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Cite this: *Org. Biomol. Chem.*, 2013, **11**, 1925

Received 17th January 2013,
Accepted 1st February 2013

DOI: 10.1039/c3ob40094h

www.rsc.org/obc

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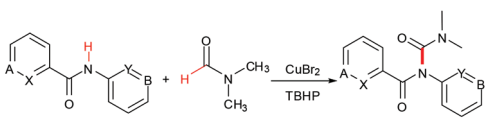
A copper-catalysed oxidative C–H/N–H cross-coupling between formamides and amides through chelation-assisted N–H activation has been developed for the preparation of various multi-substituted ureas.

N,*N*-Dimethylformamide (DMF) is not only an excellent solvent for a great many of chemical reactions, but can also be utilized as a multipurpose reagent, an effective ligand, or even as a catalyst, and thus has been given increasing attention.[1] Especially, in recent years, significant achievements have been made in transition metal catalysed aminocarbonylation reactions through the C–H bond activation of DMF. Highlights of these research efforts include the aminocarbonylation of aryl halides,[2] the addition of DMF to alkenes and alkynes,[3] and the aminocarbonylation of β-ketoesters, *ortho*-carbonyl substituted phenols and *N*-alkoxy amides *via* a cross-dehydrogenative coupling reaction.[4] In addition, a metal-free oxidative C–H/C–H cross-coupling between azoles and DMF has also been achieved by employing *tert*-butyl perbenzoate as an oxidant.[5] The C–H bond activation of DMF can usually be extended to other formamide derivatives. However, the oxidative C–H/N–H cross-coupling between formamides and amides to construct the C–N bond remains rarely developed.[4a]

Highly functionalized ureas have been paid much attention due to their applications in pharmaceuticals[6] and agrochemicals.[7] Although numerous methods such as the substitution reaction based on ureas with alkyl halides and acyl chlorides,[8] the substitution or addition reaction based on phosgene, isocyanates and their equivalents,[6a,9] the oxidative acylation starting from the thioureas,[10] and transition-metal catalysed coupling reactions[4a,11] have been reported for the preparation of multi-substituted ureas, development of the preferred and alternative method, especially starting from other readily available sources, is still necessary for synthetic and medicinal chemists. No doubt, the direct oxidative cross-coupling between formamides and amides would be an ideal strategy to form the C–N bond and prepare substituted ureas. The use of copper salts as catalysts for oxidative cross-coupling reactions has always attracted much interest due to their low toxicity and economical attractiveness.[12] Recently, copper-catalysed direct amidation of sp^2 or sp^3 C–H bonds was achieved in the presence of alkyl peroxides,[13] which demonstrated that the N–H bond of amides can be activated by copper and alkyl peroxides. In addition, according to the results of Zhu, Wang and Reddy,[4,5] the alkyl peroxide can also activate the C–H bond of formamides. Therefore, we envisioned that the copper-catalysed oxidative cross-coupling between the C–H bond of formamides and the N–H bond of amides might be achieved in the presence of an alkyl peroxide to build various multi-substituted ureas (Scheme 1).

To verify our hypothesis, the cross-coupling of *N*-phenyl benzamide with DMF was investigated by using $CuBr_2$ (5 mol%) as a catalyst and *tert*-butyl hydroperoxide (TBHP, 65 wt% in water, 1.5 equiv.) as an oxidant, but none of the desired coupling product was detected (Scheme 1, entry 1). Inspired by the chelation-assisted strategy for oxidative coupling reactions and as a continuation of our recent work,[14] we thus resorted to the directed role of pyridine.[15] *N*-Phenyl-2-picolinamide and *N*-(pyridin-2-yl)benzamide were designed and synthesized as test substrates. It was gratifying that both substrates reacted



(1) A = B = CH, X = Y = CH, n.d.;
(2) A = B = CH, X = N, Y = CH, 75%,[a]
(3) A = B = CH, X = CH, Y = N, 70%,[a]
(4) A = N, B = CH, X = Y = CH, n.d.;
(5) A = CH, B = N, X = Y = CH, n.d..

Scheme 1 Investigation of chelation-assisted N–H activation. Reactions were carried out using amide (0.5 mmol), DMF (1 mL), $CuBr_2$ (5 mol%), TBHP (65 wt% in water, 1.5 equiv.), 80 °C, 12 h, N_2. [a]Yield of isolated product. n.d. = not detected.

