HETEROCYCLES, Vol. 73, 2007, pp. 177 - 182. © The Japan Institute of Heterocyclic Chemistry
Received, 16th June, 2007, Accepted, 27th August, 2007, Published online, 28th August, 2007. COM-07-S(U)17

NEW END-ON THIOLACTONE SCAFFOLD BY AN ISOCYANIDE-BASED MULTICOMPONENT REACTION

Barbara Beck,[1] Stuti Srivastava,[1] and Alexander Dömling*

Departments of Pharmaceutical Sciences and Chemistry, University of Pittsburgh, Pittsburgh, PA 12580, USA; asd30@pitt.edu

Abstract – The three component reaction of homocysteine, an oxocomponent and an isocyanide smoothly and stereoselectively yields *N*-substituted 2-(2-oxotetrahydrothiophen-3-ylamino)acetamides. In this communication we present our preliminary results on six compounds derived from this unprecedented reaction.

INTRODUCTION

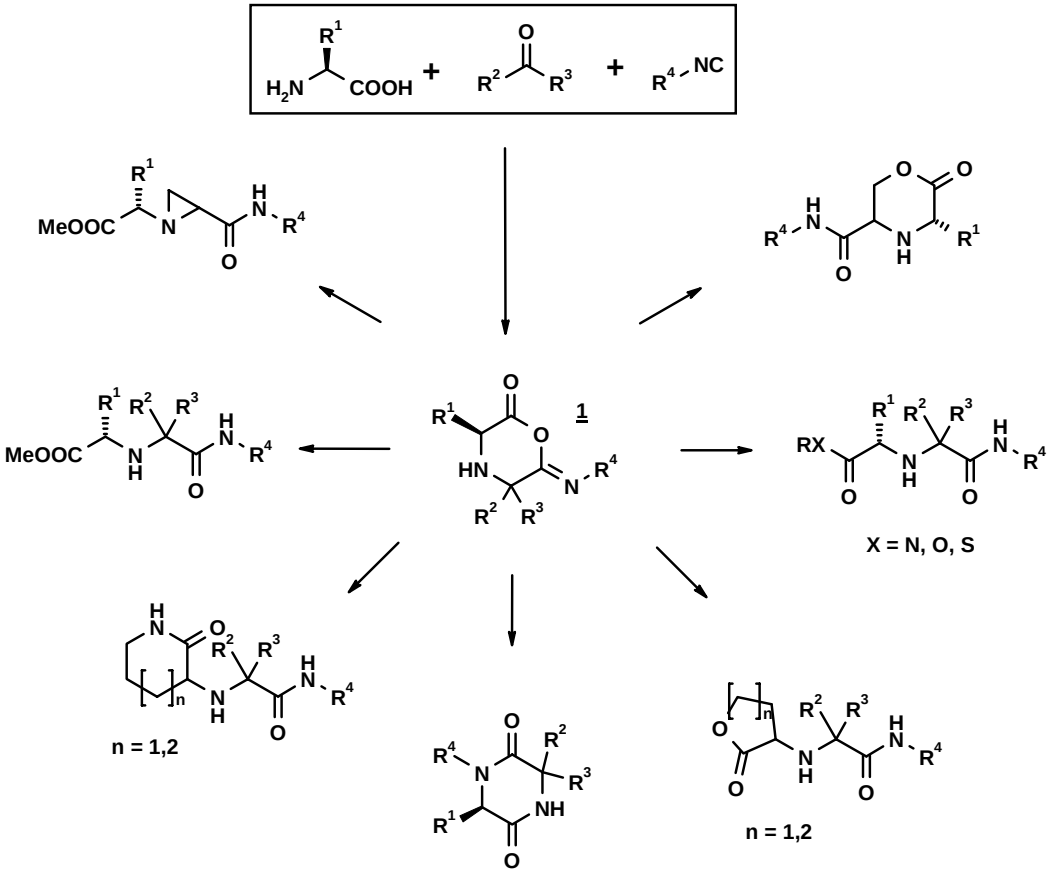
Ivar Ugi, 50 years ago, pioneered isocyanide-based multi component reactions (IMCR) for applications in combinatorial chemistry and organic chemistry (e.g. peptide synthesis), long time before the term combinatorial chemistry was even coined.[1] As an example he discovered an elegant and efficient one-pot access to the popular local anesthetic Xylocaine™ using his famous Ugi condensation in a three component variation, starting from formaldehyde, diethylamine and 2,5-dimethylphenylisocyanide.[2] More importantly, he immediately recognized that many variations are accessible as well by variations of the three starting materials. That time he called these derivatives collections of compounds, nowadays they are called libraries. Certainly the value of his work in the area of combinatorial chemistry can not be overestimated!

