Synthesis of β-lactam peptidomimetics through Ugi MCR: first application of chiral Nβ-Fmoc amino alkyl isonitriles in MCRs

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**Abstract**

Chiral Nβ-Fmoc amino alkyl isonitriles were employed in Ugi multi component reactions (Ugi 4C-3CR) to obtain functionalized β-lactam peptidomimetics with L-aspartic acid α-methyl ester/peptide ester and organic aldehydes. The reactions were carried out in MeOH. Thirteen Ugi products have been prepared in good to moderate yields with good diastereoselectivities.

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**Multi-component reactions (MCRs)** have become vital tools for assembling complex molecules and hence new MCRs are being designed for the construction of novel molecules. Isonitrile based MCRs have gained renewed attention due to their unique reactivity to function as electrophile as well as nucleophile. They have been the key components in Pessirini 3CRs and Ugi-4CRs employed widely for generating molecular libraries. Ugi-MCRs, over the years, have undergone improvements with respect to improving the yield and selectivity of the products. This work reports the synthesis of Nβ-Fmoc amino alkyl isonitriles and their application in Ugi-MCRs to obtain β-lactam peptidomimetics.

**Scheme 1.** General mechanism for the formation of β-lactam ring through Ugi 4C-3CR.

**Scheme 2.** Synthesis of Nβ-Fmoc amino alkyl isonitriles.

**Figure 1.** Representative examples of reported β-lactam peptidomimetics.
A promising application of Ugi MCR focuses on the synthesis of β-lactam derivatives. β-Lactams are powerful antibacterials and have been largely employed in one-pot synthesis of peptides and peptidomimetics. A promising application of Ugi MCR focuses on the synthesis of β-lactam derivatives. β-Lactams are powerful antibacterials and have been largely employed in one-pot synthesis of peptides and peptidomimetics. 

\[
\text{FmocHN} \quad \text{NC} \quad \text{MeOH, rt FmocHN} \quad \text{H} \quad \text{N} \quad \text{O} \quad \text{N} \quad \text{O} \quad \text{R2} \quad \text{Ph} \quad \text{COOMe}
\]

\[
\text{R2-CHO} = (\text{HCHO})_n, \text{C}_6\text{H}_5\text{CHO}, \text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{CHO}
\]

**Scheme 3.** Synthesis of β-lactam peptidomimetics.

**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isonitriles 2</th>
<th>Ugi product 3</th>
<th>Yield (%)</th>
<th>d.r.</th>
<th>HRMS [M+H]+ (obsd/calcd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>FmocHN</td>
<td>FmocHN</td>
<td>65</td>
<td>99:1</td>
<td>528.2108/528.2135</td>
</tr>
<tr>
<td>b</td>
<td>FmocHN</td>
<td>FmocHN</td>
<td>78</td>
<td>96:4</td>
<td>542.2280/542.2286</td>
</tr>
<tr>
<td>c</td>
<td>FmocHN</td>
<td>FmocHN</td>
<td>69</td>
<td>85:15</td>
<td>598.2903/598.2912</td>
</tr>
<tr>
<td>d</td>
<td>FmocHN</td>
<td>FmocHN</td>
<td>72</td>
<td>90:10</td>
<td>494.2276/494.2286</td>
</tr>
<tr>
<td>e</td>
<td>FmocHN</td>
<td>FmocHN</td>
<td>76</td>
<td>89:11</td>
<td>648.2697/648.2704</td>
</tr>
<tr>
<td>f</td>
<td>FmocHN</td>
<td>FmocHN</td>
<td>63</td>
<td>100:0</td>
<td>656.2952/656.2966</td>
</tr>
<tr>
<td>g</td>
<td>FmocHN</td>
<td>FmocHN</td>
<td>59</td>
<td>98:2</td>
<td>657.2902/657.2919</td>
</tr>
<tr>
<td>h</td>
<td>FmocHN</td>
<td>FmocHN</td>
<td>53</td>
<td>95:5</td>
<td>568.2429/568.2442</td>
</tr>
</tbody>
</table>

* a, β-Amino acid component employed was H-Asp(β-OH)-OMe.
* b, Isolated yields after column chromatography.
* c, Diastereomeric ratios of the products were measured by 1H NMR of the purified products.

the yield and diastereoselectivity. They have been largely employed in one-pot synthesis of peptides and peptidomimetics.
show an array of bioactivities, such as inhibition of ser, cys, and HIV-1 proteases. They also find synthetic applications as β-amino acid precursors and in the synthesis of short peptide segments. Despite the widespread utility of β-lactam units, there is still requirement for highly functionalized β-lactam units (Fig. 1).

