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Ammonium Chloride Promoted Ugi Four-Component, Five-Center Reaction of α-Substituted α-Isocyano Acetic Acid: A Strong Solvent Effect

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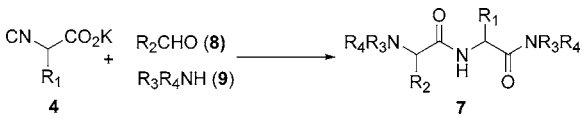
ABSTRACT



Conditions have been developed for the multicomponent synthesis of di- and tetrapeptide (7) based on the unique reactivity of α-isocyano acetic acid (4 and its α -substituted derivatives) by an Ugi four-component, five-center reaction. Simply mixing 4, a carbonyl compound (aldehyde or ketone, 8), and a secondary amine (9) (ratio: 1:1:2) in toluene in the presence of 1.5 equiv of ammonium chloride afforded the desired product in good to excellent yield as a mixture of two diastereomers.

In 1921, Passerini[1] pioneered the use of isocyanides and successfully developed a three-component synthesis of α-acyloxycarboxamide by reaction of a carboxylic acid, an aldehyde, and an isonitrile.[2] However, the most important breakthrough came in 1959 when Ugi described a four-component synthesis of α-acylamino amide from an aldehyde, an amine, an acid, and an isocyanide.[3] This reaction, named after Ugi (Ugi 4CR or U-4CR) has become one of the most investigated transformations during the past decade, in conjunction with the enabling technologies such as high-throughput screening and combinatorial chemistry.[4]

The ability of isonitrile to undergo facile α-addition with a nucleophile and an electrophile under mild conditions made it a popular reactant for the development of novel MCRs.[5] Incorporation of additional functionalities into the isocyanide derivatives would naturally increase further the versatility of these synthons and indeed many new functionalized isonitriles have been synthesized.[6,7,8] Among them, α-isocyano acetate[6,7,9] (**1**, Figure 1) and α-toluenesulfonylmethyl isocyanide[8,10] (TosMIC, **2**) are notable examples. The names of Schöllkopf and Van Leusen stand for many pioneering developments in this field and particularly on α-metalated

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(1) (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126−129. (b) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181−189. (c) Passerini, M. *Gazz. Chim. Ital.* **1922**, *52*, 432−435.

(2) Banfi, L.; Riva, R. In *Organic Reactions*; Charette, A. B., Eds.; John Wiley & Sons, Inc.: New York, 2005, in press.

(3) (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386. (b) Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267−268.

(4) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210.

(5) For recent reviews on multicomponent reactions, see: (a) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321−3329. (b) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306−313. (c) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51−80. (d) Orru, R. V. A.; De Greef, M. *Synthesis* **2003**, 1471−1499. (e) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101−4111. (f) Jacobi von Wangelin, A.; Neumann, H.; Gördes, D.; Klaus, S.; Strübing, D.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 4286−4294. (g) Murakami, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 718−720.

(6) Marcaccini, S.; Torroba, T. *Org. Prep. Proced. Int.* **1993**, *25*, 141−208.

(7) (a) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 789−804. (b) Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 339−348.

(8) Van Leusen, D.; Van Leusen, A. M. In *Organic Reactions*; Oveman, L. E., Ed.; John Wiley & Sons, Inc.: New York, 2001; Vol. 57, pp 417−666.

(9) (a) Suzuki, M.; Nunami, K.-I.; Moriya, T.; Matsumoto, K.; Yoneda, N. *J. Org. Chem.* **1978**, *26*, 4933−4935. (b) Bon, R. S.; Hong, C.; Bouma, M. J.; Schmitz, R. F.; De Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. *Org. Lett.* **2003**, *5*, 3759−3762.

