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Published in:
Acs combinatorial science

DOI:
10.1021/acscombsci.5b00189

ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

Versatile Protecting-Group Free Tetrazolomethane Amine Synthesis by Ugi Reaction

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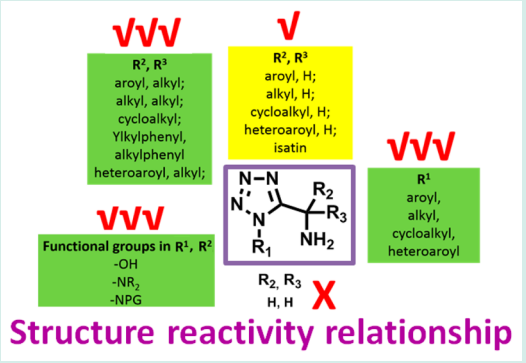
Supporting Information

ABSTRACT: The use of ammonia in the Ugi reaction is often problematic due to low yields and multiple side reactions. Here, we report the use of ammonia in the tetrazole Ugi variation providing a clean, good-to-high yielding reaction, especially with ketones as oxo components. The scope and limitations of this reaction and a structure−reactivity relationship are provided by performing >85 reactions. The primary amine component of the α-amino tetrazole is a versatile starting material for further reactions.



KEYWORDS: *aminomethyltetrazole, multicomponent reaction, Ugi reaction, ammonia*

Scaffold diversity is a very important quality criterion for high-throughput screening (HTS) libraries.[1] In the framework of the European Lead Factory, a very high quality library of 500 K is currently assembled based on chemical and property features including 3D character, water solubility, being precedence-less, unusual scaffolds, and target class coverage to name just a few.[2] Among many robust classical organic chemistries, multicomponent reactions (MCRs) are very popular for assembling HTS libraries.[1a,3] This is based on the unique features of MCRs, including scaffold and compound diversity, very large chemical space, ease of synthesis, convergence, one-pot synthesis, and convergence, which can lead to considerable time and operational savings.[4] The isocyanide-based multicomponent reaction between an oxo, 1° or 2° amine, an isocyanide, and an acid component is known as the Ugi reaction.[3a,4b,c] The specific scaffold formed depends mostly on the nature of the acid component, e.g., carboxylic acid, thiocyanate, water, phenoles, and hydrogen azide form α-aminoacylamides, thiohydantoines, α-aminoamides, α-phenylaminoamides, and α-amino tetrazoles, respectively.[3b,4b,c] Additional scaffold diversity can also be accomplished by postcondensations of suitable orthogonal building blocks besides variations in the primary Ugi components.[3c,5] Besides variations in the acid component, the amine component turns out to be versatile as well and 1° or 2° amines and acylated and sulfonated hydrazines generally react smoothly.[6] An exception is ammonia, which is reported to react sluggishly and often results in poor yields with a lot of side products.[7] Notable exceptions comprise, for example, the synthesis of tetrazolobenzodiazepines, thiazoles, and isoquinolines, where ammonia is an effective component.[8] Another productive result of ammonia in an IMCR is the use of ammonium formate yielding α-aminoformylamides (Scheme 1).[9] However, because of the often unsatisfactory results of ammonia, trityl amine and other protected forms of ammonia have recently been introduced as ammonia surrogates.[10] Highly substituted primary amines—the potential reaction products of ammonia in the tetrazole Ugi-3CR—are among the most versatile building blocks in organic chemistry, and therefore new methods to produce those in high diversity are highly sought. Therefore, we report here for the first time the use of ammonia in the Ugi tetrazole variation leading to unprotected α,α-disubstituted α-amino tetrazoles in good to excellent yields (Scheme 1). In the second part of this study, we report on the synthesis of *N*,*N*-di-unprotected α-amino tetrazoles.

