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A Convenient Synthesis of Unsymmetrically Substituted Ureas via Carbamoyl Azides of α-*N*-Protected Amino Acids

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A simple and efficient two-step synthesis of unsymmetrically substituted ureas containing an amino acid derivative is reported. The procedure involves the reaction between the carbamoyl azides of α-*N*-protected amino acids and ammonium hydroxide or a primary or a secondary amine. The reaction proved to be very fast (0.5 h) with small, highly reactive ammonium hydroxide and slower (4 h) with sterically hindered *tert*-butylamine. The ^{1}H NMR spectra of the synthesized, new, unsymmetrical ureas carried out in [D_6]DMSO suggest that the protons in the –$^{\alpha}$CH–NHCONH–CH– moiety assume a *trans* conformation. Moreover, analysis of the mass spectra (EI and ESI) revealed some interesting common features. The reported synthesis represents the first example of the potential value of carbamoyl azides as versatile chiral starting materials for many synthetic purposes.

Introduction

The development of new synthetic protocols for the preparation of ureas has recently attracted interest because of the presence of this moiety in many biologically active compounds,[1] agrochemicals, resin precursors, dyes and additives to petrochemicals, and polymers.[2] To date, the general procedures described for the synthesis of unsymmetrical ureas involve the reaction between isocyanates and amines.[3] In turn, isocyanates[4] are usually prepared by bubbling phosgene gas into a solution of an amine at high temperature[3c,5] or at room temperature in the presence of a base.[3e,6] Hazards involved in the handling of phosgene, as well as the drastic conditions required, discourage the use of these procedures. Triphosgene represents a preferred choice,[5a,6a,6b,7] but its use is not fully satisfactory, as the excess amount of the precursor remains as a contaminant present in the reaction mixture. Alternative safer derivatives[8] such as various carbonates,[9] *S*,*S*-dimethylthiocarbonate (DMDTB),[10] *N*,*N*′-carbonyldiimidazole (CDI),[3a,3c,11] and 1,1′-carbonylbisbenzotriazole (CBBT)[12] have been extensively used in the carbonylation of amines to form substituted ureas. Some of these methods are multistep processes and, in addition, require long reaction times and obnoxious preparations of reagents (DMDTC, CBBT) that use toxic starting material.

Alternative syntheses of ureas involve the reaction of amines with NCO equivalent compounds like carbamates,[3a,3c,13] or formamides (in the presence of a Ru catalyst).[14] All these methods require the initial preparation of the reagents, long reaction times, and the final isolation of the reactive intermediate from the excess amount of the reagent.[13b] In recent years, much attention has been paid to alternative routes for the synthesis of unsymmetrical ureas, and most of these procedures are based on the catalyzed[15] carbonylation of amines by using carbon monoxide[16] or carbon dioxide[17] in the presence of metal complexes, as well as sulfur,[18] selenium,[16b,19] and phosphorus compounds,[20] or *N*,*N*′-dicyclohexylcarbodiimide.[21] All these carbonylation have been generally carried out at high temperatures under moderate to high pressure of CO or CO_2.

Recently, we have proposed a fast and simple one-pot synthesis of α-*N*-protected carbamoyl azides[22] starting from α-*N*-protected amino acids. Taking into account that this functional group can be considered as a NCO equivalent, we now report the use of these intermediates as suitable building blocks in the synthesis of unsymmetrical ureas.

Results and Discussion

The simple and convenient synthesis of unsymmetrical ureas **1** with a substituent bearing the chiral moiety of an α-amino acid here reported has been successfully accomplished by a two-step reaction sequence (Scheme 1).

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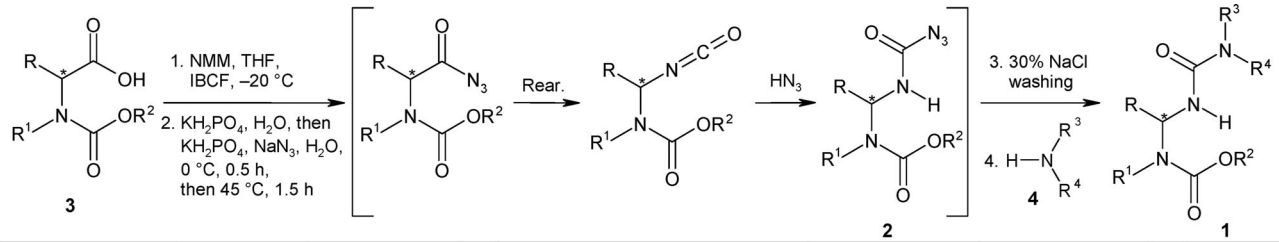


