Chapter 1  Application of 1-propanephosphonic acid cyclic anhydride (T3P) as an efficient promoter for the synthesis of urea and carbamate derivatives through Lossen rearrangement

In this chapter, an efficient synthesis of hydroxamic acids from carboxy acids employing 1-propanephosphonic acid cyclic anhydride (T3P) under ultrasonication is described. Further, the application of T3P to activate the hydroxamates, leading to isocyanates via the Lossen rearrangement has also been delineated. The isocyanates were trapped with suitable nucleophile in situ to obtain the corresponding ureas and carbamates.

1.1. INTRODUCTION

Peptides are the primary means of intercellular communication in various diverse biological systems.\(^1\) Proteins play significant role in key biological functions and they have unique intrinsic properties which make them particularly attractive as therapeutic agents. Biological role of peptides is associated with low toxicity and high specificity, so that even a short peptide can offer a plethora of combinatorial possibilities as a unique messenger. The benefits conferred by these molecules also include drawbacks such as unspecific binding, easy hydrolysis by proteases and poor solubility.\(^2\) This has lead to the development of analogs of natural peptides bearing one or more non-amide bonds which are termed as "peptidomimetics". The unnatural linkages employed to construct such architectures have been shown to improve peptides' in vivo shelf-life, solubility, bio-availability, target specificity significantly. Synthesis of backbone modified peptides and their screening is essential to meet the growing demands for the development of new molecular entities for discovering drug candidates.\(^3\)-\(^6\) Thus, several classes of peptidomimetics such as ureidopeptides, peptidyl carbamates, sulfopeptides, peptoids, hydrazino peptides, aminoox peptides and heterocycle-linked peptides have been synthesized (Figure 1.1) and studied.\(^7\)-\(^16\)

Among these, decoration of peptide backbone by inserting urea moiety has been one of the extensively studied sub-areas under peptidomimetics. The ureidopeptidomimetics are relatively rigid compared to native peptides owing to strong hydrogen bonding property. Hence, they possess metabolic stability, improved pharmacokinetic properties, absorption
and lower toxicity. Several biologically active ureidopeptides related to potent HIV-1 protease inhibitors, TAR binding fragment of TAT proteins, aspartic peptidases, γ-secretases, aspartic acid protease, angiotensins, microbial alkaline proteinase inhibitors and [Leu\(^5\)]enkephaline have been prepared. Apart from this, unsymmetrical urea derivatives find extensive applications in agriculture, petrochemicals, pharmaceuticals and biology. For example, diuron (A) is a commercially available herbicide, a simple urea derivative with
morpholine ring (B) acts as antileukemic agent, substituted urea (C) is used as HIV-1 protease inhibitor and D as a RTK-inhibitor (Figure 1.2). Given the wide spread applicability, there has been significant interest in the development of new and simple protocols for the preparation of ureidopeptidomimetics.

**Figure 1.2.**

Principally, the formation of an urea involve the reaction of an amine with an isocyanate or a related intermediate. In particular, to access ureidopeptides, there are reports which describe the conversion of N-terminus of an amino acid ester into isocyanate followed by reaction with another amino acid ester. Also, in a different approach, carboxy terminus of N-protected amino acid has been converted into isocyanate and then trapped with amino acid ester. Thus, reaction of an amine group (present at the N-terminus of an amino acid or the one inserted on C-termini through a series of functional group transformations) with carbonylating reagents such as carbonyldiimidazole (CDI) or N,N’-disuccinimidyl carbonate
(DSC) to obtain ‘isocyanate’ like reactive intermediate (also called active carbamates) that yields urea upon reaction with another amine is also an additional useful route.

Goldschmidt and Wick synthesized the isocyanates by refluxing hydrochloride salt of amino acid esters in toluene while sparging with gaseous phosgene. In a modified protocol, Nowick et al., employed a solution of phosgene in toluene or triphosgene under organic or biphasic reaction conditions to obtain the isocyanato esters. Further, the isocyanato esters were made to react with another amino acid ester to yield ureido peptides which possessed carboxy termini on both sides (Scheme 1.1).

\[ \text{Scheme 1.1} \]

A reaction of \(N,N'-\text{carbonyldiimidazole (CDI)}\) with an amine in the presence of base generates imidazolyl carbamate which reacts with another molecule of amine to afford symmetric ureas as described by Pena et al. Ogura and co-workers investigated the reaction of an amine with \(N,N'-\text{disuccinimidyl carbonate (DSC)}\), and the formation of urea in this case followed through the active succinimidyl carbamate intermediate. Similarly, treatment of the primary amines with \(p\)-nitrophenyl chloroformate leads to \(p\)-nitrophenyl carbamate which is then transformed into the corresponding urea by reaction with amines. Katritzky et al., described the synthesis of ureas by the reaction of amine with the carbamoylbenzotriazole intermediate employing 1,1'-carbonyl-bis-benzotriazole (CBT, Scheme 1.2). These methods are well practiced in organic chemistry, and also adopted to a certain extent, with suitable modifications in peptide chemistry as well.
On the other hand, ureidopeptides are also obtained by the reaction of an amino acid ester with the isocyanates obtained from the modification of carboxy group of an N-protected amino acid. In this approach, the N→C sequence of the peptide backbone is retained.

In general, the key intermediates \textit{i.e.}, N\textsuperscript{\textit{\textalpha}}-protected amino acid derived isocyanates are obtained either by the Curtius rearrangement of N-protected amino acid azide,\textsuperscript{36-44} or the Hofmann rearrangement of N-protected amino acid amide\textsuperscript{45-47} or the Lossen rearrangement of corresponding hydroxamic acid.\textsuperscript{48-50} In the first method, activated carboxylic acids in the form of acid chloride or mixed anhydride are subjected to azidolysis or the carboxylic acids are directly converted into acyl azides employing azide-transfer reagent such as diphenylphosphoryl azide (DPPA) and then the acyl azides, under thermal conditions, rearranged to afford isocyanates.\textsuperscript{41,51-56} Hofmann rearrangement involves oxidant-mediated conversion of an amide into isocyanate as described by Lipton and coworkers during the synthesis of ureidopeptides\textsuperscript{45-47} (\textbf{Scheme 1.3}). The acid azide method is compatible with
common N-protecting groups. However, the explosive nature of acyl azides under the high temperature conditions used for carrying out the rearrangement makes it synthetically less attractive—particularly for large scale reactions. In amino acid chemistry, the acid chloride method is not compatible with Boc- as well as Z-amino acids. For example, Boc-amino acid chlorides degrade to oxazolidin-2,5-diones. On the other hand, the Hofmann protocol using bis[trifluoroacetoxy]phenylidene (PIFA) or phenylidene diacetate (PIDA) is particularly useful in Boc- and Z- chemistry. However, its utility in base sensitive Fmoc chemistry is not satisfactory. In addition, the byproduct trifluoroacetic acid can catalyze the hydrolysis of isocyanates and it also deprotects Boc group there by reducing the yields of corresponding urea derivative. Therefore a simple and scalable protocol for mild generation of isocyanates which tolerates different urethane protecting groups is desirable.

![Scheme 1.3](image)

**Scheme 1.3**

The Lossen rearrangement (LR), which involves the transformation of hydroxamic acids into isocyanates through the migration of electron deficient nitrogen atom, is a valid alternative for an easy access to isocyanates. In this chemistry, hydroxamic acids are activated to create a suitable leaving group for subsequent rearrangement. It also belongs to the category of named classical carboxy degradation reactions that provides useful isocyanate
intermediates from carboxylic acid derivatives. We became interested in the use of LR due to its apparent simplicity and relatively mild reaction conditions.

The essential precursor for the LR is a hydroxamic acid. Apart from the use of hydroxamic acid as starting compound for the LR, hydroxamic acids are also valuable compounds for their pharmacokinetic merits. They are an imperative class of chelators of hard metal ions such as Fe(III), which have found applications in therapeutic, diagnostic and separation chemistry. Ruthenium catalyzed oxidation of hydroxamic acids produces acyl nitroso derivative which can be subjected to in situ hetero Diels-Alder reaction with cyclohexa-1,3-diene. Most importantly, amino acid derived hydroxamic acids act as chiral ligands in the vanadium catalyzed epoxidation (Scheme 1.4) and in asymmetric transfer hydrogenation of ketones.

![Scheme 1.4](image)

**SCHEME 1.4**

There are several protocols for the preparation of hydroxamic acids. El-Faham et al., reported the preparation of hydroxamic acids starting from carboxylic acid employing tetramethylfluoroformamidinium hexafluorophosphate (TFFH) and benzyltriphenylphosphonium dihydrogen trifluoride (PTF). Najera’s group used 2-mercaptopyridone-1-oxide-based thiouronium salts A and B for the preparation of hydroxamates directly from carboxylic acids. O-Alkyl hydroxamic acids are obtained by the treatment of carboxylic
acids with the coupling agent, phosphoric acid diethyl ester 2-phenyl-benzimidazol-1-yl ester C (Scheme 1.5).  

$$\begin{align*}
\text{A} & \quad \text{NH}_2\text{OH.HCl, TEA} \\
\text{B} & \quad \text{Me, Bn} \\
\text{C} & \quad \text{Bn, Et}
\end{align*}$$

**SCHEME 1.5**

Hydroxamic acids have also been obtained starting from aldehydes by performing the Angeli–Riminis reaction on a solid-supported \( N \)-hydroxybenzenesulfonamide in the presence of sodium methoxide in THF at rt (Scheme 1.6).  

$$\begin{align*}
\text{R}\cdot\text{O.H} & \quad \text{MeONa} \\
\text{MeONa} & \quad \text{THF, rt, 6-12 h}
\end{align*}$$

**SCHEME 1.6**

Hypervalent iodine(III) reagents (diacetoxyiodo)benzene (DIB) or Kosers reagent \{[hydroxy(tosyloxy)iodo]benzene (HTIB)} mediated oxidation of various aliphatic and aromatic aldoximes has also been employed in the preparation of \( N \)-acetoxy or \( N \)-hydroxy amides (Scheme 1.7).
Several protocols have been reported for the synthesis of amino acid derived hydroxamic acids. Giacomelli et al., developed a simple one-flask protocol for the preparation of amino/peptide acid derived hydroxamates starting from corresponding acids using cyanuric chloride (Scheme 1.8). Microwave assisted transformation of Boc-amino acid esters into corresponding hydroxamic acids was reported by Mordini's group.

