

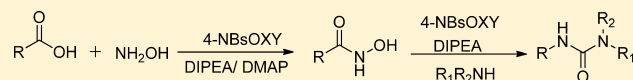
Ethyl 2-Cyano-2-(4-nitrophenylsulfonyloxyimino)acetate-Mediated Lossen Rearrangement: Single-Pot Racemization-Free Synthesis of Hydroxamic Acids and Ureas from Carboxylic Acids

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Supporting Information

ABSTRACT: Ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate (4-NBsOXY) mediated Lossen rearrangement and its application for the synthesis of ureas is demonstrated. Required hydroxamic acids for the Lossen rearrangements were synthesized from carboxylic acids using the same reagent. Finally, reaction of an amine with the produced isocyanate resulted in urea. Good yields without racemization were achieved under milder and simpler reaction conditions. Reactions are compatible with common *N*-protecting groups, such as Boc, Fmoc, Cbz, and benzyl, as well as various OH protecting groups, such as ^tBu and Bzl. Conversion from carboxylic acid to urea is achieved in one pot. Most importantly, byproducts Oxyma [ethyl 2-cyano-2-(hydroxyimino)acetate] and 4-nitrobenzenesulfonic acid can be recovered easily and can be recycled to prepare the reagent. Thus, the method is environmentally friendly and cost-effective.



Yields upto 92 %
38 examples

INTRODUCTION

The urea linkages and hydroxamic acids have interesting applications in medicinal chemistry¹ and in structural chemistry.² Many urea based compounds are potentially used in pharmaceutical industry. For example, unsymmetrically substituted ureas are potential inhibitors of HIV-1 protease,³ microbial alkaline protease,⁴ and several other classes of enzymes.⁵ They have important application in dye chemistry as well. Similarly, hydroxamic acids exhibit a wide range of biological activities such as antihypertensive drugs, antibacterial,⁶ inhibitors of various metalloproteases,⁷ inhibition of peptide deformylase (PDF),⁸ and orally active human epidermal growth factor receptor-2 sheddase inhibitor for the treatment of cancer.⁹ Some hydroxamates are known as highly potent tumor necrosis factor converting enzyme inhibitors (TACE, ADAM17)¹⁰ and strong bidentate metal ion chelators.¹¹

Numerous synthetic methods for the synthesis of ureas have been developed. Urea and its derivatives were synthesized via azide, isocyanate, or carbamate intermediates. Several coupling reagents have been used in the last two decades such as CDI (*N,N*-carbonyldiimidazole),¹² *N,N*-disuccinimidocarbonate,¹³ EDC (1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide)/DMAP (*N,N*-dimethylpyridin-4-amine),¹⁴ 1,1-carbonylbisbenzotriazole,¹⁵ and PPh₃-CCl₄-TEA system.¹⁶ Some other methods involve Me³SiCl,¹⁷ cyanuric chloride,¹⁸ bromodimethylsulfonium bromide (BDMS),¹⁹ Zr(IV) catalyst,²⁰ β -elimination of haloform,²¹ Zn(OTf)₂,²² *N,O*-bis-(ethoxycarbonyl)hydroxylamine,²³ and *N*-(*tert*-butyloxycarbonyl)-*O*-methanesulfonylhydroxamic acid.²⁴ However, a major disadvantage of most of the coupling reagents invented to date is the generation of undesired byproducts and chemical waste as well as racemization.

On the other hand, hydroxamic acids were prepared by the reaction of carboxylic acid or *N*-protected amino acids with hydroxylamine hydrochloride in the presence of alkyl chloroformate,¹⁴ cyanuric chloride,²⁵ TFFH (tetramethylfluoroformamidinium hexafluorophosphate),²⁶ coupling reagents,²⁷ and other important methods.²⁸ They also can be prepared from esters using KCN²⁹ and from *N*-acyloxazolidinone using samarium triflate.³⁰ The major drawback of these methods is the usage of toxic reagents and harsh reaction conditions. These methods also cause racemization and are hence not applicable to amino acids. Thus, simpler and more efficient methods for preparation of hydroxamic acids from *N*-protected amino acids are still needed.

Here we describe an alternative method for synthesizing racemization-free hydroxamic acids at ambient conditions without using any acid chlorides or strong bases. We also have extended the same methodology for conversion of the hydroxamic acid, which was prepared in the first step, to ureas via Lossen rearrangement using the same coupling reagent. Finally, a one-pot protocol for the whole conversion is described.

RESULTS AND DISCUSSION

Ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate (4-NBsOXY, **1**) (Figure 1) was used as a new coupling reagent for preparation of hydroxamic acids and a new reagent for Lossen rearrangement to convert the obtained hydroxamic acids to urea. Compound **1** can be easily prepared by the reaction of Oxyma and sulfonyl chloride in the presence of

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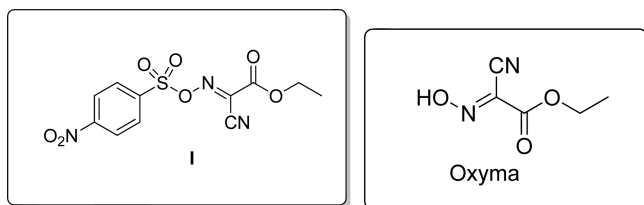


Figure 1. Ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate (**I**, 4-NBsOXY) and Oxyma (ethyl 2-cyano-2-(hydroxyimino)acetate).

DIPEA using a reported protocol.³¹ This reagent is stable at room temperature and can be stored for long periods of time. Oxyma was largely used as a racemization suppressant in peptide synthesis.³²

Hydroxamic acids were prepared by preactivation of the carboxylic acids with **I** (1 equiv) in the presence of DIPEA and a catalytic amount of DMAP (*N,N*-dimethylpyridin-4-amine) (0.1 mol %) at room temperature, for 30 min in anhydrous THF, followed by the addition of hydroxylamine hydrochloride in DMF with DIPEA (1.5 equiv). It required 2 h for complete conversion at room temperature as monitored by TLC.³³

For optimization, we screened a variety of bases, e.g., DIPEA, NMM (*N*-methylmorpholine), Et₃N, and DABCO (1,4-diazabicyclo[2.2.2]octane), using the reaction between benzoic acid and hydroxylamine hydrochloride (Table 1). We found DIPEA and a catalytic amount of DMAP (0.1 mol %) afforded higher yields. DMAP may act as an acyl-transfer catalyst as known for Steglich esterification.³⁴

Table 1. Optimization of the Reaction Conditions^a

entry	base (1 mmol)	DMAP (mmol %)	yield ^b (%)
1	DIPEA	0.1	82
2	DIPEA		61
3	NMM	0.1	73
4	NMM		52
5	Et ₃ N	0.1	50
6	DABCO	0.1	30

^aReaction conditions: substrate **1a** (122 mg, 1 mmol), 4-NBsOXY (327 mg, 1 mmol), DMAP (12.2 mg, mmol), DIPEA (322.5 mg, 2.5 mmol), hydroxylamine hydrochloride (103.5 mg, 1.5 mmol), and THF (2 mL), at room temperature, time of the reaction fixed to 2.5 h.
^bIsolated yield.

Under these optimized conditions, this methodology was applied to a wide variety of carboxylic acids that included aromatic, aliphatic, and long-chain carboxylic acids (Table 2). This methodology was also successfully applied to amino acids with excellent yield. The reactions were compatible with common *N*-protecting groups, e.g., Bn (entry 6), Cbz (entries 7 and 8), Fmoc (entries 9–14), and Boc (entries 15–17).

We investigated the racemization probability of the current protocol by comparison of the HPLC profile of *DL*-Boc-phenylalanine hydroxamic acid (**2p**) and *L*-Boc-phenylalanine hydroxamic acid (**2o**) (chiral column, 5 μ m, 2.1 \times 150 mm, isocratic gradient of 10% 2-propanol in hexane, 20 min). Two peaks with retention times of 3.06 and 3.81 min, corresponding to the two enantiomers of *DL*-Boc-phenylalanine hydroxamic

acid (**2p**), were observed in the HPLC profile of **2p**, whereas a single peak at 3.24 min, corresponding to the single enantiomer, was noted at the HPLC profile of *L*-Boc-phenylalanine hydroxamic acid (**2o**) (Figure 2). Thus, there was no detectable racemization for the preparation of hydroxamic acids using the present reagent.

A possible reaction mechanism is shown in Figure 3 and Scheme 1. At first, the active Oxyma ester of carboxylic acid (**III**) may form via transient intermediate **II**. Intermediate **III** could be isolated and characterized by ¹H and ¹³C NMR and HRMS (see the Experimental Section and the Supporting Information, Figure S113–115). In a second step, hydroxylamine hydrochloride reacts with **III** to produce the desired hydroxamic acid. DMAP may act as an acyl-transfer catalyst as known for Steglich esterification.³⁴ We commenced the reaction using benzoic acid and 4-NBsOXY in the presence of DIPEA/DMAP and recorded the C¹³ NMR in CDCl₃ in an NMR tube. At the initial stage, the peak for the carbonyl carbon (a) of benzoic acid was noted at δ 172.8 ppm as well as the carbonyl carbon (b) and the aromatic carbon at para position (c) of 4-NBsOXY was noted at 155.5 and 151.9 ppm, respectively. At 30 min, four new peaks replaced those; two peaks at 160.4 and 156.7 ppm (d and e) correspond to intermediate **III** and the other two peaks at 151.7 and 148.0 ppm (f and g) correspond to the byproduct 4-nitrobenzenesulfonic acid. Hydroxylamine hydrochloride was then added. NMR was checked after 90 min of the addition of hydroxylamine hydrochloride. The peaks d and e shifted to 164.7 ppm (h), 158.7 ppm (i), which correspond to **2a** and the byproduct, Oxyma, respectively. Intermediate **III** was isolated and characterized with various spectroscopic techniques. These observations clearly support the proposed mechanism as depicted in Figure 3. Time-dependent ¹H NMR experiments (Supporting Information, Figure S152–161) also confirm that. However, the possibility of direct conversion of intermediate **II** to the hydroxamic acid **2a** cannot be obviated. In our method, most probably, the reaction proceeds via intermediate **III**, as (a) we could isolate **III** and (b) we are adding hydroxylamine hydrochloride after formation of **III** (30 min). A plausible pathway explaining the involvement of DMAP is also proposed on the basis of the existing literature (Scheme 1).³⁴

Finally, urea was prepared via Lossen rearrangement of hydroxamic acids into the corresponding isocyanate by the reaction of **I** (1 equiv) in the presence of DIPEA. Stirring was continued at 0 $^{\circ}$ C for 90 min followed by the addition of amine to the reaction mixture at room temperature. The reaction was completed within 4 h.