For the synthesis of β-lactam derivatives, Staudinger reaction involving [2+2] cycloaddition of ketenes and ketones has been the widely used protocol. Solid phase synthetic protocols are also described mainly based on [2+2] cycloaddition of ketenes with resin bound isonitriles. Among them L-aspartic acid and aldehydes. The reaction also represents a simple method to insert β-lactam units into the peptide backbone.

A probable accepted mechanism for the formation of β-lactam derivatives is represented in Scheme 1. Condensation of β-amino acid with appropriate aldehyde affords protonated Schiff’s base, which reacts with an isonitrile to generate an oxazepine intermediate. The latter would be transferred to β-lactam derivative through intramolecular N-O-acyl migration (Scheme 1).

In the first part of our work, N'-Fmoc-amino alkyl isonitriles 2, the key intermediates for the proposed reaction were prepared following the reported procedure. In brief, N'-Fmoc-amino alkyl isocyanates (obtained from N'-Fmoc-amino acids) were directly formulated by treating with formic acid under DMAP catalyzed Goldschmidt–Wick condition with 98% formic acid and the resulting formamides were reacted with Burgess reagent under neutral condition. All the isonitriles were obtained in good yield with the retention of chiral integrity (Scheme 2).

In the next part, syntheses of different β-amino acid components 1 required for Ugi multi component condensation were undertaken. Starting with Z-Asp(β-OBn)-OH, employing standard peptide coupling protocols, several di and tripeptide methyl esters were prepared. After removal of Z and benzyl esters of Asp residue under catalytic hydrogenolysis (Pd/C, H2), the required H-Asp-Xaa-OMe derivatives were obtained in good yield.

Having the key reactants in hand, we focused on the assembly of β-lactam derived peptidomimetics. In a typical reaction a solution of peptide derivatives is represented in Scheme 1. Condensation of β-amino acid with appropriate aldehyde affords protonated Schiff’s base, which reacts with an isonitrile to generate an oxazepine intermediate. The latter would be transferred to β-lactam derivative through intramolecular N-O-acyl migration (Scheme 1).

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of the present protocol, a series of β-lactam derivatives were prepared by varying the isonitriles derived from N-Fmoc-amino acids and aldehyde components (3a–j) keeping H-Asp-OMe as a common reactant.26 All the reactions were complete with in 24–28 h under rt, resulting in the β-lactam derivatives in moderate to good yield with diastereomeric ratio varying from 100:0 to 85:15 (Table 1). It is known from the literature, a good diastereoselectivity is achieved during β-lactam synthesis through Ugi 4C-3CR due to the formation of seven membered oxapinone intermediate. Further, an attempt to decrease the reaction time and to improve the yields of the Ugi adducts was undertaken with compound N-Fmoc-Phe-Ψ[CH(NC)2]Ce as the model reactant. The reaction was also carried out at reflux for 8–10 h or ultrasonication at 80 °C for 7–9 h during which complete disappearance of the isonitrile was observed, but these conditions did not improve the yield significantly or the diastereoselectivity. Hence, mild conditions were eventually chosen to synthesize title molecules (Scheme 3). Isonitriles derived from several side chain functionalized amino acids viz Fmoc-Ser(Obn)-OH, Fmoc-Asp(β-Obn)-OH, Fmoc-Lys(Z)-OH were also used in the reaction and the products were obtained in good yield without the formation of byproducts.

Encouraged by these results, additional set of peptidomimetics 31–m bearing endo-β-lactam units were prepared by utilizing peptide esters with N-terminal Asp residue 1b–e. Ugi reaction was carried out by varying all the three components. Compared to the reactions involving 1a as β-amino acid component, those involving 1b–e were sluggish and even after running the reaction to 48 h, only moderate yields were obtained (Fig. 2).27 All the compounds were isolated as stable ones and characterized through IR, mass, 1H NMR and 13C NMR analyses.

In conclusion, we have accomplished the first application of chiral N-Fmoc–amino-alkyl isonitriles in Ugi multi component reactions through the synthesis of peptide mimics with β-lactam units. β-Lactams have been synthesized in solution through Ugi 4C-3CR through one-pot condensation of N-Fmoc-amino alkyl isonitriles, L-ascpartic acid x-methyl ester/peptide ester, and commercially available aldehydes.

