Multicomponent Reactions

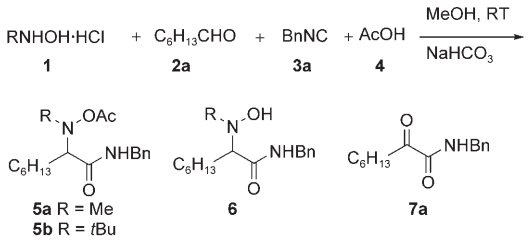
DOI: 10.1002/anie.200704840

Synthesis of α-Ketoamides by a Molecular-Sieves-Promoted Formal Oxidative Coupling of Aliphatic Aldehydes with Isocyanides**

Jean-Marie Grassot, Géraldine Masson, and Jieping Zhu**

The α-ketoamide functionality has been found in a number of biologically important natural products, such as FK 506[1] and cyclotheonamide.[2] The facile formation of stable tetrahedral adducts between the highly electrophilic α-oxo group and nucleophilic residues (OH, SH) at the active site of enzymes make α-ketoamides an excellent basis for the development of enzyme inhibitors. Indeed, this structural motif has often been incorporated strategically at the P1 position of designed protease inhibitors.[3] α-Ketoamides[4] have been prepared mainly by the following strategies: 1) amidation of α-keto acids;[5] 2) oxidation of α-hydroxyamides,[6] α-cyanoamides,[7] and α-aminoamides (transamination);[8] 3) oxidation of acyl cyanophosphoranes followed by amidation of the resulting α,β-diketone nitrile;[9] 4) transition-metal-catalyzed double carbonylative amination of aryl halides;[10] 5) reaction of isocyanides with aromatic acyl chlorides or anhydrides followed by hydrolysis of the resulting α-ketoimidoyl chloride.[11] In spite of the availability of these synthetic methodologies, a general and efficient synthesis of α-ketoamides is still in high demand.

In connection with our ongoing project on the development of novel multicomponent reactions,[12] we had occasion to examine the Ugi four-component reaction (4CR)[13,12k] of *N*-methylhydroxylamine (**1a**), heptanal (**2a**), benzyl isocyanide (**3a**), and acetic acid (**4a**).[14,15] Under the conditions of Guanti and co-workers (MeOH, room temperature), we obtained the expected Ugi 4CR adduct **5a** and the non-acylated adduct **6** (R = Me) in 45 and 18% yield, respectively (Scheme 1). However, the unexpected product *N*-benzyl-2-oxooctanamide (**7a**) was also isolated in 10% yield (Table 1, entry 1). The formation of **7a** corresponds to a formal oxidative coupling of an aldehyde with an isocyanide.[16] The simple reaction conditions and the lack of a one-pot synthesis of α-ketoamides prompted us to examine in detail this unprecedented transformation. We report herein our preliminary results.



Scheme 1. Use of *N*-alkyl hydroxylamines **1** in the Ugi 4CR. Bn = benzyl.

Table 1: Optimization of the reaction conditions for the synthesis of α-ketoamides.[a]

Entry	c[b] [mol L^{-1}]	R	Additive	Yield [%][c] 5	6	7
1	0.4	Me (**1a**)	none	45	18	10
2	0.4	Me (**1a**)	$MgSO_4$	25	5	20
3	0.4	Me (**1a**)	3-Å MS	38	5	10
4	0.4	Me (**1a**)	4-Å MS	13	0	58
5	0.4	Me (**1a**)	4-Å MS	18	0	47[d]
6	1.0	Me (**1a**)	4-Å MS	0	0	65
7	1.0	Me (**1a**)	4-Å MS	0	0	60[e]
8	1.0	*t*Bu (**1b**)	4-Å MS	57	0	0
9	1.0	Bn (**1c**)	4-Å MS	0	0	55

[a] General conditions: **1**/**2a**/**3a**/AcOH 1.1:1.0:1.0:9 (molar ratio), $NaHCO_3$ (2 equiv). [b] Concentration of **2a**. [c] Yield of the product after purification by chromatography. [d] Just 3 equivalents of AcOH were used. [e] PhCOOH was used instead of AcOH.