We screened various solvents using the reaction between benzhydroxamic acid (1 mmol) and benzylamine (1 mmol) (Table 3). THF was found to be the best solvent. Use of CHCl₃, CH₃CN, ethyl acetate, acetone, and DMF also gave good results. Starting material **2a** completely disappeared in all solvents other than water. In the case of water, 74% (82 mg) of the starting material (**2a**) was recovered.

We synthesized various ureas (Table 4) to explore the scope of this method under the above optimized reaction condition. The reaction works with aliphatic, aromatic, and long-chain containing hydroxamic acids with good yields (70–92%). Yields of the products were good even when aniline (**3a**, **3e**, and **3q**) or a secondary amine (**3d**) was used as a nucleophile. Selectivity of the reaction was checked with ethanol amines (**3f**); selective attachment of the amino group was noted in this

Table 2. Wide Scope of the Synthesis of Hydroxamic Acid Using I^a

Entry	Acid	Product			Entry	Acid	Product		
		Structure	Id	Yield ^a			Structure	Id	Yield ^a
1			2a	82	10			2j	81
2			2b	79	11			2k	80
3			2c	76	12			2l	75
4			2d	74	13			2m	77
5			2e	81	14			2n	75
6			2f	81	15			2o	80
7			2g	78	16			2p	81
8			2h	78	17			2q	80
9			2i	80					

^aIsolated yield. Reaction condition was similar to that mentioned in Table 1.

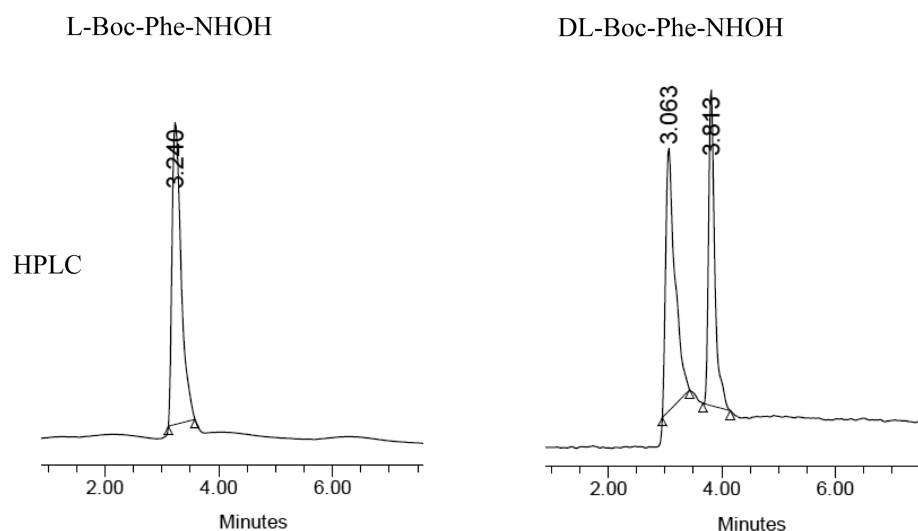


Figure 2. HPLC profile diagrams of products 2o and 2p.

case. A few drops of water were necessary for solubility of free glycine (3g), and 81% yield was obtained.

This methodology was compatible with common amine protecting groups, such as Boc, Fmoc, Cbz, and benzyl, 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 (70 to 90%) in all cases including the sterically hindered amino acids, e.g., leucine, valine, phenylalanine, and phenylglycine. All the products were characterized using ¹H and ¹³C NMR, HRMS, and IR. The product 3g was characterized using XRD data also (Supporting Information, Figure S181).

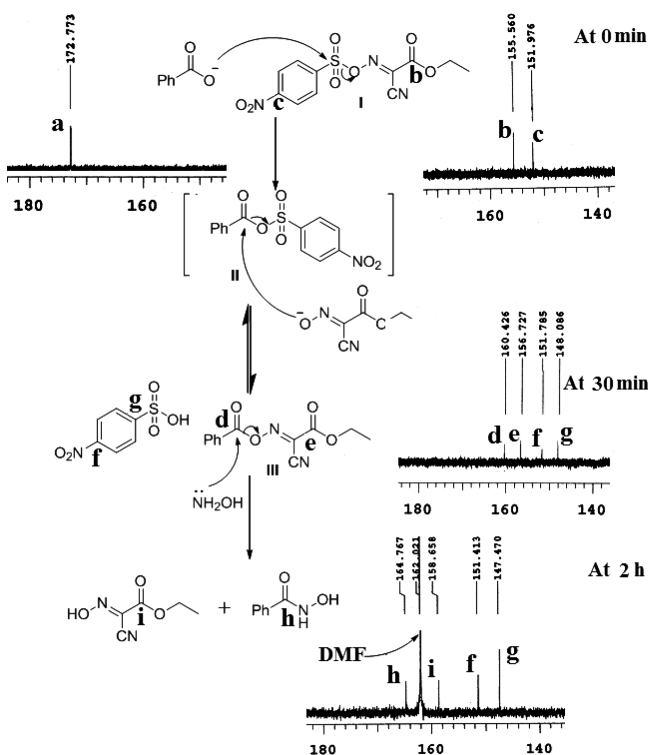
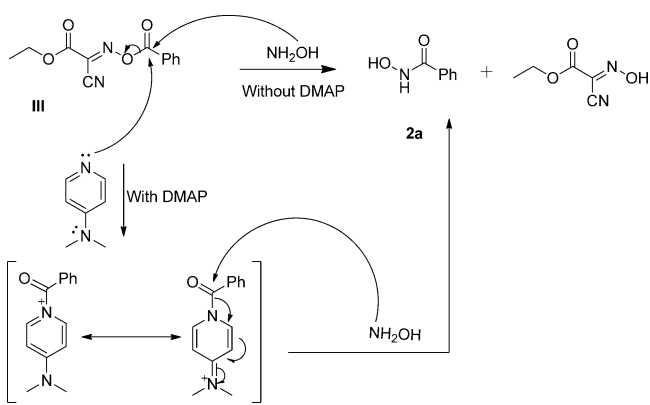


Figure 3. Plausible reaction mechanism for the synthesis of ureas from hydroxamic acids by I as noticed using C^{13} NMR experiments.

Scheme 1. Plausible Mechanism for the Involvement of DMAP³³



A possible reaction mechanism is shown in Figure 4. At first, substrate 2a reacts with I and an active O-sulfonylated intermediate (IV) forms at 0 °C. In the second step, IV undergoes Lossen rearrangement to isocyanate V, which was characterized by 1H and ^{13}C NMR and HRMS (Supporting Information, Figures S116–118). Finally, nucleophilic amine reacts with V to produce urea 3a. To identify the intermediate, we performed the reaction between hydroxamic acid and 4-NBsOXY in the presence of DIPEA in an NMR tube using $CDCl_3$ as a solvent, and ^{13}C NMR was recorded at the specified time interval. Initially, three peaks were present, one at 166.8 ppm (1) corresponding to the carbonyl carbon of the hydroxamic acid (2a) and the other two peaks at 155.5 and 151.9 ppm (2 and 3) corresponding to the carbonyl carbons of 4-NBsOXY. At 90 min, the peaks 1, 2, and 3 were replaced by 4, 5, and 6, respectively. The peak at 162.2 ppm (4) corresponds to the carbonyl carbon of Oxyma, and the peaks

Table 3. Synthesis of Ureas from Hydroxamic Acids Using I in Various Solvents^a

entry	solvent	isolated yield (%)
1	$CHCl_3$	87
2	CH_3CN	85
3	THF	91
4	EtOAc	87
5	acetone	82
6	DMF	80
7	H_2O	20

^aReaction conditions: substrate 2a (137 mg, 1 mmol), 4-NBsOXY (327 mg, 1 mmol), DIPEA (193.5 mg, 1.5 mmol), amine (107 mg, 1 mmol), and solvent (2 mL), temperature (first 90 min at 0 °C and then 4 h at room temperature), total reaction time 5.5 h.

at 151.4 and 148.1 ppm (5 and 6) correspond to 4-nitro benzenesulfonic acid. Finally, one new peak appeared at 155.7 ppm (7) after the addition of cyclohexyl amine, which corresponds to the carbonyl carbon of urea. These observations support the proposed mechanism depicted in Figure 4.

Finally, we achieved a one-pot synthesis of ureas from carboxylic acids using I and obtained up to 71% yield. The one-pot protocol requires 2 equiv of I: 1 equiv for activation of carboxylic acid into Oxyma ester (III) which converts into hydroxamic acid followed by the addition of hydroxylamine hydrochloride and a further 1 equiv of I for conversion of hydroxamic acid into urea via isocyanate (Lossen rearrangement). The scope of the one-pot protocol was investigated with a variety of N-protected amino acids. All of the amino acids, even with bulky side chains, produced good yields (Table 5).

