Hydantoin-Free Synthesis of Peptide Ester Isocyanates, Isothiocyanates, and Dipeptidyl Ureas: The Application of Zinc Dust in a Carbonylation Procedure without Base

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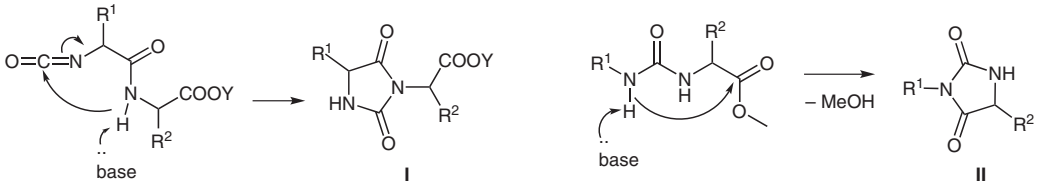
Abstract: Non-Schotten–Baumann conditions are described for the hydantoin-free synthesis of peptide ester isocyanates using activated zinc dust as a non-basic HCl scavenger. Also, the procedure gives no N-acylated products in the case of the conversion of amino acid and peptide amides into isocyanates.

Key words: zinc dust, peptide ester isocyanates, isothiocyanates, base-free synthesis, peptidyl ureas, thioureas

Peptide isocyanates as well as amino acid ester isocyanates constitute synthetic building blocks for the assembly of peptides and a plethora of backbone-modified peptide mimics such as azapeptides, carbazapeptides, peptidyl ureas, heterocycles, and β-lactams, and in the construction of artificial secondary structures.[1] Peptide isocyanates are generally generated by the treatment of peptide esters or resin-bound peptides with carbonylating agents such as phosgene or triphosgene and activated carbonates. In either case, the formation of isocyanates is frequently associated with the co-formation of varying levels of peptide hydantoins **I** as side products (Scheme 1). This side reaction is a major contributor to the decrease in yield and homogeneity of peptide isocyanates. Hydantoin formation takes place through an intramolecular nucleophilic attack by the nitrogen of the peptide bond of the N-terminal amino acid of the peptide on the isocyanato group or activated urethane. This ring-closure process is facilitated by the application of high temperatures[2] or by conditions that can cause ionization of the weakly nucleophilic amide nitrogen, such as the presence of base. The role of the base as the source of this side reaction has been observed by several workers. Nowick et al., obtained appreciable amounts of hydantoins during the treatment of peptide esters with phosgene in the presence of pyridine (base is invariably required to neutralize the liberated HCl, which otherwise will lead to inactivation of the amine through protonation), in the synthesis of peptide isocyanates.[3] A similar observation has been reported by Chong and Patello during the conversion of resin bound N^{α}-Fmoc-protected peptides into isocyanates by treatment with trichloro(methyl)silane in the presence of triethylamine.[4] Consequently, Nowick et al. used modified Schotten–Baumann conditions (CH_2Cl_2–aq Na_2CO_3 biphasic solvent system) without the addition of a tertiary amine base to make isocyanates.[3] Although this method drastically improved the yields, it could not completely overcome hydantoin formation, at least in a few sequence specific examples. Hydantoin formation has also been observed during the activation (either as isocyanate or activated carbamate) of the amino terminus of resin-bound peptides and furthermore, the exclusion of base has been shown to avoid this side reaction.[5] An alternative approach that has been proposed as protection against hydantoin formation is protection of the amide bond with groups such as 2-hydroxy-4-methoxybenzyl (Hmb), so that the generated isocyanate is unable to rearrange into hydantoin.[6]

In pursuit of a mild, straightforward, and hydantoin-free synthesis of peptide isocyanates, we envisaged the use of activated zinc dust as a non-basic HCl scavenger[7] and commercial phosgene in toluene as the carbonylation reagent in organic solvent (non-Schotten–Bauman conditions). Zinc dust serves two purposes in the proposed synthesis viz. trapping of the HCl liberated during the reaction; and deprotonation, in the initial step, of the peptide esters when prepared and used as hydrochloride salts. The use of a tertiary amine for the latter purpose has certain



Scheme 1 Hydantoin formation in the presence of base

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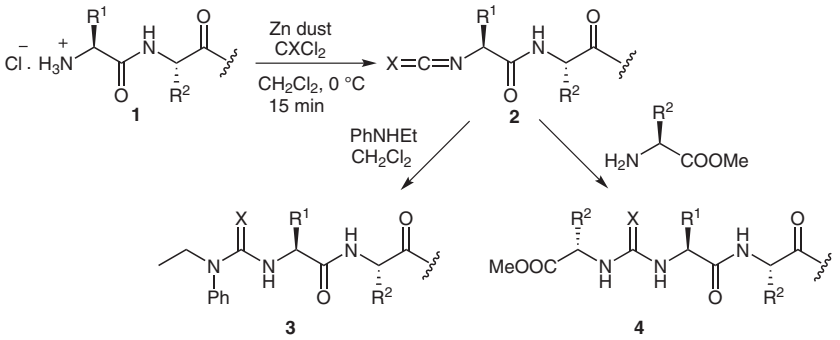


Scheme 2 Synthesis of peptide ester isocyanates and isothiocyanates, and peptidyl ureas and thioureas

limitations per se.[8] Furthermore, since non-Schotten–Baumann conditions are employed, the loss in the yield of the isocyanates (which inherently do not possess an acceptable degree of stability) due to possible hydrolysis by exposure to aqueous solutions (as in Schotten–Baumann condition as reported previously[3]) can be overcome. Phosgene in toluene is a commercially available reagent and unlike gaseous phosgene it can be handled with convenience. Its use offers several advantages with respect to the present synthesis.[9] Accordingly, we herein report an efficient and hydantoin-free synthesis of peptide isocyanates through carbonylation under neutral and non-Schotten–Bauman conditions using zinc as an HCl scavenger. The procedure has been extended to the preparation of peptide ester isothiocyanates and further to the one-pot, two-stage preparation of N,N′-unsymmetrically substituted dipeptidyl ureas and thioureas.

