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Facile direct synthesis of unsymmetrical ureas from *N*-Alloc-, *N*-Cbz-, and *N*-Boc-protected amines using DABAL-Me_3

Soosung Kang [a, **], Hee-Kwon Kim [b, c, *]

[a] College of Pharmacy and Graduate School of Pharmaceutical Sciences, Ewha Womans University, Seoul, 03760, Republic of Korea
[b] Department of Nuclear Medicine, Molecular Imaging & Therapeutic Medicine Research Center, Chonbuk National University Medical School and Hospital, Jeonju, 54907, Republic of Korea
[c] Research Institute of Clinical Medicine of Chonbuk National University-Biomedical Research Institute of Chonbuk National University Hospital, Jeonju, 54907, Republic of Korea

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ABSTRACT

A practical synthetic method for the direct synthesis of unsymmetrically substituted ureas from *N*-Alloc-, *N*-Cbz-, and *N*-Boc-protected amines is described. In this study, efficient direct conversion of the Alloc-, Cbz-, and Boc-carbamate compounds to ureas was achieved in the presence of DABAL-Me_3, an air stable and easily handled reagent. Using this reaction method, both protected aromatic and aliphatic amines were successfully transformed into various trisubstituted and tetrasubstituted ureas with high yields without side product. Our findings offer promising guidelines for direct preparation of useful ureas from *N*-Alloc-, *N*-Cbz-, and *N*-Boc-carbamates.

1. Introduction

Urea is a structure frequently found in many natural products and biologically active compounds including antitumor agents,[1] antagonists of natural receptors,[2] anti-mycobacterial agents,[3] enzyme inhibitors,[4] inhibitors of HIV protease.[5] and plant growth regulators.[6] The urea has unique properties such as rigidity and polarity, and it can form hydrogen bonding when gels were formed from ureas or self-assemblies of urea oligomers were achieved. Thus, the synthetic method of urea has been utilized to prepare various useful organic materials. Particularly, preparation of a variety of molecular gels and self-assembling molecular capsules has been successfully achieved via reactions to produce urea structures.[7]

Several synthetic protocols for the synthesis of urea units have been reported.[8] A commonly used traditional method for the preparation of ureas involves reaction of isocyanate generated from the treatment of phosgene with the corresponding amines, or reaction of carbamoyl chlorides with the corresponding amines.[9] Even though these approaches have been widely employed, the syntheses of ureas should be carried out more carefully under safe environment due to toxicity related to phosgene and the instability of carbamoyl chloride intermediates. Alternatively, 1,1′-carbonyldiimidazole (CDI) and *p*-nitrophenyl carbamates have been used in the preparation of various urea units.[10] The synthesis of urea derivatives using CDI and *p*-nitrophenyl carbamates is often achieved in good yield.

Amines are a popular functional group in organic chemistry. In many multi-step syntheses, amines are used as a protected type by a carbamate protecting group to prevent the generation of unwanted side products during reactions. In particular, allylcarbamate (Alloc-carbamate), benzyl-carbamate (Cbz-carbamate), and Boc-carbamate are widely employed as protecting groups of amines in process chemistry and medicinal chemistry,[11] because Alloc-, Cbz-, and Boc-protected amines are readily prepared from primary or secondary amines using several methods, including treatment with allyl chloroformate or benzyl chloroformate.

* Corresponding author. Department of Nuclear Medicine, Molecular Imaging & Therapeutic Medicine Research Center, Chonbuk National University Medical School and Hospital, Jeonju, 54907, Republic of Korea.
** Corresponding author.
E-mail addresses: sskang@ewha.ac.kr (S. Kang), hkkim717@jbnu.ac.kr (H.-K. Kim).

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0040-4020/

However, in order to produce ureas from both protected amines, two separate reaction procedures are needed: removal of the protecting group of amines and generation of urea by the attack of another nucleophile amine. Thus, development of effective direct preparation of ureas from both protected amines is valuable challenge to multi-step organic chemistry. However, the direct conversion of Alloc-carbamate or Cbz-carbamate or Boc-carbamate to unsymmetrical ureas has not been extensively reported, because Alloc-, Cbz-, and Boc-protected amines are weakly activated. To the best of our knowledge, practical and simple direct synthesis of urea from Alloc-carbamate or Cbz-carbamate or Boc-carbamate using easily handled reagents has not yet been reported. Herein, we are pleased to describe a novel direct preparation method of various unsymmetrical ureas from Alloc-, Cbz-, and Boc-protected amines that is easily applicable to multi-step organic synthesis.

2. Results and discussion

Alloc-protected aniline was selected as the model substrate and *n*-butylamine was used as the nucleophilic amine in the initial study to find optimized conditions for the synthesis of unsymmetrical ureas from Alloc-protected amines. In the optimization study, the synthetic yield of the corresponding urea was evaluated after the reaction proceeded for 2 h.

We first attempted the reaction experiment with a series of commercial available and widely used reagents such as triethylamine, $NaHCO_3$, K_2CO_3, DMAP, and DBU, but product was either not observed or had a low yield (Table 1, entries 1–5). We next used Lewis acids, including $TiCl_4$, and $SnCl_4$, as a direct conversion reaction agent from Alloc-protected amines into unsymmetrical ureas, and obtained a slightly greater yield (Table 1, entries 6 and 7). It was discovered that bis(trimethylaluminum)-1,4-diazabicyclo [2.2.2]octane adduct (DABAL-Me_3) is an air stable, white solid that can be easily handled (see Fig. 1). In particular, DABAL-Me_3 has been used for several organic reactions such as the synthesis of amides and the asymmetric synthesis of chiral alcohols because reactions using DABAL-Me_3 do not require an inert reaction environment such as N_2 gas.[12] In this study, DABAL-Me_3 was employed for the direct urea formation reaction, and the target urea was synthesized with a significantly higher yield (95%), indicating that DABAL-Me_3 is effective for direct urea synthesis from Alloc-protected amines (Table 1, entry 8).

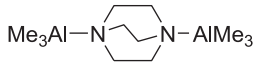


Fig. 1. Bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct.

Next, several solvents were examined to further optimized reaction conditions. Reactions in THF and 1,4-dioxane resulted in low yield synthesis of urea. When CH_3CN was used as a reaction solvent, the synthetic yield of urea was enhanced to 44%, but was still unsatisfactory. However, when toluene was employed in the reaction, the yield of target urea increased significantly (95%), indicating that toluene was the most effective solvent for direct urea formation from Alloc-protected amines.

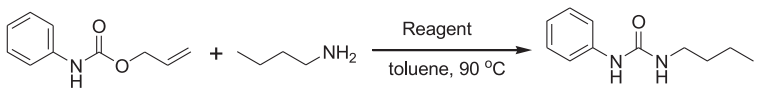
The effect of temperature on the reaction was also investigated, and elevated reaction temperature increased the yield of the desired urea (95% for reaction at 90 °C, and 95% for reaction at 105 °C; Table 2). We chose a reaction temperature of 90 °C for the next study of urea synthesis because 90 °C was lower than 105 °C with the same transformation yield.

