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

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A B S T R A C T
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 peptidotimetics. 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 peptidomimeticlike 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, isocyano 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 peptidotimetics. The Cu-catalyzed azide–alkyne cycloaddition (click chemistry) is a robust 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 peptidotimetic and glycopeptidotimetic scaffolds involving multistep protocol. Our interest in the development of a useful strategy for accessing cyclic neoglyco-peptidotimetics 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 azide and alkyne groups required to operate post-MCR step, in a sequential manner so as to modify the Ugi-product to obtain desired products. Till recently, isocyano 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 peptidotimetics. The Cu-catalyzed azide–alkyne cycloaddition (click chemistry) is a robust 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 peptidotimetic and glycopeptidotimetic scaffolds involving multistep protocol. Our interest in the development of a useful strategy for accessing cyclic neoglyco-peptidotimetics led us to explore a sequential combination of Ugi-MCR and azide–alkyne cycloaddition as a tool to synthesize the title compounds.

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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. 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. 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. Poc-amino acids were prepared by

![Scheme 1](image)

**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Poc-Xaa-[CH2NC] (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-AcO-AcO-AcO</td>
<td>75</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>Leu</td>
<td>CHO</td>
<td>Gly</td>
<td>BzlO-BzlO-BzlO-BzlO</td>
<td>71</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>Gly</td>
<td>CHO</td>
<td>Leu</td>
<td>AcO-AcO-AcO-AcO</td>
<td>69</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>Val</td>
<td>OCHO</td>
<td>Leu</td>
<td>AcO-AcO-AcO-AcO</td>
<td>73</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>Leu</td>
<td>CHO</td>
<td>Gly</td>
<td>AcO-AcO-AcO-AcO</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>Ala</td>
<td>OHC</td>
<td>Phe</td>
<td>AcO-AcO-AcO-AcO</td>
<td>67</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>Isoleucine</td>
<td>HCHO</td>
<td>Val</td>
<td>BzlO-BzlO-BzlO-BzlO</td>
<td>72</td>
<td>59</td>
</tr>
<tr>
<td>8</td>
<td>Phe</td>
<td>OCHO</td>
<td>Ala</td>
<td>BzlO-BzlO-BzlO-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 termonis was modified into methylene isonitrile through a series of operations as described previoulsy 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).

isolation in moderate yield and characterized. is made to participate in the intramolecular cycloaddition with an the first time in MCR reactions and the alkyne moiety of Poc group tions in a sequential manner. Poc-amino alkyl isonitrile is used for the major reaction.

because the ring strain is less due to which mono-cyclization is formed as a major component along with only a small amount of problem will not be so serious if the ring size is large so as to keep the isomers were not separated any further. The same protocol was subjected to Cu catalyzed azide–alkyne cycloaddi-

During the cyclization reactions, dimerization and oligomeriza-

the isomers were not separated any further. The same protocol was still not good. As expected, the product was a product. The desired cyclic glycopeptidomimetic afforded the target compound along with small amounts of dimer 120:40 mL). The resulting solution was allowed to stir for 10 h at rt. In order to the major reaction.