We started the project with an extensive screening of the reaction conditions, including azide source, solvents, ammonia sources, reagent ratios, reaction time, and temperature for a representative reaction (Table 1). As ammonia sources, we tried ammonium chloride and ammonium hydroxide; the azide source was $TMSN_3$ or sodium azide. The solvent was pure methanol or a methanol−water mixture to increase salt

Received: December 16, 2015
Revised: January 29, 2016
Published: February 5, 2016

DOI: 10.1021/acscombsci.5b00189
ACS Comb. Sci. 2016, 18, 170−175

Scheme 1. Previous and Present Work on Ammonia and Surrogates As Components in Ugi-Type Reactions

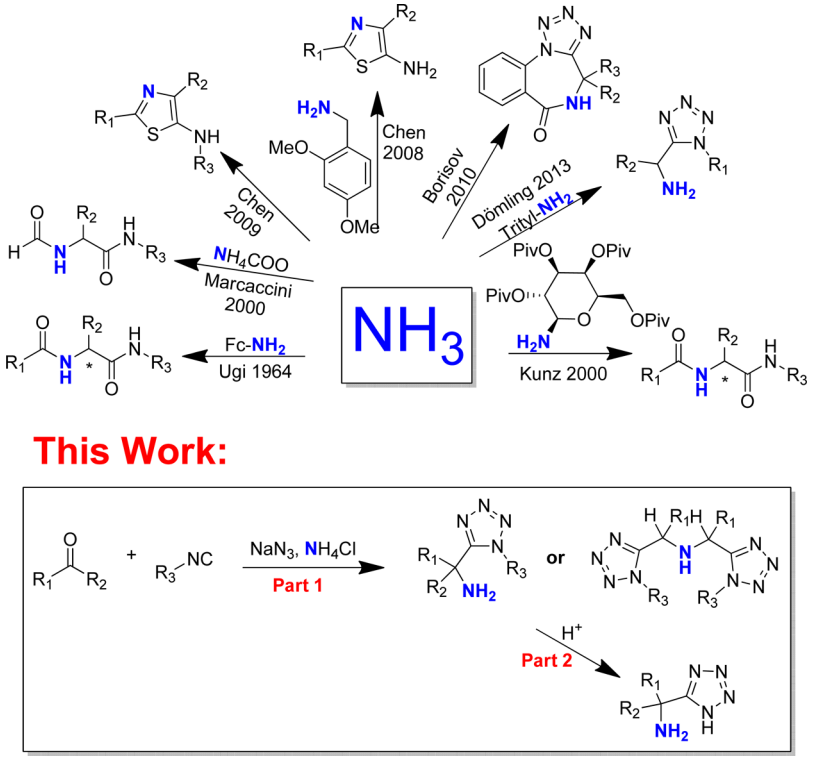
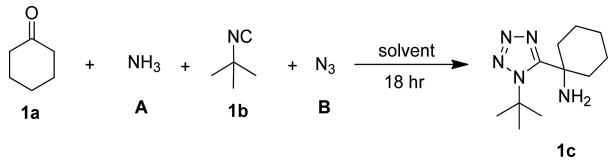


Table 1. Screening of the Reaction Conditions



ammonia source (A)	azide source (B)	solvent	temperature	isolated % yield
NH_4OH (1 equiv)	$TMSN_3$ (1 equiv)	MeOH	r.t.	18
NH_4OH (2 equiv)	$TMSN_3$ (2 equiv)	MeOH	r.t.	32
NH_4OH (3 equiv)	$TMSN_3$ (3 equiv)	MeOH	r.t.	45
NH_4OH (3 equiv)	$TMSN_3$ (3 equiv)	MeOH	60 °C	17
NH_4OH (3 equiv)	NaN_3 (3 equiv)	MeOH	r.t.	32
NH_4Cl (3 equiv)	$TMSN_3$ (3 equiv)	MeOH	r.t.	37
NH_4Cl (3 equiv)	NaN_3 (3 equiv)	Water	r.t.	trace
NH_4Cl (3 equiv)	NaN_3 (3 equiv)	MeOH:H_2O (1:1)	r.t.	67
NH_4Cl (3 equiv)	NaN_3 (3 equiv)	MeOH:H_2O (3:1)	r.t.	80
NH_4Cl (1.5 equiv)	NaN_3 (1.5 equiv)	MeOH:H_2O (3:1)	r.t.	82

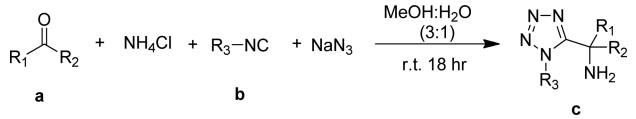
solubility; reagent ratios varied between equimolar up to 3-fold excess. Finally, the temperature varied between room temperature and 60 °C to obtain the product between 18% and almost quantitative yield. For the representative reaction, the optimized conditions included ammonium chloride and sodium azide in 1.5 molar excess in a methanol−water mixture (3:1) at room temperature in 1 M concentration, and the target compound could be isolated in satisfactory 82% yield.

