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Isocyanates of N^{α}-[(9-Fluorenylmethyl)oxy]carbonyl Amino Acids: Synthesis, Isolation, Characterization, and Application to the Efficient Synthesis of Urea Peptidomimetics

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The Curtius rearrangement of Fmoc-amino acid azides **1** was carried out in toluene by refluxing the solution for 30 min. The resulting isocyanates **2** have been isolated as crystalline solids and are fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. They are found to be stable for several months when stored at 4 °C. The acyl azides of Asp, Glu, Ser, Tyr, and Lys with side-chain protection having *tert*-butyl, benzyl, and Boc groups were also converted to the corresponding isocyanates **2h**−**m**. The rearrangement of Fmoc-amino acid azides in toluene to isocyanates **2** under microwave irradiation was also accomplished. The direct exposure of solid azides to microwaves for 60 s led to the completion of the rearrangement. The resulting isocyanates, after recrystallization, were found to be analytically pure. The scale-up of the rearrangement, under microwave irradiation as tested up to 0.75 mol, posed no problems and led to the isolation of the isocyanates in 91−96% yield. The utility of isocyanates as building blocks in the synthesis of urea peptides **4** is demonstrated. Further, the coupling of isocyantes **2** directly with *N*,*O*-bis(trimethylsilyl) derivatives of amino acids **6** resulted in urea peptide acids **7** with good yield in high purity. Thus, the synthesis of urea peptide acids **7d**−**g** containing Asp, Glu, Ser, and Tyr with a free side-chain functional group have been carried out.

Introduction

Recently, there is a considerable effort on the insertion of urea moiety as a replacement for the amide bond in peptides to obtain peptidomimetics.[1−4] It is widely believed that such molecules are relatively rigid compared with peptides and possess metabolic stability and improved pharmacokinetic properties such as absorption, transport characteristics, and lower toxicity. The Rana group demonstrated that a small Tat-derived oligourea binds TAR RNA specifically with high affinity and interacts in the widened major groove of TAR RNA similar to Tat peptides.[5] On the other hand, the Nowick group has developed artificial β-sheets of greater size comprising diurea molecular scaffolds and peptide strands.[6]

The synthesis of unsymmetrical ureas involves the reaction of an isocyanate and primary amine.[7] The isocyanates derived from hydrochloride salts of amino acid esters and peptide esters have been prepared from the corresponding amino component by refluxing in toluene while sparging with gaseous phosgene over a period of several hours[8] or by the addition of a solution of phosgene in toluene either under biphasic conditions using aqueous sodium carbonate solution[9] or by using excess of pyridine.[10]

The use of triphosgene [bis(trichloromethyl)carbonate] instead of phosgene, though reported to result in contaminants,[9] is a preferred alternative with a view to develop green chemistry.[11]

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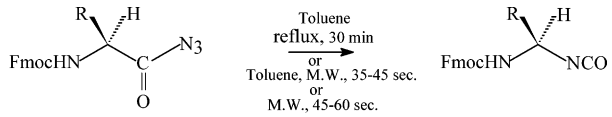
Interest in monomeric building blocks that are useful in the synthesis of ureas has led to the development of carbamates such as *p*-nitrophenyl carbamates,[12] 2,4,5-trichlorophenyl carbamates,[13] and (phenoxycarbonyl)-tetrazole.[14] The carbamates can be prepared by the reaction of isocyanates and substituted phenol. Alternatively, chloroformates are treated with monoprotected diamines which are obtained by the reduction of alkyl azides[15] or of nitriles[16] or by the conversion of isocyanates to N,N^1-diacyl-1,1-diamino derivatives from which one of the acyl groups had to be suitably deprotected.[17] Several other routes and reagents such as the use of azido *p*-nitrophenyl carbamates,[18] N,N^1-carbonyldiimidazole,[19] $1,1^1$-carbonylbisbenzotriazole,[20] or N,N^1-disuccinimido carbonate[21] and thermolytic cleavage of oxime−carbamate resins[22] have been explored for the synthesis of urea peptides. Thus, the application of the above approaches, in principle, needs the conversion of α-amino group of amino acid esters or peptide esters to isocyanates which can be used directly or via carbamates to prepare urea peptides. These methods, in general, involve multiple steps and further require preparation of reagent, long reaction time, and use of large excess of reagents. However, the conversion of N^{α}-[(9-fluorenylmethyl)oxy]-carbonyl (Fmoc)-protected α-amino acids to their isocyanates using Curtius rearrangement via acid azides as key intermediates is yet to be exploited.[17,23,24] We describe in this paper the synthesis, isolation, and characterization of Fmoc-protected isocyanates from aliphatic and aromatic amino acid azides and also include amino acids having functional side chains protected by *tert*-butyl and benzyl groups. We also demonstrate the utility of the isocyanates in the synthesis of urea dipeptide esters and free acids.

SCHEME 1



1 **2**

R : H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH_2C_6H_5$, C_6H_5,
a b c d e f g

$CH2COO^tBu$, $CH_2CH_2COO^tBu$, CH_2O^tBu, $CH_2C_6H_5O^tBu$, $CH_2OCH_2C_6H_5$,
h I J k l

$(CH_2)_4NHBoc$
m

Results and Discussion

Preparation of Isocyanates. Similar to acid chlorides and acid fluorides,[25,26] acid azides of Fmoc-protected amino acids have been shown by us to be crystalline solids with a long-shelf life at room temperature as well as stability during washing with aqueous media.[27] Treatment of the acid chlorides of Fmoc-amino acids with NaN_3 gave the corresponding acid azides **1**. The isocyanates **2a**−**g*** have been prepared upon heating Fmoc-protected acyl azides in toluene at 65 °C (Scheme 1). The course of the reaction was followed by TLC and IR and was found to be complete in ca. 30 min. The resulting isocyanates **2a**−**g***, after the evaporation of toluene under reduced pressure, were isolated as solids in 83−92% yields. In general, there was no need to subject them to any purification steps and they can be employed directly in further reactions. Recrystallization from dichloromethane (DCM) and *n*-hexane gave analytically pure samples. A list of isocyanates **2a**−**g*** made along with their physical constants is given in Table 1. They are completely soluble in solvents such as dichloromethane, chloroform, ethyl acetate, and tetrahydrofuran and were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. Their IR spectra contain a sharp peak characteristic of carbonyl stretching vibrational frequency at around 2247−2257 cm^{-1}. Isocyanates are found to be stable crystalline solids that can be stored at 4 °C for months without any decomposition. However, storage at room temperature for more than 24 h led to their decomposition.