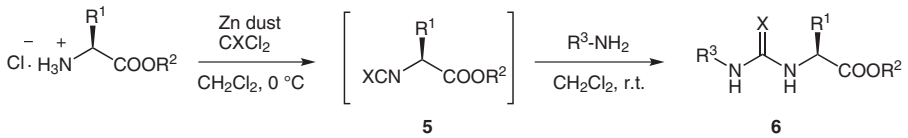
The peptide esters employed as starting materials were prepared as the hydrochloride salts through catalytic hydrogenolysis of the corresponding N^{α}-Z-protected dipeptide esters in the presence of concentrated hydrochloric and acetic acid.[10] In a typical reaction, a suspension of H-Leu-Gly-OMe·HCl (a peptide whose isocyanate has shown to be sensitive to hydantoin formation[3]) and activated zinc dust in anhydrous dichloromethane was stirred at room temperature to convert the hydrochloride salt into the free amino peptide ester. The solution was cooled to 0 °C and treated with phosgene in toluene to produce the desired isocyanate [IR: 2249 cm^{-1}] (Scheme 2). The excess zinc, and the zinc chloride formed were filtered off and the unreacted phosgene was removed through evaporation in vacuo.

The product was not analyzed further in the isocyanate form since peptide ester isocyanates, unlike amino acid ester isocyanates (which are distillable liquids), are not stable to isolation. This has compelled the authors who first described these compounds to analyze them as their urea adducts. The yield and purity of isocyanates were correlated to the corresponding data of the latter.[3] In the present study, we adopted a similar approach for the characterization of the peptide isocyanates. Accordingly, isocyanate **2a** was treated with *N*-ethylaniline to afford the ureido compound **3a**.[11,12] Using the same procedure, OCN-Val-Ala-OMe (**2b**) and OCN-Val-Cys(Me)-Ala-OMe (**2c**), which have also been shown to possess a tendency to form the hydantoin, were prepared. In no case was the expected hydantoin formed. The isocyanates were also coupled with amino acid methyl esters to obtain peptide-urea hybrids **4a**–**d** (Table 1).

The synthesis of peptide isothiocyanates is associated with the formation of peptide thiohydantoins via similar mechanism discussed for the formation of the peptide hydantoin.[13] The application of the present protocol allowed us to prepare peptide ester isothiocyanates. Treatment of dipeptide ester with thiophosgene (2.1 equiv) in presence of zinc dust produced isothiocyanates **2d**, **2e**, and **2i**, which were trapped with *N*-ethylaniline as well as amino acid methyl esters. HPLC as well as ^{1}H NMR analysis of the thioureas confirmed the absence of thiohydantoin.

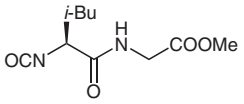
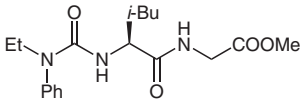
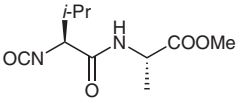
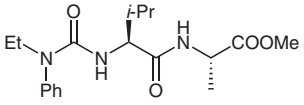
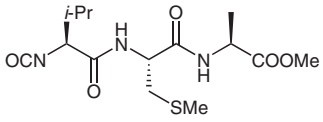
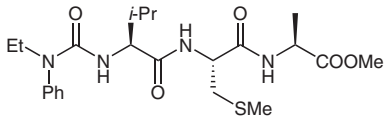
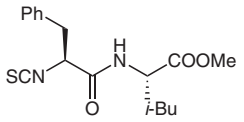
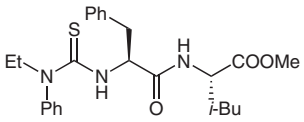
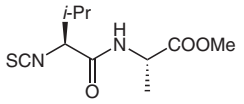
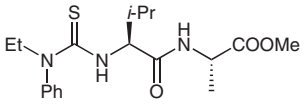
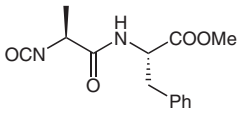
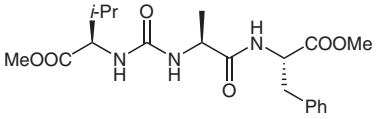
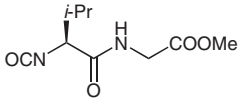
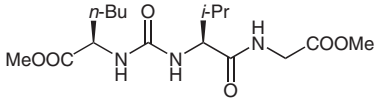
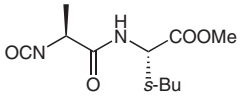
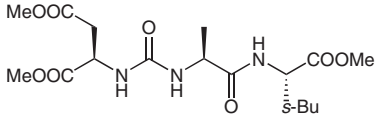
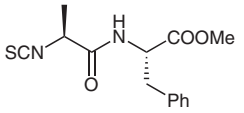
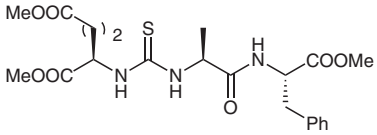
This procedure was extended to the one-pot, two-stage preparation of N,N′-unsymmetrically substituted dipeptidyl ureas **6a**–**f** (Table 2) by treating the hydrochloride salts of amino acid esters with phosgene in toluene in presence of activated zinc dust followed by coupling of the isocyanates **5** directly with amino acid methyl esters [obtained by deprotonation of corresponding HCl salts] with activated zinc dust (Scheme 3).

Ureas **6g**, **6h** as well as thioureas **6i** and **6j** were also prepared by coupling the isocyanates and isothiocyanates (prepared by treating the amino acid esters with thiophosgene under similar conditions) with functionalized alkyl- and arylamines including glycosylamine (Table 2). Such compounds are extensively used as catalysts in asymmetric synthesis.[14] Since the synthesis is devoid of base, the



Scheme 3 Synthesis of N,N′-unsymetrically substituted dipeptidyl ureas

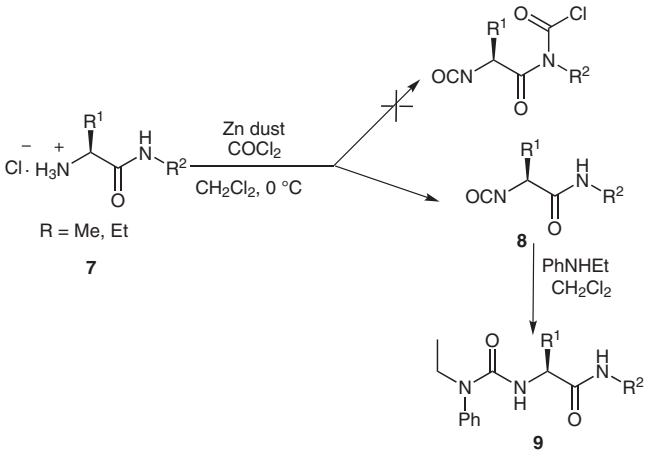
Table 1 Peptide Isocyanates and Isothiocyanates **2** and Peptidyl Ureas and Thioureas **3** and **4** Prepared

Entry	Peptide isocyanate or isothiocyanate **2**		Peptidyl urea or thiourea		Yield (%)	Mp (°C)
1	**2a**		**3a**		91	142–144
2	**2b**		**3b**		89	136–137
3	**2c**		**3c**		86	gum
4	**2d**		**3d**		91	gum
5	**2e**		**3e**		85	131–133
6	**2f**		**4a**		93	158–160
7	**2g**		**4b**		91	167–168
8	**2h**		**4c**		87	149–150
9	**2i**		**4d**		88	gum

known base-catalyzed cyclization into hydantoin **II** (Scheme 1) of compounds that contain an ureido linkage α to the ester bond[15] is precluded. Furthermore, in the one-pot protocol yields are increased.

