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

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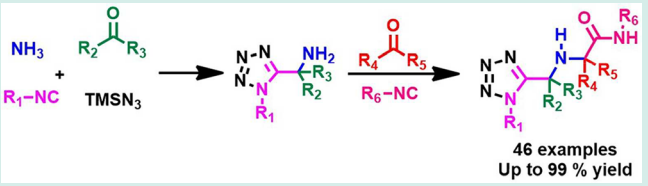
Supporting Information

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-1*H*-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.



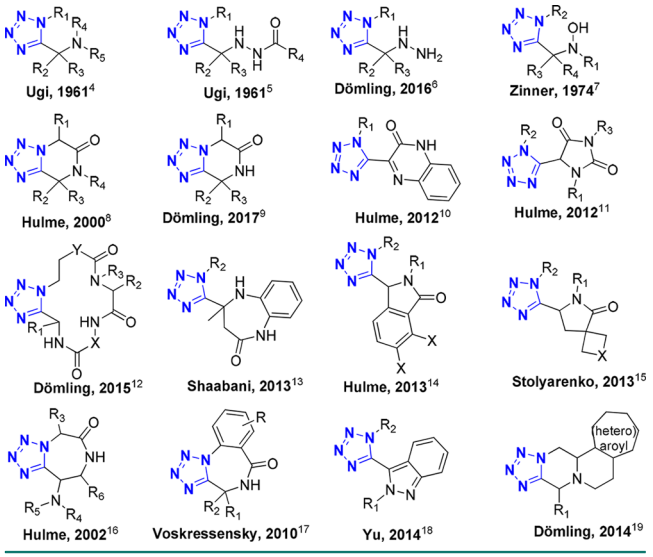
KEYWORDS: *Ugi reaction, library-to-library approach, high-throughput screening, structure-based drug design, European Lead factory*

High-throughput screening (HTS) often yields poor or no results for difficult post-genomic targets, such 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

Scheme 1. Sixteen Recently Disclosed Mono-, Bi-, Tri-, and Macrocyclic Tetrazole Scaffolds Accessible via Multicomponent Reactions



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

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Scheme 2. Ugi-3CR Reaction Presented Herein

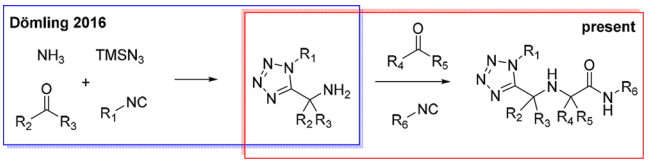
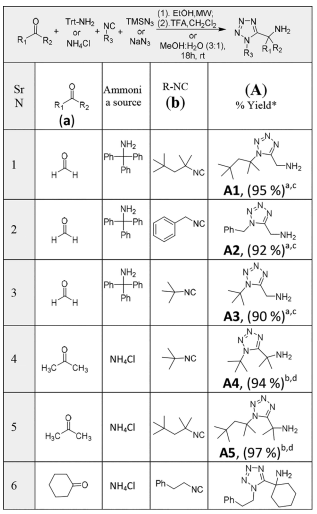


Table 1. Scale-up Synthesis of α-Aminomethyl Tetrazoles



Sr N	(a)	Ammonia source	R-NC (b)	(A) % Yield*
1				**A1**, (95 %)[a,c]
2				**A2**, (92 %)[a,c]
3				**A3**, (90 %)[a,c]
4		NH_4Cl		**A4**, (94 %)[b,d]
5		NH_4Cl		**A5**, (97 %)[b,d]
6		NH_4Cl		
7		NH_4Cl		**A7**, (82 %)[b,d]
8		NH_4Cl		**A8**, (77 %)[b,d]
9		NH_4Cl		**A9**, (74 %)[b,c]
10		NH_4Cl		**A6**, (90 %)[bd] **A10** (50%)[b,c]

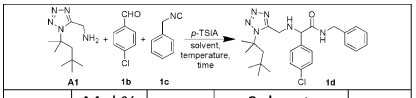
*Isolated yield. [a]Synthesized according to the method reported in ref 21. [b]Synthesized according to the method reported in ref 20. [c]Reaction run in 10 mmol scale. [d]Reaction run at 25 mmol scale.

