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Chemoselective isocyanide insertion into N-H bond using iodine-DMSO: A metal-free access to substituted ureas

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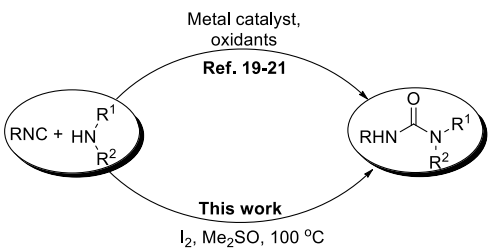
Insertion of isocyanide into N-H bond gives entry to many medicinally important and structurally diverse complex nitrogen-containing heterocycles. Although the transition metal catalyzed isocyanide insertion to N-H bond is very common, polymerization of isocyanide in the presence of a transition metal and its strong coordination with metals are the common drawbacks. On the other hand, inertness of most of the isocyanides towards amines in the absence of a metal catalyst has stymied the growth of the metal-free approach for isocyanide insertion into amine. As a result, only a handful of metal catalysed methods with limited substrate scope are reported for synthesis of ureas *via* isocyanide insertion into amine and no metal-free version is reported yet. Interestingly, no report on chemoselective isocyanide insertion into amine is reported in the literature. We have employed I_2-DMSO reagent system for chemoselective synthesis of ureas, where the isocyanides react with aliphatic amines only while the aromatic amines need a nucleophilic activator (DABCO) to facilitate the formation of ureas. This method gave direct and chemoselective entry to the ureas by evading the commonly used yet toxic isocyanates.

The chemistry of the isocyanides is profoundly different from the rest of organic chemistry because of both divalent and tetravalent nature of carbon of the isocyanide group that can exist as electrophilic carbene and nucleophilic zwitterion. Ever since the synthetic applications of this dual philicity of isocyanide in the Passerini and Ugi reactions, isocyanides have been proven as a versatile C1 building block for synthesis of numerous biologically relevant heterocycles *via* C−C, C−N, and C−O bond formation reactions. Specially the application of isocyanide insertion to amine has taken unprecedented stride for the synthesis of huge libraries of heterocycles having tremendous structural and medicinal significance. Yet, most of the reported achievements mainly focus on the metal catalyzed insertion of isocyanides into amines for the synthesis of nitrogen-containing compounds.

Although most of the synthesis involving isocyanide insertion into amines are catalyzed by electrophilic metal catalysts to activate the weakly nucleophilic isocyanides, the use of isocyanide is handicapped by polymerization in the presence of a transition metal,[1] and strong coordination with metals leading to reduction of catalytic activity. Its metal-free version also experiences significant challenges due to the inertness of amines towards isocyanides, except those activated by electron-withdrawing groups.[2] Only recently, a couple of methods have been reported for metal-free isocyanides insertion into amines; (i) synthesis of perfluoroalkyl substituted amidines *via* somophilic isocyanide insertion using triethylamine at 100 °C[3] and (ii) I_2/CHP catalyzed carbodiimide synthesis.[4]

The interest on ureas has recently been tremendously reinvigorated due to their applications in the field of stereoselective organocatalysis,[5] supramolecular chemistry,[6] and drug discovery. The presence of urea scaffold in various natural products,[7] agrochemicals[8] and pharmaceuticals that work as antimalarial,[9] HIV protease inhibitors,[10] p38-MAP kinase inhibitors,[11] raf kinase inhibitor,[12] antitumor,[13] antinociceptive,[14] antiglycation,[15] CCK-B receptor antagonists,[16] endothelin antagonists,[17] acyl-CoA cholesterol acyltransferase (ACAT) inhibiting activity,[18] L-8 Receptor antagonsts,[19] neuropeptide Y Y5 receptor antagonists,[20] and glucokinase activators[21] have contributed enormously to the recent developments of new synthetic methodologies. Majority of the reported methods for the synthesis of urea proceed through isocyanate intermediate,[22] albeit other interesting methods have also been reported.[23] Some of these methods have not found desired applications due to their toxicity, poor stability, low yields, long reaction time, multi-step synthetic design, high cost and challenging reaction conditions. However, no method has addressed chemoselective synthesis of ureas starting from aliphatic and aromatic amines.



