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Effective approach to ureas through organocatalyzed one-pot process

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ABSTRACT

An efficient approach to N, N′-unsymmetrically substituted ureas **9** has been developed through the ammonolysis process of *N*-Boc protected anilines **7** with amines prompted by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD). Moreover, a convenient protocol for the synthesis of the symmetric N, N'-substituted ureas **12** by one-pot diammonolysis process of Boc_2O with amines catalyzed by DABCO has also been achieved. With broad substrate scope and mild conditions, these two methods demonstrate practical preparation of both unsymmetrical and symmetrical ureas.

Introduction

The discovery of convenient methods for the formation of carbon-nitrogen bond has always been a focused area in synthetic organic chemistry, due to wide application in both natural product synthesis and industrial research and production.[1] As a prime instance, efficient methods toward preparation of urea and its analogous are very important in synthetic and medicinal chemistry, because these chemical subunits serve as substructures for numerous pharmaceuticals,[2] agrochemicals,[3] as well as materials science.[4] For example, the urea units are present in PI3K inhibitors (BEZ235, PKI-587)[5], VEGFR inhibitors (Sorafenib, ABT-869, Lenvatinib, PD173074),[6] TRPV antagonists (SB705498),[7] and p38-MAP kinase inhibitors (BIBR796)[8] (Fig. 1). Moreover, urea-containing scaffolds are frequently used in the design of bifunctional organocatalysts.[9] Accordingly, tremendous efforts have been devoted to developing methods for the construction of urea motifs, and a number of powerful approaches have been reported.[10–16,18] However, most of the traditional methods for the preparation of urea or its derivatives involve the use of phosgene,[10] metal-catalysts,[11] isocyanate,[12] azide,[13] carbonyl imidazole derivatives[14] and microwave-accelerated conditions,[15] which are highly toxic, unstable, or challenging for large scale application. To pursue green processes, several methods through transition metal-catalyzed oxidative carbonylation of amines with CO[16] or direct carbonylation of amine by CO_2[17] are developed in recent years. However, the use of high pressure of CO/CO_2 gas still limits lab-scale application in medicinal chemistry.

With continuous focus in exploring practical synthetic methods for the synthesis of natural products and compounds with medicinal interests,[18] we decided to develop a convenient method for the construction of urea scaffolds. The most straightforward urea synthesis uses activated carbamates as the starting materials or key intermediates. For example, very recently, Me_3SiCl, SiI_2H_2 or Tf_2O/Base were reported to activate the Boc-protected amines[19] (Fig. 2. Eq. 1). Starting from unprotected amines, urea formation can also be achieved with the promotion of 4-dimethylaminopyridine (DMAP) in the presence of Boc anhydride[20] (Fig. 2. Eq. 2). Herein, we present efficient approach to obtain ureas with catalytic amount of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (Fig. 2. Eq. 3) or 1,4-Diazabicyclo[2.2.2]octane;triethylenediamine (DABCO) (Fig. 2. Eq. 4).

Results and discussion

As shown in Table 1, the reaction of Boc-protected 3-bromoaniline (**7a**) with benzylamine was used as the template for our investigation. Firstly, at room temperature, in DCM or acetonitrile as the solvent, only trace amount (≤5%) of urea product **9a** was observed with 10% TBD, while no reaction can be detected with catalytic

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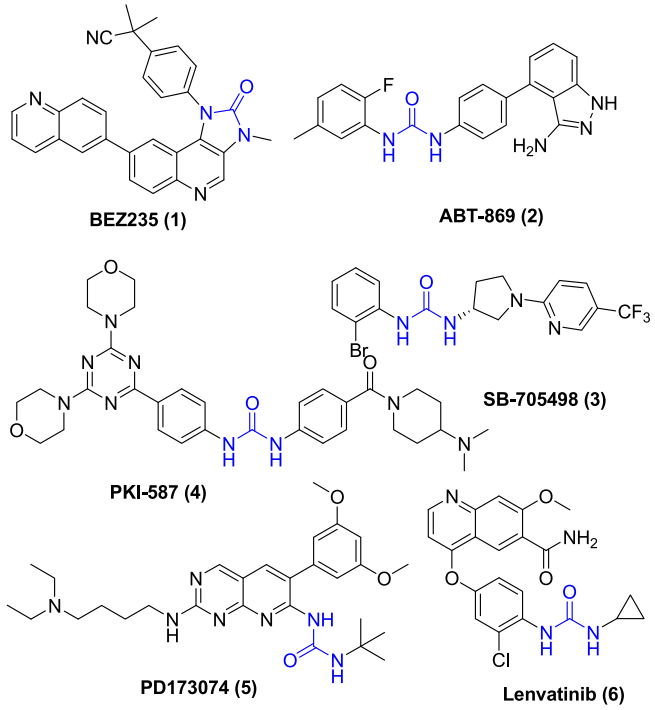


Fig. 1. Examples of bioactive molecules containing urea units.