1−2 mmol scale under identical reaction conditions (entry 1−10, Table 1).

For the optimization of the reaction conditions, we tested the Ugi three-component reaction (U-3CR) of *tert*-octyltetrazolo-5-methylamine (**A1**), *p*-chlorobenzaldehyde (**1b**), and benzyl isocyanide (**1c**) with various Lewis acids, such as $Sc(OTf)_3$, $Al(OTf)_3$, $Cu(OTf)_3$, $Zn(OTf)_3$, $ZnCl_2$, $HClO_4$, $TiCl_4$, $ZrCl_4$, BCl_3, $B(OH)_3$, CH_3SO_3H, *p*-TSA in 10 to 20 mol % and HCl in methanol (1 equiv), in solvents, such as toluene, dichloromethane, and methanol. Disappointingly, all initial attempt failed to provide good yield of product **1d**. Then, we increasing the reaction time with various temperature combinations from room temperature to 55 °C, but again we did not obtain satisfactory product **1d** formation. Next, we following the procedures of List[22] and Li[23] and we tested this reaction with 10% phenyl phosphinic acid[22] in toluene and 20% *p*-toluenesulfinic acid (*p*-TSIA)[23] in methanol. Encouragingly, *p*-toluenesulfinic acid (20 mol %) in methanol stand out giving the desired product in moderate yield (**1d**, 40%). Thus, we selected *p*-TSIA to optimize the reaction conditions further with respect to solvent, temperature, reaction time and ratio of *p*-TSIA (Table 2).

We observed that rising the reaction temperature (entry 3, Table2) and using methanol−water as 9:1 mixture to promote this reaction (entry 4, Table 2), also did not improve the yield. By changing the solvent from methanol to dichloromethane we found only trace product formation (entry 5, Table 2). Finally, we decided to use *p*-TSIA in an (semi)stochiometric amounts (entry 6−8, Table 2). Surprisingly, we observed the stochiometric use of *p*-TSIA at room temperature gave the product **1d** in excellent 96% yield, while rising the temperature again resulted in lower yields.

Table 2. Optimize the Reaction Conditions with *p*-TSIA



Entry	Mol % of *p*-TSIA	Time (h)	Solvent, temperature (°C)	Yield (%)[a]
1	0	18	MeOH, rt	traces
2	20	18	MeOH, rt	40
3	20	48	MeOH, 55	35
4	20	18	MeOH: H_2O (9:1), rt	38
5	20	18	CH_2Cl_2, rt	traces
6	50	18	MeOH, rt	55
7	100	18	MeOH, rt	96[b]
8	100	18	MeOH, 55	65

[a]% yield confirmed by SFC-MS. [b]Isolated yield.

With these optimized reaction conditions in hand we initiated our study to explore the scope and limitations of the *N*-alkyl tetrazolo-5-methylamines (**A**), oxo components (**B**), and isocyanides (**C**) (Table 3).

First, the reaction of various oxo-components (aldehydes and ketones) and isocyanides with *N*-*tert*-octyl tetrazolo-5-methylamine (**A1**) as the amine component was studied (Table 3, entries 1−22). Aromatic, substituted aromatic and heterocyclic aldehydes, for example indole-3-carboxaldehyde (Table 3, **12b,** 73%) gave good yields (Table 3, entries 1−12). The electronic properties of aromatic aldehydes did not influence the yields of the reactions (Table 3, entry 4−11). Aliphatic aldehydes and ketones including sterically demanding cyclic ketones, similarly, gave excellent yields (Table 3, entries 13−22). Moreover, the reaction of **A3** with bulky 1-adamantyl isocyanide (**26c**) also gave good yield (**26d**, 71%). Use of hydrophilic 2-morpholinoethyl isocyanide resulted in lowering of the yield (**23d,** 63%), presumably due to loss of material during workup.

