Novel Direct Synthesis of Asymmetrical Urea Compounds from Trichloroethyl Carbamates Using Catalytic DBU

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Urea is one of the most common structures present in biologically active compounds,[1,2] and a variety of pharmaceuticals including enzyme inhibitors, anticancer agents, and antimycobacterial agents contain the urea structure.[3–6] In addition, urea units are commonly used to synthesize a number of useful organic compounds including molecular gels and chemical sensors due to their rigidity and polarity.[7–12] Several synthetic protocols have been developed for the production of urea-containing structures.[13,14] Among existing protocols, reactions of amines with isocyanate generated from phosgene or with carbamoyl chloride remain prevelent.[15] However, the instability of carbamoyl chloride intermediates and the toxicity of phosgene remain significant drawbacks of these methods.

Amines are commonly used during chemical synthesis in the form of carbamate-protecting groups. Two separate steps are generally employed to synthesize urea from carbamate-protected amines, namely, deprotection of the amine group and generation of a new urea via treatment with other amines. In this way, direct preparation of urea structures from carbamate-protected amines is an attractive method that can reduce costs, time, and waste. Among the many different types of amine protecting groups, 2,2,2-trichloroethyl carbamate (Troc-carbamate) is prevalent.[16,17] Generally, primary or secondary amines are easily protected via reaction with 2,2,2-chloroethyl chloroformate to generate Troc-carbamates (Troc-protected amines). However, transformation of Troc-caramate to asymmetrical ureas has not been studied in great detail due to the weakly active nature of Troc-protected amines.[18]

The development of practical reagents for the direct conversion of Troc-protected amines to urea remains a challenge. In particular, organocatalysts are considered an attractive method for synthesizing asymmetrical urea compounds.[19,20] We are currently interested in identifying catalytic amounts of organic base reagents to treat Troc-protected amines to directly synthesize target asymmetrical urea compounds in high yield. Indeed, a direct synthetic protocol of urea compounds from Troc-protected amines using an organic catalyst has not yet been reported. Herein, we are pleased to present our organic catalytic reagent-mediated method for preparing asymmetrical urea molecules from Troc-protected molecules.

Troc-protected aniline was used to optimize the amounts of organic catalysts needed for preparing asymmetrical urea from Troc-protected amines. First, reactions with Troc-protected amine **1a** were screened with a series of commercially available organic catalysts containing one or two nitrogen atoms, namely, pyridine, N,N-Diisopropylethylamine (DIPEA), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo [4.3.0]non-5-ene (DBN), 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), and 4-dimethylaminopyridine (DMAP) (Figure 1).

Reactions were carried out using 1 equiv of Troc-protected aniline, 1.4 equiv of benzylamine, and 0.5 equiv of organic catalysts. After performing the reaction for 4 h, the effect of each reagent on the synthetic yield of the desired urea was investigated. Likewise, the structures and purity of the resulting urea compounds were determined by ^{1}H and ^{13}C NMR spectroscopy and HRMS. Our initial screening results indicated that the catalytic activities of the organic catalysts varied significantly according their structures, as shown in Table 1. The catalytic activities of pyridine, DIPEA, DABCO, and DMAP were considered moderate and low, respectively, while both DBN and DBU had high activity over a reaction time of 4 h. Based on the above results, we further investigated the use of DBN and DBU at lower catalytic amounts (0.2 equiv and 0.05 equiv). Reactions performed using 0.2 equiv of DBN or DBU as the catalyst resulted in synthetic yields of the target urea of 65% and 83%, respectively, while use of 0.05 equiv of DBN or DBU had corresponding synthetic yields of less than 28% and 41% after a reaction time of 10 h, respectively (Table 1, entries 5, 6, 8, and 9). Together, these results suggested that the loading amount of DBN and DBU influenced the yield of the corresponding urea compounds. Based on the

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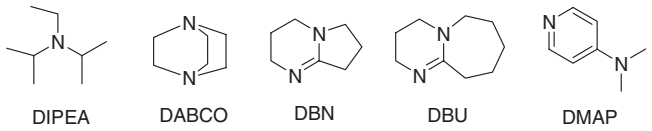


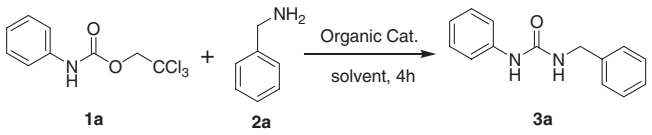
Figure 1. Structure of organic reagents used for screening.

conversion yield, a catalytic amount of DBU of 0.2 equiv (20 mol%) was selected for further optimization of the urea preparation protocol, although it should be noted that reactions containing 0.5 equiv of DBU resulted in a sufficient yield of the desired product.

