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# 'Atypical Ugi' tetrazoles†

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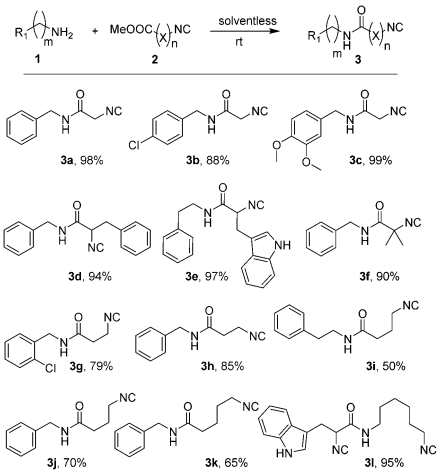
**Amino acid-derived isocyano amides together with $TMSN_3$, oxo-components and 1° or 2° amines are common substrates in the Ugi tetrazole reaction. We surprisingly found that combining these substrates gives two different constitutional isomeric Ugi products A and B. A is the expected classical Ugi product whereas B is an isomeric product ('atypical Ugi') of the same molecular weight with the tetrazole heterocycle migrated to a different position. We synthesized, separated and characterized 22 different isomorphic examples of the two constitutional isomers of the Ugi reaction to unambiguously prove the formation of A and B. Mechanistic studies resulted in a proposed mechanism for the concomitant formation of A and B.**

1,5-Disubstituted tetrazoles are well-known bioisosteres of carboxylic acids and *cis*-amides and thus widely used in chemical biology and medicinal chemistry.[1] One of the most competitive synthetic pathways towards this important scaffold is the Ugi tetrazole reaction (Scheme 1).[2] Recently, we introduced a straightforward way for the synthesis of α-, β- and higher amino acid-derived isocyano amides.[3] Isocyano acetamides are very versatile building blocks and have been used in Ugi and Passerini multicomponent reactions as well as in heterocycle syntheses, for example for the synthesis of tetrazoles,[4] imidazoles,[5] iminohydantoins,[6] oxazoles[7] and for the production of functional materials such as giant vesicles,[8] PEGylated polymers,[9] proline-like β-turn mimics,[10] functional β-sheet mimics,[11] tryptase and FXa inhibitors,[12] inhibitors of hepatitis C virus NS3 protease,[13] Src-family kinase p56Lck inhibitors,[14]




Scheme 1 Structures and yields of isocyano amides synthesized and used in this study.

erythropoietin mimicking small molecules,[15] selenopeptido mimetics,[16] hydrogels,[17] polyisocyanides for bioscaffolding,[18] peptide ligations,[19] polyamines,[20] spirocycles,[21] functionalized fullerenes,[22] natural product sandramycin,[23] dendrimers[24] and artificial macrocycles[25] (Fig. 1). The chemistry of isocyanoacetate and derivatives has been recently comprehensively reviewed.[26] In an ongoing effort to synthesize diversely substituted macrocycles using isocyanide based multicomponent reactions (IMCR), we reported the first time use of the Ugi tetrazole variation for macrocyclic ring closure using amino acid derived isocyanides.[27]

During analysis of several X-ray structures of tetrazole products including macrocycles, we noted beside the formation of the expected classical tetrazole products, the formation of constitutional isomeric Ugi products in considerable amounts where the tetrazole heterocycle was formally migrated from the isocyanide position to the amide position introduced by the amino acid-derived isocyano amide (Fig. 2). Surprised by the unexpected formation of the atypical isomer we investigated the reaction more thoroughly and want to report here synthesis