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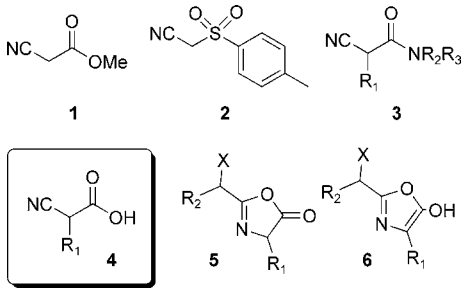
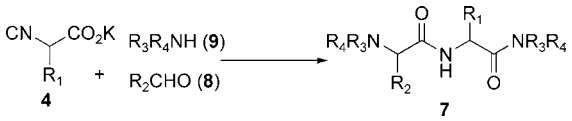


Figure 1. Functionalized isocyanides.

isocyanides. The importance of α-metalated isocyanides rests partly on the nucleophilicty of α-carbanion, to which electrophilic centers can become attached, and partly on the fact that the divalent isocyanide carbon makes subsequent heterocyclization possible.

We have been working on the chemistry of α-isocyano acetamides (**3**)[11] and have uncovered its unique reactivity profile that is completely different from that of α-isocyano acetates.[12] This was illustrated by developing a number of novel MCRs for the synthesis of complex polyheterocycles[13,14] and macrocycles.[15] As a continuation of our work in this field, we became interested in the reactivity of α-isocyanoacetic acid (**4**) and its use in the development of novel multicomponent reactions (Scheme 1). In a broad sense

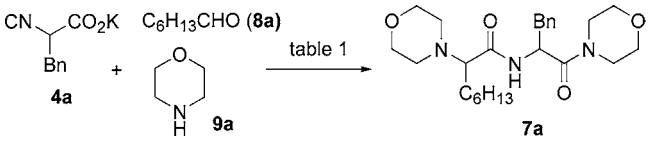
Scheme 1



and in accord with our previous studies on isocyano acetamide, we envisaged a multicomponent synthesis of oxazolone **5**[16] (Figure 1) that, in principle, can be further functionalized, either directly or via its tautomer 5-hydroxy oxazole **6**. As a prelude of this investigation, we report herein a multicomponent synthesis of peptide **7** by an Ugi four-component, five-center reaction (ABC_2 type, Scheme 1).[17,18]

The Ugi reaction of isocyanoacetic acid has received only sporadic attention, and the only recorded example in the open literature was the one reported from the group of Bossio, Marcaccini, and Pepino.[19,20] The reaction of potassium isocyanoacetate, an amine salt and a ketone in refluxing ethanol, was found to be limited in scope and was applicable only to anilines and ketones. When aliphatic aldehyde was used as carbonyl input, a very complex reaction mixture was produced under these conditions. As a first step of our long-term project, we decided to reexamine this reaction using morpholine **9a**, heptanal **8a**, and potassium 2-isocyano-3-phenylpropanoate **4a** as model substrates.[21] Guided by our previous work on isocyano acetamide, toluene was selected as solvent in combination with a weak Brönstedt acid or Lewis acid (Table 1).[11b] As is seen, by mixing compounds **4a**, **8a**, and **9a** together (ratio: 1:1:2) in toluene in the presence of 1.5 equiv of ammonium chloride (NH_4Cl, entry 1), the dipeptide **7a** was isolated in 90% yield as a mixture of two diastereomers.[13,22] The dramatic effect of ammonium chloride

Table 1. Multicomponent Synthesis of **7a**: Effect of the Additive, Solvent, and Temperature[a]



entry	solvent	T (°C)	additive	yield[b] (%)
1	toluene	rt	NH_4Cl	90
2	toluene	rt		17
3	toluene	rt	LiBr	16
4	toluene	rt	CSA	44
5	EtOH	rt	NH_4Cl	30
6	toluene	60 °C	NH_4Cl	83

[a] Reaction time: 18 h. Additive: 1.5 equiv. [b] Isolated yield.

(10) Recent examples, see: (a) Kulkarni, B. A.; Ganesan, A. *Tetrahedron Lett.* **1999**, *40*, 5633−5636. (b) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516−1524.