We next examined the effect of temperature on conversion yield at room temperature and 80°C. We found that reaction temperature affected the yield of the corresponding ureas. Although there was no reactivity at room temperature and no desired product was obtained from a reaction at room temperature, reaction yield increased with increasing reaction temperature: reactions carried out at 80°C resulted in a higher yield (83%) than reactions at 30°C (2%), 40°C (4%), and 60°C (32%) (Table 1, entries 9, 11–14).

Reaction conditions were next optimized by investigating different types of solvents. Reactions performed in 1,4-dioxane and THF resulted in a low yield of urea, while reactions performed in toluene and MeCN were more effective for synthesizing the desired product (74% and 83%, respectively, Table 1 entries 9 and 17). Based on these data, reaction conditions consisting of 20 mol % DBU, MeCN, and 80°C were chosen for subsequent studies.

Table 1. Screening of reaction conditions for preparing urea structures.[a]



1a 2a 3a

Entry	Catalyst (equiv)	Solvent	Temperature (°C)	Yield[b] (%)
1	Pyridine (0.5)	MeCN	80	NR[c]
2	DIPEA (0.5)	MeCN	80	7
3	DABCO (0.5)	MeCN	80	11
4	DMAP (0.5)	MeCN	80	NR[c]
5[d]	DBN (0.05)	MeCN	80	28
6	DBN (0.2)	MeCN	80	65
7	DBN (0.5)	MeCN	80	71
8[d]	DBU (0.05)	MeCN	80	41
9	DBU (0.2)	MeCN	80	83
10	DBU (0.5)	MeCN	80	85
11	DBU (0.2)	MeCN	r.t.	NR[c]
12	DBU (0.2)	MeCN	30	2
13	DBU (0.2)	MeCN	40	4
14	DBU (0.2)	MeCN	60	32
15	DBU (0.2)	1,4-Dioxane	80	8
16	DBU (0.2)	THF	80	58
17	DBU (0.2)	Toluene	80	74

[a] Reaction conditions: Troc-carbamate (1.0 mmol), amine (1.4 mmol), DBU (0.2 mmol), MeCN, 4 h.
[b] Isolated yields after purification of flash column chromatography.
[c] No reaction.
[d] Reaction conducted for 10 h.

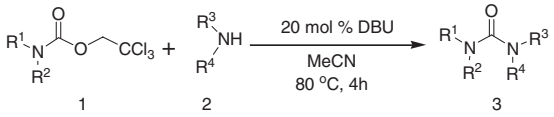
We next examined the scope of our novel catalytic protocol for preparing various ureas under the optimized experimental conditions (Table 2). First, aromatic compounds were used to assess the synthesis of asymmetrical ureas. Specifically, Troc-protected aniline was reacted with a variety of amines such as aromatic groups and aliphatic groups, affording the corresponding asymmetrical ureas (**3a**–**3f**) in high yield for 4 h. Reactions of Troc-protected aromatic amines bearing electron-donating and electron-withdrawing groups with different amines also produced the desired asymmetrical urea compounds in high yield.

We also investigated the scope of the synthetic protocol employing catalytic DBU by studying Troc-protected benzyl compounds. We found that the reaction method was useful for the direct synthesis of several corresponding ureas from Troc-protected benzyl compounds. Specifically, introduction of 20 mol % of DBU to reactions successfully generated benzylurea (**3g**–**3i**) in high yield, confirming that DBU is a useful catalytic agent for generating urea compounds from Troc-protected amines. We also extended the synthetic method to Troc-protected compounds prepared from secondary amines. Treatment of Troc-protected methylaniline compound **2a** with several amines in the presence of DBU indicated that the method was efficient for direct synthesis of the desired asymmetrical trisubstituted urea in high yield for 4 h. For instance, the trisubstituted ureas **3k** and **3l** were readily prepared in good yield from the same DBU-mediated method (83% for compound **3k** and 85% for compound **3l**).