During 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/DIPEA in acetonitrile and CuBr/[1,8-Diazabicycloc[5.4.0]undec-7-ene] (DBU) in toluene were explored. Both systems yielded only 40% and 46% of the cyclized product 6d. In light of these results, the CuSO₄/sodium ascorbate was finally chosen and thus was utilized in the synthesis of 6a–6h. In a typical reaction, CuSO₄ (0.02 equiv, 0.64 mg), sodium ascorbate (0.3 equiv, 7.6 mg) were added to the solution of linear peptide component 5d (100 mg 0.128 mmol) in BuOH/water (3:1; 120:40 mL). The resulting solution was allowed to stir for 10 h at rt. The reaction was monitored by RP-HPLC. A simple work-up 11. (a) Marcaccini, S.; Torroba, T. 12. (a) Vishwanatha, T. M.; Narendra, N.; Sureshbabu, V. V. 13. (a) Nixey, Y.; Kelly, M.; Hulme, K. 14. (a) Armstrong, R. W.; Ameijde, J.; Aerts, K. L.; Kawai, T. K.; Lohse, C.; Moawad, A.; Schatz, C.; Sutherland, A. G.; Dushin, R. G. 15. Domling, A.; Ugi, I. Angew. Chem., Int. Ed. 2000, 39, 3168–3210. 16. (a) Semple, J. E.; Owens, T. D.; Nguyen, K.; Levy, O. E. Org. Lett. 2000, 2, 2769–2772; (b) Tsuchida, S.; De, J. E. J. Org. Chem. 2001, 66, 3301–3304. 17. Ramachary, D. B.; Kishor; M; Babul Reddy, G. 18. (a) Altamura, M.; Dragoni, E.; Infantino, A. S.; Legnani, L.; Ludbrook, S. B.; Menchi, G.; Toma, L.; Nativi, C. Bioorg. Med. Chem. Lett. 2009, 19, 3841–3844; (b) Hadzic, B.; Butz, D.; Schneidereit, T.; Steudle, J.; Wohlbewen, W.; Sussmuth, R.; Stegmann, E. Chem. Biol. 2007, 14, 1078–1089; (c) Chen; J.; Warren, J. D.; Bu, W.; Chen; G.; Wana, Q.; Danishefsky, S. J. Tetrahedron Lett. 2006, 47, 1969–1972.

5d


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 C_{1}H_{2}O (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) \nu_{max} = 1692, 1735, 2122, 3340 cm\textsuperscript{-1}; \nu_{R} = 0.21 (EtOAc: n-hexane, 40:60); RP-HPLC \nu_{R} = 16.8 (20–100% CH_{3}CN, 30 min); \textsuperscript{1}H NMR (DMSO-d_{6}, 400 MHz) \nu_{0.93} (d, 6H, \textsuperscript{J} = 6.8 Hz), \nu_{0.98} (d, 6H, \textsuperscript{J} = 7.2 Hz), \nu_{1.20} (s, 12H), \nu_{1.73} (m, 1H), \nu_{1.89} (m, 2H), \nu_{2.32} (m, 1H), \nu_{3.48} (m, 2H), \nu_{4.16} (m, 1H), \nu_{4.26} (d, 2H, \textsuperscript{J} = 5.8 Hz), \nu_{4.54} (t, 1H, \textsuperscript{J} = 4.8 Hz), \nu_{4.63} (m, 1H), \nu_{4.66} (m, 1H), \nu_{4.96} (m, 1H), \nu_{5.23} (s, 1H), \nu_{5.28} (s, 1H), \nu_{5.66} (s, 1H), \nu_{6.12} (s, 1H), \nu_{6.24} (d, 1H, \textsuperscript{J} = 6.2 Hz), \nu_{6.86} (br, 2H), \nu_{7.16} (s, 1H), \nu_{7.21} (s, 1H); \textsuperscript{13}C NMR (DMSO-d_{6}, 100 MHz) \nu_{17.4}, \nu_{20.9}, \nu_{21.9}, \nu_{22.2}, \nu_{30.6}, \nu_{40.4}, \nu_{45.3}, \nu_{56.4}, \nu_{58.2}, \nu_{58.3}, \nu_{59.2}, \nu_{64.3}, \nu_{67.6}, \nu_{69.5}, \nu_{69.7}, \nu_{76.3}, \nu_{79.2}, \nu_{106.4}, \nu_{110.2}, \nu_{120.6}, \nu_{141.8}, \nu_{142.1}, \nu_{152.1}, \nu_{157.4}, \nu_{170.6}, \nu_{171.2}, \nu_{173.2}; HRMS calcd for C_{35}H_{48}N_{6}O_{14} m/z 799.3100 [M+Na]^+, found 799.3104.