(11) (a) Sun, X.; Janvier, P.; Zhao, G.; Bienaymé, H.; Zhu, J. *Org. Lett.* **2001**, *3*, 877−880. (b) Janvier, P.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560−2567.

(12) For a short account, see: Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133−1144.

(13) (a) González-Zamora, E.; Fayol, A.; Bois-Choussy, M.; Chiaroni, A.; Zhu, J. *J. Chem. Soc. Chem. Commun.* **2001**, 1684−1685. (b) Gámez-Montaño, R.; Zhu, J. *J. Chem. Soc. Chem. Commun.* **2002**, 2448−2449. (c) Janvier, P.; Bienaymé, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4291−4294. (d) Gámez-Montaño, R.; González-Zamora, E.; Potier, P.; Zhu, J. *Tetrahedron* **2002**, *58*, 6351−6358. (e) Fayol, A.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3633−3635. (f) Fayol, A.; Zhu, J. *Org. Lett.* **2004**, *6*, 115−118.

(14) (a) Wang, Q.; Xia, Q.; Ganem, B. *Tetrahedron Lett.* **2003**, *44*, 6825−6827. (b) Wang, Q.; Ganem, B. *Tetrahedron Lett.* **2003**, *44*, 6829−6832.

(15) (a) Zhao, G.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2001**, *123*, 6700−6701. (b) Janvier, P.; Bois-Choussy, M.; Bienaymé, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 811−814.

(16) For reviews, see: (a) Mukerjee, A. K.; Kumar, P. *Heterocycles* **1981**, *16*, 1995−2034. (b) Mukerjee, A. K. *Heterocycles* **1987**, *26*, 1077−1097.

(17) Ugi four-component, five-center reactions using α-amino acid as input: (a) Demharter, A.; Hörl, W.; Herdtweck, E.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 173−175. (b) Park, S. J.; Keum, G.; Kang, S. B.; Koh, H. Y.; Kim, Y.; Lee, D. H. *Tetrahedron Lett.* **1998**, *39*, 7109−7112. (c) Zimmer, R.; Ziemer, A.; Gruner, M.; Brudgam, I.; Hartl, H.; Reissig, H. U. *Synthesis* **2001**, 1649−1658. (d) 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. (e) Gedev, S.; Van der Eycken, J.; Fulöp, F. *Org. Lett.* **2002**, *4*, 1967−1969.

(18) Ugi four-component, five-center reactions using rigid *β*-amino acid as input: Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron Lett.* **2004**, *45*, 587−590.

(19) Bossio, R.; Marcaccini, S.; Paoli, P.; Pepino, R. *Synthesis* **1994**, 672−674.

(20) An additional example without specifying the yield was cited as unpublished results in the book of Ugi: Gokel, G.; Lüdke, G.; Ugi, I. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971; p 159.

(21) Prepared by saponification of the corresponding methyl ester. It was kept as the potassium salt since the free acid is unstable even at the refrigerator conditions. See: Takiguchi, K.; Yamada, K.; Mamoru, S.; Nanami, K.; Kimiaki, H.; Kazuo, M. *Agric. Biol. Chem.* **1989**, *53*, 77−82.

on the reaction outcome is readily seen if one compared the results of entries 1 and 2. In fact, in its absence, the multicomponent reaction proceeded sluggishly to provide the dipeptide in only 17% yield (entry 2). Other additives such as lithium bromide and camphrosulfonic acid were less efficient for this particular reaction. The superiority of toluene relative to ethanol as reaction medium is also evident since the same reaction carried out in ethanol afforded the dipeptide (**7a**) in only 30% yield (entry 5). The Passerini reaction, which is usually favored in a nonpolar aprotic solvent, was not observed under these conditions. It is interesting to note that potassium 2-isocyano-3-phenylpropanoate **4a** was only partly soluble in toluene, and so was NH_4Cl. However, as the reaction proceeds, **4a** was gradually dissolved and was completely consumed. The temperature had little or no effect on the yield of the product although the reaction proceeded faster. Indeed, when the same reaction was carried out at 60 °C, the desired dipeptide **7a** was isolated in 83% yield.