Scheme 1 Synthesis of urea *via* isocyanide insertion into N-H bond

Interestingly, the synthesis of ureas *via* isocyanide insertion into N-H bond is hardly explored. Only a few metal catalysts *viz.* bulk gold,[24] cobalt(II) acetylacetonate,[25] and $Cu(OAc)_2$[26] have recently been reported for the synthesis of ureas *via* insertion of isocyanide into N-H bond. But these methods are plagued by limited substrate scope,[24-26] formation of byproducts[24] and poor reactivity with amines.[24] Despite the limitations of metal catalyzed methods, a metal-free approach

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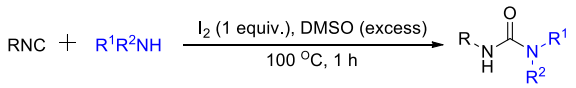
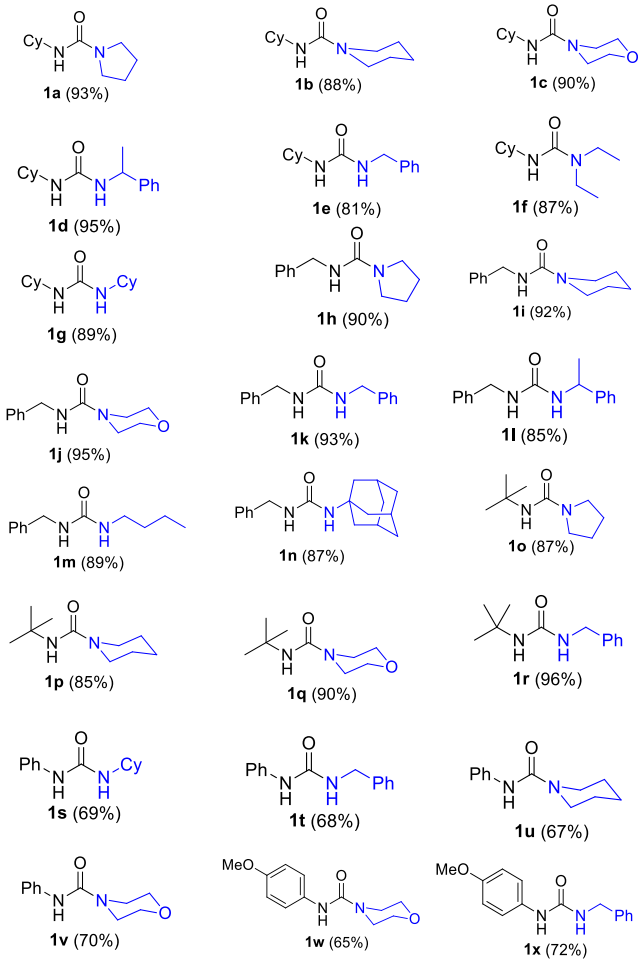
to synthesize ureas *via* isocyanide insertion into N-H bond has not been explored due to poor reactivity of isocyanide with amines in the absence of a metal catalyst (Scheme 1).

Table 1 Synthesis of symmetrical and unsymmetrical ureas from aliphatic amines[a,b]



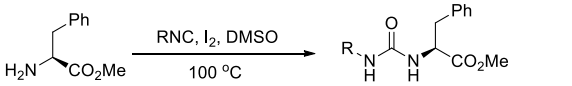


[a]Reactions are carried out at 1 mmol scale; [b]Isolated yields are reported.

Given its low cost, ready availability, ease of handling, nontoxic, and nonmetallic nature, the I_2-DMSO reagent system is finding interesting applications in organic synthesis because hydroiodic acid generated from iodine in the catalytic process is oxidised by DMSO to regenerate iodine.[27] In continuation of our interest on development of iodine mediated chemical transformations,[28] we envisioned that highly reversible nature of binding between isocyanide and iodine[29] in forming isocyanide diiodide adduct may be put into use for activation of weakly nucleophilic isocyanide group. The isocyanide diiodide can, in principle, facilitate double nucleophilic addition in the presence of an amine and DMSO to form urea *via* insertion of isocyanide into N-H bond. Our investigations led to a hitherto unknown chemoselective isocyanide insertion into amine that could exploit the difference of nucleophilicity between aliphatic and aromatic amines for chemoselective synthesis of urea derivatives.