Furthermore, we extend the scope and limitation analysis toward the amine component using several other *N*-alkyl tetrazolo-5-α,α-disubstituted methylamines, such as **A4**−**A10** (Table 3, entries 28−52). For example, the gem-dimethyl moiety is frequently used to improve PKPD and target engagement properties of compounds.[24] Use of *N*-*tert*-butyl tetrazolo-5-α,α-dimethyl methylamine (**A4**) provided the product in 42−81% yields (Table 3, entry 28−36). Aromatic aldehydes gave excellent yields (Table 3, entry 33−35). When we used bulkier *N*-*tert*-octyl tetrazolo-5-α,α-dimethyl methylamine (**A5**), yields dropped as compared to *N*-*tert*-octyl tetrazolo-5-methylamine (**A1**). In this case, aromatic heterocyclic aldehydes failed to give any products (Table 3, entries 41−44).

Next, we investigated combinations of bulky α,α-disubstituted methylamines 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 45−52).

The same reaction strategy was also applied to *N*-*H*-tetrazolo-5-methylamine,[25,26] as 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*-*tert*-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).

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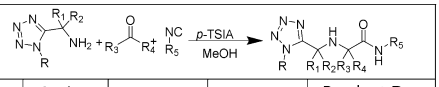
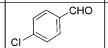
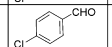
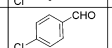
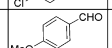
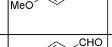
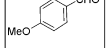
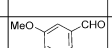
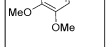
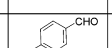
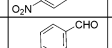
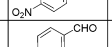
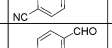
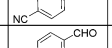
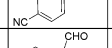
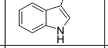
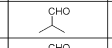
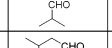
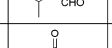
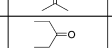
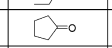
Table 3. Ugi-3CR of Different Amino Methyl Tetrazoles with Different Oxo Components and Isocyanides



sr	Amine A	Oxo comp. B	Isocyanide C	Product **D**, % Yield
1	**A1**			**1d**, 96
2	**A1**			**2d**, 97
3	**A1**			**3d**, 98
4	**A1**			**4d**, 97
5	**A1**			**5d**, 97
6	**A1**			**6d**, 99
7	**A1**			**7d**, 94
8	**A1**			**8d**, 94
9	**A1**			**9d**, 95
10	**A1**			**10d**, 96
11	**A1**			**11d**, 99
12	**A1**			**12d**, 73
13	**A1**			**13d**, 97
14	**A1**			**14d**, 97
15	**A1**			**15d**, 85
16	**A1**			**16d**, 90
17	**A1**			**17d**, 79
18	**A1**			**18d**, 37
19	**A1**			**19d**, 87
20	**A1**			**20d**, 96
21	**A1**			**21d**, 97[a]
22	**A1**			**22d**, 98[b]
23	**A2**			**23d**, 63
24	**A2**			**24d**, 78
25	**A3**			**25d**, 79
26	**A3**			**26d**, 71
27	**A3**			**27d**, 86
28	**A4**			**28d**, 52
29	**A4**			**29d**, 81
30	**A4**			**30d**, 73
31	**A4**			**31d**, 42
32	**A4**			-
33	**A4**			**33d**, 78
34	**A4**			**34d**, 75
35	**A4**			**35d**, 71
36	**A4**			-
37	**A5**			**37d**, 43
38	**A5**			**38d**, 61
39	**A5**			**39d**, 54
40	**A5**			**40d**, 17
41	**A5**			-
42	**A5**			-
43	**A5**			-
44	**A5**			-
45	**A6**			**45d**, 96
46	**A6**			**46d**, 84
47	**A6**			**47d**, 94
48	**A7**			**48d**, 61
49	**A8**			**49d**, 71
50	**A9**			**50d**, 80[c]
51	**A9**			**51d**, 84[d]
52	**A10**			**52d**, 80 %

*Isolated yields. [a]Cis/trans ratio 4:3. [b]Cis/trans ratio 19:1. [c]Cis/trans ratio 3:2. [d]Cis/trans ratio 5:1.