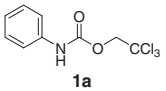
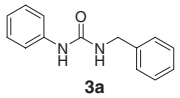
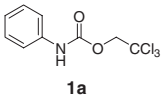
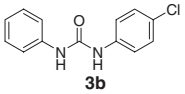
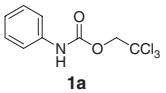
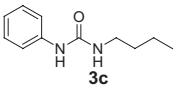
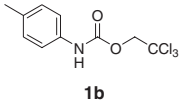
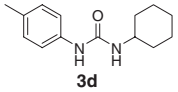
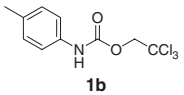
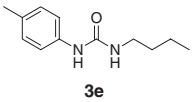
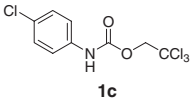
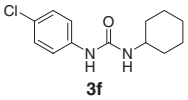
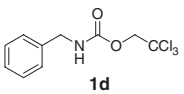
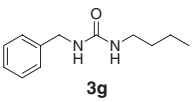
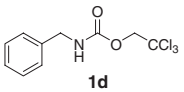
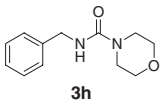
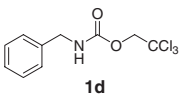
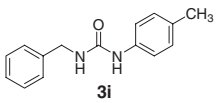
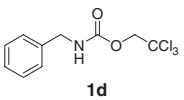
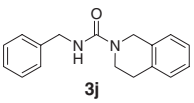
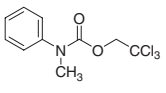
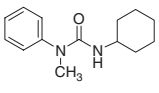
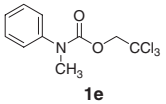
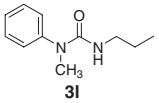
To the best of our knowledge, this is the first study to report on the directed preparation of trisubstituted ureas from Troc-protected compounds using catalytic amounts of DBU. Encouraged by our results thus far, the catalytic reagent system using DBU was next applied to additional reactions of Troc-protected hydroisoquinoline compound **1f** and Troc-protected dibenzyl amine **1g**, a more sterically hindered amine, to further expand the scope of preparation of Troc-protected compounds from secondary amines. Importantly, Troc-protected hydroisoquinolines were successfully converted into the corresponding trisubstituted ureas in high yield (73–85%) with the optimized catalytic protocol using DBU and various amines (Table 2, entries 15–17). In addition, the reactions of Troc-protected dibenzyl amines **1g** resulted in the target trisubstituted ureas **3q** and **3r** in yields of 81% and 72%, respectively (Table 2, entries 18 and 19).

Finally, we applied our catalytic method to generate bis-urea structures to establish the wide utility of the DBU organic catalyst. As shown in Scheme 1, treatment of 1 equiv of Troc-protected *m*-xylylenediamine **1h** with 2.8

Table 2. Scope of urea formation from amines.[a]

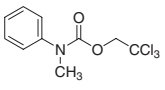
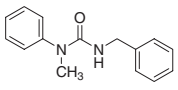
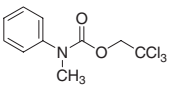
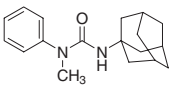
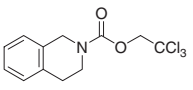
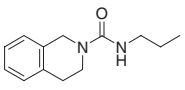
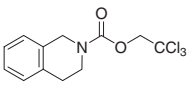
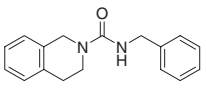
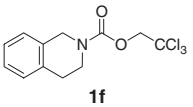
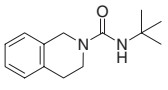
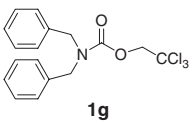
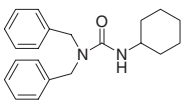
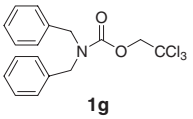
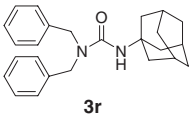
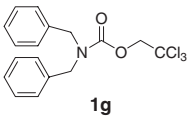


