PAPER

Various cyclization scaffolds by a truly Ugi 4-CR†

Mantosh K. Sinha,[a] Kareem Khoury,[a] Eberhardt Herdtweck[b] and Alexander Dömling*[a,c]

Efficient access to a large chemical space based on new scaffolds with defined 3D conformations and highly variable in the side chains is needed to find novel functional materials. Four heterocyclic scaffolds based on a four component Ugi reaction of α-amino acids, oxo components, isocyanides and primary or secondary amines suitably functionalized are described. A handful of examples are described for each scaffold.
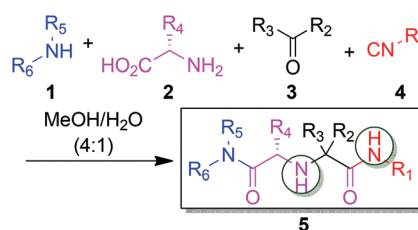
Ivar Ugi, half a century ago, pioneered the use of multicomponent reaction technology (MCR) for the discovery of novel agents with preferred properties.[1] MCR is now widely recognized for its impact on drug discovery projects and is strongly endorsed by academia in addition to industry.[2] Recent reviews on chemistry and biology of MCRs give comprehensive proof for the increasing number of marketed products based on MCRs including Boceprevir,[3] Retosiban,[4] or Mandipropamid,[5] just to name a few. Based on the sheer number of theoretically accessible MCR products, recent trends in drug discovery are geared toward leveraging MCR chemistry for use in various virtual screening tools.[6] For example, the recently introduced ANCHOR.QUERY freeware offers >25 million virtual MCR compounds for structure- and web-based drug design purposes.[6c] While there are hundreds of different MCRs described in chemical literature, only a few are highly variable in all starting materials, such as the Ugi, Passerini, and van Leusen reactions.[1,7] The size of the chemical space of different MCR scaffolds has major implications for the usefulness of a particular MCR serving as a suitable virtual search space. Amongst the different strategies for the design of molecular complexity using MCR chemistry,[8] post-Ugi secondary cyclization has been a very fruitful strategy in the past to accomplish novel scaffolds.

We have recently introduced a stereoselective Ugi-type reaction using four highly variable starting materials: primary or secondary amine **1**, α-amino acid **2**, oxo component **3**, and isocyanide **4**, thus comprising a novel truly 4-CR (Scheme 1).[9] Herein, we would like to report on the design of Ugi postcondensation reactions leading to four highly variable heterocyclic scaffolds.

Due to the well-known functional group compatibility of the Ugi starting materials, we envisioned the construction of heterocyclic scaffolds involving the unique and reactive secondary amine formed during our Ugi reaction variation. Several intramolecular lactamizations based on different Ugi scaffolds have been reported in the past.[10] However, our synthesis differs from them by (1) yielding a different scaffold and (2) using much milder conditions of cyclization. By introducing methyl 2-formylbenzoate as an oxo component and some optimization of the reaction conditions, we could in fact see the formation of the expected isoindolinone scaffold (Table 1).

One equivalent amount of amino acids, isocyanide, primary or secondary amine and methyl 2-formylbenzoate were added together in a microwave vial in one-tenth molar concentration for one hour at 80 °C. The crude reaction mixture was checked *via* supercritical fluid chromatography-mass spectrometry (SFC-MS) and both masses for the Ugi product and the newly cyclized product **7** could be seen from the mixture of **6**. Work-up was done to remove any unreacted amino acid and the reaction was heated again in ethanol. SFC-MS then revealed that only cyclized product **7** remained. Either one diastereomer precipitated out (**7a** and **7b**) or a crude mixture was

[a]*University of Pittsburgh, Biomedical Science Tower 3, 3501 Fifth Avenue, Pittsburgh, PA 15261, USA*

[b]*Technische Universität München, Department Chemie, Lehrstuhl für Anorganische Chemie, Lichtenbergstrasse 4, D-85747 Garching bei Munchen, Germany*

[c]*University of Groningen, Department of Drug Design, A. Deusinglaan 1, 9713 AV Groningen, The Netherlands. E-mail: a.s.s.domling@rug.nl*

Scheme 1 The previously reported Ugi 4-CR of α-amino acid, oxo-component, isocyanide and primary or secondary amine.

