Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5987–5990
Tetrahedron Letters

Preparation of peptide-like bicyclic lactams via a sequential Ugi reaction—olefin metathesis approach ☆

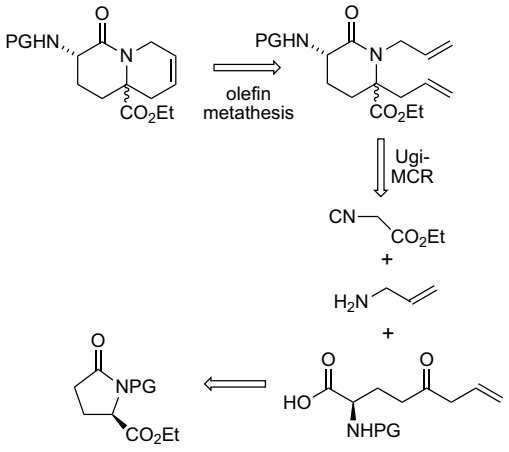
Ralf Krelaus and Bernhard Westermann*

Leibniz-Institute of Plant Biochemistry, Department of Bioorganic Chemistry, Weinberg 3, 06120 Halle (Saale), Germany

Received 27 April 2004; revised 27 May 2004; accepted 11 June 2004

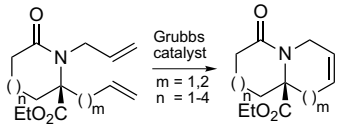
Abstract—Bicyclic lactams, suitable for incorporation into conformationally restricted peptide mimics, can be synthesized by using olefinic starting materials for the Ugi multicomponent reaction, setting up an olefin metathesis reaction, that is easily carried out with the Grubbs catalyst. The influence of the different starting materials is evaluated. In addition, the utilization of chiral, non-racemic amines is described.

The Ugi multicomponent reaction (MCR) is a very versatile reaction for the preparation of peptides and peptide mimics due to its high product diversity.[2] This is of particular interest for the synthesis of compound ensembles required for the discovery of new lead structures. This intriguing and simple reaction is remarkably flexible. For suitable starting materials, a high degree of functionalization in the amine, the carboxylic acid, the isocyanide, and the carbonyl compound are tolerated. However, the Ugi reaction has rarely been used to synthesize lactams.[3] In such cases, the classical Ugi 4-component-4-center reaction would have to be reduced to a 3-component-4-center reaction (Scheme 1).



Scheme 1.

In the preceding paper we have presented our approach to the synthesis of bicyclic lactams, materials, that can be used as peptide mimics.[4] We are thus also interested in new pathways to obtain these products in a more straightforward and short synthesis that would also allow diversification. A retrosynthetic scheme is presented in Scheme 1. Key steps for the synthesis of bicyclic lactams are a ring opening reaction of pyroglutamic acid, an Ugi multi component reaction (MCR) and a ring closing olefin metathesis. Recently, we have reported the use of olefin metathesis on suitable lactams with the first generation Grubbs catalyst (Scheme 2).[5]

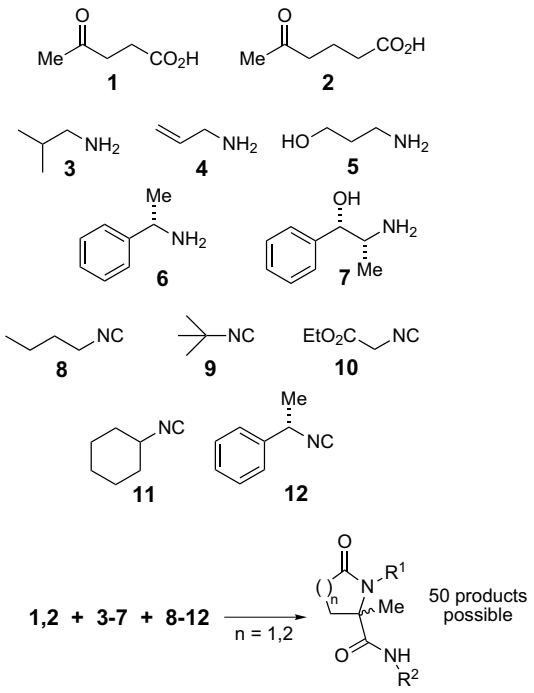


Scheme 2.