We determined racemization in our method of urea synthesis from carboxylic acid using the reaction starting from DL-Boc-phenylalanine (3s) and L-Boc-phenylalanine (3r). In both cases, the methyl ester of phenylglycine was used as nucleophile. Analytical HPLC profiles of products 3r and 3s (symmetry C_8 , 5 μm , 3.0 \times 150 mm analytical column, CH_3CN in H_2O with 0.1% formic acid, linear gradient from 0 to 100% CH_3CN in H_2O up to 10 min, then 10 to 20 min 100% CH_3CN) were compared. Two peaks with retention times of 10.73 and 11.17 min, which correspond to the two diastereomers present in the product, appeared in the HPLC profile of 3s. On the other hand, a single peak at 10.89 min was observed in the HPLC profile of 3r, which corresponds to the single stereoisomeric product (Figure 5). This implies the current method does not cause any racemization. The singlet at δ 3.71 ppm for methoxy proton of 3r and two singlets at δ 3.70 ppm and δ 3.68 ppm for the same of 3s in 1H NMR confirm that (Figure 5). Many other peaks in 1H and ^{13}C NMR also support that.

Stepwise conversion of the Fmoc-L-Ala-OH to hydroxamic acid and that to urea (with methyl ester of leucine) was performed by 4-nitrobenzenesulfonyl chloride, it worked as expected (yield ~50%). However, the one-pot protocol for the same synthesis with 4-nitrobenzenesulfonyl chloride decreased the yield to 30%. Moreover, 1.5% racemization (Supporting Information, Figure S138) was observed. On the other hand, use of I gave 61% yield for the same reaction under the same conditions without detectable racemization (Supporting Information, Figure S131). Thus, use of I is better than that of the 4-nitrobenzenesulfonyl chloride.

Table 4. Wide Scope of the Synthesis of Ureas Using I^a

Entry	Acid	Amine	Product		Entry	Acid	Amine	Product													
			Id	Yield ^a				Id	Yield ^a												
1		A Ph-NH ₂	3a	83	7			3m	82												
		B	3b	91			8			3n	80										
		C	3c	90					9			3o	79								
		D	3d	82							10			3p	81						
		E	3e	74									11			3q	74				
		F	3f	91											12			3r	89		
		G	3g	81													13			3s	88
2			3h	88	14															3t	85
		3					3i	92											15		
							3j	87	15												
							3k	90													
							3l	89													

^aIsolated yield; the products were characterized by NMR, ESI-MS, and IR; all amino acids were L-amino acids except **13**, which had a DL configuration.

From the available literature we found only one report for one-pot conversion of carboxylic acids into urea that uses carbonyl diimidazole.¹² However, that reaction needs 60 °C temperature and does not ensure retention of chiral integrity. On the other hand, our method works at room temperature and retains chiral integrity. Most importantly, byproducts generated in our method, Oxyma and 4-nitrobenzenesulfonic acid, were easily recovered by simple acid–base workup or a column chromatographic separation after acid wash of the reaction mixture. Chlorination of the recovered 4-nitrobenzenesulfonic acid with sulfonyl chloride at 60 °C in toluene gave 4-nitrobenzenesulfonyl chloride, which was treated with the recovered Oxyma in the presence of DIPEA to regenerate I. NMR spectra of the recovered byproducts were as good as the commercial sample (Supporting Information, Figure S173–178). Characteristic spectra of the regenerated I and the products synthesized using that were also identical with those spectra of the products obtained using other batch of the reagent I. Thus, this is the first report of a racemization free

one-pot synthesis of urea from carboxylic with a recyclable reagent.

CONCLUSIONS

In summary, we have developed an efficient method for the racemization-free synthesis of ureas and hydroxamic acids under milder reaction conditions utilizing ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate (4-NBsOXY) as a recyclable reagent. The reaction is compatible with common N-protecting groups, such as, Boc, Fmoc, Cbz, benzyl, and various side-chain alcohol protecting groups of amino acids including ^tBu and OBzl. Mechanistic investigation suggests a Lossen rearrangement mediated urea formation. We described a one-pot synthesis protocol of ureas from carboxylic acids with reasonable yields using 4-NBsOXY (I). Furthermore, the byproduct, Oxyma and 4-nitrobenzenesulfonic acid, can be recovered easily and reused for reagent preparation. This is the first report of one-pot racemization-free synthesis of urea from carboxylic acid, which is performed with a recyclable reagent.

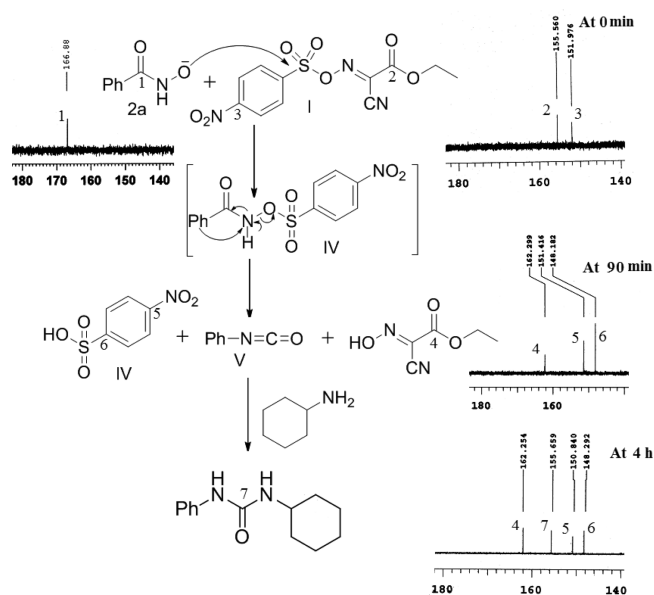


Figure 4. Plausible reaction mechanism for synthesis of urea with ^{13}C NMR.

EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial sources. All amino acids are L-amino acids except glycine unless otherwise noted. NMR spectra were recorded on 600 and 400 MHz spectrometers using CDCl_3 and CD_3OD as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are reported in ppm, and spin–spin coupling constants (J) are given in hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). High-resolution mass spectra were recorded on a Q-TOF ESI-MS instrument and Q-TOF LC/MS system. Reactions were monitored using thin-layer chromatography with silica gel G254. Purification of the reaction products was carried out by column chromatography using silica gel (60–120 mesh) using eluent EtOAc/hexane. Solvents were removed under reduced pressure using a Buchi rotary evaporator. HPLC analysis was carried out with a chiral column (5 μm , 2.1 \times 150 mm) and symmetry C_8 (5 μm , 3.5 \times 150 mm) column coupled to a UV–visible detector, and HPLC grade solvents were used for HPLC analysis. Melting points were determined using a dedicated melting point measuring apparatus, and FT-IR spectra were recorded on a FT-IR spectrometer. X-ray data were collected on a diffractometer equipped with a CCDc area detector using Mo $K\alpha$ radiation. The structures were solved by direct methods using SHELLX-97 (Göttingen, Germany) software.

General Procedure for the Synthesis of Ethyl 2-Cyano-2-(4-nitrophenylsulfonyloxyimino)acetate (4-NBsOXY, I) from Sulfonyl Chloride and Oxyma. 4-Nitrobenzenesulfonyl chloride (1 mmol) was added to a stirred solution of Oxyma (1 mmol) and DIPEA (1 mmol) in DCM (2 mL) under nitrogen at 0 °C. Then the reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting solution was extracted with DCM (2 \times 10 mL) and 5% citric acid (2 \times 5 mL), washed with brine (2 \times 5 mL), and dried over anhydrous CaCl_2 . It was then dried in vacuo and purified by recrystallization using hexane. Characterization data including the XRD structure are reported.³¹

General Procedure for the Synthesis of Hydroxamic Acids 2a–m. 4-NBsOXY (I, 1 mmol) was added to a stirred solution of carboxylic acid (1 mmol), DIPEA (1 mmol), and DMAP (0.1 mmol) in THF (2 mL) at room temperature. The reaction mixture was stirred for 30 min followed by the addition of hydroxylamine hydrochloride in DMF (0.5 mL) and DIPEA (1.5 mmol). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction

Table 5. One-Pot Synthesis of Ureas from Carboxylic Acids with 4-NBsOXY (I)^a

Entry	Acid	Amine	Time	Product	
				Id	yield ^b
1			8 h	3b	68
2			8 h	3k	69
3			8 h	3m	62
4			8 h	3n	61
5			8 h	3p	63
6			8 h	3q	45
7			8 h	3r	71
8			8 h	3s	69

^aReaction conditions: acid (1 mmol), hydroxamic acid (1.5 mmol), 4-NBsOXY (2 mmol), amine (1 mmol), DMAP (0.1 mmol), and DIPEA (3 mmol), temperature (at first 2.5 h at rt, 90 min at 0 °C, and rt for 4 h). ^bIsolated yield.

mixture was concentrated using a rotary evaporator and then diluted with 15 mL of ethyl acetate, washed with 5% HCl (2 \times 10 mL), 5% NaHCO_3 (2 \times 10 mL), and saturated NaCl solution (2 \times 10 mL), and dried over anhydrous Na_2SO_4 . Evaporation of the organic layer gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate.