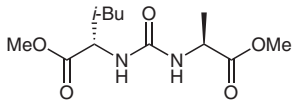
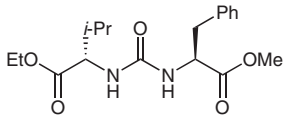
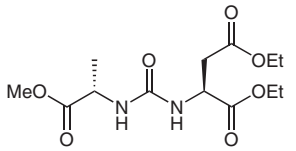
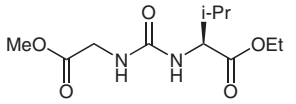
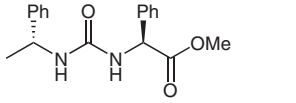
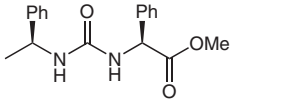
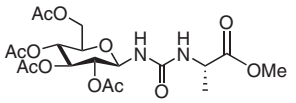
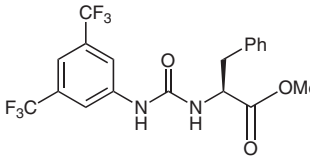
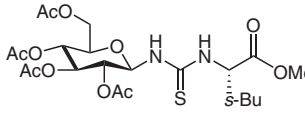
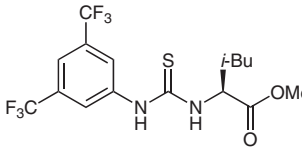
During the preparation of isocyanates of amino acid amides, acylation of the amide bond by phosgene, especially in case of unhindered alkyl amides, has been observed. It was envisaged that zinc dust mediated carbonylation could prevent this undesired acylation since ionization of the amide nitrogen does not take place. Consequently, isocyanates **8a–c** were prepared from amino acid methyl and ethyl amides **7** and coupled directly to *N*-ethylaniline to give the products **9**, which were analyzed (Table 3). In all cases, no N-acylated amide was detected (Scheme 4).[3]

In conclusion, the use of activated zinc as an HCl scavenger during the synthesis of peptide ester isocyanates and isothiocyanates ensures neutral condition and avoids the



Scheme 4 Synthesis of isocyanato amino acid amides **8** and urea adducts **9**

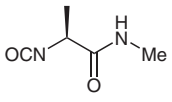
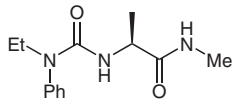
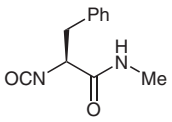
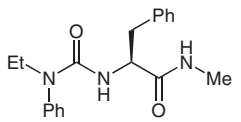
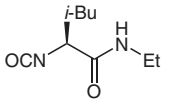
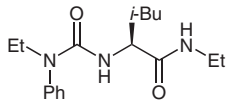
Table 2 N,N′-Unsymmetrical Dipeptidyl Ureas **6**

Entry	Urea derivative **6**		Yield (%)	Mp (°C)
1	**6a**		89	109–110
2	**6b**		85	169–171
3	**6c**		91	81–83
4	**6d**		82	92–94
5	**6e**		88	gum
6	**6f**		85	gum
7	**6g**		84	171–172
8	**6h**		82	121–123
9	**6i**		75	106–108
10	**6j**		92	gum

formation of hydantoin side products. The procedure furnishes quantitative yields and is free from racemization (see experimental part). The protocol can be extended to the preparation of dipeptidyl ureas. Furthermore, isocyanates from amino acid amides can be prepared without acylation of the amide nitrogen. We anticipate that the procedure would be advantageous for preparation of homogenous samples of bioactive compounds from peptide and amino acid isocyanates.

All solvents were distilled prior to use and reagents were used as received from Sigma-Aldrich. Melting points were determined on a Buchi model 150 melting point apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Nicolet model impact 400 D FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz and 100 MHz Bruker spectrometers, respectively. HRMS were recorded on Q-Tof micromass mass spectrometer. Elemental analysis was performed on a Thermo Finnigan FLASH EA 1112 CHN analyzer. Optical rotations were measured on Jasco P2000 digital polarimeter.

Table 3 Urea Adducts **9** Prepared

Entry	Isocyanato amide **8**		Urea adduct **9**		Yield (%)
1	**8a**		**9a**		75
2	**8b**		**9b**		69
3	**8c**		**9c**		71

Activation of Zinc Dust

Commercial zinc must be washed from surface oxides to make it pure sufficiently to carry out reactions; this is called activation of zinc powder. Typically, commercial Zn (400 g) is stirred in 10% HCl (150 mL) for 2 min, filtered, washed with H_2O (300 mL) and acetone (100 mL), and then dried under vacuum at r.t. for 10 min.

Methyl (*S*)-2{(*S*)-2-[3-Ethyl-3-phenylureido]-3-methylbutanamido}propanoate (3b); Typical Procedure

[*Caution: Phosgene is toxic and should be handled with utmost care: use a fume hood.*] To a soln of Val-Ala-OMe·HCl (**1a**, 1.190 g, 5.0 mmol) in anhyd CH_2Cl_2 (50.0 mL), was added activated Zn dust (0.812 g, 25.0 mmol) and stirred for 10 min at r.t. and then cooled to 0 °C. To this, 1.93 M phosgene in toluene (5.2 mL, 20.0 mmol; Sigma-Aldrich) was transferred through a syringe and the mixture was stirred at this temperature for another 10–15 min till completion of the reaction (TLC and IR analysis). The solid residue was filtered off and the filtrate was subjected to evaporation in vacuo. The crude isocyanate (1.106 g, 93%) was then dissolved in anhyd CH_2Cl_2 (20.0 mL) and *N*-ethylaniline (1.21 mL, 9.6 mmol) was added in a single portion at r.t. The mixture was stirred overnight, the solvent was removed under reduced pressure, and the residue was recrystallized (*n*-hexane) to afford the urea **3b** (2.07 g, 89%) as a white solid. The crude product was analyzed by HPLC and NMR analysis, which found no hydantoin formation.