With these optimized conditions in hand, we elaborated the scope and limitations by varying the isocyanide and oxo components (Tables 2 and 3). Although optimization of an IMCR is often done with a limited number of different starting materials of each class, we performed an in-depth scope and limitation study by choosing >70 oxocomponents and >15 isocyanides with different kinds of substitutions, including small, bulky, aliphatic, aromatic, and heteroaromatic, and taking into account multiple different functional groups. We believe a meaningful scope and limitation investigation is the basis for a parallel synthesis project with a high recovery rate of isolated high quality target compounds. Currently, mostly small scale scope and limitation studies are performed based on only a few similar substituents and are not suitable for a meaningful prediction of synthesizability of a specific chemical space.

The first major finding of this study was that ketones work much better than the corresponding aldehydes (Scheme 1). In the ketone class of oxo component starting materials, we found acyclic ketones and cyclic ketones to work. Aliphatic cyclic ketones generally worked very well, and ring sizes from 5 to 7 were investigated (entries 1−29). Introduction of a tertiary amine into the side chain of the ring is also well-tolerated (25c). Surprisingly, even highly sterically hindered tricyclic camphor works well (28c). Psychoactive tropinone, however, for unknown reasons could not be brought to work under the employed conditions (entry 29). The aromatic cyclic ketone 2-cyclopentanone (8a) also gave satisfactory yields (8c, 72%). Piperidinones with a wide variety of *N*-functionalizations, including basic *N*-methyl, *N*-benzyl, *N*-phenylethyl, and neutral Cbz and Boc gave good to excellent yields (entries 9−21), although the α,β-unsaturated cyclohexenone derivative (entry 22) worked only in very low yields and the *O*-protected cyclic

DOI: 10.1021/acscombsci.5b00189
ACS Comb. Sci. 2016, 18, 170−175

Table 2. Ketones as an Oxo-Component in the Ugi Reaction



a b c

Sr N	(a)	R–NC (b)	(c) % Yield
1			**1c** 82
2			**2c** 84 %
3			**3c** 89 %
4			**4c** 93 %
5			**5c** 29 %
6			**6c** 83 %
7			**7c** 93 %
8			**8c** 72 %
9			**9c** 66 %
10			**10c** 71 %
11			**11c** 92 %
12			**12c** 55 %
13			**13c** 88 %
14			**14c** 96 %
15			**15c** 97%

Sr N	(a)	R–NC (b)	(c) % Yield
16			**16c** 68 %
17			**17c** 90 %
18			**18c** 92 %
19			**19c** 88 %
20			**20c** 89 %
21			**21c** 88 %
22			**22c** 10 %
23			-
24			-
25			**25c** 49 %
26			**26c** 88 %
27			**27c-cis**, 34% ; **27c-trans** 60%
28			**28c** 57 %
29			-

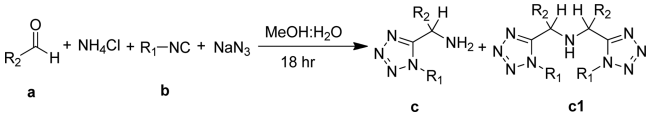
Sr N	(a)	R–NC (b)	(c) % Yield
30			**30c** 89 %
31			**31c** 87 %
32			**32c** 92 %
33			**33c** 88 %
34			**34c** 81 %
35			**35c** 76 %
36			**36c** 78 %
37			**37c** 76 %
38			**38c** 79 %
39			**39c** 80 %
40			**40c** 75 %
41			**41c** 70 %
42			**42c** 80 %
43			**43c** 45%
44			**44c** 78 %
45			**45c** 97 %
46			**46c** 79 %
47			**47c** 39 %