To utilize the olefin metathesis for cyclization to form the bicyclic heterocycle, olefinic starting materials have to be used in order to do a Ugi MCR reaction. Very recent reports utilized olefinic starting materials in the

Keywords: Ugi reaction; Olefin metathesis; Isocyanide; Peptide mimic.
☆ See Ref. 1.
* Corresponding author. Tel.: +49-345-5582-1340; fax: +49-345-5582-1309; e-mail: bwesterm@ipb-halle.de

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.06.052



Scheme 3.

Ugi reaction.[6] Due to the limited information available, we were interested in studying the influence of these functional groups in the Ugi reaction. Here, we present our results using olefinic starting compounds in an Ugi 3-component-4-center reaction. In addition, we demonstrate the use of chiral, nonracemic starting compounds.

In preliminary experiments we applied the Ugi reaction to lactams **13** (Scheme 3). For this, ketocarboxylic acids **1** and **2** in the presence of amines **3**–**7** and isocyanides **8**–**12** were used. Levulinic acid **1** and its homologue **2** were chosen, because the methyl group in these substrates allows easy characterization of the products. In racemates, it appears as a singlet in the ^{1}H NMR spectra. While employing chiral, nonracemic starting materials, the diastereomeric ratio of the Ugi products can be determined by integration of the two singlets. For the formation of diastereomers, amines **6** and **7**, and isocyanide **12** were used as chiral, nonracemic starting materials. With these, the influence of stereocenters can be studied. In the case of amines, allyl amine **4** was used to introduce olefins.

In Table 1 the results of the Ugi reaction using levulinic acid **1** are presented.[7] It can be seen that the yield of the Ugi reaction is highly dependent on the isocyanide. With the very lipophilic isocyano butane **8**, the yields (**13**–**15**) are very high (81–92%), whereas ethyl 2-isocyano acetate leads to **16**–**18** in low to moderate yields (7–51%).

Furthermore, the olefinic moieties of lactams **14** and **17** are not affected under the conditions of the Ugi reaction. Therefore, olefinic building blocks such as allyl amine **4** can be employed. While using the chiral amine **6**, no

Table 1. Results of the Ugi MCR reaction of **1** with isocyanides **8**, **10**, and amines **3**, **4**, **6** as starting materials

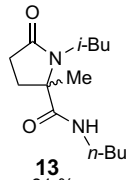
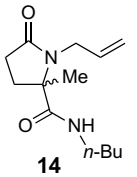
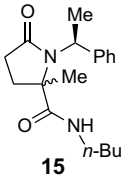
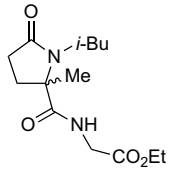
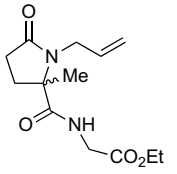
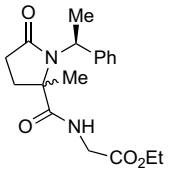
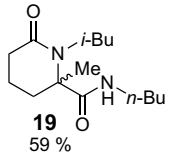
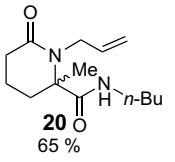
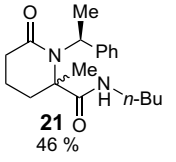
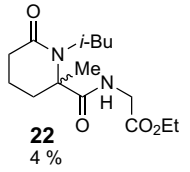
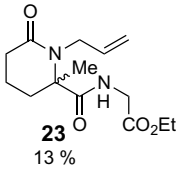
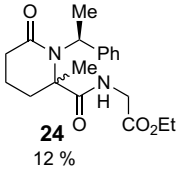
	3	**4**	**6**
8	 **13** 81 %	 **14** 86 %	 **15** 92 %
10	 **16** 12 %	 **17** 51 %	 **18** 7 %

Table 2. Results of the Ugi MCR reaction of **2** with isocyanides **8**, **10**, and amines **3**, **4**, **6** as starting materials

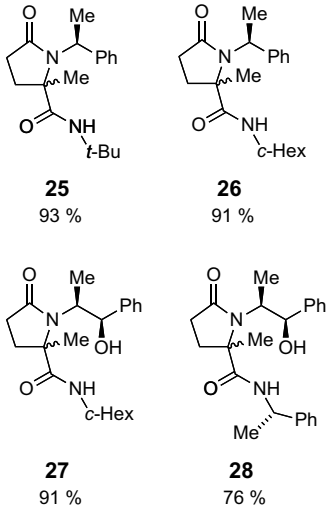
	3	**4**	**6**
8	 **19** 59 %	 **20** 65 %	 **21** 46 %
10	 **22** 4 %	 **23** 13 %	 **24** 12 %

diastereomeric excess was observed; in both cases (**15**, **18**) a 1:1 ratio is obtained. The same pattern of reactivity and selectivity is achieved using δ-keto carboxylic acid **2**, leading to products **19**–**24** (Table 2) in lower yields, compared to the products formed by using **1**.

