Improved Synthesis of Unsymmetrical Ureas via Carbamates

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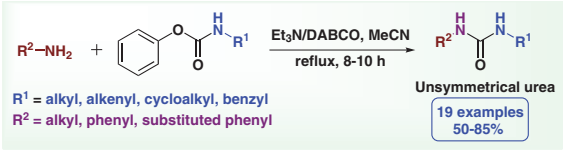

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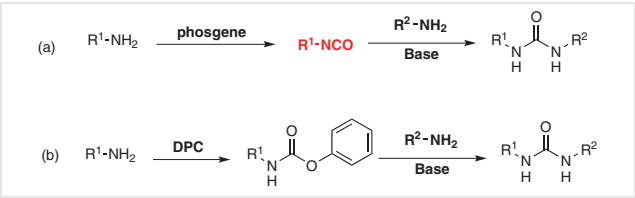
Abstract An efficient, cost-effective, easy and green method is reported for the preparation of *N*,*N*′-alkyl aryl ureas and *N*,*N*′-dialkylureas via carbamates. This improved procedure is devoid of any hazardous reagents such as phosgene and isocyanates, and shows broad substrate scope with good to excellent yields. As compared to previous reports, this procedure offers an operationally simple, potentially scalable, and, significantly, benign way to synthesize these important urea motifs.

Key words carbamates, ureas, unsymmetrical ureas, amine, scale-up, organic synthesis

Urea scaffolds are of high importance in fields such as pharmaceuticals, agrochemicals, material science, and organocatalysis, and they are required for many biologically active natural products.[1] *N*,*N*′-Alkyl aryl ureas and *N*,*N*′-dialkyl ureas with different alkyl groups either di-, tri-, or tetra-substituted, constitute very important classes of nitrogen-containing compounds that display a wide range of pharmacological and physiological activities.[2] Numerous methods have been developed for the preparation of urea motifs, and a large number of robust approaches have been reported.[3] Most of the conventional reported methods for the synthesis of urea and its surrogates[4] include use of metal catalyst,[5] phosgene,[6] isocyanates,[7] azides,[8] chloroformate,[9] or carbonyl imidazole derivatives,[10] or they are microwave-assisted[11] reactions. However, the above methods use highly toxic, hazardous and unstable substances, which are not suitable for scale-up operations. In addition to above methods, green approaches have recently been developed such as the use of transition-metal-catalyzed oxidative carbonylation of amines with CO,[12] or direct carbonylation of amines with CO_2.[13] These methods have found use in laboratory-scale applications, especially in medicinal chemistry. Our quest to develop green and scalable processes led us to explore the possibility of preparing *N*,*N*′-alkyl aryl ureas and *N*,*N*′-dialkyl ureas, i.e., unsymmetrical ureas, *via* carbamates through *in situ* generation of the isocyanates from the rearrangement of carbamates followed by reaction of the isocyanates with amines to generate ureas.

Typically, isocyanates have been used for the synthesis of ureas (Scheme 1). Isocyanates, in turn, are synthesized using phosgene and its surrogates such as diphosgene and triphosgene; other frequently used methods to generate isocyanates involve Curtius rearrangement,[14] Hoffmann rearrangement,[15] and Lossen rearrangement.[16] In this study, urea derivatives are synthesized from the reaction of amines with carbamates via isocyanates, which are generated from the carbamates *in situ*. Carbamates were synthesized by carbamoylation reaction of carbonates with amines. Although both alkyl[17,18] and aryl[19] carbonates have been utilized previously, alkyl carbonates showed restricted reactivity compared to aryl carbonates due to the formation of various side products.[20] The low reactivity of carbamates of alky carbonates with nucleophiles is related to the high pK_a values of the released alkyl alcohols compared to the low pK_a value of the aryl alcohols. Hence, compared to *O*-aryl carbamate, the alkyl counterparts do not react efficiently. This aspect makes aryl carbonates an attractive ecofriendly alternative for the synthesis of *O*-aryl carbamates, especially with aromatic amines.[16] A literature search also revealed that *N*-alkyl *O*-aryl carbamates have been synthesized from the reaction of aliphatic amines with chloroformates.[21] As many drugs such as cefoxitine, linezolide,

darunavir, brecanavir, irinotecan, ritonavir, and URB524 contain aliphatic *N*-side chains, the *N*-alkyl *O*-aryl carbamates are required for the synthesis of these molecules.[18]