A particular useful variation of the Ugi reaction is the use of unprotected α-amino acids as components incorporating the carboxylic acid and amine functionality.[3] Depending on the nature of the amino acid and the other starting materials a variety of different general scaffolds are accessible: imino dicarboxylic acid derivatives, (di)ketopiperazines, aziridines, 2-keto-morpholines, δ-lactones, isoindoles, isoquinolines and γ-,δ-lactams (Scheme 1).[4-11] Importantly, the absolute configuration of the chiral α-amino acids

[1] Contributed equally to the present work.

remains unchanged during this reaction, thus the reactions are stereoselective. Recently, selective and potent T-type Ca^{2+} channel inhibitors have been discovered in such α-amino acid derived Ugi libraries.[10]

Scheme 1. The diversity of Ugi-type reactions using α-amino acids.



RESULTS AND DISCUSSION

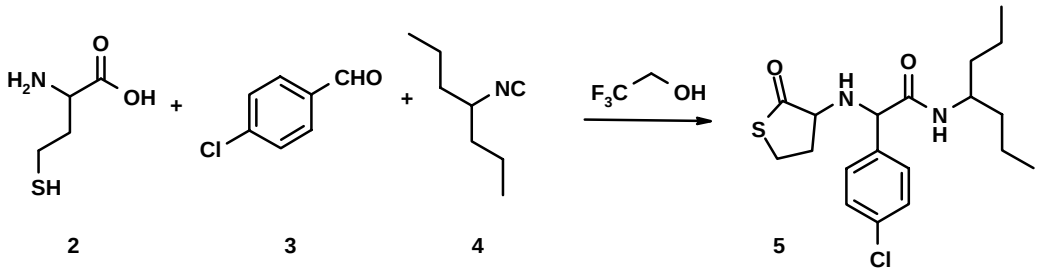
Recognizing the usefulness of the chemistry of α-amino acid-based Ugi reactions we would like to add a novel scaffold to the toolbox of isocyanide-based multi component reactions[11] and communicate our recent findings on the one-pot synthesis of thio-γ-lactones by Ugi reactions.

The thiolactone moiety is of general interest as part of bioactive natural products, e.g. in thiolactomycin. Moreover, thioesters and lactones are discussed to be critical to the origin of the world: "*The thioester bond is what biochemists call a high-energy bond, equivalent to the phosphate bonds in adenosine triphosphate (ATP), which is the main supplier of energy in all living organisms. ...*

It is revealing that thioesters are obligatory intermediates in several key processes in which ATP is either used or regenerated. Thioesters are involved in the synthesis of all esters, including those found in complex lipids. They also participate in the synthesis of a number of other cellular components, including peptides, fatty acids, sterols, terpenes, porphyrins and others. In addition, thioesters are formed as key intermediates

in several particularly ancient processes that result in the assembly of ATP. In both these instances, the thioester is closer than ATP to the process that uses or yields energy. In other words, thioesters could have actually played the role of ATP in a thioester world initially devoid of ATP. Eventually, [these] thioesters could have served to usher in ATP through its ability to support the formation of bonds between phosphate groups."[12]

In an attempt to design novel bioactive small molecules, particularly potential protease inhibitors, we reacted the α-amino acid homocystein with aldehydes and isocyanides in trifluorethanol to yield *N*-substituted 2-(2-oxotetrahydrothiophen-3-ylamino)acetamides. The scaffold design is based on the known 6-membered α-adduct of the α-amino acid derived Schiff base onto the isocyano carbon **1**, representing the mechanistically most significant hallmark of Ugi reactions. This cyclic hetero carbonic acid anhydride represents a strong acylating intermediate and can react in an intermolecular (e.g. with methanol as the solvent) or intramolecular fashion (with nucleophilic side chains in one of the starting materials) and thus determines the structural fate of the formed scaffold. The ratio inter- vs. intramolecular acylation can be governed by the choice of solvent. E.g. if trifluorethanol as a non nucleophilic solvent is used the intramolecular reaction pathway is dominant.



Scheme 2. The reaction of homocysteine **2**, 4-chlorobenzaldehyde **3** and 4-isocyanoheptane **4** in TFE yields **5**.