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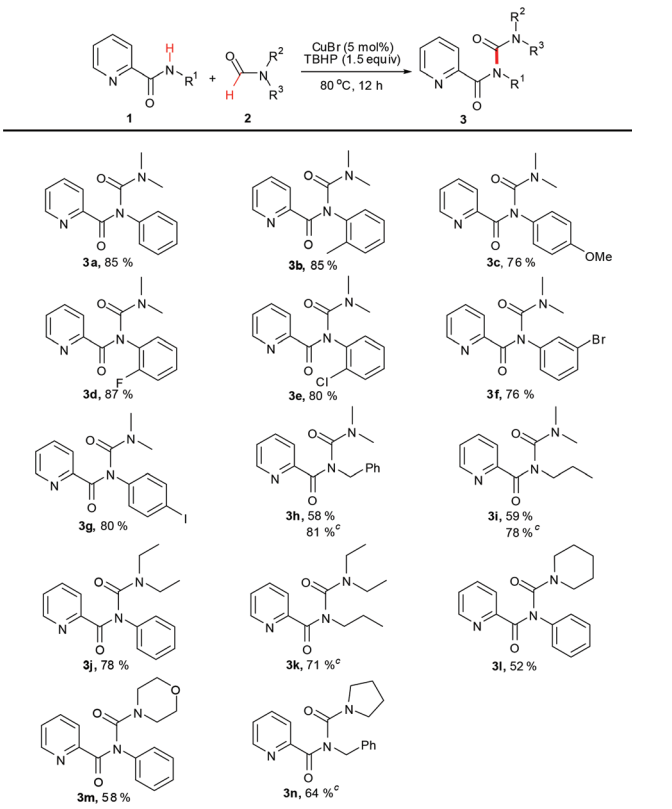
†Electronic supplementary information (ESI) available: Detailed experimental procedures, analytical data. See DOI: 10.1039/c3ob40094h

smoothly with DMF affording the corresponding coupling products in 75% and 70% yields in the presence of $CuBr_2$ and TBHP (Scheme 1, entries 2 and 3). Next, to get further support for the chelation-assisted role of the 2-pyridyl group, *N*-phenyl-3-picolinamide and *N*-(pyridin-3-yl)benzamide were synthesized and subjected to the cross-coupling reaction with DMF. It was no surprise that the coupling reaction did not occur under the same conditions (Scheme 1, entries 4 and 5).

Subsequently, *N*-phenyl-2-picolinamide (**1a**) was chosen as the standard substrate for screening out the optimal reaction condition (ESI, Table S1†). Catalytic effects of various transition metal salts on the cross-coupling of **1a** with DMF were firstly evaluated in the presence of TBHP. Almost all of the common copper salts were available, but CuBr was the most effective one (Table S1,† entries 1–8). $CoCl_2{\cdot}6H_2O$ was also able to work in this transformation, affording the coupling product in 59% yield (Table S1,† entry 9). Other transition metal catalysts such as $Pd(OAc)_2$, $FeCl_3$ and $NiCl_2{\cdot}6H_2O$ did not show significant catalytic activities (Table S1,† entries 10–12). After screening a series of peroxides and other oxidants, TBHP turned out to be still the best choice (Table S1,† entries 2 and 14–19). Higher temperature was not beneficial for this reaction (Table S1,† entry 23), meanwhile, yields were slowly decreasing with lowering of the reaction temperature (Table S1,† entries 2 and 20–22). It was worth noting that the cross-coupling reaction could also occur even at room temperature giving the coupling product in a moderate yield (Table S1,† entry 22). Although a high coupling yield could be obtained in just one hour (75%, Table S1,† entry 24), 12 h was finalized as the optimal reaction time for higher yields and generality (Table S1,† entries 2 and 24–27). Attempts to reduce the amount of formamide by loading 3 equivalents of DMF in no or another solvent led to a low reactivity (Table S1,† entries 28–32). Not surprisingly, TEMPO, a common radical scavenger, could strongly inhibit the reaction (Table S1,† entry 33), which indicated that the reaction was likely to proceed by a radical mechanism.

With the optimized conditions in hand, the scope of oxidative cross-coupling between formamides and *N*-substituted-2-picolinamides was investigated. A variety of *N*-aryl-2-picolinamides were found to be competent substrates and could efficiently couple with DMF, affording the corresponding multi-substituted ureas in good to excellent yields (Table 1, **3a–3g**). Especially, this catalytic system could be tolerant to not only fluoride, chloride and bromide but also the more challenging iodide to give various halogenated *N*-aryl ureas, which provided an opportunity for further synthetic transformations (Table 1, **3d–3g**). *N*-Alkyl-2-picolinamides showed lower activities under the same reaction conditions, providing the coupling products in moderate yields. On increasing the loading of TBHP to 2.5 equivalents, good yields could be obtained (Table 1, **3h–3i**). Other *N*,*N*-dialkyl formamides were also available for coupling with *N*-aryl or alkyl substituted 2-picolinamides to produce a diversity of substituted ureas (Table 1, **3j–3n**).