Previously, Sureshbabu et al., reported the magnesium oxide mediated synthesis of Nα-Fmoc-amino acid hydroxamates employing the corresponding acid chlorides. However, due to the instability of the acid chlorides, the protocol could not be extended to N-Boc or Z-protected amino acids (Scheme 1.9).

To bring about the Lossen transformation, the hydroxamic acids are activated using the reagents such as carbodiimides, p-toluenesulfonyl chloride, 1,1'-carbonyldiimidazole and cyanuric chloride. The O-activated hydroxamic acids are then rearranged through the
displacement of N-hydroxy group followed by C to N migration to afford the isocyanate intermediate (Scheme 1.10).

![Scheme 1.10](image)

**SCHEME 1.10**

Hoare *et al.*, demonstrated conversion of hydroxamic acid with water soluble carbodiimide 1-benzyl-3-(3-dimethylaminopropyl)carbodiimide (BDC) to a quantitative formation of isocyanate under mild conditions (Scheme 1.11).\(^4\)

\[
\begin{align*}
R^1 \text{NHOH} + NR^2 & \rightarrow R^1\text{N}=C=O \\
R^2 &= \text{Bn} \\
R^3 &= 3\text{-dimethylaminopropyl}
\end{align*}
\]

**SCHEME 1.11**

Carbodiimide mediated LR of hydroxamic acid was also reported by Needs and co-workers, wherein, the galacturonic acid residues of pectin was initially converted to corresponding hydroxamic acid and then treated with carbodiimide. The resulting isourea derivative underwent LR through an alkaline hydrolysis into isocyanate (Scheme 1.12).\(^5\)
Sureshbabu et al., reported a facile LR of $N^\alpha$-urethane-protected amino acid hydroxamates into isocyanates employing 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) in the presence of catalytic amount of 4-dimethylaminopyridine (DMAP) at rt. Subsequent coupling with amino acid ester afforded corresponding urea derivative (Scheme 1.13).86

Scheme 1.13

$p$-Toluenesulfonyl chloride or 2-chloro-1-methylpyridinium iodide induced LR was described by Bauer and Pihuleac.87 Treatment of a solution of hydroxamic acid in dry CH$_2$Cl$_2$ with $p$-TsCl and pyridine at rt followed by reflux for 30 min afforded corresponding isocyanate in a good yield (Scheme 1.14).

Scheme 1.14
Cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, TCT) was also employed to promote LR, as reported by Papot et al. A series of carbamates, thiocarbamates and ureas were prepared by trapping the isocyanates with alcohol, thiol or amine. Initially, hydroxamic acid was treated with cyanuric chloride in the presence of NMM in dichloroethanol (DCE) at 0 °C and the temperature was raised to reflux after the addition of suitable nucleophile to afford corresponding urethane product in quantitative yield (Scheme 1.15).  

\[ \text{O} \quad \text{R}^1\text{NHOH} \quad \xrightarrow{[\text{1. TCT, NMM, DCE, 0} \ ^\circ \text{C}]} \quad \text{R}^1\text{O} \quad \text{X} \quad \text{R}^2 \quad \xrightarrow{[\text{2. R}^3\text{XH, reflux}]} \quad \text{X} = \text{O, S, NH} \]

SCHEME 1.15

Dube et al., reported the carbonyl diimidazole (CDI) mediated LR. Reaction of hydroxamic acid with CDI in CH\textsubscript{3}CN lead to the formation of dioxazolone within 10 min at ambient temperature, which after heating at 80 °C for 30 min afforded corresponding isocyanate. Later, the isocyanate was trapped with hydroxyl or amino compound to obtain carbamate and urea derivatives respectively (Scheme 1.16).  

\[ \text{O} \quad \text{R}^1\text{NHOH} \quad \xrightarrow{[\text{CDI in CH} \textsubscript{3} \text{CN}]} \quad \text{[R}^1\text{O}\text{N} = \text{C}=\text{O}] \quad \xrightarrow{-\text{CO}_2} \quad \text{R}^1\text{N} = \text{C}=\text{O} \quad \text{R}^2\text{R}^3\text{NH} \quad \text{R}^1\text{R}^2\text{R}^3\text{NH} \quad \text{R}^4\text{OH} \quad \text{R}^1\text{R}^2\text{R}^3\text{NH} \quad \text{R}^4\text{OH} \]

SCHEME 1.16

Recently, Yadav and co-workers reported the bromodimethylsulfonium bromide (BDMS)-mediated LR of hydroxamic acids to the corresponding isocyanates which were
subsequently trapped in situ with various amines to afford unsymmetrical ureas (Scheme 1.17).\(^{90}\)

\[
\begin{align*}
\text{O} & \text{N-OH} \quad \xrightarrow{\text{Br}^+ \text{Br}^- \text{NMM}} \quad \xrightarrow{\text{DMSO}} \quad \xrightarrow{\text{HN-}^\text{R}^2 \text{R}^3 \text{DCE, 0-80 °C}} \\
\text{R}^1 & \text{N-C=O} \\
\text{R}^1 & \text{N-C=O} \\
\end{align*}
\]

**SCHEME 1.17**

However, few drawbacks posed by several methods are the accumulation of isocyanate before the complete activation of hydroxamic acid leading to self-condensed byproduct, complicated experimental procedures, high temperature and long duration.\(^{48-50,84,91-94}\) In spite of several reports available for the synthesis of ureidopeptides via LR, complexities associated with the existing protocols demand an efficient protocol for the facile activation of hydroxamic acids leading to isocyanates.

During our search for a new promoter for LR, we came across 1-propanephosphonic acid cyclic anhydride (T3P), one of the economic and efficient coupling agents and also a water scavenger.\(^{95}\) Advantages such as high-yielding reactions, broad functional group tolerance, low epimerization and easy workup procedures make the reagent meritorious over several contemporaries. The byproducts are water soluble and eliminate the need for chromatographic purification (Figure 1.3).

**FIGURE 1.3. 1-Propanephosphonic acid cyclic anhydride**
Meudt and co-workers employed T3P as dehydrating agent for the synthesis of nitriles and isonitriles from corresponding carboxy amides and formamides respectively.\textsuperscript{96} T3P has also been employed to obtain alkenes \textit{via} the dehydration of primary, secondary and tertiary alcohols under mild conditions without any isomerization (Scheme 1.18).\textsuperscript{97}

\begin{center}
\begin{equation}
\text{Scheme 1.18}
\end{equation}
\end{center}

The dehydration property of T3P was exploited for the synthesis of \(S\)-alkyl(aryl)imidazole derivatives by the cyclization of corresponding aminoacrylic acid esters (Scheme 1.19).\textsuperscript{98}

\begin{center}
\begin{equation}
\text{Scheme 1.19}
\end{equation}
\end{center}

Meudt \textit{et al.}, employed T3P as an oxidizing agent for the preparation of aldehydes and ketones from corresponding primary and secondary alcohols respectively. The protocol

14
is a modification of Swern oxidation, which eliminates the use of hazardous oxalyl chloride (Scheme 1.20).\textsuperscript{99}

\[
\begin{array}{c}
R\text{-}OH & \xrightarrow{T3P, 0-10 \, ^\circ\text{C}} & R\text{-}H \\
\text{DMSO, EtOAc (1:1)} & & \\
\text{OH} & \xrightarrow{T3P, 0 \, ^\circ\text{C}} & \text{O} \\
\text{NH} \text{Boc} & \text{OMe} & \text{NH} \text{Boc} \\
\end{array}
\]

**SCHEME 1.20**

T3P is a superior, traceless and environmentally benign promoter for N-acylation.

Appendino's group reported a 12 h reaction protocol for the T3P-mediated synthesis of hydroxamic acids at rt (Scheme 1.21).\textsuperscript{100} T3P has also been employed in the synthesis of Weinreb amides, nitriles and \(\beta\)-lactams.\textsuperscript{101-103}

\[
\begin{array}{c}
\text{R OH} & \xrightarrow{T3P, TEA, \text{CH}_2\text{CN}} & \text{R NHOOH} \\
\text{NH}_2\text{OHHCl} & & \\
\end{array}
\]

**SCHEME 1.21**

T3P is mainly used as an effective and mild condensation reagent in peptide and peptidomimetic synthesis (Scheme 1.22).\textsuperscript{104,105}

\[
\begin{array}{c}
Pg\text{HN COOH} + H_2\text{N COOMe} & \xrightarrow{T3P, DIPEA} & Pg\text{HN} \xrightarrow{\text{R}^1} \text{H}_2\text{N COOMe} \\
\text{R}^1 \text{R}^2 \text{EtOAc} & & \text{R}^1 \text{R}^2 \\
\end{array}
\]

**SCHEME 1.22**

We reasoned that T3P, being a carboxy activator, can be employed for the preparation of hydroxamates from the corresponding acids and being a dehydrating agent, could be a suitable promoter for the LR via \(O\)-activation. To the best of our knowledge, except for a
couple of examples of the LR of benzoic acid hydroxamates to Boc/Z-protected anilines,\textsuperscript{106} a systematic study on the T3P-mediated LR for the conversion of hydroxamates into isocyanates was not carried out. Thus, we herein describe the T3P-promoted LR of hydroxamates derived from aromatic acids, as well as $N^\text{a}$-protected amino acids into isocyanates and conversion of the latter into urea, carbamate and thiocarbamate derivatives.
1.2. PRESENT WORK

1.2.1. Synthesis of hydroxamic acids

The synthesis of hydroxamic acids from diverse range of carboxylic acids including Fmoc/Boc/Z-α-amino acids employing T3P is described. In addition, application of T3P to effect LR on hydroxamic acids to furnish ureas, ureidopeptides, carbamates and thiocarbamate is also delineated.

