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Advanced Synthesis & Catalysis

Ethyl 2-(*tert*-Butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma): An Efficient Reagent for the Racemization Free Synthesis of Ureas, Carbamates and Thiocarbamates via Lossen Rearrangement

Srinivasa Rao Manne,[a] Kishore Thalluri,[a] Rajat Subhra Giri,[a] Jyoti Chandra,[a] and Bhubaneswar Mandal[a,*]

[a] Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, Assam – 781039, India
Fax: (+91)-358-258-2349
Phone: (+91)-361-258-2319; e-mail: bmandal@iitg.ernet.in

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Abstract: Boc-Oxyma (Ethyl 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate) has been reported previously as an efficient coupling reagent for the synthesis of amides, peptides, esters, thioesters and hydroxamic acids. It is known for its excellent racemization suppression capability, and also as an environment friendly reagent as it generates only Oxyma as solid byproduct that can be recovered easily and recycled for the synthesis of the same reagent. In this update, we report a simple, efficient, environment friendly, chemoselective and racemization free method for the synthesis of ureas, carbamates and thiocarbamates from hydroxamic acids via Lossen rearrangement by using Boc-Oxyma. We have achieved racemization free di- and tripeptidyl ureas with very good yield by using this protocol. A rigorous mechanistic investigation is also incorporated.

Keywords: Boc-Oxyma; Hydroxamic acid; Lossen Rearangement; Ureas; Carbamates, thiocarbamates; Racemization free.

Introduction

Urea is an important structural unit having widespread utilities in pharmaceutical, medicinal and material sciences.[1] Due to the presence of hydrogen bonding, it serves as a backbone for the preparation of ureidopeptides that are important in drug discovery.[2] For example, Syringolins is a class of proteasome inhibitors having promising antitumor activity.[3] Therefore, research devoted towards the efficient and high-yielding methods for the preparation of ureas has received much attention.

The classical methods such as Hofmann,[4] Curtius,[5] and Lossen rearrangement,[6] have been proven to be the practical methods for the synthesis of diverse ureas. However, use of strong hypervalent iodine reagents in Hofmann and potentially explosive azides in Curtius rearrangement limit the practical utility for large scale synthesis as well as for the preparation of complex natural products. Alternatively, the Lossen rearrangement provides access to isocyanates under relatively mild conditions. To date, several synthetic methods have been developed for the synthesis of ureas through Lossen rearrangement, for example, phosgene and its derivatives such as triphosgene[7] are widely used reagents for synthesis of ureas; together with chloroformates,[8] cyanuric chloride,[9] 1,1′-carbonyldiimidazole,[10] 1-propanephosphonic acid cyclic anhydride (T3P),[11] *N*,*N*′-dicyclohexylcarbodiimide,[12] *N*-benzyl-*N*′-(3-dimethylaminopropyl)carbodiimide,[13] Zr(IV)-catalyst,[14] Pd-catalyzed[15] and 2-chloro-1-methylpyridinuim iodide.[16]

On the other hand, Boc-Oxyma (**I**, Ethyl 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate, Figure 1)

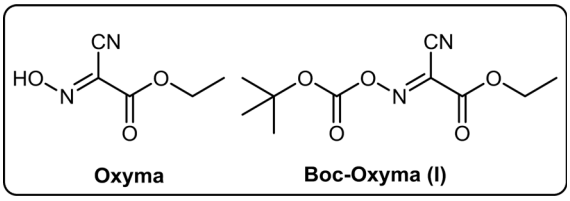


Figure 1. Ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma) and Ethyl 2-(tert-butoxycarbonyloxyimino)-2-cyanoacetate **I** (Boc-Oxyma).

has been described previously as an efficient coupling reagent. It readily activates the carboxylic acid group for the formation of amides, peptides, esters, thioesters[17] and hydroxamic acids.[18] Notable feature of Boc-Oxyma is in its excellent racemization suppression capability. Also, it is an environment friendly reagent as it generates only Oxyma as solid byproduct that can be recovered easily and can be recycled for the synthesis of the same reagent. Herein, we report a novel method for the synthesis of ureas from hydroxamic acids using Boc-Oxyma as an efficient reagent for urea synthesis via Lossen rearrangement.

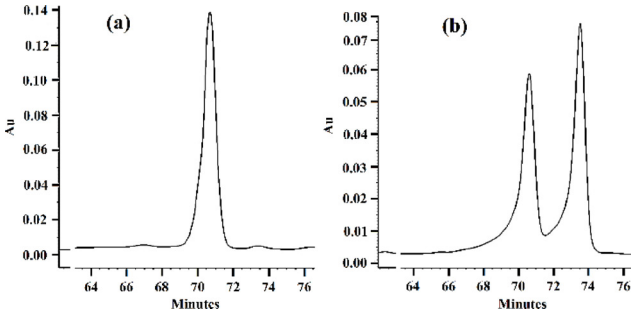
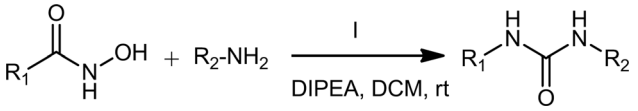


Figure 2. HPLC profiles of products (a) L & (b) DL form of Bz-Phe-Phg-OMe dipeptidyl ureas. (C18 analytical column and a linear gradient of 5% to 30% acetonitrile in water during the first 20 min, then linear gradient of acetonitrile in water from 30% to 70% till 200 min were used for proper seperation.).

Results and Discussion

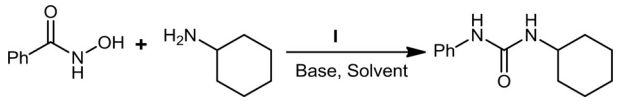
I was synthesized easily by the reaction of Oxyma (ethyl 2-hydroxyimino 2-cyanoacetate) with Boc_2O in the presence of DIPEA at 0–5 °C for 1 h. After that the solvent (chloroform) was evaporated completely and then used in the reaction directly without purification. We hypothesized, hydroxamic acids, which was prepared by using **I**[18] from carboxylic acids, could further be O-activated by **I** (1 equiv.) in the presence of DIPEA, and then could be converted into the corresponding isocyanate via Lossen rearrangement which subsequently be trapped in situ with nucleophiles, such as amines or alcohols in an one-pot manner (Scheme 1) to generate ureas or carbamates, respectively.