As the amino acid chlorides bearing the side chains with *tert*-butyl protection are unstable, the mixed anhydride method using isobutyloxy carbonyl chloride and treatment with NaN_3 was used for the synthesis of the acid azides **1h**−**m**. Thus, the isocyanates **2h**−**m** derived from glutamic acid, aspartic acid, serine, tyrosine, and lysine bearing *tert*-butyl, benzyl, or Boc groups have been obtained as crystalline solids with good yields (78−85%, Table 2). Their conversion into the corresponding isocyanates **2h**−**m** was found to be straightforward and smooth without the formation of any contaminants.

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TABLE 1. Conversion of Fmoc-amino Acid Azide 1a−g*[a] to the Corresponding Isocyanate 2a−g*[a]

reactant 1	product 2	method[b]	time	yield[c] (%)	mp (°C)	IR[d] (cm^{-1})	$[\alpha]^{25}_D$ (*c* 1, $CHCl_3$)	^1H NMR (δ, $CDCl_3$)	^{13}C NMR (δ, $CDCl_3$)
Gly	**2a**	A	30 min	83	142	2255		3.2 (2H, d), 4.2 (1H, t), 4.4	27.3, 47.0, 66.6, 120.0,
		B	45 s	88				(2H, d), 5.5 (1H, br), 7.25−7.8	124.8, 126.1, 127.1, 127.6,
		C	60 s	94				(8H, m)	143.2, 144.0, 156.5
Ala	**2b**	A	30 min	87	111	2257	−33.4	1.2 (3H, d), 3.80 (1H, m), 4.2	17.3, 47.1, 48.7, 66.6,
								(1H, t), 4.4 (2H, d), 5.2 (1H,	120.0, 124.7, 126.6, 127.1,
								d), 7.2−7.85 (8H, m)	127.7, 141.2, 143.5, 156.5
Val	**2c**	A	30 min	89	154	2247	−38.8	0.95 (6H, d), 1.9 (1H, m), 3.85	18.6, 19.4, 29.3, 47.2, 59.0,
								(1H, t), 4.1 (2H, d), 4.29	66.7, 119.9, 12 124.8,
								(1H, t), 5.1 (1H, d), 7.3−7.5	126.4, 126.9, 127.6,
								(8H, m)	141.2, 144.0, 156.9
Leu	**2d**	A	30 min	86	112	2248	−23.2	0.95 (6H, d), 1.5−1.8 (3H, m),	22.1, 23.0, 24.6, 40.2, 47.4,
		B	40 s	91				4.15 (1H, t), 4.4(3H, m),	51.3, 66.6, 122.0, 124.8,
		C	60 s	96				5.15 (1H, br), 7.25−7.8 (8H, m)	126.8, 127.1, 127.5, 141.3,
									143.6, 156.8.
Ile	**2e**	A	30 min	92	104	2252	−32.7	0.9 (6H, d), 1.7−2.0 (3H, m),	11.2, 15.6, 25.3, 35.6,
								4.2 (1H, t), 4.3−4.4 (3H, m),	47.2, 57.3, 66.6, 119.9,
								5.15 (1H, br), 7.2−7.85 (8H, m)	125.1, 126.9, 127.2, 127.7,
									141.5, 143.9, 156.8.
Phe	**2f**	A	30 min	86	124	2257	−43.62	2.45 (2H, m), 4.2 (1H, t),	37.4, 47.2, 54.5, 66.5,
		B	40 s	89				4.3−4.4 (3H, m), 5.15	120.0, 124.8, 126.8, 127.1,
		C	50 s	95				(1H, br), 7.2−7.85 (13H, m)	127.7, 127.9, 128.5, 129.4,
									137.6, 141.5, 144.1, 156.6.
Phg	**2g**	A	30 min	89	164	2248	−33.2	4.2 (1H, t), 4.35−4.5 (3H, m),	47.4, 56.1, 66.6, 120.0,
								5.8 (1H, br) 7.2−7.8 (13H, m)	124.8, 126.0, 126.9, 127.6,
									127.8, 128.7, 129.3, 138.0,
									141.5, 144.2, 156.8.
Phg[b]	**2g**[b]	A	30 min	86	161	2249	+33.0	4.05 (1H, t), 4.3−4.5 (3H, m),	47.3, 56.1, 66.5, 119.9,
								5.8 (1H, br), 7.3−7.8 (13H, m)	124.8, 126.0, 126.9, 127.6,
									127.8, 128.8, 129.5, 138.0,
									141.3, 144.1, 156.7

[a*] D-configuration. [b] Method A: reflux in toluene. Method B: microwave irradiation in toluene. Method C: microwave irradiation using solid powder. All compounds except Gly, unless specified, had the L-configuration. [c] Isolated yield after crystallization. [d] Vibrational frequency of isocyanate carbonyl group.

Microwave-Assisted Synthesis of Isocyanates. In recent years, microwave-accelerated organic syntheses has gained prominence in developing alternative route for the synthesis of organic compounds with higher yields and without impurities in shorter periods of time circumventing the use of large quantities of solvents accompanied by tedious workup procedures.[28] To the best of our knowledge, the Curtius rearrangement of acid azides to its isocyanates under microwave irradiation is not yet reported.[28] In the present study, it was found that the exposure of acid azides **1** in limited amount of toluene to microwaves for 45 s. using an unmodified domestic microwave oven at its 60% power gave the isocyanates **2** in 85−91% yield.

Further improvements in organic syntheses have been achieved by carrying out the reactions in solid state which avoid the handling of large quantities of toxic solvents such as toluene has gained a lot of attention in recent studies.[29] In line with such studies, it is now found that the direct exposure of naked powdered solid acid azides **1** as such to microwaves for 60 s resulted in complete rearrangement to isocyanates **2**. The reaction was found to be clean and complete. The recrystallization of the resulting isocyanates gave analytically pure compounds. The bifunctional amino acids bearing *tert*-butyl, benzyl, and Boc groups for side chain protection were also converted to the corresponding isocyanates **2h**−**m** by this procedure. More importantly, it has led to the isolation of the isocyanates **2** in about 9−14% more yield when compared with the conventional procedure. Thus, the use of toluene in the classical thermal heating of acyl azides **1** is completely circumvented.