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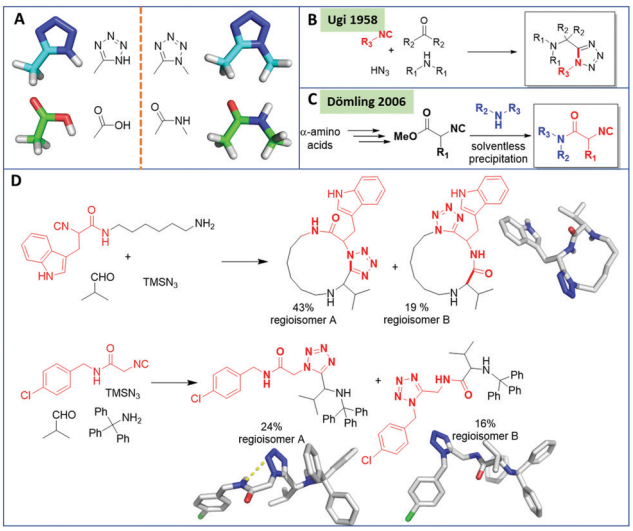


Fig. 1 Bioisostery of 1,5-disubstituted tetrazoles (A), tetrazole Ugi reaction (B), isocyanoacetamide synthesis (C). Herein reported: surprising finding of two constitutional Ugi tetrazole isomers (D).

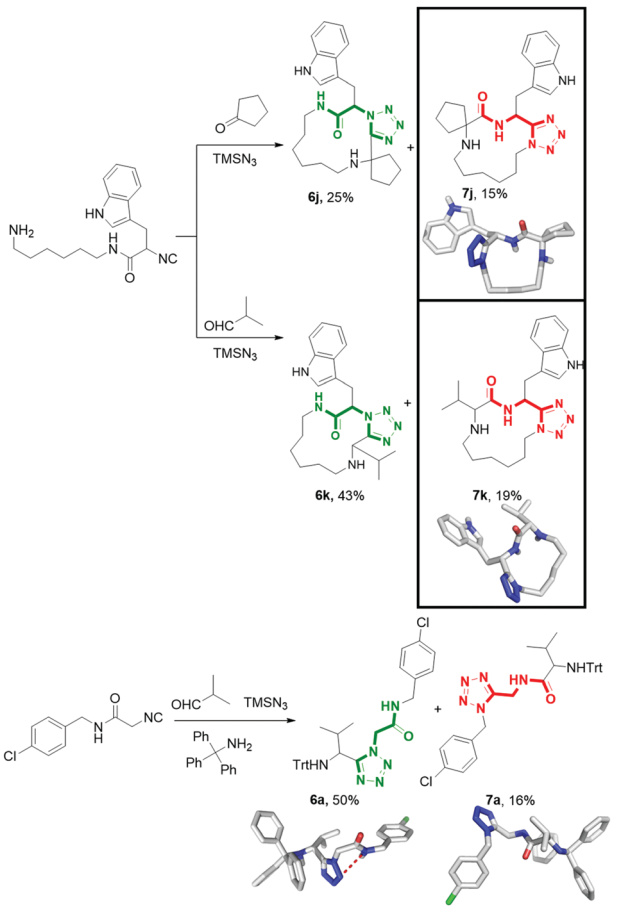


Fig. 2 Observation of the 'atypical Ugi' tetrazole products besides expected products, highlighted as red and green bolded structures respectively and X-ray structures. In **6a** the red dotted line indicates an intramolecular hydrogen bond (Trt = trityl).

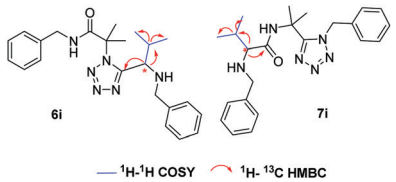


Fig. 3 $^{1}H-^{1}H$ COSY and $^{1}H-^{13}C$ HMBC correlations to differentiate between compounds **6i** and **7i**.

and separation of 22 compounds, analytical and structural evidence for the formation of both isomers, and a mechanistic proposal.

We thoroughly investigated the structural influence of the substrates and reaction conditions on the ratio of A/B. Numerous examples were characterized by different means, $^{1}$H-NMR, $^{13}$C-NMR, 2D COSY and HMBC, for example in Fig. 3 the key proton which is labeled by star * correlates to 157.5 ppm (tetrazole-C) in compound **6i** and correlates to 173.7 ppm (carbonyl-C) in compound **7i** (ESI†). Also, multiple compounds were characterized by unambiguous X-ray structure analyses.

