A simple protocol for the synthesis of triazole-linked cyclic glycopeptidomimetics: a sequential Ugi-MCR and azide–alkyne cycloaddition approach

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Article info

Article history:
Received 26 March 2012
Revised 6 April 2012
Accepted 7 April 2012
Available online 14 April 2012

Keywords:
Cyclic glycopeptidomimetic
Poc-amino alkyl isonitrile
Ugi multi-component reaction
Click chemistry

Abstract

Sequential combination of Ugi-MCR and click chemistry has been employed for the synthesis of triazole linked cyclic glycopeptidomimetics. The protocol employs Poc-amino alkyl isonitriles, sugar-1-amines, azido acids, and simple aldehydes as precursors. The dual nature of the propargyloxycarbonyl (Poc) group was explored for amine protection as well as cycloaddition with an azide. All the cyclic glycopeptidomimetics are isolated and characterized.

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Affluence of cyclic glycopeptides in natural sources and the knowledge about their biological and structural significance emphasize the importance of the development of synthetic methodologies for such molecules and related analogs. From the biochemist's perspective, glycopeptide cyclization is an interesting aspect of study that may lead to valuable architectural repertoire possessing structurally and pharmacologically useful properties.

Cyclic glycopeptides do not possess ionizable N- and C-terminals rendering them with improved membrane permeability and stability to in vivo enzymatic degradation. However, cyclization is, in general, yield-limiting and synthetically a difficult step. This evokes to suitably design the sites for gluing the head to tail affording a ring structure in an efficient manner through the establishment of a native or non-native linkage. On the other hand, substantial focus has been paved toward development of new protocols for the construction of glycopeptidomimetics and peptidomimetics. In the former, the carbohydrate is linked to peptide backbone through a non-native linkage and in the latter class of molecules, one or more amide bonds in the backbone are replaced by artificial tethers.

Multi-component reactions such as Ugi-MCR and Passerini-3CR are being utilized for accessing complex molecules from simple substrates. Isonitrile based MCRs, especially those involving isocyanate esters have emerged as tools of choice to access peptide-like constructs. It is useful to tag MCRs with another reaction(s) in a sequential manner so as to modify the Ugi-product to obtain desired products. Till recently, isocyanate esters, prepared by N-modification of amino acid esters were the isonitrile components generally used in the MCRs. Sureshbabu and co-workers described another class of amino acid derived isonitriles by modifying the C-terminus of N-protected amino acids and the resulted N-protected amino alkyl isonitriles have been employed as key substrates in a couple of MCRs to obtain a few peptidomimetics. The Cu-catalyzed azide–alkyne cycloaddition (‘click’ chemistry) is a robust chemical transformation in bridging two components. This reaction has accelerated the research in drug discovery due to the efficient and non-sensitive reaction conditions, thus ideal for the synthesis of a library of compounds. Triazole has been used as a surrogate to the native bond in the synthesis of cyclic peptidomimetic and glycopeptidomimetic scaffolds involving multistep protocol. Our interest in the development of a useful strategy for accessing cyclic neoglyco-peptidomimetics led us to explore a sequential combination of Ugi-MCR and azide–alkyne cycloaddition as a tool to synthesize the title compounds.

The present study involves the design of suitable starting components for MCR that would yield a linear molecule which can be cyclized through click reaction. A combination of an isonitrile, amine, aldehyde, and a carboxy compound would lead to a linear peptidic derivative wherein the isonitrile and carboxy acid components flank at either terminus. This directed us to deposit the alkyne and azide groups required to operate post-MCR step, in the isonitrile and carboxy substrates before initiating the MCR. In this context, it is to note that both azide and alkyne groups are compatible to Ugi reaction conditions. The azido acid was an
immediate choice as one of the components because it serves as amino acid precursor in peptide bond formation. Another key aspect is to obtain a linear peptidic unit possessing both isonitrile and alkyne groups as terminals. The dual utility of propargyloxy-carbonyl (Poc) group can be explored for amino protection as well as a reactant for Huisgen’s cycloaddition reaction.15 Thus, Poc-protected amino alkyl isonitriles are chosen as suitable substrates in this protocol. The sugar component was selected as an amino component which can be prepared easily. The aldehydes were selected from the commercially available sources.

