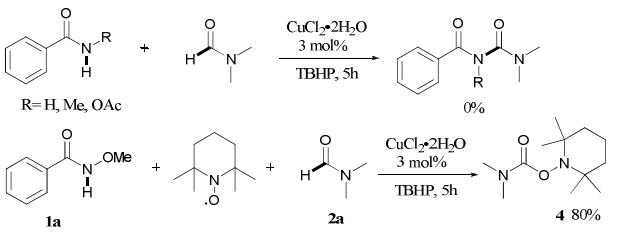


[a] Reaction conditions: **1** (0.5 mmol), 52 equiv formamides, 52 equiv formamides, room temperature, TBHP (3.0 equiv), 5 h. [b] Yield of isolated product. [c] 6 equiv piperidine-1-carbaldehyde, DMSO as solvent (2 mL).

To show the synthetic utility of this method, a variety of *N*-substituted groups were subjected to the optimized conditions. As expected, the desired *N*-acyl ureas were obtained in satisfactory yields. It is important to point out that increasing chain length of the aliphatic groups made slightly influence on the isolated yield of the corresponding products. Meanwhile, the yields decreased slowly when the aliphatic groups cause big steric effects (Table 3, **3m-3t**). In addition, the scope of the *N*, *N*-disubstituted formamides was also screened, both acyclic and cyclic formamides, were effective substrates and gave the desired *N*-acyl ureas with satisfied yields (Table 3, **3u-3w**). Moreover, the yield of **3v** can be improved to 43% when DMSO was used as solvent. To our delight, the aliphatic *N*-methoxyamide can also be applied in this reaction and provided the product in 52% yield (**3x**).

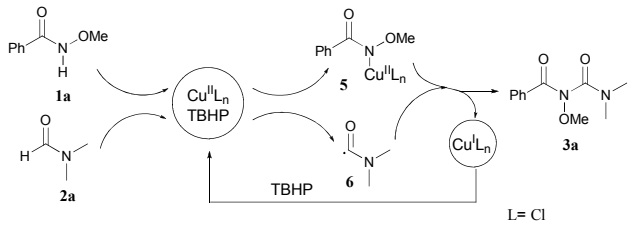
To gain insights into this reaction, several control experiments were carried out to elucidate the mechanism. Firstly, no product could be detected between benzamide and DMF under the standard reaction conditions. Later, we changed other *N*-substituted groups such as Me and OAc, the reaction also could not happen, which indicated that *N*-alkoxy group is essential for the *N*-acyl urea synthesis. The electron-donating group *N*-alkoxy may change the electronegativity of

amide nitrogen and make it more active to undergo the reaction. Furthermore, the addition of radical inhibitors such as 1, 1-diphenylethylene and TEMPO (2, 2, 6, 6-tetramethylpiperidine-*N*-oxyl) blocked the reaction respectively, and no product was detected. To our delight, the TEMPO adduct **4** was detected instead of the *N*-acyl urea during the reaction of *N*-methoxybenzamide **1a** and DMF **2a** under the optimized conditions (Scheme 2).



Scheme 2. Investigations into the reaction mechanism.

From the above results, we believe that the reaction proceeded via the C–H bond activation of *N*, *N*-substituted formamides by a radical mechanism.[13] A hypothesized mechanism of this transformation is shown in Scheme 3. Firstly, the proposed initiated complex **5** generated in *situ* under the copper-catalyst and oxidant TBHP. Next, the radical intermediate **6** was formed through the abstraction of hydrogen from the DMF facilitated by Cu^{II} and TBHP.[14] Further the radical intermediate **6** would couple with the complex **5**, and produced the desired *N*-acyl urea **3a** under reductive elimination.



Scheme 3.The proposed reaction mechanism.

In summary, the first efficient and direct synthesis of *N*-acyl ureas catalyzed by copper from two different amides *via* C–H/N–H bond activation have been developed under mild conditions. This novel and distinct protocol provides an efficient method for the construction of multisubstituted ureas, which avoids using harsh reaction conditions such as toxic materials, high temperature and high CO pressure. The two different amides *N*-alkoxyaromaticamides and *N*, *N*-disubstituted formamides are easily available from the commercial source or laboratory. Further investigations to explore the mechanistic details and the synthetic applications are currently ongoing.

Notes and references

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

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