Sr N	(a)	R–NC (b)	(c) % Yield
48			**48c** 75 %
49			**49c** 52 %
50			**50c** 42 %
51			**51c** 82 %
52			**52c** 97 %
53			--
54			--
55			**55c** 26 %
56			--
57			--
58			--
59			**59c** 17 %
60			**60c** 84 %
61			**61c** 64 %
62			**62c** 61 %
63			**63c** 93 %
64			--

1,3-diketone (entry 24) did not work at all. Finally, the highly deactivated isatine (entry 55) also reacted; however, only low yields could be obtained. Next, we investigated acyclic ketones (entries 30−64). Acetone, which often causes problems in IMCRs, worked well in high isolated yields (entries 30−33). Longer aliphatic ketones worked equally well (entries 34−48). Acetophenone with decreased carbonyl activity worked only with poor yields (entry 59). The even less electrophilic diphenylketone and the heteroaromative acetylfurane derivative did not react at all (entries 56−57). Phenylacetone as well as sterically hindered diphenylacetone worked in good to excellent yields (entries 60−63). The free hydroxyl group of hydroxyl acetone was well-tolerated (entries 49−51). The dimethoxyacetale-protected pyruvate derivative reacted nearly quantitatively (entry 52), whereas acetylacetone did not work nearly as well as an acrylate derivative (entry 64). The general observation was that, using aldehydes as the oxo component in our IMCR reactions, the yields were lower (Scheme 1). This was due to the fact that the less-hindered primary amine moiety of the product was available to participate in a second Ugi tetrazole reaction as the amine source, effectively creating a cascade of reactions in situ leading to dimer products. This phenomenon is solely observed with aldehydes, and no traces of ketone-derived dimers could be detected. Some of these dimers have been isolated, and their crystal structures were determined (67c1, 68c1). This dimerization could be reduced to some extent by using excess ammonium chloride (4 equiv). Among the aldehydes tested, only pivaldehyde (entry 74) gave satisfactory yield comparable to those of the ketone products. Pivaldehyde with a fully blocked α-position cannot enolize, and therefore side reactions cannot take place. In contrast, enolizable aliphatic aldehydes gave mixed results mostly below 40% (entries 67−73). Surprisingly, rather highly enolizable phenylacetaldehyde also worked in 17% yield (entry 73). Benzaldehydes and substituted derivatives reacted poorly or not at all, as well as heteroaromatic pyridine and indole derivatives (entries 75−88). Moreover, in the case of all aldehydes, we additionally observed 5-unsubstituted tetrazole as a major side product, which is formed by the reaction between azide and isocyanide according to Oliveri-Mandala and Alagna. Next, we turned to investigate the differential reactivity of the isocyanide input. Isocyanides are the limiting building blocks in many IMCRs because they are−albeit commercially available in a great manifold−often very expensive. Often, synthetic groups

DOI: 10.1021/acscombsci.5b00189
ACS Comb. Sci. 2016, 18, 170−175

Table 3. Aldehyde as an Oxo-Component in the Ugi Reaction



Sr N	(a)	R–NC (b)	(c) % Yield
65			**65c1** 35 %
66			**66c1** 29 %
67			**67c1** 9 %
68			**68c1** 17 %
69			**69c1** 18 %
70			**70c1** 13 %
71			**71c1** 23 %
72			**72c1** 12 %
73			**73c1** 17 %
74			**74c** 70 %
75			**75c** 12 %
76			**76c** 23 %
77			**77c** 20 %

Sr N	(a)	R–NC (b)	(c) % Yield
78			--
79			--
80			--
81			--
82			--
83			--
84			--
88			--
86			--
87			--
88			--

Figure 1. Structure–reactivity relationship of IMCR synthesis of unprotected α,α-disubstituted α-amino tetrazoles.

therefore only investigate commercially available cheap isocyanides that are not representative of the great manifold

Table 4. Deprotection of the *tert*-Octyl Group

Sr. N	Compound (c)	Deprotected tetrazole (d)	% Yield
1	**2c**	**1d**	86
2	**7c**	**2d**	93
3	**8c**	**3d**	93
4	**10c**	**4d**	92
5	**14c**	**5d**	94
6	**21c**	**6d**	92
7	**27c-*cis***	**7d**	93
8	**31c**	**8d**	91

