The Ugi reaction of cyanoacetic acid as a route to tetramic acid derivatives.

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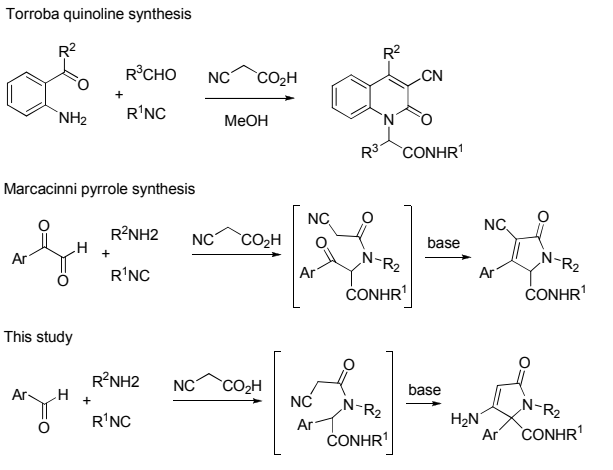
Abstract: Ugi adducts of cyanoacetic acid and aromatic aldehydes are easily cyclized under basic condition leading to one-pot formation of aminopyrrolinone derivatives.

Key words: Ugi, isocyanide, cyanoacetic, aminopyrolidinones.

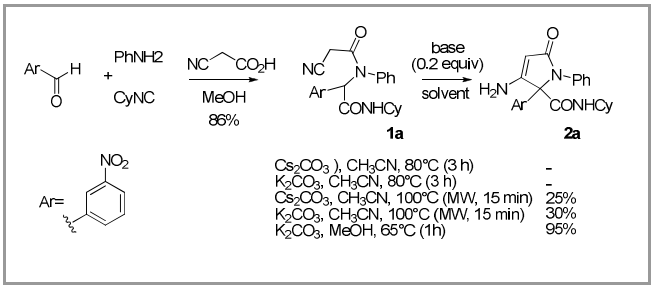
The Ugi reaction is one of the most efficient tools for the fast assembly of heterocyclic scaffolds.[1] Since the rebirth of this reaction thirthy years ago, many two to three-steps strategies towards nitrogen heterocycles have been reported thanks to the hudge functional tolerance of the Ugi coupling used in the first step of these sequences.[2] The interest of cyanoacetic acid in Ugi reactions was first explored by Marcaccini et al. His initial report on the preparation of pyrrolinones[3] was latter extended by him an others to the synthesis of quinolines,[4] pyridones[5] and pyridazinones.[6] In all the studies with this acid, the multicomponent process is followed by a knoevenagel reaction involving the cyanoacetamide CH_2 group and a carbonyl function properly positioned . Two variations on this strategy by Marcacini and Torroba are displayed in Scheme 1.



Scheme 1 Cyanoacetic acid in Ugi reactions.

Whereas these studies have largely emphasized on the nucleophilic potential of the cyanoacetamide moiety, the ability of the cyano group to be trapped by internal nucleophiles have been completly underestimated. We surmised that the choice of an aromatic aldehyde in order to raise the acidity of the peptidyl position might give a chance to this site to compete for deprotonation with acetamido CH_2 group (Scheme 1).[7] Such strategy if efficient would complement nicely the pyrrolinone synthesis reported by Marcacini.

In order to test this hypothesis, aniline was added to a solution of 3-nitrobenzaldehyde in methanol followed by addition of cyclohexyl isocyanide and cyanoacetic acid to give the Ugi product **1a** in 86% isolated yield (Scheme 2). Heating **1a** in acetonitrile at 80°C with either potassium carbonate or cesium carbonate failed to give any cyclization. However we were delighted to observe the formation of the expected product **2a** in moderate yield after microwave heating at higher temperature. Replacing acetonitrile by methanol led to dramatic increase in yield as **2a** was then obtained in 95% isolated yield after refluxing the mixture for one hour.