General Procedure for the Synthesis of Urea 3a–r. 4-NBsOXY (1 mmol) was added to a stirred solution of hydroxamic acid (1 mmol) and DIPEA (1.5 mmol) in THF (2 mL) at 0 °C. Then the reaction mixture was stirred at the same temperature for 90 min followed by the addition of amine (1 mmol) and stirring at room temperature for more 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated using a rotary evaporator and then diluted with 15 mL of ethyl acetate, washed with 5% HCl (2 \times 10 mL), 5% NaHCO_3 (2 \times 10 mL), and saturated NaCl solution (2 \times 10 mL), and dried over anhydrous Na_2SO_4 , and the evaporation of the solvent gave a residue

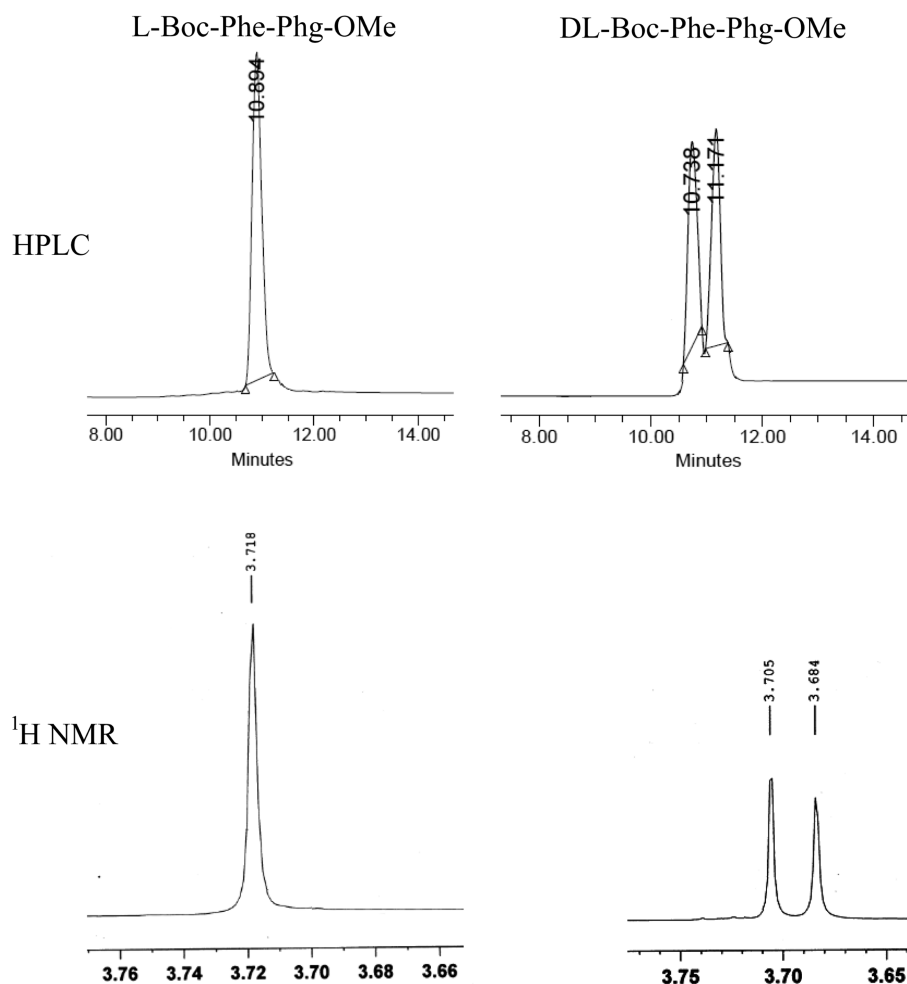


Figure 5. HPLC profile diagrams and ^1H NMR spectra of products **3r** and **3s** (Phe = phenylalanine, Phg = phenylglycine, L-Boc-Phe-Phg-OMe indicates the urea prepared from L-Boc-Phe-OH and Phg-OMe; similarly, DL-Boc-Phe-Phg-OMe indicates the urea prepared from DL-Boc-Phe-OH and Phg-OMe).

that was purified on silica gel column chromatography using hexane and ethyl acetate.

General Procedure for the Synthesis of Urea from Carboxylic Acids (One-Pot Protocol). 4-NBsOXY (1 mmol) was added to a stirred solution of carboxylic acid (1 mmol), DIPEA (1 mmol), and DMAP (0.1 mmol) in THF (2 mL) at room temperature. Then the reaction mixture was stirred for 30 min followed by the addition of hydroxylamine hydrochloride in DMF (0.5 mL) and DIPEA (1.5 mmol) and stirred for more 2 h at room temperature. 4-NBsOXY (1 mmol) and DIPEA (1 mmol) were added again to the above reaction mixture at 0°C and stirring continued for 90 min at the same temperature followed by addition of amine (1 mmol) and stirring at room temperature for further 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated using rotary evaporator and then diluted with 15 mL of ethyl acetate, washed with 5% HCl (2×10 mL), 5% NaHCO_3 (2×10 mL), and saturated NaCl solution (2×10 mL), and dried over anhydrous Na_2SO_4 . The obtained residue that was purified on silica gel column chromatography using hexane and ethyl acetate

Bz-Oxya (Intermediate III): white solid (226 mg, 92%); ^1H NMR (600 MHz, CDCl_3) δ 8.20–8.18 (d, $J = 7.8$ Hz, 2H), 7.72–7.70 (t, $J = 7.8$ Hz, 1H), 7.56–7.53 (t, $J = 7.8$ Hz, 2H), 4.53–4.49 (q, $J = 7.2$ Hz, 2H), 1.45–1.43 (t, $J = 7.2$, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 160.8, 157.1, 135.3, 131.8, 130.7, 129.3, 125.9, 107.2, 64.7, 14.1; HRMS (ESI) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_4\text{Na}$ 269.0538, found 269.0555

Isocyanatobenzene (Intermediate V): colorless liquid (109 mg, 90%); ^1H NMR (600 MHz, CDCl_3) δ 7.37–7.36 (d, $J = 7.8$ Hz, 2H), 7.28–7.26 (t, $J = 7.2$ Hz, 2H), 7.03–7.01 (t, $J = 7.8$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 132.6, 128.7, 127.6, 127.0, 124.1; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_6\text{NO}$ 120.0449, found 120.0456.

N-Hydroxybenzamide (2a):³⁵ white solid (122 mg, 82%); mp 125–127 $^\circ\text{C}$; ^1H NMR (600 MHz, CDCl_3) δ 7.72–7.71 (d, $J = 7.8$ Hz, 2H), 7.50–7.48 (t, $J = 7.2$ Hz, 1H), 7.41–7.38 (t, $J = 7.8$ Hz, 2H), 3.20 (br, 1H); ^{13}C NMR (150 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 166.8, 131.9, 131.5, 128.6, 127.0; FT-IR (KBr) 3296, 3058, 2758, 1643, 1612, 1573, cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_8\text{NO}_2$ 138.0555, found 138.0553.

N-Hydroxy-2-phenylacetamide (2b): white solid (119 mg, 79%); mp 130–132 $^\circ\text{C}$; ^1H NMR (600 MHz, CDCl_3) δ 7.34–7.24 (m, 5H), 3.49 (s, 2H), 2.30 (br, 1H); ^{13}C NMR (150 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 169.36, 134.25, 126.3, 129.1, 128.7, 128.5, 127.2, 40.0; FT-IR (KBr) 3190, 3029, 2923, 1685, 1630, 1545 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{10}\text{NO}_2$ 152.0712, found 152.0718.

N-Hydroxyfuran-2-carboxamide (2c): white solid (96 mg, 76%); mp 122–123 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 8.81 (br, 2H), 7.63–7.62 (d, $J = 7.2$ Hz, 1H), 7.31–7.30 (d, $J = 7.2$ Hz, 1H), 6.54–6.53 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.4, 147.0, 144.3, 119.3, 112.1 FT-IR (KBr) 3304, 3066, 2972, 1693, 1646, 1540 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_5\text{H}_6\text{NO}_3$ 128.0348, found 128.0348.

N-Hydroxypicolinamide (2d): white solid (102 mg, 74%); mp 125–126 °C; ^1H NMR (400 MHz, CDCl_3) δ 10.5 (br, 2H), 8.48–8.47 (d, $J = 4.2$ Hz, 1H), 8.07–8.06 (d, $J = 7.8$ Hz, 1H), 7.78–7.75 (m, 1H), 7.37–7.34 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.2, 149.5, 148.4, 137.6, 126.7, 122.5. FT-IR (KBr) 3324, 3166, 2961, 1683, 1626, 1550, cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_6\text{H}_7\text{N}_2\text{O}_2$ 139.0508, found 139.0510.

N-Hydroxydodecanamide (2e): white solid (174 mg, 81%); mp 75–76 °C; ^1H NMR (600 MHz, CDCl_3) δ 2.46–2.44 (t, $J = 7.8$ Hz, 2H), 1.61–1.57 (m, 2H), 1.28–1.23 (m, 16H), 0.86–0.84 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 171.7, 33.1, 32.0, 29.7, 29.6, 29.4, 29.4, 29.3, 25.6, 22.7, 14.1; FT-IR (KBr) 3258, 2915, 2847, 1663, 1623, 1469, 1423, 720, 649 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{26}\text{NO}_2$ 216.1964, found 216.1964.

N-(1-(hydroxyamino)-4-methyl-1-oxopentane-2-yl)benzamide (2f): white solid (202 mg, 81%); mp 122 °C; ^1H NMR (600 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 7.76–7.75 (d, $J = 7.8$ Hz, 2H), 7.47–7.46 (t, $J = 7.2$ Hz, 1H), 7.38–7.37 (t, $J = 5.4$ Hz, 2H), 4.53–4.51 (m, 1H), 2.9 (br, 1H), 1.69–1.66 (m, 2H), 1.26–1.23 (m, 1H), 0.91–0.90 (d, $J = 6$ Hz, 3H), 0.88–0.87 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 169.7, 168.2, 133.3, 131.8, 128.4, 128.1, 127.1, 126.8, 49.5, 40.9, 24.7, 22.4, 21.8; FT-IR (KBr) 3301, 2956, 2461, 1642, 1612, 1535, 1425, 866, 693 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_3$ 251.1396, found 251.1376.

Benzyl (2-(hydroxyamino)-2-oxoethyl)carbamate (2g): white solid (174 mg, 78%); mp 119–121 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.44–7.17 (m, 5H), 5.16 (s, 2H), 3.95–3.94 (d, $J = 5.4$ Hz, 2H), 0.9 (br, 1H); ^{13}C NMR (150 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 167.4, 157.2, 136.1, 128.5, 128.2, 128.0, 67.2, 41.9; FT-IR (KBr) 3318, 2943, 1705, 1672, 1536, 770, 697 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{O}_4$ 225.0875, found 225.0886.