Scheme 1. Synthesis of ureas from hydroxamic acids by **I.**

Initially, we commenced the optimization studies with benzhydroxamic acid **1a** as a model substrate in DCM. Cylohexylamine was used as the amine nucleophile. In a set of base sources screened, DIPEA exhibited superior results compared to NMM (*N*-methylmorpholine), Et_3N, NMI, DMAP, DBU and DABCO (1,4-diazabicyclo [2.2.2] octane). The reaction worked best in DCM solvent. However, the reaction also proceeded well in $CHCl_3$, THF, CH_3CN, EtOAc, CH_3OH, and DMF with very good yield (Table 1).

Table 1. Optimization of the reaction conditions.[a]

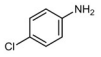
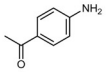
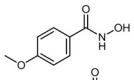
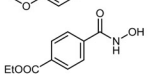
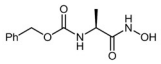
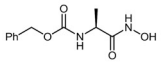
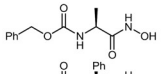
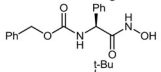
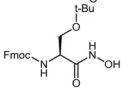
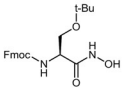
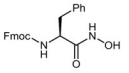
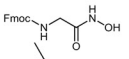
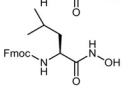
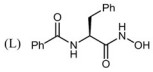
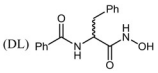
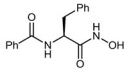
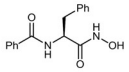
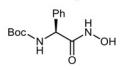
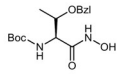


Entry	Base	Solvent	Yield (%)[b]
1	DBU	DCM	71
2	NMM	DCM	74
3	DABCO	DCM	55
4	NMI	DCM	54
5	DMAP	DCM	77
6	NEt_3	DCM	75
7	DIPEA	DCM	90
8	DIPEA	$CHCl_3$	85
9	DIPEA	THF	83
10	DIPEA	CH_3CN	81
11	DIPEA	EtOAc	87
12	DIPEA	CH_3OH	79
13	DIPEA	DMF	82
14	DIPEA	H_2O	45

[a] Reaction conditions: benzhydroxamic acid (127 mg, 1 mmol), Boc-Oxyma (242 mg, 1 mmol.), base (2.5 mmol), cylohexylamine (99 mg, 1 mmol), solvent (2 ml), temperature: first 15 min at 0 °C, and then 6 h at room temperature after addition of amine, total reaction time 6–7 h.
[b] Isolated yield.

Interestingly, the reaction worked well with aliphatic as well as aromatic amines, such as aniline and its derivatives (Table 2, products 3c–3f). Substituted aromatic carboxylic acids also generated good yield (products 3g & 3h). Systematic investigation on the electronic effect of the substituents revealed that the electron withdrawing substituents hindered the reaction to a certain extent. Reaction proceeded well for amino acid derivatives with common amine protecting groups, such as Boc, Fmoc, CBz, and Bz (benzoyl), as well as various side-chain alcohol protecting groups of amino acids, such as tBu and Bzl. The yields were found to be good to excellent in all the cases including the sterically hindered amino acids, e.g., leucine, isoleucine, phenylalanine, and phenylglycine. The reaction worked well with aliphatic, β-amino alcohols and methyl ester of amino acids as nucleophile.

Table 2. Wide scope of the synthesis of ureas by using **I.**[a].

Entry	Hydroxamic acid	Amine	Product id	Yield[b]
1			**3a**	90
			**3b**	89
			**3c**	90
			**3d**	82
			**3e**	76
			**3f**	73
2			**3g**	87
3			**3h**	70
4			**3i**	85
5			**3j**	81
6			**3k**	83
7			**3l**	78
8			**3m**	82
9			**3n**	80
10			**3o**	77
11			**3p**	83
12			**3q**	75
13			**3r**	83
14			**3s**	81
15			**3t**	80
16			**3u**	84
17			**3v**	85
18			**3w**	74
19			**3x**	79

[a] Reaction conditions: hydroxamic acid (1 mmol), Boc-Oxyma (242 mg, 1 mmol.), DIPEA (317 mg, 2.5 mmol), amine (1 mmol), DCM (2 ml), temperature: first 15 min at 0 °C and then 6 h at room temperature after addition of amine, total reaction time 6–7 h.

[b] Isolated yield

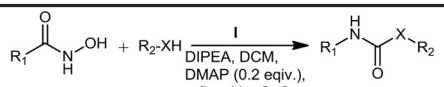
Usually, carbamates are formed in presence of hydroxyl group in Lossen rearrangement. Interestingly, although tertiary butanol was present as a byproduct in the reaction mixture, no trace of hydroxyl addition was observed. Also, when we used β-amino alcohols, chemoselective addition of amine occurred resulting in peptidyl ureas with free hydroxyl group (entries 11, 12, 16 and 19) as sole products. These ureas are very important intermediates for preparing anticancer agents.[19]

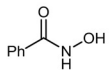
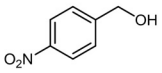
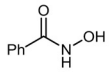
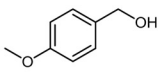
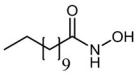
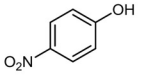
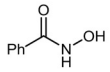
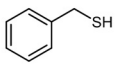
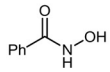
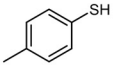
Design of peptidomimetics often helps to obtain better active pharmaceutical ingredients, and replacement of peptide bond by peptidyl urea is a common technique for peptidomimetic design as it allows generation of H-bond donor and acceptors at desired sites. Moreover, some naturally occurring small peptidyl ureas have been isolated that have been demonstrated to inhibit HIV proteases[20] and microbial alkaline proteases.[21] Here, to extend the scope of our methodology, we synthesized tripeptidyl ureas from hydroxamic acid of dipeptides using methyl ester of amino acids in good yield (Scheme 2).

Finally, we could extend this protocol for the synthesis of carbamates and thiocarbamates (Table 3) also, but addition of DMAP and refluxing condition was required. The requirement of such harsher condition may be accounted for the relatively lower nucleophilicity of the alcohol group than the amine functional group. To a chilled solution of hydroxamic in DCM, Boc-Oxyma, DIPEA and 0.2 equiv. of DMAP were added, and the mixture was stirred for 15 minutes. Then, the nucleophile (alcohol or thiol) was added, and the reaction mixture was refluxed for more five hours to obtain the desired product.

