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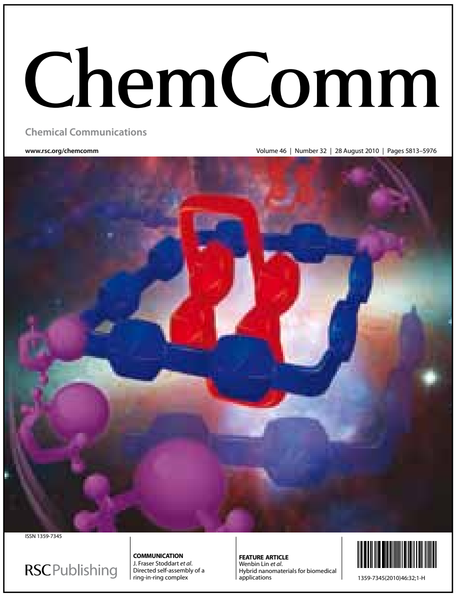
ChemComm
Chemical Communications
www.rsc.org/chemcomm
Volume 46 | Number 32 | 28 August 2010 | Pages 5813–5976
ISSN 1359-7345
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COMMUNICATION

Copper-mediated Tandem Reaction through Isocyanides N–H Bond Insertion: Efficient Access to Unsymmetrical Tetrasubstituted Ureas †

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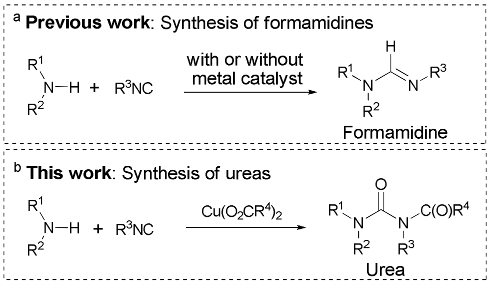
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A copper-mediated multi-component reaction was developed through isocyanides insertion into N–H bonds of less active secondary arylamines. This approach leads to an efficient synthesis of unsymmetrical tetrasubstituted ureas in one pot.

Isocyanides have proven to be versatile building blocks in organic synthesis because of their synthetic possibilities capable of reacting with electrophiles, nucleophiles and even radicals,[1] and have been widely applied to the synthesis of various complicated compounds and heterocyclic systems.[2] Efficiency of isocyanides as strong ligands for metals have early been recognized,[3] and transitional metal-enabled cascade sequences through isocyanide insertions have recently made this class of reactions a powerful tool in synthetic chemistry,[4] which led to a variety of heterocyclic compounds.[5] In comparison, reactions based on isocyanide insertion into N–H bond are barely explored. The reason may due to that most isocyanides, except those activated by electron-withdrawing groups, are inert towards amines in the absence of metal catalysts.[6] A few examples involving isocyanide insertion into N–H bond of certain amines were investigated to give formamidines under the catalysis of metal ions (Scheme 1a).[7] This metal-catalyzed formation of formamidine undergoes initial coordination (η^1) of the isocyanide to the metal ion followed by attack of the amine on the isocyanide and then elimination. Among these reactions, alkyl amines usually undertook the reaction smoothly, while less active aryl primary amines (e. g. aniline) and aryl secondary amines (e. g. *N*-methyl-aniline) required more vigorous conditions,[7b] which limited their utilizations in organic synthesis.[8]



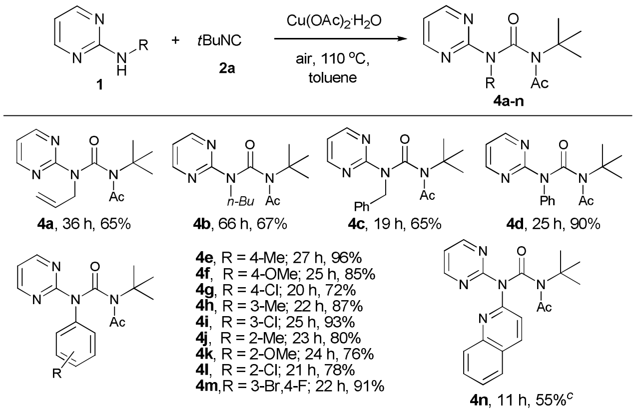
Scheme 1 Isocyanides insertion into N–H bond of amines.