All thiourea compounds were prepared following a similar procedure outlined in the typical procedure by using thiophosgene (2.1 equiv) as the thiocarbonylating agent.

Methyl (*S*)-2-[2-(3-Ethyl-3-phenylureido)-4-methylpentanoamido]acetate (3a)

White solid; yield: 91%; mp 142–144 °C; R_f = 0.42 ($CHCl_3$–MeOH, 7:3).

IR (KBr): 3384, 1752, 1677, 1638 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.1 Hz, 3 H), 0.98 (d, *J* = 5.6 Hz, 3 H), 1.05 (t, *J* = 5.4 Hz, 3 H), 1.49 (dd, *J* = 4.8, 6.9 Hz, 2 H), 1.69–1.73 (m, 1 H), 2.98–3.04 (m, 2 H), 3.52 (s, 3 H), 4.09 (s,

2 H), 4.29–4.33 (m, 1 H), 5.98 (br s, 1 H), 6.03 (br s, 1 H), 6.98 (d, *J* = 4.8 Hz, 1 H), 7.11–7.45 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 19.6, 21.1, 21.3, 31.5, 39.8, 40.1, 50.5, 52.6, 120.4, 120.5, 124.6, 128.8, 128.9, 138.4, 154.9, 168.5, 171.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{27}N_3NaO_4$: 372.1899; found: 372.1879.

Anal. Calcd for $C_{18}H_{27}N_3O_4$: C, 61.87; H, 7.79; N, 12.03; O, 18.32. Found: C, 61.70; H, 7.81; N, 12.16; O, 18.22.

Methyl (*S*)-2[(*S*)-2-(3-Ethyl-3-phenylureido)-3-methylbutanamido]propanoate (3b)
White solid; yield: 89%; mp 136–137 °C; R_f = 0.51 ($CHCl_3$–MeOH, 7:3).

IR (KBr): 3298, 1724, 1691, 1611 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.4 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 1.08 (t, *J* = 5.8 Hz, 3 H), 1.32 (d, *J* = 7.1 Hz, 3 H), 2.53–2.58 (m, 1 H), 3.01–3.08 (m, 2 H), 3.58 (s, 3 H), 4.43 (d, *J* = 3.8 Hz, 1 H), 4.59–4.62 (m, 1 H), 5.96 (br s, 1 H), 6.03 (br s, 1 H), 6.97 (d, *J* = 2.8 Hz, 1 H), 7.08–7.22 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3, 16.1, 16.5, 17.0, 29.5, 45.0, 47.8, 50.6, 60.1, 119.8, 120.0, 123.6, 128.9, 129.0, 138.6, 154.5, 170.0, 170.3.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{27}N_3NaO_4$: 372.1899; found: 372.1855.

Anal. Calcd for $C_{18}H_{27}N_3O_4$: C, 61.87; H, 7.79; N, 12.03; O, 18.32. Found: C, 61.88; H, 7.59; N, 12.08; O, 18.30.

Methyl (*S*)-2-{(*R*)-2-[(*S*)-2-(3-Ethyl-3-phenylureido)-3-methylbutanamido]-3-(methylthio)propanamido}propanoate (3c)
Gum; yield: 86%; R_f = 0.19 ($CHCl_3$–MeOH, 7:3).

IR (neat): 3291, 1738, 1647 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 5.6 Hz, 3 H), 0.81 (d, *J* = 5.9 Hz, 3 H), 1.08 (t, *J* = 6.0 Hz, 3 H), 1.32 (d, *J* = 4.9 Hz, 3 H), 1.98 (s, 3 H), 2.55–2.58 (m, 1 H), 2.61–2.68 (m, 2 H), 3.11–3.15 (m, 2 H), 3.58 (s, 3 H), 4.31 (d, *J* = 2.9 Hz, 1 H), 4.49–4.52 (m, 1 H), 4.77–4.80 (m, 1 H), 5.65 (br s, 1 H), 5.77 (br s, 1 H), 6.19 (br s, 1 H), 6.99 (d, *J* = 3.2 Hz, 1 H), 7.08–7.16 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3, 15.8, 16.0, 16.9, 17.0, 29.8, 35.4, 44.6, 48.0, 50.8, 51.1, 59.5, 119.7, 120.0, 123.6, 128.5, 128.8, 138.7, 154.6, 171.0, 171.2, 171.5.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{34}N_4NaO_5S$: 489.2148; found: 489.2123.

Anal. Calcd for $C_{22}H_{34}N_4O_5S$: C, 56.63; H, 7.34; N, 12.01; O, 17.14; S, 6.87. Found: C, 56.68; H, 7.22; N, 12.00; O, 17.31; S, 6.55.

Methyl (*S*)-2-[(*S*)-2-(3-Ethyl-3-phenylthioureido)-3-phenylpropanamido]-4-methylpentanoate (3d)
Gum; yield: 91%; R_f = 0.51 ($CHCl_3$–MeOH, 9:1).

IR (KBr): 3301, 1750, 1698, 1451 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 5.8 Hz, 3 H), 0.92 (d, *J* = 5.5 Hz, 3 H), 1.10 (t, *J* = 6.1 Hz, 3 H), 1.77–1.79 (m, 1 H), 1.85 (dd, *J* = 3.6, 6.2 Hz, 1 H), 2.89–2.96 (m, 2 H), 3.36–3.41 (m, 2 H), 3.56 (s, 3 H), 3.83–3.91 (m, 1 H), 4.21 (t, *J* = 6.8 Hz, 1 H), 5.96 (br s, 1 H), 6.55 (br s, 1 H), 6.61 (d, *J* = 2.9 Hz, 1 H), 7.01 (br s, 1 H), 6.78–7.31 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.6, 21.3, 21.5, 22.0, 36.8, 39.1, 48.1, 49.4, 50.6, 59.9, 123.9, 125.5, 126.0, 126.1, 127.7, 127.9, 128.5, 128.9, 129.1, 129.4, 138.8, 139.5, 170.8, 171.2, 182.3.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{33}N_3NaO_3S$: 478.2140; found: 478.2125.