1	R, R^1	R^2	R^3, R^4	1	R, R^1	R^2	R^3, R^4
aba	$(CH_3)_2CH$, H	Et	H, H	**dca**	Ph, H	*t*Bu	H, H
abc	$(CH_3)_2CH$, H	Et	*c*Hex, H	**dcd**	Ph, H	*t*Bu	Bn, H
bad	$(CH_3)_2CHCH_2$, H	Me	Bn, H	**ebc**	$PhCH_2$, H	Et	*c*Hex, H
bbc	$(CH_3)_2CHCH_2$, H	Et	*c*Hex, H	**ebd**	$PhCH_2$, H	Et	Bn, H
bcc	$(CH_3)_2CHCH_2$, H	*t*Bu	*c*Hex, H	**edg**	$PhCH_2$, H	Bn	$(CH_2)_5$
bda	$(CH_3)_2CHCH_2$, H	Bn	H, H	**edh**	$PhCH_2$, H	Bn	$(CH_2)_2O(CH_2)_2$
bdh	$(CH_3)_2CHCH_2$, H	Bn	$(CH_2)_2O(CH_2)_2$	**fbb**	$CH_3S(CH_2)_2$, H	Et	*t*Bu, H
ccb	$(CH_2)_3$	*t*Bu	*t*Bu, H	**fbf**	$CH_3S(CH_2)_2$, H	Et	*c*Hex, Me
cce	$(CH_2)_3$	*t*Bu	Et, Et	**gad**	1*H*-indole-3-CH_2, H	Me	Bn, H
ccf	$(CH_2)_3$	*t*Bu	*c*Hex, Me	**gbe**	1*H*-indole-3-CH_2, H	Et	Et, Et
dba	Ph, H	Et	H, H	**gbh**	1*H*-indole-3-CH_2, H	Et	$(CH_2)_2O(CH_2)_2$
dbi	Ph, H	Et	(*R*)-MeCHPh, H				

2,3	R, R^1	R^2	2,3	R, R^1	R^2
ab	$(CH_3)_2CH$, H	Et	**dc**	Ph, H	*t*Bu
ba	$(CH_3)_2CHCH_2$, H	Me	**eb**	$PhCH_2$, H	Et
bb	$(CH_3)_2CHCH_2$, H	Et	**ed**	$PhCH_2$, H	Bn
bc	$(CH_3)_2CHCH_2$, H	*t*Bu	**fb**	$CH_3S(CH_2)_2$, H	Et
bd	$(CH_3)_2CHCH_2$, H	Bn	**ga**	1*H*-indole-3-CH_2, H	Me
cc	$(CH_2)_3$	*t*Bu	**gb**	1*H*-indole-3-CH_2, H	Et
db	Ph, H	Et			

4	R^3, R^4
a	H, H
b	*t*Bu, H
c	*c*Hex, H
d	Bn, H
e	Et, Et
f	*c*Hex, Me
g	$(CH_2)_5$
h	$(CH_2)_2O(CH_2)_2$
i	(*R*)-MeCHPh, H

Scheme 1. Synthesis of unsymmetrical ureas **1**. Reagents: NMM = *N*-methylmorpholine; IBCF = isobutyl chloroformate.

The first step consists of the one-pot synthesis of α-*N*-protected carbamoyl azide **2**, performed according to our previously described method,[22] just by applying some suitable operative optimizations (see Experimental Section). Under the present conditions, the procedure gave a satisfactory result even with *N*-Boc-proline (**3cc**), which as previously reported[22] afforded only the corresponding 1-*tert*-butyloxycarbonyl-2-isocyanatopyrrolidine when the reaction was carried out at room temperature (3 h). In the second step, the separated, suitably washed organic phase containing carbamoyl azide **2** was cooled down to 0 °C and amine **4** (1.5 equiv. with respect to **3**) was slowly added. The mixture was then stirred at room temperature for 0.5–4 h, affording, after convenient workup and purification, unsymmetrical urea **1** in a 72–96% overall yield.

