Tetrahedron Letters 53 (2012) 7088–7092

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A green one-pot synthesis of *N*-alkyl-2-(2-oxoazepan-1-yl)-2-arylacetamide derivatives via an Ugi four-center, three-component reaction in water

Mohammad Ali Rasouli [a], Mohammad Mahdavi [b], Parviz Rashidi Ranjbar [a], Mina Saeedi [b], Abbas Shafiee [b], Alireza Foroumadi [b,c,*]

[a] School of Chemistry, University College of Science, University of Tehran, PO Box 14155-6455, Tehran, Iran
[b] Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medicinal Sciences, Tehran, Iran
[c] Drug Design & Development Research Center, Tehran University of Medicinal Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Received 9 July 2012
Revised 29 September 2012
Accepted 18 October 2012
Available online 24 October 2012

Keywords:
N-Alkyl-2-(2-oxoazepan-1-yl)-2-arylacetamides
Multicomponent reactions (MCRs)
Heterocycles
Azepan-2-ones

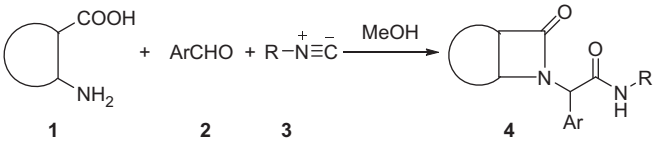
ABSTRACT

This work describes a green and efficient one-pot synthesis of *N*-alkyl-2-(2-oxoazepan-1-yl)-2-arylacetamide derivatives via an Ugi four-center, three-component reaction of 6-aminohexanoic acid, aromatic aldehydes, and isocyanide derivatives in water under reflux conditions in the absence of a catalyst.

Practical application of multicomponent reactions (MCRs) in modern organic synthesis has been proved repeatedly. They have become efficient and important tools in the synthesis of cyclic and acyclic compounds due to their atom economy, simple procedures, straightforward reaction design, facile execution, and convergence.[1] The Ugi four-component coupling[2] is one of the most common examples of MCRs. A literature survey revealed that a wide range of heterocycles[3] has been prepared, and many successful drug discoveries have been accomplished[4] through Ugi reactions. Several modifications of the classic Ugi reaction have been described, which usually involve variation of one of the components, or the introduction of a linkage between two of them. A useful variation of the Ugi reaction involves the use of amino acids as reactants incorporating both the carboxylic acid and amine functionality (Schemes 1 and 2).[5]

Various reports on the synthesis of cyclic amides (lactams)[5,6] using the Ugi reaction encouraged us, in connection with our ongoing research interest in the development of new and efficient methods for the preparation of novel heterocycles, especially bioactive molecules,[7] to investigate a practical protocol for the preparation of novel *N*-alkyl-2-(2-oxoazepan-1-yl)-2-arylacetamide derivatives **9** (Scheme 3).

We focused our attention on *N*-alkyl-2-(2-oxoazepan-1-yl)-2-arylacetamides as these compounds possess an azepan-2-one (caprolactam) scaffold, which represents a bioactive moiety in many drugs.[8] A detailed study by Fox et al. described the synthesis of 3-(acylamino)azepan-2-one derivatives as stable broad-spectrum chemokine inhibitors resistant to metabolism in vivo (Fig. 1).[9] Also, Warshawsky et al. reported that the azepan-2-ones are valuable as inhibitors of matrix metalloproteinase.[10]



Scheme 1. Synthesis of alicyclic β-lactams **4** via the reaction of β-amino acids **1**, aromatic aldehydes **2**, and isocyanides **3**.[5a]

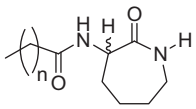
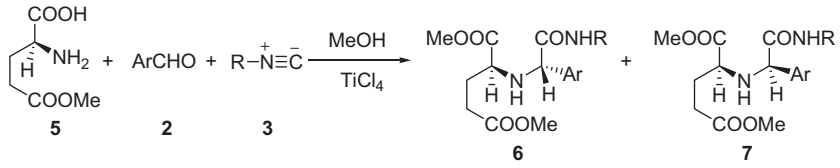


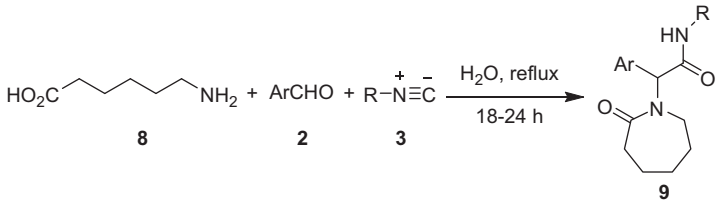
Figure 1. 3-(Acylamino)azepan-2-one derivatives as chemokine inhibitors.