4792 | *Org. Biomol. Chem.*, 2013, **11**, 4792–4796

This journal is © The Royal Society of Chemistry 2013

Table 1 Cyclization of the Ugi 4-CR to yield the isoindolone scaffold

Comp	R₁—NC	[aldehyde/ester]	[amino acid]	[amine]	Yield[a] [%]
7a	(diphenylmethyl isocyanide)	(methyl 2-formylbenzoate, CO_2Me)	(H₂N, leucine, CO_2H)	(1,2-diphenylethylamine)	35
7b	(diphenylmethyl isocyanide)	(methyl 2-formylbenzoate, CO_2Me)	(H₂N, phenylalanine, CO_2H)	(phenethylamine)	50
7c	(benzyl isocyanide)	(methyl 2-formylbenzoate, CO_2Me)	(H₂N, leucine, CO_2H)	(morpholine)	42
7d	(benzyl isocyanide)	(MeO, dimethoxy 2-formylbenzoate, CO_2Me, OMe)	(H₂N, leucine, CO_2H)	(morpholine)	40

[a] Overall yield in one step.

purified *via* SFC (**7c** and **7d**). When primary amines were used (**7a** and **7b**), crude SFC traces revealed diastereomeric ratios of 7 : 3 and only the major diastereomer precipitated (see ESI-21, ESI-25†). When secondary amines were used (**7c** and **7d**), SFC traces using chiral cell OD revealed four stereoisomers in equal ratio, thus suggesting the racemization of the amino acid stereocenter by secondary amines as previously discovered[9] (see ESI-28, SI-29†).

As reported previously, the Ugi reaction generally works well with aromatic and aliphatic aldehydes and ketones. Another available building block of suitable bifunctional orthogonal starting materials is the β-ketoester. In fact, when employing 2-oxocyclohexane carboxylic acid ethyl ester under heating conditions at 85 °C, SFC-MS revealed the formation of the Ugi product as well as trace amounts of the corresponding pyrrolidinedione scaffold **9** (Table 2). Upon addition of 3 equivalents of cesium carbonate, complete cyclization of the Ugi product to the pyrrolidinedione **9** was observed. Benzyl 3-oxobutanoate also produced similar pyrrolidinedione **9d**.

Several analogous reactions were performed and all yielded the products in satisfactory yields (Table 2). The finding of this reaction is remarkable since few other orthogonal methods exist to access the pyrrolidinedione scaffold by isocyanide

Fig. 1 Structure of pyrrolidinedione product **9a** in solid state.

based MCRs.[11] Stereochemical analysis SFC-MS revealed that compound **9c** gave a single diastereomer. However, **9b** (9 : 1) and **9d** (9.5 : 0.5) formed a mixture of two distereomers (see ESI-38, ESI-41†). The major distereomers were isolated using preparative TLC plates. Pyrrolidinedione **9a** is exclusively formed as the *cis* relative stereoisomer. The X-ray structure of

Table 2 Cyclization of the Ugi 4-CR to yield the pyrrolidinedione scaffold

Comp	R_1—NC		$H_2N \overset{CO_2H}{\underset{R_4}{\diagdown}}$	$HN \overset{R_5}{\underset{R_6}{\diagdown}}$	Yield[a] [%]
9a	(benzyl isocyanide)	CO₂Et cyclohexanone	H_2N—CO₂H	H_2N—(butyl)	40
9b	(cyclohexyl isocyanide)	CO₂Et cyclohexanone	H_2N—CO₂H (Ala)	H_2N—(phenethyl)	49
9c	(phenethyl isocyanide)	CO₂Et cyclohexanone	H_2N—CO₂H (Trp)	H_2N—(ethoxyethyl)	45
9d	(tryptamine isocyanide)	CO₂Bn	H_2N—CO₂H (Phe)	H_2N—(isopropyl)	34

[a] Overall yield in two steps in one pot (crude Ugi product was directly used for the cyclization).