Scheme 1 Unsymmetrical urea synthesis via (a) isocyanate and (b) carbamate

The low pK_a of aryl alcohol makes it a synthetic challenge to prepare *N*-alkyl-*O*-aryl carbamates from the reaction of aryl carbonates with primary amines. Urea is expected to be a by-product of these reactions. Because of the low cost of aryl carbonates such as diphenyl carbonate (DPC), our investigation started with the reaction of diphenyl carbonate with primary aliphatic amines to produce carbamates as key intermediates, which were then converted into unsymmetrical ureas (Scheme 2).

Our earlier study[19] with *n*-butylamine and diphenyl carbonate afforded phenyl butyl carbamate (**3c**, 78%) and optimized reaction conditions. Various aliphatic amines reacted with diphenyl carbonate in water/THF mixture (9:1) at room temperature to give *N*-alkyl-*O*-phenyl carbamates (Figure 1). A series of carbamates of alkyl amines were synthesized and employed in this study to synthesize unsymmetrical ureas. A patent application describing the initial results of the unsymmetrical urea synthesis has also been filed.[20]

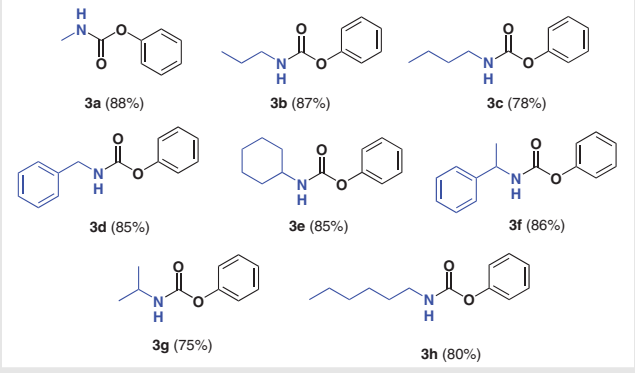
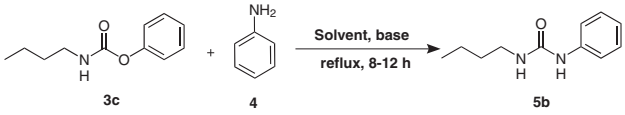


Figure 1 *N*-Substituted carbamates employed for the synthesis of unsymmetrical ureas

The carbamates listed in Figure 1 were further utilized to synthesize *N*,*N*′-alkyl aryl ureas and *N*,*N*′-dialkyl ureas. Our first experiments involved reaction of phenyl butyl carbamate with aniline under a range of reaction conditions (Table 1). No reaction was observed upon reflux in either acetonitrile or *N*,*N*-dimethylformamide (DMF) without a base (entries 1 and 2). Then, the use of inorganic and organic bases were investigated (entries 3–14). The use of inorganic base K_2CO_3 in acetonitrile gave 42% yield of the desired product, and the yield was further increased to 50% when NaOH, Cs_2CO_3, or LiOH were used.

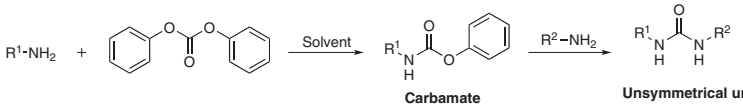
Table 1 Optimization of the Reaction Conditions for the Synthesis of *N*,*N*′-Alkyl Aryl Ureas



Entry	Reaction conditions[a]	Yield (%)[b]
1	MeCN, reflux, 12 h	nd
2	DMF, reflux, 12 h	nd
3	MeCN, K_2CO_3, reflux, 12 h	42
4	MeCN, NaOH, reflux, 12 h	45
5	MeCN, Cs_2CO_3, reflux, 12 h	50
6	MeCN, LiOH, reflux, 12 h	50
7	MeCN, Et_3N, reflux, 12 h	60
8	MeCN, pyridine, reflux, 12 h	62
9	MeCN, DMAP, reflux, 12 h	65
10	MeCN, Et_3N (1:2), reflux, 12 h	63
11	MeCN, Et_3N (1:4), reflux, 12 h	70
12	MeCN, Et_3N (1:6), reflux, 12 h	80
13	Et_3N, reflux, 12 h	75
14	MeCN, DABCO, reflux, 8–10 h	80

[a] Reaction conditions (1.0 mmol scale): **3c** (1.1 equiv), 4 (1.0 equiv), cerium(IV) ammonium nitrate (CAN; 3 mL), inorganic base (1.0 equiv).
[b] Isolated yield. nd = not detected.

