

A new practical method for the synthesis of unsymmetrical ureas via high-pressure-promoted condensation of 2,2,2-trichloroethyl carbamates (Troc-carbamates) with amines[☆]

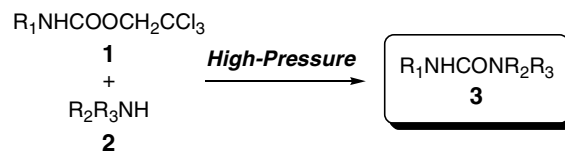
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Abstract—A new practical method for the synthesis of unsymmetrical ureas was achieved by condensation between 2,2,2-trichloroethyl carbamates (Troc-carbamates) and primary or secondary amines under high-pressure conditions.
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Ureas are an important class of compounds in organic, bioorganic, supramolecular, and medicinal chemistry.² They are typically prepared by condensing amines with phosgene or isocyanate derivatives.^{2,3} However, mainly due to the high toxicity and instability of these materials, the corresponding carbamates are frequently employed as convenient starting substrates to achieve the in situ formation of isocyanate intermediates. A survey of the literature reveals that the relative ease of urea formation can be roughly correlated with the p*K*_a value of the alcohol component,⁴ for example, *p*-nitrophenol⁵ > 2,4,5-trichlorophenol⁶ > phenol⁷ > 1,2,2,2-tetrachloroethanol⁸ > chloromethanol.⁹ Although in some instances non-activated alkyl carbamates can also serve as substitutes for isocyanates, acid/base catalysts or organometallic techniques are needed to achieve the required transformations.¹⁰ In the present work, we propose a new practical protocol for the synthesis of unsymmetrical ureas **3** via the uncatalyzed/direct condensation of 2,2,2-trichloroethyl carbamates (Troc-carbamates, **1**) with primary or secondary amines **2** under neutral and mild conditions by applying a high-pressure technique (Scheme 1).¹¹



Scheme 1.

Troc-carbamates **1** were readily prepared from amine precursors by conventional treatment with 2,2,2-trichloroethyl chloroformate.¹² Since these Troc-protected amines are only weakly activated, it is not surprising that there are only a few reports on the use of these substrates for the synthesis of ureas.^{10c,h,13} We thought that at high pressure the desired reactions should proceed smoothly without the use of any catalysts or additives, since condensation reactions of this type are accompanied by large molecular contraction, and hence are highly favorable at high pressure.¹⁴ We describe here the realization of this expectation.

The results are summarized in Table 1.¹⁵ Thus, when a mixture of Troc-protected aniline (**1a**) and benzylamine (**2a**, 1.2 equiv) in THF was reacted at 0.8 GPa and 80 °C for 30 h, the corresponding *N*-benzyl-*N'*-phenylurea (**3a**) was obtained in an almost quantitative yield (entry 3). For comparison, we also examined the same reaction at normal pressure in refluxing THF with or without the use of a base, and the superiority of high-pressure technique was established (entries 1 and 2). This method

Keywords: High-pressure reaction; 2,2,2-Trichloroethyl carbamates; Amines; Ureas; Condensation.

[☆] See Ref. 1.

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is applicable to a wide variety of aliphatic amines including long-chain amine **2b** and sterically hindered amine **2f** (entries 4–8). The reaction of **1a** with ethylenediamine (**2g**) proceeded cleanly to afford bis-urea **3g** in 84% yield (entry 9). Due to their decreased amine nucleophilicity, the reactions using *t*-butyl glycinate (**2h**) and *p*-methoxyaniline (**2i**) were relatively slow even at high pressure (entries 10 and 11). Troc-protected cyclohexylamine (**1b**), an aliphatic amine carbamate, was less reactive than **1a**, and the reaction with **2c** gave dicyclohexylurea (**3j**) after 72 h at 100 °C in 69% yield along with unreacted **1b** (28%) (entry 12).