Synthesis of Urea Dipeptides. Reacting isocyanates **2** with amino acid esters **3** in the presence of a base like *N*-ethyldiisopropylamine (DIEA) or *N*-methyl morpholine (NMM) at room-temperature resulted in the urea derivatives **4a**−**k** (Scheme 2). The reaction proceeds rapidly, and the starting materials were generally consumed within 20 min. All the compounds **4a**−**k** made have been separated out as solids. Subsequent filtration and recrystallization using dimethyl sulfoxide (DMSO)−water mixture gave analytically pure compounds. Unlike in the case of carbamates which involve the formation of *N*-hydroxysuccinimide, 2,4,5-trichloro phenol, as byproducts and hence have to be separated by aqueous wash, the use of isocyanates for urea derivatives synthesis is not only rapid but also the workup as well as the isolation of the products is simple. Thus, the entire protocol starting from using isolated acid azides **1** to urea derivatives **4** is executed in an organic phase which circumvents the exposure of isocyanates to aqueous media.

Synthesis of N^{α}-Fmoc-Protected Urea Dipeptide Acids. The urea derivatives are almost completely insoluble in most of the organic solvents regularly

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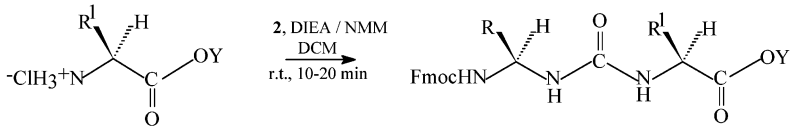
TABLE 2. Conversion of Fmoc-amino Acid Azide 1h−m to the Corresponding Isocyanate 2h−m

reactant **1**	product **2**	method[a]	time	yield[b] (%)	mp (°C)	IR[c] (cm^{-1})	$[\alpha]^{25}_D$ (*c* 1, $CHCl_3$)	^1H NMR (δ, $CDCl_3$)	^{13}C NMR (δ, $CDCl_3$)
Asp (O^{t}Bu)	**2h**	A	30 min	78	148	2256	−31.2	1.35 (9H, s), 2.8 (2H, m), 4.1−4.45 (4H, m), 5.1 (1H, s), 7.2−7.7 (8H, m)	28.1, 37.4, 47.0, 50.1, 66.5, 81.4, 119.9, 124.8, 127.1, 127.5, 127.7, 141.2, 144.0, 156.3, 172.3.
		B	40 s	86					
		C	50 s	91					
Glu (O^{t}Bu)	**2i**	A	30 min	85	86	2255	−29.5	1.4 (9H, s), 1.8−2.35 (4H, m), 3.80 (1H, m), 3.9 (1H, t), 4.3 (2H, d), 5.25 (1H, s), 7.2−7.75 (8H, m)	19.1, 28.1, 36.9, 48.9, 50.2, 66.6, 81.6, 120.0, 125.0, 127.0, 127.3, 127.5, 141.1, 143.8, 156.5, 171.2
		B	40 s	88					
		C	50 s	94					
Ser (^{t}Bu)	**2j**	A	30 min	82	91	2248	−44.9	1.25 (9H, s), 3.6 (2H, m), 3.85 (1H, m), 4.1 (1H, t), 4.35 (2H, d), 5.1 (1H, br), 7.2−7.8 (8H, m)	28.9, 46.6, 51.7, 62.3, 66.6, 73.5, 120.0, 125.0, 126.8, 127.2, 127.4, 141.0, 144.3, 156.4
		B	40 s	87					
		C	55 s	93					
Tyr (^{t}Bu)	**2k**	A	30 min	83	113	2257	−22.5	1.2 (9H, s), 3.1 (2H, d), 3.95 (1H, t), 4.3- 4.45 (3H, m), 5.9 (1H, br), 7.2−7.9 (13H, m)	28.6, 36.6, 47.4, 54.5, 66.5, 78.4, 120.0, 124.4, 125.1, 127.4, 127.9, 128.1, 131.9, 132.6, 141.3, 144.0, 154.2, 156.6
		B	40 s	85					
		C	55 s	91					
Ser (OBzl)	**2l**	A	30 min	79	148	2252	−27.6	3.1 (2H, s), 3.7 (2H, d), 4.1 (1H, t), 4.35−4.5 (3H, m), 5.1 (1H, br), 7.2−7.9 (13H, m)	37.6, 46.6, 51.9, 62.5, 66.6, 120.0, 124.9, 126.6, 127.3, 127.5, 127.8, 128.5, 129.4, 137.6, 141.0, 143.8, 156.6
		B	45 s	87					
		C	60 s	93					
Lys (Boc)	**2m**	A	30 min	81	71	2256	−18.9	1.2−1.55 (15H, m), 3.1 (2H, m), 3.6 (1H, m), 4.15 (1H, t), 4.35 (2H, m), 4.65 (1H, m), 5.3 (1H, d), 7.25−7.8 (8H, m)	22.6, 29.9, 30.5, 28.2, 39.6, 47.2, 52.9, 66.6, 79.3, 120.0, 124.8, 126.8, 127.0, 127.2, 127.8, 141.3, 144.0, 156.5, 156.9
		B	35 s	87					
		C	45 s	92					

[a] Method A: reflux in toluene. Method B: microwave irradiation in toluene. Method C: microwave irradiation using solid powder. All compounds except Gly, unless specified, had the L-configuration. [b] Isolated yield after crystallization. [c] Vibrational frequency of isocyanate carbonyl group.

