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Efficient Synthesis of Conformationally Constrained, Aminotriazoloazepinone-containing Di- and Tripeptides via a One-Pot Ugi-Huisgen tandem Reaction

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Herein we describe a catalyst-free procedure employing an Ugi-4CR between a β-azido-α-amino acid, propargylamine, an isocyanide and an aldehyde, followed by a thermal azide-alkyne Huisgen cycloaddition to generate a 16-member library of aminotriazoloazepinone-bearing di- and tripeptides with up to four points of diversification and high atom economy.

Di- to oligopeptides incorporating a cyclic conformationally constrained amino acid, typically having ring sizes of 3 to 8 atoms, have found use in the synthesis of peptidomimetics with widely different applications, such as for instance immunomodulatory agents,[1] dipeptide thrombin inhibitors,[2] antagonists of Grb2,[3] STAT3 inhibitors (e.g. **1**, Fig. 1),[4] inhibitors of hepatitis C N53 protease,[5] inducers of 3_{10} helices,[6] RGD-motif mimetics,[7] and the mimicry of β-, γ- and reverse-turns.[8] Such constraints, placed upon individual amino acid residues in peptides, limit rotation around the φ, ψ and χ torsional angles, and can increase the biological activity, receptor selectivity, circulatory half-life, cellular permeability and resistance to enzymatic hydrolysis of the peptidomimetic, while providing structural diversity and functional versatility. Dipeptide lactams have been widely used as constraints in the synthesis of biologically active peptidomimetics[9] and, more specifically, seven-membered lactams have proven their utility as important scaffolds in medicinal chemistry and are considered to be part of the 'privileged scaffolds',[10] alongside the structurally related benzodiazepine core. Azepinones are often found in pharmaceutical molecules[9,11] such as the sodium channel blocker **2** for the treatment of neuropathic pain,[12] the antihypertensive agent gemopatrilat **3**, and κ-opioid antagonists[13] **4** *inter alia*.

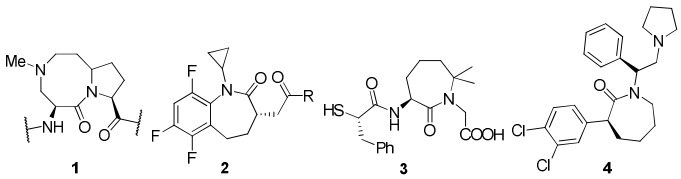


Fig. 1 – Selected examples of lactam-constrained peptidomimetics

Azepinones derived from amino acids such as the amino-benzazepinone (Aba) **5**, amino-indoloazepinone (Aia) **6**, **7** and amino-triazoloazepinone (Ata) **8** scaffolds (Figure 2) could also serve as privileged scaffolds following their use in a range of peptide and peptidomimetic ligands, including those for opioid receptors.[14] Recently, our group was able to show the facile generation of Aia scaffolds with an additional point of diversification in **7** (R_3, Fig. 2), through diastereoselective Ugi-3CRs,[15] thus increasing the potential of this scaffold for medicinal chemistry purposes. Additionally, biheterocyclic systems bearing seven-membered lactams fused with a triazole ring represent an interesting class of bioactive molecules that have received limited synthetic attention.[16]

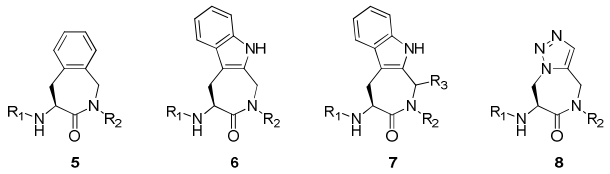
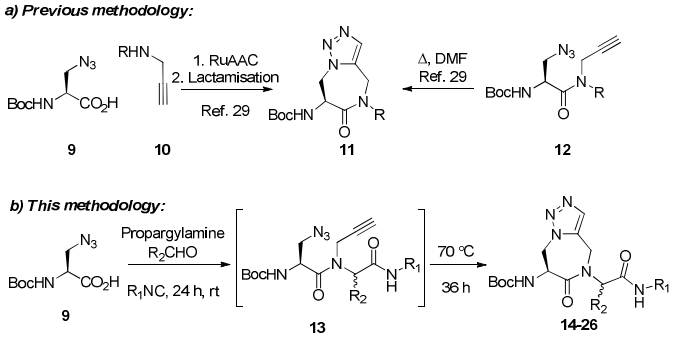


