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With unprotected amino acids to tetrazolo peptidomimetics†

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Here we describe the direct usage of C,N-unprotected amino acids in Ugi-tetrazole reactions to produce a novel class of acid-tetrazole compounds. Surprisingly, only the tetrazole Ugi product is found and not traces of other possible Ugi type reactions. Based on this reaction pathway we have designed the synthesis of novel tetrazole-peptidomimetics. A high level of structural diversity can be achieved using this isocyanide based multicomponent reaction (IMCR), providing a platform for the production of functionalized building blocks for novel bioactive molecules and nontraditional scaffolds which previously were not accessible.

There have been enormous developments in both the Ugi- and Ugi-tetrazole reactions since 1959, which provide a general route to diverse peptides, peptidomimetics and other complex molecules.¹ In multicomponent reactions (MCRs), isocyanide based multicomponent reactions (IMCRs) are highly convergent processes which have had a great impact in pharmaceutical and drug discovery research.² Although IMCRs have proven to be a solution for many common problems in synthetic chemistry such as diversity, complexity and harsh conditions, novel scaffolds, for example, by the use of bi-functional substrates, are of high interest.³

N-Substituted amino acids are interesting scaffolds as their parent amino acids play a key role in biochemistry and are the structural units of peptides, proteins and enzymes. Moreover protected amino acid derived Ugi/Ugi-tetrazole products can efficiently act as biomimetics undergoing competing interactions at the active site of enzymes and cell receptors. In 1996, Ugi reported the use of α -amino acids as bifunctional educts in the Ugi-5-center-4-component reaction (U-5C-4CR) instead of the amine and acid components in the familiar Ugi-4-component reaction (U-4CR).⁴ Later on, very effective variations of the Ugi-reaction were reported by using amino acids as one of the

starting components.⁵ Yudin *et al.*, Orru *et al.* and Paixão *et al.* have shown the great impact of the direct use of amino acids in Ugi-type reactions.^{5c,d,h} Our group also reported a “truly” four-component reaction for the synthesis of iminodicarboxamides by employing amino acids directly in an U-5C-4CR.^{5e} In 2013, Lämmerhofer *et al.* reported the synthesis of phosphopeptidomimetics by utilizing aminophosphonic acids in U-5C-4CR.^{5g} Even though unprotected amino acids and aminophosphonic acids are utilized in various Ugi-type reactions, to the best of our knowledge, this is the first study on the use of unprotected amino acids in the Ugi-tetrazole reaction (Scheme 1).

This finding is of importance since tetrazole is a known bioisostere of carboxylic acid with often superior pharmacokinetic/pharmacodynamic (PKPD) properties.⁶ Although the Ugi tetrazole

Scheme 1 Reported direct use of amino acids in Ugi-type reactions and our methodology.

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reaction has been developed tremendously in recent years, the use of unprotected amino acids is unprecedented and surprising.⁷

Therefore we report herein a mild and efficient technology for the synthesis of highly substituted N,C-unprotected but N-substituted acid-tetrazoles **4** and peptido-tetrazoles **6** using Ugi-tetrazole/Ugi reactions from natural N,C-unprotected amino acids, di and tripeptides and commercially available aldehydes/ketones, amines and isocyanides [Scheme 1b]. In continuation of our previous tetrazole work, we decided to explore the direct usage of amino acids in the Ugi-tetrazole reaction.⁸ We expected that the reaction of L-proline **1a** with paraformaldehyde **2a**, benzyl isocyanide **3a** and sodium azide would lead to the Ugi-tetrazole (**4a**) or U-5C-4CR or U-4CR product, all in principle are possible reaction pathways for these reactants. Initial attempts in DCM interestingly furnished the Ugi-tetrazole product (**4a**) without any other possible by-products, however in only 15% yield, with the remainder being recovered as the starting materials. A subsequent solvent optimization exercise of this amino acid based Ugi-tetrazole reaction is summarized in Table 1.