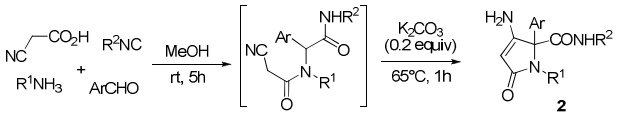


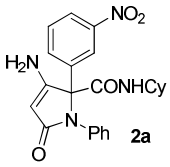
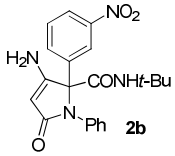
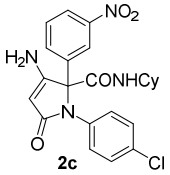
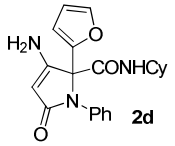
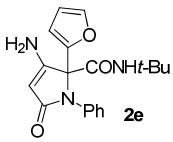
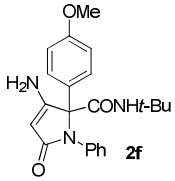
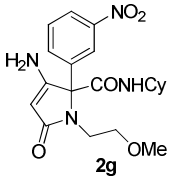
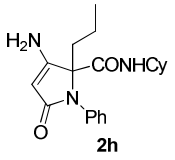
Scheme 2 Cyclization of Ugi product **1a** to pyrrolinone **2a**.

The further interest of methanol for the cyclization step is associated with an easier conversion of this sequence into a one-pot procedure. After completion of the Ugi step, the solution was diluted with methanol to reach [0.2 M], the base was added and the mixture heated under reflux. Using this one-pot procedure **2a** could be still directly obtained from the Ugi components in a 74% isolated yield. These conditons were selected for the rest of the study allowing the preparation of pyrrolinones **2a**-**2g** in good to moderate yields (Table 1, entries 1-7).[8] Best yields were obtained with aniline derivatives (Table 1, entries 1-6). The cyclized products usually precipitate during the reaction. The choice of an aliphatic amine leads to the expected product but with a lower 50% isolated yield (Table 1, entry 7). In this case, the cyclization to **2g** already started during the Ugi step and the final product was simply recovered letting the Ugi mixture stand at room tenperature for one day. Finally, the importance of tuning the acidity of the peptidyl position through a proper choice of the

starting aldehyde component was confirmed by the attempted formation of pyrrolinone **2h** from n-butyraldehyde. Whereas the intermediate Ugi adduct could be easily formed, the following cyclization was not observed and prolonged heating led to an untractable mixture.

Table 1



Entry	2	Yield (%)	Entry	2	Yield (%)
1	 **2a**	74	2	 **2b**	82
3	 **2c**	77	4	 **2d**	79
5	 **2e**	70	6	 **2f**	72
7	 **2g**	50[a]		 **2h**	0

[a]:**2g** was obtained during the Ugi reaction without added base

Pyrrolidinones are important heterocyclic scaffolds. They are found in many natural products[9] and represent important targets for both pharmaceutical[10] and agrochemical[11] industries. The aminopyrrolinones **2** are aminoanalogues of tetramic acid, they have been used as herbicides,[12] antibacterial[13] and have shown interesting activities for the treatment of epilepsy.[14] The main synthetic routes for these products involve the preparation of an intermediate aminonitrile (by a Strecker reaction) which may be acylated and cyclized under basic conditions[15] or the amination of a preformed tetramic acid derivative[16] (Scheme 3).

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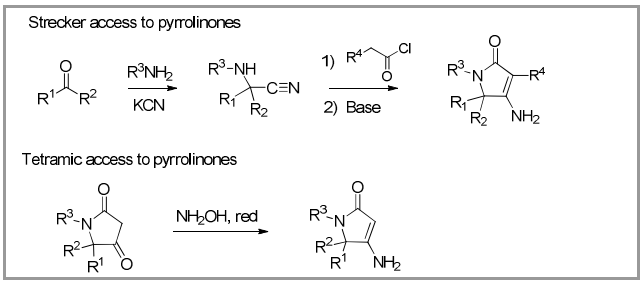

Scheme 3 Known synthetic routes towards 4-aminopyrrolin-2-ones.

To conclude, we have extended the diversity offered by cyanoacetic acid in Ugi reactions. Our approach offers an interesting complement to the Ugi-Knoevenagel preparation of pyrrolinones by Marcaccini et al. Compared with the latter, the enamine moiety of pyrrolinones 2 may be associated with interesting nucleophilic behavior for the preparation of fused heterocyclic systems. This direction as well as the extension of this strategy to Passerini couplings and furan preparation will be further explored.

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References

(1) For reviews, see: (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed*. **2000**, *39*, 3168-3210. (b) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J*. **2000**, *6*, 3321-3329. (c) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53-66. (d) Dömling, A. *Curr. Opin. Chem. Bio.* **2002**, *6*, 306-313. (e) "Multicomponent reactions"; Zhu, J.; Bienaymé, H. Eds Wiley-VCH: Weinheim, **2005**. (f) Dömling, A. *Chem. Rev*. **2006**, *106*, 17-89. (g) "Multicomponent reactions in organic synthesis": Zhu, J.; Wang, Q.; Wang, M. Eds Wiley-VCH: Weinheim, **2014**.