The postulated mechanism for the Ugi reaction includes the Mum-rearrangement.[1] It can be assumed that the transition state during this rearrangement, which will be six-membered for levulinic acid **1**, is favorable to the seven-membered transition state for **2**. This might explain the higher yields for the formation of the γ-lactams.

To examine the influence of the isocyano substrate further, isocyanides **9**, **11**, and **12** in the presence of the chiral amines **6** and **7** were used. The corresponding lactams **25**–**28** were also obtained in high yields, indicating that isocyanides with a high CH-acidity at the α-center of the isocyanides are not favorable.[8]

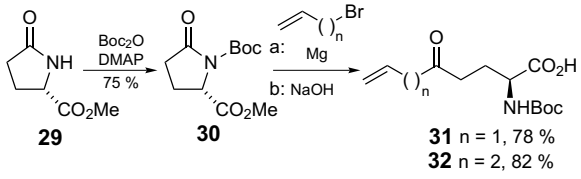
It is interesting to note that even by employing two chiral substrates, no diastereoselectivity can be observed. Lactam **28** is obtained as a 1:1 mixture of diastereomers.



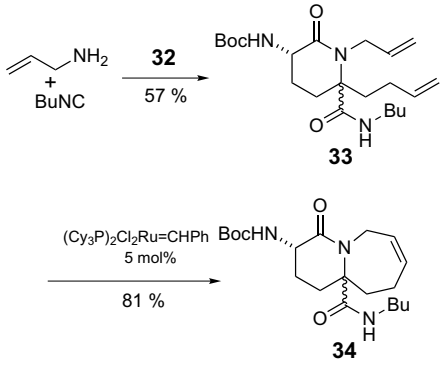
For the synthesis of bicyclic lactams an easy approach toward unsaturated keto carboxylic acids is required.

Protection of pyroglutamic ester **29** affords lactam **30**. Ring opening nucleophilic attack by Grignard reagents derived from allyl bromide and 3-butenyl bromide, respectively, achieves the synthesis of the two-centered, olefinic amino acids. Subsequently, the Ugi reaction employing **32** in the presence of allyl amine leads to highly functionalized lactam **33** bearing two olefinic moieties (Scheme 4).

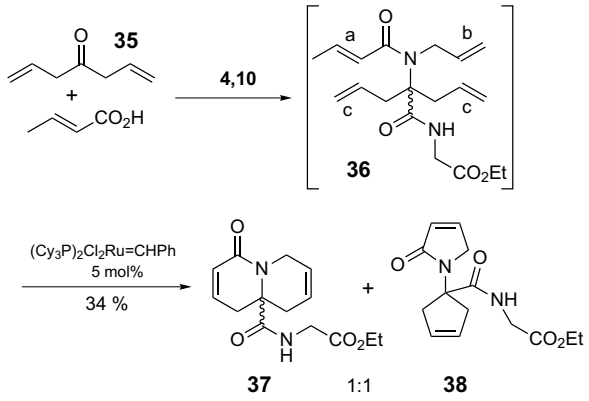
In agreement with our previous results, a 1:1 ratio of diastereomers was obtained. In the next step, a ring closing olefin metathesis (RCM) using the Grubbs catalyst was carried out (Scheme 5). In the presence of $[Ru(PCy_3)_2Cl_2]$=CHPh (5 mol%) the bicyclic product **34** is formed in 81% yield. The whole sequence starting



Scheme 4.



Scheme 5.



Scheme 6.

from pyroglutamic acid requires only five steps to this peptide mimics making it a very short synthesis of this highly complex molecule.

An even shorter route can be envisioned by utilizing an Ugi reaction to the tetraolefinic amide **36**, setting up a double RCM directly (Scheme 6).

Carbonyl compound **35** can be obtained by oxidation of the commercially available alcohol. For the carboxylic acid we chose crotonic acid, anticipating that a distinction in the RCM reaction should exist if one of the double bonds is disubstituted. Two modes of cyclization are possible: cyclization of a/c and b/c leading to **37** and cyclization of a/b and c/c leading to **38**.