Further we examined the stereochemical aspects of this protocol. For that, we synthesized two peptidyl ureas Bz–L-Phe-L-Phg-OMe and Bz-DL-Phe-L-Phg-OMe by using **I** from L and DL form of Bz-phenylalanine hydroxamic acid, respectively, with methyl ester of phenylglycine. We compared HPLC profiles of the products. Single peak appeared in the HPLC profile of the L-isomer indicating the presence of single stereoisomeric product. On the other hand, distinct twin peaks appeared in HPLC profile of the DL analogue in the same gradient indicating the presence of two diastereomers (Supporting Information, Figures S64, S65, S70, and S71). These results imply that no detectable racemization occurred during the conversion executed by the current protocol.

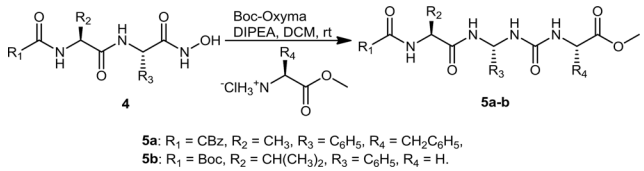
Table 3. Synthesis of carbamates and thiocabamates.[a].



Entry	$R_1CONHOH$	R_2XH	Product id	Yield[b]
1			**6a**	77
2			**6b**	80
3			**6c**	76
4			**6d**	71
5			**6d**	74

[a] Reaction conditions: Hydroxamic acid (1 mmol), Boc-Oxyma (242 mg, 1 mmol.), DIPEA (2.5 mmol), DMAP (0.2 mmol) amine (1 mmol), DCM (2 ml), temperature: first 15 min at 0 °C and then 5 h at reflux after addition of the nuleophile, total reaction time 5–6 h.

[b] Isolated yield



Scheme 2. Synthesis of tripeptidyl ureas from hydroxamic acid derivatives of dipeptides by **I.**

To understand the mechanism, we performed the reaction between hydroxamic acid and Boc-Oxyma in the presence of DIPEA in an NMR tube using $CDCl_3$ as a solvent, and ^{13}C and ^{1}HNMR spectra were recorded at the specified time intervals. Initially, the hydroxamic acid reacted with Boc-Oxyma and formed a stable intermediate II quickly within 15 minutes (Figure 3 and Supporting Information, Figures S114 – 128), evident by the appearance of the peaks at 164.2 (A′), 136.4 (B′) from 166.8 ppm (A) and 131.9 (B) corresponding to the carbonyl carbon and the adjascent aromatic carbon of the hydroxamic acid, respectively. The carbonyl carbons of Boc-Oxyma 157.1 (C), 148.7 (D) was converted into 163.7 (C′), 153.2 (D′) corresponding to the intermediate II, respectively. Presence of the intermediate II and Oxyma could be verified by ESI (-Ve mode, Figure S119 and +Ve mode, Figure S120) and ^{1}HNMR spectra (Figure S126) recorded till 5 min before addition of amine. Finally, two new peaks appeared slowly at 155.5 ppm (A″) and 140.3 ppm (B″), after the addition of the tertiarybutyl amine, which corresponds to the carbonyl carbon of urea and the aromatic carbon, respectively. Now, if the reaction progress via a classical Lossen rearrangement mechanism, then the intermediate II should rearrange directly to the isocyanate IV and nucleophilic amine addition may take place then. But, unlike our previous work on Lossen rearrangement,[22] all our efforts to isolate the isocyanate went in vain, rather intermediate II could be isolated. Possibility of the formation of the cyclic intermediate III from II and its conversion to IV as reported by Pascal Dubé and co-workers[10a] was also considered (Figure 3), but no characteristic peak of III was observed either in ^{1}HNMR or in ^{13}CNMR spectra (Figure S121, S122 and S128).

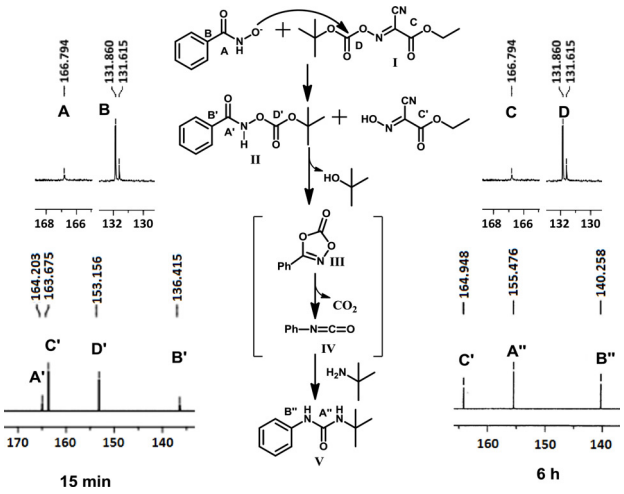


Figure 3. Plausible reaction mechanism for the synthesis ureas via the current protocol.

Furthermore, the characteristic quartret of the Oxyma that appeared within 5 min remained unchanged during the whole course of the reaction eliminating any possibility of further reaction of Oxyma with II. Also, the time resolved conversion of ^{13}CNMR peaks (Figure S121 and S122) as well as ^{1}HNMR peaks (Figure S128) indicated absence of any further intermediate(s). Therefore, it was inferred that either direct attack of amine on the intermediate II resulted in urea, CO_2 and tert-butanol formation via a rearrangement that occurred in a concerted manner or the conversion of II to III or IV and subsequent attack by amine was so fast that it was impossible to get a trace of the interemediates III and IV.

All the products were purified by column chromatography and chartacterized using various spectro-

scopic tools. The chemical structure of the product 3b (Table 2) was further confirmed by X-ray crystallographic analysis (Figure 4).

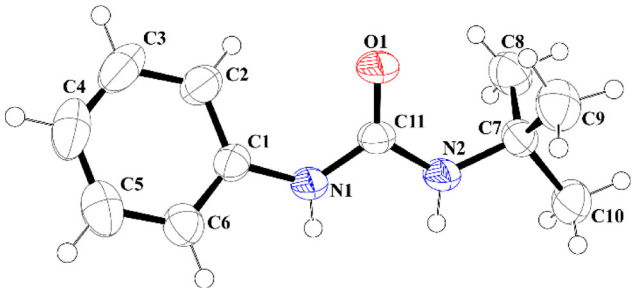


Figure 4. X-ray crystallographic structure of 3b in table 2 (ORTEP diagram with ellipsoid of 50% probability, CCDC No. 1484427.).