* Corresponding author. Tel.: +98 21 66954708; fax: +98 21 66461178.
E-mail address: aforoumadi@yahoo.com (A. Foroumadi).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.075

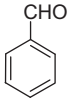
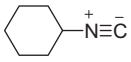
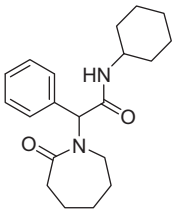
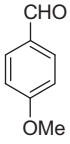
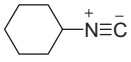
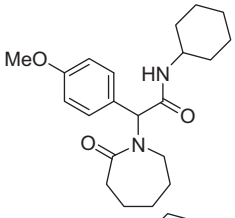
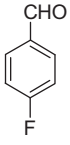
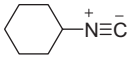
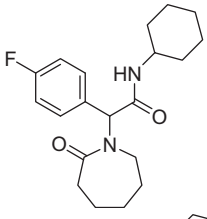
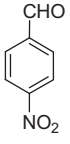
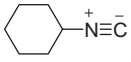
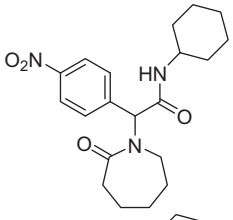
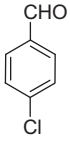
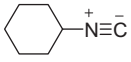
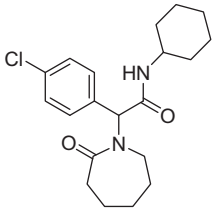


Scheme 2. Titanium catalysis in the Ugi reaction of glutamate (an α-amino acid) (**5**), aromatic aldehydes **2**, and isocyanides **3**.[5b]



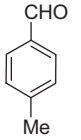
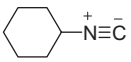
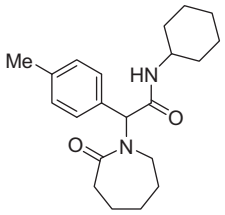
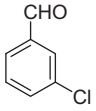
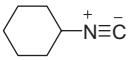
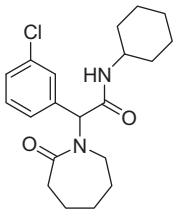
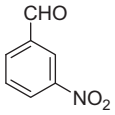
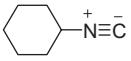
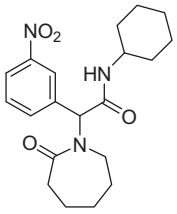
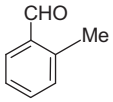
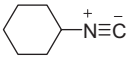
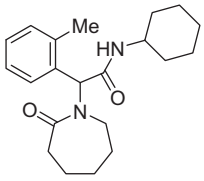
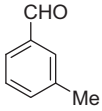
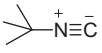
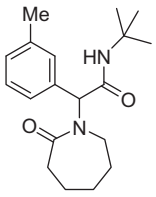
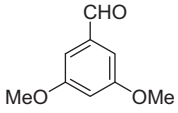
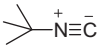
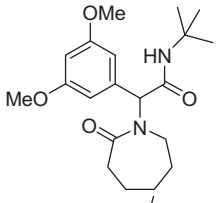
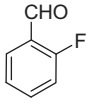
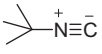
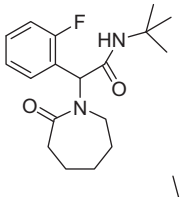
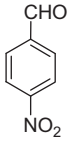
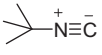
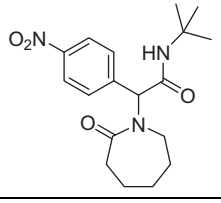
Scheme 3. Ugi three-component reaction of 6-aminohexanoic acid (**8**), aromatic aldehydes **2**, and isocyanides **3**.

