Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 587–590
Tetrahedron Letters

U-4C-3CR versus U-5C-4CR and stereochemical outcomes using suitable bicyclic β-amino acid derivatives as bifunctional components in the Ugi reaction

Andrea Basso,* Luca Banfi, Renata Riva and Giuseppe Guanti*

Dipartimento di Chimica e Chimica Industriale, Università degli Studi di Genova, Via Dodecaneso 31, 16146 Genova, Italy

Received 9 September 2003; revised 24 October 2003; accepted 30 October 2003

Abstract—Intramolecular Ugi reactions with bicyclic β-amino acids have been performed and the effects of the configuration and *N*-alkylation have been studied. We have proven that preferential ring contraction or nucleophilic attack by the solvent depend not only on the presence of *N*-alkylation but also on the relative disposition of the carboxyl group and the amine. Excellent results in terms of stereoselectivity have been obtained in the case of *N*-alkyl-3-*exo*-amino-7-oxabicyclo[2.2.1]-2-*endo*-carboxylic acids.

The Ugi four-component reaction (U-4CR) is a valuable tool in organic chemistry for generating α-amino acid derivatives in a very straightforward manner by condensing an aldehyde, an amine, a carboxylic acid and an isocyanide in one pot.[1] Intramolecular versions of the Ugi reaction have also been reported, where two of the four functional groups are present on the same molecule. The possibility of generating β-lactam rings using β-amino acids as bifunctional compounds is known as the Ugi-4-centre-3-component reaction (U-4C-3CR).[2a–f] This reaction evolves through a seven-membered ring intermediate (Fig. 1, $R^3 = H$, $n = 2$),[2c] to give the β-lactam derivative via a ring-contraction step.

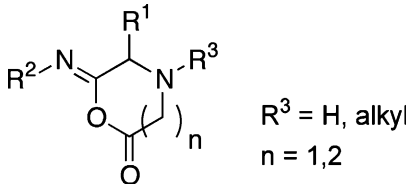


Figure 1. Cyclic intermediate for Ugi intramolecular reactions with α- and β-amino acids.

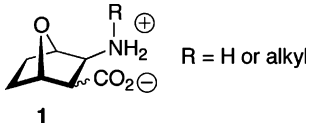
It has been reported that α-amino acids can react in an intramolecular version of the Ugi reaction (Ugi-5-centre-4-component reaction, U-5C-4CR)[3a] via a similar mechanism; in this case the six-membered ring intermediate (Fig. 1, $R^3 = H$, $n = 1$) cannot evolve via a ring contraction but reacts with a nucleophile, such as methanol used as the solvent, to give, α,α′-imino dicarboxylic acid derivatives with very high conversions and good diastereoselectivities.[3a–f] This reaction has been reported with various α-amino acids, mainly with primary amino groups, although proline[3b,f] is also reported to react in the same way.

We recently became interested in the synthesis of pharmacologically relevant molecules via the Ugi multicomponent reaction and therefore we have investigated both the classical condensation and its intramolecular versions. In this communication we report the results that we have obtained performing the intramolecular Ugi reaction with racemic β-amino acid derivatives of general formula **1** (Fig. 2), where the amino group can be either primary or secondary and the carboxyl group either *exo* or *endo*. The alkylated amine, reacting with an aldehyde, would form an iminium zwitter ionic species analogous to that formed when proline is employed in the same reaction, while the primary amine would react like any other amino acid. The choice for compounds of formula **1** was made in order to have a rigid scaffold, able in principle to exert more influence on the stereoselectivity than would flexible counterparts.

Keywords: Multicomponent reactions; Intramolecular Ugi reaction; β-Amino acids; Chiral auxiliary; Stereoselective Ugi reaction; Ugi with secondary amines.

* Corresponding authors. Tel.: +39-010-3536117; fax: +39-010-3536-118 (A.B.), tel./fax: +39-010-3536105 (G.G.); e-mail addresses: andreab@chimica.unige.it; guanti@chimica.unige.it

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.10.193

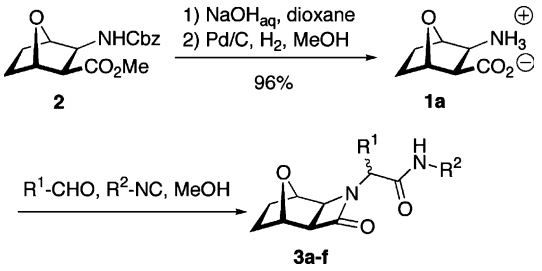


1

Figure 2. General formula for β-amino acid derivatives employed in the Ugi intramolecular reactions.