Conclusion

In summary, we have demonstrated a simple, efficient, environment friendly, chemoselective and racemization free method for the synthesis of ureas, carbamates and thiocarbamates directly from hydroxamic acid via Lossen rearrangement by using Boc-Oxyma. Importantly, all the hydroxamic acid substrates used in this article were obtained from the corresponding carboxylic acids using the same reagent, Boc-Oxyma. Also it is worth mention that Boc-Oxyma produces only Oxyma as a solid byproduct in the reaction that can be easily recovered and reused for the synthesis of the same reagent. This is one of the advantages over the use of the other reagents for the purpose. Therefore, the use of the current method can reduce chemical waste generation in industries.

Experimental Section

General procedure for the synthesis of urea: Boc-Oxyma (1 mmol) was added to a stirred solution of hydroxamic acid (1 mmol) and DIPEA (1.5 mmol) in 2 mL of DCM at 0 °C. Then the reaction mixture was stirred at the same temperature for 15 min followed by the addition of amine (1 mmol) and stirring at room temperature for more 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with 15 mL of DCM and washed with 5% HCl (2×10 mL), 5% $NaHCO_3$ (2×10 mL), saturated NaCl solution (2×10 mL) and dried over anhydrous $CaCl_2$ and the evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate.

General procedure for the synthesis carbamates and thiocarbamates: Boc-oxyma (1 mmol) was added to a stirred solution of hydroxamic acid (1 mmol), DIPEA (1.5 mmol) and DMAP (0.2 mmol) in 2 mL of DCM at 0 °C. Then the reaction mixture was stirred at the same temperature for 15 min followed by the addition of alcohols or thiols (1 mmol) and then stirred at reflux for more 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with 15 mL of DCM and washed with 5% HCl (2×10 mL), 5% $NaHCO_3$ (2×10 mL), saturated NaCl solution (2×10 mL) and dried over anhydrous $CaCl_2$ and the evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate.

Cyclohexyl-3-phenylurea 3a. White solid; (98 mg, 90%), mp 125–127 °C; ^{1}HNMR (600 MHz, $CDCl_3$) δ 7.27-7.26 (m, 4H), 7.05-7.03 (m, 1H), 6.77 (s, 1H), 4.99 (s, 1H), 3.65–3.63 (m, 1H), 1.94–1.91 (m, 2H), 1.68–1.64 (m, 3H), 1.35–1.31 (s, 2H), 1.12–1.06 (m, 3H); ^{13}CNMR (100 MHz, $CDCl_3$,) δ 155.7, 139.5, 129.1, 122.8, 120.0, 48.8, 33.7, 25.6, 25.0; FT-IR (KBr) 3328, 2932, 2853, 1680, 1629, 1558, 1317 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{19}N_2O$ 219.1497, found 219.1486.

1-(*tert*-Butyl)-3-phenylurea 3b. White solid; (170 mg, 89%), mp 166–168 °C; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.28–7.26 (m, 4H), 7.05–7.02 (m, 1H), 6.63 (s, 1H), 4.96 (s, 1H), 1.35 (s, 9H); ^{13}CNMR (100 MHz, $CDCl_3$,) δ 155.4, 139.2, 129.3, 123.4, 120.7, 120.6, 50.8, 29.5; FT-IR (KBr) 3361, 2924, 2853, 1647, 1539, 1211 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{17}N_2O$ 193.1341, found 193.1347.

1-Phenyl-3-(p-tolyl)urea 3c White solid; (101 mg, 90%), mp 196–198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.55 (s, 1H) 7.44–7.42 (d, J=7.6 Hz, 2H), 7.34–7.32 (d, J=8.4 Hz, 2H) 7.28–7.24 (t, J=7.6 Hz, 2H), 7.08–7.06 (d, J=8.4 Hz, 2H) 6.96–6.93 (t, J=7.2 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6,) δ 152.6, 139.8, 137.1, 130.6, 129.2, 128.8, 121.7, 118.3, 118.1, 20.3; FT-IR (KBr) 3301, 2922, 2852, 1789, 1635, 1535 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{15}N_2O$ 227.1184, found 227.1185.

1,3-Diphenylurea 3d White solid; (86 mg, 82%), mp 225–227 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 2H), 7.45–7.43 (d, J=8 Hz, 4H), 7.28–7.24 (t, J=7.6 Hz, 4H) 6.97–6.93 (t, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6,) δ 152.6, 139.7, 128.8, 121.8, 118.2; FT-IR (KBr) 3328, 2924, 2845, 1790, 1662, 1552 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{13}N_2O$ 213.1028, found 213.1024.

1-(4-chlorophenyl)-3-phenylurea 3e White solid; (93 mg, 76%), mp 238–240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.70 (s, 1H), 7.49–7.43 (m, 4H), 7.33–7.25 (m, 4H), 6.99–6.95 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6,) δ 152.5, 139.5, 138.7, 128.8, 128.6, 127.3, 125.3, 122.0, 119.7, 118.3; FT-IR (KBr) 3440, 2922, 2852, 1636, 1594, 1563 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{12}ClN_2O$ 247.0638, found 247.0640.

1-(4-acetylphenyl)-3-phenylurea 3f White solid; (92 mg, 73%), mp 190–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 8.36 (br s, 1H), 8.03 (br s, 1H), 7.86–7.84 (d, J=8.4 Hz, 2H), 7.49–7.47 (d, J=8.8 Hz, 2H), 7.40–7.38 (d, J=8 Hz, 2H), 7.30–7.27 (m, 2H), 7.06–7.03 (t, J=7.2 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 153.3, 144.1, 138.4, 131.1, 130.0, 129.1, 123.4, 119.6, 117.8, 26.4; FT-IR (KBr) 3440, 2921, 2848, 16631, 1638, 1598 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{15}N_2O_2$ 255.1134, found 255.1129.