Anal. Calcd for $C_{25}H_{33}N_3O_3S$: C, 65.90; H, 7.30; N, 9.22; O, 10.53; S, 7.04. Found: C, 65.80; H, 7.16; N, 9.31; O, 10.28; S, 6.98.

Methyl (*S*)-2-[(*S*)-2-(3-Ethyl-3-phenylthioureido)-3-methylbutanamido]propanoate (3e)
Yellow solid; yield: 85%; mp 131–133 °C; R_f = 0.48 ($CHCl_3$–MeOH, 8:2).

IR (KBr): 3291, 1735, 1648, 1550 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 5.8 Hz, 3 H), 0.81 (d, *J* = 4.9 Hz, 3 H), 1.08 (t, *J* = 6.0 Hz, 3 H), 1.36 (d, *J* = 3.1 Hz, 3 H), 2.18–2.22 (m, 1 H), 3.39–3.40 (m, 2 H), 3.41 (d, *J* = 4.8 Hz, 1 H), 3.51 (s, 3 H), 4.55–4.58 (m, 1 H), 5.89 (br s, 1 H), 6.29 (br s, 1 H), 6.49 (d, *J* = 5.2 Hz, 1 H), 6.48–7.04 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 16.9, 17.1, 17.3, 29.8, 47.1, 49.6, 50.8, 65.5, 123.3, 125.8, 126.3, 128.5, 128.7, 139.8, 170.9, 171.0, 183.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{27}N_3NaO_3S$: 365.1773; found: 365.1759.

Anal. Calcd for $C_{18}H_{27}N_3O_3S$: C, 59.15; H, 7.45; N, 11.50; O, 13.13; S, 8.77. Found: C, 59.05; H, 7.36; N, 11.50; O, 13.22; S, 8.69.

Methyl (*R*)-2-{3-[(*S*)-1-[(*S*)-1-Methoxy-1-oxo-3-phenylpropan-2-ylamino]-1-oxopropan-2-yl]ureido}-3-methylbutanoate (4a)
White solid; yield: 93%; mp 158–160 °C; R_f = 0.31 ($CHCl_3$–MeOH, 7:3).

IR (KBr): 3208, 1751, 1742, 1670 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 4.2 Hz, 3 H), 0.82 (d, *J* = 5.2 Hz, 3 H), 1.44 (d, *J* = 7.1 Hz, 3 H), 2.65–2.72 (m, 2 H), 2.98–3.02 (m, 1 H), 3.55 (s, 3 H), 3.59 (s, 3 H), 4.38 (d, *J* = 2.6 Hz, 1 H), 4.51–4.68 (m, 1 H), 4.71–4.78 (m, 1 H), 5.85 (br s, 1 H), 6.11 (br s, 1 H), 6.18 (br s, 1 H), 7.02–7.19 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8, 17.0, 17.2, 29.1, 36.8, 50.5, 50.6, 51.3, 52.5, 56.8, 120.3, 125.8, 127.3, 128.0, 128.2, 138.1, 155.8, 170.8, 171.0, 171.5.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{29}N_3NaO_6$: 430.1954; found: 430.1948.

Anal. Calcd for $C_{20}H_{29}N_3O_6$: C, 58.95; H, 7.17; N, 10.31; O, 23.56. Found: C, 58.81; H, 7.12; N, 10.19; O, 23.50.

Methyl (*R*)-2-{3-[(*S*)-1-(2-Methoxy-2-oxoethylamino)-3-methyl-1-oxobutan-2-yl]ureido}hexanoate (4b)
White solid; yield: 91%; mp 167–168 °C; R_f = 0.36 ($CHCl_3$–MeOH, 6:4).

IR (KBr): 3301, 2918, 1734, 1759, 1660 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 7.2 Hz, 3 H), 0.83 (d, *J* = 5.6 Hz, 3 H), 0.88 (d, *J* = 5.1 Hz, 3 H), 1.01 (d, *J* = 3.1 Hz, 3 H), 1.12–1.16 (m, 2 H), 2.56–2.60 (m, 1 H), 2.86–2.90 (m, 1 H), 3.48 (s, 3 H), 3.54 (s, 3 H), 4.03 (s, 2 H), 4.35 (d, *J* = 4.8 Hz, 1 H), 4.40 (d, *J* = 6.1 Hz, 1 H), 5.85 (br s, 1 H), 6.01 (br s, 1 H), 6.15 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8, 13.6, 15.7, 15.8, 23.8, 29.5, 34.4, 39.6, 50.8, 51.0, 55.1, 59.8, 156.6, 168.9, 170.8, 171.1.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{29}N_3NaO_6$: 382.1954; found: 382.1939.

Anal. Calcd for $C_{16}H_{29}N_3O_6$: C, 53.47; H, 8.13; N, 11.69; O, 26.71. Found: C, 53.40; H, 8.03; N, 11.88; O, 26.69.

Dimethyl (*R*)-2-{3-[(*S*)-1-(2*S*,3*S*)-1-Methoxy-3-methyl-1-oxopentan-2-ylamino]-1-oxopropan-2-yl]ureido}succinate (4c)
White solid; yield: 87%; mp 149–150 °C; R_f = 0.49 ($CHCl_3$–MeOH, 6:4).

IR (KBr): 3298, 1717, 1735, 1756, 1679, 1547 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.78 (t, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 4.2 Hz, 3 H), 1.18–1.21 (m, 2 H), 1.39 (d, *J* = 5.0 Hz, 3 H), 2.55–2.65 (m, 2 H), 2.86–2.88 (m, 1 H), 3.51 (s, 3 H), 3.53 (s, 3 H), 3.55 (s, 3 H), 4.38 (d, *J* = 3.6 Hz, 1 H), 4.55–4.59 (m, 1 H), 4.96–5.02 (m, 1 H), 5.68 (br s, 1 H), 5.91 (br s, 1 H), 6.25 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.6, 14.8, 16.6, 24.9, 35.5, 35.9, 49.8, 50.5, 50.8, 51.0, 51.2, 52.4, 156.6, 170.8, 171.1, 171.3, 172.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{29}N_3NaO_8$: 426.11852; found: 426.1860.

Anal. Calcd for $C_{17}H_{29}N_3O_8$: C, 50.61; H, 7.25; N, 10.42; O, 31.73. Found: C, 50.49; H, 7.33; N, 10.30; O, 31.48.