Initial experiments indicated that the reaction is sensitive to a number of parameters. It is crucial to use an excess of acetic acid (9 equiv) in methanol to obtain the α-ketoamide **7a**. Only the corresponding nitrone (65%) was isolated when the reaction was performed in CH_2Cl_2, whereas a complex mixture of products was produced in THF. The addition of $MgSO_4$ to the reaction mixture led to a slight increase in the yield of **7a** (Table 1, entry 2). No beneficial effect was observed when the reaction was performed in the presence of 3-Å molecular sieves (MS, Table 1, entry 3). However, when the 3-Å MS were simply exchanged for 4-Å MS under otherwise identical conditions, the yield of **7a** increased significantly (Table 1, entry 4). The contrast between the effects of 3-Å and 4-Å MS is intriguing. However, examples of the different behavior of these two zeolites in a given transformation have been reported previously.[17] The reaction was improved further by increasing the substrate concentration (Table 1, entry 6). Benzoic acid can also

[*] J.-M. Grassot, Dr. G. Masson, Dr. J. Zhu
Institut de Chimie des Substances Naturelles, CNRS
91198 Gif-sur-Yvette Cedex (France)
Fax: (+33) 1-6907-7247
E-mail: masson@icsn.cnrs-gif.fr
zhu@icsn.cnrs-gif.fr
Homepage: http://www.icsn.cnrs-gif.fr/article.php3?id_article=122

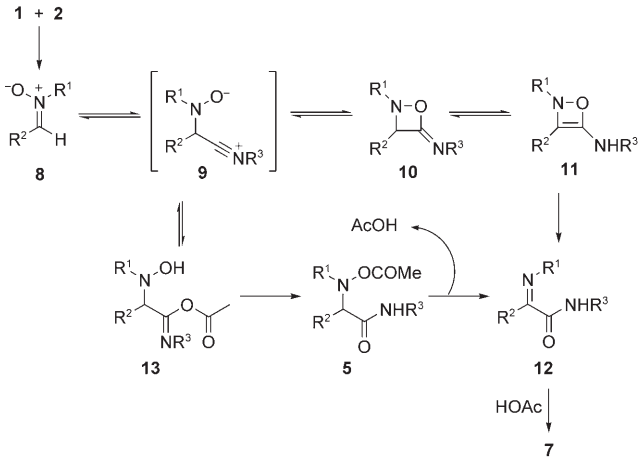
[**] Financial support from the CNRS and this institute is gratefully acknowledged. J.M.G. thanks this institute for a doctoral fellowship. We thank Professor G. Guanti for helpful discussions.

Supporting information for this article, including experimental procedures, product characterization, and copies of the ^{1}H and ^{13}C NMR spectra of compounds **5a**, **6a**, and **7a**–**7n**, is available on the WWW under http://www.angewandte.org or from the author.

mediate this coupling reaction to afford **7a** in 60% yield (Table 1, entry 7). The nature of the substituent on the N atom of the hydroxylamine influenced the efficiency of the reaction. The use of *N*-*tert*-butylhydroxylamine hydrochloride (**1b**) led to only the α-acyloxyamino amide **5b** (Table 1, entry 8), whereas the reaction of *N*-benzylhydroxylamine hydrochloride (**1c**) afforded the α-ketoamide **7a**, albeit in slightly reduced yield (55%; Table 1, entry 9).