(2) In 1(e): Marcaccini, S; Torroba, T "Post-condensation Modifications of the Passerini and Ugi Reactions" chap. 2, 33-72.

(3) (a) Bossio, R.; Marcaccini, S.; Pepino, R. *Synthesis* **1994**, 765-766.

(4) (a) Marcaccini, S.; Pepino, R.; Pozo, M. C.; Basurto, S.; Garcia-Valverde, M.; Torroba, T.*Tetrahedron Lett.* **2004**, *45*, 3999-4001. (b) Gordon, C. P.; Young, K. A.;

Hizartzidis, L.; Deane, F. M.; McCluskey, A. *Org. Biomol. Chem.* **2011**, *9*, 1419-1428.

(5) Neo, A. G.; Carillo, R. M.; Barriga, S.; Moman, E.; Marcaccini, S.; Marcos, C. F. *Synlett* **2007**, 327-329.

(6) Marcos, C. F.; Marcaccini, S.; Pepino, R.; Polo, C.; Torroba, T. *Synthesis* **2003**, 691-694.

(7) For some Ugi post-condensations involving the peptidyl position of Ugi adducts: (a) Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Synthesis* **1997**, 1389-1390. (b) Salcedo, A.; Neuville, Luc; Zhu, J. *J. Org. Chem.* **2008**, *73*, 3600-3603. (c) El Kaïm, L.; Grimaud, L.; Ibarra, T.; Montano-Gamez, R. *Chem. Comm.***2008**, *11*, 1350-1352. (d) El Kaïm, L.; Grimaud, L.; Wagschal, S. *J. Org. Chem.* **2010**, *75*, 5343–5346. (e) El Kaim, L.; Le Goff, X. –F.; Grimaud, L.; Schiltz, A. *Org. Lett.* **2011**, *13*, 534-536. (f) Ben Abdessalem, A.; Abderrahim, R.; Agrebie, A.; Dos Santos, A.; El Kaïm, L.; Komesky, A. *Chem. Commun*. **2015**, *51*, 1116-1119.

(8) Typical procedure given for **2a**: To a stirred solution of 3-nitrobenzaldehyde (305 mg, 2 mmol) in anhydrous methanol (0.5 M) under argon at room temperature was added aniline (187 mg, 2 mmol). After 5 min, cyclohexylisocyanide (222 mg, 2 mmol) and cyanoacetic acid (171 mg, 2 mmol) were sequentially added. The resulting mixture was stirred at room temperature for 4 h. Subsequently, anhydrous methanol was added to obtain a 0.2 M solution and K_2CO_3 (0.2 equiv.) was added. The resulting mixture was stirred and heated at 65 ºC for 1 h. Evaporation of the solvent under reduced pressure, addition of dichloromethane and extraction afforded the crude which was purified by silica gel column chromatography (petroleum ether /diethyl ether, 2:8). **2a** was obtained as a white solid (MP: 231-233 ºC) in 74% isolated yield (620 mg, 1.48 mmol). Rf = 0.17 (2:8, petroleum ether:diethyl ether).**^{1}H NMR (400 MHz, DMSO):** δ (ppm) = 8.31 (t, *J* = 2.0 Hz, 1 H, ArH), 8.18 (d, *J* = 8.5 Hz, 1 H, NH), 8.10 (ddd, *J* = 0.9, 2.3, 8.2 Hz, 1 H, ArH), 7.70–7.68 (m, 1 H, ArH), 7.56–7.52 (m, 1 H, ArH), 7.13–7.12 (m, 4 H, ArH), 6.96–6.92 (m, 1 H, ArH), 6.60 (s, 2 H, NH_2), 4.87 (s, 1 H, CH), 3.76–3.67 (m, 1 H, CH), 1.66–1.65 (m, 3 H, CyH), 1.57–1.55 (m, 2 H, CyH), 1.35–1.17 (m, 4 H, CyH), 1.04–0.97 (m, 1 H, CyH). **^{13}C NMR (100 MHz, DMSO):** δ = 172.8 (CO), 165.9 (CO), 164.5 (CNH_2), 147.2 (ArC), 139.2 (ArC), 137.8 (ArC), 135.1 (ArC), 129.5 (ArC), 128. 2 (ArC), 124.1 (ArC), 123.8 (ArC), 123.5 (ArC), 122.9 (ArC), 88.3 (CH), 75.0, (C_{quat}), 48.9 (CH), 31.7 (CyC), 25.1 (CyC), 25.0 (CyC), 25.0 (CyC). **FT-IR (*ν*, cm^{-1}):** 1693 (CO), 1673 (CO), 1617 (NH_2), 1529 (NO_2), 1348 (NO_2). **HRMS (ESI+/TOF)**: *m/z* calcd. for $C_{23}H_{25}N_4O_4^+$ 421.1870, found 421.1886.