SCHEME 2



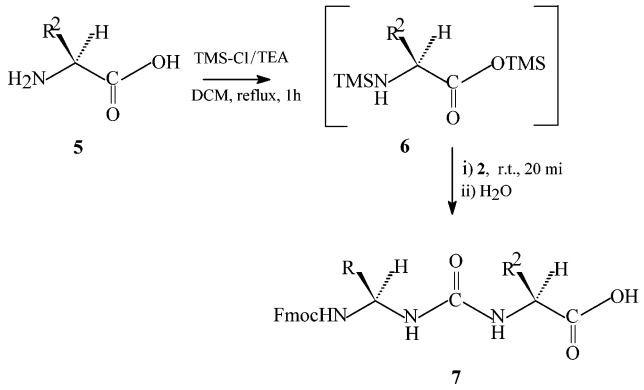
3 **4**

Compound **4**	R	R^1	Y
4a	CH_3	$CH_2CH(CH_3)_2$	CH_3
4b	$CH(CH_3)_2$	H	CH_3
4c	$CH(CH_3)CH_2CH_3$	H	CH_3
4d	C_6H_5	$CH_2C_6H_5$	CH_3
4e	C_6H_5	$CH_2C_6H_5$	CH_3
4f	$CH_2OCH_2C_6H_5$	H	CH_3
4g	CH_2COO^tBu	H	CH_3
4h	$CH_2CH_2COO^tBu$	$CH_2C_6H_5$	CH_3
4i	CH_3	CH_2OBzl	CH_3
4j	$CH(CH_3)_2$	$CH_2CH(CH_3)_2$	$CH_2C_6H_5$
4k	$CH(CH_3)CH_2CH_3$	$CH_2C_6H_5$	$CH_2C_6H_5$

employed in organic synthesis. Although this has led to isolation of analytically pure compounds directly, further chain lengthening of the compounds, if necessary, is difficult to execute. Employment of *N*,*O*-bis(trimethyl silyl) derivatives of amino acids[30,31] are known to aid solubility and enhance the rate of acylation reactions. In the present study, the isocyanates **2** were reacted with

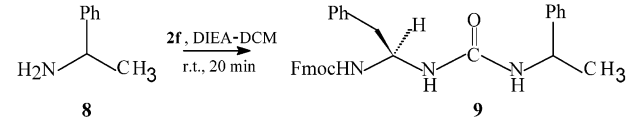
(30) Bolin, D. R.; Sytwu, I.-I.; Humiec, F.; Meienhofer, J. *Int. J. Pept. Protei. Res.* **1989**, *33*, 353.

SCHEME 3



Compound 7	R	R^2
7a	$CH(CH_3)_2$	$CH_2CH(CH_3)_2$
7b	$CH_2C_6H_5$	$CH_2CH(CH_3)_2$
7c	$CH_2C_6H_5$	$CH_2OCH_2C_6H_5$
7d	$CH_2C_6H_5$	CH_2COOH
7e	$CH(CH_3)CH_2CH_3$	CH_2CH_2COOH
7f	$CH_2C_6H_5$	CH_2OH
7g	$CH(CH_3)CH_2CH_3$	$CH_2C_6H_4OH$

SCHEME 4



6a−**g** at room temperature to obtain urea derivatives **7a**−**g** containing the free carboxyl terminal in a single step (Scheme 3). The reaction was found to be complete in about 20 min. and all the urea derivatives made were fully characterized. Extending the procedure, Asp and Glu containing urea peptides **7d** and **7e** with β- or γ-free carboxyl groups and Ser and Tyr urea peptides **7f** and **7g** with free hydroxyl group have also been prepared in good yield. Further, our attempts for the direct reactions of a free amino acid **5** with the isocyanate **2** in the presence of aqueous sodium carbonate solution at O °C resulted in the desired product **7** but in lower yield (23%).

The isocyanates prepared in the present work and the coupling of isocyanates to obtain urea peptides was considered to be unlikely to racemize given the nature of the acid azides and mild conditions employed during these transformations. Nevertheless, isocyanates were determined to be enantiomerically pure by ^{1}H NMR analysis of the urea adducts **9** with 1-phenylethylamine. Ureas **9a** and **9b** were prepared by reaction of **2f** with (*R*)-(+)- and (*S*)-(−)-1-phenylethylamine. Equimolar mixtures of diastereomers **9a** and **9b** were prepared by reaction of **2f** with racemic 1-phenylethylamine (Scheme 4). The methyl group resonances of **9a** (δ 1.29 and 1.31) and **9b** (δ 1.27 and 1.29) clearly separated by 0.02 ppm in the ^{1}H NMR spectra in DMSO-d_6 solution. Further, the determined optical rotations of 9a and 9b also confirmed that the optical purity of the isocyanates.

(31) For the synthesis of protected dipeptide acids using bis-TMS amino acids, see: Bambino, F.; Brownles, R. T. C.; Chiu, F. C. K. *Tetrahedron Lett.* **1991**, *32*, 3407.

Conclusions

In summary, isocyanates can be prepared readily from Fmoc-amino acid azides. They have been isolated as crystalline solids, fully characterized and are optically pure. Though not stable for long periods at room temperature, they have been found to be stable at 4 °C for several months without any decomposition. They react cleanly and in good yields with amino acid esters to form urea derivatives. They can also be prepared easily starting from powdered Fmoc-amino acid azides, upon microwave irradiation, in almost quantitative yields without any side products**.** It is a simple and rapid approach avoiding the necessity of using toluene. The scaling up of this procedure has not posed any problems. Isocyanates can be coupled with *N*,*O*-bis(trimethylsilyl) derivatives of amino acids to obtain urea peptide derivatives containing free carboxyl terminal which aid in their solubility, thus making them more useful as building blocks for the synthesis of oligourea peptides.

Experimental Section

Melting points were determined using a capillary method and are uncorrected. LG domestic microwave oven operating at 2450 MHz was used for the preparation of isocyanates. All solvents were freshly distilled prior to use. Fmoc-amino acid azides, prepared by the reported procedures,[27] were isolated, recrystallized, and characterized prior to use.

General Procedure for the Preparation of Fmoc-Protected Isocyanates 2. Method A. The Fmoc-amino acid azide **1** (1 mmol) dissolved in toluene (10 mL) was heated at 65 °C under nitrogen atmosphere. After the completion of the reaction (Tables 1 and 2), the solvent was removed under reduced pressure to get the crude isocyanate **2**, which was recrystallized using DCM and *n*-hexane.

Method B. A mixture of Fmoc-amino acid azide **1** (1 mmol) and toluene (5 mL) in a beaker was exposed to microwave irradiation at its 60% power until the reaction was complete (Tables 1 and 2). The residue was recrystallized using *n*-hexane to get the corresponding isocyanate **2**.