The utility of this method is apparent from the results with **1c**, where chemoselective transformation was observed at the Troc-carbamate position in providing **3k** without any effect from the *N*-Boc group (entry 13). The reaction of aminopyridine carbamates such as **1d** and **1e** proceeded without any difficulty to give the desired mono- and bis-urea **3l** (99%) and **3m** (96%),

respectively (entries 14 and 15). As expected, the secondary amine carbamate, Troc-protected piperidine (**1f**), could not be converted into the trisubstituted urea **3n** (entry 16).^{10h}

These results suggest that the present transformation should involve the in situ formation of the isocyanate intermediate **4** through the well-known base-promoted elimination of trichloroethanol (Scheme 2).

Consistent with this proposal, the present work confirms that the relative ease of urea formation was simply governed by either the nucleophilicity of amine base **2** (compare entries 5 and 11) or the acidity of an NH-proton of Troc-carbamate **1** (compare entries 5 and 12).²¹

We then investigated the application of this method to the formation of carbohydrate-based ureas, since these compounds attract considerable attention from medicinal and synthetic chemists due to their importance as

Table 1. High-pressure-promoted condensation of Troc-carbamates **1** with amines **2**^a

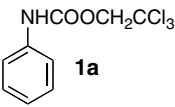
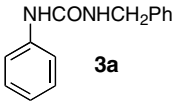
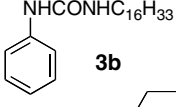
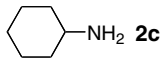
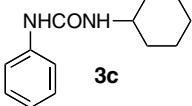
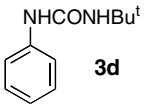

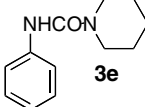
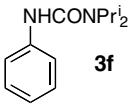
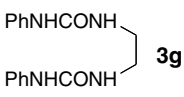
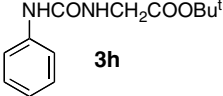
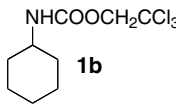
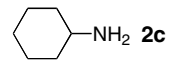
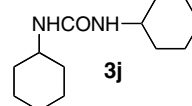
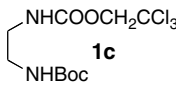
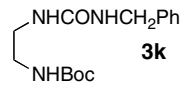
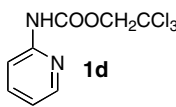
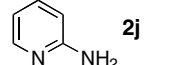
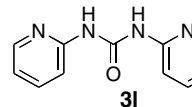
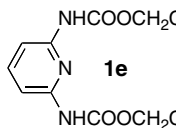
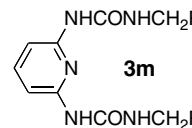
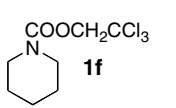

Entry	Troc-carbamate	Amine	Temperature (°C), time (h)	Product, mp (°C)	Yield ^b (%)
1 ^c 2 ^d 3		PhCH ₂ NH ₂ 2a	75, 30		Trace
			75, 30	3a	55 (42)
			80, 30		97
4		C ₁₆ H ₃₃ NH ₂ 2b	80, 48		90–91
5		 2c	80, 30		191–192 (lit. ^{5b} 193)
				3c	100
6		<i>t</i> -BuNH ₂ 2d	80, 30		171–172.5 (lit. ^{5b} 160–161)
				3d	97
7		 2e	100, 72		171–172 (lit. ^{10h} 169.5–171)
				3e	92
8		<i>i</i> -Pr ₂ NH 2f	100, 30		121–123 (lit. ¹⁷ 112–113)
				3f	91
9 ^c		H ₂ NCH ₂ CH ₂ NH ₂ 2g	80, 72		278–279 (lit. ¹⁸ 251–256)
				3g	84
10		NH ₂ CH ₂ COOBu ^t 2h	80, 72		128–129
				3h	62 (31)

Table 1 (continued)