1-(4-methoxyphenyl)-3-phenylurea 3g White solid; (105 mg, 87%), mp 191–193 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.46 (s, 1H), 7.44–7.42 (d, J = 7.6 Hz, 2H), 7.36–7.34 (d, J = 9.2 Hz, 2H), 7.28–7.24 (t, J = 7.6 Hz, 2H), 6.96–6.92 (t, J = 7.6 Hz, 1H), 6.87–6.85 (d, J = 9.2 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.5, 152.8, 139.9, 132.7, 128.8, 121.6, 120.0, 118.1, 114.0, 55.1; FT-IR (KBr) 3298, 2923, 2853, 1720, 1560, 1246 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_2$ 243.1134, found 243.1131.

Ethyl 4-(3-phenylureido)benzoate 3h White solid; (99 mg, 70%), mp 170–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.95 (s, 1H) 7.81–7.78 (d, J = 8.4 Hz, 2H), 7.23–7.21 (d, J = 8.8 Hz, 2H), 7.18–7.13 (m, 4H), 6.99–6.98 (m, 1H), 4.33–4.28 (q, J = 7.2 Hz, 2H) 1.36–1.32 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 154.0, 143.1, 137.7, 130.8, 129.2, 124.6, 124.3, 121.2, 118.9, 61.1, 14.4; FT-IR (KBr) 3441, 2922, 2842, 1708, 1600, 1542 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{16}H_{17}N_2O_3$ 285.1239, found 285.1241.

(*S*)-Methyl 5-methyl-3,7-dioxo-1-phenyl-2-oxa-4,6,8-triazadecan-10-oate 3i. White solid; (131 mg, 85%), mp 160–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.37–7.30 (m, 5H), 5.18 (br, 1H), 5.08 (s, 2H), 3.93 (s, 2H), 3.72 (s, 3H), 1.47–1.45 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 171.8, 157.9, 156.5, 136.2, 128.6, 128.2, 128.0, 66.9, 56.0, 52.3, 41.8, 21.3; FT-IR (KBr) 3367, 2964, 2926, 1723, 1697, 1626, 1276 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{20}N_3O_5$ 310.1404, found 310.1403.

(5*S*,9*S*)-Methyl 9-benzyl-5-methyl-3,7-dioxo-1-phenyl-2-oxa-4,6,8-triazadecan-10-oate 3j. White solid; (161 mg, 81%), mp 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 5H), 7.23–7.18 (m, 3H), 7.12–7.10 (d, J = 7.2 Hz, 2H), 5.64 (br, 2H), 5.17 (br, 1H), 5.03 (s, 2H), 4.73–4.68 (m, 1H), 3.65 (s, 3H), 3.11–3.06 (m, 1H), 3.02–2.96 (m, 1H), 1.42–1.41 (d, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 156.8, 156.1, 136.6, 136.3, 129.4, 128.6, 128.5, 128.2, 128.1, 126.9, 66.9, 56.1, 54.3, 52.2, 38.5, 21.5; FT-IR (KBr) 3298, 2924, 2849, 1737, 1697, 1640, 1502, 1267 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{21}H_{26}N_3O_5$ 400.1872, found 400.1869.

Benzyl ((*S*)-1-(3-((S)-1-hydroxy-4-methylpentan-2-yl)ureido) ethyl)carbamate 3k. White solid; (140 mg, 83%), mp 151–153 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 5.91 (br, 1H), 5.73 (br, 1H), 5.58 (br, 1H), 5.20 (br, 1H), 5.08 (s, 2H), 3.84 (s, 1H), 3.64–3.61 (m, 1H), 3.46–3.43 (m, 1H), 1.64–1.51 (m, 1H), 1.43–1.42 (d, J = 5.4 Hz, 3H), 1.39–1.23 (m, 2H), 0.90–0.88 (t, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.3, 136.0, 128.4, 128.1, 127.8, 66.8, 66.6, 55.8, 50.6, 40.3, 24.7, 23.0, 22.1, 21.3; FT-IR (KBr) 3447, 2953, 2921, 2849, 1697, 1645, 1539, 1263 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{28}N_3O_4$ 338.2080, found 338.2077.

Benzyl ((S)-(3-((S)-1-hydroxy-4-methylpentan-2-yl)ureido)(-phenyl)methyl)carbamate 3l. White solid; (155 mg, 78%), mp 192–194 °C; ^{1}H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.35–7.24 (m, 10H), 6.16 (br, 1H), 5.03 (s, 2H), 3.77 (s, 1H), 3.56–3.54 (m, 1H), 3.34 (br, 1H), 1.60–1.58 (m, 1H), 1.24 (br, 2H), 0.87–0.85 (t, J = 6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 158.2, 156.2, 136.1, 128.4, 128.3, 127.9, 127.8, 127.7, 125.7, 66.7, 65.6, 60.9, 50.0, 40.4, 24.6, 22.8, 21.8; FT-IR (KBr) 3311, 2954, 2924, 2853, 1679, 1618, 1438, 1259 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{22}H_{30}N_3O_4$ 400.2236, found 400.2230.

(*S*)-Methyl 5-(tert–butoxymethyl)-1-(9H-fluoren-9-yl)-3,7-dioxo-2-oxa-4,6,8-triazadecan-10-oate 3m. White solid; (192 mg, 82%), mp 135–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.75 (d, J = 7.6 Hz, 2H), 7.60–7.58 (d, J = 7.2 Hz, 2H), 7.42–7.38 (t, J = 7.2 Hz, 2H), 7.33–7.29 (t, J = 7.2 Hz, 2H), 5.87–5.85 (d, J = 8 Hz, 1H), 5.52–5.50 (d, J = 7.6 Hz, 1H), 5.33 (br, 1H), 4.43–4.39 (m, 2H), 4.25–4.22 (t, J = 7.2 Hz, 1H), 3.98–3.97 (d, J = 5.2 Hz, 2H), 3.68 (s, 3H), 3.59–3.51 (m, 2H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 157.5, 156.8, 143.9, 141.4, 127.9, 127.2, 125.2, 120.1, 67.4, 63.9, 58.9, 52.2, 47.2, 42.2, 27.5; FT-IR (KBr) 3328, 2974, 2924, 1698, 1644, 1539, 1245 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{25}H_{32}N_3O_6$ 470.2291, found 470.2286.