When amine **4** was directly added to the crude mixture containing carbamoyl azide **2**, the reaction was slower and required a large excess of **4** (2–3 equiv. with respect to **3**), because the presence of water and KH_2PO_4 reduced the availability of free amine **4** in the organic phase [Equation (1)].

$$H_2PO_4^{\ominus} + \underset{\mathbf{4}}{R^3R^4NH} \rightleftharpoons HPO_4^{2-} + R^3R^4\overset{\oplus}{N}H_2$$

R^3R^4NH (**4**) and $R^3R^4NH_2^{\oplus}$ partially soluble in water (1)

With the aid of ESI-MS analysis we observed that, with the exception of small, highly reactive ammonium hydroxide (**4a**) and sterically hindered *tert*-butylamine (**4b**), the rate of this reaction was not influenced by the nature of carbamoyl azide **2** or amine **4**.

Purification of the crude urea (CU**1**) obtained after evaporation of THF was carried out in three different ways (Table 1): (i) When CU**1** was a solid or an oil derived from the reaction of **2** with amine **4** slightly soluble in water [e.g., cyclohexylamine (**4c**), benzylamine (**4d**), *N*-methylcyclohexylamine (**4f**), or (*R*)-(+)-1-phenylethylamine (**4i**)], the residue was dissolved in EtOAc, washed with aqueous 0.6 M HCl (1.2 equiv. with respect to **4**) and brine, and the separated organic phase was dried with Na_2SO_4 and concentrated (Method A). (ii) When CU**1** was an oil obtained from the reaction of **2** with amine **4** soluble in water [e.g., ammonium hydroxide (**4a**), *tert*-butylamine (**4b**), *N*,*N*-diethylamine (**4e**), piperidine (**4g**), or morpholine (**4h**)], the residue was dissolved in EtOAc, washed with water and brine, and the separated organic phase was finally dried with Na_2SO_4 and concentrated (Method B). (iii) When CU**1** was a solid obtained from the reaction of **2** and amine **4** soluble in water, the residue was simply thoroughly washed with water and dried (Method C).

In order to exclude the possibility of racemization under our experimental conditions, 1-[1-(ethoxycarbonylamino)-1-phenylmethyl]-3-(1-phenylethyl)urea (**1dbi**) was prepared

Table 1. Yields and some properties of unsymmetrical ureas **1** prepared.

Product[a]	Purification method[b]	Yield [%][c]	M.p. [°C]	$[\alpha]_D^{20}$ (*c*, solvent)
1aba	C	83	169–171, white solid	–32.5 (0.4, MeOH)
1abc	A	94	194–195, white solid	–26.7 (0.3, DMSO)
1bad	A	88	132–134 (decomp.), white solid	–7.2 (0.7, MeOH)
1bbc	A	80	141 (decomp.), white solid	–17.4 (0.2, MeOH)
1bcc	A	72	142–144, white solid	–7.5 (0.4, MeOH)
1bda	C	96	133–134, white solid	–11.1 (0.3, MeOH)
1bdh	B	95	116 (decomp.), white solid	+7.4 (0.7, $CHCl_3$)
1ccb	B	95	110–112, white solid	–6.5 (0.3, $CHCl_3$)
1cce	B	93	85–87, white solid	–22.9 (0.5, $CHCl_3$)
1ccf	A	88	159–161, white solid	–62.9 (0.3, $CHCl_3$)
1dba	C	88	179–181, white solid	–15.0 (0.2, MeOH)
1dbi	A	89	181–183, white solid	–16.6 (0.2, MeOH)
1dca	C	89	176–177, white solid	–33.3 (0.2, MeOH)
1dcd	A	85	151–153, white solid	+10.0 (0.3, MeOH)
1ebc	A	90	173–175, white solid	+12.9 (0.3, DMSO)
1ebd	A	75	164–166, white solid	–35.0 (0.3, DMSO)
1edg	C	89	149–151, white solid	–27.3 (0.3, DMSO)
1edh	C	91	158–160, white solid	–20.0 (0.4, DMSO)
1fbb	C	84	133–135, white solid	–9.6 (0.5, $CHCl_3$)
1fbf	A	86	170–171, white solid	–45.2 (0.5, DMSO)
1gad	A	90	157–159 (decomp.), white solid	–38.5 (0.3, DMSO)
1gbe	B	93	70–71 (decomp.), white solid	+9.5 (0.2, $CHCl_3$)
1gbh	B	96	76–78, white solid	–25.0 (0.3, MeOH)