Sr. N	Compound (c)	Deprotected tetrazole (d)	% Yield
9	**36c**	**9d**	90
10	**44c**	**10d**	94
11	**48c**	**11d**	97
12	**55c**	**12d**	76
13	**59c**	**13d**	80
14	**60c**	**14d**	80
15	**63c**	**15d**	87
16	**72c1**	**16d**	78
17	**74c**	**17d**	81

of isocyanides. In fact, the standard isocyanides often used in synthetic papers are *tert*-butyl and cyclohexyl isocyanides, which are poor probes for isocyanide reactivity because they are generally very reactive due to their electron-donating substituents. Thus, they can give the impression of having generally excellent reactivity whereas other isocyanides are much less reactive and can sometimes give considerably lower yields. Here, we screened 15 different isocyanides, including bulky aliphatic, aromatic, and heteroaromatic isocyanides. All tested isocyanides resulted in product formation. Aliphatic isocyanides generally worked well, even aromatic and heteroaromatic ones (entries 5, 33, 61). Aromatic-substituted isocyanides also generally worked well, e.g., 13b and 16b, which have several electron-donating substituents. The least reactive isocyanide was 4-nitro-2-methoxyphenyl isocyanide, which is of potential use as cleavable isocyanide (5b).

The many starting materials we tested allow for the formulation of a structure–reactivity relationship (SRR)