Table 1 Oxidative cross-coupling of formamides with *N*-substituted-2-picolinamides[a,b]

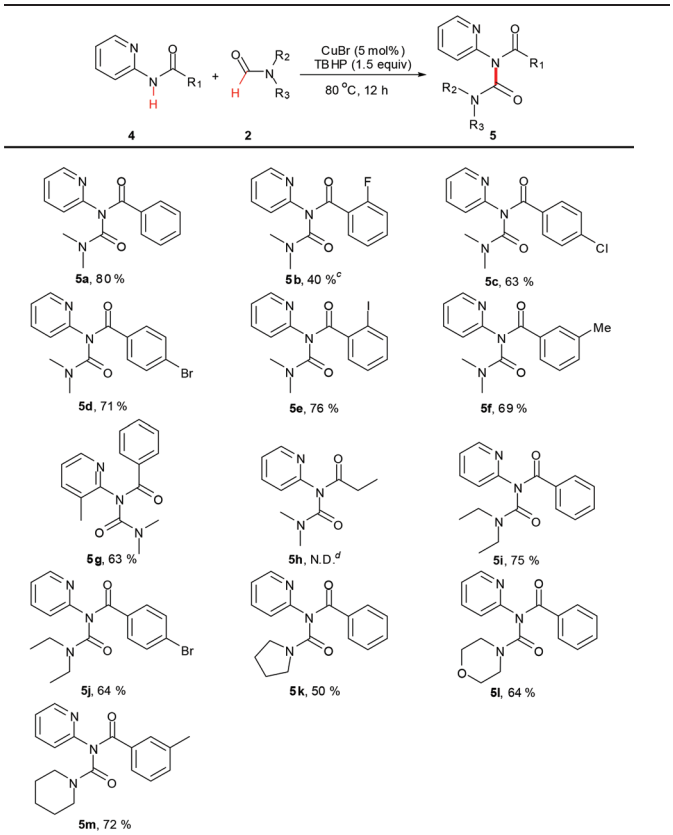


[a] Conditions: *N*-substituted-2-picolinamide (0.5 mmol, 1.0 equiv.), formamide (1 mL), CuBr (5 mol%), TBHP (65 wt% in water, 1.5 equiv.), 80 °C, 12 h, N_2. [b] Isolated yield. [c] 2.5 equiv. TBHP.

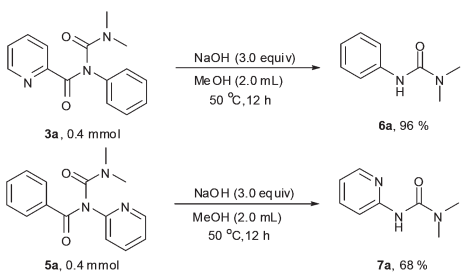
The optimized condition was also applicable to the cross-coupling of formamides with *N*-(pyridin-2-yl)amides. A series of *N*-(pyridin-2-yl)arylamides could successfully couple with DMF to produce the corresponding substituted ureas in moderate to good yields (Table 2, **5a–5g**). 2-Fluorobenzamides may be prone to decompose in the course of the reaction, especially during heating, and thus the coupling of **4b** with DMF only gave the desired product in 40% yield at room temperature. It is worth noting that *N*-(3-methylpyridin-2-yl)benzamide with steric hindrance could undergo the coupling process to afford the benzoyl urea **5g** in 63% yield. However, it was unexpected that when *N*-(pyridin-2-yl)propanamide was employed as the coupling substrate, the corresponding product was not detected (Table 2, **5h**), which might be attributed to the unstable imine intermediate.

Many a tri-substituted urea exhibits extensive pharmaceutical activities with potential applications such as anti-melanoma therapeutics,[6a] antiobesity therapeutics,[6d] and anti-HIV drugs.[6e] So, it is necessary to remove the 2-pyridoyl group from the coupling product to get a tri-substituted urea. After several attempts, we were pleased to find that when **3a** was treated with NaOH in methanol at 50 °C, the tri-substituted urea **6a** was obtained with a high yield of 96% (Scheme 2). The

Table 2 Oxidative cross-coupling of formamides with *N*-(pyridin-2-yl)-amides[a,b]



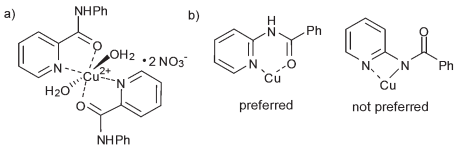
[a] Conditions: *N*-(pyridin-2-yl)amide (0.5 mmol, 1.0 equiv.), formamide (1 mL), CuBr (5 mol%), TBHP (65 wt% in water, 1.5 equiv.), 80 °C, 12 h, N_2. [b] Isolated yield. [c] rt. [d] Not detected.