Table 3 Pictet–Spengler cyclization of the Ugi 4-CR to yield the tricyclic 3,9-diazabicyclo[3.3.1]nonane scaffold

Comp	R_1—NC	$R_2 \overset{O}{\underset{R_3}{\diagdown}}$	Yield[a] [%]
11a	(phenethyl isocyanide)	acetone	44
11b	(benzyl isocyanide)	cyclohexanone	40
11c	(cyclohexyl isocyanide)	cyclohexanone	48
11d	(phenethyl isocyanide)	cyclobutanone	30

[a] Overall yield in two steps in one pot (crude Ugi product was directly used for the Pictet–Spengler reaction).

9a shows the solid state conformation and also proves the overall structure of the scaffold (Fig. 1).

The Pictet–Spengler reaction recently became popular for performing Ugi post-condensation reactions to yield complex
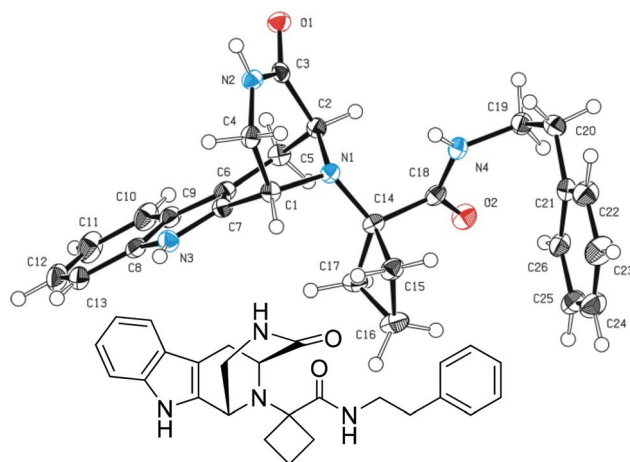
Fig. 2 Structure of Ugi/Pictet–Spengler product **11d** in solid state.

polycyclic scaffolds.[12] For example, the use of suitable starting materials allows for the convergent synthesis of the important schistosomiasis medication Praziquantel.[13] The two required functional groups of the Pictet–Spengler reaction, an electron rich aromatic group such as tryptophan and an oxo group, can be conveniently introduced via the α-amino acid component and the primary amine component respectively (Table 3). By performing the Pictet–Spengler reaction under formic acid at room temperature conditions, we indeed could isolate the strained tricyclic 3,9-diazabicyclo[3.3.1]nonane system **11** from

4794 | *Org. Biomol. Chem.*, 2013, **11**, 4792–4796

This journal is © The Royal Society of Chemistry 2013

Table 4 Cyclization of the Ugi 4-CR to yield bicyclic tetrahydroimidazo-[1,2-a]pyrazine-2,6(3H,5H)-dione scaffold

Comp	R$_1$—NC	$\begin{matrix}R_2\\R_3\end{matrix}$=O	Yield[a] [%]
13a	(benzyl) NC	(acetone) =O	63
13b	(benzyl) NC	(cyclohexanone) =O	87
13c	(phenethyl) —NC	(cyclopentanone) =O	40
13d	(phenethyl) —NC	(cyclohexanone) =O	54

[a] Overall yield in two steps in one pot (crude Ugi product was directly used for the cyclization).

Fig. 3 Bicyclic Ugi/condensation product **13c** in solid state.

Fig. 4 Principal moment of inertia (PMI) calculated for 1000 randomly generated compounds for each of the four scaffolds **7** (green triangles), **9** (light blue triangles), **11** (purple triangles) and **13** (navy blue triangles) compared to 1000 randomly chosen compounds from the Zinc Library[15] (yellow squares). PMI of specific compounds from this paper can be seen in all four graphs as red squares.

mixture **10**. Several analogous reactions show the general character of this transformation (Table 3).

Indolo annulated tricyclic 3,9-diazabicyclo[3.3.1]nonane systems or substructures thereof occur in several alkaloids, such as **11d**. The herein described convergent synthesis could therefore be of use in the synthesis of the corresponding backbones. A crystal structure analysis of **11d** has been performed supporting the proposed scaffold structure (Fig. 2).

As a final example of how our new Ugi variation, together with carefully chosen orthogonal functional groups in the other starting materials which can be used for the synthesis of novel and complex scaffolds, involves the use of other electron

rich aromatic α-amino acids such as phenylalanine (Table 4). Using similar conditions as seen in Table 3 the bicyclic tetrahydroimidazo[1,2-a]pyrazine-2,6(3H,5H)-dione scaffold **13** was obtained from mixture **12** (Table 4). In all cases, the formation of only the *trans* diastereomer was observed. A crystal structure analysis of **13c** has been performed showing the formation of the *trans* stereoisomer and supporting the proposed overall scaffold structure (Fig. 3).