As expected, the Ugi reaction led to the tetraolefinic intermediate **36**, which was cyclized without further purification. After the RCM reaction, **37** and **38** were isolated in a 1:1 ratio. This formation of analogous products was observed very recently by Ma and Ni.[9] They found that the outcome of the RCM is highly dependent on whether a quaternary center or a tertiary stereogenic center is formed. In the case of formation of the quaternary center, both products are formed to the same extent.

In conclusion, we have shown that bicyclic lactams can be synthesized by a sequence of Ugi reaction and ring closing olefin metathesis. The 3-component-4-center Ugi reaction seems to be advantageous for the preparation of highly olefin-functionalized lactams. It can be selectively bicyclized with the Grubbs catalyst. The Ugi reaction toward a tetraolefinic intermediate followed by a RCM should be by far the shortest route toward such products, although the selectivity in the RCM will require further studies.

Acknowledgements

Financial support was provided by the Fonds der Chemischen Industrie and the Graduiertenstiftung NRW (grant to R.K.), which is gratefully acknowledged.

References and notes

1. The work has been carried out mainly at the University of Paderborn, Germany. It has been presented, in part, at the Chemiedozententagung, abstract A33, Cologne, Germany, **2002**.
2. Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
3. (a) Harriman, G. C. B. *Tetrahedron Lett.* **1997**, *38*, 5591–5594; (b) Short, K. M.; Mjalli, M. M. *Tetrahedron Lett.* **1997**, *38*, 359–362; (c) Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett.* **1998**, *39*, 2725–2728; (d) Marcaccini, S.; Pepino, R.; Torroba, T.; Miguel, D.; Garcia-Valverde, M. *Tetrahedron Lett.* **2002**, *43*, 8591–8593; (e) Zimmer, R.; Ziemer, A.; Gruner, M.; Brüdgam, I.; Hartl, H.; Reissig, H. U. *Synthesis* **2001**, 1649–1658.
4. Westermann, B.; Diedrichs, N.; Krelaus, R.; Walter, A.; Gedrath, I. *Tetrahedron Lett.*, see preceding paper, doi:10.1016/j.tetlet.2004.06.051.
5. (a) Diedrichs, N.; Westermann, B. *Synlett* **1999**, 1127–1129; (b) Diedrichs, N.; Krelaus, R.; Gedrath, I.; Westermann, B. *Can. J. Chem.* **2002**, *80*, 686–691.
6. (a) Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709–712; (b) Hebach, C.; Kazmaier, U. *Chem. Commun.* **2003**, 596–597; (c) Beck, B.; Larbig, G.; Magnin-Lachaux, M.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 1047–1050.
7. General procedure for the synthesis of lactam **13**: levulinic acid **1** (1.00 g, 8.6 mmol) was dissolved in dry methanol (43 mL) and isobutylamine **3** (0.79 g, 10.8 mmol) was added. The mixture was stirred for 30 min at room temperature to allow formation of the imine. 1-Isocyanobutane **8** (0.71 g, 8.6 mmol) was added and the mixture is stirred for two days at room temperature.
   The solvent was removed and the remaining oil was dissolved in dichloromethane and washed successively with diluted hydrochloric acid and sodium carbonate solution. The organic phase was dried over sodium sulfate and filtered. Solvent was removed in vacuum to result 2-(*R*,*S*)-*N*-butyl-1-isobutyl-2-methyl-5-oxo-2-pyrrolidine-carboxamide **13** (yield 81%) as a yellow oil, which was characterized without further purification.
   ^{1}H NMR ($CDCl_3$) 0.93 (d, $J = 6.6$ Hz, 6H), 0.93 (t, $J = 6.9$ Hz), 1.22–1.55 (m, 4H), 1.56 (s, 3H), 1.83–2.10 (m, 2H), 2.26–2.47 (m, 2H), 2.72 (dd, $J_1 = 6.9$ Hz, $J_2 = 13.8$ Hz, 1H), 3.20–3.42 (m, 4H), 5.90 (br s, 1H). ^{13}C NMR ($CDCl_3$) 14.1, 20.5, 20.7, 21.1, 24.0, 28.6, 30.0, 32.0, 33.5, 40.0, 49.3, 68.3, 173.8, 176.7. HRMS calcd for $C_{14}H_{26}N_2O_2$ $[M]^+$ m/e 254.19943, found m/e 254.20132.
8. Orru, R., personal communication.
9. (a) Ma, S.; Ni, B. *Org. Lett.* **2002**, *4*, 639–641; (b) Ma, S.; Ni, B. *Chem. Eur. J.* **2004**, online preprint.