An Efficient Procedure for the Synthesis of Morpholin-2-one-3-carboxamide Derivatives in Good Diastereoselectivity by the Ugi Reaction

Deguang Zhu, Ruijiao Chen, Haibo Liang, Sheng Li, Li Pan, Xiaochuan Chen*

Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. of China
Fax +86(28)85413712; E-mail: chenxc@scu.edu.cn
Received 17 November 2009

Abstract: A series of 5-substituted morpholin-2-one-3-carboxamide derivatives were efficiently synthesized by a Ugi three-component reaction involving chiral 5,6-dihydro[1,4]oxazin-2-one substrates, isocyanides and carboxylic acids. The newly formed chiral center in the product was obtained in good diastereoselectivity.

Key words: Ugi reaction, isonitrile, multicomponent reaction, diastereoselectivity, morpholin-2-one

The Ugi reaction is a very efficient tool that has been used to quickly prepare various pharmacological compounds, such as peptides and heterocyclces, and is widely applied in combinatorial and medical chemistry.[1] Morpholinone derivatives have attracted much attention due to their potential biological and synthetic applications.[2] In 2001, the synthesis of morpholin-2-one-5-carboxamide (**I**) through the Ugi condensation was described by Kim and co-workers (Figure 1).[3] In a subsequent study, the morpholin-2-one compounds were found to exhibit potent and selective T-type Ca^{2+} channel blocking activities.[4] However, to our best knowledge, construction of the morpholin-2-one-3-carboxamide skeleton (**II**) has not yet been reported.

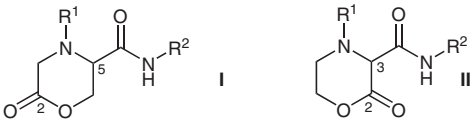
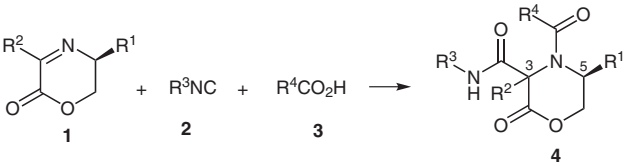


Figure 1

Herein, we wish to present a new Ugi three-component reaction (U-3CR) based on 5,6-dihydro[1,4]oxazin-2-one substrates **1** with isocyanides **2** and carboxylic acids **3** that can be used to effectively synthesize morpholin-2-one-3-carboxamide derivatives **4** (Scheme 1). Such compounds contain the 2-amidomalonyl subunit, which is present in numerous bioactive and pharmacological compounds.[5]

Chiral 5,6-dihydro[1,4]oxazin-2-ones **1a–c** (Figure 2), as preformed cyclic imines for the Ugi reaction, were conveniently prepared from the corresponding natural (*S*)-amino alcohols by literature procedures.[6] Optimal conditions were then sought for the Ugi reaction of **1a** with *tert*-butyl isocyanide (**2a**) and acetic acid (**3a**), which was used as a model reaction (Table 1).



Scheme 1 The Ugi three-component reaction of **1**

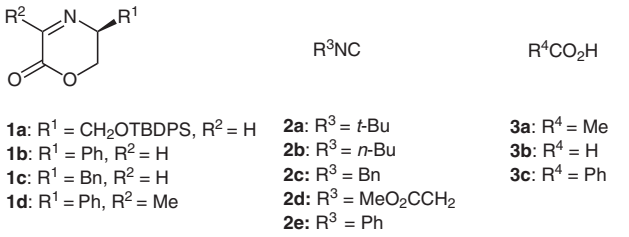


Figure 2 Substrates **1** and **2** and **3**

Screening of solvents revealed that when the reaction was performed in 2,2,2-trifluoroethanol (TFE) it proceeded much faster than in other solvents, to afford **4a** in 70% yield (Table 1, entry 7). Elevating the reaction temperature did not deliver an improvement in the yields (Table 1, entry 9). A similar yield was also obtained using CH_2Cl_2 as solvent but, in this case, prolonged reaction time was necessary for full consumption of **1a** (Table 1, entry 5). In the presence of excess **3a**, the required reaction time in CH_2Cl_2 was shortened, however, only a slight improvement in yield was observed (Table 1, entry 6). Decreasing the amount of **2a** and **3a** led to a reduction in both yield and reaction rate (Table 1, entry 7). Reactions performed in other solvents or at lower temperature often gave diminished yield or failed to proceed. Therefore the U-3CR was preferably carried out in either TFE or CH_2Cl_2 at room temperature.