The dependency of the formation of A and B on the α-amino acid isocyanide was investigated with glycine, phenylalanine, tryptophan and valine. Thus, we synthesized several different amino acid-derived isocyanides as their amides, by simply mixing the amine and isocyanoester under solvent-free conditions and generally could obtain the isocyanoamides in good to excellent yields (Scheme 1). However, no influence of the amino acid side chain towards A/B selectivity was observed. Isocyanoamides are α-acidic and the p$K_a$ of an amide is 2–4 units lower than the corresponding ester.[26] Moreover, anionic α-isocyanides are important intermediates in several heterocycle formations such as oxazoles or oxazolidines.[28] To investigate the potential involvement of such isocyano carbaniones we reacted blocked α,α-dimethyl isocyanoacetamide **3f**. However, even with this isocyanide, unable to form carbanions, the formation of A and B was observed. Thus, an isocyano carbanion-based mechanism could be ruled out.

More elucidating was the investigation of the dependency on the distance between the isocyanide and the amide group, *e.g.* derived from α-, β-, γ-amino acids. As shown above, all α-amino acid derived isocyanoacetamides **3a–3f** gave mixtures of A and B (Scheme 2). Also, β-amino acid β-alanine-derived isocyanide **3g** and **3h** gave A and B, although only small amounts of B were formed (Scheme 3). Even more pronounced with γ-amino acid derived **3i** and **3j** and with δ-amino acid derived **3k** no B could be detected anymore by SFC analysis of the crude reaction. Thus, a clear dependence of the A/B ratio on the distance between the amide group and the isocyanide was established.

Next, we investigated the formation of A and B in dependency of the azide source. In the original description of the tetrazole multicomponent reaction, Ugi used stock solutions of hydrogen azide in benzene or alternatively amine hydrochloride together with sodium azide. Later, TMS-azide was introduced as a safe *in situ* hydrogen azide which now completely superseded the isolation of the toxic and explosive hydrogen azide.

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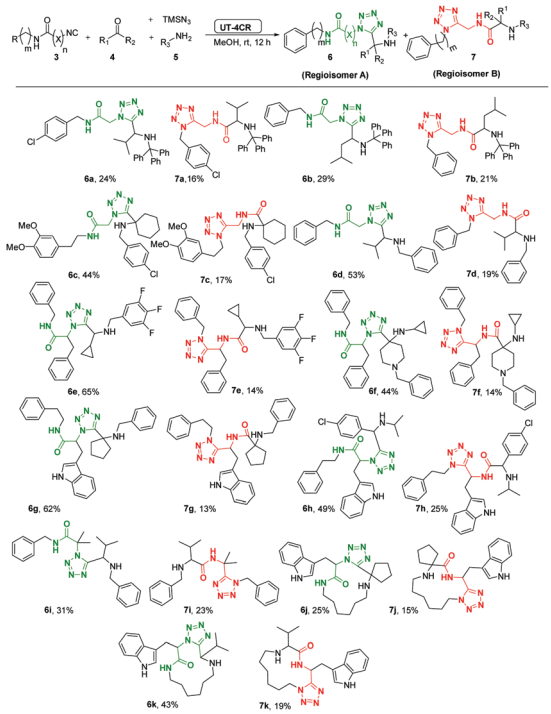
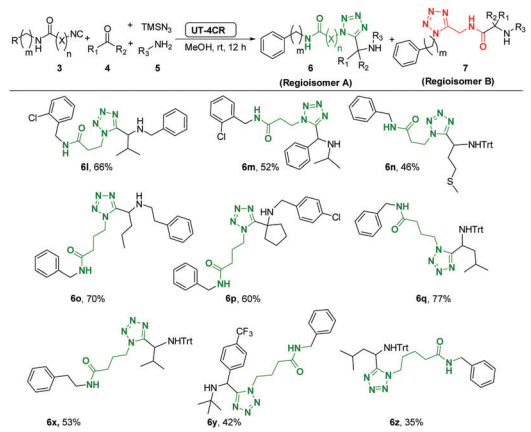



Scheme 2 'Crazy Ugi' tetrazole products beside expected products from α-amino acid derived isocyanoacetamides, highlighted as red and green bolded structures respectively.