With our previous experience and published work on ultrasound-accelerated reactions, we reasoned that ultrasonic waves may enhance the rate of conversion of carboxy acids to hydroxamic acids. Practically, this was the case and we could reduce the reaction time from 12 h (as reported by Appendino’s group) to 60 min under ultrasonication. In an initial experiment, a solution of p-nitrobenzoic acid (1mmol) and an equimolar quantity of T3P in CH₃CN in the presence of N-methylmorpholine (NMM) was stirred at 0 °C to facilitate the activation. After 15 min, hydroxylamine (obtained by the treatment of hydroxylamine hydrochloride salt with NMM) was added at once and the reaction was run under ultrasonication for another 30 min to allow for the completion of the reaction (Scheme 1.23). A simple workup led to the isolation of N-hydroxy-4-nitrobenzamide 1.2b in good yield (86%); a single recrystallization from THF–n-hexane gave analytically pure sample as a crystalline solid. Five more hydroxamic acids, 1.2a and 1.2c–f were also made in a similar way, starting from phenylacetic acid, 2-thiophenic acid, 2-furoic acid, benzoic acid and p-bromobenzoic acid (Table 1.1).
\[
\begin{align*}
R'\text{CONHOH} & \xrightarrow{T3P, NMM, \text{CH}_3\text{CN}, 0 ^\circ \text{C}} [R'\text{CONHOH}] \xrightarrow{\text{NH}_2\text{OH, CH}_3\text{CN}, \ddag} R'\text{CONHOH}
\end{align*}
\]

**SCHEME 1.23.** Synthesis of organic hydroxamic acids

**TABLE 1.1.** List of Hydroxamates 1.2

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R'CONHOH</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
<th>HRMS [M+Na]^+ Obsd (calcd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2a</td>
<td>![Structure]</td>
<td>88</td>
<td>Oil 79</td>
<td>174.0535 (174.0531)</td>
</tr>
<tr>
<td>1.2b</td>
<td>![Structure]</td>
<td>86</td>
<td>135-137</td>
<td>205.01 (205.02)</td>
</tr>
<tr>
<td>1.2c</td>
<td>![Structure]</td>
<td>85</td>
<td>122-123</td>
<td>165.9944 (122-123) ^79 (165.9939)</td>
</tr>
<tr>
<td>1.2d</td>
<td>![Structure]</td>
<td>89</td>
<td>120-121</td>
<td>128.0341 (119-122) ^75 (128.0348) ^b</td>
</tr>
<tr>
<td>1.2e</td>
<td>![Structure]</td>
<td>85</td>
<td>125-127</td>
<td>160.0368 (126-127) ^79 (160.0374)</td>
</tr>
<tr>
<td>1.2f</td>
<td>![Structure]</td>
<td>83</td>
<td>184-185</td>
<td>237.9486 (184-185) ^80 (237.9480)</td>
</tr>
</tbody>
</table>

^aESI-MS, ^bM+H.
The present protocol was extended to prepare a series of \( N^a \)-protected amino acid hydroxamates 1.4. Thus, a solution of \( N^a \)-Boc-Phe-OH in CH\(_3\)CN in the presence of NMM was treated with T3P at 0 °C for 15 min. After the addition of hydroxylamine, the mixture was subjected to ultrasonication. Satisfactorily, the reaction proceeded smoothly and was complete in about 90 min, to yield \( N^a \)-Boc-Phe-NHOH (1.4h) in 89% yield. Similarly, Fmoc- and Z-protected \( \alpha \)-amino acids were also converted into corresponding hydroxamates 1.4 (Scheme 1.24, Table 1.2). This is a common and mild protocol for the synthesis of hydroxamates compatible with all the three commonly employed urethane-protected amino acids (Fmoc, Boc and Z).

![Scheme 1.24. Synthesis of amino acid derived hydroxamates](image)

**TABLE 1.2. List of \( N \)-Urethane-Protected Amino Acid Hydroxamates 1.4**

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Pg-Xaa-NHOH</th>
<th>Yield (%)</th>
<th>Time (min)</th>
<th>Mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4a</td>
<td>Fmoc-Ala</td>
<td>97</td>
<td>90</td>
<td>128(128)(^{33})</td>
</tr>
<tr>
<td>1.4b</td>
<td>Fmoc-Phe</td>
<td>93</td>
<td>80</td>
<td>151-152(150-152)(^{31})</td>
</tr>
<tr>
<td>1.4c</td>
<td>Fmoc-Glu(O'Bu)</td>
<td>95</td>
<td>85</td>
<td>132-133(131-133)(^{56})</td>
</tr>
<tr>
<td>1.4d</td>
<td>Fmoc-Ser(Bn)</td>
<td>93</td>
<td>110</td>
<td>163-164(164)(^{33})</td>
</tr>
</tbody>
</table>
1.2.2. Lossen rearrangement of hydroxamic acids

In the next stage, T3P mediated LR of the hydroxamates was undertaken. In a typical experiment, a chilled solution of hydroxamate 1.2b and T3P in tetrahydrofuran (THF) in the presence of NMM was stirred for about 30 min. After the completion of O-activation of the hydroxamate (confirmed by TLC analysis), the mixture was refluxed for 90 min. The IR spectrum of the reaction mixture showed a strong peak at around 2240 cm⁻¹, corresponding to the isocyanate. The O-activation of hydroxamic acids took little longer time than that required for carboxy activation as shown for the preparation of hydroxamates, and an excess of T3P is required to drive the reaction towards completion. After confirming the formation of isocyanates, our next objective was to trap them with nucleophiles including amines, alcohols and thiol. Towards this end, after stirring a solution of hydroxamate 1.2b along with T3P and NMM in THF at 0 °C for 30 min, the reaction mixture was refluxed in the presence of p-methylaniline. After completion of the reaction (3 h), a simple workup led to the isolation of urea 1.5c in 86% yield. The generality of this reaction was confirmed by the
synthesis of ureas 1.5a, 1.5e, 1.5f, carbamates 1.5d, 1.5g, 1.5h, and thiocarbamate 1.5b

(Scheme 1.25, Table 1.3).

SCHEME 1.25. Synthesis of organic ureas, carbamates and thiocarbamate

TABLE 1.3. List of Ureas/Carbamates 1.5

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R'NHCOXR²</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
<th>HRMS [M+Na]+ Obsd (calcd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5a</td>
<td></td>
<td>85</td>
<td>Gum¹¹⁴</td>
<td>283.0619 (283.0614)</td>
</tr>
<tr>
<td>1.5b</td>
<td></td>
<td>75</td>
<td>Gum</td>
<td>272.1091 (272.1085)</td>
</tr>
<tr>
<td>1.5c</td>
<td></td>
<td>86</td>
<td>187-188 (188)¹¹⁴</td>
<td>294.0849 (294.0855)</td>
</tr>
<tr>
<td>1.5d</td>
<td></td>
<td>75</td>
<td>92-93 (93)¹¹⁴</td>
<td>233.07 (233.05)²</td>
</tr>
<tr>
<td>1.5e</td>
<td></td>
<td>89</td>
<td>244 (245)¹¹⁴</td>
<td>318.9511 (318.9517)</td>
</tr>
<tr>
<td>1.5f</td>
<td></td>
<td>91</td>
<td>176</td>
<td>219.0751 (219.0746)</td>
</tr>
</tbody>
</table>
The utility of the present protocol for the preparation of ureidopeptidomimetics was also studied. To a chilled solution of Boc-Phe-NHOH (1.4h) in THF, T3P and NMM were added, and the mixture was stirred for 30 min. After adding H-Val-OMe (obtained by deprotonation of the corresponding hydrochloride salt using Zn dust$^{108,109}$), the mixture was refluxed for two hours to obtain the ureidopeptide, albeit in low yield. The not-so-encouraging result obtained using the thermal method led us to test the feasibility of this transformation under ultrasonication. To our delight, when the reaction mixture, after the O-activation step was subjected to ultrasonication, the activated hydroxamic acid underwent the LR and the isocyanate formed reacted in situ with the amine to afford urea 1.6c in a shorter duration (an hour) in good yield (85%; Scheme 1.26, Table 1.4). A few Boc- and Z-protected amino acid hydroxamates were also subjected to the LR and the corresponding ureas 1.6c–g were isolated as analytically pure ones (Table 1.4). Fmoc-Protected ureidopeptides precipitated as solids from the reaction mixture and a single recrystallization step led to crystalline products (1.6a and 1.6b). The protocol was also extended to the preparation of a few active carbamates 1.7a–c by trapping the intermediate isocyanates with substituted phenols (Scheme 1.26, Table 1.4). All products were isolated and characterized by NMR and mass spectroscopy.
SCHEME 1.26. Synthesis of ureidopeptides and active carbamates