The preparation of the substrates was straightforward and simple. Briefly, azido acids were prepared by a reaction of amino acids with imidazole-1-sulfonyl azide as reported by Goddard-Borger.16 For the preparation of 2,3,4,6-tetra-O-acetyl glucosyl-1-amine, glucose was reacted with acetyl chloride and the resulting 1,2,3,4,6-penta-O-acetyl-α,β-D-glucopyranose was reacted with HBr in AcOH to obtain 2,3,4,6-tetra-O-acetyl glycopyranosyl-1-bromide. Replacement of bromide with azide followed by catalytic hydrogenation of the azido group afforded 2,3,4,6-tetra-O-acetyl glucopyranosyl-1-amine.17 Poc-amino acids were prepared by

![Scheme 1. Synthesis of triazole linked cyclic glycopeptidomimetics 6 via Ugi products 5.](image)

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Poc-Xaa-{[CH$_2$NC]} (1)</th>
<th>Aldehyde (2)</th>
<th>Azido acid (3)</th>
<th>Sugar amines (4)</th>
<th>Ugi-product (5) Yield (%)</th>
<th>Cyclic product (6) Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phe</td>
<td>OHC</td>
<td>Ala</td>
<td>AcO</td>
<td>75</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>Leu</td>
<td>CHO</td>
<td>Gly</td>
<td>BzlO</td>
<td>71</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>Gly</td>
<td>CHO</td>
<td>Leu</td>
<td>AcO</td>
<td>69</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>Val</td>
<td>CHO</td>
<td>Leu</td>
<td>AcO</td>
<td>73</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>Leu</td>
<td>CHO</td>
<td>Gly</td>
<td>AcO</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>Ala</td>
<td>H</td>
<td>Phe</td>
<td>AcO</td>
<td>67</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>Isoleucine</td>
<td>HCHO</td>
<td>Val</td>
<td>BzlO</td>
<td>72</td>
<td>59</td>
</tr>
<tr>
<td>8</td>
<td>Phe</td>
<td>HCHO</td>
<td>Ala</td>
<td>BzlO</td>
<td>65</td>
<td>60</td>
</tr>
</tbody>
</table>
treating amino acids with Poc-OPfp according to Chandrasekaran and co-workers.18 The carbonyl terminus was modified into methylene isonitrile through a series of operations as described previously by us.19

The Ugi MCR was initiated by mixing equimolar quantities of the four reactants in MeOH. In a typical reaction, Poc-Val-SR/S1/OC-52/2011).2011

Click reaction is very efficient in bringing out the cyclization with-2

out considerable byproducts. The resulting cyclic neoglyco-

mimetic was isolated in moderate yield and characterized.

The reaction was monitored by RP-HPLC. A simple work-up

procedure for the preparation of Ugi products 5a–h: To a stirred solution of aldehyde (5 mL) Poc-AA-

1

was subjected to Cu catalyzed azide–alkyne cycloaddi-

tion, and thus the ring strain is less due to which mono-cyclization is

problem will not be so serious if the ring size is large so as to keep

the strain at minimum.22 In the present case, when the linear mol-

5d

of furfural

the four reactants in MeOH. In a typical reaction, Poc-Val-


ity and thus was utilized in the synthesis of

chemical.

was monitored through TLC. After 24 h, the crude reaction mixture

2

was column chromatographed to obtain the desired linear peptidic

was monitored through TLC. After 24 h, the crude reaction mixture

2d

of 15-membered ring

at 95°C for 10 min, then it was subjected to Cu catalyzed azide–alkyne cycloaddi-

tions in a sequential manner. Poc-amino alkyl isonitrile is used for

was subjected to Cu catalyzed azide–alkyne cycloaddi-

tion, and thus was utilized in the synthesis of

was monitored through TLC. After 24 h, the crude reaction mixture

2d

of 15-membered ring

at 95°C for 10 min, then it was subjected to Cu catalyzed azide–alkyne cycloaddi-

tion, and thus was utilized in the synthesis of

was monitored through TLC. After 24 h, the crude reaction mixture

2d

of 15-membered ring

at 95°C for 10 min, then it was subjected to Cu catalyzed azide–alkyne cycloaddi-