In additions, we investigated the use of DABAL-Me_3 in a series of amounts, including 0.5 equiv, 1.2 equiv, 2.0 equiv, and 3.0 equiv in toluene. The results suggested that the synthetic yield was influenced by the amount of DABAL-Me_3. When 0.5 equiv. of DABAL-Me_3 was used, we obtained a 45% yield of the desired urea. Addition of an enhanced amount of DABAL-Me_3 into the reaction resulted in an increase yield of the conversion to corresponding urea. However, levels greater than 1.2 equiv. of DABAL-Me_3 did not increase synthetic yield any further during urea formation.

Thus, based on our primary optimization results, the reaction conditions of 1.2 equiv. of DABAL-Me_3, toluene, and 90 °C were chosen for the next studies. The structure and purity of the prepared urea compounds were confirmed by analysis with HRMS and ^1H and ^{13}C NMR spectroscopy.

With the optimized reaction conditions in hand, we examined the scope of this procedure for the direct synthesis of ureas (Table 3). First, reactions of Alloc-protected anilines, an aromatic compound, were investigated for the direct synthesis of unsymmetrical ureas. Reactions of Alloc-protected aniline with different amines in the presence of DABAL-Me_3 produced the corresponding unsymmetrical ureas (**3a-3c**) at high yield (Table 3, entries 1–3). In particular, the reactions of Alloc-protected aniline with secondary

Table 1
Screening of reaction conditions for the preparation of urea structure[a].



1a 2a 3a

Entry	Reagent	Time	Temp.	Yield[b] (%)
1	triethylamine	2 h	90 °C	NR
2	$NaHCO_3$	2 h	90 °C	NR
3	K_2CO_3	2 h	90 °C	4
4	DMAP	2 h	90 °C	NR
5	DBU	2 h	90 °C	NR
6	$TiCl_4$	2 h	90 °C	5
7	$SnCl_4$	2 h	90 °C	8
8	DABAL-Me_3	2 h	90 °C	95
9	None	2 h	90 °C	NR

[a] Reaction conditions: 1**a** Alloc-protected amine (1.0 mmol), amine (1.2 mmol), reagent (1.2 mmol), toluene (5 mL), 2 h.
[b] Isolated yield after column purification.

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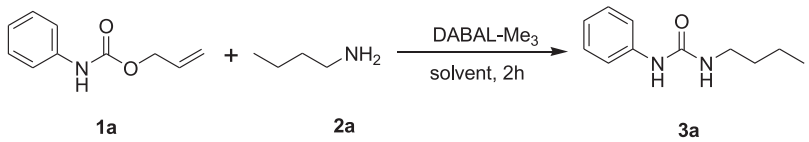
Table 2
Screening of reaction conditions for the preparation of urea structures[a].



1a 2a 3a

Entry	DABAL-Me_3 (equiv)	Solvent	Temp.	Yield[b] (%)
1	1.2	THF	reflux	32
2	1.2	1,4-dioxane	90 °C	24
3	1.2	CH_3CN	reflux	44
4	1.2	toluene	90 °C	95
5	1.2	toluene	40 °C	12
6	1.2	toluene	65 °C	41
7	1.2	toluene	105 °C	95
8	0.5	toluene	90 °C	45
9	2.0	toluene	90 °C	95
10	3.0	toluene	90 °C	96

[a] Reaction conditions: 1**a** Alloc-protected amine (1.0 mmol), amine (1.2 mmol), DABAL-Me_3 (1.2 mmol), solvent (5 mL), 2 h.
[b] Isolated yield after column purification.

amines **2c** generated the desired trisubstituted urea **3c** with 90% yield (Table 3, entry 3).

In addition, Alloc-protected benzyl amine was employed to extend the scope of this protocol, and the reaction method using DABAL-Me_3 was proven useful for the preparation of unsymmetrical benzylureas (Table 3, entries 4–10). In particular, the treatment of Alloc-protected benzyl amine with different aromatic amines containing electron-donating (methyl, methoxy, and piperonyl) and electron-withdrawing (chloro, nitro, and cyano) groups under the same reaction conditions provided unsymmetrical ureas at high yield (Table 3, entries 5–10). These findings clearly demonstrate that DABAL-Me_3 was an efficient conversion reagent to turn Alloc-protected amines into unsymmetrical ureas during the reaction process.

Next, the scope of our method using DABAL-Me_3 was extended to prepare trisubstituted and tetrasubstituted ureas from Alloc-protected compounds prepared from secondary amines. The reaction of various amines with Alloc-protected methylaniline **1c** and piperidine **1d** in the presence of DABAL-Me_3 readily yielded the desired unsymmetrical trisubstituted ureas with yields ranging from 82 to 96% in 2 h (Table 3, entries 11–16). In particularly, the reaction protocol using secondary amines such as Alloc-protected methylaniline and piperidine provided tetrasubstituted ureas with good yields (91% for compound **3m** and 82% for compound **3p**, respectively).

Furthermore, we evaluated the impact of steric hindrance on the reaction scope of Alloc-protected amines by performing the reaction of Alloc-protected dibenzyl compounds (**1e**) with two bulky phenyl groups (Table 3, entries 17–19). Under the same optimized conditions, trisubstituted and tetrasubstituted ureas were successfully prepared from Alloc-protected dibenzyl compounds with yields ranging from 86% to 92% (Table 3, entries 17–19). These findings demonstrate that Alloc-protected amines were readily converted into the desired ureas in high yields via DABAL-Me_3-mediated reactions.

Cbz-protected amines are widely found in numerous multi-step organic synthesis strategies. Thus, our novel direct urea formation method using DABAL-Me_3 was applied for the conversion of *N*-Cbz-protected amines to unsymmetrical ureas, as shown in Table 4. We found that the reaction of different Cbz-protected amines from aniline, benzylamine, and methylaniline with primary and secondary amines successfully generated the corresponding ureas in high yields (Table 4, entries 1–8). The reaction of Cbz-protected amines with different aromatic amines containing electron-donating (methyl, methoxy, and piperonyl) and electron-withdrawing (chloro, nitro, and cyano) groups to generate unsymmetrical ureas was also examined, and then it was discovered that the reaction method using DABAL-Me_3 readily yield unsymmetrical ureas from Cbz-protected amines with high yield (Table 4, entries 3–7). Next, Cbz-protected 2-(4-chlorophenyl)ethylamine was utilized as a substrate to assess its reaction with a variety of amines to yield ureas. The reaction using Cbz-protected 2-(4-chlorophenyl)ethylamine confirmed that treatment of several amines including aromatic amines, aliphatic amines, ally amines (unsaturated amine), cyclic amines, and secondary amines in the presence of DABAL-Me_3 led to successful synthesis of ureas at high yields (Table 4, entries 9–17).