Benzyl (2-(hydroxyamino)-2-oxo-1-phenylethyl)carbamate (2h): white solid (234 mg, 78%); mp 157–158 °C; ^1H NMR (600 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 7.33–7.16 (m, 10H), 5.18 (s, 1H), 5.08 (s, 2H), 3.74 (br, 1H); ^{13}C NMR (150 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 167.8, 156.1, 137.2, 136.0, 128.8, 128.7, 128.4, 128.3, 128.1, 127.9, 127.0, 126.8, 67.1, 56.1; FT-IR (KBr) 3348, 3266, 2915, 1715, 1647, 1497, 751, 697 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_4$ 301.1188, found 301.1209.

(9H-Fluoren-9-yl)methyl (2-(hydroxyamino)-2-oxoethyl)carbamate (2i): white solid (249 mg, 80%); mp 127–128 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.76–7.75 (d, $J = 6.6$ Hz, 2H), 7.58–7.57 (d, $J = 6.6$ Hz, 2H), 7.40–7.38 (t, $J = 6.6$ Hz, 2H), 7.32–7.30 (t, $J = 5.4$ Hz, 2H), 4.39–4.38 (d, $J = 7.2$ Hz, 2H), 4.19–4.16 (t, $J = 6.6$ Hz, 1H), 3.71–3.70 (d, $J = 6$ Hz, 2H), 3.37 (br, 1H); ^{13}C NMR (150 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 167.4, 157.3, 143.7, 141.2, 127.7, 127.1, 125.0, 119.9, 67.2, 47.0, 41.9; FT-IR (KBr) 3342, 3259, 2922, 1695, 1667, 1551, 1281, 737, 698 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4\text{Na}$ 335.1008, found 335.0999.

(9H-Fluoren-9-yl)methyl (3-(hydroxyamino)-3-oxopropyl)carbamate (2j): white solid (264 mg, 81%); mp 170–171 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.66–7.65 (d, $J = 7.2$ Hz, 2H), 7.51–7.48 (d, $J = 7.2$ Hz, 2H), 7.31–7.28 (t, $J = 7.2$ Hz, 2H), 7.22–7.20 (t, $J = 7.2$ Hz, 2H), 4.26–4.25 (d, $J = 6.6$ Hz, 2H), 4.11–4.09 (t, $J = 6.6$ Hz, 1H), 3.67 (br, 1H), 3.30–3.28 (t, $J = 6$ Hz, 2H), 2.21–2.19 (t, $J = 6$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.6, 156.4, 143.8, 141.4, 127.8, 127.2, 125.2, 120.1, 67.4, 53.2, 47.2, 27.4; FT-IR (KBr) 3304, 3066, 2972, 1693, 1646, 1540 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_4$ 327.1345, found 327.1346.

(9H-Fluoren-9-yl)methyl (1-(hydroxyamino)-1-oxopropane-2-yl)carbamate (2k): white solid (260 mg, 80%); mp 128–129 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.78–7.77 (d, $J = 4.8$ Hz, 2H), 7.61–7.59 (d, $J = 7.8$ Hz, 2H), 7.46–7.44 (t, $J = 6$ Hz, 2H), 7.31–7.29 (t, $J = 7.8$ Hz, 2H), 4.41–4.40 (d, $J = 6.6$ Hz, 2H), 4.31–4.27 (m, 1H), 4.12–4.11 (t, $J = 6.6$ Hz, 1H), 2.5 (br, 1H), 1.39–1.38 (d, $J = 6$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ

170.3, 156.3, 143.6, 141.1, 127.6, 127.6, 124.9, 119.8, 66.9, 49.1, 46.9, 18.0; FT-IR (KBr) 3426, 3306, 2925, 1685, 1618, 1533 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_4$ 327.1345, found 327.1331.

(9H-Fluoren-9-yl)methyl (1-(hydroxyamino)-3-methyl-1-oxobutane-2-yl)carbamate (2l): white solid (265 mg, 75%); mp 173–174 °C; ^1H NMR (600 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 7.74–7.73 (d, $J = 7.2$ Hz, 2H), 7.55–7.51 (d, $J = 6.6$ Hz, 2H), 7.38–7.36 (t, $J = 7.2$ Hz, 2H), 7.29–7.27 (t, $J = 7.8$ Hz, 2H), 5.9 (br, 1H), 4.41–4.38 (d, $J = 7.2$ Hz, 2H), 4.33–4.30 (m, 1H), 4.18–4.16 (t, $J = 7.2$ Hz, 1H), 2.15–1.93 (m, 1H), 0.92–0.90 (d, $J = 6.6$ Hz, 3H), 0.89–0.87 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 168.8, 156.8, 143.8, 141.3, 127.8, 127.1, 125.0, 120.0, 67.2, 58.3, 47.1, 30.9, 19.0, 18.4; FT-IR (KBr) 3305, 3208, 2925, 2467, 1686, 1647, 1536; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4$ 355.1658, found 355.1650.

(9H-Fluoren-9-yl)methyl (1-(hydroxyamino)-1-oxopropane-2-yl)(methyl)carbamate (2m): white solid (262 mg, 77%); mp 160–161 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.69–7.67 (d, $J = 7.6$ Hz, 2H), 7.48–7.46 (d, $J = 7.6$ Hz, 2H), 7.34–7.30 (t, $J = 7.2$ Hz, 2H), 7.25–7.21 (t, $J = 7.6$ Hz, 2H), 4.61–4.59 (m, 1H), 4.36–4.34 (d, $J = 6.6$ Hz, 2H), 4.15–4.12 (t, $J = 6.6$ Hz, 1H), 2.72 (s, 3H), 1.26–1.25 (t, $J = 7.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.9, 157.0, 143.7, 141.3, 127.7, 127.1, 125.1, 120.0, 68.0, 51.8, 47.2, 29.7, 14.2; FT-IR (KBr) 3304, 3066, 2972, 1693, 1646, 1540 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{NaO}_4$ 363.1321, found 363.1320.

(9H-Fluoren-9-yl)methyl (1-(hydroxyamino)-2-methyl-1-oxopropane-2-yl)carbamate (2n): white solid (255 mg, 75%); mp 172–174 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.76–7.75 (d, $J = 7.2$ Hz, 2H), 7.58–7.57 (d, $J = 7.2$ Hz, 2H), 7.41–7.38 (t, $J = 7.2$ Hz, 2H), 7.33–7.31 (t, $J = 7.2$ Hz, 2H), 4.43–4.42 (d, $J = 6.6$ Hz, 2H), 4.18–4.17 (t, $J = 6.6$ Hz, 1H), 1.44 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.5, 155.6, 143.8, 141.4, 127.9, 127.2, 125.0, 120.1, 66.5, 55.6, 47.2, 25.3; FT-IR (KBr) 3304, 3066, 2972, 1693, 1646, 1540 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{NaO}_4$ 363.1321, found 363.1324.

tert-Butyl (1-(hydroxyamino)-1-oxo-3-phenylpropane-2-yl)carbamate (2o): white solid (224 mg, 80%); mp 135 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.30–7.29 (d, $J = 6.6$ Hz, 2H), 7.24–7.22 (d, $J = 7.2$ Hz, 1H), 7.14–7.13 (t, $J = 7.2$ Hz, 2H), 4.24–4.20 (m, 1H), 3.07–3.0 (dd, $J = 6.6$ Hz, 1H), 2.97–2.94 (dd, $J = 6.6$ Hz, 1H), 2.03 (br, 1H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 168.9, 155.8, 136.4, 129.3, 128.5, 126.9, 80.4, 53.4, 38.7, 28.2; FT-IR (KBr) 3350, 3309, 2918, 2927, 1672, 1662, 1513 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_4$ 281.1501, found 281.1542.

tert-Butyl (3-(benzyloxy)-1-(hydroxyamino)-1-oxobutane-2-yl)carbamate (2q): white solid (259 mg, 80%); mp 168–169 °C; ^1H NMR (600 MHz, CDCl_3) δ 7.35–7.28 (m, 5H), 5.4 (br, 1H) 4.57 (s, 2H), 4.52–4.50 (m, 1H), 4.30 (br, 1H), 4.11 (m, 1H), 1.42 (s, 9H), 1.17–1.16 (d, $J = 6$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.4, 156.0, 137.8, 128.6, 128.0, 80.6, 74.4, 71.8, 56.5, 28.4, 15.8; FT-IR (KBr) 3331, 3260, 2983, 1679, 1637, 1525; HRMS (ESI) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_5\text{Na}$ 347.1583, found 347.1584.

1,3-Diphenylurea (3a):³⁶ white solid (176 mg, 83%); mp 225–226 °C; ^1H NMR (400 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 7.90 (s, 2H), 7.33–7.31 (d, $J = 7.6$ Hz, 4H), 7.22–7.18 (t, $J = 8$ Hz, 4H), 6.96–6.92 (t, $J = 7.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 152.7, 138.3, 129.0, 128.9, 123.0; FT-IR (KBr) 3336, 2891, 2870, 1685, 1600, 1534 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}$ 213.1028, found 213.1018.

1-Benzyl-3-phenylurea (3b):³⁷ white solid (205 mg, 91%); mp 173–174 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.31–7.22 (m, 10H), 4.85 (br, 1H), 4.39–4.38 (d, $J = 7.4$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.6, 139.3, 137.6, 128.7, 128.5, 127.7, 127.6, 127.2, 122.7, 43.8; FT-IR (KBr) 3226, 2971, 2830, 1666, 1630, 1555; HRMS (ESI) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}$ 227.1184, found 227.1185.