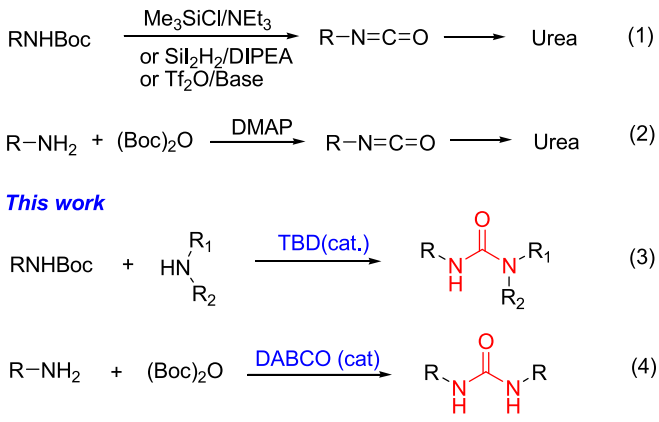
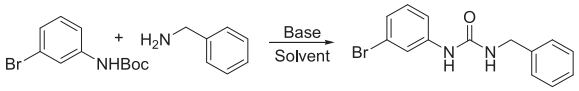


Fig. 2. Our strategy to urea derivatives.

amount of DMAP or DABCO (Table 1, entries 1–4). When the reaction mixture was heated at 60 °C, the desired **9a** was obtained in 65% yield (Table 1, entry 5). The reaction was not satisfactory in NaH/THF condition (Table 1, entry 6). To further investigate this reaction, different temperatures and amounts of TBD were screened, and the results indicated that the optimal reaction temperature is 83 °C, and the amount of TBD slightly affected the yield of **9a** (Table 1 entries 7–9).

Next, we turned our attention to investigate the substrates scope of this direct approach to urea from Boc-protected amine **7** with different amines **8**. As shown in Table 2, when substituted benzylamines **8a-e** were examined under the above optimal conditions, the desired products were generated in excellent yields (Table 2, entries 2–5). Reaction also proceeded smoothly with simple alkyl amines **8f-h** to give urea **9f-h** with high yields (Table 2, entries 6–7). It is noteworthy to mention that even amines with sterically bulky substituents such as adamantane **8i** also afforded desired products in reasonable yield (51% for 9i) (Table 2, entry

Table 1
Optimization of the reaction conditions.[a]



Entry	Base (equiv)	Solvent	Temp (°C)	Y% (**9a**)
1	DMAP (0.1)	DCM	rt	0[c]
2	DABCO (0.1)	DCM	rt	0[c]
3	TBD (0.1)	DCM	rt	<5[c]
4	TBD (0.1)	MeCN	rt	5[c]
5	TBD (0.1)	MeCN	60	65[b]
6	NaH (0.1)	THF	60	<5[c]
7	TBD (0.1)	MeCN	83	86[b]
8	TBD (0.05)	MeCN	83	78[b]
9	TBD (0.1)	MeCN	100	84[b]

[a] The reactions were performed with **7a** (1.0 mmol), benzylamine (2.0 mmol), base in solvent (5 mL) under nitrogen atmosphere and the solution was refluxed for 16 h.
[b] Isolated yield.
[c] Checked by LC–MS.

9). Various substituted Boc-protected anilines **7** were also examined and the results were summarized in Table 2 entries 10–13. Electronically different substitutions on the aromatics rings (7**j-l**) can be tolerated. No reaction can be observed when the NH on the Boc-protected amine is masked (Table 2, entry 13).

To test if this method can apply to secondary amine for urea formation, we investigated the reaction of Boc-protected amine **7a** with pyrrolidine. The result showed that the desired urea **10** was smoothly produced in high yield (97%).

Encouraged by above results (Table 2), we decided to investigate symmetric urea formation through one-pot process using amine **11a** (Table 3). Recent years, Knölker and co-workers observed that isocyannates reacted with primary amines under $(Boc)_2O$/DMAP conditions could smoothly produce ureas.[6] With this goal in mind, 3-bromoaniline was firstly treated by di-tert-butyl pyrocarbonate and only little N-Boc-protected 3-bromoaniline **7a** was obtained (Table 3, entry 1). To our surprise, when triethylamine (TEA) was added, the urea **12a** was obtained in 90% yield (Table 1 entry 2). When the amount of Boc_2O was reduced, the yield of 12a was declined (Table 3, entries 3). To obtain the optimal condition, a variety of bases were screened. The results indicated that the triethylenediamine (DABCO) was the best choice for the one-pot formation of urea (Table 3, entries 4–10). Almost quantitatively yield of **12a** can be obtained with 0.01–0.1 equivalent of DABCO and 0.5 equivalent of Boc_2O (Table 3, entries 10–12). It is noteworthy to mention that even in the solvent of water urea also was obtained as major product (Table 3, entry 13). Corresponding isocyanate was obtained by addition of H_2SO_4 at -30 °C (Table 3, entry 14).

Next, we turned our attention to investigate the substrate scope for this one-pot urea formation. As shown in Table 4, a variety of amines were examined under the above optimal conditions (Table 3, entry 10). When substituted aromatic amines were used, the corresponding ureas were obtained in excellent yields (Table 4, entries 1–14). The condition can be applied to substituted benzylamines, with desired ureas produced in moderate yields (Table 4, entries 15–16). When tert-butylamine was used, the yield of **12q** was generated in 86% yield (Table 4, entry 17). However, the phenethylamine only gave product **12r** in 56% yield (Table 4, entry 18). Notably, when sterically hindered amines were employed, the desired ureas were also produced in excellent yields (Table 4, entries 19–20). In addition, heterocyclic substrates, such as 8-aminoquinoline (Table 4, entry 21), were tolerated as well, demon-