Entry	Troc-carbamate	Amine	Temperature (°C), time (h)	Product, mp (°C)	Yield ^b (%)
11		MeO-C ₆ H ₄ -NH ₂ 2i	100, 72	NHCONHC ₆ H ₄ -p-OMe 3i	198 (lit. ¹⁹ 191–193) 41 (50)
12	 1b	 2c	100, 72	 3j	231–232 (lit. ⁹ 232) 69 (28)
13	 1c	PhCH ₂ NH ₂ 2a	80, 72	 3k	149–150 70 (12)
14	 1d	 2j	100, 72	 3l	181–183 (lit. ²⁰ 174–176) 99
15 ^f	 1e	PhCH ₂ NH ₂ 2a	100, 72	 3m	225–226 96
16	 1f	PhCH ₂ NH ₂ 2a	100, 30	 3n	No reaction

^a Unless otherwise noted, all reactions were performed with Troc-carbamate (1.0 mmol) and amine (1.2 mmol) in THF (ca. 1.5 mL).

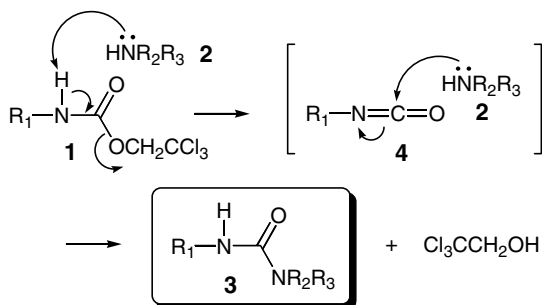
^b Isolated yields. Value in parentheses indicates the recovered starting Troc-carbamate.

^c At atmospheric pressure (1 atm).

^d 0.1 equiv of triethylamine was added.

^e 0.6 equiv of ethylenediamine was added.

^f 2.4 equiv of benzylamine was added.

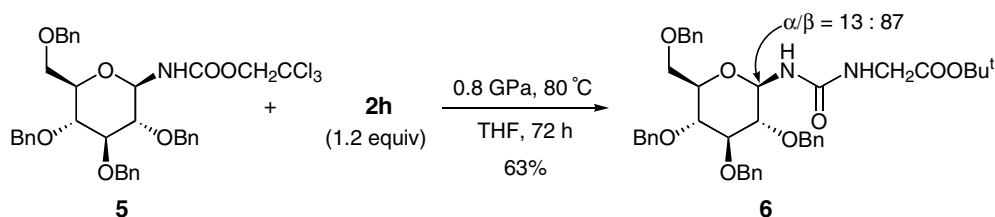


Scheme 2.

glycopeptide mimetics.²² Thus, as outlined in Scheme 3, treatment of Troc-protected glucosylamine **5** with *t*-butyl

glycinate (**2h**) at 0.8 GPa and 80 °C produced a novel type of the glucose–glycine conjugate derivative **6** in 63% yield accompanying by some extent of anomerization ($\alpha/\beta = 13:87$).²³ This result indicates the great synthetic value of this method for devising other types of glycopeptides.

In conclusion, we have found a new practical method for preparing a variety of unsymmetrical ureas **3** via the direct condensation of Troc-carbamates **1** with primary or secondary amines **2** under high-pressure conditions. The fact that this method does not require any catalyst or additive and the byproduct formed was only trichloroethanol makes this system clean and convenient. Furthermore, the utility of this method



Scheme 3.

was established by the highly chemoselective transformation at the Troc group and the easy access to glycoconjugated urea derivatives.