(9) (a) Hayashi, Y.; Shoji, M.; Yamaguchi, S.; Mukaiyama, T.;Yamaguchi, J.; Kakeya, H.; Osada, H. *Org. Lett.* **2003**, *5*, 2287−2290. (b) Yamaguchi, J.; Kakeya, H.; Uno, T.; Shoji, m.; Osada, H.; Hayashi, Y.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *40*, 3170−3175. (c) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, 114, 10677−10678.

(10) (a) Husain, A.; Alam, M. M.; Shaharyar, M.; Lal, S. J. *Enzym Inhib. Med. Ch.* **2010**, *25*, 54−61. (b) Hashem, A. I.; Youssef, A. S.; Kandeel, K. A.; Abou-Elmagd, W. S. *Eur. J. Med. Chem.* **2007**, *42*, 934−939. (c) Kenda, B. M.; Matagne, A. C.; Talaga, P. E.; Pasau, P. M.; Differding, E.; Lallemand, B. I.; Frycia, A. M.; Moureau, F. G.; Klitgaard, H. V.; Gillard, M. R.; Fuks, B.; Michel, P. *J. Med. Chem.* **2004**, *47*, 530−549.

(11) (a) Daniel Bellus, D.; Fory, W. U.S. Patent 4,013,445, Mar 22, 1977. (b) Nobuyuki, O.; Toshihiro, N.; Akira, T.; Shigehiko, T.; Yasunori, O. U.S. Patent 5 312 929, May 17, 1994.

(12) Baasner, B.; Fischer, R.; Widdig, A.; Lürssen, K.; Santel, H.-J.; Schmidt, R. R. US Patent, 5 338 560, 1994.

(13) Matsuo, K.; Tanaka, K. *Yakugaku Zasshi* **1984**, 104,1004–1008

(14) Arnold, T.; Unverferth, K.; Lankau, H.-J.; Rostock, A.; Tober, C.; Rundfeldt, C.; Bartsch, R. US Patent, 6 500 821, 2002.

(15) (a) Lee, C.-W.; Lira, R.; Dutra, J.; Ogilvie, K.; O'Neill, B. T.; Brodney, M.; Helal, C.; Young, J.; Lachapelle, E.; Sakya, S.; Murray, J. C. *J. Org. Chem*. **2013**, *78*, 2661-2669.(b)Zali-Boeini,H.; Mobin, M.; Hajibabaei, K.; Ghani, M. J. Org. Chem. 2012, 77, 5908-5812.

(16) (a) Pinheiro, S.; da Silva Júnior, R. C.; Silva de Souza, A.; Walkimar de M. Carneiro , J.; Muri, E. M. F.; Antunes, O. A. C. *Tetrahedron Lett*. **2009**, *50*, 2402-2404. (b) Hosseini, M.; Grau, J. S.; Sørensen, K. K.; Søtofte, I.; Tanner, D.; Murray, A.; Tønder, J. E.*Org. Biomol. Chem*.**2007**, *5*, 2207–2210.

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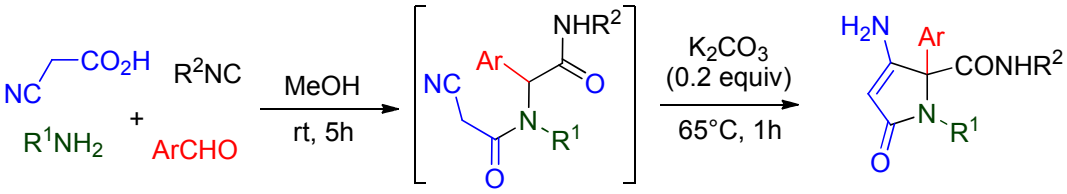
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NC
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R1NH2
+
ArCHO
MeOH
rt, 5h
NHR2
Ar
NC
O
N
R1
O
K2CO3
(0.2 equiv)
65°C, 1h
H2N
Ar
CONHR2
N
R1
O