Subsequently, under the optimized conditions, various cyclic imines, isocyanides and carboxylic acids were reacted to provide morpholin-2-one-3-carboxamide derivatives **4** in moderate to good yield (Table 2).[7] When formic acid (**3b**) was used as the acid component, the reactions were accelerated dramatically even when less acid was used (1.5 equiv), due to its stronger acidity (Table 2, entry 3 vs entry 2); the reactions completed at a similar rate and gave

SYNLETT 2010, No. 6, pp 0897–0900
Advanced online publication: 18.02.2010
DOI: 10.1055/s-0029-1219533; Art ID: W18109ST

Table 1 Optimization of the U-3CR with **1a**, **2a** and **3a**[a]

Entry	Solvent	Time (h)	Temp (°C)	Yield of **4a** (%)
1	MeOH	3 d	r.t.	39[b]
2	toluene	40	r.t.	58
3	THF	40	r.t.	trace
4	CH_2Cl_2	50	r.t.	48[b]
5	CH_2Cl_2	50	r.t.	67
6	CH_2Cl_2	5	r.t.	73[c]
7	TFE	4	r.t.	70
8	TFE	6	–30	51
9	TFE	4	60	68

[a] General conditions: **1a** (1 equiv), **2a** (2 equiv), **3a** (2.2 equiv), r.t.
[b] **1a** (1 equiv), **2a** (1.5 equiv), **3a** (1.6 equiv) were used.
[c] **1a** (1 equiv), **2a** (2 equiv), **3a** (20 equiv) were used.

yields comparable to those obtained when the reaction was carried out in TFE (Table 2, entry 5 vs entry 6). The substituents in imines **1** (R^1) had no clear influence on the yield of the reaction (Table 2, entries 3, 6 and 11). Aliphatic and aromatic isocyanides were well tolerated in the reaction. Finally, imine **1d**,[8] containing a methyl group at R^2, was tested under the same reaction conditions. Unfortunately, in these cases, the reactions were sluggish and the desired product was only obtained in low yield, together with substantial amounts of *N*-formamide formed from hydrolysis of the isocyanide. This could be explained by the steric hindrance of the methyl group.

As optically active 5,6-dihydro[1,4]oxazin-2-one derivatives have been successfully used to explore asymmetric Mannich reactions with phenol,[6c,9] we were interested in the possibility of introducing asymmetric induction into the U-3CR. Until now, controlling the stereochemistry in the Ugi reaction has been a challenging issue; the limited number of cases that have delivered good selectivity were achieved by induction with chiral amines, including 1-phenylethylamines,[10] α-aminoferrocenylamines,[11] aminosugars[12] and some amino acids.[13] In most of the examples above, the chiral auxiliaries need to be subsequently cleaved from the Ugi products. It is therefore desirable to develop further asymmetric Ugi reactions that meet various requirements of modern synthetic processes. In principle, although two diastereomeric products could be formed in our reactions, we could not identify two separable Ugi products by silica gel chromatography. Nonetheless, examination of the ^{1}H NMR spectra of these compounds revealed that most proton signals appeared either in pairs or as broadened peaks, however, it was difficult to conclude whether these pairs of signals were due to rotameric or disastereomeric protons. We also noted that the choice of the solvent used in the reaction had no effect on the ratio of the paired signals. For an example, the products **4b** obtained separately in different solvents (CH_2Cl_2, TFE and toluene) showed the same ratio of paired signals (about 3.4:1) in their ^{1}H NMR spectra. Hence, we decided to carry out further experiments in order to determine the diastereoselectivity of the reaction.

The ^{1}H NMR spectrum of **4f** consisted of two sets of peaks that appeared in a ratio of 1.8 to 1. Lactone **4f** was then reduced with $LiBH_4$ to yield two separable diastereomers **5a** and **5b** in 70% and 15% yield respectively (Scheme 2). The paired signals in the ^{1}H NMR spectra of both products showed that each product contained two rotamers (**5a** in a ratio of 7:1, **5b** in a ratio of 2:1). This suggested that the paired signals in the NMR spectrum did not arise from two diastereomers but from two rotamers. Otherwise, four set of peaks should have been observed. We also believe that the minor isomer **5b** was generated from the epimerization of the C-3 chiral center during reduction because of the highly acidic nature of the H-3 proton due to the presence of two carbonyl functional groups in **4f**.