1-Cyclohexyl-3-phenylurea (3c):³⁸ white solid (196 mg, 90%); mp 168–169 °C; ^1H NMR (600 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 7.31–7.26 (m, 4H), 7.07–7.06 (t, $J = 6.8$ Hz, 1H), 6.63 (s, 1H), 4.88–4.87 (d, $J = 6.8$ Hz, 1H), 3.65–3.62 (m, 1H), 1.96–1.94 (m, 2H); 1.69–1.67 (m, 2H), 1.59–1.57 (m, 1H), 1.38–1.34 (m, $J =$

4.8 Hz, 2H), 1.17–1.14(m, 3H), ¹³C NMR (100 MHz, CDCl₃, few drops of CD₃OD for solubility) δ 156.0, 139.4, 129.1, 122.9, 120.2, 48.9, 33.7, 25.7, 25.0; FT-IR (KBr) 3236, 2961, 2810, 1685, 1620, 1585 cm⁻¹; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₁₃H₁₉N₂O 219.1497, found 219.1497.

N-Phenylpiperidine-1-carboxamide (3d): white solid (167 mg, 82%); mp 170–171 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.50–7.48 (d, *J* = 7.2 Hz, 2H), 7.35–7.34 (t, *J* = 7.2 Hz, 2H), 7.04–7.05 (t, *J* = 7.6 Hz, 1H), 3.40–3.34 (m, 4H), 2.6 (br, 1H), 1.45–1.41 (m, 6H); ¹³C NMR (150 MHz, CDCl₃, few drops of CD₃OD for solubility) δ 156.7, 131.8, 131.6, 128.6, 127.0, 45.0, 28.4, 24.4; FT-IR (KBr) 3126, 2971, 2790, 1635, 1625, 1555 cm⁻¹; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₁₉H₁₇N₂O 205.1341, found 205.1333.

1-(4-Cyanophenyl)-3-phenylurea (3e): white solid (175 mg, 74%); mp 170–172 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.85–7.83 (d, *J* = 7.8 Hz, 1H), 7.60–7.55 (m, 4H), 7.40–7.38 (d, *J* = 7.6 Hz, 2H), 7.31–7.27 (t, *J* = 7.8 Hz, 2H), 7.04–7.03 (d, *J* = 7.2 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 152.8, 143.8, 138.4, 133.2, 128.7, 123.4, 119.6, 119.5, 118.4, 104.6; FT-IR (KBr) 3304, 3066, 2972, 1693, 1646, 1540, cm⁻¹; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₁₄H₁₂N₃O 238.0980, found 238.0978.

1-(2-Hydroxyethyl)-3-phenylurea (3f): white solid (163 mg, 91%); mp 120–121 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.83 (br, 1H), 7.27–7.17 (m, 4H), 6.98–6.96 (t, *J* = 7.4 Hz, 1H), 5.9 (br, 1H), 3.58–3.55 (t, *J* = 5.2 Hz, 2H), 3.26–3.24 (t, *J* = 5.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃, few drops of CD₃OD for solubility) δ 157.2, 139.2, 139.1, 128.8, 122.6, 119.5, 119.3, 61.7, 42.3; FT-IR (KBr) 3116, 2991, 2872, 1695, 1635, 1524 cm⁻¹; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₉H₁₃N₂O₂ 181.0977, found 181.0974.

2-(3-Phenylureido)acetic acid (3g): white solid (161 mg, 81%); mp 96–97 °C; ¹H NMR (400 MHz, CD₃OD) δ 7.38–7.40 (d, *J* = 8 Hz, 2H), 7.21–7.19 (d, *J* = 8.4 Hz, 2H), 7.10–7.06 (t, *J* = 8 Hz, 2H), 6.84–6.80 (t, *J* = 7.6 Hz, 2H), 3.7 (s, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 170.6, 158.3, 140.8, 129.9, 129.7, 128.5, 123.8, 120.5, 42.6; FT-IR (KBr) 3216, 2951, 2892, 1772, 1665, 1645, 1544 cm⁻¹; HRMS (ESI) *m/z* [M - H]⁻ calcd for C₉H₉N₂O₃ 193.0613, found 193.0616.

1,3-Dibenzylurea (3h):³⁹ white solid (211 mg, 88%); mp 172–173 °C; ¹H NMR (400 MHz, CDCl₃, few drops of CD₃OD for solubility) δ 7.32–7.22 (m, 10H), 6.82 (br, 2H), 4.37–4.36 (d, *J* = 7.4 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃, few drops of CD₃OD for solubility) δ 161.5, 137.7, 128.7, 127.7, 127.0, 42.0; FT-IR (KBr) 3296, 3058, 2092, 1643, 1612, 1573 cm⁻¹; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₁₅H₁₇N₂O 241.1341, found 241.1336.

Methyl 2-phenyl-2-(3-undecylureido)acetate (3i): white solid (334 mg, 92%); mp 78–80 °C; ¹H NMR (600 MHz, CDCl₃, few drops of CD₃OD for solubility) δ 7.32–7.27 (m, 5H), 5.42(s, 1H), 3.72 (s, 3H), 3.08–3.06 (t, *J* = 7.2 Hz, 2H), 1.58–1.53 (m, 2H), 1.44–1.39 (m, 2H), 1.25–1.18 (m, 14H), 0.84–0.82 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃, few drops of CD₃OD for solubility) δ 172.9, 158.1, 137.1, 128.8, 128.3, 127.3, 127.1, 57.2, 52.5, 40.1, 35.0, 31.9, 30.0, 29.5, 29.3, 26.8, 25.3, 22.6, 13.9; FT-IR (KBr) 3326, 2921, 2850, 1732, 1634, 1568 cm⁻¹; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₁H₃₅N₂O₃ 363.2648, found 363.2650.

Methyl 2-(3-(1-benzamido-3-methylbutyl)ureido)propanoate (3j): white solid (291 mg, 87%); mp 196–197 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.76–7.75 (d, *J* = 7.2 Hz, 2H), 7.36–7.21 (m, 3H), 5.64 (br, 1H), 5.13 (m, 1H), 4.30–4.25 (m, 1H), 3.65 (s, 3H), 1.63–1.59 (m, 2H), 1.36–1.25 (m, 3H), 0.85–0.84 (d, *J* = 5.4 Hz, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 174.3, 167.5, 157.6, 134.0, 131.5, 128.9, 128.3, 127.4, 56.4, 52.0, 49.2, 43.6, 27.6, 22.2, 18.5; FT-IR (KBr) 3365, 3317, 2956, 1744, 1660, 1637, 1567 cm⁻¹; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₁₇H₂₆N₃O₄ 336.1923, found 336.1924.

Methyl 2-(3-(1-benzamido-3-methylbutyl)ureido)-2-phenylacetate (3k): white solid (357 mg, 90%); mp 202–203 °C; ¹H NMR (600 MHz, CDCl₃, few drops of CD₃OD for solubility) δ 7.80–7.80 (d, *J* = 7.8 Hz, 1H), 7.73–7.71 (d, *J* = 7.2 Hz, 1H), 7.51–7.27 (m, 8H), 5.42–5.40 (d, *J* = 7.2 Hz, 1H), 5.34–5.31 (m, 1H), 3.71 (s, 3H), 1.81–1.74 (m, 2H), 1.69–1.65 (m, 1H), 0.93–0.91 (d, *J* = 6.6 Hz, 3H), 0.90–0.89 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃, few drops of CD₃OD for solubility) δ 172.1, 168.4, 157.6, 136.7, 136.4,

133.8, 131.7, 128.7, 128.6, 128.3, 127.2, 127.1, 57.5, 57.3, 52.3, 42.8, 24.8, 22.1, 22.0; FT-IR (KBr) 3365, 3317, 2956, 1744, 1660, 1637, 1567 cm⁻¹; HRMS (ESI) *m/z* [M + Na]⁺ calcd for C₂₂H₂₇N₃O₄Na 420.1899, found 420.1896.

Methyl 2-(3-(1-benzamido-2-methylpropyl)ureido)-4-methylpentanoate (3l): white solid (323 mg, 89%); mp 200 °C; ¹H NMR (600 MHz, CDCl₃) δ 8.09–8.07 (d, *J* = 7.8 Hz, 1H), 7.74–7.73 (d, *J* = 7.2 Hz, 2H), 7.43–7.28 (m, 3H), 4.88–4.86 (m, 1H), 4.28–4.25 (m, 1H), 3.65 (s, 3H), 2.18–2.16 (m, 1H), 1.65–1.50 (m, 2H), 1.28–1.24 (m, 1H), 0.96–0.95 (d, *J* = 6.6 Hz, 3H), 0.92–0.91 (d, *J* = 6.6 Hz, 3H), 0.86–0.84 (d, *J* = 6.6 Hz, 3H), 0.79–0.68 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 174.7, 168.2, 158.2, 134.0, 131.7, 128.5, 127.4, 63.7, 52.0, 49.5, 41.2, 32.2, 28.3, 24.8, 22.9, 21.8, 19.0; FT-IR (KBr) 3345, 2960, 1748, 1637, 1625, 1560 cm⁻¹; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₁₉H₃₀N₃O₄ 364.2236 found 364.2235.

Methyl 9-isobutyl-3,7-dioxo-1,5-diphenyl-2-oxa-4,6,8-triazadecan-10-oate (3m): white solid (350 mg, 82%); mp 189–190 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.43–7.21 (m, 5H), 6.27–6.26 (d, *J* = 6 Hz, 1H), 5.86–5.85 (br, 2H), 5.08 (s, 2H), 4.50–4.46 (m, 1H), 3.68 (s, 3H), 1.67–1.63 (m, 2H), 1.54–1.52 (m, 1H), 0.92–0.90 (d, *J* = 8.4 Hz, 3H), 0.89–0.88 (d, *J* = 8.4 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 175.0, 157.3, 156.3, 136.2, 128.9, 128.7, 128.6, 128.2, 128.1, 127.4, 127.2, 126.0, 125.8, 67.1, 61.3, 52.2, 51.7, 49.7, 41.6, 24.9, 22.9, 22.0; FT-IR (KBr) 3299, 3034, 2958, 1726, 1689, 1636, 1571 cm⁻¹; HRMS (ESI) *m/z* [M + Na]⁺ calcd for C₂₃H₂₉N₃O₅Na 450.2005, found 450.2006.