Next, scaled-up urea formation from *N*-Alloc-protected amines was carried out (Scheme 1). A gram-scale reaction was successfully achieved. The reaction of *N*-Alloc-protected benzylamine **1b** (10.5 mmol, 1.0 equiv., 2.00 g) with aniline **2h** (12.6 mmol, 1.2 equiv.) gave the corresponding product **3b** in a 90% yield under the optimized reaction conditions, indicating that the reaction method was both scalable and practical.

To further examine the substrate scope for the urea synthesis method using DABAL-Me_3, amines bearing Boc and Fmoc group were evaluated. As shown in Table 5. We found that the reaction of Boc-protected benzylamine and aniline in the presence of DABAL-Me_3 successfully yielded the corresponding ureas in high yields (Table 5, entries 1–4). In additions, unsymmetrical ureas were prepared via the treatment of Fmoc-protected benzylamine and aniline with DABAL-Me_3 (Table 5, entries 5–7).

3. Conclusions

In conclusion, a novel method for the direct synthesis of unsymmetrical ureas from *N*-Alloc-, *N*-Cbz-and *N*-Boc-protected amines has been developed. In this study, after investigation of several reagents, we employed DABAL-Me_3, an air stable reagent, to increase activation of *N*-Alloc-, *N*-Cbz- and *N*-Boc-protected amines for direct preparation of target unsymmetrical ureas, including trisubstituted and tetrasubstituted ureas, with high yields. Our results suggest that this novel direct DABAL-Me_3-mediated transformation of *N*-Alloc-, *N*-Cbz, and *N*-Boc-protected amines into

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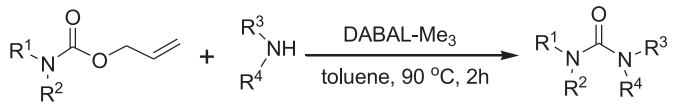
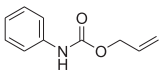
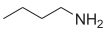
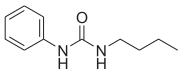
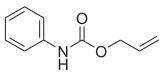
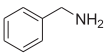
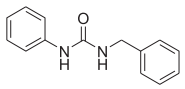
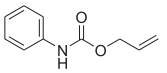
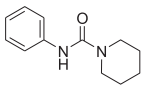
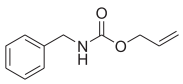
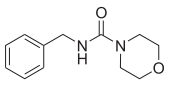
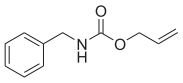
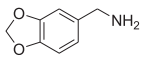
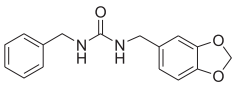
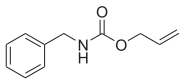
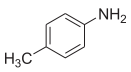
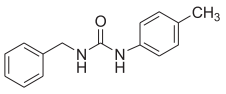
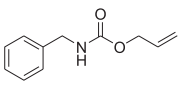
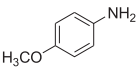
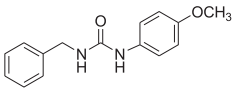
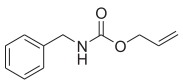
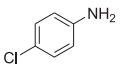
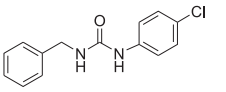
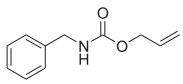
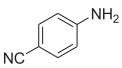
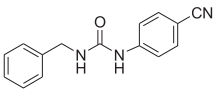
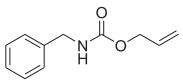
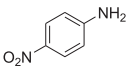
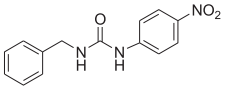
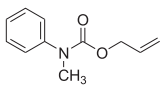
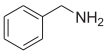
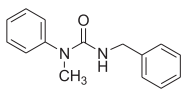
Table 3
Scope of urea formation from Alloc-protected amines[a].



1 2 3

Entry	Alloc-carbamate		Amine		Product		Yield[b] (%)
1		**1a**		**2a**		**3a**	95
2		**1a**		**2b**		**3b**	94
3		**1a**		**2c**		**3c**	90
4		**1a**		**2d**		**3d**	93
5		**1b**		**2e**		**3e**	91
6		**1b**		**2f**		**3f**	88
7		**1b**		**2g**		**3g**	90
8		**1b**		**2h**		**3h**	92
9		**1b**		**2i**		**3i**	91
10		**1b**		**2j**		**3j**	90
11		**1c**		**2b**		**3k**	93

unsymmetrical substituted ureas is practical and applicable to the synthesis of many different ureas.

4. Experimental section

4.1. General procedure

All chemicals were purchased from Sigma-Aldrich and used without further purification. DABAL-Me_3 is a free-flowing solid and has a hydrolytic stability. The reagent can be treated without the need for an inert atmosphere, and can be weighed out freely in the laboratory as well as stored in standard container. Proton and ^{13}C NMR spectra were recorded on a 600 MHz & 150 MHz respectively JNM-ECA600 spectrometer. The chemical shifts are reported in δ units (ppm) relative to tetramethylsilane (TMS) and the coupling constants (J) quoted in Hz. Reaction progress was monitored by thin-layer chromatography (TLC) analysis. TLC analysis was performed using an aluminum plate with silica gel 60 F_{254} and TLC spots were visualized by UV light (254 nm) exposure. Flash chromatography was performed using 230–400 mesh silica gel and analytical grade solvent. HRMS spectrometry was performed on a water Q-TOF mass spectrometer to obtain high-resolution mass

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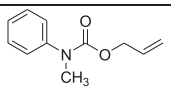
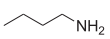
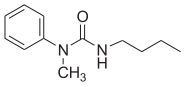
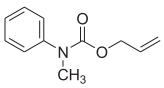
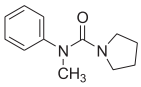
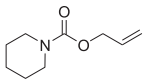
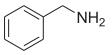
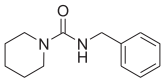
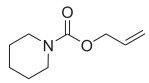
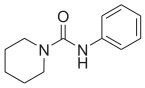
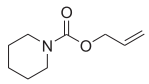
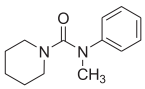
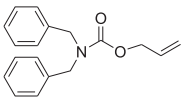
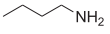
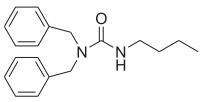
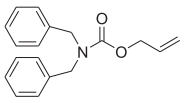
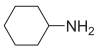
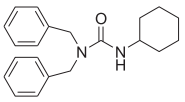
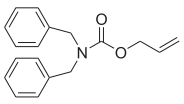
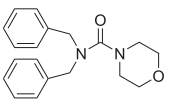
Entry	Alloc-carbamate		Amine		Product		Yield[b] (%)
12		**1c**		**2a**		**3l**	96
13		**1c**		**2k**		**3m**	91
14		**1d**		**2b**		**3n**	94
15		**1d**		**2l**		**3o**	91
16		**1d**		**2m**		**3p**	82
17		**1e**		**2a**		**3q**	92
18		**1e**		**2n**		**3r**	91
19		**1e**		**2d**		**3s**	86

[a]Reaction conditions: Alloc-carbamate (1.0 mmol), amine (1.2 mmol), DABAL-Me_3 (1.2 mmol), toluene (5 mL), 90 °C for 2 h, [b]Isolated yields after column purification.

spectra.