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- General procedure*: A mixture of Troc-carbamate (**1**, 1.0 mmol) and amine (**2**, 1.2 mmol) in THF (ca. 1.5 mL) was placed in a Teflon reaction vessel, and the mixture was allowed to react at 0.8 GPa at the appropriate temperature and for the specified time (Table 1). After the mixture was cooled and the pressure was released, the mixture was concentrated in vacuo. The crude product was purified by silica gel column chromatography (elution with CHCl₃–MeOH) to afford the pure urea **3**.
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- pK_a values calculated by Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67: 2c-H⁺ 10.57, 2i-H⁺ 5.21; PhNHC(=O)CH₃ 15.1, C₆H₁₃NHC(=O)CH₃ 16.2.
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- Unreacted **5** (35%) was also recovered as an anomeric mixture (α/β = ca. 10:90). Compound **6** (β -anomer): mp 120–122 °C; $[\alpha]_D^{23}$ –19.1 (c 0.98, CHCl₃); FTIR (KBr) ν 3322, 1736, 1643, 1577, 1158, 1094, 1069 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.46 (9H, s), 3.36 (1H, t, *J* = 8.8 Hz), 3.52 (1H, dt, *J* = 9.3, 3.0 Hz), 3.65–3.75 (4H, m), 3.73 (1H, dd, *J* = 18.1, 4.9 Hz), 3.88 (1H, dd, *J* = 18.1, 5.4 Hz), 4.45 (1H, d, *J*_{AB} = 12.0 Hz), 4.50 (1H, d, *J*_{AB} = 11.0 Hz), 4.56 (1H, d, *J*_{AB} = 12.0 Hz), 4.71 (1H, d, *J*_{AB} = 11.5 Hz), 4.79 (1H, d, *J*_{AB} = 11.5 Hz), 4.79 (1H, d, *J*_{AB} = 11.0 Hz), 4.87 (1H, d, *J*_{AB} = 11.0 Hz), 4.87 (1H, t, *J* = 8.8 Hz), 4.89 (1H, d, *J*_{AB} = 11.0 Hz), 4.94 (1H, d, *J* = 8.8 Hz), 5.14 (1H, br), 7.10–7.13 (2H, m), 7.22–7.35 (18H, m); ¹³C NMR (100 MHz, CDCl₃): δ 28.0 (×3), 42.7, 68.3, 73.4, 74.6, 74.9, 75.7, 75.9, 77.7, 80.1, 81.4, 81.9, 85.9, 127.6(8) (×2), 127.7(4), 127.8 (×4), 128.0 (×2), 128.1, 128.3 (×2), 128.3(6) (×2), 128.4(2) (×2), 128.6 (×2), 128.7 (×2), 137.8, 137.9, 138.0, 138.4, 156.6, 169.6. Compound **6** (α -anomer): colorless gum; $[\alpha]_D^{23}$ +60.3 (c 0.73, CHCl₃); FTIR (KBr) ν 3347, 1743, 1650, 1558, 1155, 1072 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.45 (9H, s), 3.61–3.67 (1H, m), 3.70–3.76 (4H, m), 3.77 (1H, dd, *J* = 18.1, 5.1 Hz), 3.85 (1H, dd, *J* = 18.1, 5.9 Hz), 3.93 (1H, dt, *J* = 10.0, 3.0 Hz), 4.45 (1H, d, *J*_{AB} = 12.0 Hz), 4.50 (1H, d, *J*_{AB} = 11.2 Hz), 4.59 (1H, d, *J*_{AB} = 12.0 Hz), 4.62 (1H, d, *J*_{AB} = 11.7 Hz), 4.65 (1H, d, *J*_{AB} = 11.7 Hz), 4.78 (1H, d, *J*_{AB} = 10.7 Hz), 4.81 (1H, d, *J*_{AB} = 11.2 Hz), 4.88 (1H, d, *J*_{AB} = 10.7 Hz), 5.27 (2H, br s), 6.02 (1H, dd, *J* = 5.9, 5.1 Hz), 7.14–7.16 (2H, m), 7.24–7.32 (18H, m); ¹³C NMR (100 MHz, CDCl₃): δ 28.1 (×3), 42.5, 68.4, 69.8, 72.8, 73.5, 74.9, 75.8, 77.2, 78.0, 78.1, 81.7, 81.9, 127.6(7) (×3), 127.7(2), 127.8(7) (×2), 127.9(5) (×2), 128.1(0) (×2), 128.1(5), 128.3(4) (×2), 128.3(8) (×3), 128.3(9) (×2), 128.6 (×2), 137.1, 137.9, 138.2, 138.3, 158.4, 169.4.