DOI: 10.1021/acscombsci.5b00189
ACS Comb. Sci. 2016, 18, 170–175

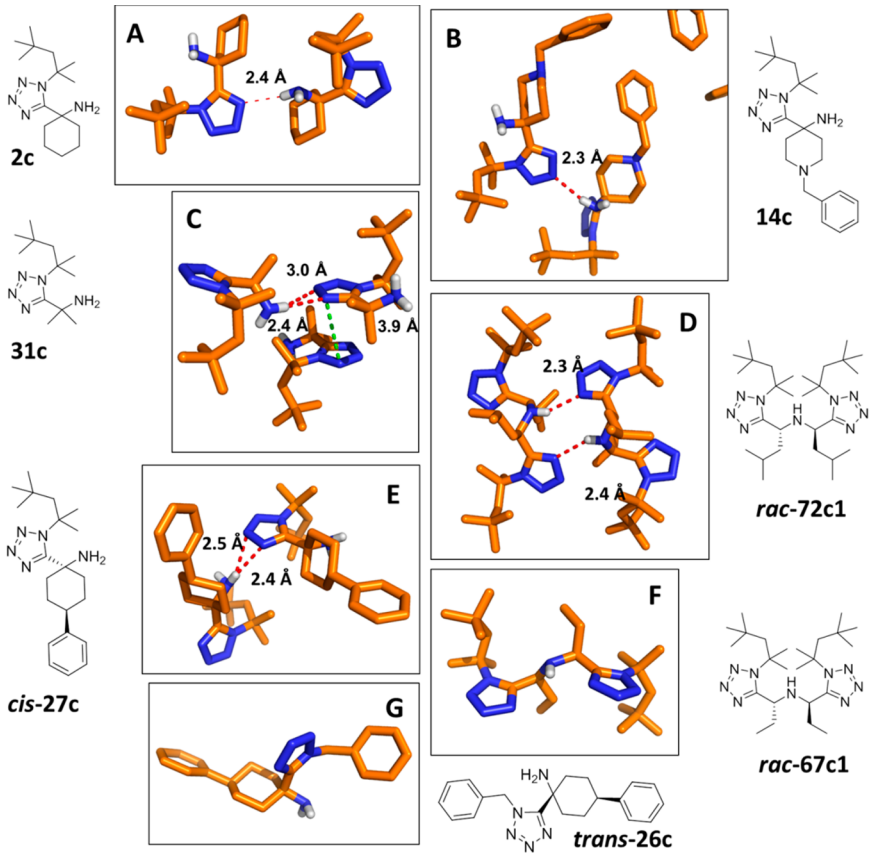


Figure 2. Structures of several *N*-protected tetrazoles as seen in the solid state by X-ray structure analysis. The structures are shown as orange sticks with nitrogens shown as blue sticks. Interactions are shown as dotted lines. (A) Compound 2c forming a hydrogen bridge of 2.4 Å length between the amine NH and the N4 of an adjacent molecule; moreover, the benzyl side chains undergo parallel and T-shaped pi-pi interactions. (B) Compound 14c forming a hydrogen bridge of 2.3 Å length between the amine NH and the N3 of an adjacent molecule. (C) Compound 31c makes several intermolecular contacts: hydrogen bridges of 2.3 and 3.0 Å length between the amine NH and the N3 and N4 of an adjacent molecule, respectively; moreover, two tetrazoles are parallel aligned with a distance of approximately 3.9 Å in a way that their dipole momentum is antiparallel (green dotted lines). (D) Compound *rac*-72c1 constitutes a tetrazole resulting from a double Ugi reaction. (E) Compound *cis*-27c forming a bifurcated, almost symmetrical hydrogen bridge of 2.4 and 2.5 Å length between the amine NH and the N3 and N4 of an adjacent tetrazole molecule. (F) Compound *rac*-67c1 constitutes a tetrazole resulting from a double Ugi reaction and undergoes no hydrogen bonding. (G) The polar moieties of *trans*-26c are enveloped by hydrophobic groups, and thus no hydrogen bonding is formed.

analogous to the medicinal chemistry structure−activity relationship (SAR), which is summarized in Figure 1.

Fully unprotected α-amino tetrazoles are an interesting class of α-amino acid bioisosteres and are poorly described. Therefore, we also want to report here the synthesis of this compound class using the above-described IMCR approach. Among the different tested convertible isocyanides, we found that 1,1,3,3-tetramethylbutyl isocyanide (Walborsky's reagent) is well-compatible with the herein used α-amino tetrazoles. It can be cleaved with 6 N HCl at 65−75 °C for 36−48 h. Generally, all 17 reactions tested gave good to excellent yields, and the unprotected α-amino tetrazoles were isolated as HCl salts. It is interesting to note that the Boc group of the *N*-Boc piperidinone-derived α-amino tetrazole is stable under the acidic deprotection conditions used. Table 4 summarizes the structures and yields of the fully unprotected α-amino tetrazoles synthesized.

Several of the *tert*-octyl-protected tetrazoles crystallized nicely, and their solid state structures have been solved (Figure 2). Interestingly, the tetrazoles form a multitude of intermolecular contacts, including mono and bifurcated hydrogen bonds, dipol−dipol interactions, and hydrophobic interactions. The understanding of typical binding interactions can be useful in the rational structure-based design of inhibitors.

In summary, we described an in depth scope and limitation study on the use of ammonia in the Ugi tetrazole variation leading to primary α-amino tetrazoles. The study is significant for several reasons. First, we provide the first procedure for a high yielding primary α-amino tetrazole IMCR. Second, we studied more than 88 diverse reactions and thus can provide detailed insight into the scope and limitations of the reaction. Third, α-amino tetrazoles are a highly underused scaffold in medicinal chemistry, and the resulting easily accessible primary α-amino tetrazoles can be used in a manifold of other organic and multicomponent reactions and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00189.

General methods; preparation of compounds c and d; ^{1}H NMR, ^{13}C NMR, and SFC-MS data and spectra of

DOI: 10.1021/acscombsci.5b00189
ACS Comb. Sci. 2016, 18, 170−175

compounds c, c1, and d; and crystal structure determinations (PDF)

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Author Contributions

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

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under Grant Agreement No. 115489, resources of which are composed of financial contributions from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in-kind contribution, the NIH (1R01GM097082-01), and was also supported by the European Regional Development Fund in the framework of the Polish Innovation Economy Operational Program (Contract No. POIG.02.01.00-12-023/08).

REFERENCES

(1) (a) Hulme, C.; Dietrich, J. Emerging molecular diversity from the intra-molecular Ugi reaction: iterative efficiency in medicinal chemistry. *Mol. Diversity* **2009**, *13*, 195−207. (b) Langdon, S. R.; Brown, N.; Blagg, J. Scaffold diversity of exemplified medicinal chemistry space. *J. Chem. Inf. Model.* **2011**, *51*, 2174−2185.