Dimethyl (*R*)-2-{(*S*)-3-[(*S*)-1-methoxy-1-oxo-3-phenylpropan-2-ylamino]-1-oxopropan-2-yl]thioureido}pentanedioate (4d)
Gum; yield: 88%; R_f = 0.45 ($CHCl_3$–MeOH, 8:2).

IR (KBr): 3284, 2958, 1724, 1759, 1762, 1669, 1550, 1451 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 4.8 Hz, 3 H), 2.18 (dd, *J* = 3.9 Hz, 2 H), 2.23–2.26 (m, 2 H), 2.96–3.01 (m, 2 H), 3.36 (t, *J* = 7.0 Hz, 1 H), 3.50 (s, 3 H), 3.52 (s, 3 H), 3.58 (s, 3 H), 3.61–3.63 (m, 1 H), 4.71–4.74 (m, 1 H), 6.01 (br s, 1 H), 6.81–7.19 (m, 5 H), 7.25 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.3, 25.4, 27.1, 36.6, 50.8, 51.3, 51.4, 52.0, 55.1, 58.8, 125.4, 126.1, 126.9, 127.3, 128.1, 138.9, 170.8, 171.3, 172.0, 180.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{29}N_3NaO_7S$: 467.1726; found: 467.1708.

Anal. Calcd for $C_{21}H_{29}N_3O_7S$: C, 53.95; H, 6.25; N, 8.99; O, 23.95; S, 6.86. Found: C, 53.79; H, 6.20; N, 8.80; O, 23.70; S, 6.60.

Methyl (*S*)-2-{3-[(*S*)-1-Methoxy-1-oxopropan-2-yl]ureido}-4-methylpentanoate (6a)
White solid; yield: 89%; mp 109–110 °C; R_f = 0.36 (*n*-hexane–EtOAc, 7:3).

$[\alpha]_D^{24}$ –25.6 (*c* 0.1, MeOH).

IR (KBr): 3301, 1744, 1755, 1671 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 5.4 Hz, 3 H), 0.82 (d, *J* = 6.2 Hz, 3 H), 1.36 (d, *J* = 2.9 Hz, 3 H), 1.78–1.82 (m, 3 H), 3.56 (s, 3 H), 3.59 (s, 3 H), 4.08 (t, *J* = 3.1 Hz, 1 H), 4.43–4.48 (m, 1 H), 5.22 (br s, 1 H), 5.56 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 20.6, 20.9, 21.4, 38.8, 49.9, 50.6, 50.9, 51.2, 156.6, 171.0, 171.2.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{29}N_3NaO_7S$: 297.1426; found: 297.1411.

Anal. Calcd for $C_{12}H_{22}N_2O_5$: C, 52.54; H, 8.08; N, 10.21; O, 29.16. Found: C, 52.41; H, 8.00; N, 10.09; O, 29.11.

Ethyl (*S*)-2-{3-[(*S*)-1-Methoxy-1-oxo-3-phenylpropan-2-yl]ureido}-3-methylbutanoate (6b)
White solid; yield: 85%; mp 169–171 °C; R_f = 0.45 (*n*-hexane–EtOAc, 7:3).

$[\alpha]_D^{24}$ –22.0 (*c* 0.35, MeOH).

IR (KBr): 3291, 1744, 1735, 1669, 1451 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 5.2 Hz, 3 H), 0.86 (d, *J* = 6.0 Hz, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 2.91–2.96 (m, 1 H), 3.03–3.13 (m, 2 H), 3.56 (s, 3 H), 4.04–4.09 (m, 2 H), 4.12 (d, *J* = 4.2 Hz, 1 H), 4.38–4.41 (m, 1 H), 5.18 (br s, 1 H), 5.72 (br s, 1 H), 6.98–7.15 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 16.9, 17.0, 29.5, 35.1, 50.4, 54.1, 57.6, 60.9, 124.5, 125.8, 126.7, 127.2, 127.8, 138.4, 156.6, 170.2, 171.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{26}N_2NaO_5$: 373.1739; found: 373.1711.

Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 7.99; O, 22.83. Found: C, 61.59; H, 7.36; N, 7.82; O, 22.88.

Diethyl (*S*)-2-{3-[(*S*)-1-Methoxy-1-oxopropan-2-yl]ureido}succinate (6c)
White solid; yield: 91%; mp 81–83 °C; R_f = 0.45 (*n*-hexane–EtOAc, 7:3).

$[\alpha]_D^{24}$ –21.1 (*c* 0.8, MeOH).

IR (KBr): 3291, 1760, 1771, 1669 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 4.8 Hz, 3 H), 1.28 (t, *J* = 5.2 Hz, 3 H), 1.44 (d, *J* = 6.1 Hz, 3 H), 2.55–2.61 (m, 2 H), 3.58 (s, 3 H), 4.04–4.11 (m, 4 H), 4.33–4.38 (m, 1 H), 4.96–4.98 (m, 1 H), 5.15 (br s, 1 H), 5.28 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 13.9, 16.0, 35.8, 49.1, 49.9, 50.6, 50.4, 60.8, 155.7, 170.2, 170.9, 172.1.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{22}N_2NaO_7$: 341.1325; found: 341.1309.

Anal. Calcd for $C_{13}H_{22}N_2O_7$: C, 49.05; H, 6.97; N, 8.80; O, 35.18. Found: C, 48.98; H, 6.89; N, 8.82; O, 35.10.

Ethyl (*S*)-2-[3-(2-Methoxy-2-oxoethyl)ureido]-3-methylbutanoate (6d)
White solid; yield: 82%; mp 92–94 °C; R_f = 0.40 (*n*-hexane–EtOAc, 6:4).

$[\alpha]_D^{24}$ –52.2 (*c* 0.6, MeOH).

IR (KBr): 3285, 1745, 1669, 1516 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 5.1 Hz, 3 H), 0.82 (d, *J* = 4.9 Hz, 3 H), 2.96–3.01 (m, 1 H), 3.58 (s, 3 H), 3.60 (s, 3 H), 3.91 (s, 2 H), 4.28 (d, *J* = 6.1 Hz, 1 H), 5.09 (br s, 1 H), 5.18 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 16.8, 29.1, 41.2, 50.5, 50.9, 56.8, 156.6, 168.9, 170.4.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{20}N_2NaO_5$: 283.1270; found: 283.1244.

Anal. Calcd for $C_{11}H_{20}N_2O_5$: C, 50.76; H, 7.74; N, 10.76; O, 30.73. Found: C, 50.59; H, 7.79; N, 10.65; O, 30.70.