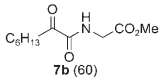
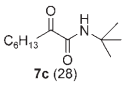
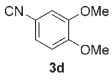
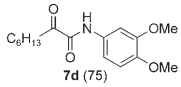
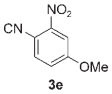
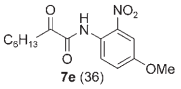
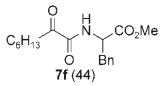
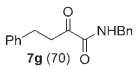
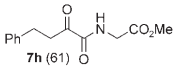
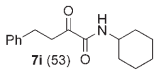
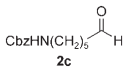
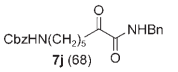
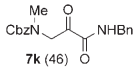
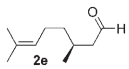
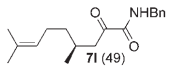
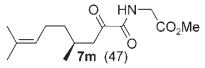
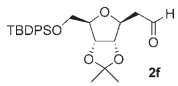
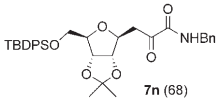
The generality of this formal oxidative coupling of aldehydes with isocyanides was next examined with *N*-methylhydroxylamine hydrochloride (**1a**) and acetic acid (**4**) as mediators. Both aromatic and aliphatic isocyanides, including α-isocyanoacetates, underwent the desired reaction to provide α-ketoamides in moderate to good yields (Table 2). However, the coupling product was obtained in low yield with sterically hindered *tert*-butyl isocyanide (Table 2, entry 2). The amide **7e**, which can serve as a precursor to α-keto-octanoic acid, was also obtained in low yield, certainly because of the low nucleophilicity of the convertible isocyanide **3e** (Table 2, entry 4).[18] Aliphatic aldehydes, including functionalized aldehydes, are effective substrates (Table 2, entries 1–9). The coupling reaction proceeded well with 6-(*N*-benzyloxycarbamoyl)hexanal (**2c**). With α-aminoaldehydes, double protection of the α-amino group was crucial for the reaction to occur smoothly (Table 2, entry 10). However, the reaction of aromatic aldehydes with isocyanides afforded the corresponding α-ketoamides in only low yield. The chiral aldehydes (*S*)-citronellal (**2e**) and **2f** were transformed efficiently into the corresponding α-ketoamides **7l**, **7m**, and **7n** without racemization (Table 2, entries 11–13).

A plausible reaction sequence that accounts for the formation of α-ketoamides is shown in Scheme 2. The condensation of an N-substituted hydroxylamine **1** and an aldehyde **2** gives a nitrone **8**, which reacts with an isocyanide **3** to afford the nitrilium intermediate **9**. The species **9** can conceivably be transformed into an α-ketoamide **7** through two different mechanistic pathways: Intramolecular trapping of the nitrilium moiety by the tethered oxygen nucleophile would lead to the 4-imino-1,2-oxazetidine intermediate **10**. The fragmentation of **10** via its enamine form **11** would provide the α-iminoamide **12**, the hydrolysis of which would afford the observed product **7**. Alternatively, the classic Ugi reaction pathway would lead to the formation of α-acyloxy-amino amides **5** via an imidate intermediate **13**. The β elimination of acetic acid would then afford an α-imino-amide **12**, which would be hydrolyzed to **7**.



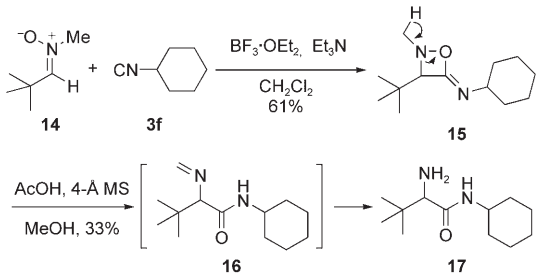
Scheme 2. Reaction pathway leading to α-ketoamides **7**.

Table 2: Synthesis of α-ketoamides by the coupling of an aldehyde with an isocyanide.[a]

Entry	Aldehyde	Isocyanide	Product (yield [%][b])
1	 **2a**	 **3b**	 **7b** (60)
2	**2a**	 **3c**	 **7c** (28)
3	**2a**	 **3d**	 **7d** (75)
4	**2a**	 **3e**	 **7e** (36)
5	**2a**	 **3f**	 **7f** (44)
6	 **2b**	BnNC **3a**	 **7g** (70)
7	**2b**	**3b**	 **7h** (61)
8	**2b**	 **3g**	 **7i** (53)
9	 **2c**	**3a**	 **7j** (68)
10	 **2d**	**3a**	 **7k** (46)
11	 **2e**	**3a**	 **7l** (49)
12	**2e**	**3b**	 **7m** (47)
13	 **2f**	**3a**	 **7n** (68)

[a] All reactions were carried out in methanol at room temperature in the presence of the hydrochloride salt of *N*-methylhydroxylamine and acetic acid. [b] Yield of the product after chromatography on silica gel. Cbz = carbobenzyloxy, TBDPS = *tert*-butyldiphenylsilyl.