As a starting point, we chose the reaction of cyclohexyl isocyanide with cyclohexylamine as the model reaction for the said synthesis. A series of model reactions were conducted in DMSO by varying the amount of the iodine and the temperature (Table 1S in the ESI). Although the reaction was complete with 20 mol% of the iodine within 20 h at 100 °C, the optimum conditions required 1 equiv. of iodine to complete the reaction within 1h at 100 °C. With the optimized conditions in place, a few alkyl isocyanides were reacted with various alkyl amines to study the scope of the reaction (Table 1). Our protocol gave both symmetrical and unsymmetrical ureas with consumate ease. There was practically no difference in yield of urea derivatives for the reaction of alkyl isocyanides with 1° and 2° amines. The electron rich aryl isocyanides (entries 2a-i), which are less prone to undergo insertion into N-H bond, also gave excellent yield of both di-and trisubstituted urea derivatives with 1° and 2° amines.

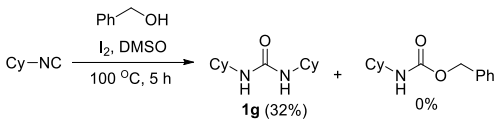
In order to see if this protocol can be applied for synthesis of chiral ureas, we carried out the reaction of phenylalanine methyl ester with benzyl isocyanide and also cyclohexyl isocyanide to achieve excellent yields (Scheme 2). Chiral HPLC analyses revealed complete retention of configuration without any racemization. At the same time, the methyl ester functionality was found to be compatible to our reaction conditions.



2a: R = $PhCH_2$-, 90% (99%ee)
2b: = Cyclohexyl, 93% (99%ee)

Scheme 2 Synthesis of chiral ureas

The scope of our method was tested for the synthesis of carbamates. Surprisingly, when the reaction of cyclohexyl isocyanide with benzyl alcohol was carried out under similar reaction conditions (Scheme 3), the formation a symmetrical urea was detected instead of the desired carbamate product. In the absence of amine, CyNC might have formed isocyanate in the absence of an amine[30] which subsequently formed dicyclohexylurea via moisture-curing process for isocyanates, presumably involving adventitious water.[31]



Scheme 3 Reaction of isocyanide with alcohol

Interestingly, the cyclohexyl isocyanide did not react with aniline also under our reaction conditions, instead *N,N'*-dicyclohexyl urea was formed (Scheme 4[a]). This observation suggests that the electrophilicity of cyclohexyl isocyanide diiodide might not be enough to react with aromatic amines under our optimized reaction

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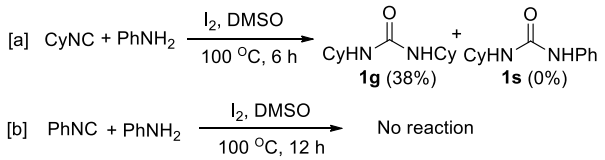
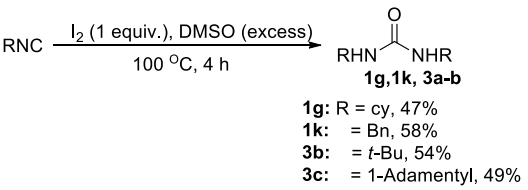
conditions. Notably, when yet less electrophilic phenyl isocyanide was treated with aniline under similar reaction conditions, the desired product did not form at all after prolong exposure (Scheme 4[b]). It might be due to poor philicity of both phenyl isocyanide diiodide and aniline under the given reaction conditions.



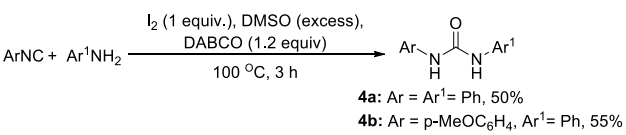
Scheme 4 Reaction of isocyanides with aniline

The fact that *N*,*N*′-dicyclohexylurea was formed rather than formation of the desired unsymmetrical olefin, we performed the reaction in the absence of aromatic amine to achieve complete conversion of the starting isocyanide with 47% isolated yield. Since, no literature report is available for synthesis of symmetrical ureas from isocyanide without employing amine, we explored the substrate scope for synthesis of symmetrical ureas directly from the alkyl isocyanides. Our findings on synthesis of symmetrical ureas from the reaction of alkyl isocyanide with iodine and DMSO at 100 °C are shown at Scheme 5. We propose that the reaction might follow the same mechanism (Scheme S1 in the ESI) as explained in case of Scheme 3.