Methyl 1-(9H-fluoren-9-yl)-9-isobutyl-5-methyl-3,7-dioxo-2-oxa-4,6,8-triazadecan-10-oate (3n): white solid (362 mg, 80%); mp 201–203 °C; ¹H NMR (600 MHz, CDCl₃, few drops of CD₃OD for solubility) δ 7.77–7.76 (d, *J* = 7.2 Hz, 2H), 7.56–7.55 (d, *J* = 7.2 Hz, 4H), 7.41–7.39 (t, *J* = 7.4 Hz, 2H), 7.32–7.30 (t, *J* = 7.4 Hz, 2H), 5.55 (br, 1H), 5.22–5.20 (m, 1H), 4.41–4.35 (m, 3H), 4.24–4.20 (t, *J* = 7.4 Hz, 1H), 3.73 (s, 3H), 1.63–1.43 (m, 6H), 0.95–0.94 (d, *J* = 6.6 Hz, 3H), 0.91–0.89 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃, few drops of CD₃OD for solubility) δ 174.8, 157.5, 156.6, 143.9, 141.3, 127.8, 127.2, 125.1, 120.0, 67.0, 55.9, 51.6, 49.5, 47.1, 41.6, 24.8, 22.9, 21.8, 21.2; FT-IR (KBr) 3294, 2955, 2926, 1730, 1694, 1637, 1573 cm⁻¹; HRMS (ESI) *m/z* [M + Na]⁺ calcd for C₂₅H₃₁N₃O₅Na 476.2161, found 476.2159.

Methyl 1-(9H-fluoren-9-yl)-5-isopropyl-3,7-dioxo-9-phenyl-2-oxa-4,6,8-triazadecan-10-oate (3o): white solid (396 mg, 79%); mp 158–160 °C; ¹H NMR (600 MHz, CDCl₃, few drops of CD₃OD for solubility) δ 7.77–7.75 (d, *J* = 6.6 Hz, 2H), 7.63–7.62 (d, *J* = 7.8 Hz, 2H), 7.43–7.27 (m, 9H), 6.9 (br, 1H), 5.48–5.45 (m, 2H), 4.86 (m, 1H), 4.33–4.19 (m, 3H), 3.66 (s, 3H), 2.06–2.03 (m, 1H), 0.92–0.89 (d, *J* = 7.2 Hz, 6H); ¹³C NMR (150 MHz, CDCl₃, few drops of CD₃OD for solubility) δ 170.6, 155.0, 154.0, 142.5, 139.4, 136.3, 127.2, 126.6, 126.1, 125.6, 123.8, 118.4, 64.1, 62.0, 55.3, 50.7, 45.5, 31.0, 16.8; FT-IR (KBr) 3365, 3298, 2952, 1724, 1692, 1636, 1564 cm⁻¹; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₉H₃₂N₃O₅ 502.2342, found 502.2346.

Methyl 9-benzyl-1-(9H-fluoren-9-yl)-5,5-dimethyl-3,7-dioxo-2-oxa-4,6,8-triazadecan-10-oate (3p): white solid (405 mg, 81%); mp 180–182 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.94–7.93 (d, *J* = 7.2 Hz, 2H), 7.82–7.80 (d, *J* = 7.8 Hz, 2H), 7.59–7.56 (t, *J* = 7.2 Hz, 3H), 7.51–7.45 (m, 5H), 7.36–7.34 (t, *J* = 7.2 Hz, 1H), 6.3 (s, 1H), 5.49–5.47 (d, *J* = 8.4 Hz, 1H), 4.85–4.80 (m, 1H), 4.59–4.58 (d, *J* = 5.2 Hz, 2H), 4.41–4.39 (t, *J* = 6.4 Hz, 1H), 3.88 (s, 3H), 3.36–3.33 (dd, *J* = 6 Hz, 1H), 3.27–3.22 (dd, *J* = 6.4 Hz, 1H), 1.70 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 172.3, 155.1, 152.1, 143.6, 141.0, 135.9, 129.1, 128.3, 128.2, 127.5, 126.9, 126.8, 125.0, 119.7, 66.7, 60.3, 56.0, 52.0, 46.9, 38.0, 28.1; FT-IR (KBr) 3304, 3066, 2972, 1693, 1646, 1540 cm⁻¹; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₉H₃₁N₃NaO₅ 524.2161, found 524.2164.

Ethyl 4-(3-(1-(9H-fluoren-9-yl)methoxy)carbonyl(methylamino)ethyl)ureido)benzoate (3q): white solid (360 mg, 74%); mp 174–175 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.09 (s, 1H), 7.92–7.90 (d, *J* = 7.2 Hz, 1H), 7.75–7.72 (d, *J* = 7.2 Hz, 3H), 7.59–7.25 (m, 8H), 5.60 (s, 1H), 5.30 (s, 1H), 4.41–4.33 (m, 4H), 4.21–4.18 (t, *J* = 6.6 Hz, 1H), 2.75 (s, 3H), 1.38–1.36 (t, *J* = 7.2 Hz, 3H), 1.19–1.17-

(t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 158.9, 156.6, 143.7, 141.4, 139.4, 130.9, 127.9, 127.3, 125.2, 125.1, 124.4, 120.2, 118.3, 114.2, 67.8, 63.2, 60.9, 47.3, 31.7, 18.8, 14.5; FT-IR (KBr) 3257, 2966, 2872, 1699, 1653, 1590 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{29}\text{N}_3\text{NaO}_5$ 510.2005, found 510.2004

Methyl 6-benzyl-10,10-dimethyl-4,8-dioxo-2-phenyl-9-oxa-3,5,7-triazaundecan-1-oate (3r): white solid (380 mg, 89%); mp 129–130 $^\circ\text{C}$; ^1H NMR (600 MHz, CDCl_3) δ 7.36–7.18 (m, 10H), 5.55 (br, 1H), 5.46–5.45 (d, $J = 6$ Hz, 1H), 5.32–5.31 (m, 1H), 3.71 (s, 3H), 3.07–3.03 (m, 2H), 1.32 (s, 9H), ^{13}C NMR (150 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 171.7, 156.8, 155.5, 136.6, 136.3, 129.1, 128.6, 128.5, 128.2, 128.1, 126.9, 126.3, 79.5, 58.7, 57.0, 52.1, 40.2, 27.9; FT-IR (KBr) 3388, 3341, 3061, 2983, 1738, 1681, 1635, 1504 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{30}\text{N}_3\text{O}_5$ 428.2185, found 428.2193.

DL-Methyl 6-benzyl-10,10-dimethyl-4,8-dioxo-2-phenyl-9-oxa-3,5,7-triazaundecan-1-oate (3s): white solid (380 mg, 88%); mp 129–130 $^\circ\text{C}$; ^1H NMR (600 MHz, CDCl_3) δ 7.38–7.16 (m, 10H), 5.42–5.41 (d, $J = 6$ Hz, 1H), 5.09–5.05 (m, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.08–3.05 (m, 2H), 2.84–2.81 (m, 2H), 1.39 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3 , few drops of CD_3OD for solubility) δ 172.3, 157.0, 155.9, 136.9, 129.4, 128.9, 128.8, 128.5, 127.3, 127.2, 126.7, 80.1, 60.3, 60.1, 57.6, 57.3, 52.7, 52.6, 40.4, 28.3, 28.2; FT-IR (KBr) 3388, 3341, 3061, 2983, 1738, 1681, 1635, 1504 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{30}\text{N}_3\text{O}_5$ 428.2185, found 428.2193.

Methyl 6-(1-(benzyloxy)ethyl)-2,10,10-trimethyl-4,8-dioxo-9-oxa-3,5,7-triazaundecan-1-oate (3t): white solid (347 mg, 85%); mp 140–142 $^\circ\text{C}$; ^1H NMR (600 MHz, CDCl_3) δ 7.35–7.29 (m, 5H), 5.41–5.39 (m, 1H), 5.02 (br, 1H), 4.62–4.60 (d, $J = 6$ Hz, 2H), 4.44–4.37 (m, 2H), 3.72 (s, 3H), 1.44 (s, 9H), 1.36–1.34 (d, $J = 7.2$ Hz, 3H), 1.21–1.20 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 174.3, 156.8, 155.2, 137.7, 128.4, 127.8, 80.2, 71.0, 61.8, 52.1, 49.1, 27.8, 18.4, 15.8; FT-IR (KBr) 3327, 3030, 2979, 1733, 1688, 1641, 1569; HRMS (ESI) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{31}\text{N}_3\text{O}_6\text{Na}$ 432.2111, found 432.2123.

Methyl 2-benzyl-6-(1-(benzyloxy)ethyl)-10,10-dimethyl-4,8-dioxo-9-oxa-3,5,7-triazaundecan-1-oate (3u): white solid (397 mg, 82%); mp 157–159 $^\circ\text{C}$; ^1H NMR (600 MHz, CDCl_3) δ 7.43–7.11 (m, 10H), 5.35 (br, 1H), 5.29–5.27 (m, 1H), 5.04 (br, 1H), 4.70–4.68 (m, 1H), 4.63–4.61 (d, $J = 6$ Hz, 2H), 4.38–4.36 (d, $J = 11.4$ Hz, 1H), 3.62 (s, 3H), 3.11–3.07 (dd, $J = 6.6$ Hz, 1H), 3.03–3.0 (dd, $J = 6.6$ Hz, 1H), 1.40 (s, 9H), 1.22–1.21 (d, $J = 6$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 173.1, 156.6, 155.6, 137.8, 136.7, 129.3, 128.6, 128.4, 128.0, 126.8, 80.4, 76.3, 71.2, 62.2, 54.6, 52.0, 38.6, 28.4, 16.0; FT-IR (KBr) 3326, 2981, 2933, 1723, 1666, 1627, 1527 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{36}\text{N}_3\text{O}_6$ 486.2604, found 486.2602.