Table 1
Synthesis of *N*-alkyl-2-(2-oxoazepan-1-yl)-2-arylacetamide derivatives **9**[14]

Entry	Aldehyde **2**	Isocyanide **3**	Product **9**		Time (h)	Yield[a] (%)
1				**9a**	20	80
2				**9b**	19	77
3				**9c**	19	87
4				**9d**	18	92
5				**9e**	19	75

(*continued on next page*)

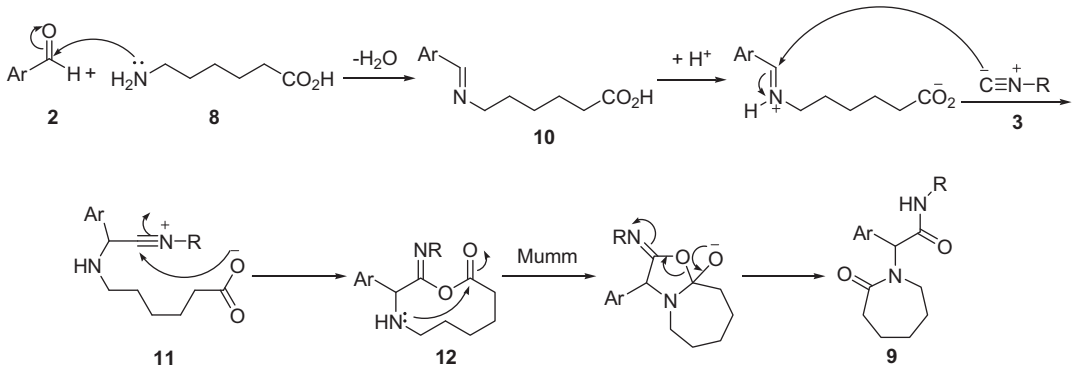
Table 1 (*continued*)

Entry	Aldehyde **2**	Isocyanide **3**	Product **9**		Time (h)	Yield[a] (%)
6				**9f**	21	77
7				**9g**	22	74
8				**9h**	22	82
9				**9i**	48	10[b]
10				**9j**	22	62
11				**9k**	22	69
12				**9l**	24	73
13				**9m**	20	82

[a] Isolated yields.
[b] Yield refers to chromatographic analysis.

Herein, we describe the reaction of 6-aminohexanoic acid (**8**), aromatic aldehydes **2**, and isocyanides **3** (Scheme 3), as a suitable procedure for replacing traditional synthetic methods toward azepan-2-ones.[11]

To optimize the conditions for the preparation of *N*-alkyl-2-(2-oxoazepan-1-yl)-2-arylacetamide derivatives **9**, we began our studies by investigating the reaction of 6-aminohexanoic acid (**8**), *p*-methoxybenzaldehyde, and cyclohexyl isocyanide (Table 1, entry



Scheme 4. A possible mechanism for the synthesis of *N*-alkyl-2-(2-oxoazepan-1-yl)-2-arylacetamides **9**.

2) in different organic solvents and water. It should be noted that when the model reaction was run in polar protic solvents such as methanol, ethanol, and water, similar results were obtained with respect to the yield and reaction time. As regards the use of aqueous media in multicomponent reactions,[12] we selected water as a green medium for the above mentioned reaction to produce *N*-cyclohexyl-2-(4-methoxyphenyl)-2-(2-oxoazepan-1-yl) acetamide (**9b**). Water as the solvent has been used in isocyanide-based multicomponent reactions and is recommended not only due to environmentally issues, but it also has other advantages including simple product isolation and safety.[5c,13]

We found that when the reaction was carried out at ambient temperature, no product was obtained and heating at reflux was required. Also our investigations revealed that using stoichiometric amounts of starting materials gave a moderate yield of **9b** (50%); increasing the amount of cyclohexyl isocyanide led to 1.2 mmol to the formation of product **9b** in a much better yield of 77%.

In order to show the generality and scope of this novel protocol, we used various aromatic aldehydes and isocyanides in the reaction in Scheme 3 under the optimized conditions. The results are summarized in Table 1.