4.2. General procedure for the preparation of urea compounds from alloc-protected amine (**3a**-**3s**)

To a solution of butylamine (0.099 g, 1.355 mmol) in toluene (5 mL) DABAL-Me_3 (0.347 g. 1.356 mmol) was added. The mixture was stirred for 20 min at 40 °C. **1a** (0.200 g, 1.129 mmol) were added and allowed to stir for 2 h at 90 °C. The reaction mixture was quenched by the addition of 1 M HCl (2 mL) and extracted with CH_2Cl_2 (2 × 20 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** (0.206 g, 95%).

4.2.1. 1-Butyl-3-phenylurea (**3a**)

White solid; mp 128–130 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.16 (t, J = 7.8 Hz, 2H), 6.82 (t, J = 7.2 Hz, 1H), 6.04 (t, J = 5.4 Hz, 1H), 3.03 (dd, J = 6.6, 12.5 Hz, 2H), 1.38–1.35 (m, 2H), 1.28–1.24 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 155.7, 141.1, 129.1, 121.3, 118.0, 39.5, 32.4, 20.5, 14.7; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{11}H_{17}N_2O$ = 193.1335, found 193.1346. Data are consistent with that previously reported.[13]

4.2.2. 1-Benzyl-3-phenylurea (**3b**)

Yellow solid; mp 173–174 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.49 (s, 1H), 7.37–7.17 (m, 9H), 6.86 (m, 1H), 6.56 (s, 1H), 4.26 (d, J = 6.0 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 155.8, 140.9, 140.8, 129.2, 128.8, 127.6, 127.2, 121.6, 118.2, 43.3; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{14}H_{15}N_2O$ = 227.1179, found 227.1178. Data are consistent with that previously reported.[14]

4.2.3. N-Phenylpiperidine-1-carboxamide (**3c**)

White solid; mp 169–171 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.31 (d, J = 7.8 Hz, 2H), 7.26–7.23 (t, J = 7.8 Hz, 2H), 6.99 (t, J = 1.8, 1H), 6.48 (s, 1H), 3.42 (m, 4H), 1.63–1.57 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 139.4, 128.9, 122.9, 119.9, 45.3, 25.8, 24.5; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{12}H_{17}N_2O$ = 205.1335, found 205.1344. Data are consistent with that previously reported.[15]

4.2.4. N-Benzylmorpholine-4-carboxamide (**3d**)

White solid; mp 138–140 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33–7.25 (m, 5H), 4.79 (s, 1H), 4.41 (s, 2H), 3.67 (t, J = 4.8 Hz, 4H), 3.34 (t, J = 4.8 Hz, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.7, 139.2, 128.8, 127.9, 127.5, 66.6, 45.1, 44.1; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{12}H_{17}N_2O_2$ = 221.1290, found 221.1285. Data are consistent

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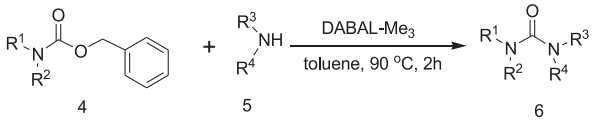
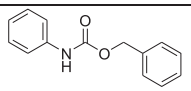
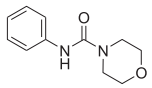
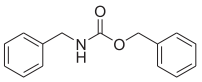
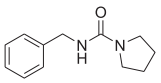
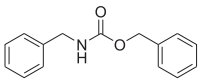
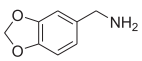
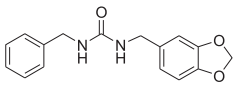
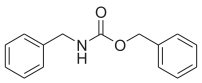
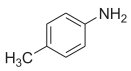
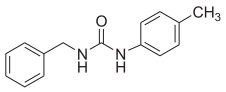
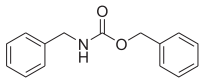
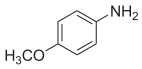
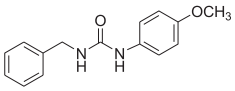
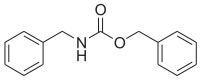
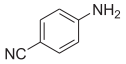
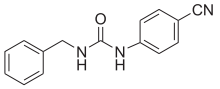
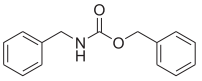
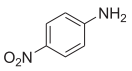
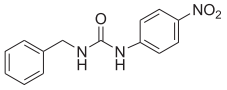
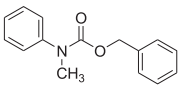
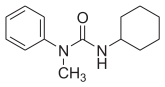
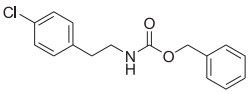
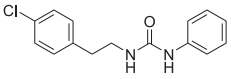
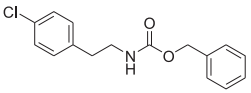
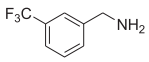
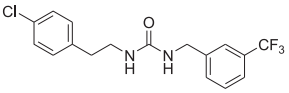
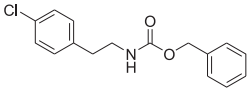
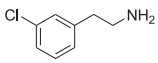
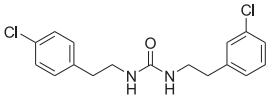
Table 4
Scope of urea formation from Cbz-protected amines[a].



4 5 6

Entry	Cbz-carbamate		Amine		Product		Yield[b] (%)
1		**4a**		**5a**		**6a**	91
2		**4b**		**5b**		**6b**	94
3		**4b**		**5c**		**6c**	90
4		**4b**		**5d**		**6d**	87
5		**4b**		**5e**		**6e**	92
6		**4b**		**5f**		**6f**	90
7		**4b**		**5g**		**6g**	88
8		**4c**		**5h**		**6h**	91
9		**4d**		**5i**		**6i**	81
10		**4d**		**5j**		**6j**	72
11		**4d**		**5k**		**6k**	95

with that previously reported.[16]