In all of the above entries, the undesired product obtained was *N*,*N*-dibutyl urea arising from the reaction of *n*-butylamine – generated from the hydrolysis of the carbamate with the carbamate. Organic bases gave higher yields of the desired ureas, and finally the optimal yields were achieved when the reaction was carried out either in 1:4 or 1:6 v/v mixture of acetonitrile and triethylamine (entry 12)

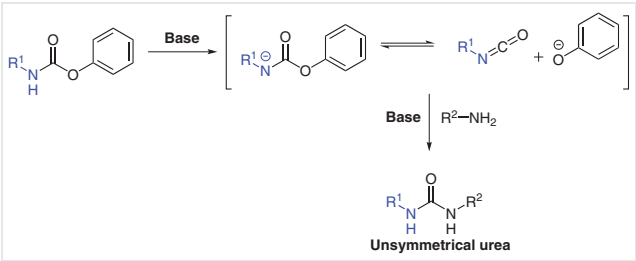


Scheme 2 New route to unsymmetrical urea derivatives via carbamate

at reflux for 12 hours. However, good yield was also achieved when triethylamine was used as a solvent, also at reflux (entry 13), and the inclusion of a tertiary amine base like 1,4-diazabicyclo[2.2.2]octane (DABCO) gave very good yield at reflux for 8–10 h (entry14).

Thereafter, the optimized reaction conditions were applied to synthesize other *N*,*N*′-alkyl aryl ureas and *N*,*N*′-dialkyl ureas. A total of eighteen ureas were prepared, as shown in Figure 2. Aromatic amines reacted with alkyl carbamates in Et_3N/DABCO, at reflux, to afford unsymmetrical ureas **5a–p**; in a similar manner, alkyl amine gave dialkyl ureas **5q–s** in good to excellent isolated yield. For dialky ureas, higher yields can be attributed to the high pK_a of the alkyl amines, and reactions also proceeded smoothly and cleanly. However, observed trends in the yields of *N*,*N*′-alkyl aryl ureas can be correlated to the nature of the substituents present on the aromatic rings of the amine. In the case of **5a–d**, which are aniline-based urea molecules, similar yields of ca. 70% were obtained. *p*-Halo substituted ureas **5e–i** were formed in slightly reduced yield (ca. 60% isolated yield), except for *p*-bromoaniline (**5e**, 78%). *m*-Nitroaniline urea **5j** was isolated in 55% yield, whereas ureas bearing substituents with an electron-donating inductive effect and or mesomeric effect such as **5k–n** gave higher yields of 75–80%. 2-Amino benzothiazole derived ureas gave lower yields of ca. 50–65%, as expected for amines of lower basicity compared to aniline. Although different bases and solvents were tried, and reactions conditions were also varied using different temperatures, the optimal yield was always obtained only when the reaction was carried out in triethylamine as solvent at reflux for up to 10 hours.

From a mechanistic viewpoint, as also reported in the literature,[18] the reactions of carbamates of secondary amines at elevated temperature proceed *via* formation of an isocyanate intermediate. Base is required to extract hydrogen from the carbamate to generate the isocyanate intermediate, which is then rapidly trapped by an amine molecule to produce the desired unsymmetrical urea (Scheme 3).