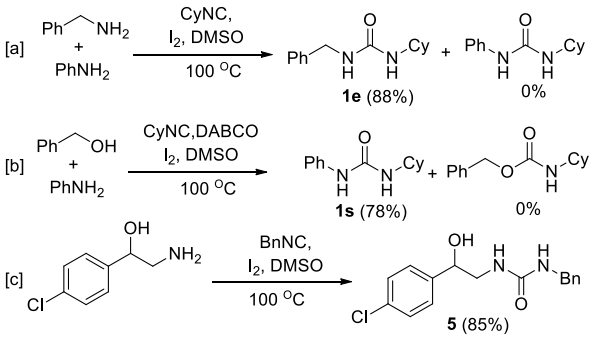
Scheme 5 Synthesis of symmetrical urea from isocyanide without using amine

Given the fact that isocyanide dichloride, despite being more electrophilic, reacts with aromatic amine only at very high temperature,[32] we assumed that the reaction between less electrophilic isocyanide diiodide and aromatic amine is not favorable. Therefore, we proposed to add a highly nucleophilic amine to activate the isocyanide diiodide. After screening various amines (Table 2S in the ESI), it was observed that addition of a one equivalent of DABCO facilitated the formation of diarylureas (Scheme 6).



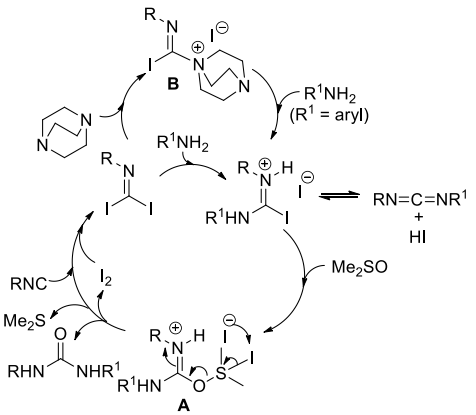
Scheme 6 Synthesis of symmetrical urea from isocyanide without using amine

Both intra- and intermolecular chemoselectivity were studied (Scheme 7). Reaction of cyclohexyl isocyanide (2 equiv.) with an equimolar mixture of benzylamine and aniline under the optimized conditions gave only *N*-Benzyl-*N*′-cyclohexylurea in 88% yield (Scheme 7[a]). The reaction of 2-(4-aminophenyl)ethylamine with cyclohexyl isocyanide (1 equiv.) led to formation of urea derivative with aliphatic amine and the protection of aromatic amine was not detected (Scheme 7[b]). The reaction of cyclohexyl isocyanide (2 equiv.) with 2-amino-1-phenylethanol under the optimized conditions gave the urea derivative in 85% yield leaving the hydroxy group unaffected (Scheme 7[c]).



Scheme 7 Reaction of isocyanides with aniline

The fact that the reaction of isocyanides under Johnson and Daughhetee[30] conditions takes 24 h to give very low yield of isocyanate, while the same reaction under our reaction conditions takes only 4 h with no trace of isocyanate, we propose that the reaction might follow altogether a different route (Scheme 6). Initially, upon treatment with I_2, isocyanides form its diiodide derivative. The diiodide derivative reacts with amine to form highly electrophilic hydroiodide salt of *N*,*N*′-disubstituted carbamimidic iodide which then react with DMSO to form the complex **A** that leads to generation of urea derivative along with dimethyl sulphide and iodine. The less nucleophilic aromatic amines might not have reacted with isocyanide diiodide under our reaction conditions. The addition of highly nucleophilic DABCO might have activated the isocyanide diiodide by forming a complex **B** which facilitated the reaction of aromatic amines to form similar hydroiodide derivative of *N*,*N*′-disubstituted carbamimidic iodide. The source of oxygen was confirmed by ^{18}O isotopic study, where it was observed that the reaction of benzyl isocyanide with benzyl amine in the presence of iodine and Me_2SO[18] under the optimized reaction conditions led to the formation of ^{18}O labelled *N*,*N*′-dibenzyl urea (m/z 243.1425 for M+H peak).



Scheme 9 Plausible mechanism

In conclusion, our method provides a concise entry to diverse array of symmetrical and unsymmetrical ureas *via* a simple metal-free process of isocyanide insertion into N-H bond. The method also represents a chemoselective isocyanide insertion to N-H bond. Additionally, a novel amine-free protocol for the synthesis of symmetrical dialkylureas is developed. Broad substrate scope, short reaction time and use of cheap reagents in our protocol provide an alternative to the existing methods for isocyanide insertion into N-H that have limited substrate scopes. It is worthwhile to speculate that activation of isocyanide with readily available iodine may open new vistas in organic synthesis involving double nucleophilic addition to isocyanide diiodide.

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Notes and references

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