[a] Satisfactory elemental analyses obtained: C ±0.15, H ±0.10, N ±0.14. [b] See Experimental Section. [c] Isolated yields.

by reaction of *N*-ethoxycarbonyl-L-phenylglycine (**3db**) with (*R*)-(+)-1-phenylethylamine (**4i**), and its ^1H and ^{13}C NMR spectra were compared with those obtained from the reaction of racemic *N*-ethoxycarbonyl-DL-phenylglycine (*rac*-**3db**) with **4i**. The spectra of the diastereoisomeric mixture of 1-[1-(ethoxycarbonylamino)-1-phenylmethyl]-3-(1-phenylethyl)urea (diast-**1dbi**) obtained from *rac*-**3db** evidenced two sets of peaks for each proton and carbon signal, respectively. In contrast, when we carried out the reaction with **3db**, the corresponding spectra of **1dbi** did not exhibit a similar complexity.

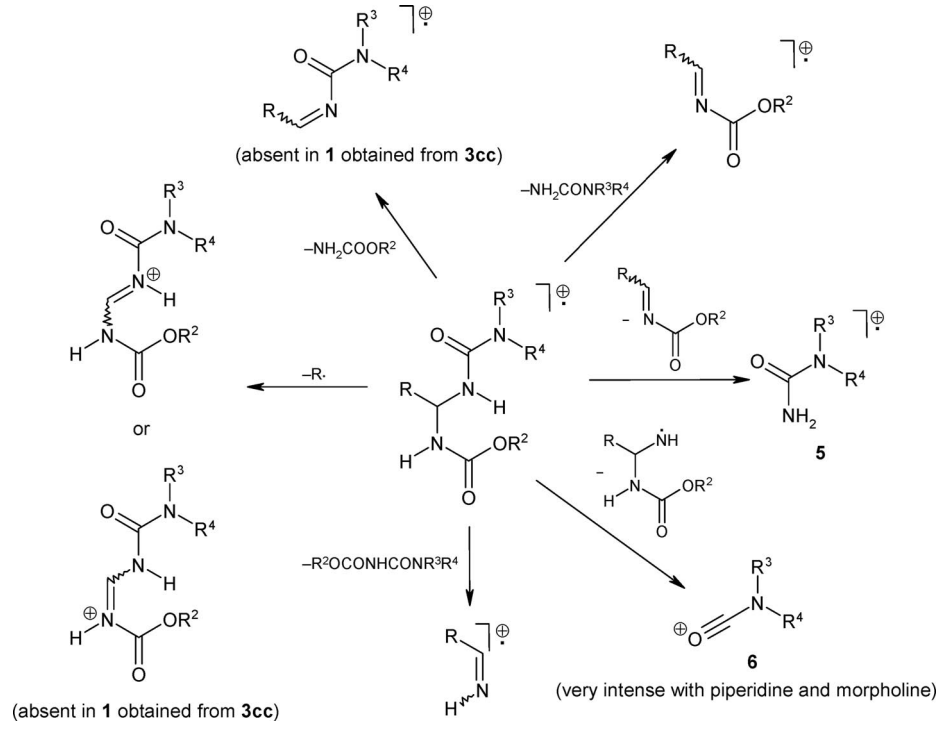
The results obtained and some properties of unsymmetrical ureas **1** are reported in Table 1. Data pertinent to synthesized **1** are collected in the Supporting Information (Table S1).

All the ^1H NMR spectra of unsymmetrical ureas **1** carried out in [D_6]DMSO exhibited a broad doublet (J = 7.9–9.1 Hz) in the range δ = 5.7–6.7 ppm (Supporting Information, Table S1) assigned (^1H–^1H decoupling experiments) to the proton on the urea nitrogen atom linked to the α-carbon atom of the starting amino acid. Similarly, when the amine involved in the reaction was cyclohexylamine (**4c**) or (*R*)-(+)-1-phenylethylamine (**4i**), the resulting ureas, for example, 1-[1-(ethoxycarbonylamino)-2-methylpropyl]-3-cyclohexylurea (**1abc**), 1-[1-(ethoxycarbonylamino)-3-methylbutyl]-3-cyclohexylurea (**1bbc**), 1-[1-(*tert*-butoxycarbonylamino)-3-methylbutyl]-3-cyclohexylurea (**1bcc**), 1-[1-(ethoxycarbonylamino)-2-phenyl]-3-cyclohexylurea (**1ebc**), and 1-[1-(ethoxycarbonylamino)-1-phenylmethyl]-3-(1-phenylethyl)urea (**1dbi**), exhibited a broad doublet (J = 7.9 Hz) in the range δ = 5.6–6.8 ppm attributed to the other urea N-H proton. These results indicate that both αCH-NH and, when present, NH–CH bonds assume a *trans* conformation.[23]