Scheme 3 Tetrazole products from β- and γ-amino acid derived isocyanoacetamides, highlighted as red and green bolded structures respectively (Trt = trityl).

Unfortunately, no difference in A to B ratio was observed using different azide sources.

The formation of A and B dependent on the reaction temperature was investigated by SFC-MS as shown in Fig. S1 in the ESI.† The change of the temperature of the reaction from room temperature to 0 °C and −10 °C showed a slight increase in the formation of the minor product B. Thus we speculate that the minor product is the thermodynamic product, however it did not greatly change the overall distribution of the major/minor product. Several X-ray structures of the two products A and B involving different substituents provide unambiguous

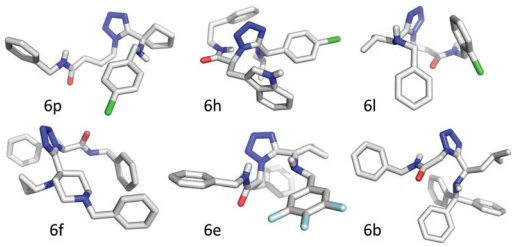
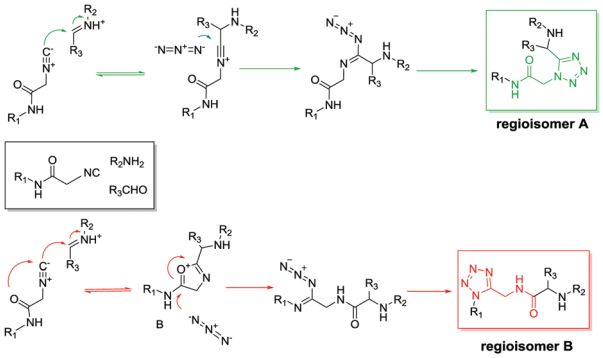



Fig. 4 X-ray structures for some 'normal' Ugi tetrazole products.

proof of the formation and give some first insight into possible solid-state conformations (Fig. 2 and Fig. 4). The plausible mechanism of the reaction is shown in Scheme 4. It is conceivable that initially the condensation of the oxo-component and amino group affords the Schiff base. Then, nucleophilic addition of carbenoid C atom of the isocyanide onto the iminium group followed by the addition of the azide anion onto the C atom of the nitrilium ion and 1,5-dipolar electrocyclization leads to the formation of regioisomer **A**. On the other hand, the nucleophilic addition of carbenoid C atom of the isocyanide onto the iminium group with the addition of the O atom of amide group onto the C atom of the nitrilium ion formed oxazolidine intermediate which followed by the addition of the azide anion leads to the formation of regioisomer **B**.

Similar oxazolidine intermediates were also previously postulated in a macrocyclization and peptide formation.[29] In conclusion, we report for the first time a competing Ugi tetrazole reaction with commonly used isocyanoamides as substrates. We investigated in detail the reaction by performing many different substrate combinations, reaction conditions, reagent conditions and standard chemical analyses and multiple crystal structures. Based on our results and literature analysis we propose a competing mechanism which is based on an intramolecular carbonyl oxygen attack to the isocyanide and addition to the imine *via* a five- or six-membered intermediate. This α-adduct intermediate preferentially reacts with the azide ion to ultimately cyclize to the 'atypical Ugi' product. The knowledge of this side reaction in the context of the Ugi tetrazole reaction is of high importance since it is an often-used reaction in the chemical community.




Scheme 4 Proposed mechanistic explanation of the formation of the two tetrazole isomers.

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## Conflicts of interest

There are no conflicts to declare.

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