Methyl (*S*)-2-Phenyl-2-{3-[(*R*)-1-phenylethyl]ureido}acetate (6e)
Gum; yield: 88%; R_f = 0.55 (*n*-hexane–EtOAc, 7:3).

$[\alpha]_D^{24}$ –10.2 (*c* 1.0, MeOH).

IR (neat): 3288, 1733, 1666 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (d, *J* = 4.1 Hz, 3 H), 3.59 (s, 3 H), 4.91–4.94 (m, 1 H), 5.13 (br s, 1 H), 5.43 (s, 1 H), 5.56 (br s, 1 H), 7.05–7.23 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4, 50.8, 51.5, 56.7, 124.4, 124.5, 125.6, 125.8, 126.9, 127.0, 127.4, 128.4, 128.6, 128.9, 134.6, 142.8.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{20}N_2NaO_3$: 335.1372; found: 335.1366.

Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97; O, 15.37. Found: C, 69.18; H, 6.36; N, 8.98; O, 15.29.

Methyl (*S*)-2-Phenyl-2-{3-[(*S*)-1-phenylethyl]ureido}acetate (6f)

Gum; yield: 85%; R_f = 0.55 (*n*-hexane–EtOAc, 7:3).

$[\alpha]_D^{24}$ +22.2 (*c* 1.0, MeOH).

IR (neat): 3300, 1735, 1665 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (d, *J* = 5.8 Hz, 3 H), 3.50 (s, 3 H), 4.01–4.13 (m, 1 H), 5.18 (br s, 1 H), 5.55 (br s, 1 H), 5.61 (s, 1 H), 7.11–7.28 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 50.1, 51.9, 55.5, 124.1, 124.5, 125.5, 125.9, 127.3, 127.6, 128.1, 128.4, 128.5, 129.0, 134.1, 141.2.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{20}N_2NaO_3$: 335.1372; found: 335.1359.

Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97; O, 15.37. Found: C, 69.11; H, 6.51; N, 8.68; O, 15.30.

Methyl (*S*)-2-[3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glycopyranosyl)ureido]propanoate (6g)

White solid; yield: 84%; mp 171–172 °C; R_f = 0.49 (*n*-hexane–EtOAc, 6:4).

$[\alpha]_D^{24}$ +41.6 (*c* 1.0, MeOH).

IR (KBr): 3300, 1741, 1735, 1665 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 6.9 Hz, 3 H), 2.01 (s, 3 H), 2.06 (s, 3 H), 2.12 (s, 3 H), 2.19 (s, 3 H), 3.55 (s, 3 H), 3.90 (t, *J* = 8.6 Hz, 1 H), 4.10 (d, *J* = 6.4 Hz, 2 H), 4.29 (d, *J* = 10.2 Hz, 1 H), 4.44–4.51 (m, 1 H), 5.01 (dd, *J* = 3.3, 10.5 Hz, 1 H), 5.52 (t, *J* = 9.6 Hz, 1 H), 6.01 (dd, *J* = 0.82, 3.6 Hz, 1 H), 6.78 (br s, 1 H), 6.91 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 20.0, 20.3, 20.9, 21.0, 50.8, 51.7, 61.6, 67.2, 69.5, 69.9, 70.5, 78.2, 155.5, 169.2, 170.1, 171.0, 171.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{28}N_2NaO_{12}$: 499.1540; found: 499.1512.

Anal. Calcd for $C_{19}H_{28}N_2O_{12}$: C, 47.90; H, 5.92; N, 5.88; O, 40.30. Found: C, 47.78; H, 5.75; N, 5.35; O, 40.12.

Methyl (*S*)-2-{3-[3,5-Bis(trifluoromethyl)phenyl]ureido}-3-phenylpropanoate (6h)

White solid; yield: 82%; mp 121–123 °C; R_f = 0.45 (*n*-hexane–EtOAc, 8:2).

$[\alpha]_D^{24}$ –15.8 (*c* 1.0, $CHCl_3$).

IR (KBr): 3288, 1733, 1666, 1498 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.98–3.16 (m, 2 H), 3.55 (s, 3 H), 4.77 (dd, *J* = 2.6, 4.8 Hz, 1 H), 5.85 (br s, 1 H), 6.09 (br s, 1 H), 7.02 (d, *J* = 5.4 Hz, 1 H), 7.11 (d, *J* = 3.9 Hz, 1 H), 7.18–7.23 (m, 2 H), 7.42 (s, 1 H), 7.87 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.8, 55.0, 117.6, 119.7, 119.9, 123.6, 123.7, 125.5, 127.7, 127.8, 128.5, 128.8, 130.5, 130.9, 135.8, 138.9, 155.2, 170.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{16}F_6N_2NaO_3$: 457.0963; found: 457.0911.

Anal. Calcd for $C_{19}H_{16}F_6N_2O_3$: C, 52.54; H, 3.71; F, 26.24; N, 6.45; O, 11.05. Found: C, 52.50; H, 3.19; F, 25.88; N, 6.59; O, 11.00.

Methyl (*S*)-3-Methyl-2-[3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glycopyranosyl)thioureido}pentanoate (6i)

White solid; yield: 75%; mp 106–108 °C; R_f = 0.40 (*n*-hexane–EtOAc, 7:3).

$[\alpha]_D^{25}$ –3.8 (*c* 1.0, $CHCl_3$).

IR (KBr): 3211, 1739, 1734, 1698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.1 Hz, 3 H), 1.02 (d, *J* = 8.2 Hz, 3 H), 1.13–1.18 (m, 2 H), 2.00 (s, 3 H), 2.04 (s, 3 H), 2.14 (s, 3 H), 2.19 (s, 3 H), 2.41–2.49 (m, 1 H), 3.25 (d, *J* = 3.2 Hz, 1 H), 3.59 (s, 3 H), 4.11–4.23 (m, 2 H), 4.31 (dd, *J* = 3.6, 11.4 Hz, 1 H), 4.38–4.44 (m, 1 H), 4.61–4.77 (dd, *J* = 2.8, 7.9 Hz, 1 H), 5.11 (dd, *J* = 2.9, 9.6 Hz, 1 H), 5.43 (t, *J* = 5.8 Hz, 1 H), 6.01 (br s, 1 H), 7.11 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 15.1, 20.1, 20.5, 20.9, 21.2, 24.8, 35.8, 50.9, 58.6, 59.3, 67.8, 69.1, 72.1, 75.4, 86.1, 169.6, 170.4, 171.1, 171.5, 171.8, 181.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{34}N_2NaO_{11}S$: 557.1781; found: 557.1745.