■ ASSOCIATED CONTENT

■ Supporting Information

^1H and ^{13}C NMR and HRMS spectra of **2a–q**, **3a–u**, **III**, and **IV**, data for racemization studies mechanistic data, and XRD crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>

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Notes

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■ REFERENCES

- (1) (a) Kozikowski, A. P.; Zhang, J.; Nan, F.; Petukhov, P.; Grajkowska, A. E.; Wroblewski, J. T.; Yamamoto, T.; Bzdega, T.; Wroblewska, B.; Neale, J. H. *J. Med. Chem.* **2004**, *47*, 1729–1738. (b) Flipo, M.; Beghyn, T.; Charton, J.; Leroux, A. V.; Deprez, P. B.; Deprez-Poulain, R. *Bioorg. Med. Chem.* **2007**, *15*, 63–67.
- (2) (a) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111–1239. (b) Cheng, R. P.; Gellman, S. H.; De-Grado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232. (c) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. A. *Chem. Rev.* **2001**, *101*, 3893–4012. (d) Flipo, M.; Charton, J.; Hocine, A.; Dassonneville, S.; Deprez, B.; Deprez-Poulain, R. *J. Med. Chem.* **2009**, *52*, 6790–6802. (e) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180.
- (3) Lam, P. Y.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C. H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R. *Science* **1994**, *263*, 380–384.
- (4) Broadbridge, R. J.; Sharma, R. P.; Akhtar, M. *Chem. Commun.* **1998**, 1449–1450.
- (5) Kozikowski, A. P.; Zhang, J.; Nan, F. P.; Petukhov, A.; Grajkowska, E.; Wroblewski, J. T.; Yamamoto, T.; Bzdega, T.; Wroblewska, B.; Neale, J. H. *J. Med. Chem.* **2004**, *47*, 1729–1738.
- (6) (a) Weber, G. *Cancer Res.* **1983**, *43*, 3466–3492. (b) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49–56. (c) Miller, M. J. *Chem. Rev.* **1989**, *89*, 1563–1579.
- (7) (a) Flipo, M.; Beghyn, T.; Leroux, V.; Florent, I.; Deprez, B. P.; Deprez-Poulain, R. F. *J. Med. Chem.* **2007**, *50*, 1322–1334. (b) Chen, Y. F.; Lopex-Sanchez, M.; Savoy, D. N.; Billadieu, D. D.; Dow, G. S.; Kozikowski, A. P. *J. Med. Chem.* **2008**, *51*, 3437–3448.
- (8) (a) Boularot, A.; Giglione, C.; Petit, S.; Duroc, Y.; Alves de Sousa, R.; Larue, V.; Cresteil, T.; Dardel, F.; Artaud, I.; Meinel, T. *J. Med. Chem.* **2007**, *50*, 10–20. (b) Capkova, K.; Yoneda, Y.; Dickerson, T. J.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6463.
- (9) Yao, W.; Zhuo, J.; Burns, D. M.; Xu, M.; Zhang, C.; Li, Y. L.; Qian, D. Q.; He, C.; Weng, L.; Shi, E.; Lin, Q.; Agrios, C.; Burn, T. C.; Caulder, E.; Covington, M. B.; Fridman, J. S.; Friedman, S.; Katiyar, K.; Hollis, G.; Li, Y.; Liu, C.; Liu, X.; Marando, C. A.; Newton, R.; Pan, M.; Scherle, P.; Taylor, N.; Vaddi, K.; Wasserman, Z. R.; Wynn, R.; Yeleswaram, S.; Jalluri, R.; Bower, M.; Zhou, B. B.; Metcalf, B. *J. Med. Chem.* **2007**, *50*, 603–606.
- (10) Zhu, Z.; Mazzola, R.; Sinning, L.; McKittrick, B.; Niu, X.; Lundell, D.; Sun, J.; Orth, P.; Guo, Z.; Madison, V.; Ingram, R.; Beyer, B. M. *J. Med. Chem.* **2008**, *51*, 725–736.
- (11) (a) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, H. J. A. *Chem. Rev.* **1999**, *99*, 2735. (b) Cheng, M.; De, B.; Pikul, S.; Almstead, N. G.; Natchus, M. G.; Anastasio, M. V.; McPhail, S. J.; Snider, C. E.; Taiwo, Y. O.; Chen, L.; Dunaway, C. M.; Gu, F.; Dowty, M. E.; Mieling, G. E.; Janusz, M. J.; Wang-Weigand, S. *J. Med. Chem.* **2000**, *43*, 369–380.
- (12) (a) Dube, P.; Nathel, F. N.; Vetelino, M.; Couturier, M.; Aboussafy, L. C.; Pichette, S.; Jorgensen, L. M.; Hardink, M. *Org. Lett.* **2009**, *15*, 5622–5625. (b) Zhang, X.; Rodrigues, J.; Evans, L.; Hinkle, B.; Ballantyne, L.; Pena, M. *J. Org. Chem.* **1997**, *62*, 6420–6423.
- (13) Takeda, K.; Akagi, Y.; Saiki, A.; Tsukahara, T.; Ogura, H. *Tetrahedron Lett.* **1983**, *24*, 4569–4572.
- (14) Narendra, N.; Chennakrishnareddy, G.; Sureshbabu, V. V. *Org. Biomol. Chem.* **2009**, *7*, 3520–3526.
- (15) Katritzky, A. R.; Pleyne, D. P. M.; Yang, B. *J. Org. Chem.* **1997**, *62*, 4155–4158.
- (16) Porwanski, S.; Menuel, S.; Marsura, X.; Marsura, A. *Tetrahedron Lett.* **2004**, *45*, 5027–5029.
- (17) Gastaldi, S.; Weinreb, M. S.; Stien, D. *J. Org. Chem.* **2000**, *65*, 3239–3230.
- (18) Hamon, F.; Prie, G.; Lecornue, F.; Papot, S. *Tetrahedron Lett.* **2009**, *50*, 6800–6802.

- (19) Yadav, D. K.; Yadav, A. K.; Srivastava, V. P.; Watal, G.; Yadav, L. D. S. *Tetrahedron Lett.* **2012**, *53*, 2890–2893.
- (20) Han, C.; Porco, A. J. *Org. Lett.* **2007**, *9*, 5717–5720.
- (21) Braverman, S.; Cherkinsky, M.; Kedrova, L.; Reiselman, A. *Tetrahedron Lett.* **1999**, *40*, 3235–3238.
- (22) Lebel, H.; Leogane, O. *Org. Lett.* **2006**, *8*, 5717–5720.
- (23) Anilkumar, R.; Chandrasekhar, S.; Sridhar, M. *Tetrahedron Lett.* **2000**, *41*, 5291–5293.
- (24) Stafford, A. J.; Gonzales, S. S.; Barrett, G. D.; Suh, M. E.; Feldman, L. P. *J. Org. Chem.* **1998**, *63*, 10040–10044.
- (25) Giacomelli, G.; Porcheddu, A.; Salaris, M. *Org. Lett.* **2003**, *5*, 2715–2717.
- (26) El-Faham, A.; Khattab, S. N.; Abdul-Ghani, M. *ARKIVOC* **2006**, *xiii*, 57–63.
- (27) (a) Gissot, A.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **2005**, *70*, 6925–6928. (b) Woo, S. C. J.; Fenster, E.; Dake, R. G. *J. Org. Chem.* **2004**, *69*, 8984–8986.
- (28) (a) Fei, Z.; Kong, W.; Wang, H.; Peng, J.; Sun, F.; Yin, Y.; Bajwa, J.; Jiang, X. *Org. Process Res. Dev.* **2012**, *16*, 1436–1441. (b) Pirung, C. M.; Chau, L. H. J. *J. Org. Chem.* **1995**, *60*, 8084–8085. (c) Thouin, E.; Lubell, D. W. *Tetrahedron Lett.* **2000**, *41*, 457–460. (d) Choi, J.; Park, G. J.; Pang, P. Y. *Tetrahedron Lett.* **2008**, *49*, 1103–1106.
- (29) Ho, C. Y.; Strobel, E.; Ralbovsky, J.; Gallemmo, R. A., Jr. *J. Org. Chem.* **2005**, *70*, 4873–4875.
- (30) Sibi, M. P.; Hasegawa, H.; Ghorpade, S. R. *Org. Lett.* **2002**, *4*, 3343–3346.
- (31) Nani Babu, P.; Dharm, D.; Shubhasmin, R.; Krishna, C. N.; Bhubaneswar, M. *Eur. J. Org. Chem.* **2013**, *2013*, 2627–2633.
- (32) El-Faham, A.; Subiros-Funosas, R.; Prohens, R.; Albericio, F. *Chem.—Eur. J.* **2009**, *15*, 9404–9416.
- (33) In a separate experiment, we added hydroxylamine hydrochloride to the reaction mixture at 0 time (i.e., at the starting of the reaction, without preactivation of acid). In that case, only 4-nitrosulfonyl hydroxamic acid was formed (90%) within 30 min by direct reaction of the hydroxyl amine to **I**; the product **2a** was hardly observed (Supporting Information, Figures S179–180).
- (34) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522–524.
- (35) Porcheddu, A.; Giacomelli, G. *J. Org. Chem.* **2006**, *71*, 7057–7059.
- (36) Li, Q. X.; Wang, K. W.; Han, X. Y.; Zhang, C. *Adv. Synth. Catal.* **2010**, *352*, 2588–2598.
- (37) Oh, K. H.; Park, E. J.; Sung, D. D.; Lee, I. *J. Org. Chem.* **2004**, *69*, 3150–3153.
- (38) Vinogradova, V. E.; Fors, P. B.; Buchwald, L. S. *J. Am. Chem. Soc.* **2012**, *134*, 11132–11135.
- (39) Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* **2004**, *69*, 4741–4750.