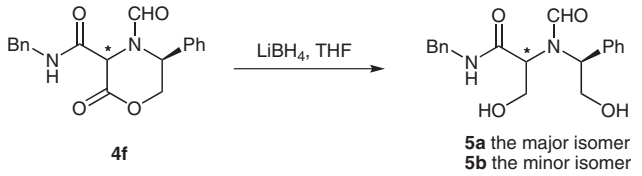
Table 2 Synthesis of 5-Substituted Morpholin-2-one-3-carboxamide Derivatives **4a–p**[a]

Entry	R^1	R^2	R^3	R^4	Solvent	Time (h)	Product	Yield (%)
1	$CH_2OTBDPS$	H	*t*-Bu	Me	TFE	4	**4a**	70
2	$CH_2OTBDPS$	H	*t*-Bu	Me	CH_2Cl_2	50	**4a**	67
3	$CH_2OTBDPS$	H	*t*-Bu	H	CH_2Cl_2	8	**4b**	74
4	$CH_2OTBDPS$	H	*n*-Bu	H	CH_2Cl_2	12	**4c**	66
5	Ph	H	*t*-Bu	H	CH_2Cl_2	2.5	**4d**	71
6	Ph	H	*t*-Bu	H	TFE	2.5	**4d**	73
7	Ph	H	CH_2CO_2Me	Me	TFE	4	**4e**	78
8	Ph	H	Bn	H	CH_2Cl_2	4	**4f**	58
9	Ph	H	CH_2CO_2Me	H	CH_2Cl_2	4	**4g**	80
10	Bn	H	*t*-Bu	H	CH_2Cl_2	7	**4h**	71

Table 2 Synthesis of 5-Substituted Morpholin-2-one-3-carboxamide Derivatives **4a–p**[a] (continued)

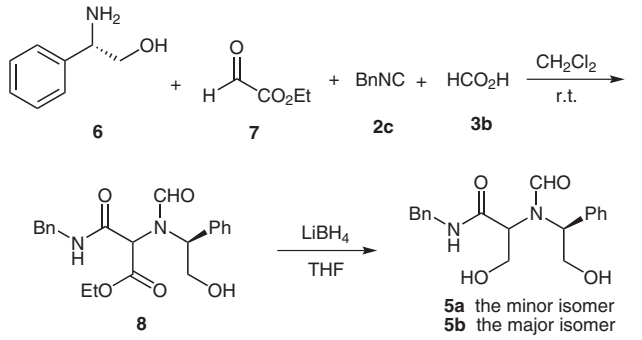
Entry	R^1	R^2	R^3	R^4	Solvent	Time (h)	Product	Yield (%)
11	Bn	H	*t*-Bu	Me	TFE	4	**4i**	62
12	Bn	H	*t*-Bu	Ph	TFE	5	**4j**	66
13	Bn	H	Bn	Me	TFE	4	**4k**	55
14	Bn	H	CH_2CO_2Me	Me	TFE	4.5	**4l**	64
15	Bn	H	CH_2CO_2Me	Ph	TFE	5	**4m**	67
16	Bn	H	Ph	H	TFE	5	**4n**	75
17	Ph	Me	*t*-Bu	H	TFE	30	**4o**	31[b]
18	Ph	Me	*n*-Bu	H	TFE	40	**4p**	37

[a] Reaction conditions: the reactions were carried out at r.t., and **1**, **2** and **3** were used in a ratio of 1:1.5:1.5 (**3b** as acid component) or 1:2:2.2 (**3a** or **3c** as acid component).
[b] Carried out at r.t. with **1/2/3** = 1:1.5:2.2.



Scheme 2 Reduction of compound **4f**

Starting from optically pure (*S*)-2-amino-2-phenylethanol (**6**), the four-component condensation with ethyl glyoxylate (**7**), **2c** and **3b** was performed in CH_2Cl_2 to give a Ugi product mixture containing **8** in 70% yield after column chromatography. The product was then treated with $LiBH_4$ to afford **5a** and **5b** in a 1:3.5 ratio (Scheme 3). Interestingly, a reversal of stereoselectivity was observed with our U-3CR compared to the normal U-4CR.