Over the last decade, more interests in urea derivatives have remarkably revived in many fields as hydrogen-bond donors in organocatalysts, significant scaffolds in supramolecular chemistry, and owing to their increasingly important roles in drug discovery.[9] Such characteristics have made the molecules significant synthetic targets and, therefore, have resulted in sustained interest in developing new methods for the preparation of this valuable structural unit.[10,11] Among them, however, many methods are suffered from use of toxic phosgene and unstable carbamoyl chloride intermediates.[12] Furthermore, preparation of multi-substituted especially those tetrasubstituted unsymmetrical ureas normally requires multi-steps.[13] A bulky gold promoted formation of trisubstituted ureas was discussed by Angelici from isocyanide and active alkyl secondary amines, albeit in low to moderate yields.[14] Herein, we reported a copper mediated multi-component reaction, whereby a sequential one C–O bond and two C–N bonds formation is described from easily accessible isocyanides, arylamines and copper carboxylates to give unsymmetrical tetrasubstituted ureas (Scheme 1b). To our knowledge, the given approach features a new mode of isocyanides insertion into N–H bond of less active secondary arylamines in the presence of copper reagents.

Preliminary investigation was started by examining the reaction of *N*-(2-pyrimidyl)allylamine **1a** with *tert*-butyl isocyanide in the presence of CuCl in toluene, however, no apparent reaction occurred (entry 1, Table S1 in the ESI†). Intriguingly, when anhydrous $Cu(OAc)_2$ (1.5 equiv) was used instead, the unexpected tetrasubstituted urea **4a**, rather than the anticipated formamidine product, was isolated in 30% yield (entry 2). An extensive screening concerning copper resources (entries 2–5), solvent (entries 6–8), temperature (entries 9–10), and atmosphere (entries 11–12) revealed that the use of $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv) as catalyst and reagent in toluene at 110 ^{o}C under air, turned out to be the best choice and resulted in **4a** in 65% yield. As a comparison, the combination of catalytic amount of $Cu(OAc)_2{\cdot}H_2O$ and 2.0 equivalents of NaOAc as an acetate source appeared less satisfying than the direct use of copper acetate, and gave only trace amount of product (entry 13), which indicated that stoichiometric of copper acetate was crucial to proceed this reaction. No reaction could be observed in the absence of copper catalyst (entry 14) or using catalytic amount of $Pd(OAc)_2$ and excess of NaOAc (entry 15).[15]

Having developed conditions for the formation of ureas, we then extended the reaction with a range of substrates. A variety of pyrimidine-based amines bearing alkyl or aryl substituents were investigated under the optimized conditions. As illustrated in Table 1, all examined substrates proceeded efficiently to give the desired ureas with good to excellent yields, regardless of their different electronic properties. Reactions involving allyl, alkyl and benzyl substitutions led to good product yields (**4a**–**c**). Substrates containing aryl groups could also undertake this reaction and generally gave urea products very smoothly (**4d**–**m**), which is remarkable considering their notoriously poor nucleophilicity. Furthermore, substrate **4n** with one additional quinoline substituent could also afford the desired product in 55% yield, albeit at higher temperature under oxygen atmosphere. However, methylaniline failed to give any urea product under the same condition or using additional *t*BuOK as base in the reaction. This remarkable difference of pyrimidyl from phenyl group may come from the coordination effect between one of the nitrogen atoms of pyrimidyl group and the copper center in the reaction, despite its even poor nucleophilicity than methylanaline due to the electronic deficient property of pyrimidyl substituent.

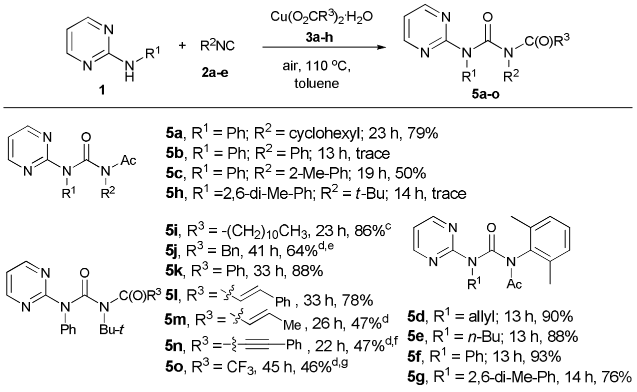
Table 1 Scope of pyrimidyl amines[a,b]



[a] Reaction conditions: amine **1** (0.5 mmol), **2a** (3.0 equiv), $Cu(OAc)_2·H_2O$ **3a** (2.0 equiv), 110 °C, air, toluene (3.0 mL). [b] Isolated yield. [c] O_2, *m*-xylene, 130 °C, the yield based on the conversion of 56%.