(2) (a) Besnard, J.; Jones, P. S.; Hopkins, A. L.; Pannifer, A. D. The Joint European Compound Library: boosting precompetitive research. *Drug Discovery Today* **2015**, *20*, 181−186. (b) Nelson, A.; Roche, D. Innovative approaches to the design and synthesis of small molecule libraries. *Bioorg. Med. Chem.* **2015**, *23*, 2613.

(3) (a) Dömling, A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. *Chem. Rev.* **2006**, *106*, 17−89. (b) Dömling, A.; Wang, W.; Wang, K. Chemistry and Biology Of Multicomponent Reactions. *Chem. Rev.* **2012**, *112*, 3083−3135. (c) Hulme, C.; Bienaymé, H.; Nixey, T.; Chenera, B.; Jones, W.; Tempest, P.; Smith, A. L. Library Generation via Postcondensation Modifications of Isocyanide-Based Multicomponent Reactions. *Methods Enzymol.* **2003**, *369*, 469−496.

(4) (a) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. Multicomponent Reaction Design in the Quest for Molecular Complexity and Diversity. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234−6246. (b) Ugi, I. Von Isocyaniden via Vierkomponenten-Kondensation zu Antibiotica-Synthesen. *Angew. Chem.* **1982**, *94*, 826−835. (c) Ugi, I. Recent progress in the chemistry of multicomponent reactions. *Pure Appl. Chem.* **2001**, *73*, 187−191.

(5) (a) Basso, A.; Banfi, L.; Guanti, G.; Riva, R. A novel intramolecular Ugi reaction with 7-azabicyclo[2.2.1]heptane derivatives followed by post-condensation acylations: a new entry to azanorbornyl peptidomimetics. *Org. Biomol. Chem.* **2009**, *7*, 253−258. (b) Keating, T. A.; Armstrong, R. W. Postcondensation Modifications of Ugi Four-Component Condensation Products: 1-Isocyanocyclohexene as a Convertible Isocyanide. Mechanism of Conversion, Synthesis of Diverse Structures, and Demonstration of Resin Capture. *J. Am. Chem. Soc.* **1996**, *118*, 2574−2583. (c) Borisov, R.; Polyakov, A.; Medvedeva, L.; Khrustalev, V.; Guranova, N.; Voskressensky, L. Concise Approach toward Tetrazolo[1,5-a][1,4]benzodiazepines via a Novel Multicomponent Isocyanide-Based Condensation. *Org. Lett.* **2010**, *12*, 3894−3897.

(6) (a) Basso, A.; Banfi, L.; Guanti, G.; Riva, R.; Riu, A. Ugi multicomponent reaction with hydroxylamines: an efficient route to hydroxamic acid derivatives. *Tetrahedron Lett.* **2004**, *45*, 6109−6111. (b) Nikbakht, A.; Ramezanpour, S.; Balalaie, S.; Rominger, F. Efficient and stereoselective synthesis of α-hydrazino tetrazoles through a pseudo five-component domino reaction. *Tetrahedron* **2015**, *71*, 6790−6795. (c) Zinner, G.; Hantelmann, O. Hydroxylamine in der Vierkomponenten-Kondensation nach Ugi, III. *Arch. Pharm.* **1975**, *308*, 321−325. (d) Zinner, G.; Moderhack, D.; Hantelmann, O.; Bock, W. Hydroxylamine in der Vierkomponenten-Kondensation nach Ugi, I. *Chem. Ber.* **1974**, *107*, 2947−2955. (e) Zinner, G.; Moderhack, D.; Kliegel, W. Hydroxylamin-Derivate, XXXVII. Hydroxylamine in der Vierkomponenten-Kondensation nach Ugi. *Chem. Ber.* **1969**, *102*, 2536−2546. (f) Shaw, A. Y.; McLaren, J. A.; Nichol, G. S.; Hulme, C. Hydrazine-mediated cyclization of Ugi products to synthesize novel 3-hydroxypyrazoles. *Tetrahedron Lett.* **2012**, *53*, 2592−2594. (g) Shaw, A. Y.; Xu, Z.; Hulme, C. Ugi/Robinson−Gabriel reactions directed toward the synthesis of 2,4,5-trisubstituted oxazoles. *Tetrahedron Lett.* **2012**, *53*, 1998−2000. (h) Thompson, M. J.; Chen, B. Versatile assembly of 5-aminothiazoles based on the Ugi four-component coupling. *Tetrahedron Lett.* **2008**, *49*, 5324−5327. (i) Basso, A.; Banfi, L.; Guanti, G.; Riva, R. One-pot synthesis of α-acyloxyaminoamides via nitrones as imine surrogates in the Ugi MCR. *Tetrahedron Lett.* **2005**, *46*, 8003−8006.