1 2 3

Entry	Troc-carbamate	Urea	Yield[c] (%)
1	 **1a**	 **3a**	83
2	 **1a**	 **3b**	84
3	 **1a**	 **3c**	85
4	 **1b**	 **3d**	87
5	 **1b**	 **3e**	86
6	 **1c**	 **3f**	81
7	 **1d**	 **3g**	84
8	 **1d**	 **3h**	77
9	 **1d**	 **3i**	85
10	 **1d**	 **3j**	77
11	 **1e**	 **3k**	83
12	 **1e**	 **3l**	85

(*continued overleaf*)

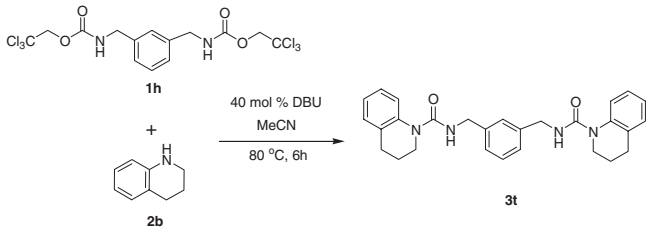
Table 2 (*continued*)

Entry	Troc-carbamate	Urea	Yield[c] (%)
13	 **1e**	 **3m**	83
14	 **1e**	 **3n**	75
15	 **1f**	 **3o**	84
16	 **1f**	 **3j**	85
17	 **1f**	 **3p**	73
18	 **1g**	 **3q**	81
19	 **1g**	 **3r**	72
20	 **1g**	**3s**	70[b]

[a] Reaction conditions: Troc-carbamate (1.0 mmol), amine (1.4 mmol), DBU (0.2 mmol), MeCN, 80°C for 4 h.
[b] Reaction conditions: Troc-carbamate (1.0 mmol), amine (1.4 mmol), DBU (0.2 mmol), MeCN, 80°C for 10 h.
[c] Isolated yields after purification of flash column chromatography.

equiv of 1,2,3,4-tetrahydroquinoline **2b** in the presence of DBU successfully afforded the desired bis-urea compound **3t** (67% yield).

In conclusion, we report here a novel method for the direct synthesis of asymmetrical urea compounds from Troc-protected amines. Reactions were carried out in the presence of catalytic amounts of DBU in MeCN for the synthesis of a variety of target urea structures. Furthermore, the use of DBU was successfully extended to the preparation of bis-urea compounds. Our results indicate that direct synthesis of asymmetrical substituted urea compounds from Troc-protected amines using a DBU catalyst is a practical method.



Scheme 1. Synthesis of a bis-urea compound.

Experimental

General Procedure for the Preparation of Urea Compounds (3a–3s). To a solution of Troc-protected aniline **1a** (0.26 g, 1.03 mmol) in MeCN (10 mL) benzylamine (0.15 g, 1.40 mmol) and DBU (0.03 g, 0.20 mmol) were added at room temperature and allowed to stir for 4 h at 80°C. The reaction mixture was cooled down to room temperature and extracted with CH_2Cl_2 (2 × 30 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was then purified by flash column chromatography on silica gel with hexane–EtOAc as eluent to afford the desired product **3a** (0.193 g, 83%).

General Procedure for the Preparation of Bis-Urea Compound (3t). To a solution of Troc-protected *m*-xylylenediamine **1h** (0.47 g, 1.03 mmol) in MeCN (10 mL) 1,2,3,4-tetrahydroquinoline **2b** (0.38 g, 2.85 mmol) and DBU (0.06 g, 0.40 mmol) were added at room temperature and allowed to stir for 6 h at 80°C. The reaction mixture was cooled down to room temperature and extracted with CH_2Cl_2 (2 × 30 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was then purified by flash column chromatography on silica gel with hexane–EtOAc as eluent to afford the desired product **3t** (0.312 g, 67%).

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Supporting Information. Additional supporting information is available in the online version of this article.

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