To probe the reaction mechanism, the authentic 4-imino-1,2-oxazetidine **15** was prepared by treating the nitrone **14** with the isocyanide **3g** in the presence of $BF_3{\cdot}OEt_2$ (Scheme 3).[19] When **15** was submitted to our reaction conditions, the α-aminocarboxamide **17** was isolated exclusively in 33% yield. This mode of fragmentation, that is, preferential deprotonation of the N-methyl group followed by N–O bond cleavage, is in accord with results reported previously.[19]



Scheme 3. Fragmentation of a 4-imino-1,2-oxazetidine under acidic conditions.

These findings, and the fact that the α-acyloxyamino amide **5a** was isolated from the reaction mixture, indicate that the Ugi mechanism operates effectively. Indeed, to make the reaction proceed towards the α-ketoamide, the nonproductive sequence that leads to the 4-imino-1,2-oxazetidine **10** must be avoided. One should be able to favor entropically the Ugi pathway by increasing the substrate concentration and the number of equivalents of acetic acid used (although the acid is regenerated according to the proposed mechanism). This conclusion is in accord with our experimental observations. A control experiment indicated that the molecular sieves promote the β elimination of α-acyloxyamino amides **5**. Indeed, when a solution of **5a** in methanol was stirred in the presence of 4-Å MS, the α-ketoamide **7a** was formed in 89% yield.[20,21]

In summary, we have developed a novel synthesis of α-ketoamides by a formal oxidative coupling of an aldehyde with an isocyanide.[22] The reaction is carried out under mild conditions in the presence of both *N*-methylhydroxylamine and acetic acid as mediators. We also demonstrated the importance of selecting a particular zeolite for this transformation. Although multicomponent reactions form a proven technology for creating structural complexity and diversity,[23] their use as a means for the development of fundamental transformations has attracted far less attention.[24] We believe that the use of small and cheap molecules to initiate/terminate a reaction sequence could be a useful strategy for the development of novel reactions.

Experimental Section

Typical procedure: Heptanal (**2a**; 112 μL, 0.80 mmol) was added to a solution of **1a** (74 mg, 0.88 mmol, 1.1 equiv), $NaHCO_3$ (132 mg, 1.57 mmol, 2 equiv), and 4-Å molecular sieves (600 mg) in methanol (0.80 mL), and the resulting mixture was stirred for 30 min at room temperature. Benzyl isocyanide (**3a**; 100 μL, 0.84 mmol, 1.05 equiv) and acetic acid (400 μL, 9 equiv) were then added, and stirring was continued for 24 h at room temperature. The reaction mixture was then filtered, and the solvent was removed in vacuo. The crude product was purified by flash chromatography (SiO_2, 10% ethyl acetate in heptane) to afford **7a** (128 mg, 65%) as a white solid.

Received: October 18, 2007
Published online: December 18, 2007

Keywords: isocyanides · ketoamides · multicomponent reactions · nitrones · Ugi reaction