*4.2.5. 1-(benzo[d][1,3]dioxol-5-ylmethyl)-3-benzylurea (**3e**)*

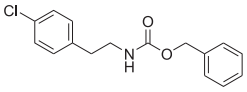
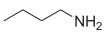
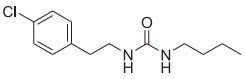
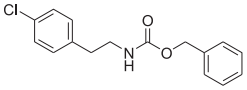
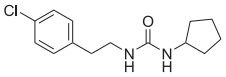
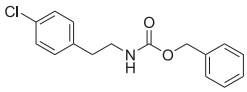
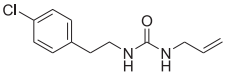
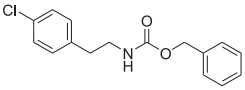
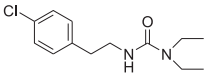
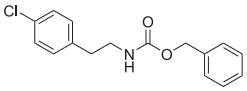
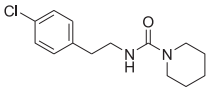
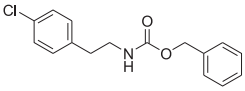
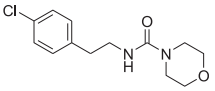
White solid; mp 162–164 °C.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.22 (m, 5H), 6.85–6.72 (m, 3H), 6.42–6.38 (m, 2H), 5.98 (s, 2H), 4.23–4.22 (d, J = 6 Hz, 2H), 4.14–4.13 (d, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 147.6, 146.3, 141.3, 136.3, 128.6 (2C), 127.4 (2C),127.0, 120.5, 108.4, 108.1, 101.1, 43.4, 43.2; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{16}H_{17}N_2O_3$ = 285.1239, found 285.1235. Data are consistent with that previously reported.[17]

*4.2.6. 1-Benzyl-3-p-tolylurea (**3f**)*

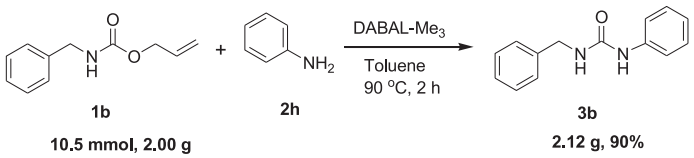
White solid; mp 183–185 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.31–7.11 (m, 7H), 6.89 (m, 2H), 6.51 (s, 1H), 4.24 (d, J = 6.0 Hz, 2H), 2.18 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.8, 140.9, 138.4, 130.3, 129.6, 128.8, 127.6, 127.2, 118.3, 43.3, 20.8; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{15}H_{17}N_2O$ = 241.1335, found 241.1345. Data are consistent with that previously reported.[18]

*4.2.7. 1-Benzyl-3-(4-methoxyphenyl)urea (**3g**)*

White solid; mp 168–170 °C; ^{1}H NMR (400 MHz, DMSO-d_6)

Entry	Cbz-carbamate		Amine		Product		Yield[b] (%)
12		4d		5l		6l	79
13		4d		5m		6m	81
14		4d		5n		6n	84
15		4d		5o		6o	83
16		4d		5p		6p	75
17		4d		5a		6q	67

[a] Reaction conditions: Cbz-carbamate (1.0 mmol), amine (1.2 mmol), DABAL-Me_3 (1.2 mmol), toluene (5 mL), 90 °C for 2 h, [b] Isolated yields after column purification.



Scheme 1. The gram-scale reaction of *N*-Alloc-protected benzylamines with aniline.

δ 8.35 (s, 1H), 7.24–7.35 (m, 7H), 6.83 (d, $J = 12$ Hz, 2H), 6.51 (t, $J = 6$ Hz, 1H), 4.29 (d, $J = 6$ Hz, 2H) 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 147.6, 140.9, 140.2, 128.8 (2C), 127.6 (2C),127.2, 125.5 (2C), 117.3 (2C), 43.2; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{15}H_{17}N_2O_2 = 257.1290$, found 221.1288. Data are consistent with that previously reported.[19]

*4.2.8. 1-Benzyl-3-(4-chlorophenyl)urea (**3h**)*

White solid; mp 190–192 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.40–7.38 (m, 2H), 7.29–7.21 (m, 7H), 6.62 (s, 1H), 4.25 (d, $J = 6.0$ Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 155.6, 140.8, 140.0, 129.0, 128.8, 127.6, 125.0, 120.3, 119.7, 43.2; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{14}H_{14}ClN_2O = 261.0789$, found 261.0798. Data are consistent with that previously reported.[20]

*4.2.9. 1-Benzyl-3-(4-cyanophenyl)urea (**3i**)*

White solid; m.p 177–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.68–7.58 (m, 4H), 7.34–7.31 (m, 5H), 6.87 (t, $J = 5.6$ Hz,1H), 4.32 (d, $J = 5.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 155.9, 145.4, 140.4, 133.6 (2C), 128.8 (2C), 127.6 (2C), 127.3, 119.9, 117.9 (2C), 102.9, 43.2; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{15}H_{14}N_3O = 252.1137$, found 252.1139.

*4.2.10. 1-Benzyl-3-(4-nitrophenyl)urea (**3j**)*

Yellow solid; mp 216–218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.16–8.13 (m, 2H), 7.66–7.63 (m, 2H), 7.36–7.25 (m, 5H), 6.95 (t, J = 6, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 152.9, 139.9, 139.2, 129.3, 129.1, 125.8, 122.4, 120.1, 118.8; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{14}H_{14}N_3O_3 = 272.1035$, found 272.1037.

*4.2.11. 3-Benzy-1-methyl-1-phenylurea (**3k**)*

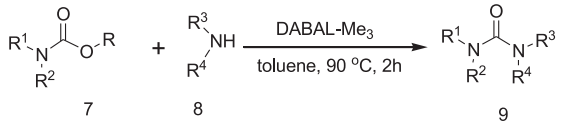
White solid; mp 92–94 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41–7.38 (m, 2H), 7.29–7.20 (m, 8H), 4.66 (s, 1H), 4.38 (d, $J = 5.4$ Hz, 2H), 3.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 134.4, 139.6, 130.2, 128.9, 127.5, 127.4, 127.2, 44.8, 37.4; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{15}H_{17}N_2O = 241.1335$, found 241.1346. Data are consistent with that previously reported.[21]

*4.2.12. 3-Butyl-1-methyl-1-phenylurea (**3l**)*

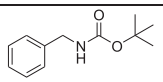
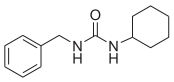
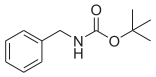
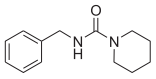
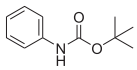
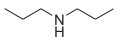
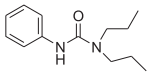
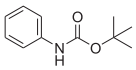
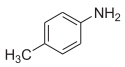
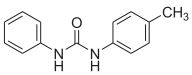
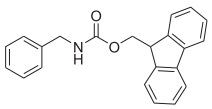
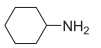
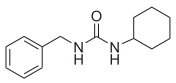
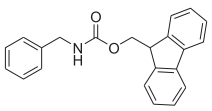
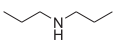
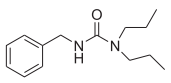
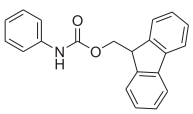
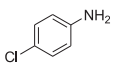
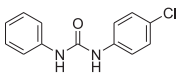
White solid; mp 46–48 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40–7.37 (m, 2H), 7.28–7.20 (m, 3H), 4.28 (brs, 1H), 3.23 (s, 3H), 3.13 (m, 2H), 1.36–1.33 (m, 2H), 1.23–1.19 (m, 2H), 0.84 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.4, 143.5, 130.1, 127.4, 127.2, 40.6, 37.2, 32.4, 20.1, 13.9; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{12}H_{19}N_2O = 207.1492$, found 207.1498. Data are consistent with

Please cite this article in press as: Kang S, Kim H-K, Facile direct synthesis of unsymmetrical ureas from *N*-Alloc-, *N*-Cbz-, and *N*-Boc-protected amines using DABAL-Me_3, Tetrahedron (2018), https://doi.org/10.1016/j.tet.2018.06.011

Table 5
Scope of urea formation from Boc- and Fmoc-protected amines[a].