1.2.3. Test for racemization

The protocol was revisited to check if there is any possibility of racemization in the course of the reaction. A set of diastereomeric ureidopeptides, Fmoc-Phg$^\text{L}$-L-Ala-OMe (1.6f) and Fmoc-Phg$^\text{D}$-D-Ala-OMe (1.6g), were prepared starting from racemization-prone Fmoc-Phg-OH and their $^1$H NMR spectrum were examined for the methyl group resonances of the alanly residue. Distinct doublets were observed at $\delta = 1.28$ and 1.30 ppm for 1.6f and at $\delta = 1.29$ and 1.32 ppm for 1.6g. This clearly indicates the presence of a single diastereomer in each sample. This, in turn, suggests that Fmoc-Phg-NHOH (1.4e) is epimerically pure, and also the urea derivatives prepared from it via the LR to the extent detectable by NMR analysis. This evidences that the conversion of $N$-protected amino acid into hydroxamic acid employing T3P and later the T3P promoted LR are all free from racemization at the level detectable by $^1$H NMR.
### TABLE 1.4. List of Ureidopeptides 1.6 and Active Carbamates 1.7

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Urea/Carbamate</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6a</td>
<td><img src="image" alt="Structure 1.6a" /></td>
<td>96</td>
<td>180 (181)&lt;sup&gt;114&lt;/sup&gt;</td>
</tr>
<tr>
<td>1.6b</td>
<td><img src="image" alt="Structure 1.6b" /></td>
<td>84</td>
<td>140-141 (140)&lt;sup&gt;39&lt;/sup&gt;</td>
</tr>
<tr>
<td>1.6c</td>
<td><img src="image" alt="Structure 1.6c" /></td>
<td>85</td>
<td>138-139</td>
</tr>
<tr>
<td>1.6d</td>
<td><img src="image" alt="Structure 1.6d" /></td>
<td>79</td>
<td>139</td>
</tr>
<tr>
<td>1.6e</td>
<td><img src="image" alt="Structure 1.6e" /></td>
<td>89</td>
<td>142-143 (142-144)&lt;sup&gt;114&lt;/sup&gt;</td>
</tr>
<tr>
<td>1.6f</td>
<td><img src="image" alt="Structure 1.6f" /></td>
<td>91</td>
<td>170</td>
</tr>
<tr>
<td>1.6g</td>
<td><img src="image" alt="Structure 1.6g" /></td>
<td>90</td>
<td>170</td>
</tr>
<tr>
<td>1.7a</td>
<td><img src="image" alt="Structure 1.7a" /></td>
<td>91</td>
<td>142</td>
</tr>
<tr>
<td>1.7b</td>
<td><img src="image" alt="Structure 1.7b" /></td>
<td>85</td>
<td>117-118 (117)&lt;sup&gt;116&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
In outline, a facile conversion of aromatic acids as well as \( N^e \)-protected amino acids into hydroxamates under ultrasonication using T3P as carboxy activator is described. Further, the T3P was employed to mediate the LR of these hydroxamates. The generated isocyanates were utilized to synthesize urea, carbamate and thiocarbamate derivatives by treating with suitable nucleophiles. The protocol is mild, rapid and free from racemization.
1.3. EXPERIMENTAL

Melting points were determined using capillary method. All the amino acids used, except glycine, are of L-configuration unless otherwise specified. Optical rotations were determined using automatic AA-10 polarimeter (Optical Activity, UK). The purity of the amino acid derivatives and peptides was determined by thin layer chromatography (TLC) on precoated silica gel-G (GF-254 purchased from Merck) plates. TLC plates were exposed either to iodine vapors for 5 min or for UV fluorescence to visualize the spots. IR spectra were recorded on a Nicolet model impact 400D FT-IR spectrometer (KBr pellets, 3 cm\(^{-1}\) resolution). \(^1\)H and \(^13\)C NMR spectra were recorded using Bruker AMX 300 MHz and 75 MHz spectrometer respectively using TMS as an internal standard. High-resolution mass spectra (HR-MS) were recorded on Q-Tof micromass mass spectrometer. The ultrasound bath (Elma, T 310/H) was German made and operated at 35 kHz. The RP-HPLC experiments were carried out in Agilent 1100 series instrument having G1311A VWD at \(\lambda = 254\) nm, flow 0.5 mL/min, column: Agilent eclipse XDB-C-18, pore size-5\(\mu\)m, diameter x length = 4.6 x 150 mm; method: gradient 0.1% TFA, water-CH\(_3\)CN; CH\(_3\)CN 30-100% in 30 min.

**The solvents used for the present work were purified as follows:**

1. **Acetonitrile:** Treated with anhydrous CaCl\(_2\) for 24 h and distilled over P\(_2\)O\(_5\).
2. **Dichloromethane:** Distilled over CaSO\(_4\) or from P\(_2\)O\(_5\) and passed through a column of basic Al\(_2\)O\(_3\) and stored in a brown bottle over molecular sieves (4 Å).
3. **Diethylamine:** Distilled and stored in a brown bottle.
4. **1,4-Dioxane:** Distilled and stored in a brown bottle.
5. **Ethyl acetate**: Treated with $\text{K}_2\text{CO}_3$ overnight, filtered and distilled over $\text{P}_2\text{O}_5$.

6. **Ethyl chloroformate**: Distilled and stored in a brown bottle.

7. **n-Hexane**: Distilled and stored over sodium wire.

8. **N-Methylmorpholine**: Refluxed over sodium wire for 2 h, distilled and stored over sodium wire.

9. **Tetrahydrofuran**: Shaken with KOH pellets for 2 h, decanted, refluxed over sodium wire in presence of benzophenone till the solution became blue, distilled and stored over sodium wire.

10. **Toluene**: Washed with 10% by volume of conc. $\text{H}_2\text{SO}_4$ till the $\text{H}_2\text{SO}_4$ layer became pale yellow, washed, distilled and stored over sodium wire.

11. **Methanol**: Refluxed over magnesium turnings (5.0 g / lit.) in the presence of traces of iodine and distilled.

**1.3.1. Synthesis of Fmoc-amino acids**$^{110}$

To a solution of the amino acid (10 mmol) in 10% $\text{Na}_2\text{CO}_3$ solution (20 mL) at 0 °C a solution of Fmoc-OSu (3.37 g, 10 mmol) in 1,4-dioxane (25 mL) was added slowly over a period of 30 min with vigorous stirring and the reaction was continued for another 2 h at the same temperature. It was diluted with water (100 mL), washed with ether (3 x 50 mL). The aqueous phase was acidified using cold 6N $\text{HCl}$ to pH 2. The liberated Fmoc-amino acid was extracted with EtOAc (4 x 25 mL). The organic phase was washed with 1N $\text{HCl}$, water and saturated brine solution, dried over anhydrous $\text{Na}_2\text{SO}_4$ and evaporated under reduced pressure.
1.3.2. Synthesis of Z-amino acids

To a vigorously stirred solution of amino acid (10 mmol) in 4N NaOH (2.5 mL) and acetone (2.5 mL) at 0 °C, benzylxycarbonyl chloride (1.8 mL, 10 mmol) was added in ten small portions during 2 h period maintaining the pH at 9-10 using 4N NaOH. Stirring was continued at 0 °C and at rt overnight. The reaction mixture was diluted with water (10 mL) and extracted with ether (3 x 50 mL). The aqueous phase was acidified with 6N HCl and the compound separated was extracted with EtOAc (3 x 20 mL). The organic extract was washed with water and saturated brine solution, dried over anhydrous Na₂SO₄ and the solvent removed in vacuo.

1.3.3. Synthesis of Boc-amino acids

A mixture of the amino acid (10 mmol), Boc-ON (11 mmol), Et₃N (13 mmol), dioxane (7 mL) and water (7 mL) was stirred at rt till it becomes homogeneous. The reaction mixture was diluted with water (10 mL) and extracted with ether (3 x 50 mL). The aqueous phase was acidified with 10% KHSO₄ or citric acid solution and the Boc-amino acid was extracted into EtOAc (4 x 20 mL). The combined organic layer was washed with water (3 x 20 mL), dried over anhydrous Na₂SO₄ and evaporated in vacuo to get the title compound.

1.3.4. Methyl esters of amino acids

Thionyl chloride (0.10 mL, 1.5 mmol) was added slowly with stirring into methanol (10 mL) cooled in an ice-bath. Amino acid (10 mmol) was then added in portions during half an hour and stirring was continued for 2 h below 0 °C. After an additional stirring for 2 h at rt, the reaction mixture was refluxed for an hour and cooled. The solvent was evaporated and
the residue was triturated with dry ether. The separated solid was filtered, washed with ice-cold alcohol and dried to yield amino acid ester hydrochloride salt.

1.3.5. **General procedure for the synthesis of hydroxamic acids 1.2 and 1.4**

![Chemical Structure](image)

To a chilled (0 °C) solution of an aromatic acid 1.1 or N-protected amino acid 1.3 (1 mmol) and NMM (0.12 mL, 1.1 mmol) in CH$_3$CN (10 mL) was added 50% T3P in EtOAc (0.71 mL, 1.2 mmol). The reaction mixture was stirred at the same temperature for 15 min and then subjected to ultrasonication after the addition of NH$_2$OH (83 mg, 1.2 mmol; obtained by neutralization of the corresponding hydrochloride salt with NMM) until the reaction was completed. The mixture was diluted with EtOAc (15 mL), washed with H$_2$O and brine. The organic phase was dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under reduced pressure and the residue was recrystallized (THF/n-hexane).

**1.3.5.1. N-Hydroxy-2-phenylacetamide (1.2a)**

Yield: 133 mg (88%); oil; $R_f = 0.32$ (CHCl$_3$ and MeOH, 9:1); IR (KBr): 1638 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 2.22$ (bs, 1H), 3.62 (s, 2H), 7.32 (m, 5H), 8.21 (br, 1H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 34.1, 126.8, 127.9, 128.6, 128.9, 164.4$.

HR-MS: $m/z$ calcd for C$_8$H$_9$NO$_2$: 174.0531 [M+Na]$^+$; found: 174.0535.