The initial experiment for the cyclization of 5d, the catalytic

system comprising CuSO4·5H2O/sodium ascorbate in BuOH/water was used. It led to 6d in 62% yield in about 10 h at rt. In order to improve the yield as well as to reduce the duration of reaction, other catalysts CuI/DPPEA in acetoinonitrile and CuI/1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene were explored. Both sys-
tems yielded only 40% and 46% of the cyclized product 6d. In light of these results, the CuSO4/sodium ascorbate was finally chos-""
C_{35}H_{48}N_{6}O_{14} m/z 799.3100 [M+Na]^+. Found 799.3101, 155.3, 169.1, 173.2; HRMS Calcd for C_{35}H_{48}N_{6}O_{14} m/z 799.3100 [M+Na]^+. Found 799.3101.


23. Typical procedure for the preparation of triazole linked cyclic neoglycopeptidomimetic 6d: To a 250 mL round-bottomed flask charged with linear peptidic component 5d (0.10 g, 0.128 mmol, 1 equiv) in tBuOH (120 mL) and H_{2}O (40 mL) were added sodium ascorbate (7.6 mg, 0.038 mmol, 0.3 equiv), CuSO_{4}, and \( \text{C}_{5} \text{H}_{12} \text{O}_{2} \) (0.64 mg, 0.0025 mmol, 0.02 equiv). The solution was then stirred at rt for about 10 h. Completion of the reaction was monitored by RP-HPLC. The reaction mixture was then filtered through a pad of celite to remove the salts and washed thoroughly with EtOAc (3 × 25 mL). Crude product was then isolated by giving water (1 × 30 mL) and brine (1 × 30 mL) wash. The product was purified via chromatography (60% EtOAc in hexane) to afford triazole linked cyclic neoglycopeptidomimetic 6d (62 mg, 62% yield) as a solid.

Characterization data for compound 6d: Brown solid; mp = 137–141 °C; IR (KBr) \( \tilde{\nu}_{\text{max}} \) = 1692, 1735, 2122, 3340 cm\(^{-1}\); \( \tilde{\nu}_{\text{IR}} \) = 0.21 (EtOAc: n-hexane, 40:60); RP-HPLC \( R_{t} = 16.8 (20–100\% \text{ CH}_{3}\text{CN}, 30 \text{ min}) \); \(^{1}\text{H} \text{ NMR} \) (DMSO-\( \text{d}_{6} \), 400 MHz): \( \tilde{\nu}_{\text{max}} \) (J = 6.8 Hz), 0.98 (d, 6H, J = 6.8 Hz), 1.20 (s, 12H), 1.73 (m, 1H), 1.89 (m, 2H), 2.32 (m, 1H), 3.48 (m, 2H), 4.16 (m, 1H), 4.26 (d, 2H, J = 5.8 Hz), 4.54 (t, 1H, J = 4.8 Hz), 4.63 (m, 1H), 4.66 (m, 1H), 4.96 (m, 1H), 5.23 (m, 2H), 5.28 (s, 2H), 6.06 (s, 1H), 6.12–6.21 (m, 2H), 6.24 (d, 1H, J = 6.2 Hz), 6.86 (br, 2H), 7.16 (s, 1H), 7.21 (s, 1H); \(^{13}\text{C} \text{ NMR} \) (DMSO-\( \text{d}_{6} \), 100 MHz): \( \nu_{\text{max}} \) = 17.4, 20.9, 21.9, 22.2, 30.6, 40.4, 45.3, 56.4, 58.2, 58.3, 59.2, 64.3, 67.6, 69.5, 69.8, 76.3, 79.2, 106.4, 110.2, 120.6, 141.8, 142.1, 152.1, 157.4, 170.6, 171.2, 173.2; HRMS calcd for C_{35}H_{48}N_{6}O_{14} m/z 799.3100 [M+Na]^+. Found 799.3104.