In a first attempt we reacted racemic homocysteine with **3** and **4** in trifluorethanol (Scheme 2).[13] The solution became clear after a couple of hours and a solid precipitated out of the solution after another couple of hours. Isolation of the solid by filtration and analysis by NMR revealed the formation of a new compound which was in accordance with the designed thiolactone scaffold, e.g. the formation of a downfield signal for the thioester carbonyl carbon at 210 ppm in the ^{13}C NMR is very indicative. Luckily, a diffraction quality crystal could be grown and the corresponding X-ray structure analysis confirmed the predicted structure (Figure 1).[14]

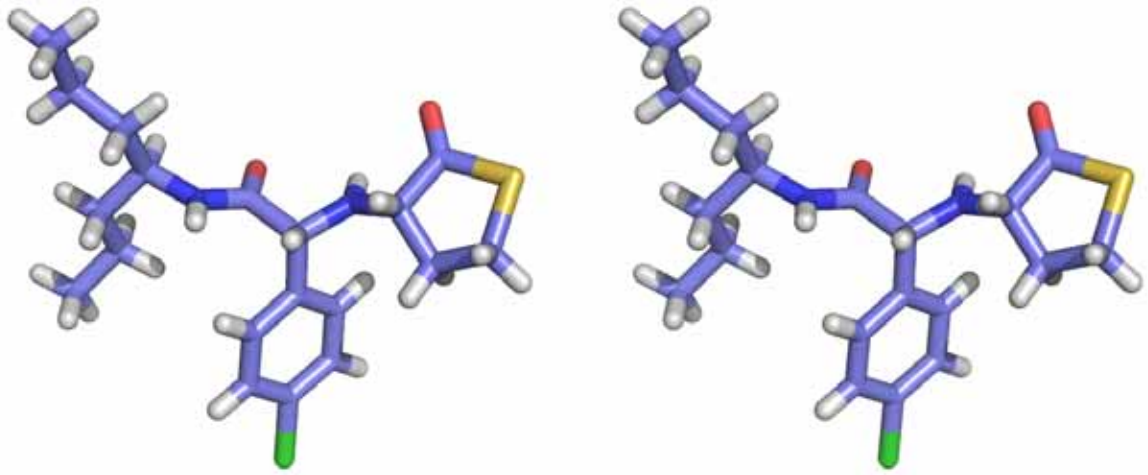
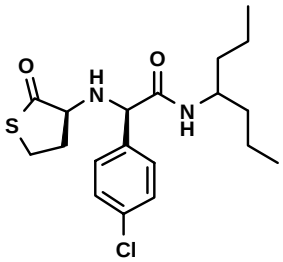
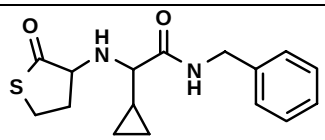
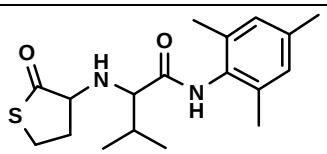
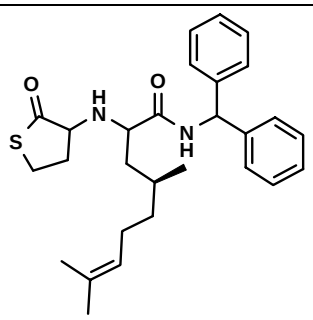
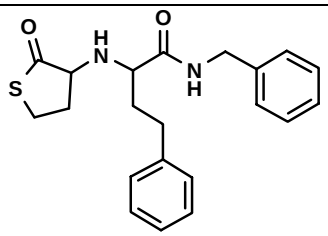
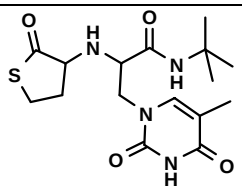


Figure 1. Stereopicture of the x-ray structure of γ-thiolactone **5**. The picture was generated using PyMol (www.pymol.com).

Next, we performed some variations in the aldehyde and isocyanide component. All performed reactions yielded the expected γ-lactone. Gratifyingly, we observed that in most of the reactions the product precipitated out of the solution. Experimentally simple filtration yielded NMR pure products in good yields (Table 1). The compounds were generally formed as mixture of diastereomers, e.g. **5** in a ratio of 85:15. During precipitation, however, mostly one diastereomere was isolated.

Table 1. Structures and yields of γ-thiolactones prepared.

no	structure	yield [%]	no	structure	yield [%]
5		30	**8**		77
6		25	**9**		43

7		73	**10**		45

In summary, we have described a novel 3-component isocyanide-based multicomponent reaction of isocyanides, homocystein and aldehydes yielding *N*-substituted 2-(2-oxotetrahydrothiophen-3-ylamino)acetamides. Noteworthy, the described scaffold is unprecedented in chemical literature and is of interest with potential inherent protease inhibitory properties. The experimental protocol of this new isocyanide-based multi component reaction is very simple thus making this reaction potentially amenable to automation. Current investigations in our laboratorium are targeted towards the synthesis of libraries of γ-thiolactone and their biological investigation.