(5*S*,9*S*)-Methyl 5-(tert–butoxymethyl)-1-(9H-fluoren-9-yl)-3,7-dioxo-9-phenyl-2-oxa-4,6,8-triazadecan-10-oate 3n. White solid; (218 mg, 80%), mp 162–164 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77–7.75 (d, J = 7.8 Hz, 2H), 7.53–7.48 (m, 2H), 7.41–7.39 (t, J = 7.2 Hz, 2H), 7.34–7.28 (m, 4H), 7.19 (br, 3H), 5.79–5.77 (d, J = 8.4 Hz, 2H), 5.50–5.47 (m, 2H), 5.40 (br, 1H), 4.30–4.24 (m, 2H), 4.08 (br, 1H), 3.69 (s, 3H), 3.60–3.54 (m, 2H), 1.19 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2, 156.6, 156.3, 144.0, 143.8, 141.4, 137.1, 128.8, 128.4, 127.9, 127.5, 127.2, 125.2, 120.1, 67.5, 63.9, 58.9, 57.5, 52.7, 47.1, 27.5; FT-IR (KBr) 3321, 2974, 2934, 1698, 1644, 1536, 1243 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{31}H_{36}N_3O_6$ 546.2604, found 546.2600.

(*S*)-Methyl 5-benzyl-1-(9H-fluoren-9-yl)-3,7-dioxo-2-oxa-4,6,8-triazadecan-10-oate 3o. White solid; (182 mg, 77%), mp 160–162 °C; ^{1}H NMR (600 MHz, $CDCl_3$, few drops of CD_3 OD for solubility) δ 7.76–7.75 (d, J = 7.2 Hz, 2H), 7.53–7.52 (d, J = 6 Hz, 2H), 7.40–7.38 (t, J = 7.2 Hz, 2H), 7.28 (br, 4H), 7.23–7.21 (m, 3H), 5.16 (br, 1H), 4.32 (br, 2H), 4.17 (br, 1H), 3.94 (s, 2H), 3.70 (s, 3H), 3.15 (br, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 171.6, 157.9, 156.4, 143.8, 141.2, 136.8, 129.2, 128.4, 127.6, 127.0, 126.7, 125.0, 119.8, 66.7, 60.4, 52.0, 47.0, 41.6, 40.2; FT-IR (KBr) 3299, 2922, 2852, 1692, 1649, 1536, 1259 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{27}H_{28}N_3O_5$ 474.2029, found 474.2028.

(*S*)-(9*H*-fluoren-9-yl)Methyl ((3-(1-hydroxy-3-methylbutan-2-yl)ureido)methyl)carbamate 3p. White solid; (165 mg, 83%), mp 174–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.77–7.75 (d, J = 7.6 Hz, 2H), 7.58–7.57 (d, J = 7.2 Hz, 2H), 7.41–7.38 (t, J = 7.6 Hz, 2H), 7.32–7.28 (m, 2H), 4.46 (s, 2H), 4.34–4.33 (d, J = 6 Hz, 2H), 4.22–4.20 (t, J = 8 Hz, 1H), 3.66–3.64 (m, 1H), 3.52–3.50 (d, J = 7.6 Hz, 2H), 1.79–1.82 (m, 1H), 0.94–0.89 (m, 6H); ^{13}C NMR (150 MHz, DMSO-D_6) δ 157.6, 156.6, 143.8, 140.7, 127.7, 127.1, 125.3, 120.1, 65.7, 61.8, 61.3, 55.7, 46.6, 28.1, 19.7; FT-IR (KBr) 3315, 2955, 2923, 2852, 1692, 1647, 1532, 1260 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{22}H_{27}N_3O_4$ 398.2080, found 398.2085.

(9*H*-fluoren-9-yl)Methyl ((S)-1-(3-((S)-1-hydroxypropan-2-yl)ureido)-3-methylbutyl)carbamate 3q. White solid;

(159 mg, 75%), mp 157–159 °C; ^{1}HNMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.77–7.75 (d, J = 6.8 Hz, 2H), 7.59–7.57 (d, J = 6.4 Hz, 2H), 7.42–7.38 (t, J = 7.6 Hz, 2H), 7.33–7.30 (t, J = 7.2 Hz, 2H), 4.97 (br, 1H), 4.37–4.35 (d, J = 7.6 Hz, 2H), 4.20 (br, 1H), 3.80 (br, 1H), 3.53–3.39 (m, 2H), 1.62 (br, 1H), 1.25 (br, 3H), 1.14–1.06 (m, 1H), 0.92 (br, 6H); ^{13}CNMR (150 MHz, $CDCl_3$, few drops of CD_3 OD for solubility) δ 158.4, 156.8, 143.6, 141.2, 127.6, 127.0, 124.9, 119.8, 66.7, 57.8, 57.7, 47.8, 47.0, 43.2, 24.7, 22.1, 21.9, 17.1; FT-IR (KBr) 3328, 2959, 2923, 2851, 1694, 1634, 1534, 1235 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{32}N_3O_4$ 426.2393, found 426.2393.

Methyl 2-(3-((R)-1-benzamido-2-phenylethyl)ureido)-2-phenylacetate 3r. White solid; (179 mg, 83%), mp 137–139 °C; ^{1}HNMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.74–7.09 (m, 15H), 5.37 (br, 1H), 5.32 (s, 1H), 3.55 (s, 3H), 3.21–3.16 (m, 2H); ^{13}CNMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 172.3, 168.5, 157.2, 136.7, 134.6, 131.8, 129.4, 129.3, 128.9, 128.8, 128.58, 128.53, 128.46, 128.40, 127.3, 127.2, 127.1, 126.8, 59.9, 57.3, 52.6, 39.9; FT-IR (KBr) 3372, 2923, 2852, 1738, 1641, 1559, 1166 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{26}N_3O_4$ 432.1923, found 432.1913.

***Methyl ((1-benzamido-2-phenylethyl)carbamoyl)glycinate 3s.** White solid; (174 mg, 81%), 137–139 °C; ^{1}HNMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.63–7.13 (m, 15H), 5.38 (br, 1H), 5.30 (s, 1H), 3.62 (s, 3H), 3.57 (s, 3H), 3.28–3.27. (m, 2H), 3.19–3.16 (m, 2H); ^{13}CNMR (100 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 172.2, 168.6, 168.5, 157.4, 157.2, 137.1, 136.8, 136.7, 133.9, 133.8, 131.8, 129.4, 129.3, 128.9, 128.8, 128.57, 128.55, 128.4, 128.3, 127.3, 127.26, 127.24, 126.7, 59.9, 57.4, 57.3, 52.66, 52.62, 39.8; FT-IR (KBr) 3372, 2923, 2852, 1738, 1641, 1559, 1166 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{26}N_3O_4$ 432.1923, found 432.1913.