Scheme 3 Possible mechanism of unsymmetrical urea formation via isocyanate generation *in situ*

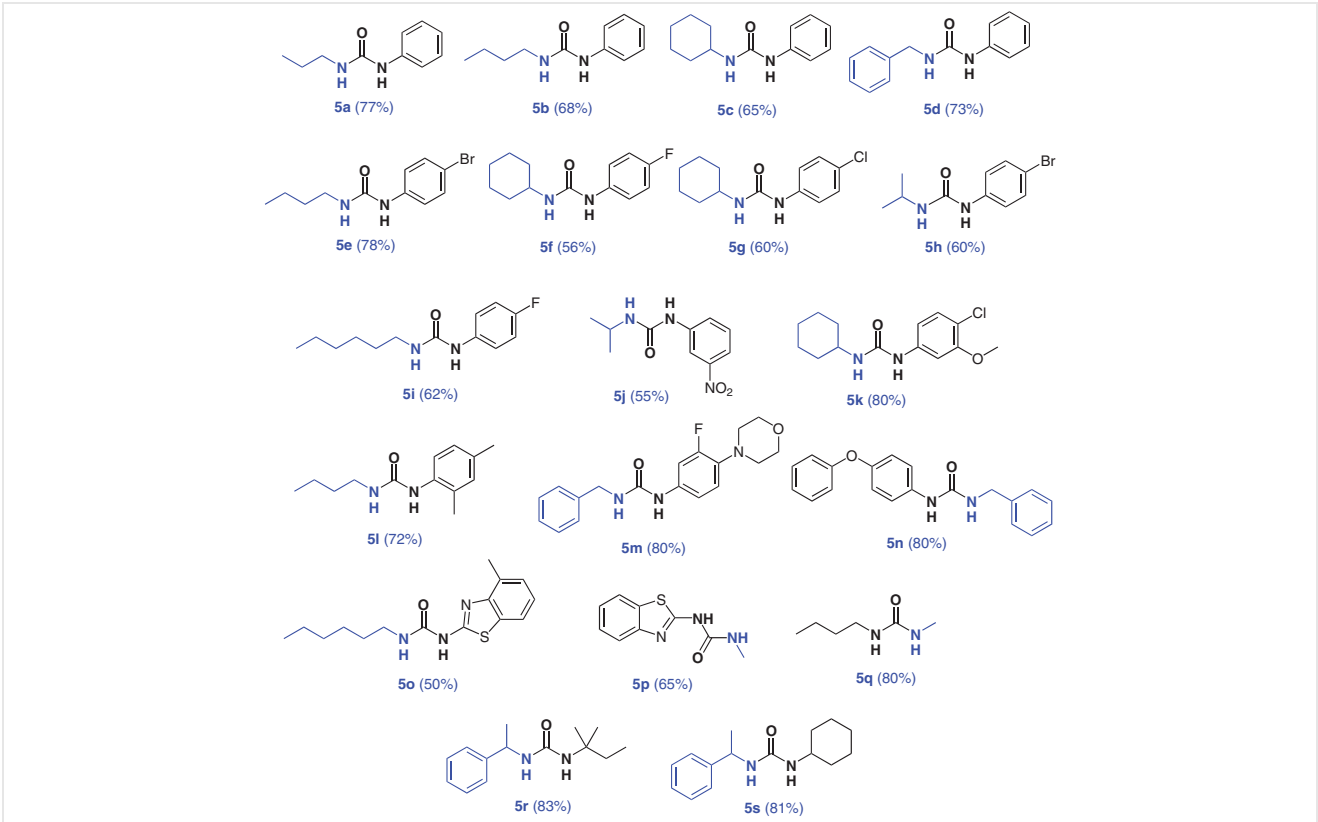


Figure 2 Synthesis of unsymmetrical ureas via *N*-alkyl-*O*-phenyl carbamates

In conclusion, an efficient, cost-effective, easy, and green method has been developed for the preparation of *N*,*N*′-alkyl aryl ureas and *N*,*N*′-dialkyl ureas without any use of hazardous, unstable, irritant, toxic, or moisture-sensitive reagents such as phosgene, isocyanates, or chloroformates. This efficient procedure has broad substrate scope, and consistently affords *N*,*N*′-alkyl aryl ureas and *N*,*N*′-dialkyl ureas in good to excellent yields. In addition, the procedure is operationally simple, potentially scalable, and, significantly, benign as compared to current methodologies available for the synthesis of these important motifs.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2157-5925.

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