ACKNOWLEDGEMENT

We thank Kareem Khoury, Sukhpreet Kaur and Kelly Hey for their help in the preparation of some compounds.

REFERENCES AND NOTES

1. I. Ugi, R. Meyr, U. Fetzer, and C. Steinbrückner, *Angew. Chem*., 1959, **71**, 386.
2. I. Ugi and C. Steinbrückner, DE-B 1,103,337, **1959**.
3. G. Gockel, G. Lüdcke, and I. Ugi, 'Organic Chemistry: Isonitrile Chemistry,' Vol. 20, ed. by I. Ugi, Academic Press, Inc., New York, 1971, p. 158.
4. A. Demharter, W. Hörl, E. Herdtweck, and I. Ugi, *Angew. Chem., Intl. Ed. Engl.*, 1996, **35**, 173; K. Sun, F.-L. Chen, and M.-J. Chung, *Mol. Div.*, 2003, **6**, 213.
5. I. Ugi, A. Demharter, W. Hörl, and T. Schmid, *Tetrahedron*, 1996, **52**, 11657.
6. S. J. Park, G. Keum, S. B. Kang, H. Y. Koh, Y. Kim, and D. H. Lee, *Tetrahedron Lett*., 1998, **39**, 7019.
7. Y. B. Kim, S. J. Park, G. Keum, M. S. Jang, S. B. Kang, D. H. Lee, and Y. Kim, *Bull. Korean Chem. Soc.*, 2002, **23**, 1277.
8. D. Kadzimirsz, D. Hildebrandt, K. Merz, and G. Dyker, *Chem. Commun.*, 2006, 661.
9. Y. B. Kim, E. H. Choi, G. Keum, S. B. Kang, D. H. Lee, H. Y. Koh, and Y. Kim, *Org. Lett*., 2001, **3**, 4149.
10. I. W. Ku, S. Cho, M. R. Doddareddy, M. S. Jang, G. Keum, J.-H. Lee, B. Y. Chung, Y. Kim, H. Rhim, and S. B. Kang, *Bioorg. Med. Chem. Lett*., 2006, **16**, 5244; M. R. Doddareddy, H. K. Jung, J. Y. Lee, Y.

S. Lee, Y. S. Cho, H. Y. Koh, and A. N. Pae, *Bioorg. Med. Chem*., 2004, **12**, 1605.

11. A. Dömling, *Chem. Rev.,* 2006, **126**, 17.
12. C. de Duve, "The Beginning of Life on Earth," *American Scientist,* 1995, **83**, 430.
13. General procedure: Homocycteine (270 mg, 2 mmol) are solubilized in trifluorethanol (TFE) (10 mL) and cooled under nitrogen to -20 ^{o}C. A solution of isocyanide (2 mmol) and aldehyde (2 mmol) in TFE (5 mL) are added dropwise. The reaction mixture is stirred for 1 h in the cold and allowed to warm to rt and stirr over night. The solvent is evaporated and the residue is dissolved in EtOAc and extracted with 2x water, and brine. The organic layer is dried over magnesium sulfate and concentrated. In most cases the product can be crystallized from EtOAc to yield the major diasteromere. In the other cases the crude product is purified by column chromatography on silica gel with heptane/EtOAc elution gradient from 3/1 to 1/2.

    2-(4-Chloro-phenyl)-2-(2-oxotetrahydrothiophen-3-ylamino)-*N*-(1-propylbutyl)acetamide **5** $C_{19}H_{27}ClN_2O_2S$; MW 382.94; Yield: 115 mg (30%) [diasteriomeric ratio 85:15]; HRMS found: m/z: 383.1742 $[M+H]^+$, 405.1573 $[M+Na]^+$; ^{1}H-NMR for the major isomer ($CDCl_3$, 600 MHz): δ = 0.87-0.93 (m, 6H), 1.20-1.42 (m, 8H), 1.94-1.96 (m, 1H), 2.41-2.46 (m, 1H), 3.17-3.23 (m, 2H), 3.30-3.33 (m, 1H), 3.86-3.88 (m, 1H), 4.45 (brs, 1H), 6.38 (d, J= 8.88 Hz, 1H), 7.30-7.33 (m, 4H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 13.75, 19.01, 27.48, 30.40, 37.18, 37.31, 48.93, 64.72, 65.47, 116.12, 128.60, 129.11, 134.32, 137.61, 170.59, 207.77.
14. The X-ray structure data of compound **5** are deposited at the CCDC (Cambridge) under the accession number CCDC 657496.