All the reactions reached completion within 18–24 h to afford good yields of products which were characterized by mass spectrometry fragmentation pattern analysis, and ^{1}H and ^{13}C NMR spectroscopy.[14] For example, the peak at *m/z*: 358 for compound **9b** represents the molecular ion (calculated mass for $C_{21}H_{30}N_2O_3$). The ^{1}H NMR spectrum of **9b** consisted of multiplet signals for the cyclohexyl and 2-azepanone rings (18H, 2.29–1.14 ppm), an N-CH resonance (1H, 3.52 ppm) and an N-CH_2 signal (2H, 3.52 ppm). The proton associated with the methine group (CH), gave a singlet at 5.92 ppm. The signals due to the four aromatic protons were observed around 7.11–6.90 ppm which were observed as two doublets; 7.11 (d, J = 7.0 Hz, 2 H) and 6.90 (d, J = 7.0 Hz, 2 H). Finally, the signal at 7.86 ppm was due to C_6H_{11} N*H* group. The ^{13}C NMR spectrum of **9b** showed 19 distinct resonances in agreement with the proposed structure. Characteristic carbonyl carbon resonances were observed at 172.8 and 168.6 ppm. As expected, four signals were apparent in the aromatic region due to symmetry, and the remaining 13 signals were observed in the aliphatic region.

As can be seen in Table 1, electronic effects of substituents attached to the aromatic aldehyde did not influence the reaction outcome. In contrast, steric effects were more significant in the case of an *ortho*-substituted benzaldehyde and the rate of reaction decreased dramatically. When the reaction of 6-aminohexanoic acid, 2-methylbenzaldehyde, and cyclohexyl isocyanide was conducted under the optimized conditions, the corresponding product was obtained in poor yield (10%) after 2 days. As expected, in the case of 2,6-dimethylbenzaldehyde, no product was observed.

A mechanistic rationalization for this reaction is provided in Scheme 4. On the basis of the well-established chemistry of isocyanides,[2] the first step involves condensation of 6-aminohexanoic acid (**8**) with the aromatic aldehyde **2** leading to the formation of imine intermediate **10**. This is followed by nucleophilic attack of the isocyanide **3** on the imine, which is facilitated by protonation of imine by the carboxylic acid to form the nitrilium carboxylate intermediate **11**. Next the nitrilium carbon might be attacked by the carboxylate to form cyclic intermediate **12**, which is converted into product **9** via a Mumm rearrangement.

In conclusion, we have demonstrated that the Ugi four-center, three-component reaction of 6-aminohexanoic acid, aromatic aldehydes, and isocyanides in water represents a direct access to *N*-alkyl-2-(2-oxoazepan-1-yl)-2-arylacetamide derivatives. The present strategy may find value in synthesis, because it is operationally simple and green, the yields of the products are good, and the starting materials are readily available. Also the protocol does not need complex or expensive catalysis.

Acknowledgement

This research was supported by grants from the research council of Tehran University of Medical Sciences and the Iran National Science Foundation (INSF).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.075. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005; (b) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *J. Org. Chem.* **2005**, *70*, 575; (c) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
2. (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386; (b) Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267; (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (d) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
3. (a) Shaabani, A.; Maleki, A.; Mofakham, H.; Khavasi, H. R. *J. Comb. Chem.* **2008**, *10*, 323; (b) Shaabani, A.; Soleimani, E.; Sarvary, A.; Rezayan, A. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3968.
4. (a) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51; (b) Ugi, I.; Wischofer, E. *Chem. Ber.* **1962**, *95*, 136; (c) Nakamura, M.; Inoue, J.; Yamada, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2807.
5. (a) Gedey, S.; Van der Eycken, J.; Fülöp, F. *Org. Lett.* **1967**, *2002*, 4; (b) Godet, T.; Bonvin, Y.; Vincent, G.; Merle, D.; Thozet, A.; Ciufolini, M. A. *Org. Lett.* **2004**, *6*, 3281; (c) Kanizsai, I.; Gyónfalvi, S.; Szakonyi, Z.; Sillanpää, R.; Fülöp, F. *Green Chem.* **2007**, *9*, 357.
6. (a) Krelaus, R.; Westermann, B. *Tetrahedron Lett.* **2004**, *45*, 5987; (b) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2003**, *44*, 7655; (c) Jida, M.;

Malaquin, S.; Deprez-Poulain, R.; Laconde, G.; Deprez, B. *Tetrahedron Lett.* **2010**, *51*, 5109; (d) Zhang, J.; Jacobson, A.; Rusche, J. R.; Helrihy, W. *J. Org. Chem.* **1999**, *64*, 1074; (e) Ilyn, A. P.; Trifilenkov, A. S.; Kuzovkova, J. A.; Kutepov, S. A.; Nikitin, A. V.; Ivachtchenko, A. V. *J. Org. Chem.* **2005**, *70*, 1478; (f) Ghandi, M.; Zarezadeh, N.; Taheri, A. *Tetrahedron Lett.* **2011**, *52*, 1228; (g) Marcaccini, S.; Pepino, R.; Torroba, T.; Miguel, D.; Garcia-Valverde, M. *Tetrahedron Lett.* **2002**, *43*, 8591.