7 8 9

Entry	Carbamate		Amine		Product		Yield[b] (%)
1		**7a**		**8a**		**9a**	93
2		**7a**		**8b**		**9b**	90
3		**7b**		**8c**		**9c**	92
4		**7b**		**8d**		**9d**	88
5		**7c**		**8a**		**9e**	61[c]
6		**7c**		**8c**		**9f**	58[c]
7		**7d**		**8e**		**9g**	55[c]

[a]Reaction conditions: Boc- and Fmoc- carbamate (1.0 mmol), amine (1.2 mmol), DABAL-Me_3 (1.2 mmol), toluene (5 mL), 90 °C for 2 h, [b]Isolated yields after column purification. [c] DABAL-Me_3 (3.0 mmol) used.

that previously reported.[22]

*4.2.13. N-Methyl-N-phenylpyrrolidine-1-carboxamide (**3m**)*

Peach solid; mp 64–66 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31–7.28 (m, 2H), 7.10–7.08 (m, 3H), 3.21 (s, 3H), 3.03 (m, 4H), 1.67–1.64 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.9, 146.5, 129.3, 125.1, 124.6, 47.9, 39.8, 25.4; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{12}H_{17}N_2O = 205.1335$, found 205.1345. Data are consistent with that previously reported.[23]

*4.2.14. N-Benzylpiperidine-1-carboxamide (**3n**)*

White solid; mp 101–104 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H), 4.81 (s, 1H), 4.40–4.39 (m, 2H), 3.32–3.30 (m, 4H), 1.59–1.50 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.7, 139.8, 128.6, 127.8, 127.3, 45.1, 45.0, 25.7, 24.5; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{13}H_{19}N_2O = 219.1492$, found 219.1495. Data are consistent with that previously reported.[24]

*4.2.15. N-Phenylpiperidine-1-carboxamide (**3o**)*

White solid; mp 169–171 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.31 (d, $J = 7.8$ Hz, 2H), 7.26–7.23 (t, $J = 7.8$ Hz, 2H), 6.99 (t, $J = 1.8$, 1H), 6.48 (s, 1H), 3.42 (m, 4H), 1.63–1.57 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 139.4, 128.9, 122.9, 119.9, 45.3, 25.8, 24.5; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{12}H_{17}N_2O = 205.1335$, found 205.1344. Data are consistent with that previously reported.[15]

*4.2.16. N-Methyl-N-phenylpiperidine-1-carboxamide (**3p**)*

A colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.27 (m, 2H), 7.07–7.04 (m, 3H), 3.18 (s, 3H), 3.14–3.12 (m, 4H), 1.45–1.43 (m, 2H), 1.33–1.29 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.3, 147.3, 129.4, 124.2, 123.6, 46.7, 39.5, 25.4, 24.6; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{13}H_{19}N_2O = 219.1492$, found 219.1494. Data are consistent with that previously reported.[25]

*4.2.17. 1,1-Dibenzyl-3-butylurea (**3q**)*

White solid; mp 72–74 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.31 (m, 4H), 7.28–7.23 (m, 6H), 4.48 (s, 4H), 4.33 (s, 1H), 3.19

(m, 2H), 1.36–1.32 (m, 2H), 1.17–1.13 (m, 2H), 0.83–0.81 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.6, 137.8, 128.8, 127.5, 127.3, 50.4, 40.8, 32.3, 19.9, 13.8; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{19}H_{25}N_2O = 297.1961$, found 297.1965. Data are consistent with that previously reported.[26]

*4.2.18. 1,1-Dibenzyl-3-cyclohexylurea (**3r**)*

White solid; mp 140–142 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.31 (m, 4H), 7.27–7.21 (m, 6H), 4.47 (s, 4H), 4.2 (m, 1H), 3.68–3.64 (m, 1H), 1.83–1.81 (m, 2H), 1.52 (m, 3H), 1.31–1.27 (m, 2H), 1.07–1.04 (m, 1H), 0.91–0.96 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.9, 137.9, 128.8, 127.5, 127.3, 50.4, 49.4, 33.7, 25.7, 24.8; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{21}H_{27}N_2O = 323.2118$, found 323.2127. Data are consistent with that previously reported.[12(c)]

*4.2.19. N,N-Dibenzylmorpholine-4-carboxamide (**3s**)*

White solid; mp 106–108 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33–7.25 (m, 6H), 7.16–7.15 (m, 4H), 4.31 (s, 4H), 3.69 (t, $J = 4.8$ Hz, 4H), 3.32 (t, $J = 4.8$ Hz, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 137.3, 128.7, 127.9, 127.5, 66.7, 50.7, 47.8; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{19}H_{23}N_2O_2 = 311.1754$, found 311.1764. Data are consistent with that previously reported.[23]

*4.3. General procedure for the preparation of urea compounds from Cbz-protected amine (**6a**-**6q**)*

To a solution of morpholine (0.115 g, 1.321 mmol) in toluene (5 mL) DABAL-Me_3 (0.406 g. 1.321 mmol) was added. The mixture was stirred for 20 min at 40 °C. **4a** (0.250 g, 1.100 mmol) were added and allowed to stir for 2 h at 90 °C. The reaction mixture was quenched by the addition of 1 M HCl (4 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was dried over magnesium 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 **6a** (0.213 g, 94%).

*4.3.1. N-Phenylmorpholine-4-carboxamide (**6a**)*

White solid; mp 150–152 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33–7.25 (m, 4H), 7.03 (m, 1H), 6.58 (s, 1H), 3.67 (t, $J = 4.8$ Hz, 4H), 3.43 (t, $J = 5.4$ Hz, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.3, 138.8, 128.9, 123.5, 120.3, 66.6, 44.3; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{11}H_{15}N_2O_2 = 207.1128$, found 207.1137. Data are consistent with that previously reported.[27]

*4.3.2. N-Benzylpyrrolidine-1-carboxamide (**6b**)*

White solid; mp 119–121 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29–7.19 (m, 5H), 4.66 (s, 1H), 4.39 (s, 2H), 3.29 (m, 4H), 1.87–1.83 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.8, 140.0, 128.6, 127.8, 127.2, 45.6, 44.6, 25.6; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{12}H_{17}N_2O = 205.1335$, found 205.1346. Data are consistent with that previously reported.[28]