The scope of this reaction was next examined varying the structure of the three reactants (Figure 2). Some representative peptides synthesized are shown in Figure 3.[23] For the carbonyl input, both aldehydes and ketones in the aromatic and aliphatic series can be used, although ketones gave lower yield. Formaldehyde can also be used, thus incorporating a glycine unit into the dipeptide. Amino esters are accepted as an amine input leading to the formation of a tetrapeptide in good yield. Furthermore, when a hydrochloride salt of amine was used as input, neutralization in situ with triethylamine in toluene followed by addition of aldehyde and isocyanide provided the corresponding dipeptide in good yield. Apparently, the stoichiometric amount of $Et_3N{\cdot}HCl$ generated in situ is enough to promote the reaction and seems to play the same role as ammonium chloride. No diastereoselectivity was observed when optically pure L-α-isocyano-*β*-phenylpropionic acid (**4a**) was used as input. Three representative isocyanoacetic acid derivatives (R = Bn, **4a**; H **4b**; Ph, **4c**) derived from phenylalanine, phenylglycine, and glycine were prepared and were found to be effective reaction partners.

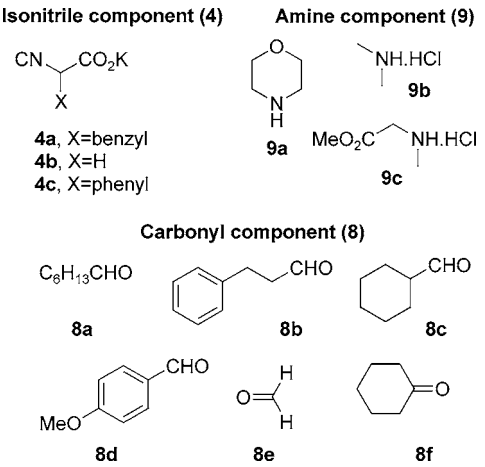


Figure 2. Structure of starting materials.