Method C. Powdered Fmoc-amino acid azide **1** (1 mmol) in a beaker was exposed to microwave irradiation at its 60% power until the rearrangement was complete (Tables 1 and 2). The resulting mass was recrystallized using DCM and *n*-hexane. Scaling up of the reaction to 0.75 mol has not posed any problems and has yielded excellent results.

General Procedure for the Preparation of Urea Peptides 4. To a stirred suspension of amino acid methyl ester hydrochloride salt **3** (1 mmol) in DCM (5 mL) was slowly added DIEA (2 mmol), and the mixture was stirred at 25 °C for few minutes. Isocyanate **2** (1 mmol) was added, and the stirring was continued till the completion of the reaction. The separated solid was filtered and recrystallized using DMSO−water to obtain the title compounds as a crystalline white solids.

Fmoc-Ala^m-Leu-OMe (4a): 0.308 g (1 mmol) of **2b**, after the reaction, gave 0.435 g (96%) of **4a**; mp 199 °C; ^{1}H NMR (δ, DMSO) 0.9 (6H, m), 1.15 (3H, d), 1.3 (2H, m), 1.5 (1H, m), 3.6 (3H, s), 3.65−3.8 (2H, m), 4.2 (1H, t), 4.41 (2H, m), 5.0 (1H, d), 6.4−6.5 (2H, m), 7.25−7.8 (8H, m); ^{13}C NMR (δ, DMSO) 17.3, 22.3, 23.2, 24.5, 40.1, 47.2, 48.8, 50.4, 61.1, 66.4, 119.9, 124.6, 127.2, 127.6, 141.5, 143.8, 155.5, 156.6, 171.5; MS (MALDI-TOF) *m*/*z* obsd 477.4 $[M + Na]^+$, 493.3 $[M + K]^+$. Anal. Calcd for $C_{25}H_{31}N_3O_5$: C, 66.21; H, 6.89; N, 9.26. Found: C, 66.11; H, 6.72; N, 9.09.

Fmoc-Val^m-Gly-OMe (4b): 0.336 g (1 mmol) of **2c**, after the reaction, gave 0.408 g (96%) of **4b**; mp 172 °C; ^{1}H NMR (δ, DMSO) 0.93 (6H, d), 1.9 (3H, m), 3.62 (3H, s), 3.81 (1H, m), 4.2 (1H, t), 4.4 (2H, m), 5.1 (1H, d), 6.4 − 6.6 (2H, m), 7.25−7.75 (8H, m); ^{13}C NMR (δ, DMSO) 18.5, 19.6, 29.2, 41.2, 47.2, 58.8, 61.2, 66.8, 119.9, 125.0, 126.0, 128.1, 141.5, 144.0, 155.5, 156.1, 170.8; ES MS *m*/*z* obsd 425.0. Anal. Calcd for $C_{23}H_{27}N_3O_5$: C, 64.92; H, 6.39; N, 9.87. Found: C, 64.68; H, 6.29; N, 9.71.

Fmoc-Ile^m-Gly-OMe (4c): 0.350 g (1 mmol) of **2e**, after the reaction, gave 0.426 g (97%) of **4c**: mp 143 °C; ^{1}H NMR (δ, DMSO) 0.8 (6H, m), 1.1−1.65 (3H, m), 2.5 (2H, m), 3.6 (3H, s), 3.8 (1H, m), 4.2−4.4 (3H, m), 5.0 (1H, d), 6.3−6.5 (2H, m), 7.3−7.9 (8H, m); ^{13}C NMR (δ, DMSO) 11.0, 14.3, 25.0, 40.4, 41.2, 46.7, 51.5, 61.5, 65.1, 120.0, 125.2, 127.0, 127.6, 140.7, 143.8, 155.0, 156.8, 171.5; ES MS *m*/*z* obsd 440.2. Anal. Calcd for $C_{24}H_{29}N_3O_5$: C, 65.59; H, 6.65; N, 9.56. Found: C, 65.38; H, 6.52; N, 9.38.

Fmoc-Phg^m-Phe-OMe (4d): 0.370 g (1 mmol) of **2g**, after the reaction, gave 0.505 g (92%) of **4d**: mp 167 °C; ^{1}H NMR (δ, DMSO) 2.85 (2H, d), 3.60 (3H, s), 3.95−4.1 (2H, m), 4.2 (1H, t), 4.4 (2H, m), 6.1 (1H, d), 6.6−6.9 (2H, m), 7.1−7.9 (18H, m); ^{13}C NMR (δ, DMSO) 37.2, 47.4, 54.1, 54.6, 61.3, 66.6, 120.1, 125.0, 126.7, 127.0, 127.2, 127.6, 128.2, 128.6, 129.0, 129.3, 137.5, 137.8, 141.3, 144.0, 155.4, 156.3, 171.1; MS (MALDI-TOF) *m*/*z* obsd 572.1 $[M + Na]^+$, 588.1 $[M + K]^+$. Anal. Calcd for $C_{33}H_{31}N_3O_5$: C, 72.11; H, 5.68; N, 7.64. Found: C, 71.98; H, 5.57; N, 7.49.

Fmoc-D-Phg^m-Phe-OMe (4e): 0.370 g (1 mmol) of **2g***, after the reaction, gave 0.50 g (91%) of **4e**: mp 181 °C; ^{1}H NMR (δ, DMSO) 2.84 (2H, d), 3.6 (3H, s), 3.93−4.1 (2H, m), 4.2 (1H, t), 4.4 (2H, m), 6.1 (1H, d), 6.6−6.9 (2H, d), 7.2−7.9 (18H, m); ^{13}C NMR (δ, DMSO) 37.3, 47.4, 54.2, 54.6, 61.4, 66.6, 120.2, 125.1, 126.8, 127.1, 127.2, 127.6, 128.2, 128.6, 129.0, 129.4, 137.5, 137.9, 141.4, 144.0, 155.6, 156.4, 171.0; MS (MALDI-TOF) *m*/*z* obsd 572.1 $[M + Na]^+$, 588.1 $[M + K]^+$. Anal. Calcd for $C_{33}H_{31}N_3O_5$: C, 72.11; H, 5.68; N, 7.64. Found: C, 72.01; H, 5.56; N, 7.46.