*4.3.3. 1-(benzo[d][1,3]dioxol-5-ylmethyl)-3-benzylurea (**6c**)*

White solid; mp 162–164 °C.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.22 (m, 5H), 6.85–6.72 (m, 3H), 6.42–6.38 (m, 2H), 5.98 (s, 2H), 4.23–4.22 (d, $J = 6$ Hz, 2H), 4.14–4.13 (d, $J = 5.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 147.6, 146.3, 141.3, 136.3, 128.6 (2C), 127.4 (2C),127.0, 120.5, 108.4, 108.1, 101.1, 43.4, 43.2; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{16}H_{17}N_2O_3 = 285.1239$, found 285.1235. Data are consistent with that previously reported.[17]

*4.3.4. 1-Benzyl-3-p-tolylurea (**6d**)*

White solid; mp 183–185 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.31–7.11 (m, 7H), 6.89 (m, 2H), 6.51 (s, 1H), 4.24 (d, $J = 6.0$ Hz, 2H), 2.18 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.8, 140.9, 138.4, 130.3, 129.6, 128.8, 127.6, 127.2, 118.3, 43.3, 20.8; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{15}H_{17}N_2O = 241.1335$, found 241.1345. Data are consistent with that previously reported.[18]

*4.3.5. 1-Benzyl-3-(4-methoxyphenyl)urea (**6e**)*

White solid; mp 168–170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.24–7.35 (m, 7H), 6.83 (d, $J = 12$ Hz, 2H), 6.51 (t, $J = 6$ Hz, 1H), 4.29 (d, $J = 6$ Hz, 2H) 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 147.6, 140.9, 140.2, 128.8 (2C), 127.6 (2C),127.2, 125.5 (2C), 117.3 (2C), 43.2; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{15}H_{17}N_2O_2 = 257.1290$, found 221.1288. Data are consistent with that previously reported.[19]

*4.3.6. 1-Benzyl-3-(4-cyanophenyl)urea (**6f**)*

White solid; m. p 177–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.68–7.58 (m, 4H), 7.34–7.31 (m, 5H), 6.87 (t, $J = 5.6$ Hz,1H), 4.32 (d, $J = 5.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl*3*) δ 155.9, 145.4, 140.4, 133.6 (2C), 128.8 (2C), 127.6 (2C), 127.3, 119.9, 117.9 (2C), 102.9, 43.2; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{15}H_{14}N_3O = 252.1137$, found 252.1139.

*4.3.7. 1-Benzyl-3-(4-nitrophenyl)urea (**6g**)*

Yellow solid; mp 216–218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.16–8.13 (m, 2H), 7.66–7.63 (m, 2H), 7.36–7.25 (m, 5H), 6.95 (t, J = 6, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 152.9, 139.9, 139.2, 129.3, 129.1, 125.8, 122.4, 120.1, 118.8; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{14}H_{14}N_3O_3 = 272.1035$, found 272.1037.

*4.3.8. 3-Cyclohexyl-1-methyl-1-phenylurea (**6h**)*

White solid; mp 112–114 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40–7.37 (m, 2H)), 7.27–7.21 (m, 3H), 4.1 (m, 1H), 3.61–3.55 (m, 1H), 3.23 (s, 3H), 1.84–1.81 (m, 2H), 1.58–1.51 (m, 3H), 1.31–1.26 (m 2H), 1.06–1.02 (m, 1H), 0.96–0.90 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.6, 143.7, 130.0, 127.3, 127.1, 49.4, 37.1, 33.7, 25.6, 24.9; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{14}H_{21}N_2O = 233.1648$, found 233.1652. Data are consistent with that previously reported.[29]

*4.3.9. 1-(4-Chlorophenethyl)-3-phenylurea (**6i**)*

White solid; mp 116–119 °C; IR ν_{max} (KBr) 3321, 1628, 1596, 1574 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40–7.20 (m, 9H), 6.89 (bs, 1H), 5.12 (bs, 1H), 3.34 (m, 2H), 2.75 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.6, 141.0, 139.1, 131.1, 129.1, 128.7, 128.5, 127.1, 121.5, 40.8, 35.6; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{15}H_{16}ClN_2O = 275.0946$, found 275,0949.

*4.3.10. 1-(4-Chlorophenethyl)-3-(3-trifluoromethylbenzyl)urea (**6j**)*

White solid; mp 121–123 °C; IR ν_{max} (KBr) 3326, 1617, 1576, 1331, 1115 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57–7.53 (m, 4H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.21 (d, $J = 8.4$ Hz, 2H), 6.52 (bs, 1H), 6.05 (bs, 1H), 4.28 (d, $J = 6.0$ Hz, 2H), 3.25 (m, 2H), 2.69 (t, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.4, 143.2, 139.2, 131.5, 131.1, 131.0, 129.5, 129.4 (q, $J = 31.2$), 128.6, 124.8 (q, $J = 270.6$ Hz), 123.7 (2C, m), 42.8, 41.2, 35.8; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{17}H_{17}ClF_3N_2O = 357.0976$, found 357.0977.

*4.3.11. 1-(3-Chlorophenethyl)-3-(4-chlorophenethyl)urea (**6k**)*

White solid; mp 119–121 °C; IR ν_{max} (KBr) 3324, 1617, 1582 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (d, $J = 8.4$ Hz, 2H), 7.30–7.15 (m, 6H), 5.88 (bs, 1H), 5.87 (bs, 1H), 3.21 (m, 4H), 2.66 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.3, 142.9, 139.3, 133.3, 131.1, 131.0, 130.5, 129.0, 128.6, 127.9, 126.4, 41.1, 40.9, 36.1, 35.8; HRMS (ESI) *m/z* $(M + H)^+$ calcd for $C_{17}H_{19}Cl_2N_2O = 337.0869$, found 337.0872.

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*4.3.12. 1-Butyl-3-(4-chlorophenethyl)urea (**6l**)*

White solid; mp 95–98 °C; IR ν_{max} (KBr) 3320, 1618, 1576, 1559 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.34 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 5.84 (t, J = 5.6 Hz, 1H), 5.77 (t, J = 5.6 Hz, 1H), 3.21 (m, 2H), 2.96 (m, 2H), 2.67 (t, J = 7.2 Hz, 2H), 1.34–1.21 (m, 4H), 1.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.4, 139.3, 131.1, 131.0, 128.6, 41.1, 39.3, 35.9, 32.6, 20.0, 14.2; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{13}H_{20}ClN_2O$ = 255.1259, found 255.1269.

*4.3.13. 1-(4-Chlorophenethyl)-3-cyclopentylurea (**6m**)*

White solid; mp 105–107 °C; IR ν_{max} (KBr) 3311, 2961, 1622, 1585 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.33 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 5.84 (d, J = 7.2 Hz, 1H), 5.64 (m, 1H), 3.82 (m, 1H), 3.20 (q, J = 6.8 Hz, 4H), 2.66 (t, J = 7.0 Hz, 2H), 1.74 (m, 2H), 1.57–1.49 (m, 4H), 1.25 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.1, 139.3, 131.1, 131.0, 128.6, 51.3, 41.0, 35.9, 33.5, 23.9; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{14}H_{20}ClN_2O$ = 267.1259, found 267.1260.