Compound **1a** was obtained from methyl 3-*exo*-(benzyl oxycarbonyl)amino-7-oxabicyclo[2.2.1]-2-*exo*-carboxylate **2** in two steps and was reacted with different combinations of aldehydes and isocyanides to give, as expected, the corresponding bicyclic β-lactams **3a–f** (Scheme 1). However, an examination of the diastereomeric ratio, determined by NMR analysis, revealed that the de's were disappointingly not higher than 42% (Table 1).[4] We recently came across a paper by Fulöp and co-workers[5] where they reported similar results with analogous bicyclic amino acids.

We then attempted the synthesis of the *N*-methylated *cis* amino acid, but when we treated compound **2** with sodium hydride and methyl iodide, we isolated, as the sole product, the *endo N*-methyl epimer **5** (Scheme 2). This epimerisation is most likely taking place on the methylated product **4**, by deprotonation of the more acidic carbon, that is the one alpha to the carboxyl group; in fact compound **2**, when treated with sodium hydride in the absence of methyl iodide, epimerised only after prolonged exposure, since in this case the more acidic proton is the NH, and epimerisation can only occur via the dianionic species.



2 1a 3a-f

Scheme 1. Synthesis of amino acid **1a** and subsequent Ugi reactions.

Table 1. Results obtained in the Ugi reaction with scaffold **1a**

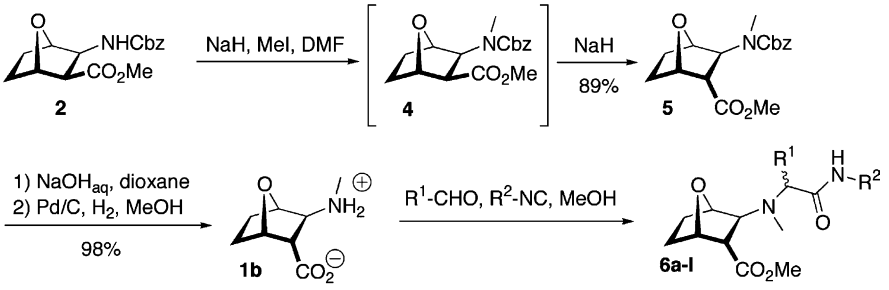
Compound	R^1	R^2	Yield (%)	Dr
3a	*i*-Pr	*t*-Bu	96	67:33
3b	*i*-Pr	*n*-Bu	84	68:32
3c	Ph	*t*-Bu	78	71:29
3d	Ph	*n*-Bu	84	71:29
3e	Bn	*t*-Bu	95	52:48
3f	Bn	*n*-Bu	90	50:50

Before looking for alternative procedures to obtain the *cis* compound, we decided to investigate the reactivity of amino acid **1b**, obtained from **5** in two steps by analogy with **1a**, in the Ugi reaction. We found that this *N*-alkylated-amino acid reacted smoothly with isovaleric aldehyde and *tert*-butyl isocyanide and after 24 h at room temperature the main product was found to be the methyl ester **6a**. In this case the postulated cyclic intermediate (Fig. 1, R = alkyl, $n = 2$), being unable to undergo intramolecular ring contraction to the corresponding β-lactam, preferably reacted intermolecularly with methanol, in analogy with α-amino acids, to generate the corresponding methyl ester (Scheme 2).

However, the most interesting outcome of this reaction was that, after an accurate NMR analysis, only one diastereoisomer was detected, while compound **1a**, with the same aldehyde and isocyanide, gave two diastereoisomers with dr 2:1.

Stimulated by this very promising result and in order to test the generality of the method, we decided to investigate the reaction with a wide combination of aldehydes and isocyanides. We were delighted to find that all the reactions were clean and reached a satisfying conversion within 72 h at room temperature and in all cases, even when extremely *unbulky* aldehydes and isocyanides were employed, only one diastereoisomer could be detected,[6] within the limits of the NMR sensitivity (Table 2),[4] meaning that this *N*-methylated *trans* amino acid could completely control the stereochemistry of the newly formed stereocentre.

With these extremely interesting results in hand, we decided to investigate if the observed stereoselectivity was due mainly to the *trans* configuration or to the presence of an *N*-alkyl group, or to the combination of the two effects. To this end we synthesised the *trans* amino acid **1c** and the corresponding *N*-propylated *cis* derivative **1d**: the first was obtained by prolonged exposure of **2** with sodium hydride, followed by ester hydrolysis and Cbz deprotection, and the latter was obtained from compound **1a** by reductive amination with propanal (Scheme 3). Both compounds were sub-