We started optimization by screening different solvents for the Ugi-tetrazole reaction of 1.0 equivalent of L-proline, 1.0 equivalent of paraformaldehyde, 1.0 equivalent of benzyl isocyanide **3a** and 1.2 equivalents of sodium azide. As expected, non-polar solvents and polar-aprotic solvents gave us very poor yield of the Ugi-tetrazole product due to the low solubility of the starting materials. Interestingly, polar-protic solvents like trifluoroethanol (TFE) and isopropanol gave only 35% and 20% yields of the Ugi-tetrazole product **4a**, respectively. Similar related reactions of C,N-unprotected dipeptides toward diketopiperazine *via* the Ugi reaction explicitly require the protic polar solvent TFE. When we used methanol as a solvent, it furnished the desired product in 78% yield after 12 h. We also tested zinc chloride as a Lewis-acid catalyst (10 mol%) but without any increase of the yield. When we

used methanol and water in a 5 : 1 ratio, the Ugi-tetrazole product was furnished in 71% yield after 12 h. Thus 1.0 equivalent of amino acid, 1.0 equivalent of aldehyde, 1.0 equivalent of isocyanide and 1.2 equivalents of sodium azide in 1.0 M of methanol or methanol:H₂O (5 : 1) for 12 h was the optimized conditions for the Ugi-tetrazole reaction.

With the optimized reaction conditions in hand, the scope of the “Ugi-tetrazole” reaction was further investigated by reacting a library of natural/unnatural α -amino acids, β -amino acids and γ/ω -amino acids with different aldehydes, isocyanides and sodium azide in methanol or a methanol:H₂O (5 : 1) solvent system to furnish an amino acid-tetrazole library **4b–p**. All the substrates **1**, **2** and **3** furnished the expected Ugi-tetrazole products **4b–p** in 27–74% yields, almost irrespective of the electronic and steric factors of the substituents present. L-Proline reacted with paraformaldehyde **2a** and glycine methyl ester isocyanide **3b** to furnish the expected Ugi-tetrazole product **4b** in 74% yield (see Table 2). Similarly, L-alanine, L-phenylalanine, 4-hydroxy-L-proline, L-isoleucine, L-valine, glycine, L-tyrosine, L-methionine and L-selenomethionine also furnished the Ugi-tetrazole products in good yields as diastereomeric mixtures. Interestingly histidine is also a valid substrate with modest yield (27% **4k**). Surprisingly, higher non α -amino acids worked as well. Thus, the reaction of β -alanine with piperonal and phenylethyl isocyanide also furnished the expected Ugi-tetrazole product **4n** in 48% yield with very low yield of the Ugi side product (β -lactam, only observed in MS, not isolatable). Next, γ -aminobutyric acid was reacted with 2-methoxy benzaldehyde and *tert*-butyl isocyanide furnishing the Ugi-tetrazole product **4o** in good 53% yield. ω -Aminovaleric acid is also a valid substrate in this reaction, and it produces the tetrazole product **4p** in 66% yield with great purity.

After synthesizing a library of acid-tetrazoles in an Ugi-tetrazole reaction, we further transformed them into biologically important peptidomimetics **6** through another Ugi-4CR. The reaction of the acid-tetrazole product **4b** with 1.0 equivalent of paraformaldehyde, 1.0 equivalent *tert*-butyl isocyanide and 1.0 equivalent of 2-(4-chlorophenyl)ethanamine in methanol at room temperature for 24 h furnished the Ugi-product **6a** in 50% yield. This compound **6** has a unique and defined structure which consists of an amino acid inside the chain, a small peptidomimetic chain but with potentially enhanced stability or biological activity and at the end a tetrazole unit which is a bioisostere for *cis*-amide groups. This interesting structural unit in one molecule was achieved only two synthetic steps. In a similar manner, the selective two-step sequential Ugi-tetrazole/Ugi-reaction strategy was demonstrated with five more substrates in good overall yields (see Table 2; **6b–f**). Finally, we investigated the synthetic utility of this methodology by reacting the N,C-unprotected dipeptide Gly-Gly and tripeptide Gly-Gly-Gly. To our great delight, these reactions also worked accordingly and afforded the products **4p** and **4q** in 69% and 58% yields, respectively (see Scheme 2).