Methyl (*R*)-((1-benzamido-2-phenylethyl)carbamoyl)glycinate 3t. White solid; (142 mg, 80%), mp 166–168 °C; ^{1}HNMR (600 MHz, $CDCl_3$) δ 7.66–7.65 (d, J = 7.2 Hz, 2H), 7.42–7.39 (t, J = 7.2 Hz, 1H), 7.27–7.25 (m, 2H), 7.21–7.16 (m, 4H), 7.13–7.10 (t, J = 7.2 Hz, 1H), 5.91 (br, 1H), 3.98–3.94 (m, 2H), 3.61 (s, 3H), 3.18–3.16 (d, J = 7.2 Hz, 2H); ^{13}CNMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 171.5, 168.6, 158.2, 137.0, 133.8, 131.8, 129.3, 128.5, 128.4, 127.1, 126.7, 59.7, 52.0, 41.7, 39.9; (KBr) 3340, 2925, 2853, 1751, 1640, 1578, 1207 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{21}N_3O_4$ 356.1610, found 356.1617.

(*R*)-*N*-(1-(3-(2-Hydroxyethyl)ureido)-2-phenylethyl)benzamide 3u. White solid; (137 mg, 84%), mp 190–192 °C; ^{1}HNMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.71–7.69 (d, J = 7.2 Hz, 2H), 7.52–7.48 (t, J = 7.2 Hz, 1H), 7.43–7.37 (m, 2H), 7.31–7.22 (m, 5H), 5.51–5.47 (t, J = 6.8 Hz, 1H), 3.61–3.58 (t, J = 5.2 Hz, 2H), 3.27–3.21 (m, 4H); ^{13}CNMR (100 MHz, $CDCl_3$, few drops of CD_3OD and DMSO- D_6 for solubility) δ 169.5, 159.8, 138.6, 135.6, 132.7, 130.5, 129.57, 129.5, 128.4, 127.7, 62.4, 60.7, 43.4, 41.7, 40.0; (KBr) 3361, 3251, 2926, 2852, 1647, 1622, 1573, 1276 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{21}N_3O_4$ 328.1661, found 328.1670.

Methyl (((*S*)-((*tert*–butoxycarbonyl)amino)(phenyl)methyl) carbamoyl)phenylalaninate 3v. White solid; (181 mg, 85%), mp 171–173 °C; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.33–7.22 (m, 8H), 7.12–7.10 (d, J = 6.8 Hz, 2H), 6.15–6.11 (m, 1H), 5.82–5.74 (m, 2H), 4.74–4.72 (m, 1H), 3.62 (s, 3H), 3.12–2.98 (m, 2H), 1.40 (s, 9H); ^{13}CNMR (100 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 173.3, 157.0, 155.6, 139.9, 136.4, 129.3, 128.5, 128.4, 127.8, 126.9, 125.8, 80.3, 60.8, 54.1, 52.1, 38.4, 28.3; FT-IR (KBr) 3368, 3328, 2926, 1744, 1677, 1620, 1211 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{30}N_3O_5$ 428.2185, found 428.2193.

(2*S*,6*S*)-Methyl 2-benzyl-6-((*S*)-1-(benzyloxy)ethyl)-10,10-dimethyl-4,8-dioxo-9-oxa-3,5,7-triazaundecan-1-oate 3w. White solid; (179 mg, 74%), mp 161–163 °C; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.37–7.16 (m, 10H), 5.35, (br, 1H), 5.18, (br, 1H), 5.03, (br, 1H), 4.71–4.67 (m, 1H), 4.64–4.62 (d, J = 6 Hz, 2H), 4.37–4.35 (d, J = 11.4 Hz, 1H), 3.63 (s, 3H), 3.11–3.00 (m, 2H), 1.42 (s, 9H), 1.23–1.22 (d, J = 6 Hz, 3H); ^{13}CNMR (150 MHz, $CDCl_3$) δ 173.1, 156.7, 156.6, 137.6, 136.8, 127.5, 127.4, 128.8, 128.5, 128.3, 128.1, 126.9, 80.7, 76.4, 71.2, 62.2, 54.8, 52.2, 38.6, 28.5, 16.1; FT-IR (KBr) 3328, 2925, 2845, 1732, 1689, 1641, 1250 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{26}H_{35}N_3O_6$ 486.2604, found 486.2608.

***tert*-Butyl ((1*S*,2*R*)-1-(3-(1-hydroxy-3-phenylpropan-2-yl) ureido)-2-methylbutyl)carbamate 3x.** White solid; (150 mg, 79%), mp 155–157 °C; ^{1}HNMR (400 MHz, DMSO-D_6) δ 7.22–7.12 (m, 5H), 6.85 (br, 1H), 6.01 (br, 1H), 4.88 (br, 1H), 4.75 (br, 1H), 3.7 (br, 1H), 3.31–3.24 (m, 2H), 2.77–2.58 (m, 2H), 1.56 (br, 1H), 3.81 (br, 1H), 1.35 (s, 9H), 1.03–1.00 (m, 2H), 0.81–0.791 (tr, J = 4.8 Hz, 1H), 0.75–0.744 (d, J = 4.4 Hz, 3H); ^{13}CNMR (100 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 158.7, 156.4, 138.4, 129.3, 128.4, 126.4, 80.2, 64.5, 62.8, 53.7, 38.7, 37.6, 28.4, 25.3, 14.7, 11.1; FT-IR (KBr) 3344, 2964, 2920, 2872, 1686, 1638, 1571, 1248 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{34}N_3O_4$ 380.2549, found 380.2552.

