Library-to-Library Synthesis of Highly Substituted α-Aminomethyl Tetrazoles via Ugi Reaction

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Supporting Information

ABSTRACT: α-Aminomethyl tetrazoles, recently made accessible by an Ugi multicomponent reaction (MCR), were shown to be excellent starting materials for a further Ugi MCR, yielding substituted N-methyl-2-(((1-methyl-1H-tetrazol-5-yl)methyl)amino)acetamides having four points of diversity in a library-to-library approach. The scope and limitations of the two-step sequence was explored by conducting more than 50 reactions. Irrespective of electron-rich and electron-deficient oxo-components and the nature of the isocyanide component, the reactions give excellent yields. Sterically less hindered α-aminomethyl tetrazoles give better yields of in further Ugi MCR. The target scaffold has four points of diversity and is finding applications to fill screening decks for high-throughput screening (HTS) in the European Lead Factory and in structure-based drug design.

KEYWORDS: Ugi reaction, library-to-library approach, high-throughput screening, structure-based drug design, European Lead factory

High-throughput screening (HTS) often yields poor or no results for difficult post-genomic targets, such as protein–protein interactions. One potential reason is the overpopulation of certain types of molecular shapes in many pharmaceutical screening libraries, which are often based on the preferential use of certain reactions, such as Suzuki–Miyaura and Buchwald–Hartwig coupling processes. In other words, libraries are often designed with synthetic chemistry in mind rather than oriented toward targets and properties.1 Library generation employs familiar steps incorporating easy-to-functionalize groups (e.g., amine, OH, −CHO) addressed with standard commercial reagents (e.g., acid chlorides, boronic acids, sulfonyl chlorides). Multicomponent reaction chemistry different from this standard library approach in that MCRs build complex scaffolds in one step after which no further functionalization is needed or performed.2 We focus here on the tetrazole functional group, a metabolically stable and drug-like fragment accessible by MCR but largely underrepresented in screening libraries. Some MCR-prepared tetrazole scaffolds are shown in Scheme 1 and have been recently reviewed.3−19

We have recently introduced a Ugi tetrazole variation in which ammonia can be used as an amine component and α-aminomethyl tetrazoles are formed in good yields and diversity.20 To take advantage of the large scope of the reaction, we decided to use the products of the Ugi tetrazole reaction as educts in another Ugi-3CR (Scheme 2), thus perusing a library-to-library approach.

α-Amino monosubstituted methyl tetrazoles can be obtained from aldehydes, whereas α-amino disubstituted methyl tetrazoles are derived from ketones.20,21 To initiate the study, we scaled up few α-amino mono or disubstituted methyl tetrazoles with selected aldehydes and ketone (Table 1). These reactions proceeded at 10−25 mmol scale in the same manner as the previously reported
Next, we investigated combinations of bulky α,α-disubstituted methylenes with N-tetrazolyl side chains, such as phenylethyl, benzyl, and cyclohexyl groups (Table 3, entry 45–52). Surprisingly, excellent results were also obtained in these cases (Table 3, entries 41–44).

The same reaction strategy was also applied to N-H-tetrazolo-5-methylamines,25,26 analogously to the report of Ley et al.27 (Scheme 3a) but no product could be isolated. However, we could synthesize a similar product (5) by acidic cleavage of the N-tet-octyl group of the intermediate Ugi adducts (14d). Usage of 6N aqueous hydrochloric acid and stirring overnight accomplished the product 5 in excellent yield (Scheme 3b).
With these overall results, we propose a plausible reaction mechanism (Scheme 4). Accordingly, the reaction proceeds with N-alkyl tetrazolo-5-methylamines to form an imine (I-1), with loss of one equivalent of water. Protonation with p-toluenesulfonic acid activates the imine to yield the iminium ion (I-2), which then undergoes nucleophilic addition to the isocyanide (C) to give the intermediate nitrilium ion species (I-4). The nucleophilic trapping of this intermediate by the p-toluenesulfonate counteranion affords the p-toluenesulfonic imidoyl species (I-5). The final step is a Mumm rearrangement with the transfer of the p-toluenesulfonate group (I-3) from the oxygen atom to the nitrogen atom of the former amine (Scheme 4) to form p-toluenesulfonic amide (I-6, pathway A). Since p-toluenesulfonate is a good leaving group, it is replaced by the nucleophile water which was generated during the imine formation process. Alternatively, water attacks
Scheme 4. Plausible Reaction Mechanism

In summary, we introduced a powerful library-to-library approach which can potentially span a large chemical space with four elements of diversity introduced by common building blocks, such as isocyanides and oxo components. A detailed analysis of the scope and limitations shows a great diversity of carbonyl components (including electron-rich and electron-deficient aldehydes, cyclic and acyclic ketones) to give mostly good to excellent yields, irrespective of the nature of the isocyanide component. Sterically less hindered N-alkyl tetrazolo-5-α,N-unsubstituted methyamines gave significantly better yields compared to N-alkyl tetrazolo-5-α,N-disubstituted methyamines. The scaffold is currently used in the European Lead Factory to enhance the screening deck. Moreover, efforts are ongoing to explore this rich and novel chemical space for islands of biological activity.

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**Notes**  
The authors declare no competing financial interest.

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