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References and notes
11. Typical procedure for H-Asp-OMe: Z-Asp(Obn)-OH (3.57 g, 1.0 mmol) was dissolved in dry THF (5 mL), and cooled to −15 °C. The THF was vaporized under reduced pressure and the residue was dissolved in CH2Cl2 (10 mL) and washed with 5% Na2CO3 (3 × 10 mL), 5% citric acid (10 mL two times), water (10 mL two times), and brine (10 mL), and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure. The product was evaporated until dryness and purified by recrystallization of the residue with ethyl alcohol. THF afforded H-Asp-OMe (4.76 g) as white solid. The later product (2.0 g) was dissolved in MeOH (20.0 mL), Pd/C (400 mg, 20 wt%) was added and the reaction mixture was stirred for 4 h under hydrogen atmosphere. After complete deprotection (TLC analysis), Pd/C was filtered out and the filtrate was evaporated under reduced pressure. Recrystallization of the crude product with MeOH:ether (5:2:50 mL of the crude product) afforded H-Asp-Phe-OMe.
24. HPLC analysis was carried out on Agilent 1100 using an Agilent EclipseXDB-C18 G1311A column (4.6 × 150 mm, 5 μm) and a gradient of 0.1% TFA-water acetonitrile; acetonitrile 30–70% in 30 min with spectrometric monitoring at λ = 238 nm. HPLC profile of the purified 3b showed two peaks one at Rt = 20.045 min and another peak at Rt = 20.098 min.


26. Spectral data for 3b: IR (KBr): ν 1738, 1745, 1665, 1558 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.81 (d, 2H, J = 7.5 Hz), 7.68 (d, 2H, J = 5.9 Hz), 7.22–7.29 (m, 4H), 7.01–7.15 (m, 5H), 6.01 (s, br, 1H), 5.90 (s, br, 1H), 5.31 and 5.55 (two s, 1H), 4.68 (d, 2H, J = 6.7 Hz), 4.41 (t, 1H, J = 3.1 Hz), 4.33–4.39 (m, 1H), 3.66–3.71 (m, 1H), 3.56 (s, 3H), 3.51 (dd, 1H, J = 8.1 Hz), 3.48 (dd, 1H, J = 4.9 Hz), 3.15–3.28 (m, 2H), 1.11 (d, 3H, J = 3.6 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 170.4, 169.5, 168.2, 155.2, 143.0, 140.8, 140.3, 136.2, 129.1, 128.7, 128.7, 128.5, 128.2, 127.8, 127.5, 127.3, 127.0, 126.8, 66.5, 59.9, 51.0, 50.5, 47.8, 46.8, 41.2, 16.8.

27. Spectral data for 3l: IR (KBr): ν 1752, 1748, 1671, 1550 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.78 (d, 2H, J = 6.5 Hz), 7.48 (d, 2H, J = 3.1 Hz), 7.22–7.28 (m, 4H), 7.05–7.19 (m, 5H), 6.36–6.89 (br, 4H), 5.36 and 5.31 (two s, 1H), 4.69 (d, 2H, J = 2.9 Hz), 4.59–4.61 (m, 1H), 4.44 (t, 1H, J = 6.8 Hz), 4.38 (d, 1H, J = 5.8 Hz), 4.31–4.35 (m, 1H), 3.85 (dd, 1H, J = 2.6, 5.9 Hz), 3.58 (s, 3H), 3.13–3.41 (m, 4H), 1.76–1.81 (m, 1H), 2.11–2.20 (m, 2H), 1.38 (d, 3H, J = 1.8 Hz), 1.08 (d, 6H, J = 8.1 Hz), 0.96 (d, 6H, J = 5.0 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 170.1, 170.9, 171.0, 167.9, 168.8, 155.0, 142.5, 140.2, 135.8, 129.8, 128.9, 128.5, 128.2, 127.8, 127.6, 127.4, 127.3, 126.7, 126.1, 125.5, 124.5, 119.4, 66.5, 59.9, 55.9, 51.4, 51.0, 49.2, 48.0, 47.1, 44.6, 40.8, 30.0, 23.1, 22.8, 17.1, 17.2, 16.8, 16.7.