Fig. 2 – Constrained scaffolds Aba **15** Aia, **6** and **7**, and Ata **8**

The Ugi three- or four-component reaction (Ugi-3CR/4CR) is one of the most important multicomponent reactions (MCRs) used in organic synthesis.[17] Since MCRs represent one of the most powerful approaches in efficient diversity-oriented synthesis, they play an important role in the development of drug discovery methodology and biological probes. The Ugi-4CR reaction, in particular, is the method of choice to synthesize dipeptide-like structures thanks to the extent of structural diversity and molecular complexity introduced in one single step.[18] This isocyanide-based multicomponent reaction involves a condensation of a carbonyl component, an amine, a carboxylic acid, and an isocyanide to present α-acylaminoamides. Concomitantly, a new stereogenic center, derived from carbonyl component (aldehyde or ketone), is created. Unfortunately, this reaction gives only linear products which thus lack any conformational constriction. Strategies exist, however, to introduce a constraint (and/or extended functionality) following the Ugi-4CR step, including the Ugi Deprotection-Cyclisation (UDC) approach,[19] in which a nucleophilic moiety in the molecule is deprotected to allow subsequent cyclisation, or the Ugi Activation-Cyclisation (UAC) sequence, in which an electrophilic moiety can be activated

for cyclisation.[20] In the literature, several other varieties of elegant MCR-post-condensation modifications have been described. These include Ugi/Diels-Alder,[21] Ugi/Buchwald–Hartwig,[22] Ugi/Heck,[23] Ugi/nucleophilic additions/substitutions,[24] Ugi/ring-closing metathesis,[25] Ugi/Aldol,[26] Ugi/Pictet-Spengler[27], and Ugi/Click[28] methodologies. The current work presents a point of diversion from other Ugi post-condensation modifications involving triazoles[22] in that the 'click'-reaction between alkyne and azide groups in the molecule occurs between two pendant side chains, rather than at either peptide *N*- or *C*-termini, or somewhere along the peptide backbone as an isosteric replacement for a central amide group.

Recently, we have reported the first preparation of amino-triazolodiazepine (Ata) scaffolds as constrained histidine mimics through both key intra- and intermolecular Huisgen cycloaddition reactions (Scheme 1a).[29] As a continuation of our studies into isocyanide-based MCRs, we envisaged that 4-aminotriazolo-azepinones could also be synthesised via an Ugi-4CR followed by a thermal [3+2] Huisgen cycloaddition.[30] As an alternative to the methodology described above, our synthetic approach to synthesize Ata-scaffold derivatives (herein dipeptides and tripeptides) is shown in Scheme 1b. The desired scaffolds could be accessed through a one-pot two-step sequence with high atom economy, a minimal number of synthetic steps and without additives, catalysts or the requirement for UDC/UAC-like chemistry.[18,27] This methodology offers several advantages over the previous work, including an appreciable increase in isolated yield (39-94% cf. 10-40% in the original work)[29] and a reduction in the number of required synthetic steps .



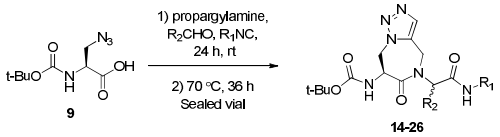
Scheme 1 - Synthetic strategies towards Ata scaffolds using previous and current methodology

In this paper we report the development of a new method towards di- and tripeptides containing 4-aminotriazolo-azepinone derivatives by condensation of Boc-protected 2-amino-3-azidopropanoic acid **9** and propargylamine with different isocyanides and aldehydes, to generate a 16-member library of 4-aminotriazolodiazepinone derivatives. 2-Amino-3-azidopropanoic acid **12** was synthesised by a reported procedure from Boc-diaminopropionic acid.[31] Recently published and optimised conditions were used to afford Ugi-3CR products of type **7**. These conditions also proved to be optimal for the current strategy.[15]

By using equimolar equivalents of the Ugi-4CR components in methanol (0.1 M) at room temperature, we were able to observe total conversion to the linear Ugi-compounds **13** in all cases. We also observed traces of the cyclic products **14-26** already pre-formed before heating. Performing this reaction in a sealed vial allowed the one-pot cyclisation by thermal, catalyst-free Huisgen cycloaddition. An optimal heating time of 36 hours was used in all but one case, **23**, where 48 hours were required for total conversion. Usually, there was a difference in HPLC retention time of around 1 minute between the open-chain Ugi-products (**13**) and cyclic products (**14-26**), which facilitated the determination of reaction completion.

Herein, the first explored point of diversification (R_1, Table 1) originated from the isocyanide component, in which we tested both aliphatic and aromatic isocyanides (Table 1, Entries **14-16**). Gratifyingly, all three compounds were synthesised in good to excellent yields. The *t*-butyl isocyanide (Entry **14**), giving the highest yield of the three at 94%, was chosen as the constant isocyanide for the exploration of possible aldehyde diversity (Entries **17-26**). A larger array of aldehydes was tested in a next step as the aldehyde functionality corresponds to the side chain of the second amino acid in these dipeptide-like structures. When examining the possible scope of aldehydes, we were pleased to observe that aromatic and heteroaromatic aldehydes were well tolerated and had no significant influence on the yield of the reaction. The products were obtained with good to excellent yields for the majority of compounds, as high as 93% for entry **26**. Aliphatic aldehydes (Entries **20** and **21**), however, gave lower isolated yields, despite conversion rates which were comparable to the ones of other aldehydes. The low yield observed when using 3'-indolyl carbaldehyde, to give **18**, can be explained in terms of its polarity and ensuing problems with purification. The difference in substitution patterns of aromatic aldehydes (e.g. **24** and **26**) and their size (e.g. **14** and **23**) had no appreciable influence on the yield and diastereoselectivity obtained in these reactions.