Fmoc-Ser(OBzl)^m-Gly-OMe (4f): A 0.414 g (1 mmol) of **2l**, after the reaction, gave 0.473 g (94%) of **4f**: mp 162 °C; ^{1}H NMR (δ, DMSO) 2.8 (2H, d), 3.3 (2H, d), 3.6 (3H, s), 3.7 (3H, d), 4.2 (1H, t), 4.42 (2H, m), 5.7 (1H, d), 6.6−6.82 (2H, m), 7.1−7.8 (13H, m); ^{13}C NMR (δ, DMSO) 17.3, 27.0, 46.5, 51.6, 61.3, 62.1, 66.5, 120.0, 124.9, 126.5, 126.8, 127.3, 128.3, 129.4, 137.6, 141.0, 143.7, 155.3, 156.2, 171.1; MS (MALDI-TOF) *m*/*z* obsd 525.8 $[M + Na]^+$, 541.8 $[M + K]^+$. Anal. Calcd for $C_{28}H_{29}N_3O_6$: C, 66.79; H, 5.80; N, 8.34. Found: 66.62; H, 5.68; N, 8.18.

Fmoc-Asp(O^{t}Bu)^m-Gly-OMe (4g): 0.408 g (1 mmol) of **2h**, after the reaction, gave 0.452 g (91%) of **4g**: mp 157 °C; ^{1}H NMR (δ, DMSO) 1.45 (9H, s), 1.9 (2H, d), 2.6 (2H, d), 3.65 (3H, s), 4.1 (1H, t), 4.3−4.4 (3H, m), 5.8 (1H, d), 6.5−6.7 (2H, m), 7.3−7.75 (8H, m); ^{13}C NMR (δ, DMSO) 27.9, 37.5, 41.5, 47.1, 50.0, 61.3, 66.8, 81.5, 120.0, 125.0, 127.5, 128.0, 141.0, 144.1, 155.5, 156.5, 170.8, 171.1; MS (MALDI-TOF) *m*/*z* obsd 519.8 $[M + Na]^+$, 536.0 $[M + K]^+$. Anal. Calcd for $C_{26}H_{31}N_3O_7$: C, 62.76; H, 6.28; N, 8.44. Found: C, 62.66; H, 6.07; N, 8.29.

Fmoc-Glu(O^{t}Bu)^m-Phe-OMe (4h): 0.422 g (1 mmol) of **2i**, after the reaction, gave 0.535 g (89%) of **4h**: mp140 °C; ^{1}H NMR (δ, DMSO) 1.42 (9H, s), 2.1 (2H, m), 2.52 (2H, br), 2.87 (2H, d), 3.65 (3H, s), 3.95−4.25 (3H, m), 4.38 (2H, d), 5.65 (1H, d), 6.75−6.9 (2H, m), 7.1−7.85 (13H, m); ^{13}C NMR (δ, DMSO) 27.6, 35.2, 37.5, 46.6, 47.2, 51.8, 54.3, 61.5, 62.4, 66.4, 66.6, 73.5, 119.8, 124.6, 126.0, 126.8, 127.2, 128.6, 129.2, 137.5, 141.1, 143.7, 155.3, 156.2, 170.8, 171.2; MS (MALDI-TOF) *m*/*z* obsd 624.1 $[M + Na]^+$, 640.1 $[M + K]^+$. Anal. Calcd for $C_{34}H_{39}N_3O_7$: C, 67.87; H, 6.53; N, 6.98. Found: C, 67.74; H, 6.42; N, 6.83.

Fmoc-Ala^m-Ser(OBzl)-OMe (4i): 0.308 g (1 mmol) of **2b**, after the reaction, gave 0.445 g (92%) of **4i**: mp 188 °C; ^{1}H NMR (δ, DMSO) 1.5 (3H, d), 3.6 (2H, d), 3.72 (3H, s), 3.81 (3H, m), 3.85 (1H, m), 5.1 (1H, d), 5.9−6.1 (2H, d), 4.2 (1H, t), 4.4 (2H, m), 7.2−7.85 (13H, m); ^{13}C NMR (δ, DMSO) 17.5, 37.8, 47.2, 49.0, 52.0, 60.7, 62.0, 66.6, 120.0, 124.8, 126.6, 127.1, 128.0, 128.5, 129.0, 138.2, 141.5, 144.0, 156.6, 155.2, 171.3; MS (MALDI-TOF) *m*/*z* obsd 540.2 $[M + Na]^+$, 556.2 $[M + K]^+$. Anal. Calcd for $C_{29}H_{31}N_3O_6$: C, 66.79; H, 5.80; N, 8.34. Found: C, 66.68; H, 5.63; N, 8.17.

Fmoc-Val^m-Leu-OBzl (4j): 0.336 g (1 mmol) of **2c**, after the reaction, gave 0.529 g (95%) of **4j**: mp 184 °C; ^{1}H NMR (δ, DMSO) 0.92 (12H, m), 1.32−1.85 (4H, m), 3.1 (2H, s), 3.7−3.8 (2H, m), 4.2 (1H, t), 4.42 (2H, m), 5.1 (1H, d), 6.6−6.7 (2H, m), 7.2−7.85 (13H, m); ^{13}C NMR (δ, DMSO) 18.5, 19.5, 22.0, 23.1, 24.5, 29.2, 37.2, 40.2, 47.2, 51.5, 59.0, 66.6, 120.0, 125.0, 126.5, 127.2, 128.0, 128.4, 129.3, 137.6, 141.2, 144.0, 155.4, 156.8, 176.4; MS (MALDI-TOF) *m*/*z* obsd 580.0 $[M + Na]^+$, 596.1 $[M + K]^+$. Anal. Calcd for $C_{33}H_{39}N_3O_5$: C, 71.07; H, 7.05; N, 7.53. Found: C, 70.96; H, 6.89; N, 7.41.