Other isocyanides were next examined to evaluate the reaction scope, and the present reaction proceeded smoothly with most of the examined isocyanides as depicted in Table 2. Cyclohexyl isocyanide also underwent this reaction smoothly to generate the corresponding urea **5a** in good yield. For aryl isocyanides, no product was observed when phenyl isocyanide was used (**5b**), presumably due to the quick polymerization of phenyl isocyanide under the reaction condition.[16] To our delight, sterically bulky 2,6-xylyl isocyanides could give ureas in good to excellent yields (**5d**–**g**), while less bulky 2-methylphenyl isocyanides gave **5c** in diminished yield. These results were correlated with the thermal stabilities of the aryl isocyanides,[17] and the detection of *N*-o-tolyl-acetamide as by-product in the synthesis of **5c** justified this perception. Highly sterically hindered urea **5g**, which was structurally confirmed by X-ray crystallographic analysis,[18] could also be obtained in 76% yield, while a combination of bulky amine and *tert*-butyl isocyanide failed to afford **5h**, which may attribute to the amplification of the different reactivity of alkyl and aryl isocyanides in this particular reaction. Most importantly, different types of copper carboxylates **3a–h** could be applied to this reaction and afforded the corresponding ureas (**5i**–**o**) in moderate to good yields, which would significantly expand the utilities of this reaction. Reactions involving functionalized copper carboxylates led to the corresponding ureas (**5l**–**n**) in moderate to good yields, and the C=C double bonds or C≡C triple bonds remained intact under the optimized conditions. The identity of **5m** was determined by spectral analysis and further confirmed by X-ray crystallographic analysis.[18] It is worth noting that urea product **5o** could be obtained in 46% yield from strong Lewis acidic copper (II) trifluoroacetate.

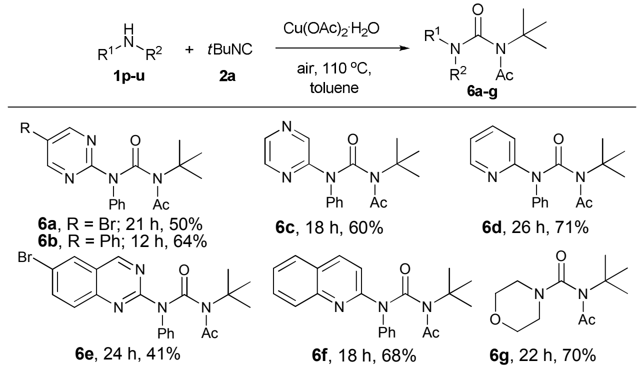
Table 2 Scope of isocyanides and copper carboxylates[a,b]



[a] Reaction conditions: amine **1** (0.5 mmol), isocyanide **2** (3.0 equiv), copper carboxylate **3** (2.0 equiv), 110 °C, air, toluene (3.0 mL). [b] Isolated yield. [c] Yield based on the conversion of 74%. [d] 90 °C. [e] 0.3 mmol scale, yield based on the conversion of 89%. [f] Isocyanide **2a** (6.0 equiv), copper carboxylate **3g** (4.0 equiv). [g] Yield was based on the conversion of 69%.

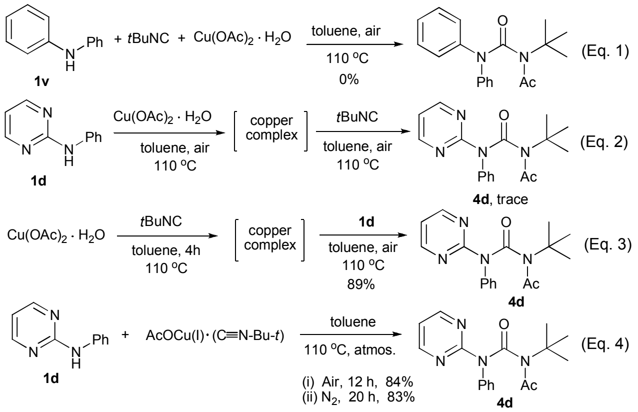
To further explore the generality of this method, various amines were investigated, and the results are summarized in Table 3. Substituted pyrimidine aryl ureas **6a** and **6b** could be obtained in moderate yields. This newly established protocol was not limited to pyrimidines. We were delighted to find that pyrazine (**6c**), pyridine (**6d**), quinazoline (**6e**) and quinoline (**6f**) were efficiently converted to desired ureas in moderate to good yields. It should be noted that strong nucleophile such as morpholine could also afford urea product **6g** successfully in good yield in the absence of the coordination assistance of nitrogen atom.