Table 1 – Substrate Scope for the creation of Ata-dipeptides by Ugi-4CR



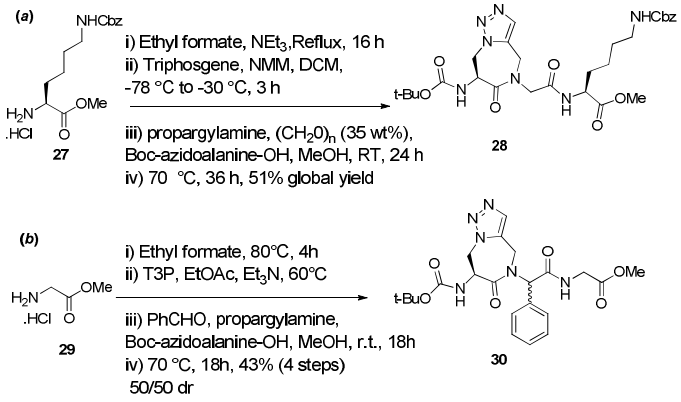
	Substrates		Product	
Comp	**R_1**	**R_2**	**Yield[a]**	**d.r.[b]**
14	t-Butyl	phenyl	94%	55/45
15	Cyclohexyl	phenyl	78%	50/50
16	Benzyl	phenyl	76%	50/50
17	t-Butyl	4'-bromophenyl	74%	53/47
18	t-Butyl	3'-indolyl	41%	58/42
19	t-Butyl	4-dimethylaminophenyl	74%	52/48
20	t-Butyl	methyl	54%[c]	51/49
21	t-Butyl	cyclohexyl	39%	64/36
22	t-Butyl	piperonyl	67%	55/45
23	t-butyl	3'-naphthyl	69%	53/47
24	t-Butyl	*m*-tolyl	75%	51/49
25	t-Butyl	4'-pyridyl	85%	54/46
26	t-Butyl	*o*-tolyl	93%	52/48

[a] isolated yield
[b] d.r. was determined by ^{1}H-NMR for all compounds except **15**, **17, 19, 21, 22** and **25** which were determined by integration of HPLC peak areas.
[c] overall yield indicated in the table; diastereoisomers were separated by preparative-HPLC giving 26% and 28%; separately analysed.

Seven of the compounds mimic (natural) amino acids either directly, such as **20** for Ala, or indirectly, **14-16** for Phe, **18** for Trp, **21** for cyclohexylalanine and **23** for 2'-naphthylalanine. Compound **17** also allows further functionalisation via palladium-catalysed couplings. For all compounds, except **18** and **19**, only one peak was

observed in the HPLC trace, but the production of two diastereomers was confirmed by ^{1}H-NMR.

In a next step, the generation of amino acid-derived isocyanides for use in these reactions became of interest, since they would generate *N*-Boc protected tripeptide esters (Scheme 2). Starting from Cbz-protected lysine methyl ester **27** (Scheme 2a), formylation via a reported method,[32] gave the desired intermediate in quantitative yield. The *N*-formyl group is dehydrated to an isocyano group using triphosgene, to present an intermediate isocyanide (not shown) without racemisation of the stereogenic centre.[33] Following a subsequent Ugi-4CR, tripeptide **28** was obtained in 51% yield as a single diastereoisomer. Work towards the incorporation of other, amino acids in to such tripeptides led to **30** (Scheme 3a), which was synthesised from the glycine methyl ester derived isocyanide **29**. In this case, the absence of a chiral centre in glycine removed the requirement for racemization-free dehydration conditions and propylphosphonic anhydride (T3P) was therefore used instead.[34] Product **30** was isolated in good yield (43% over four steps; *d.r.* 50/50).



Scheme 2 – Incorporation of amino acid-derived isocyanides into Ugi-4CRs to generate tripeptide esters.

In conclusion we have described an efficient synthesis of di- and tripeptides containing the 4-aminotriazolodiazepinone (Ata) constrained amino acid. The desired bicyclic scaffolds are formed in moderate to good yields through catalyst-free conditions and using simple experimental procedures. Since we previously showed that the Ata building block could serve as a histidine mimetic,[29] the structural complexity, facility of synthesis, and the variation in substitution patterns present in these molecules will allow their use in various His-containing bioactive peptides. Moreover, the application of other commercially available or synthetically accessible azido-alpha amino acids in the current methodology is ongoing and will be reported in due course.

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