Fmoc-Ile^m-Phe-OBzl (4k): 0.350 g (1 mmol) of **2e**, after the reaction, gave 0.569 g (94%) of **4k**: mp 192 °C; ^{1}H NMR (δ, DMSO) 0.9 (6H, m), 1.12 (2H, m), 1.55 (1H, m), 2.85 (2H, d), 2.95 (2H, s), 3.6 (1H, m), 4.0 (1H, m), 4.2 (1H, t), 4.42 (2H, m), 5.0 (1H, d), 6.6−6.8 (2H, m), 7.2−7.85 (18H, m); ^{13}C NMR (δ, DMSO) 11.3, 15.6, 25.2, 36.0, 37.3, 37.5, 47.2, 54.2, 57.2, 66.6, 120.0, 125.0, 126.7, 126.9, 127.15, 127.5, 128.0, 128.5, 129.0, 129.4, 137.4, 137.8, 141.1, 144.0, 155.4, 157.2, 177.3; MS (MALDI-TOF) *m*/*z* obsd 628.1 $[M + Na]^+$, 644.2 $[M + K]^+$. Anal. Calcd for $C_{37}H_{39}N_3O_5$: C, 73.36; H, 6.49; N, 6.94. Found: C, 73.18; H, 6.38; N, 6.86.

General Procedure for the Preparation of N^α-Fmoc-Protected Urea Peptide Acids 7. To a stirred suspension of amino acid **5** (1 mmol) in DCM (5 mL) were added trimethylsilyl chloride (TMS−Cl, 1.2 mmol) and triethylamine (TEA, 1.2 mmol) and the mixture refluxed for 1 h. The reaction mixture was cooled to room temperature, and isocyanate **2** (1 mmol) was added. It was stirred until the completion of the reaction. The solvent was evaporated, and water (10 mL) was added to the residue. The separated solid was filtered and recrystallized using DMSO−water to get the urea **7**.

In the case of Glu, Asp, Ser, and Tyr, 2.4 mmol of TMS-Cl and TEA were used.

Fmoc-Val^m-Leu-OH (7a): 0.336 g (1 mmol) of **2c**, after the reaction, gave 0.439 g (94%) of **7a**: mp 151 °C; ^{1}H NMR (δ, DMSO) 0.95 (12H, m), 1.35 (2H, m), 1.65 (1H, m), 1.82 (1H, m), 3.75−3.8 (2H, m), 4.2 (1H, t), 4.42 (2H, m), 5.1 (1H, d), 6.6−6.85 (2H, m), 7.3−7.75 (8H, m); ^{13}C NMR (δ, DMSO) 18.5, 19.3, 22.1, 23.2, 24.6, 29.1, 40.2, 47.5, 51.2, 58.6, 66.5, 120.0, 124.8, 127.1, 127.5, 141.3, 143.8, 155.8, 157.2, 180.1; MS (MALDI-TOF) *m*/*z* obsd 491.5 $[M + Na]^+$, 507.5 $[M + K]^+$. Anal. Calcd for $C_{26}H_{33}N_3O_5$: C, 66.79; H, 7.11; N, 8.99. Found: C, 66.67; H, 6.96; N, 8.83.

Fmoc-Phe^m-Leu-OH (7b): 0.384 g (1 mmol) of **2f**, after the reaction, gave 0.474 g (92%) of **7b**: mp 169 °C; ^{1}H NMR (δ, DMSO) 0.85 (6H, d), 1.4 (2H, t), 1.6 (1H, m), 2.9 (2H, m), 4.1−4.35 (5H, m), 5.2 (1H, br), 6.4−6.6 (2H, m), 7.1−7.9 (13H, m); ^{13}C NMR (δ, DMSO) 22.1, 23.0, 24.5, 37.1, 40.2, 47.3, 51.3, 54.2, 66.6, 120.0, 124.9, 126.6, 127.1, 127.5, 128.5, 129.4, 137.6, 141.2, 144.0, 156.3, 157.2, 177.9; MS (MALDI-TOF) *m*/*z* obsd 538.0 $[M + Na]^+$, 554.1 $[M + K]^+$. Anal. Calcd for $C_{30}H_{33}N_3O_5$: C, 69.88; H, 6.45; N, 8.15. Found: C, 69.32; H, 6.28; N, 8.03.

Fmoc-Phe^m-Ser(OBzl)-OH (7c): 0.384 g (1 mmol) of **2f,** after the reaction, gave 0.504 g (87%) of **7c:** mp 162 °C; ^{1}H NMR (δ, DMSO) 2.9−3.1 (4H, m), 3.7−3.85 (3H, m), 4.1−4.5 (4H, m), 5.6 (1H, d), 6.4−6.65 (2H, m), 7.1−7.95 (18H, m); ^{13}C NMR (δ, DMSO) 46.2, 51.9, 58.1, 65.0, 70.6, 75.9, 77.5, 125.3, 130.5, 131.5, 132.3, 132.68, 132.69, 132.89, 133.4, 133.45, 134.5, 143.0, 143.3, 145.9, 149.0, 160.3, 161.4, 177.8; MS (MALDI-TOF) *m*/*z* obsd 602.6 $[M + Na]^+$, 618.1 $[M + K]^+$. Anal. Calcd for $C_{34}H_{33}N_3O_6$: C, 70.45; H, 5.74; N, 7.25. Found: C, 70.32; H, 5.59; N, 7.13.

Fmoc-Phe^m-Asp-OH (7d): 0.384 g (1 mmol) of **2f**, after the reaction, gave 0.439 g (85%) of **7d**: mp 188 °C; ^{1}H NMR (δ, DMSO) 2.5 (2H, br), 2.9 (2H, d), 3.9−4.1 (3H, m), 4.4 (2H, m), 5.67 (1H, d), 6.75−6.95 (2H, m), 7.1−7.8 (13H, m); ^{13}C NMR (δ, DMSO) 37.1, 37.3, 47.3, 49.9, 54.2, 66.5, 120.0, 125.0,

126.7, 127.0, 127.6, 128.6, 129.4, 137.6, 141.5, 144.1, 157.6, 159.4, 177.9, 178.5; MS (MALDI-TOF) *m/z* obsd 504.4 $[M + Na]^+$, 522.0 $[M + K]^+$. Anal. Calcd for $C_{28}H_{27}N_3O_7$: C, 64.98; H, 5.26; N, 8.12. Found: C, 64.83; H, 5.11; N, 8.03.