Lastly, we were interested in the question of how some physiochemical properties of our scaffolds cluster and compare

This journal is © The Royal Society of Chemistry 2013

Org. Biomol. Chem., 2013, **11**, 4792–4796 | **4795**

with other commonly used virtual screening libraries. Thus we calculated the descriptors $c \log P$, rotatable bonds, molecular weight, and other drug-like properties from a randomly generated library of 1000 compounds based on all four scaffolds (ESI Fig. 1–8†). The majority of these compounds pass at least 3 out of 4 of Lipinski's rules of five; most of them, however, only fail the molecular weight rule. Interestingly the two later scaffolds (**11** and **13**) possess a low number of rotatable bonds and are highly stiff, increasing their chance of oral bio-availability. We were especially interested in the recently introduced shape descriptor principal moment-of-inertia (PMI) as a means to differentiate scaffolds based on shape.[14] These libraries were compared to 1000 randomly selected compounds from the Zinc database[15] and each library was found to possess more 3D characteristics than the zinc compounds (Fig. 4). As protein–protein interactions become an increasingly popular yet difficult target for pharmaceutical companies, novel chemical space needs to be explored.[16] With novel scaffolds that possess more 3D features, the chances to successfully probe previously unmet medical needs greatly increase. Biological activities of compounds based on the new scaffolds will be reported in due course.

Acknowledgements

Notes and references

1 I. Ugi and C. Steinbrückner, *Angew. Chem.*, 1960, **72**, 267–268.

2 A. Dömling, W. Wang and K. Wang, *Chem. Rev.*, 2012, **112**, 3083–3135.

3 S. Venkatraman, S. L. Bogen, A. Arasappan, F. Bennett, K. Chen, E. Jao, Y.-T. Liu, R. Lovey, S. Hendrata, Y. Huang, W. Pan, T. Parekh, P. Pinto, V. Popov, R. Pike, S. Ruan, B. Santhanam, B. Vibulbhan, W. Wu, W. Yang, J. Kong, X. Liang, J. Wong, R. Liu, N. Butkiewicz, R. Chase, A. Hart, S. Agrawal, P. Ingravallo, J. Pichardo, R. Kong, B. Baroudy, B. Malcolm, Z. Guo, A. Prongay, V. Madison, L. Broske, X. Cui, K.-C. Cheng, Y. Hsieh, J.-M. Brisson, D. Prelusky, W. Korfmacher, R. White, S. Bogdanowich-Knipp, A. Pavlovsky, P. Bradley, A. K. Saksena, A. Ganguly, J. Piwinski, V. Girijavallabhan and F. G. Njoroge, *J. Med. Chem.*, 2006, **49**, 6074–6086.

4 J. Liddle, M. J. Allen, A. D. Borthwick, D. P. Brooks, D. E. Davies, R. M. Edwards, A. M. Exall, C. Hamlett, W. R. Irving, A. M. Mason, G. P. McCafferty, F. Nerozzi, S. Peace, J. Philp, D. Pollard, M. A. Pullen, S. S. Shabbir, S. L. Sollis, T. D. Westfall, P. M. Woollard, C. Wu and D. M. B. Hickey, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 90–94.

5 C. Lamberth, A. Jeanguenat, F. Cederbaum, A. De Mesmaeker, M. Zeller, H.-J. Kempf and R. Zeun, *Bioorg. Med. Chem. Lett.*, 2008, **16**, 1531–1545.

6 (*a*) L. Weber, S. Wallbaum, C. Broger and K. Gubernator, *Angew. Chem., Int. Ed.*, 1995, **34**, 2280–2282; (*b*) M. Shoda, T. Harada, Y. Kogami, R. Tsujita, H. Akashi, H. Kouji, F. L. Stahura, L. Xue and J. Bajorath, *J. Med. Chem.*, 2004, **47**, 4286–4290; (*c*) D. Koes, K. Khoury, Y. Huang, W. Wang, M. Bista, G. M. Popowicz, S. Wolf, T. A. Holak, A. Dömling and C. J. Camacho, *PLoS ONE*, 2012, **7**, e32839.