**1.3.5.2. N-Hydroxy-4-nitrobenzamide (1.2b)**

Yield: 157 mg (86%); white solid; mp 135-137 °C; $R_f = 0.35$ (CHCl$_3$ and MeOH, 9:1); IR (KBr): 1642 cm$^{-1}$.
1H NMR (300 MHz, DMSO-d6): δ = 7.72 (d, J = 5.4 Hz, 2H), 7.91 (d, J = 5.4 Hz, 2H), 8.57 (s, 1H), 10.58 (s, 1H).

13C NMR (75 MHz, DMSO-d6): δ = 122.8, 128.1, 139.8, 146.8, 166.8.

ESI-MS: m/z calcd for C7H6N2O4: 205.02 [M+Na]+; found: 205.01.

1.3.5.3. N-Hydroxythiophene-2-carboxamide (1.2c)

Yield: 122 mg (85%); off-white solid; mp 122-123 °C; RF = 0.38 (CHCl3 and MeOH, 9:1); IR (KBr): 1645 cm⁻¹.

1H NMR (300 MHz, DMSO-d6): δ = 6.81-7.32 (m, 3H), 9.18 (br, 1H), 10.64 (bs, 1H).

13C NMR (75 MHz, DMSO-d6): δ = 127.6, 131.2, 135.0, 137.6, 169.3.

HR-MS: m/z calcd for C₆H₅NO₂S: 165.9939 [M+Na]+; found: 165.9944.

1.3.5.4. N-Hydroxyfuran-2-carboxamide (1.2d)

Yield: 113 mg (89%); white solid; mp 120-121 °C; RF = 0.40 (CHCl3 and MeOH, 9:1); IR (KBr): 1641 cm⁻¹.

1H NMR (300 MHz, DMSO-d6): δ = 6.80 (m, 1H), 7.21 (d, J = 6.0 Hz, 1H), 7.23 (d, J = 6.0 Hz, 1H), 8.89 (s, 1H), 10.89 (br, 1H).

13C NMR (75 MHz, DMSO-d6): δ = 118.0, 121.5, 146.3, 148.8, 172.9.

HR-MS: m/z calcd for C₇H₅NO₃: 128.0348 [M+H]+; found: 128.0341.

1.3.5.5. N-Hydroxybenzamide (1.2e)

Yield: 116 mg (85%); off-white solid; mp 125-127 °C; RF = 0.35 (CHCl3 and MeOH, 9:1); IR (KBr): 1647 cm⁻¹.

1H NMR (300 MHz, DMSO-d6): δ = 7.47-7.60 (m, 5H), 9.13 (bs, 1H).
$^1$H, 10.78 (br, 1H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 127.7, 129.3, 133.6, 143.4, 166.5$.

HR-MS: $m/z$ calcld for C$_7$H$_7$NO$_2$: 160.0374 [M+Na]$^+$; found: 160.0368.

1.3.5.6. 4-Bromo-N-hydroxybenzamide (1.2f)

Yield: 179 mg (83%); pale yellow solid; mp 184-185 °C; $R_f = 0.42$ (CHCl$_3$ and MeOH, 9:1);

IR (KBr): 1647 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 2.80$ (br, 1H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.71 (d, $J = 8.4$ Hz, 2H), 8.56 (br, 1H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 121.3, 122.5, 138.5, 146.1, 163.7$.

HR-MS: $m/z$ calcld for C$_7$H$_6$BrNO$_2$: 237.9480 [M+Na]$^+$; found: 237.9486.

1.3.5.7. (S)-(9H-Fluoren-9-yl)methyl 1-(hydroxyamino)-1-oxopropan-2-ylcarbamate $\{N^\omega$-Fmoc-Ala-NHOH$\}$ (1.4a)

Yield: 316 mg (97%); white solid; mp 128 °C; $R_f = 0.35$ (CHCl$_3$ and MeOH, 8:2); IR (KBr): 1655, 1698 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 1.42$ (d, $J = 7.2$ Hz, 3H), 3.88 (m, 1H), 4.35 (t, $J = 3.8$ Hz, 1H), 4.48 (d, $J = 6.8$ Hz, 2H), 6.89 (br, 1H), 7.32-7.91 (m, 8H), 8.85 (br, 1H), 10.65 (br, 1H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 17.9, 39.9, 47.2, 67.1, 127.5, 128.2, 128.4, 128.9, 141.5, 143.6, 157.3, 169.5$.

HR-MS: $m/z$ calcld for C$_{18}$H$_{18}$N$_2$O$_4$: 349.1164 [M+Na]$^+$; found: 349.1161.
1.3.5.8.  (S)-(9H-Fluoren-9-yl)methyl 1-(hydroxamino)-1-oxo-3-phenylpropan-2-ylcarbamate \( \{N^\alpha\text{-Fmoc-Phe-NHOH}\} \) (1.4b)

Yield: 374 mg (93%); white solid; mp 151-152 °C; \( R_f = 0.37 \) (CHCl₃ and MeOH, 8:2); IR (KBr): 1640, 1695 cm⁻¹.

\(^1\)H NMR (300 MHz, DMSO-\( d₆ \)): \( \delta = 2.72 \) (d, \( J = 5.2 \) Hz, 2H), 3.86 (m, 1H), 4.12 (t, \( J = 3.6 \) Hz, 1H), 4.25 (d, \( J = 6.8 \) Hz, 2H), 5.91 (br, 1H), 7.32-7.83 (m, 13H), 8.63 (br, 1H), 10.62 (br, 1H).

\(^{13}\)C NMR (75 MHz, DMSO-\( d₆ \)): \( \delta = 36.9, 43.2, 55.1, 65.8, 125.3, 125.9, 127.1, 127.6, 128.2, 128.7, 129.2, 137.1, 140.8, 142.3, 157.2, 170.2.

ESI-MS: \( m/z \) calcd for C\(_{24}\)H\(_{22}\)N\(_2\)O\(_4\): 425.15 [M+Na]+; found: 425.15.

1.3.5.9.  (S)-tert-Butyl 4-(((9H-fluoren-9-yl)methoxy)carbonyl)-5-(hydroxamino)-5-oxopentanoate \( \{N^\alpha\text{-Fmoc-Glu(O^tBu)-NHOH}\} \) (1.4c)

Yield: 418 mg (95%); white solid; mp 132-133 °C; \( R_f = 0.30 \) (CHCl₃ and MeOH, 8:2); IR (KBr): 1661, 1695, 1739 cm⁻¹.

\(^1\)H NMR (300 MHz, DMSO-\( d₆ \)): \( \delta = 1.37 \) (s, 9H), 1.78-1.80 (m, 2H), 2.04 (br, 1H), 2.17-2.22 (m, 2H), 3.86 (m, 1H), 4.20-4.25 (m, 3H), 7.30-7.89 (m, 8H), 8.85 (s, 1H), 10.12 (br, 1H).

\(^{13}\)C NMR (75 MHz, DMSO-\( d₆ \)): \( \delta = 27.7, 31.3, 38.5, 46.5, 51.5, 65.5, 79.6, 127.2, 127.4, 127.6, 129.0, 140.6, 142.5, 155.8, 168.0, 171.5.

HR-MS: \( m/z \) calcd for C\(_{25}\)H\(_{28}\)N\(_2\)O\(_6\): 463.1845 [M+Na]+; found: 463.1851.
1.3.5.10. (S)-(9H-Fluoren-9-yl)methyl 3-(benzyloxy)-1-(hydroxyamino)-1-oxopropan-2-ylcarbamate \( \{N^\alpha\text{-Fmoc-Ser(Bn)-NHOH}\} \) (1.4d)

Yield: 400 mg (93%); white solid; mp 163-164 °C; \( R_f = 0.32 \) (CHCl₃ and MeOH, 8:2); IR (KBr): 1661, 1697 cm⁻¹.

\(^1\)H NMR (300 MHz, DMSO-\( d_6 \)): \( \delta = 2.05 \) (bs, 1H), 3.25 (s, 2H), 3.65 (d, \( J = 4.8 \) Hz, 2H), 4.12 (t, \( J = 5.0 \) Hz, 1H), 4.26 (d, \( J = 6.4 \) Hz, 2H) 4.60 (m, 1H), 6.89 (br, 1H), 7.21-7.82 (m, 13H), 8.85 (s, 1H).

\(^13\)C NMR (75 MHz, DMSO-\( d_6 \)): \( \delta = 28.3, 47.5, 52.3, 68.4, 69.8, 127.1, 127.5, 128.3, 128.5, 128.7, 128.8, 128.9, 137.5, 141.1, 143.8, 156.1, 169.6.

HR-MS: m/z calcd for C₂₂H₂₄N₂O₅: 455.1583 [M+Na]+; found: 455.1586.

1.3.5.11. (S)-(9H-Fluoren-9-yl)methyl 2-(hydroxyamino)-2-oxo-1-phenylethylcarbamate \( \{N^\alpha\text{-Fmoc-Phg-NHOH}\} \) (1.4e)

Yield: 326 mg (84%); white solid; mp 132-133 °C; \( R_f = 0.40 \) (CHCl₃ and MeOH, 8:2); IR (KBr): 1659, 1703 cm⁻¹.

\(^1\)H NMR (300 MHz, DMSO-\( d_6 \)): \( \delta = 1.98 \) (br, 1H), 3.60 (d, \( J = 9.3 \) Hz, 1H), 4.11 (t, \( J = 4.8 \) Hz, 1H), 4.25 (d, \( J = 6.6 \) Hz, 2H), 6.55 (br, 1H), 7.20-7.81 (m, 13H), 8.71 (br, 1H).

\(^13\)C NMR (75 MHz, DMSO-\( d_6 \)): \( \delta = 44.5, 57.3, 66.5, 125.2, 125.9, 127.3, 127.8, 128.1, 128.9, 129.4, 137.8, 141.2, 142.5, 157.6, 169.2.