A plausible mechanism of this Ugi-tetrazole reaction is shown in Scheme 3 and it involves Schiff base formation, which leads to the intermediate nitrilium ion after the addition of isocyanide, followed by azide attack, and a final irreversible sigmatropic rearrangement to the tetrazole product.⁹ In the case

Table 1 Optimization for the Ugi-tetrazole reaction of L-proline^{a,b}

S. no.	Solvent (1.0 M)	Time (h)	Yield (%)
1	THF	12	<10
2	DCM	12	15
3	CH ₃ CN	12	<10
4	Toluene	12	10
5	TFE	12	35
6	Isopropanol	12	20
7	MeOH	12	78
8	MeOH + H ₂ O (1 : 1)	12	61
9	MeOH + H ₂ O (1 : 1) at 50 °C	12	50
10	MeOH + H ₂ O (5 : 1)	12	71
11	MeOH + ZnCl ₂	12	50
12	H ₂ O	12	50

^a The reactions were run using **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol) and NaN₃ (1.2 mmol) in the indicated solvent for 12 h.

^b Isolated yield.

Table 2 Two MCRs on one substrate; scope and limitations^{a,b,c,d}

^a Ugi-tetrazole reaction was carried out in MeOH or MeOH:H₂O (5:1) (1.0 M) with 1.0 equiv. of amino acid 1 relative to aldehyde 2, isocyanide 3 and 1.2 equiv. of NaN₃ at 25 °C for 12 h. ^b Ugi-reactions were carried out in MeOH (1.0 M) with 1.0 equiv. of aldehyde 2, amine 5 after 10 min of addition of 1.0 equiv. of acid-tetrazole 4 and isocyanide 3 (1.0 equiv.) at 25 °C and stirred for 24 h. ^c Yield refers to the column-purified product. ^d dr was determined by NMR analysis. ^e Reaction was carried out in MeOH:H₂O (5:1)(1.0 M).

of amino acids, the Ugi-tetrazole reaction may also proceed through pathway B, there after the addition of isocyanide 3 to the Schiff base, an *O*-acylamide (II) is formed. Due to the

Scheme 2 Di- and tripeptides in the Ugi-tetrazole reaction.

Scheme 3 Anticipated mechanistic pathways.

nucleophilic attack of the azide at the isocyanide carbon, it leads to the original intermediate (III) of the Ugi-tetrazole reaction and the subsequent rearrangement leads to the acid-tetrazole product 4.

We have performed an appropriate control experiment to investigate the competitive nature of azide anions in the Ugi-tetrazole reaction with C,N-unprotected amino acids as shown in Scheme 4. In the presence of sodium azide and an external acid (propionic acid) along with 2-amino-2-methylpropanoic acid, cyclopropanecarbaldehyde and benzyl isocyanide under standardized reaction conditions, after 12 h, we have carefully examined the NMR and ESI-HRMS spectra of the crude reaction mixture (see ESI[†]). As expected, the crude NMR spectrum and the ESI-HRMS experiment showed the major Ugi-tetrazole product (4d) along with a trace amount of the Ugi-product (7). These results indicate that the three different Ugi products are formed in substantial kinetic difference 4d >> 7 > 8.

Chemistry at its best, the 'Lego' approach is a great advantage of MCR to afford outstanding scaffold diversity. Here, we have identified a novel 'Lego-like' approach towards the synthesis of substituted amino acid-tetrazoles and tetrazole-peptidomimetics. This robust and air- and moisture-tolerant procedure is a valuable addition to MCR chemistry and expands the substrate scope to include amino acids, peptide like chains and 1,5-disubstituted tetrazoles in one molecule.

Scheme 4 Investigation of the competitive nature of the azide anion.

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