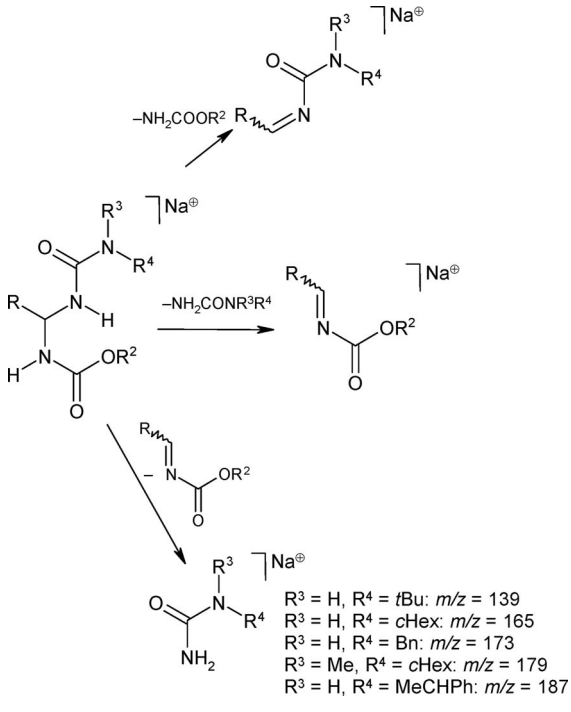
The ^{13}C NMR spectra of **1** evidence the signal of the urea C=O carbon atom in the range δ = 156.2–158.7 ppm (Supporting Information, Table S1). In detail, the four ureas obtained from ammonium hydroxide (**4a**) exhibit the highest chemical shifts at δ = 158.7, 158.0, 158.2, and 158.2 ppm for 1-(ethoxycarbonylamino)-2-methylpropylurea (**1aba**), 1-(benzyloxycarbonylamino)-3-methylbutylurea (**1bda**), ethoxycarbonylaminophenylmethylurea (**1dba**), and *tert*-butoxycarbonylaminophenylmethylurea (**1dca**), respectively.

The EI-MS of unsymmetrical ureas **1** (Supporting Information, Table S1) share the following common features (Scheme 2): (i) absence of the molecular ion, (ii) concerted 1,2-elimination of $R^2OCO\text{-}NHCONR^3R^4$, (iii) loss of urea containing the amine moiety ($NH_2CONR^3R^4$), (iv) presence of the peak corresponding to the radical ion of urea **5**, and (v) presence of acylium ion **6** (very intense when morpholine and piperidine were present). With the exception of *N*-Boc-proline derivatives **1ccb**, **1cce**, and **1ccf**, typical fragmentation processes were also the loss of the amino acid chain radical and of the carbamate moiety (Scheme 2).