Fmoc-Ile^m-Glu-OH (7e): 0.350 g (1 mmol) of **2e**, after the reaction, gave 0.432 g (87%) of **7e**; mp 184 °C; ^{1}H NMR (δ, DMSO) 0.91 (6H, d), 1.12 (2H, m), 1.52 (1H, m), 2.1−2.45 (4H, m), 3.6 (1H, m), 4.05 (1H, m), 4.21 (1H, t), 4.43 (2H, m), 4.95 (1H, d), 6.65−6.85 (2H, m), 7.25−7.76 (8H, m); ^{13}C NMR (δ, DMSO) 11.3, 15.6, 25.5, 32.1, 35.7, 38.3, 47.3, 49.9, 57.3, 66.5, 119.9, 125.0, 127.0, 127.6, 141.2, 143.9, 156.3, 158.3, 177.9, 178.2; MS (MALDI-TOF) *m/z* obsd 553.9 $[M + Na]^+$, 570.0 $[M + K]^+$. Anal. Calcd $C_{26}H_{31}N_3O_7$: C, 62.76; H, 6.28; N, 8.44. Found: C, 62.59; H, 6.16; N, 8.32.

Fmoc-Phe^m-Ser-OH (7f): 0.384 g (1 mmol) of **2f**, after the reaction, gave 0.426 g (87%) of **7f**; mp 176 °C; ^{1}H NMR (δ, DMSO) 2.85 (2H, d), 3.8 (4H, m), 4.1−4.4 (4H, m), 6.1 (1H, d), 6.8−7.0 (2H, m), 7.1−7.75 (13H, m); ^{13}C NMR (δ, DMSO) 37.5, 47.2, 52.1, 54.5, 62.5, 66.5, 120.0, 124.9, 126.8, 127.1, 127.6, 128.5, 129.1, 137.6, 141.4, 144.1, 157.6, 158.4, 178.1; MS (MALDI-TOF) *m/z* obsd 511.8 $[M + Na]^+$, 527.9 $[M + K]^+$. Anal. Calcd for $C_{27}H_{27}N_3O_6$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.11; H, 5.43; N, 8.47.

Fmoc-Ile^m-Tyr-OH (7g): 0.350 g (1 mmol) of **2e**, after the reaction, gave 0.494 g (93%) of **7g**; mp 169 °C; ^{1}H NMR (δ, DMSO) 0.9 (6H, m), 1.1 (1H, m), 1.52 (2H, m), 2.25 (1H, br), 2.85 (2H, d), 3.6 (1H, m), 4.2 (1H, t), 4.42 (2H, m), 4.95 (1H, d), 6.65−6.85 (2H, m), 7.1−7.8 (12H, m); ^{13}C NMR (δ, DMSO) 11.3, 15.4, 25.5, 35.9, 36.6, 47.5, 54.3, 57.5, 66.7, 119.9, 124.2, 124.8, 127.1, 127.6, 129.6, 132.8, 141.2, 144.1, 154.5, 156.8, 158.2, 178.4; MS (MALDI-TOF) *m/z* obsd 554.0 $[M + Na]^+$, 570.1 $[M + K]^+$. Anal. Calcd for $C_{30}H_{33}N_3O_6$: C, 67.78; H, 6.25; N, 7.90. Found: C, 67.66; H, 6.13; N, 7.79.

Test for Racemization of Isocyanate 2f. The isocyanate **2f** (0.384 g, 1 mmol) was added to a mixture of racemic 1-phenylethylamine (0.121 g, 1 mmol) and DIEA (0.147 mL, 1 mmol) in DCM (10 mL) and the mixture stirred at 25 °C for 5 min. The separated solid was filtered and recrystallized using DMSO−water. It was a near 1:1 mixture of the two diastereomers of the compound **9**: ^{1}H NMR (DMSO) δ 7.89 (2H, br), 7.65 (2H, t), 7.43−7.21 (14H, m), 6.54 (1H, d), 6.27 (1H, t), 5.18 (1H, br), 4.72 (1H, m), 4.18−4.25 (3H, m), 2.9 (2H, d), 1.30 (3/2H, J = 7 Hz, t), 1.28 (3/2H, t); MS (MALDI-TOF) *m/z* obsd 428.2 $[M + Na]^+$, 544.2 $[M + K]^+$. When this experiment was repeated using **2f** and optically pure (*R*)-(+)-1-phenylethylamine, only one diastereomer was observed. Isomer **9a** was isolated: mp 220−221 °C; $[\alpha]^{25}_D$ +12.40 (DMSO, c = 1); ^{1}H NMR (DMSO) δ 7.90 (2H, d), 7.66 (2H, d), 7.19−7.44 (14H, m), 6.53 (1H, d), 6.28 (1H, d), 5.20 (1H, br), 4.72 (1H, t), 4.17 4.26 (3H, m), 2.91 (2H, m), 1.30 (3H, d); MS (MALDI-TOF) *m/z* obsd 528.2 $[M + Na]^+$, 544.2 $[M + K]^+$. Anal. Calcd for $C_{32}H_{31}N_3O_3$: C, 76.01; H, 6.18; N, 8.31. Found: C, 75.91; H, 6.03; N, 8.19. The experiment was repeated using **2f** and optically pure (*S*)-(−)-1-phenylethylamine. The corresponding diastereomer **9b** was obtained and isolated: mp 217−218 °C; $[\alpha]^{25}_D$ −12.06 (DMSO, c = 1); ^{1}H NMR (DMSO) δ 7.89 (2H, d), 7.64 (2H, d), 7.21−7.43 (14H, m), 6.54 (1H, d), 6.26 (1H, d), 5.18 (1H, br), 4.72 (1H, t), 4.17 4.24 (3H, m), 2.91 (2H, m), 1.28 (3H, d); MS (MALDI-TOF) *m/z* obsd 528.2 $[M + Na]^+$, 544.2 $[M + K]^+$. Anal. Calcd for $C_{32}H_{31}N_3O_3$: C, 76.01; H, 6.18; N, 8.31. Found: C, 75.92; H, 6.05; N, 8.18.

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Supporting Information Available: IR spectra for **2b**, ^{1}H NMR spectra for compounds **2d**, **4c**, **7b**, **9**, **9a**, and **9b**, ^{13}C NMR spectra for compounds **2j**, **4c**, and **7c**, and mass spectra for **2l**, **4a**, **4c**, and **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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