Scheme 3 Ugi four-component reaction for the synthesis of **8** and subsequent reduction

To further verify the stereoselectivity, the ^1H NMR spectrum of **4a**, in which the paired H-3 (δ = 4.95 and 4.76 ppm) and H-5 (δ = 3.93 and 4.58 ppm) signals from two isomers were easily distinguishable and not overlapped with other proton signals,[14] was used to determine the configuration of the products. The observation of NOE correlation not between H-3 and H-5 but between H-3 and H-a (δ = 3.70 and 3.52 ppm) of each isomer reveals that both isomers of **4a** have 3,5-*trans*-configuration, namely (*S*)-configuration at C-3 (Figure 3). It also confirmed that the two rotamers of the *trans*-adduct are responsible for the paired signals in the NMR spectra. Similarly, in the ^1H NMR spectra of the other Ugi products, almost only one set of paired peaks was observed. Therefore, cyclic imines **1** have the potential to be used to develop new asymmetric Ugi reactions. In the reaction, the favorable attack on the imine from the side opposite to the C-5 substituent gave the thermodynamically more stable *trans*-isomer as the predominant isomer.

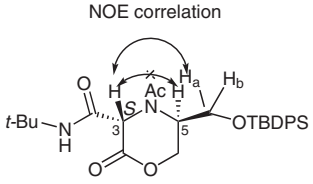


Figure 3 Configuration of the Ugi product **4a** determined by NOESY NMR analysis

In conclusion, a new Ugi reaction of chiral 5,6-dihydro[1,4]oxazin-2-one substrates **1**, isocyanides **2** and carboxylic acids **3** was developed. Using this approach, morpholin-2-one-3-carboxamide derivatives **4** were efficiently synthesized for the first time, and good diastereoselectivity of the new stereocenter at C-3 in the products was observed. The work will enrich asymmetric Ugi reactions and, currently, an extension of the reaction based on the cyclic imines is underway.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank Sichuan University Analytical and Testing Center for NMR determination. This work was supported by grants from the National Natural Science Foundation of China (No. 20802045), the National Basic Research Program of China (973 Program, No. 2012CB833200), the Setup Foundation of Sichuan University and the Youth Foundation of Sichuan University.

References and Notes

(1) For reviews, see: (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (c) Boger, D. L.; Desharnais, J.; Capps, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 4138.

(2) (a) He, Q.; Zhu, X.; Shi, M.; Zhao, M.; Zhao, J.; Zhang, S.; Miao, J. *Bioorg. Med. Chem.* **2007**, *15*, 3889. (b) Raparti, V.; Chitre, T.; Bothara, K.; Kumar, V.; Dangre, S.; Khachane, C.; Gore, S.; Deshmane, B. *Eur. J. Med. Chem.* **2009**, *44*, 3954. (c) Arcelli, A.; Balducci, D.; Neto, S. d. F. E.; Porzi, G.; Sandri, M. *Tetrahedron: Asymmetry* **2007**, *18*, 562.

(3) Kim, Y. B.; Choi, E. H.; Keum, G.; Kang, S. B.; Lee, D. H.; Koh, H. Y.; Kim, Y. *Org. Lett.* **2001**, *3*, 4149.

(4) Ku, I. W.; Cho, S.; Doddareddy, M. R.; Jang, M. S.; Keum, J. G.; Lee, J. H.; Chung, B. Y.; Kim, Y.; Rhim, H.; Kang, S. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5244.

(5) (a) Antunes, J. E.; Freitas, M. P.; da Cunha, E. F. F.; Ramalho, T. C.; Rittner, R. *Bioorg. Med. Chem.* **2008**, *16*, 7599. (b) Gao, F.; Sexton, P. M.; Christopoulos, A.; Miller, L. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4401. (c) Repine, J. T.; Himmelsbach, R. J.; Hodges, J. C.; Kaltenbronn, J. S.; Sircar, I.; Skeean, R. W.; Brennan, S. T.; Hurley, T. R.; Lunney, E.; Humblet, C. C.; Weishaar, R. E.; Rapundalo, S.; Ryan, M. J.; Taylor, D. G. Jr.; Olson, S. C.; Michniewicz, B. M.; Kornberg, B. E.; Belmont, D. T.; Taylor, M. D. *J. Med. Chem.* **1991**, *34*, 1935. (d) Gyöergydeák, Z.; Hadady, Z.; Felföeldi, N.; Krakomperger, A.; Nagy, V.; Tóth, M.; Brunyánszki, A.; Docsa, T.; Gergely, P.; Somsák, L. *Bioorg. Med. Chem.* **2004**, *12*, 4861.

(6) (a) Shafer, C. M.; Morse, D. I.; Molinski, T. F. *Tetrahedron* **1996**, *52*, 14475. (b) Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* **1996**, *61*, 2044. (c) Chen, X.; Chen, J.; Zhu, J. *Synthesis* **2006**, 4081.