1.3.5.12. (S)-Benzy1 1-(hydroxyamino)-1-oxopropan-2-ylcarbamate \( \{N^\alpha\text{-Z-Ala-NHOH}\} \) (1.4f)

Yield: 216 mg (91%); oil; \( R_f = 0.30 \) (CHCl₃ and MeOH, 8:2); IR (neat): 1665, 1698 cm⁻¹.
Chapter I

Lossen rearrangement and ureidopeptides

$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta = 1.48$ (d, $J = 5.6$ Hz, 3H), 2.17 (bs, 1H), 4.11 (m, 1H), 5.14 (s, 2H), 6.92 (br, 1H), 7.26-7.33 (m, 5H), 8.06 (s, 1H).

$^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta = 17.5, 45.8, 69.1, 127.5, 127.8, 128.4, 137.0, 155.8, 170.0$.

ESI-MS: $m/z$ calcld for C$_{11}$H$_{14}$N$_2$O$_4$: 261.09 [M+Na]$^+$; found: 261.09.

1.3.5.13. (S)-Benzy1 2-(hydroxyamino)-1-oxo-1-phenylethylcarbamate {N$^\alpha$-Z-Phg-NHOH} (1.4g)

Yield: 276 mg (92%); white solid; mp 160 °C; $R_f = 0.40$ (CHCl$_3$ and MeOH, 8:2); IR (KBr): 1662, 1695 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta = 4.12$ (d, $J = 8.6$ Hz, 1H), 5.04 (s, 2H), 7.28-7.44 (m, 10H), 8.04 (d, $J = 8.6$ Hz, 1H), 8.99 (s, 1H), 10.94 (s, 1H).

$^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta = 55.7, 65.5, 126.9, 127.0, 127.5, 127.8, 128.1, 128.5, 136.9, 138.5, 155.6, 166.5$.

HR-MS: $m/z$ calcld for C$_{18}$H$_{16}$N$_2$O$_4$: 323.1008 [M+Na]$^+$; found: 323.1011.

1.3.5.14. (S)-tert-Butyl 1-(hydroxyamino)-1-oxo-3-phenylpropan-2-ylcarbamate {N$^\alpha$-Boc-Phe-NHOH} (1.4h)

Yield: 249 mg (89%); oil; $R_f = 0.45$ (CHCl$_3$ and MeOH, 8:2); IR (neat): 1656, 1696 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta = 1.42$ (s, 9H), 2.84 (d, $J = 4.5$ Hz, 2H), 3.56 (m, 1H), 6.99 (br, 1H), 7.26-7.36 (m, 5H), 8.09 (s, 1H), 10.25 (s, 1H).
$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 27.3, 32.1, 44.8, 79.8, 126.7, 128.2, 128.9, 139.6, 156.3, 169.2$.

HR-MS: $m/z$ calcd for C$_{14}$H$_{20}$N$_2$O$_4$: 303.1321 [M+Na]$^+$; found: 303.1326.

1.3.5.15. (S)-Benzyl 4-(tert-butoxycarbonyl)-5-(hydroxyamino)-5-oxopentanoate \{N$^a$-Boc-Glu(Obn)-NHOH\} (1.4i)

Yield: 278 mg (79%); white solid; mp 81-82°C; $R_f = 0.45$ (CHCl$_3$ and MeOH, 8:2); IR (KBr): 1662, 1699, 1741 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 1.45$ (s, 9H), 2.84 (m, 2H), 2.92 (t, $J = 7.6$ Hz, 2H), 5.15 (m, 1H), 5.34 (s, 2H), 6.89 (br, 1H), 7.26-7.35 (m, 5H), 8.06 (s, 1H), 10.65 (s, 1H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 28.3, 37.8, 41.3, 49.8, 68.1, 81.1, 127.2, 127.9, 128.8, 139.0, 156.4, 169.6, 172.1$.

HR-MS: $m/z$ calcd for C$_{17}$H$_{24}$N$_2$O$_6$: 375.1532 [M+Na]$^+$; found: 375.1535.

1.3.6. General procedure for the preparation of organic ureas/carbamates 1.5

\[
\begin{align*}
1.2 & \xrightarrow{\text{T3P, NMM}} \xrightarrow{R^2-XH, \text{reflux}} 1.5 \\
 & \quad \text{X = NH, O, S}
\end{align*}
\]

To a solution of a hydroxamic acid 1.2 (1.0 mmol) in THF (10 mL) at 0 °C, NMM (0.16 mL, 1.5 mmol) and T3P (0.89 mL, 1.5 mmol) were added and the mixture was stirred for 30 min. Then, the nucleophile (amine or alcohol, 1.5 mmol) was added and the mixture was refluxed for 3 h. The solvent was removed under reduced pressure, the residue was diluted with EtOAc (15 mL), and the organic layer was washed with 10% HCl (10 mL), H$_2$O
(10 mL) and brine, then dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under reduced pressure to afford the product 1.5.

**1.3.6.1. 1-Benzyl-3-(2-chlorophenyl)urea (1.5a)**

**Yield:** 222 mg (85%); gum; $R_f = 0.50$ (n-hexane and EtOAc, 7:3); IR (neat): 1652 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 4.34 (d, $J = 5.8$ Hz, 2H), 5.43 (s, 1H), 5.57 (br, 1H), 7.15-7.53 (m, 9H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ = 47.9, 123.1, 125.1, 125.9, 126.8, 127.3, 128.9, 130.8, 136.3, 141.3, 154.5.

HR-MS: $m/z$ calcd for C$_{14}$H$_{13}$ClN$_2$O: 283.0614 [M+Na]$^+$; found: 283.0619.

**1.3.6.2. S-Cyclohexyl benzylcarbamothioate (1.5b)**

**Yield:** 187 mg (75%); gum; $R_f = 0.50$ (n-hexane and EtOAc, 7:3); IR (KBr): 1655 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 1.28-1.46 (m, 6H), 1.52-1.68 (m, 4H), 2.61 (m, 1H), 4.36 (d, $J = 6.2$ Hz, 2H), 5.98 (br, 1H), 7.12-7.22 (m, 5H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ = 22.5, 31.1, 34.6, 46.7, 47.9, 125.6, 126.7, 127.5, 139.9, 166.7.

HR-MS: $m/z$ calcd for C$_{14}$H$_{19}$NOS: 272.1085 [M+Na]$^+$; found: 272.1091.

**1.3.6.3. 1-(4-Nitrophenyl)-3-p-tolylurea (1.5c)**

**Yield:** 233 mg (86%); white solid; mp 187-188 °C; $R_f = 0.45$ (n-hexane and EtOAc, 7:3); IR (KBr): 1650 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 2.36 (s, 3H), 6.70 (s, 1H), 6.82 (br, 2H), 7.04 (s, 1H), 7.30 (d, $J = 6.8$ Hz, 2H), 7.52 (d, $J = 6.4$ Hz, 2H), 7.64 (d, $J = 5.8$ Hz, 2H).
13C NMR (75 MHz, DMSO-d6): δ = 22.5, 123.6, 123.9, 128.9, 130.1, 138.6, 139.7, 141.9, 146.1, 156.5.


1.3.6.4. Ethyl 4-nitrophenylcarbamate (1.5d)

Yield: 158 mg (75%); white solid; mp 92-93 °C; Rf = 0.40 (n-hexane and EtOAc, 7:3); IR (KBr): 1738 cm⁻¹.

1H NMR (300 MHz, DMSO-d6): δ = 1.34 (t, J = 4.4 Hz, 3H), 4.14 (m, 2H), 7.56-7.73 (m, 4H), 8.36 (s, 1H).

13C NMR (75 MHz, DMSO-d6): δ = 14.7, 62.6, 124.7, 129.8, 136.4, 141.2, 155.3.

ESI-MS: m/z calcd for C9H10N2O4: 233.05 [M+Na]+; found: 233.07.

1.3.6.5. 1-(2-Bromophenyl)-3-(thiophen-2-yl)urea (1.5e)

Yield: 264 mg (89%); white solid; mp 244 °C; Rf = 0.60 (n-hexane and EtOAc, 7:3); IR (KBr): 1648 cm⁻¹.

1H NMR (300 MHz, DMSO-d6): δ = 6.05 (bs, 1H), 6.61 (br, 1H), 6.98 (d, J = 6.2 Hz, 1H), 7.11-7.15 (m, 2H), 7.32-7.38 (m, 4H).

13C NMR (75 MHz, DMSO-d6): δ = 114.9, 121.9, 123.6, 125.2, 125.8, 126.5, 127.6, 133.3, 138.5, 141.6, 156.3.

HR-MS: m/z calcd for C11H8BrN2O3S: 318.9517 [M+Na]+; found: 318.9511.

1.3.6.6. N-(Furan-2-yl)morpholine-4-carboxamide (1.5f)

Yield: 178 mg (91%); white solid; mp 176 °C; Rf = 0.45 (n-hexane and EtOAc, 7:3); IR (KBr): 1655 cm⁻¹.
Chapter I

Lossen rearrangement and ureido peptides

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 3.52$ (t, $J = 7.2$ Hz, 4H), 3.72 (t, $J = 7.6$ Hz, 4H), 6.85 (m, 1H), 7.21 (d, $J = 6.9$ Hz, 1H), 7.43 (d, $J = 7.0$ Hz, 1H), 8.61 (br, 1H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 45.2$, 66.7, 112.3, 116.8, 143.1, 145.9, 155.8.


1.3.6.7. Benzyl phenylcarbamate (1.5g)

Yield: 191 mg (84%); white solid; mp 188 °C; $R_f = 0.50$ (n-hexane and EtOAc, 7:3); IR (KBr): 1738 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 5.11$ (s, 2H), 6.91 (br, 1H), 7.21-7.65 (m, 10H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 66.4$, 126.8, 127.1, 127.5, 129.1, 132.6, 133.4, 138.2, 143.1, 155.1.