[1] H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, M. Hashimoto, T. Taga, *J. Am. Chem. Soc.* **1987**, *109*, 5031–5033.
[2] N. Fusetani, S. Matsunaga, H. Matsumoto, Y. Takebayashi, *J. Am. Chem. Soc.* **1990**, *112*, 7053–7054.
[3] a) J. Gante, *Angew. Chem.* **1994**, *106*, 1780–1802; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699–1720; b) H.-H. Otto, T. Schirmeister, *Chem. Rev.* **1997**, *97*, 133–171.
[4] For a general review on vicinal polycarbonyl compounds, see: M. B. Rubin, R. Gleiter, *Chem. Rev.* **2000**, *100*, 1121–1164.
[5] R. P. Singh, J. M. Shreeve, *J. Org. Chem.* **2003**, *68*, 6063–6065.
[6] a) T. D. Ocain, D. H. Rich, *J. Med. Chem.* **1992**, *35*, 451–456; b) J. E. Semple, T. D. Owens, K. Nguyen, O. E. Levy, *Org. Lett.* **2000**, *2*, 2769–2772; c) L. Banfi, G. Guanti, R. Riva, *Chem. Commun.* **2000**, 985–986; d) M. Nakamura, J. Inoue, T. Yamada, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2807–2910; e) P. Xu, W. Lin, X. Zhou, *Synthesis* **2002**, 1017–1026.
[7] a) Z. Yang, Z. Zhang, N. A. Meanwell, J. F. Kadow, T. Wang, *Org. Lett.* **2002**, *4*, 1103–1105; b) J. Zhu, H. Wong, Z. Zhang, Z. Yin, J. F. Kadow, N. A. Meanwell, T. Wang, *Tetrahedron Lett.* **2005**, *46*, 3587–3589.
[8] a) T. F. Buckley, H. Rapoport, *J. Am. Chem. Soc.* **1982**, *104*, 4446–4450; b) A. Papanikos, J. Rademann, M. Medal, *J. Am. Chem. Soc.* **2001**, *123*, 2176–2181; for an application in natural product synthesis, see: c) J. Chen, X. Chen, M. Bois-Choussy, J. Zhu, *J. Am. Chem. Soc.* **2006**, *128*, 87–89.
[9] a) H. H. Wasserman, W. B. Ho, *J. Org. Chem.* **1994**, *59*, 4364–4366; b) H. H. Wasserman, A. K. Petersen, M. Xia, *Tetrahedron* **2003**, *59*, 6771–6784.
[10] F. Ozawa, H. Soyama, H. Yanagihara, I. Aoyama, H. Takino, K. Izawa, T. Yamamoto, A. Yamamoto, *J. Am. Chem. Soc.* **1985**, *107*, 3235–3245.
[11] a) J. J. Chen, S. V. Deshpande, *Tetrahedron Lett.* **2003**, *44*, 8873–8876; b) I. Ugi, U. Fetzer, *Chem. Ber.* **1961**, *94*, 1116–1121; c) L. El Kaïm, E. Pinot-Périgord, *Tetrahedron* **1998**, *54*, 3799–3806.
[12] a) P. Janvier, X. Sun, H. Bienaymé, J. Zhu, *J. Am. Chem. Soc.* **2002**, *124*, 2560–2567; b) A. Fayol, J. Zhu, *Angew. Chem.* **2002**, *114*, 3785–3787; *Angew. Chem. Int. Ed.* **2002**, *41*, 3633–3635; c) P. Janvier, H. Bienaymé, J. Zhu, *Angew. Chem.* **2002**, *114*, 4467–4470; *Angew. Chem. Int. Ed.* **2002**, *41*, 4291–4294; d) P. Janvier, M. Bois-Choussy, H. Bienaymé, J. Zhu, *Angew. Chem.* **2003**, *115*, 835–838; *Angew. Chem. Int. Ed.* **2003**, *42*, 811–814; e) A. Fayol, J. Zhu, *Org. Lett.* **2005**, *7*, 239–242; f) T. Pirali, G. C. Tron, J. Zhu, *Org. Lett.* **2006**, *8*, 4145–4148; g) T. Ngouansavanh, J. Zhu, *Angew. Chem.* **2006**, *118*, 3575–3577; *Angew. Chem. Int. Ed.* **2006**, *45*, 3495–3497; h) D. Bonne, M. Dekhane, J. Zhu, *Angew. Chem.* **2007**, *119*, 2537–2540; *Angew. Chem. Int. Ed.* **2007**, *46*, 2485–2488; i) A. Pinto, L. Neuville, J. Zhu, *Angew. Chem.* **2007**, *119*, 3355–3359; *Angew. Chem. Int. Ed.* **2007**, *46*, 3291–3295; j) T. Ngouansavanh, J. Zhu, *Angew. Chem.* **2007**, *119*, 5877–5880; *Angew. Chem. Int. Ed.* **2007**, *46*, 5775–5778; k) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144.
[13] A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300–3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210.
[14] a) A. Basso, L. Banfi, G. Guanti, R. Riva, *Tetrahedron Lett.* **2005**, *46*, 8003–8006; b) G. Zinner, D. Moderhack, W. Kliegel, *Chem. Ber.* **1969**, *102*, 2536–2546; c) D. Moderhack, *Justus Liebigs Ann. Chem.* **1973**, 359–364; d) G. Zinner, D. Moderhack, O. Hantelmann, W. Bock, *Chem. Ber.* **1974**, *107*, 2947–2955; for the use of *O*-alkyl hydroxylamines in the Ugi 4CR, see: e) A. Basso, L. Banfi, G. Guanti, R. Riva, A. Riu, *Tetrahedron Lett.* **2004**, *45*, 6109–6111.
[15] For the use of secondary amines in the Ugi 4CR, see: a) D. Bonne, M. Dekhane, J. Zhu, *Org. Lett.* **2004**, *6*, 4771–4774; b) G. B. Giovenzana, G. C. Tron, S. Di Paola, I. G. Menegotto, T. Pirali, *Angew. Chem.* **2006**, *118*, 1117–1120; *Angew. Chem. Int.*