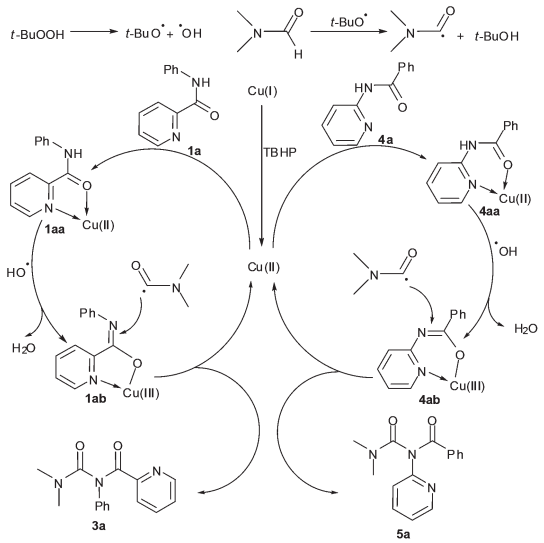
Scheme 2 Removal of the aroyl group.

benzoyl group of **5a** could also be removed under the same conditions to obtain 1,1-dimethyl-3-(pyridin-2-yl) urea (**7a**) with a yield of 68% (Scheme 2). It is worth mentioning that 2-pyridylurea derivatives are the potent inhibitors of gastric acid secretion.[16] Our method provides an alternative approach for their preparation.

To get insight into the mechanism of the oxidative C–H/N–H cross-coupling between formamides and amides, we investigated the coordination modes of copper with an amide. A Cu(II) complex with *N*-phenyl-2-picolinamide (**1a**) has been reported and its crystal structure has been confirmed by X-ray



Scheme 3 (a) Structure of $[CuL_2(H_2O)_2]\cdot(NO_3)_2$ (L = **1a**) confirmed by X-ray diffraction from the literature.[17] (b) Possible coordination of Cu with **4a**.



Scheme 4 Proposed mechanism.

diffraction (Scheme 3, a).[17] In the single crystal structure, the nitrogen atom of the pyridine and the oxygen atom of the amide coordinate to Cu(II) in a bidentate fashion. Similarly, if **4a** is considered as a bidentate ligand, it is much more likely to chelate copper forming a stable six-membered ring through *O*-bonding rather than a four-membered ring through *N*-bonding (Scheme 3, b). So we speculated that the plausible mechanism for the coupling reaction between **1a** (or **4a**) and DMF might be shown in Scheme 4. Firstly, Cu(I) is oxidized by TBHP to Cu(II), which is chelated by **1a** (or **4a**) to form **1aa** (or **4aa**). In the meantime, TBHP dissociates into a butoxy radical and a hydroxyl radical through a homolytic cleavage. A Cu(III)-complex of imine **1ab** (or **4ab**) was formed *via* depriving the hydrogen of **1aa** (or **4aa**) by the hydroxyl radical and a single electron transfer (SET) process of Cu(II). It is inferred that the complex of Cu(III) is a key intermediate, in which the imine structure is stabilized through a conjugate effect. On the other hand, an aminoacyl radical is generated from DMF by the butoxy radical.[5] The addition of the aminoacyl radical to **1ab** (or **4ab**) results in the formation of the target product **3a** (or **5a**).

In summary, we have developed a copper-catalysed oxidative C–H/N–H cross-coupling between formamides and amides through chelation-assisted N–H activation for the preparation of multi-substituted ureas. Amides containing a 2-pyridyl group turn out to be crucial in this reaction. Our methodology

is not only suitable for various formamides, but also for a relatively wide range of *N*-substituted-2-picolinamides and *N*-(pyridin-2-yl)amides. Particularly noteworthy is that the 2-pyridoyl group employed as the auxiliary coordination group can be removed to get a tri-substituted urea. Further studies are currently underway to find the applications of this strategy.

This work was supported by grants from the 973 Program (2011CB808600), the Sichuan Provincial Foundation (2012JQ0002), and the National NSF of China (Nos 21172155, 21025205 and 21021001).

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