ESI-MS: $m/z$ calcd for C$_{14}$H$_{13}$NO$_2$: 250.08 [M+Na]$^+$; found: 250.09.

1.3.6.8. Benzyl 4-bromophenylcarbamate (1.5h)

Yield: 242 mg (79%); pale yellow solid; mp 167 °C; $R_f = 0.45$ (n-hexane and EtOAc, 7:3); IR (KBr): 1742 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 5.12$ (s, 2H), 6.31 (br, 1H), 7.23-7.37 (m, 5H), 7.53 (d, $J = 8.2$ Hz, 2H), 7.78 (d, $J = 8.4$ Hz, 2H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 65.6$, 121.3, 122.9, 127.2, 127.8, 128.9, 132.4, 134.9, 141.5, 155.9.

HR-MS: $m/z$ calcd for C$_{15}$H$_{12}$BrN$_2$O$_2$: 327.9949 [M+Na]$^+$; found: 327.9941.
1.3.7. **General procedure for the preparation of ureidopeptides 1.6 and active carbamates 1.7**

![Chemical Structures]

To a solution of a \(N\)-protected amino acid hydroxamate 1.4 (1.0 mmol) in THF (10 mL) at 0 °C, NMM (0.16 mL, 1.5 mmol) and T3P (0.89 mL, 1.5 mmol) were added and the reaction mixture was stirred at 0 °C for 30 min. Then, \(H_2N\)-Xaa-COOMe or a substituted phenol (1.2 mmol) was added and the reaction mixture was subjected to ultrasonication until completion (90 min, TLC analysis). Urea products which precipitated out from the reaction mixture were collected by filtration and recrystallized (DMSO–H₂O). Otherwise, the urea or carbamate products were isolated via the same simple workup as described in the general procedure for ureas/carbamates 1.5.

1.3.7.1. **(S)-Methyl 2-(3-((S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)ethyl)ureido)-3-methylbutanoate (Fmoc-Ala-\(\psi\)NHCONH)-Val-OMe** (1.6a)

Yield: 421 mg (96%); white solid; mp 180 °C; \(R_f = 0.40\) (CHCl₃ and MeOH, 9:1); IR (KBr): 1648, 1712, 1735 cm⁻¹.

\(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 0.79\) (d, \(J = 5.7\) Hz, 6H), 1.16 (d, \(J = 5.8\) Hz, 3H), 1.72 (m, 1H), 3.55 (s, 39
3H), 4.12 (t, $J = 6.2$ Hz, 1H), 4.23 (d, $J = 6.8$ Hz, 2H), 4.51-4.82 (m, 2H), 5.13 (br, 1H), 6.31-6.37 (br, 2H), 7.22-7.94 (m, 8H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 18.3, 20.8, 31.3, 45.1, 51.3, 53.8, 59.7, 66.2, 126.5, 126.8, 127.1, 128.4, 141.1, 144.2, 156.0, 157.2, 174.1.


1.3.7.2. (S)-tert-Butyl-4-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)ureido)butanoate {Fmoc-Glu(O'Bu)-ψ[NHCONH]-Phe-OMe} (1.6b)

Yield: 505 mg (84%); white solid; mp 140-141 °C; $R_f = 0.45$ (CHCl$_3$ and MeOH, 9:1); IR: 1644, 1692, 1731 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.42 (s, 9H), 2.1 (t, $J = 7.2$ Hz, 2H), 2.52 (m, 2H), 2.87 (d, $J = 6.8$ Hz, 2H), 3.65 (s, 3H), 4.15 (t, $J = 4.4$ Hz, 1H), 4.29 (d, $J = 7.2$ Hz, 2H), 4.40-4.47 (m, 2H), 5.65 (d, $J = 6.0$ Hz, 1H), 6.75-6.91 (m, 2H), 7.54-7.85 (br, 13H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 27.8, 35.3, 37.7, 46.5, 51.8, 54.3, 61.5, 62.4, 66.6, 73.5, 119.8, 124.6, 126.1, 126.8, 127.2, 128.6, 129.2, 137.6, 141.1, 143.6, 155.3, 156.6, 170.8, 171.4.

HR-MS: m/z calcd for C$_{30}$H$_{39}$N$_3$O$_7$: 624.2686 [M+Na]$^+$; found: 624.2682.

1.3.7.3. (S)-Methyl 2-((S)-1-(tert-butoxycarbonyl)-2-phenylethyl)ureido)-3-methyl butanoate {Boc-Phe-ψ[NHCONH]-Val-OMe} (1.6c)

Yield: 334 mg (85%); white solid; mp 138-139 °C; $R_f = 0.50$ (CHCl$_3$ and MeOH, 9:1); IR (KBr): 1644, 1690, 1726 cm$^{-1}$.
\[ ^1H \text{NMR (300 MHz, DMSO-}d_6\text{):} \delta = 0.93 \text{ (d, } J = 5.8 \text{ Hz, } 6\text{H}), 1.35 \text{ (s, } 9\text{H}), 1.83 \text{ (m, } 1\text{H}), 2.85 \text{ (d, } J = 7.2 \text{ Hz, } 2\text{H}), 3.63 \text{ (s, } 3\text{H}), 3.83-3.93 \text{ (m, } 2\text{H}), 5.23 \text{ (br, } 1\text{H}), 6.35 \text{ (br, } 1\text{H}), 6.45 \text{ (d, } J = 7.0 \text{ Hz, } 1\text{H}), 7.15-7.30 \text{ (m, } 5\text{H}). \]

\[ ^{13}C \text{NMR (75 MHz, DMSO-}d_6\text{):} \delta = 18.7, 19.5, 29.5, 37.1, 54.7, 57.5, 63.1, 78.2, 126.9, 127.6, 129.1, 137.9, 155.3, 156.9, 174.5. \]

IIR-MS: m/z calcld for C\textsubscript{29}H\textsubscript{31}N\textsubscript{3}O\textsubscript{5}: 416.2161 [M+Na]\textsuperscript{+}; found: 461.2169.

1.3.7.4. (S)-Methyl 2-(3-((S)-1-((tert-butoxycarbonyl)-4-oxo-4-phenoxybutyl)ureido)-4-methylpentanoate \{Boc-Glu(Obn)-\(\psi\)[NHCONH]-Leu-OMe\} (1.6d)

Yield: 379 mg (79%); white solid; mp 139 °C; \( R_f = 0.4 \) (CHCl\textsubscript{3} and MeOH, 9:1); IR (KBr): 1656, 1702, 1742 cm\textsuperscript{-1}.

\[ ^1H \text{NMR (300 MHz, DMSO-}d_6\text{):} \delta = 0.91 \text{ (d, } J = 4.8 \text{ Hz, } 6\text{H}), 1.32 \text{ (s, } 9\text{H}), 1.42 \text{ (m, } 2\text{H}), 1.65 \text{ (m, } 1\text{H}), 2.55 \text{ (m, } 2\text{H}), 2.92 \text{ (m, } 2\text{H}), 3.65 \text{ (s, } 3\text{H}), 3.81-3.92 \text{ (m, } 2\text{H}), 5.15 \text{ (s, } 2\text{H}), 5.33 \text{ (d, } J = 4.7 \text{ Hz, } 1\text{H}), 6.35 \text{ (d, } J = 6.4 \text{ Hz, } 1\text{H}), 6.50 \text{ (d, } J = 5.8 \text{ Hz, } 1\text{H}), 7.34-7.41 \text{ (m, } 5\text{H}). \]

\[ ^{13}C \text{NMR (75 MHz, DMSO-}d_6\text{):} \delta = 22.1, 23.1, 24.7, 28.6, 37.9, 39.7, 41.9, 50.9, 61.9, 63.1, 78.7, 126.7, 127.6, 128.9, 137.7, 155.3, 156.8, 157.5, 178.1. \]

HR-MS: m/z calcld for C\textsubscript{24}H\textsubscript{27}N\textsubscript{3}O\textsubscript{5}: 502.2529 [M+Na]\textsuperscript{+}; found: 502.2531.

1.3.7.5. (S)-Methyl 2-(3-((1-(benzyloxycarbonyl)ethyl)ureido)acetate \{Z-Ala-\(\psi\)[NHCONH]-Gly-OMe\} (1.6e)

Yield: 275 mg (89%); white solid; mp 142-143 °C; \( R_f = 0.35 \) (CHCl\textsubscript{3} and MeOH, 9:1); IR (KBr): 1648, 1704, 1735 cm\textsuperscript{-1}.

\[ ^1H \text{NMR (300 MHz, DMSO-}d_6\text{):} \delta = 1.40 \text{ (d, } J = 7.8 \text{ Hz, } \text{H}). \]
Chapter I  

Lossen rearrangement and ureidopeptides

3H), 3.59 (s, 3H), 3.91 (m, 1H), 4.44 (d, J = 6.6 Hz, 2H), 5.12 (s, 2H), 5.76 (m, 1H), 6.32 (br, 2H), 7.28 (m, 5H).

$^1$H NMR (75 MHz, DMSO-$d_6$): δ = 21.5, 41.2, 49.8, 51.5, 64.9, 127.4, 127.6, 128.5, 137.0, 155.1, 156.2, 171.5.

HR-MS: m/z calcd for C$_{16}$H$_{19}$N$_3$O$_5$: 348.0962 [M+Na]$^+$; found: 348.0954.