Table 3 Scope of amines[a,b]



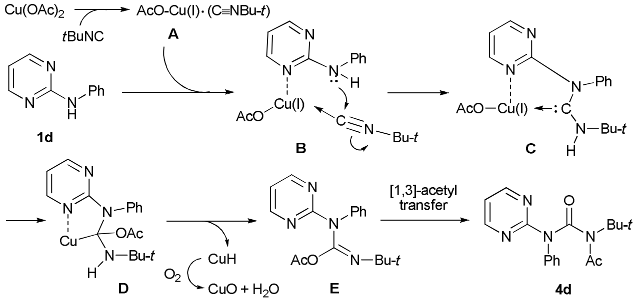
[a] Reaction conditions: amine (0.5 mmol), **2a** (3.0 equiv), $Cu(OAc)_2·H_2O$ (2.0 equiv), 110 °C, air, toluene (3.0 mL). [b] Isolated yield.

To define the possible intermediates and pathway, several control experiments were carried out as shown in Scheme 2. No corresponding urea product was observed when diphenylamine was used, and this result implied that incorporation of nitrogen atom into the substituent of poor nucleophilic amine is crucial for this transformation (Eq. 1). When the complex of **1d** and $Cu(OAc)_2·H_2O$ was treated with *tert*-butyl isocyanide, the reaction afforded only trace amount of the desired urea **4d** (Eq. 2). Evidently, the complexation effect of copper didn't take place in the initial step with substrate. However, when a Cu(II) acetate-isocyanide complex, generated from $Cu(OAc)_2·H_2O$ and *tert*-butyl isocyanide, was treated with **1d**, the urea product could be obtained in 89% yield under the standard conditions (Eq. 3), which is comparable with the result of one-step 90% yield (Table 2). Furthermore, the reaction of **1d** with synthesized acetate-isocyanide complex [AcOCu(I)•(C≡N-Bu-*t*)][19] could give urea **4d** in comparable yields under air or nitrogen atmosphere (Eq. 4). These results indicated that the Cu(I) complex might be the key intermediate during the reaction, and the incorporated nitrogen atom of the amine facilitated the subsequent insertion by coordination effect to the copper atom. The addition of TEMPO as a radical scavenger gave no significant effect in this reaction which evidenced that the radical mechanism through imidoyl radical could be ruled out.[20]



Scheme 2 Mechanistic studies.

Although the detailed reaction mechanism remained to be clarified, a plausible mechanism for this reaction was proposed on the basis of above results (Scheme 3). Initially, Cu(I) acetate-isocyanide complex **A** was formed possibly by disproportionation of Cu(II)[21] or through reduction of Cu(II) reagents by isocyanide.[3,7b] One of the nitrogen atoms of the substrate coordinated to the copper atom in complex **A** and formed intermediate **B**, which facilitated the attack of secondary amine on the isocyanide carbon atom to give rise to the diaminocarbene intermediate **C**.[22] Subsequent insertion reaction and reductive elimination of CuH process led to intermediate **E**,[23] which then afforded the urea product **4d** through a thermolytically induced 1,3-O→N acyl transfer.[24]



Scheme 3 Plausible mechanism.

In conclusion, we have successfully revealed the first copper-mediated multicomponent reaction through sequential isocyanide insertion into N–H bond of less active secondary arylamines, reductive elimination of CuH, and [1,3]-acyl transfer processes. This approach features a new mode of insertion for isocyanides and provides an efficient access to unsymmetrical tetrasubstituted ureas with operational simplicity and wide substrate scope. Further insight into the mechanism, reaction scope and the synthetic applications are under investigation.

We thank the National Natural Science Foundation of China (No. 21272149) and Innovation Program of Shanghai Municipal Education Commission (No. 14ZZ094) for financial support and Prof. Hongmei Deng (Laboratory for Microstructures, SHU) for spectra help.

Notes and references

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† Electronic Supplementary Information (ESI) available: General experimental procedures, characterization data and copies of the ^{1}H and ^{13}C NMR spectra for all compounds. See DOI: 10.1039/b000000x/

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