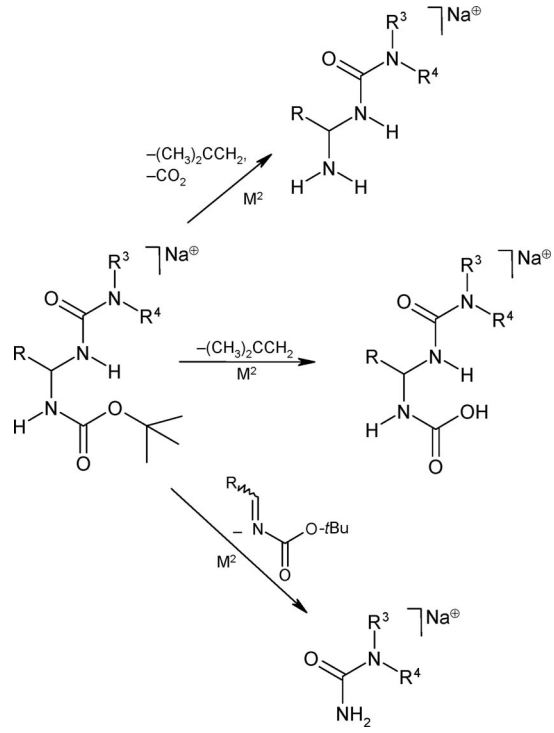
The ESI-MS of **1** (Supporting Information, Table S1) evidence only the sodium-cationized molecule $[M + Na]^+$ in the positive ion mode. With the exception of *N*-Boc-derivatives **1bcc**, **1ccb**, **1cce**, **1ccf**, **1dca**, and **1dcd**, the MS^2 spectra of $[M + Na]^+$ for **1** are characterized (Scheme 3) by the presence of two intense ions due to the loss of the carbamate molecule (NH_2COOR^2) and of the urea containing the amine moiety ($NH_2CONR^3R^4$). In addition, when the amine involved in the formation of **1** contains an alkyl group like cyclohexyl, *tert*-butyl, or benzyl, the peak (15–30% relative intensity) corresponding to the sodium-cationized urea containing the amine moiety $[NH_2CONR^3R^4 + Na]^+$ is also observed (Scheme 3).



Scheme 2.



Scheme 3.



Scheme 4.

In contrast, the MS^2 spectra of $[M + Na]^+$ for *N*-Boc-derivatives **1bcc**, **1ccb**, **1cce**, **1ccf**, **1dca**, and **1dcd** evidence, in addition to $[NH_2COR^3R^4 + Na]^+$, two fragment ions corresponding to the loss of isobutene and CO_2, as indicated in Scheme 4.

Conclusions

We have developed a simple and efficient synthesis of unsymmetrical ureas **1** starting from the carbamoyl azides of α-*N*-protected amino acids. These intermediates are use-

ful building blocks in the synthesis of ureido compounds containing a 1,1-diaminoalkyl residue. The ^{1}H NMR spectra of **1** carried out in [D$_6$]DMSO indicate that both $^{\alpha}$CH-NH and NH–CH bonds assume a *trans* conformation. Moreover, analysis of the EI-MS and ESI-MS^n points out some common fragmentation pathways involving both residues, the amine, and the protecting group of the amino acid, present as substituents in the unsymmetrical urea. We are currently investigating the use of carbamoyl azides of α-*N*-protected amino acids in the synthesis of dipeptidyl ureas.

Experimental Section

General: All *N*-protected amino acids **3** were prepared by reported procedures.[24] All solvents and reagents were purchased from Aldrich Chemical Company and used without further purification. Direct inlet mass spectra (DI-MS) were obtained with a Fisons TRIO 2000 gas chromatograph-mass spectrometer, working in the positive ion 70 eV electron impact mode. Spectra were recorded in the range 35–450 u and temperatures between 100 and 180 °C were found suitable to vaporize all the compounds into the ion source. The reactions were monitored by ESI-MS in the positive ion mode with a Finnigan LXQ (linear trap) by simply diluting the intact reaction mixture with MeCN and directly infusing the obtained solution into the ion source with the aid of a syringe pump. IR spectra were obtained with a Bruker Vector 22 spectrophotometer using the KBr technique for solids and recorded in the range 4000–400 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC-F 200 spectrometer at 200 and 50 MHz, respectively, by using $CDCl_3$ at room temperature or [D$_6$]DMSO at 40 °C as solvents. NMR peak locations are reported as δ values from TMS. Some ^{1}H multiplets are characterized by the term *app* (apparent): this refers only to their appearance and may be an oversimplification. In order to assign the $^{\alpha}$CHN*H*CONH proton resonance, ^{1}H–^{1}H decoupling experiments were performed by irradiating the $^{\alpha}$CH proton at the center of its signal. Optical rotations were determined on suitable solutions (g/100 mL) at 20 °C using a AP-300 automatic polarimeter purchased from ATAGO (Japan). Elemental analyses were performed with a Carlo Erba Mod. 1106 elemental analyzer. Melting points were determined with an automatic Mettler (Mod. FP61) melting point apparatus and are not corrected.