Anal. Calcd for $C_{22}H_{34}N_2O_{11}S$: C, 49.43; H, 6.41; N, 5.24; O, 32.95; S, 6.00. Found: C, 49.40; H, 6.21; N, 5.25; O, 32.54; S, 5.98.

Methyl (*S*)-2-{3-[3,5-Bis(trifluoromethyl)phenyl]thioureido}-4-methylpentanoate (6j)

Gum; yield: 92%; R_f = 0.55 (*n*-hexane–EtOAc, 8:2).

$[\alpha]_D^{24}$ –15.8 (c 1.0, $CHCl_3$).

IR (neat): 3129, 1703, 1638 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 5.8 Hz, 3 H), 1.01 (d, *J* = 7.1 Hz, 3 H), 1.22–1.25 (m, 2 H), 2.40–2.44 (m, 1 H), 3.28 (d, *J* = 6.2 Hz, 1 H), 3.55 (s, 3 H), 4.98 (br s, 1 H), 5.15 (br s, 1 H), 6.96 (s, 2 H), 7.09 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8, 14.6, 24.4, 35.8, 50.5, 59.4, 118.7, 123.6, 123.7, 124.5, 124.6, 129.8, 130.5, 136.8, 170.4, 175.8.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{18}F_6N_2NaO_2S$: 439.0891; found: 439.0875.

Anal. Calcd for $C_{16}H_{18}F_6N_2O_2S$: C, 46.15; H, 4.36; F, 27.38; N, 6.73; O, 7.68; S, 7.70. Found: C, 46.11; H, 4.22; F, 27.20; N, 6.59; O, 7.44; S, 7.61.

(*S*)-1-Ethyl-3-[1-(methylamino)-1-oxopropan-2-yl]-1-phenylurea (9k)

White solid; yield: 75%; mp 122–124 °C; R_f = 0.55 ($CHCl_3$–MeOH, 6:4).

$[\alpha]_D^{25}$ +35.9 (*c* 1.0, $CHCl_3$).

IR (KBr): 3200, 1708, 1649 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.0 Hz, 3 H), 1.32 (d, *J* = 4.6 Hz, 3 H), 2.55 (s, 3 H), 3.11–3.15 (m, 2 H), 4.51–4.54 (m, 1 H), 5.91 (br s, 1 H), 6.98 (d, *J* = 3.8 Hz, 1 H), 7.11–7.29 (m, 4 H), 7.75 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 16.1, 25.8, 45.0, 50.6, 120.5, 120.6, 124.2, 128.4, 128.8, 138.8, 154.6, 171.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{19}N_3NaO_2$: 272.1375; found: 272.1349.

Anal. Calcd for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85; O, 12.84. Found: C, 62.41; H, 7.32; N, 16.39; O, 12.41.

(*S*)-1-Ethyl-3-[1-(methylamino)-1-oxo-3-phenylpropan-2-yl]-1-phenylurea (9l)

White solid; yield: 69%; mp 114–116 °C R_f = 0.58 ($CHCl_3$–MeOH, 6:4).

$[\alpha]_D^{25}$ +29.5 (*c* 1.0, $CHCl_3$).

IR (KBr): 3211, 1751, 1654 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.2 Hz, 3 H), 2.51 (s, 3 H), 2.88–3.05 (m, 2 H), 3.11–3.14 (m, 2 H), 4.76–4.79 (m, 1 H), 5.91 (br s, 1 H), 6.96–7.23 (m, 10 H), 7.55 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.6, 25.4, 36.1, 44.8, 55.0, 120.6, 120.9, 123.4, 125.8, 127.6, 128.8, 129.0, 129.1, 129.3, 138.5, 138.8, 154.4, 171.2.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{23}N_3O_2$: 348.1688; found: 348.1657.

Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91; O, 9.83. Found: C, 70.05; H, 7.10; N, 12.88; O, 9.36.

(*S*)-1-Ethyl-3-[1-(ethylamino)-4-methyl-1-oxopentan-2-yl]-1-phenylurea (9m)

White solid; yield: 71%; mp 151–153 °C; R_f = 0.36 ($CHCl_3$–MeOH, 6:4).

$[\alpha]_D^{25}$ –1.9 (*c* 1.0, $CDCl_3$).

IR (KBr): 3196, 1745, 1600 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 7.2 Hz, 3 H), 0.88 (d, *J* = 5.1 Hz, 3 H), 1.05 (t, *J* = 7.2 Hz, 3 H), 1.16 (t, *J* = 6.9 Hz, 3 H), 1.65–1.69 (m, 2 H), 1.77–1.82 (m, 1 H), 3.11–3.14 (m, 2 H), 3.19–3.22 (m, 2 H), 4.41 (t, *J* = 3.1 Hz, 1 H), 5.85 (br s, 1 H), 7.02–7.71 (m, 5 H), 7.78 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2, 14.3, 20.4, 21.5, 21.7, 33.8, 39.5, 45.6, 52.5, 119.8, 120.2, 122.7, 128.8, 128.9, 138.6, 155.0, 170.7.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{17}H_{27}N_3NaO_2$: 328.2001; found: 328.1992.

Anal. Calcd for $C_{17}H_{27}N_3O_2$: C, 66.85; H, 8.91; N, 13.76; O, 10.48. Found: C, 66.49; H, 8.87; N, 13.59; O, 10.20.

Racemization Studies

The NMR spectra of the crude samples of epimeric ureas **6e** and **6f** were prepared via the present protocol by coupling the crude isocyanate derived from **5e** with (*R*)-phenylethylamine and (*S*)-phenylethylamine, respectively, showed signals as follows. A single doublet at δ = 1.41 ppm for **6e** and a single doublet at δ = 1.45 ppm for **6f** corresponding to the methyl group. The 1:1 mixture of these compounds prepared by coupling racemic (*R*/*S*)-phenylethylamine contained two methyl group doublets at δ = 1.40 and 1.43 ppm. This showed that the samples of **6e** and **6f** analyzed contained a single enantiomerically pure compound. Consequently, it was concluded that the present protocol did not destroy the integrity of the chiral centers of the components.

Supporting Information for this article is available online at http//www.thieme-connect.com/ejournals/toc/synthesis.

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