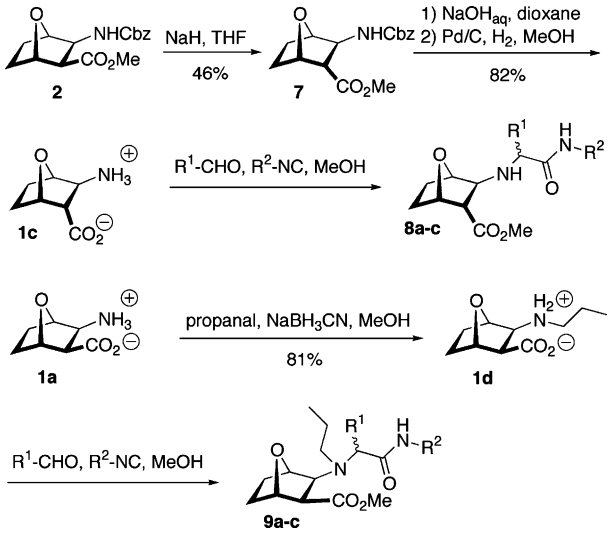
2 4 5 1b 6a-l

Scheme 2. Synthesis of amino acid **1b** and subsequent Ugi reactions.

Table 2. Results obtained in the Ugi reaction with scaffold **1b**[a]

Compound	R^1	R^2	Yield (%)
6a	*i*-Pr	*t*-Bu	50
6b	*i*-Pr	*n*-Bu	90
6c	*i*-Pr	Bn	70
6d	*i*-Pr	$(CH_2)_2CO_2$ Me	90
6e	*i*-Bu	*t*-Bu	60
6f	*i*-Bu	Bn	96
6g	Et	*t*-Bu	50
6h	Et	*n*-Bu	60
6i	Bn	*t*-Bu	50
6j	Bn	*n*-Bu	94
6k	Ph	*t*-Bu	58
6l	Ph	*n*-Bu	93

[a] In all cases the dr was higher than 95:5.



Scheme 3. Synthesis of amino acids **1c** and **1d** and subsequent Ugi reactions.

jected to Ugi reactions with various aldehydes and isocyanides and in these cases not only were the diastereoselectivities lower but also the conversion yields fell (Table 3).[4]

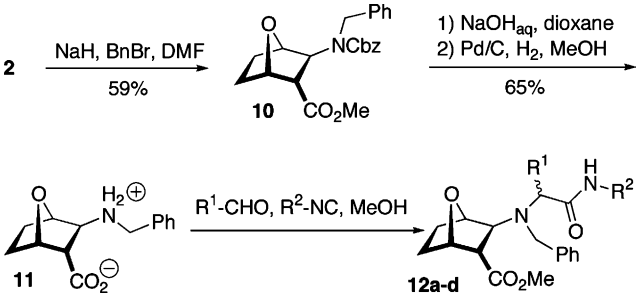
Particularly interesting was the case of compound **1c**, although the amino group was not alkylated, the *trans* configuration did not allow ring contraction, and a methyl ester was isolated in analogy with **1b**. In a recent paper[5] it was reported that *trans* cyclic β-amino acids did not react at all in such a reaction. Only in the case of the reaction with *tert*-butyl isocyanide and isobutyraldehyde was the expected methyl ester **8a** not obtained, while a small amount of a compound with an NMR spectrum consistent with a *trans* β-lactam was isolated.

Table 3. Results obtained in the Ugi reaction with scaffolds **1c** and **1d**

Compound	R^1	R^2	Yield (%)	Dr
8a	*i*-Pr	*t*-Bu	See text	—
8b	*i*-Pr	*n*-Bu	26	>95:5
8c	*i*-Bu	Bn	56	76:24
9a	*i*-Pr	*t*-Bu	5	>95:5
9b	*i*-Pr	*n*-Bu	28	89:11
9c	*i*-Bu	Bn	47	75:25

In order to study in more detail the surprising results obtained with compound **1b**, we looked also for alternative *N*-alkyl groups that could be removed at the end of the condensation (e.g., by hydrogenolysis). Compound **2** was treated with benzyl bromide and sodium hydride and the resulting *trans* derivative **10** was hydrolysed and selectively hydrogenolysed (Scheme 4). Also in this case, after condensation of **11** with different isocyanides and aldehydes, only one diastereoisomer could be detected by NMR, although yields were found to be lower, probably due to the higher steric hindrance of the benzyl group (Table 4).[4]

In a final series of experiments a Ugi reaction was performed on the unsaturated derivative **13**, prepared by modifying a literature procedure, and the sole diastereoisomer obtained (**14**) was subjected to *retro* Diels–Alder reaction and enamine hydrolysis to give the amino acid derivative **16** (Scheme 5). These results proved that compounds such as **13**, in their optically active form,[7] could be efficiently used as chiral auxiliaries in the stereoselective synthesis of α-amino amides via multicomponent Ugi reactions.