General Procedure for the Synthesis of Unsymmetrical Ureas 1: *N*-Methylmorpholine (NMM; 0.30 mL, 2.73 mmol) was slowly added to a stirred solution of α-*N*-protected amino acid **3** (2.50 mmol) in THF (15 mL). After 5 min, isobutyl chloroformate (IBCF; 0.36 mL, 2.73 mmol) was slowly added to the reaction mixture cooled down to –20 °C and stirring was continued for 20 min at the same temperature. The reaction mixture was subsequently warmed up to 0 °C and a solution of KH_2PO_4 (0.17 g, 1.25 mmol) in H_2O (1 mL) was added in one portion, followed after 5 min by a solution of KH_2PO_4 (1.70 g, 12.50 mmol) and NaN_3 (0.41 g, 6.25 mmol) in H_2O (9 mL). After 30 min at 0 °C, the mixture was warmed up to 45 °C, stirred for 1.5 h, cooled down to room temperature, and the separated organic phase was washed with 30% aqueous NaCl solution (4 mL). The THF solution containing carbamoyl azide **2** was cooled down to 0 °C, and amine **4** (3.75 mmol) was slowly added. The mixture was warmed to room temperature and stirred for an additional 2 h [ammonium hydroxide (**4a**) and *tert*-butylamine (**4b**) required 0.5 and 4 h, respectively]. THF was removed under reduced pressure, and the residue obtained, after suitable purification (see below), gave unsymmetrical urea **1** in 72–96% yield (Table 1; Supporting Information, Table S1).

Purification Methods

Method A: The residue was dissolved in EtOAc (30 mL), and the solution was washed with aqueous 0.6 M HCl (7.5 mL, 4.5 mmol) and brine (15 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo (Table 1).

Method B: The residue was dissolved in EtOAc (30 mL), and the solution was washed with water (10 mL) and brine (15 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo (Table 1).

Method C: The residue was washed three times with water and then dried in vacuo (Table 1).

Synthesis of the Carbamoyl Azide of *N*-Boc-proline 2cc: *N*-Methylmorpholine (NMM; 0.30 mL, 2.73 mmol) was slowly added to a stirred solution of α-*N*-Boc-proline **3cc** (0.54 g, 2.50 mmol) in THF (15 mL). After 5 min, isobutyl chloroformate (IBCF; 0.36 mL, 2.72 mmol) was slowly added to the reaction mixture cooled down to –20 °C and stirring was continued for 20 min at the same temperature. The reaction mixture was subsequently warmed up to 0 °C and a solution of KH_2PO_4 (0.17 g, 1.25 mmol) in H_2O (1 mL) was added, followed after 5 min by a solution of KH_2PO_4 (1.70 g, 12.50 mmol) and NaN_3 (0.41 g, 6.25 mmol) in H_2O (9 mL). After 30 min at 0 °C, the mixture was warmed up to 45 °C, stirred for 1.5 h, and the organic phase was separated and concentrated under reduced pressure. The obtained residue was dissolved in AcOEt (30 mL), washed in sequence with H_2O (10 mL), a buffer solution at ca. pH 7 (KH_2PO_4/K_2HPO_4, 20 mL), 10% HCl (10 mL), and brine (15 mL), and finally dried with Na_2SO_4. After filtration and evaporation of the solvent in vacuo, carbamoyl azide **2cc** remained in analytically pure form (0.55 g, 87% yield). M.p. 89–92 °C (decomp.). $[\alpha]_D^{20}$ = +31.4 (c = 0.4, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3279 (br.), 2982, 2940, 2891, 2253, 2147, 1693, 1524, 1400, 1374, 1222, 1168, 1120, 980, 959, 921, 865, 779, 740, 673 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 [s, 9 H, $(CH_3)_3C$], 1.63–228 (m, 4 H, CH_2CH_2), 3.08–3.30 (m, 1 H, NC*H*H), 330–356 (m, 1 H, NCH*H*), 4.00–4.28 (m, 1 H, *CH), 5.96 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.5 and 24.2, 28.1 and 28.2, 29.8 and 30.8, 46.3 and 46.6, 60.5 and 60.8, 80.1 and 80.3, 153.8 and 153.9, 155.1 (br.) ppm. DI-MS (EI): *m*/*z* (%) = 212 (1), 199 (6), 170 (12), 139 (30), 114 (48), 70 (48), 57 (100), 43 (32), 41 (80). $C_{10}H_{17}N_5O_3$ (255.28): calcd. C 47.05, H 6.71, N 27.43; found C 46.96, H 6.72, N 27.40.

Supporting Information (see footnote on the first page of this article): Spectroscopic and elemental analyses data for compounds **1**.

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