(7) (a) Just, G.; Chung, B. Y.; Grözinger, K. An attempted synthesis of an oxacepham derivative using isonitriles as β-lactam forming agents. On the stability of dihydrooxazines and the inadequacy of ammonia as the fourth component in the Ugi reaction. *Can. J. Chem.* **1977**, *55*, 274−283. (b) Kazmaier, U.; Hebach, C. Peptide Syntheses via Ugi Reactions with Ammonia. *Synlett* **2003**, *11*, 1591−1594. (c) Pick, R.; Bauer, M.; Kazmaier, U.; Hebach, C. Ammonia in Ugi Reactions - Four-Component versus Six-Component Couplings. *Synlett* **2005**, *5*, 0757−0760. (d) Moni, L.; Denißen, M.; Valentini, G.; Müller, T. J. J.; Riva, R. Diversity-Oriented Synthesis of Intensively Blue Emissive 3-Hydroxyisoquinolines by Sequential Ugi Four-Component Reaction/Reductive Heck Cyclization. *Chem. - Eur. J.* **2015**, *21*, 753−762. (e) Abbas, M.; Wessjohann, L. A. Direct synthesis of sensitive selenocysteine peptides by the Ugi reaction. *Org. Biomol. Chem.* **2012**, *10*, 9330−9333. (f) Barthelon, A.; El Kaim, L.; Gizzi, M.; Grimaud, L. Ammonia in Ugi-Smiles and Ugi Couplings. *Synlett* **2010**, *18*, 2784−2788. (g) Banfi, L.; Basso, A.; Damonte, G.; De Pellegrini, F.; Galatini, A.; Guanti, G.; Monfardini, I.; Riva, R.; Scapolla, C. Synthesis and biological evaluation of new conformationally biased integrin ligands based on a tetrahydroazoninone scaffold. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1341−1345.

(8) (a) Gulevich, A. V.; Balenkova, E. S.; Nenajdenko, V. G. The First Example of a Diastereoselective Thio-Ugi Reaction: A New Synthetic Approach to Chiral Imidazole Derivatives. *J. Org. Chem.* **2007**, *72*, 7878−7885. (b) Seganish, W. M.; Bercovici, A.; Ho, G. D.; Loozen, H. J. J.; Timmers, C. M.; Tulshian, D. A synthesis of dihydroimidazo[5,1-a]isoquinolines using a sequential Ugi−Bischler−Napieralski reaction sequence. *Tetrahedron Lett.* **2012**, *53*, 903−905. (c) Thompson, M. J.; Chen, B. Ugi Reactions with Ammonia Offer Rapid Access to a Wide Range of 5-Aminothiazole and Oxazole Derivatives. *J. Org. Chem.* **2009**, *74*, 7084−7093.

(9) Bossio, R.; Marcaccini, S.; Pepino, R. Studies on isocyanides. Synthesis of N-substituted 2-isocyanocarboxamides. *Liebigs Ann. Chem.* **1990**, *9*, 935−937.

(10) (a) Kunz, H.; Pfrengle, W. Asymmetric synthesis on carbohydrate templates: stereoselective Ugi-synthesis of α-amino acid derivatives. *J. Am. Chem. Soc.* **1988**, *110*, 651−652. (b) Sung, K.; Chen, F.-L.; Huang, P.-C. A Modified U-4CR Reaction with 2-Nitrobenzylamine as an Ammonia Equivalent. *Synlett* **2006**, *16*, 2667−2669. (c) Zhao, T.; Boltjes, A.; Herdtweck, E.; Dömling, A. Tritylamine as an Ammonia Surrogate in the Ugi Tetrazole Synthesis. *Org. Lett.* **2013**, *15*, 639−641.

DOI: 10.1021/acscombsci.5b00189
ACS Comb. Sci. 2016, 18, 170−175