Ed. **2006**, *45*, 1099 – 1102; c) Y. Tanaka, T. Hasui, M. Suginome, *Org. Lett.* **2007**, *9*, 4407 – 4410.
[16] For the insertion of isocyanides into C–O bonds of acetals, see: a) H. Pellissier, A. Meou, G. Gil, *Tetrahedron Lett.* **1986**, *27*, 2979 – 2980; b) H. Pellissier, G. Gil, *Tetrahedron Lett.* **1989**, *30*, 171 – 172; c) M. Tobisu, A. Kitajima, S. Yoshioka, I. Hyodo, M. Ospita, N. Chatani, *J. Am. Chem. Soc.* **2007**, *129*, 11431 – 11437.
[17] See, for example: a) K. Mikami, A. Yoshida, *Synlett* **1995**, 29 – 31; b) Y. Koga, M. Sodeoka, M. Shibasaki, *Tetrahedron Lett.* **1994**, *35*, 1227 – 1230.
[18] a) W. Maison, I. Schlemminger, O. Westerhoff, J. Martens, *Bioorg. Med. Chem.* **2000**, *8*, 1343 – 1360; b) W. Maison, I. Schlemminger, O. Westerhoff, J. Martens, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 581 – 584.
[19] a) D. Moderhack, M. Lorke, *J. Chem. Soc. Chem. Commun.* **1977**, 831 – 832; b) D. Moderhack, M. Lorke, *Angew. Chem.* **1980**, *92*, 46 – 47; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 45 – 46; c) D. Moderhack, M. Lorke, D. Schomburg, *Liebigs Ann. Chem.* **1984**, 1685 – 1695.
[20] M. K. Davis, *Acc. Chem. Res.* **1993**, *26*, 111 – 115.
[21] As 4-Å, but not 3-Å, molecular sieves are capable of adsorbing methanol, one of the referees suggested that MeOH-doped 4-Å MS may have a specific effect with respect to the promotion of the β-elimination step and proposed the following parallel experiments: A solution of the Ugi adduct **5** (R^1 = Me, R^2 = $PhCH_2CH_2$, R^3 = cyclohexyl) in ethanol (which can not be adsorbed by 4-Å MS) should be stirred in the presence of 4-Å MS and MeOH-doped 4-Å MS. We obtained the α-ketoamide in comparable yields from the two experiments, which indicates that the saturation of the pores with MeOH may not be important.
[22] For the direct formation of an amide from an aldehyde and an amine, see: a) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796 – 13797; b) K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126 – 8127.
[23] *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**.
[24] For the one-pot oxidative homologation of aldehydes, see: D. Bonne, M. Dekhane, J. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 6926 – 6927.