7 (*a*) L. Banfi and R. Riva, *in Organic Reactions*, John Wiley & Sons, Inc., 2004; (*b*) A. M. Van Leusen, J. Wildeman and O. H. Oldenziel, *J. Org. Chem.*, 1977, **42**, 1153–1159; (*c*) M. Passerini and L. Simone, *Gazz. Chim. Ital.*, 1921, **51**, 126–129.

8 (*a*) L. Weber, K. Illgen and M. Almstetter, *Synlett*, 1999, 366–374; (*b*) E. Ruijter, R. Scheffelaar and R. V. A. Orru, *Angew. Chem., Int. Ed.*, 2011, **50**, 6234–6246; (*c*) A. Dömling, *Curr. Opin. Chem. Biol.*, 2000, **4**, 318–323.

9 K. Khoury, M. K. Sinha, T. Nagashima, E. Herdtweck and A. Dömling, *Angew. Chem., Int. Ed.*, 2012, **51**, 10280–10283.

10 (*a*) C. F. Marcos, S. Marcaccini, G. Menchi, R. Pepino and T. Torroba, *Tetrahedron Lett.*, 2008, **49**, 149–152; (*b*) R. Zimmer, A. Ziemer, M. Gruner, I. Brüdgam, H. Hartl and H.-U. Reissig, *Synthesis*, 2001, 1649–1658; (*c*) S. Gunawan, M. Ayaz, F. De Moliner, B. Frett, C. Kaiser, N. Patrick, Z. Xu and C. Hulme, *Tetrahedron*, 2012, **68**, 5606–5611; (*d*) S. Gunawan, K. Keck, A. Laetsch and C. Hulme, *Mol. Diversity*, 2012, **16**, 601–606.

11 R. Bossio, C. F. Marcos, S. Marcaccini and R. Pepino, *Synthesis*, 1997, 1389–1390.

12 (*a*) V. Tyagi, S. Khan, V. Bajpai, H. M. Gauniyal, B. Kumar and P. M. S. Chauhan, *J. Org. Chem.*, 2012, **77**, 1414–1421; (*b*) M. A. Cano-Herrera and L. D. Miranda, *Chem. Commun.*, 2011, **47**, 10770–10772; (*c*) W. Wang, S. Ollio, E. Herdtweck and A. Dömling, *J. Org. Chem.*, 2010, **76**, 637–644; (*d*) A. Znabet, J. Zonneveld, E. Janssen, F. J. J. De Kanter, M. Helliwell, N. J. Turner, E. Ruijter and R. V. A. Orru, *Chem. Commun.*, 2010, **46**, 7706–7708; (*e*) W. Wang, E. Herdtweck and A. Dömling, *Chem. Commun.*, 2010, **46**, 770–772; (*f*) H. Liu and A. Dömling, *J. Org. Chem.*, 2009, **74**, 6895–6898.

13 (*a*) H. Cao, H. Liu and A. Dömling, *Chem.–Eur. J.*, 2010, **16**, 12296–12298; (*b*) H. Liu, S. William, E. Herdtweck, S. Botros and A. Dömling, *Chem. Biol. Drug Des.*, 2012, **79**, 470–477.

14 W. H. Sauer and M. K. Schwarz, *J. Chem. Inf. Comput. Sci.*, 2003, **43**, 987–1003.

15 (*a*) J. J. Irwin and B. K. Shoichet, *J. Chem. Inf. Model.*, 2005, **45**, 177–182; (*b*) J. J. Irwin, T. Sterling, M. M. Mysinger, E. S. Bolstad and R. G. Coleman, *J. Chem. Inf. Model.*, 2012, **52**, 1757–2768.

16 A. Dömling, R. Mannhold, H. Kubinyi and G. Folkers, *Protein-Protein Interactions in Drug Discovery (Methods and Principles in Medicinal Chemistry)*, Wiley-VCH, Weinheim, Germany, 2013.

4796 | *Org. Biomol. Chem.*, 2013, **11**, 4792–4796

This journal is © The Royal Society of Chemistry 2013