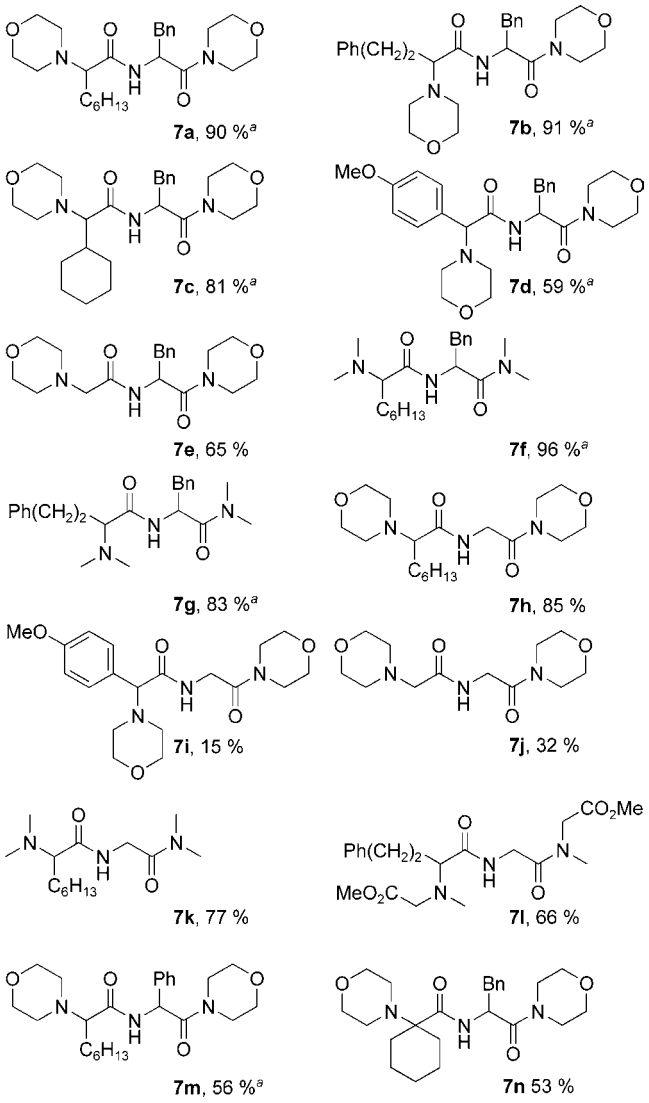


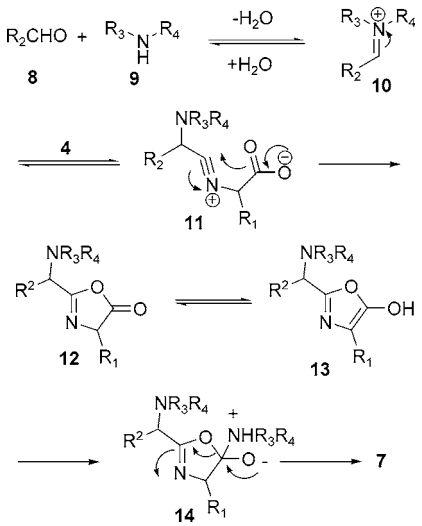
Figure 3. Isolated yields of analytically pure compounds. [a]Isolated as a mixture of two diastereomers in a 1:1 ratio.

A plausible reaction sequence that accounts for the formation of dipeptide is shown in Scheme 2. Thus, condensation of an aldehyde **8** and a secondary amine **9** gave the iminium **10**, which reacted with isonitrile **4** to afford the nitrilium intermediate **11**. Trapping of the latter by an internal carboxylate oxygen would provide the oxazolone **12** which may be in equilibrium with the 5-hydroxyoxazole **13**. An

(22) Ammonium chloride promoted Ugi reaction: Cristau, P.; Vors, J. P.; Zhu, J. *Org. Lett.* **2001**, *3*, 4079−4082.

(23) A representative procedure: A solution of amine (**9a**) (2.0 equiv) and aldehyde (**8a**) (1.0 equiv) in dry toluene (0.12 M) was stirred at room temperature in the presence of 1.5 equiv of NH_4Cl for 15 min. The potassium salt of α-substituted α-isocyano acetic acid (**4**) (1.0 equiv) was added, and the reaction mixture was stirred for 18 h at room temperature under argon atmosphere. The toluene was then removed under reduce pressure. After dilution with water, the product was extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel, eluent: ethyl acetate).

Scheme 2. Plausible Reaction Sequence



intermolecular nucleophilic attack of a second equivalent of amine **9** on the oxazolone would produce **14** which underwent fragmentation to afford the observed dipeptide **7**. We hypothesized that the role of the ammonium chloride was to promote the formation of iminium intermediate (**10**). Stronger Brönsted acid (CSA), when used in a stoichiometric amount, affected the reaction conversion. This is due probably to the protonation of amine input leading to inactive ammonium salt, as well as the instability of the oxazolone intermediate under strong acidic conditions. Weak Lewis acid (LiBr) has no apparent effect on the reaction conversion. Overall, this MCR can be considered as an Ugi 4CR (ABC_2)/five-center reaction.

In conclusion, we have shown that potassium isocyano acetic acid derivatives (**4**) can efficiently participate in a Ugi 4CR/five-center reactions leading to the formation of dipeptides or tetrapeptides. Polar protic solvents such as methanol and trifluoroethanol have frequently been used as the reaction medium for performing Ugi-type transformations. We provide herein a further example wherein nonpolar, aprotic solvent (toluene) in combination with ammonium chloride can be used advantageously. The weak acidity of ammonium chloride might explain its ability to promote this MCR in nonpolar aprotic solvent.[11b] We are currently exploiting the potential reactivity of the intermediate oxazolone in order to expand this chemistry to the synthesis of heterocycles.

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Supporting Information Available: Physical data for compounds **4a** and **7a**−**n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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