7. (a) Hosseini-Zare, M. S.; Mahdavi, M.; Saeedi, M.; Asadi, M.; Javanshir, S.; Shafiee, A.; Foroumadi, A. *Tetrahedron Lett.* **2012**, *51*, 3448; (b) Mahdavi, M.; Najafi, R.; Saeedi, M.; Alipour, E.; Shafiee, A.; Foroumadi, A. *Helv. Chim. Acta* **2012**, in press, doi: http://dx.doi.org/10.1002/hlca.201200199.; (c) Tahghighi, A.; Razmi, S.; Mahdavi, M.; Foroumadi, P.; Ardestani, S. K.; Emami, S.; Kobarfard, F.; Dastmalchi, S.; Shafiee, A.; Foroumadi, A. *Eur. J. Med. Chem.* **2012**, *50*, 124.
8. Thorsett, E. D.; Harris, E. E. U.S. Patent 4409,146, 1983; *Chem. Abstr.* **1984**, *100*, 34426s.
9. Fox, D. J.; Reckless, J.; Wilbert, S. M.; Greig, I.; Warren, S.; Grainger, D. J. *J. Med. Chem.* **2005**, *48*, 867.
10. Warshawsky, A. M.; Tsay, J. T.; Janusz, M. J.; Shen, J.; Flynn, G. A.; Dharanipragada, R. M.; Burkhart, J. P.; Beight, D. W.; Patel, M. V. U.S. Patent 6953,788 B1, 2005; *Chem. Abstr.* **2005**, *143*, 367335h.
11. (a) Ullmanns Encyclopedia of Industrial Chemistry, 6th ed., 1998, electronic release.; (b) Weissermal, K.; Arpe, H. J. *Industrial Organic Chemistry*; VCH: Weinheim, 1994.
12. (a) Pirrung, M. C.; Sarma, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 444; (b) Kumaravel, K.; Vasuki, G. *Curr. Org. Chem.* **1820**, *2009*, 13.
13. (a) Shaabani, A.; Teimouri, M. B.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2002**, *43*, 9151; (b) Yavari, I.; Kowsari, E. *Mol. Divers.* **2009**, *13*, 519; (c) Sarma, R.; Sarmah, M. M.; Lekhok, K. C.; Prajaparti, D. *Synlett* **2010**, 2847.
14. General procedure for the preparation of *N*-alkyl-2-(2-oxoazepan-1-yl)-2-arylacetamide derivatives **9**: A mixture of 6-aminohexanoic acid (**8**) (1 mmol), aromatic aldehyde **2** (1 mmol), and isocyanide **3** (1.1 mmol) in H_2O or methanol (10 mL) was heated at reflux for 18–24 h. After completion of the reaction, according to Table 1, the mixture was cooled to room temperature and left to stand overnight. The precipitated product was filtered off and dried. All the products were analytically pure without the need for recrystallization. *N*-Cyclohexyl-2-(4-methoxyphenyl)-2-(2-oxoazepan-1-yl) acetamide (**9b**): Yield: 77%, white solid. Mp 287 °C; IR (KBr): 3267, 3086, 2925, 2849, 1651, 1638, 1563, 1514, 1443 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H = 7.86 (s, 1H, NH), 7.11 (d, J = 7.0 Hz, 2H, ArH), 6.90 (d, J = 7.0 Hz, 2H, ArH), 5.92 (s, 1H, CH), 3.74 (s, 3H, OMe), 3.52 (m, 1H, NCH, cyclohexyl), 3.19 (m, 2H, NCH_2, 2-azepanone), 2.29–1.14 (m, 18H, cyclohexyl and 2-azepanone); ^{13}C NMR (DMSO-d_6, 125 MHz,): δ_C = 172.8, 168.6, 158.8, 130.1, 128.7, 113.8, 59.2, 55.1, 47.7, 44.4, 32.4, 32.2, 32.0, 26.5, 25.2, 24.7, 24.6, 24.5, 23.1; MS m/z (%) = 358 (M^+, 5), 278 (5), 239 (10), 165 (10), 57 (60); Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81; Found: C, 70.15; H, 8.66; N, 7.95.