Scheme 3. (a) Ugi-3CR Reaction of *N-H*-Tetrazolo-5-methylamine and (b) Deprotection of *N-tert*-Octyl Group

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*-toluenesulfinic 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*-toluenesulfinate counteranion affords the *p*-toluenesulfinic imidoyl species (**I-5**). The final step is a Mumm rearrangement with the transfer of the *p*-toluenesulfinate group (**I-3**) from the oxygen atom to the nitrogen atom of the former amine (Scheme 4) to form *p*-toluenesulfinic amide (**I-6**, pathway A). Since *p*-toluenesulfinate is a good leaving group, it is replaced by the nucleophile water which was generated during the imine formation process. Alternatively, water attacks

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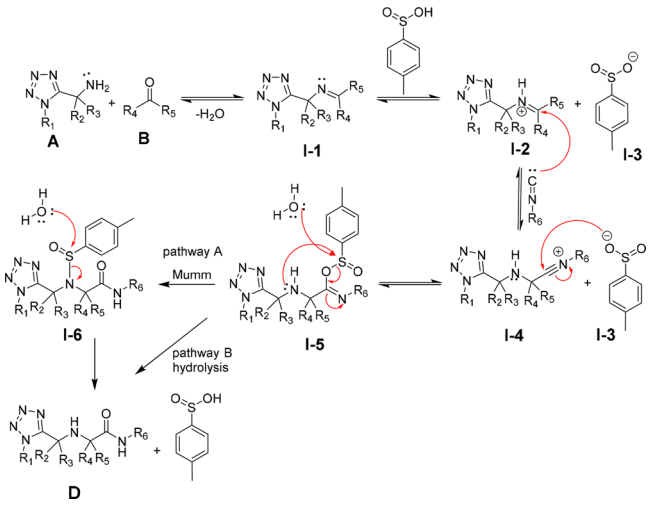
Scheme 4. Plausible Reaction Mechanism



p-toluenesulfinic imidoyl species (**I-5**) to give product **D** without Mumm rearrangement (pathway B).

To confirm the structures of the final Ugi 3-CR products we could grow several crystals in ethanol for X-ray structure analysis. The resulting structures of **1d**, **2d**, **17d**, **18d**, and **22d** are shown in Figure 1 and give some insight into the hydrogen bonding pattern of the α-amino tetrazole moiety.

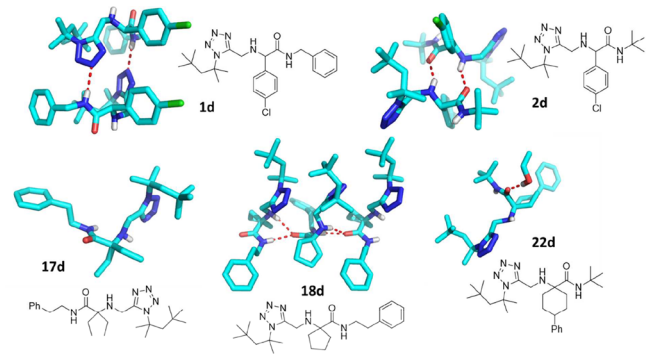


Figure 1. Crystal structure analysis and hydrogen bonding interactions (red dotted lines) of **1d**, **2d**, **17d**, **18d**, and **22d**. Compound **1d** for example is a noncovalent dimer formed by hydrogen bonds between tetrazole-N3 and the amide NH of the adjacent molecule.

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,α-unsubstituted methylamines gave significantly better yields compared to *N*-alkyl tetrazolo-5-α,α-disubstituted methylamines. The scaffold is currently used in the European Lead Factory to enhance the screening deck.[28] Moreover, efforts are ongoing to explore this rich and novel chemical space for islands of biological activity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.7b00137.

Crystallographic information file for compound **1d** (CIF)
Crystallographic information file for compound **2d** (CIF)
Crystallographic information file for compound **17d** (CIF)
Crystallographic information file for compound **18d** (CIF)
Crystallographic information file for compound **22d** (CIF)
General methods, preparations of compound **d**, ^{1}H NMR, ^{13}C NMR and SFC-MS data and ^{1}H NMR and ^{13}C NMR spectra for compounds **1d**−**52d** and **5**, crystal structure determination, (PDF)

■ AUTHOR INFORMATION

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The manuscript was written through contributions of P.P. and A.D. The crystallographic study contributed by K.K and K.J.

Notes

The authors declare no competing financial interest.

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