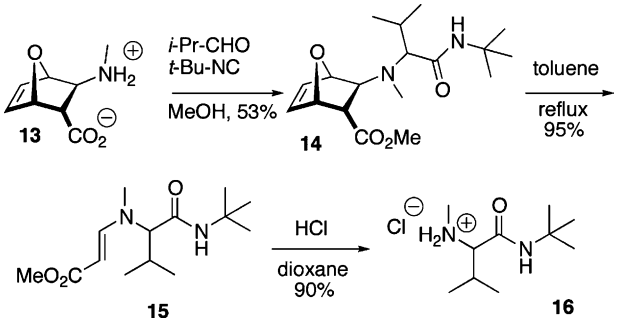


Scheme 4. Synthesis of amino acid **11** and subsequent Ugi reactions.

Table 4. Results obtained in the Ugi reaction with scaffold **11**[a]

Compound	R^1	R^2	Yield (%)
12a	*i*-Pr	*t*-Bu	11
12b	Bn	*n*-Bu	55
12c	Ph	*t*-Bu	30
12d	Bn	*t*-Bu	49

[a] In all cases the dr was higher than 95:5.



Scheme 5. Ugi reaction with an unsaturated bicyclic amino acid and subsequent removal of the chiral auxiliary.

In conclusion this paper reports for the first time the different reactivities of bicyclic β-amino acids in the intramolecular Ugi reaction. We have demonstrated that configuration and *N*-alkylation can play an important role in the outcome of the reaction and we have obtained excellent results in terms of diastereoselectivity with compound **1b**. Finally, we have proven that compounds such as **13** can be successfully employed as chiral auxiliaries and removed at the end of the condensation under very mild conditions. We are currently preparing optically active compounds such as **1b** and **13**[7] in order to obtain, via an intramolecular Ugi reaction, chiral amino acid derivatives and we will investigate, on a molecular basis, with the aid of molecular modelling tools, the reasons for the high stereoselectivity observed. This will hopefully clarify some of the obscure points on the mechanism of the Ugi reaction that are, after about 50 years from its discovery, still debated.

Acknowledgements

The authors wish to thank Dr. Francesca Tarchino for her precious collaboration with this work and Università di Genova and MIUR (COFIN 2002) for financial support.

References and Notes

1. Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169–3210.
2. (a) Ugi, I.; Steinbruckner, C. *Chem. Ber.* **1961**, *94*, 2802–2814; (b) Isenring, H. P.; Hofheinz, W. *Synthesis* **1981**, 385–387; (c) Obrecht, R.; Toure, S.; Ugi, I. *Heterocycles* **1984**, *21*, 271–277; (d) Kehagia, K.; Ugi, I. *Tetrahedron* **1995**, *51*, 9523–9530; (e) Dömling, A.; Kehagia, K.; Ugi, I. *Tetrahedron* **1995**, *51*, 9519–9522; (f) Nitta, H.; Hatanaka, M.; Ishimura, T. *J. Chem. Soc., Chem. Commun.* **1987**, 51–52.
3. (a) Gokel, G.; Lüdke, G.; Ugi, I. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic: New York, 1971; p 158; (b) Demharter, A.; Hörl, W.; Herdtweck, E.; Ugi, I. *Angew. Chem., Int. Ed.* **1996**, *35*, 173–175; (c) Ugi, I.; Demharter, A.; Hörl, W.; Schmid, T. *Tetrahedron* **1996**, *52*, 11657–11664; (d) Zimmer, R.; Ziemer, A.; Gruner, M.; Brudgam, I.; Hartl, H.; Reissig, H. U. *Synthesis* **2001**, 1649–1658; (e) Park, S. J.; Keum, G.; Kang, S. B.; Koh, H. Y.; Kim, Y.; Lee, D. H. *Tetrahedron Lett.* **1998**, *39*, 7109–7112; (f) Kim, Y. B.; Choi, E. H.; Keum, G.; Kang, S. B.; Lee, D. H.; Koh, H. Y.; Kim, Y. S. *Org. Lett.* **2001**, *3*, 4149–4152.
4. Yields refer to isolated products purified by flash chromatography. All new compounds have been fully characterised by NMR and MS.
5. Gedey, S.; Van der Eycken, J.; Fulöp, F. *Org. Lett.* **2002**, *4*, 1967–1969.
6. To confirm unambiguously the absence of the second diastereoisomer, the two diastereoisomers of compound **6f** were independently prepared via an alternative procedure and their NMR spectra were compared with the one of the crude material of the Ugi reaction of compound **1b** with isobutyric aldehyde and benzyl isocyanide, confirming that only one diastereoisomer could be detected within the limits of the NMR sensitivity.
7. Optically active **13** and related compounds can be prepared by desymmetrisation of diesters[8] or anhydrides[9] of *exo*-3,6-epoxy-1,2,3,6-tetrahydro-phthalic acids prior to the Curtius rearrangement generating the amino acid moiety.
8. Guanti, G.; Banfi, L.; Narisano, E.; Riva, R.; Thea, S. *Tetrahedron Lett.* **1986**, *27*, 4639–4642.
9. Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965–2983.