*4.3.14. 1-Allyl-3-(4-chlorophenethyl)urea (**6n**)*

White solid; mp 107–109 °C; IR ν_{max} (KBr) 3326, 1623, 1595 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.34 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.00 (t, J = 5.6 Hz, 1H), 5.89 (t, J = 5.6 Hz, 1H), 5.80 (m, 1H), 5.08 (dd, J = 17.2, 1.6 Hz, 1H), 5.08 (dd, J = 10.0, 1.6 Hz, 1H), 3.63 (m, 2H), 3.24 (q, J = 6.8 Hz, 2H), 2.68 (t, J = 7.2, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.2, 139.2, 137.3, 131.1, 131.0, 128.6, 114.7, 42.1, 41.1, 35.9; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{12}H_{16}ClN_2O$ = 239.0946, found 239.0946.

*4.3.15. 3-(4-Chlorophenethyl)-1,1-diethylurea (**6o**)*

Colorless gel; IR ν_{max} (KBr) 3345, 2974, 1625, 1533, 1492, 1281, 1091 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.25 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 4.50 (t, J = 5.2 Hz, 1H), 3.44 (q, J = 6.8 Hz, 2H), 3.21 (q, J = 7.2 Hz, 4H), 2.80 (t, J = 6.8 Hz, 2H), 1.08 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.1, 138.1, 132.0, 130.2, 128.5, 41.9, 41.1, 35.8, 13.8; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{13}H_{20}ClN_2O$ = 255.1259, found 255.1289.

*4.3.16. N-(4-Chlorophenethyl)piperidine-1-carboxamide (**6p**)*

White solid; mp 115–118 °C; IR ν_{max} (KBr) 3338, 2934, 2855, 1622, 1539, 1492, 1271 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.33 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.50 (t, J = 5.2 Hz, 1H), 3.24 (m, 6H), 2.71 (t, J = 7.2 Hz, 2H), 1.50 (m, 2H), 1.38 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.7, 139.4, 131.0, 130.9, 128.6, 44.7, 42.1, 35.7, 25.8, 24.7; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{14}H_{20}ClN_2O$ = 267.1259, found 267.1257.

*4.3.17. N-(4-Chlorophenethyl)morpholine-4-carboxamide (**6q**)*

White solid; mp 100–102 °C; IR ν_{max} (KBr) 3346, 2858, 1627, 1575, 1263 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.33 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.63 (t, J = 5.6 Hz, 1H), 3.52 (m, 4H), 3.22 (m, 6H), 2.71 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.0, 139.3, 131.1, 131.0, 128.6, 66.4, 44.3, 42.1, 35.6; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{13}H_{18}ClN_2O_2$ = 269.1051, found 269.1056.

*4.4. General procedure for the preparation of urea compounds from Boc- and Fmoc-protected amine (**9a**-**9g**)*

To a solution of cyclohexylamine (0.126 g, 1.275 mmol) in toluene (5 mL) DABAL-Me_3 (0.327 g. 1.275 mmol) was added. The mixture was stirred for 20 min at 40 °C. **6a** (0.220 g, 1.063 mmol) were added and allowed to stir for 2 h at 90 °C. The reaction mixture was quenched by the addition of 1 M HCl (4 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was dried over magnesium 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 **9a** (0.230 g, 93%).

*4.4.1. 1-Benzyl-3-cyclohexylurea (**9a**)*

White solid; mp 133–134 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.34 (m, 5H), 4.33 (s, 2H), 3.52 (m, 1H), 1.91 (dd, J = 3.2, 14.8 Hz, 2H), 1.66 (m, 3H), 1.31 (m, 3H), 1.09 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 139.4, 128.6, 127.4, 127.2, 19.1, 44.4, 33.9, 25.6, 24.9; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{14}H_{21}N_2O$ = 233.1648, found 233.1658. Data are consistent with that previously reported.[30]

*4.4.2. N-Benzylpiperidine-1-carboxamide (**9b**)*

White solid; mp 101–103 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.37 (m, 5H), 4.74 (s, 1H), 4.46 (d, J = 5.2 Hz, 2H) 3.36 (t, J = 5.6 Hz, 4H), 1.61 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ157.5, 139.6, 128.6, 127.8, 127.2, 24.1, 45.02, 25.6, 24.4; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{13}H_{19}N_2O$ = 219.1492, found 219.1499. Data are consistent with that previously reported.[24]

*4.4.3. 3-Phenyl-1,1-dipropylurea (**9c**)*

White solid; mp 70–72 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7,41 (m, 2H), 7.29 (m, 2H), 7.03 (m, 1H), 6.34 (s, 1H), 3,28 (t, J = 7.2 Hz, 4H), 1.66 (m, 4H), 0,97 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 139.3, 128.8, 122.7, 119.7, 49.5 (2C), 21.9 (2C), 11.4 (2C); HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{13}H_{21}N_2O$ = 221.1648, found 221.1658. Data are consistent with that previously reported.[31]

*4.4.4. 1-Phenyl-3-p-tolylurea (**9d**)*

White solid; mp 212–213 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.55 (s, 1H), 7.44–7.46 (m, 2H), 7.26–736 (m, 4H), 7.07 (d, J = 8.0 Hz, 2H), 6.96 (m, 1H) 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 140.2, 137.7, 137.6, 131.1, 130.9, 129.6, 129.2, 122.1, 118.7, 118.7, 118.6, 118.5, 20.8; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{14}H_{15}N_2O$ = 227.1179, found 227.1189. Data are consistent with that previously reported.[32]

*4.4.5. 3-Benzyl-1,1-dipropylurea (**9f**)*

White solid; mp 43–45 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.37 (m, 5H), 4.65 (s, 1H), 4.67 (d, J = 4.8 Hz, 2H), 3.19 (t, J = 8.0 Hz, 4H), 1.55–1.65 (m, 4H), 0.92 (t, J = 7.2 Hz, 6H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 139.9, 128.6, 127.6, 127.1, 49.2 (2C), 44.9, 21.8 (2C), 11.39 (2C); HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{14}H_{23}N_2O$ = 235.1805, found 235.1815. Data are consistent with that previously reported.[33]

*4.4.6. 1-(4-Chlorophenyl)-3-phenylurea (**9g**)*

White solid; mp 248–250 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.70 (s, 1H), 7.44–7.50 (m, 4H), 7.31–7.33 (m, 4H), 7.26–7.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 139.9, 139.2, 129.3, 129.1, 125.8, 122.4, 120.1, 118.8; HRMS (ESI); HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{13}H_{12}ClN_2O$ = 247.0633, found 247.0689. Data are consistent with that previously reported.[28]

Conflicts of interest

There are no conflicts to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.06.011.

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