1.3.7.6. (S)-Methyl 2-(3-((9H-fluoren-9-yl)methoxy)carbonyl)(phenyl)methyl ureido)proponoate (Fmoc-Phg-$\gamma$[NHCONH]-Ala-OMe) (1.6f)

Yield: 431 mg (91%); white solid; mp 170 °C; $R_f = 0.40$ (CHCl$_3$ and MeOH, 9:1); IR (KBr): 1647, 1715, 1738 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.29 (d, J = 6.0 Hz, 3H), 3.65 (s, 3H), 4.29 (t, J = 5.4 Hz, 1H), 4.40 (d, J = 6.4 Hz, 2H), 4.69 (m, 1H), 5.09 (m, 1H), 6.15 (m, 2H), 6.75 (br, 1H), 7.25-7.65 (m, 13H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 18.1, 47.5, 49.8, 52.5, 58.6, 65.6, 125.1, 125.8, 126.3, 126.9, 127.5, 127.9, 128.1, 141.3, 143.5, 143.9, 155.8, 156.7, 170.8.

HR-MS: m/z calcd for C$_{27}$H$_{27}$N$_3$O$_5$: 496.1848 [M+Na]$^+$; found: 496.1841.

1.3.7.7. (R)-Methyl 2-(3-((9H-fluoren-9-yl)methoxy)carbonyl)(phenyl)methyl ureido)proponoate (Fmoc-Phg-$\gamma$[NHCONH]-r-Ala-OMe) (1.6g)

Yield: 426 mg (90%); white solid; mp 170 °C; $R_f = 0.40$ (CHCl$_3$ and MeOH, 9:1); IR (KBr): 1647, 1715, 1738 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.30 (d, J = 9.0 Hz, 3H), 3.55 (s, 3H), 4.10 (t, J = 4.8 Hz, 1H), 4.21 (d, J = 6.2 Hz, 2H), 4.41 (m, 1H), 4.85 (m, 1H), 5.79 (m, 2H), 6.62-6.78 (br, 1H), 7.20-7.90 (m, 13H).
Chapter I

Lossen rearrangement and ureidoamides

\(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta = 18.9, 46.8, 49.1, 52.1, 58.7, 65.5, 125.3, 125.9, 126.2, 126.9, 127.6, 127.9, 128.3, 141.5, 143.7, 144.1, 156.3, 157.6, 171.4.

HR-MS: \(m/z\) calcd for C\(_{27}\)H\(_{27}\)N\(_3\)O\(_5\): 496.1848 [M+Na]\(^+\); found: 496.1840.

1.3.7.8. Fmoc-Phe-\(\psi\)[NHCO-OTcp] (1.7a)

Yield: 529 mg (91 %); white solid; mp 142 °C; \(R_f = 0.35\) (n-hexane and EtOAc, 7:3); IR (KBr): 1695, 1742 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 2.85\) (d, \(J = 6.2\) Hz, 2H), 3.81 (m, 1H), 4.11 (t, \(J = 4.6\) Hz, 1H), 4.25 (d, \(J = 7.0\) Hz, 2H), 6.58 (br, 2H), 7.23-8.15 (m, 15H).

\(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta = 38.9, 47.6, 52.5, 66.7, 120.0, 122.5, 124.6, 125.0, 127.1, 127.2, 127.8, 128.7, 129.1, 129.8, 132.0, 136.9, 141.2, 143.4, 151.4, 155.8, 156.6.

HR-MS: \(m/z\) calcd for C\(_{39}\)H\(_{23}\)Cl\(_3\)N\(_2\)O\(_4\): 603.0621 [M+Na]\(^+\); found: 603.0626.

1.3.7.9. Boc-Glu(OBu)-\(\psi\)[NH-CO-OPfp] (1.7b)

Yield: 441 mg (85 %); white solid; mp 117-118 °C; \(R_f = 0.4\) (n-hexane and EtOAc, 7:3); IR (KBr): 1698, 1737, 1755 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 1.32\) (s, 9H), 2.15 (m, 2H), 2.42 (t, \(J = 5.8\) Hz, 2H), 4.85 (m, 1H), 5.11 (s, 2H), 6.11-6.32 (br, 2H), 7.25-7.41 (m, 5H).

\(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta = 26.2, 27.8, 34.9, 52.4, 63.5, 80.1, 127.5, 128.2, 128.9, 137.9, 140.5, 141.3, 143.9, 150.4, 155.3, 156.1, 171.2.

HR-MS: \(m/z\) calcd for C\(_{23}\)H\(_{23}\)F\(_3\)N\(_2\)O\(_6\): 541.1374 [M+Na]\(^+\); found: 541.1369.
1.3.7.10. Fmoc-Ala-$\psi$[NH-CO-OPnp] (1.7c)

Yield: 398 mg (89 %); white solid; mp 170-171 °C; \( R_f \) = 0.3 (n-hexane and EtOAc, 7:3); IR (KBr): 1711, 1743 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \( \delta = 1.14 \) (d, \( J = 6.2 \) Hz, 3H), 3.85 (m, 1H), 4.13 (d, \( J = 6.6 \) Hz, 2H), 4.26 (t, \( J = 3.6 \) Hz, 1H), 6.66-6.72 (br, 2H), 7.26-8.12 (m, 12H).

\(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \( \delta = 18.3, 48.0, 48.6, 66.6, 120.2, 122.4, 125.6, 125.8, 126.8, 127.6, 128.2, 141.9, 145.1, 145.7, 157.1, 157.9.\)

HR-MS: \( m/z \) calcd for \( \text{C}_{26}\text{H}_{21}\text{N}_3\text{O}_6 \): 448.1509 [M+H]*; found: 448.1514.
1.4. SPECTRA

$^1$H NMR spectrum of $N$-hydroxy-2-phenylacetamide 1.2a

$^{13}$C NMR spectrum of $N$-hydroxy-2-phenylacetamide 1.2a
Chapter I  
Lossen rearrangement and ureidopeptides

HR-MS spectrum of N-hydroxy-2-phenylacetamide 1.2a

1H NMR spectrum of N-hydroxythiophene-2-carboxamide 1.2c
$^{13}$C NMR spectrum of $N$-hydroxyfuran-2-carboxamide 1.2d

$^1$H NMR spectrum of $N$-hydroxybenzamide 1.2e
$^{13}$C NMR spectrum of $N$-hydroxybenzamide 1.2e

$^1$H NMR spectrum of $N^\alpha$-Fmoc-Ala-NHOH 1.4a
Chapter I  
Lossen rearrangement and ureidopeptides

$^{13}$C NMR spectrum of $N^\alpha$-Fmoc-Ala-NHOH 1.4a

$^1$H NMR spectrum of $N^\alpha$-Fmoc-Glu(O'Bu)-NHOH 1.4c
Chapter I
Lossen rearrangement and ureidopeptides

IR-MS spectrum of $N^\alpha$-Fmoc-Glu(O'Bu)-NHOH 1.4c

$^1$H NMR spectrum of $N^\alpha$-Z- Ala-NHOH 1.4f
$^1$H NMR spectrum of $N^\omega$-Z-Phg-NHOH 1.4g

$^1$H NMR spectrum of $N^\omega$-Boc-Phe-NHOH 1.4h
$^1$H NMR spectrum of 1-benzyl-3-(2-chlorophenyl)urea 1.5a

$^{13}$C NMR spectrum of 1-benzyl-3-(2-chlorophenyl)urea 1.5a
Chapter I

Lossen rearrangement and ureidopeptides

HR-MS spectrum of S-cyclohexyl benzylcarbamothioate 1.5b

\(^1\)H NMR spectrum of benzyl phenylcarbamate 1.5g
HR-MS spectrum of Fmoc-Ala-\(\psi\)[NHCONH]-Val-OMe \textbf{1.6a}

HR-MS spectrum of Fmoc-Glu(O'Bu)-\(\psi\)[NHCONH]-Phe-OMe \textbf{1.6b}
$^1$H NMR spectrum of Boc-Phe-$\psi$[NHCONH]-Val-OMe 1.6c

HR-MS spectrum of Boc-Glu(Obn)-$\psi$[NHCONH]-Leu-OMe 1.6d
$^{13}$C NMR spectrum of Z-Ala-$\psi$[NHCONH]-Gly-OMe 1.6e

$^1$H NMR spectrum of Fmoc-Phg-$\psi$[NHCONH]-Ala-OMe 1.6f
Chapter I

Lossen rearrangement and ureidopeptides

$^1$H NMR spectrum of Fmoc-Phg-$\psi[\text{NHCONH}]$-$\alpha$-Ala-OMe 1.6g

$^1$H NMR spectrum of Fmoc-Phe-$\psi[\text{NHCO-OTcp}]$ 1.7a
Chapter I

Lossen rearrangement and ureidopeptides

$^1$H NMR spectrum of Boc-Glu(Obn)-ψ[NH-CO-OPfp] 1.7b

$^1$H NMR spectrum of Fmoc-Ala-ψ[NH-CO-OPnp] 1.7c

58
RP-HPLC trace of N\textsuperscript{\textalpha}-Fmoc-Ala-NHOH 1.4a (λ = 254 nm, flow: 0.5 mL/min; column: Agilent eclipse XDB-C-18, pore size - 5μm, diameter x length = 4.6 x 150 mm; method: gradient 0.1% TFA water-CH\textsubscript{3}CN; CH\textsubscript{3}CN 30-100% in 30 min)

RP-HPLC trace of Fmoc-Ala-\psi[NHCONH]-Val-OMe 1.6a (λ = 254 nm, flow: 0.5 mL/min; column: Agilent eclipse XDB-C-18, pore size - 5μm, diameter x length = 4.6 x 150 mm; method: gradient 0.1% TFA water-CH\textsubscript{3}CN; CH\textsubscript{3}CN 30-100% in 30 min)

59


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Chapter I

Lossen rearrangement and ureidopeptides


Chapter I  Lossen rearrangement and ureidopeptides