(5*S*,8*R*,12*S*)-Methyl 12-Benzyl-5-methyl-3,6,10-trioxo-1,8-diphenyl-2-oxa-4,7,9,11-tetraazatridecan-13-oate 5a. White solid; (100 mg, 75%), mp 193–195 °C; ^{1}HNMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 8.33–8.31 (d, J = 7.6 Hz, 1H), 7.38–7.13 (m, 15H), 6.36–6.35 (d, J = 6.8 Hz, 1H), 5.08–5.07 (d, J = 5.2 Hz, 2H), 4.68–4.65 (t, J = 6.4 Hz, 1H), 4.20–4.18 (m, 1H), 3.68 (s, 3H), 3.13–2.98 (m, 2H), 1.34–1.32 (d, J = 7.2 Hz, 3H); ^{13}CNMR (150 MHz, DMSO-D_6) δ 173.3, 172.5, 156.6, 156.2, 141.3, 137.2, 129.6, 128.8, 128.79, 128.7, 128.3, 128.1, 127.9, 127.1, 126.3, 65.9, 58.4, 54.3, 52.3, 50.5, 49.0, 38.1, 18.3; FT-IR (KBr) 3302, 3020, 2925, 1735, 1682, 1558, 1260 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{33}N_4O_6$ 533.2400, found 533.2407.

(6*R*,9*S*)-Methyl 9-isopropyl-13,13-dimethyl-4,8,11-trioxo-6-phenyl-12-oxa-3,5,7,10-tetraazatetradecan-1-oate 5b. White solid; (156 mg, 72%), mp 180–183 °C; ^{1}HNMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.31–7.18 (m, 5H), 6.53–6.49 (m, 2H), 5.65 (br, 1H), 3.96–3.77 (m, 3H), dt3.65 (s, 3H), 1.99–1.97 (m, 1H), 1.38 (s, 9H); 0.85–0.84 (d, J = 6.8 Hz, 6H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 172.4, 171.7, 157.8, 156.1, 139.4, 128.5, 128.4, 127.5, 126.19, 126.13, 79.8, 60.8, 58.6, 52.3, 42.1, 29.8, 28.5, 19.2, 18.3 cm^{-1}; FT-IR (KBr) 3340, 3271, 2964, 2917, 2870, 1703, 1657, 1558, 1206 cm^{-1};

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{33}N_4O_6$ 437.2400, found 437.2404.

4-Nitrobenzyl phenylcarbamate 6a. Light yellow solid; (105 mg, 77%), mp 121–123 °C; ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.24–8.22 (d, $J=8$ Hz, 2H), 7.56–7.54 (d, $J=8$ Hz, 2H), 7.40–7.38 (d, $J=7.6$ Hz, 2H), 7.34–7.30 (t, $J=7.6$ Hz, 2H), 7.11–7.07 (t, $J=7.2$ Hz, 1H), 6.81 (br, 1H), 5.29 (s, 2H); ^{13}CNMR (150 MHz, $CDCl_3$) δ 153.0, 147.8, 143.6, 137.5, 129.3, 128.4, 124.0, 123.9, 119.2, 65.5 cm^{-1}; FT-IR (KBr) 3343, 2932, 1705, 1535, 1511, 1235 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{13}N_2O_4$ 273.0875, found 273.0888.

4-Methoxybenzyl phenylcarbamate 6b. White solid; (102 mg, 80%), mp 87–89 °C; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.38–7.25 (m, 6H), 7.07–7.03 (t, $J=7.6$ Hz, 1H), 6.91–6.89 (d, $J=7.2$ Hz, 2H), 6.67 (br, 1H) 5.13 (s, 2H), 3.81 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) 159.8, 153.6, 137.9, 130.3, 129.1, 128.2, 123.5, 118.8, 114.1, 66.9, 55.4 cm^{-1}; FT-IR (KBr) 3315, 2945, 2828, 1701, 1533, 1236 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{15}H_{15}NO_3Na$ 280.0950, found 280.0964.

4-Nitrophenyl undecylcarbamate 6c. Pale yellow solid; (128 mg, 76%), mp 83–85 °C; ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.25–8.23 (d, $J=9.2$ Hz, 2H), 7.32–7.30 (d, $J=8.8$ Hz, 2H), 3.30–3.25 (m, 2H), 1.60–1.55 (m, 4H), 1.26–1.25 (m, 14H), 0.89–0.86 (t, $J=6.4$ Hz, 3H), ; ^{13}CNMR (100 MHz, $CDCl_3$) 156.1, 153.3, 144.8, 125.3, 122.1, 41.6, 32.0, 29.8, 29.79, 29.77, 29.72, 29.5, 29.4, 26.9, 22.8, 14.3 cm^{-1}; FT-IR (KBr) 3342, 2922, 2852, 1703, 1542, 1352, 1217 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{29}N_2O_4$ 337.2127, found 337.2148.

***S*-Benzyl phenylcarbamothioate 6d.** White solid; (87 mg, 71%), mp 84–86 °C; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.40–7.39 (d, $J=5.6$ Hz, 2H), 7.36–7.35 (d, $J=4.8$ Hz, 2H), 7.31–7.29 (m, 4H), 7.25–7.24 (t, $J=2.4$ Hz, 1H), 7.12–7.09 (t, $J=4.8$ Hz, 1H), 4.22 (s, 2H); ^{13}CNMR (100 MHz, $CDCl_3$) 165.6, 138.0, 137.7, 129.2, 129.0, 128.7, 127.4, 124.7, 120.0, 34.6 cm^{-1}; FT-IR (KBr) 3243, 3038, 2925, 1653, 1535, 1242, 1165, 751, 701 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{14}NOS$ 244.0796, found 244.0796.

***S*-*p*-Tolyl phenylcarbamothioate 6e.** White solid; (90 mg, 74%), mp 129–131 °C; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.51–7.49 (d, $J=8$ Hz, 2H), 7.37–7.35 (d, $J=8$ Hz, 2H), 7.30–7.25 (m, 4H), 7.15 (br, 1H), 7.11–7.09 (t, $J=2.4$ Hz, 1H), 7.12–7.09 (d, $J=7.2$ Hz, 1H), 2.40 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) 165.0, 140.6, 137.7, 135.8, 130.6, 129.2, 124.7, 124.6, 119.6, 21.5 cm^{-1}; FT-IR (KBr) 3258, 3012, 2976, 1662, 1541, 1233, 1196, 784, 695 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{14}NOS$ 244.0796, found 244.0818.

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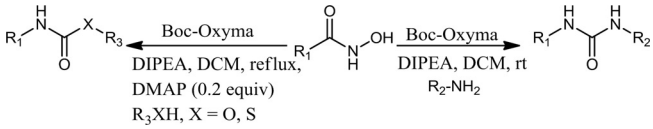
Ethyl 2-(*tert*-Butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma): An Efficient Reagent for the Racemization Free Synthesis of Ureas, Carbamates and Thiocarbamates via Lossen Rearrangement



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