(7) General procedure for the synthesis of **4**: To a solution of **1** were added, successively, acid **3** and isocyanide **2** under inert atmosphere. The resulting mixture was stirred at room temperature until completion (TLC), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel column to give product **4**

(8) Harwood, L. M.; Vines, K. J.; Drew, M. G. B. *Synlett* **1996**, 1051.

(9) (a) Tohma, S.; Endo, A.; Kan, T.; Fukuyama, T. *Synlett* **2001**, 1179. (b) Tohma, S.; Rikimaru, K.; Endo, A.; Shimamoto, K.; Kan, T.; Fukuyama, T. *Synthesis* **2004**, 909.

(10) (a) Ugi, I.; Dffermann, K. *Angew. Chem. Int. Ed.* **1963**, *2*, 624. (b) Ugi, I.; Kaufhold, G. L. *Ann. Chem.* **1967**, *709*, 11. (c) Madson, U.; Frydenvang, K.; Ebert, B.; Johemsen, T. N.; Brehm, L.; Krogsgaard-Larsen, P. *J. Med. Chem.* **1996**, *39*, 183. (d) Eberle, G.; Ugi, I. *Angew. Chem. Int. Ed.* **1976**, *15*, 492.

(11) (a) Merquarding, D.; Hoffman, P.; Heitzer, H.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 1969. (b) Demharter, A.; Ugi, I. *J. Prakt. Chem.* **1993**, *335*, 244. (c) Siglmuller, F.; Herrmam, R.; Ugi, I. *Tetrahedron* **1986**, *42*, 5931.

(12) (a) Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* **1988**, *110*, 651. (b) Kunz, H.; Pfrangle, W. *Tetrahedron* **1988**, *44*, 5487. (c) Lehnhoff, S.; Goebel, M.; Karl, R. M.; Klosel, R.; Ugi, I. *Angew. Chem. Int. Ed.* **1995**, *34*, 1104. (d) Drabik, J. M.; Achatz, J.; Ugi, I. *Proc. Est. Acad. Sci. Chem.* **2002**, *51*, 156.

(13) (a) Demharter, A.; Hörl, W.; Herdtweck, E.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 173. (b) Dyker, G.; Breitenstein, K.; Henkel, G. *Tetrahedron: Asymmetry* **2002**, *13*, 1929. (c) Park, S. J.; Keum, G.; Kang, S. B.; Koh, H. Y.; Kim, Y.; Lee, D. H. *Tetrahedron Lett.* **1998**, *39*, 7109. (d) Ugi, I.; Demharter, A.; Hörl, W.; Schmid, T. *Tetrahedron* **1996**, *52*, 11657. (e) Zimmer, R.; Ziemer, A.; Gruner, M.; Brudgam, I.; Hartl, H.; Reissig, H. U. *Synthesis* **2001**, 1649.

(14) **4a**: $[\alpha]_D^{28}$ +4 (*c* 0.5, $CHCl_3$). IR (neat): 3337, 2963, 2932, 1752, 1666, 1539, 1463, 1391, 1289, 1108 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (two rotamers) = 7.66–7.61 (m, 4 H), 7.46–7.40 (m, 6 H), 5.98 (s, 1 H), 4.95 (s, 0.8 H), 4.82 (dd, *J* = 2.7, 11.5 Hz, 1 H), 4.76 (s, 0.2 H), 4.71 (dd, *J* = 1.3, 11.4 Hz, 0.8 H), 4.58 (m, 0.2 H), 4.47 (dd, *J* = 2.8, 12.0 Hz, 0.2 H), 3.93 (m, 0.8 H), 3.86 (dd, *J* = 4.0, 9.6 Hz, 0.2 H), 3.70 (t, *J* = 10.6 Hz, 0.8 H), 3.59 (dd, *J* = 5.3, 10.7 Hz, 0.8 H), 3.52 (t, *J* = 9.6 Hz, 0.2 H), 1.89 (s, 0.6 H), 1.82 (s, 2.4 H), 1.36 (s, 1.8 H), 1.33 (s, 7.2 H), 1.06 (s, 7.2 H), 1.05 (s, 1.8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (two rotamers) = 169.9, 169.8, 165.7, 163.3, 162.2, 162.1, 135.4, 135.3, 132.5, 131.9, 130.2, 130.1, 127.9, 127.7, 127.6, 66.7, 65.8, 62.7, 61.0, 60.7, 60.2, 52.9, 52.6, 52.2, 50.0, 29.6, 28.3, 26.6, 21.1, 20.4, 19.0 ppm. HRMS: *m/z* $[M + Na]^+$ calcd for $C_{28}H_{38}N_2O_5Si$: 533.2448; found: 533.2437.