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Synthesis of Passerini−Ugi Hybrids by a Four-Component Reaction Using the Glycolaldehyde Dimer

Riccardo Mossetti, Tracey Pirali, and Gian Cesare Tron*

Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche and Drug and Food Biotechnology Center, Università degli Studi del Piemonte Orientale "A. Avogadro", Via Bovio 6, 28100 Novara, Italy

tron@pharm.unipmn.it

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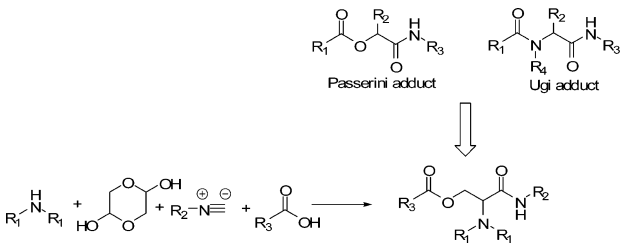
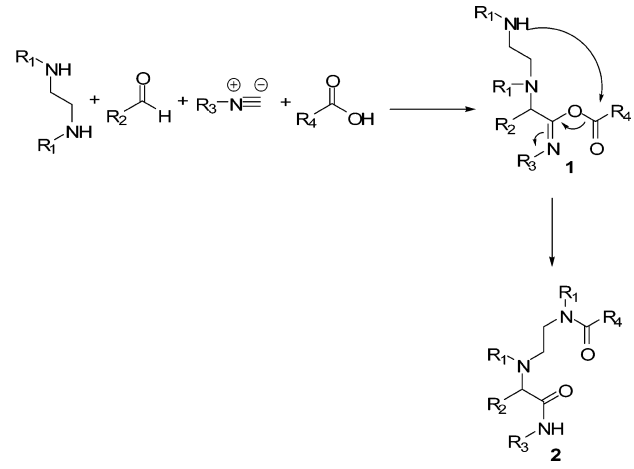


Passerini−Ugi hybrid adducts can be obtained through a four-component reaction by using glycolaldehyde dimer.

Over the past decades, multicomponent reactions (MCRs) have demonstrated their ability and efficiency in the generation of chemical diversity.[1] For this reason, MCRs are featured in many diversity-oriented projects, whose biological relevance has been validated by the discovery of novel biological probes and drug leads.[2] The Ugi four-component reaction[3] and the Passerini three-component reaction[4] are the two most important and used isocyanide-mediated MCRs.[5]

To broaden their potentiality, both intramolecular variations, where two of the four functional groups belong to the same molecule, and post-transformation strategies have been performed, giving easy access to a vast array of heterocycles.[6] However, a limitation of these reactions lies in the fact that in all of the final adducts the obtainable molecular skeletons always follow the same connectivity, namely, NCCNC and NCCOC for Ugi and Passerini products, respectively. Recently, we tried to modify the scaffold extension of the Ugi reaction and reported that the combination of two secondary amines in the same molecule is effective in generating a new multicomponent reaction where the classical Ugi scaffold was split,[7] as the use of a secondary amine in the Ugi reaction can give origin to a different mechanisms of reaction. Indeed, after the formation of the iminium ion and the isocyanide and carboxylic acid attack, the imino anhydride intermediate generated (**1**) can no longer undergo the Mumm rearrangement, as meanwhile the nitrogen atom has become a tertiary amine.[8] The intermediate can now undergo different synthetic fates: (a) being attacked by acyl acceptors in the presence of nucleophilic solvents (e.g., methanol)[9] to give an α-amino amide, (b) being attacked by the isocyanide nitrogen atom in presence of non-nucleopilic solvents to give the acylating agent α-amino imide,[9,10] or (c) being intramolecularly intercepted by another secondary nitrogen atom to give the new scaffold **2**[7a] (Scheme 1).

SCHEME 1. Different Mechanisms of the Ugi Reaction with a Secondary Amine



Searching for new MCRs using this strategy, we planned to generate a novel skeleton that could formally be viewed as a hybrid between Ugi and Passerini products.[11] To achieve this task, we thought that the imino anhydride intermediate could also be intercepted by nucleophiles other than the nitrogen atom and reasoned that the incorporation of a hydroxyl group in the aldehyde component, using the commercially available glycolaldehyde dimer and the presence of a secondary amine, could give rise to an *O*-acyl Mumm rearrangement, typical of the Passerini reaction, with the formation of a new molecular

(1) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005 and references therein.

(2) (a) Weber, L. *Curr. Med. Chem.* **2002**, *9*, 1241–1253. (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80. (c) Akritopoulou-Zanze, I. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324–331.

(3) (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386–388. (b) Marcaccini, S.; Torroba, T. *Nat. Protoc.* **2007**, *2*, 632–639.

(4) (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126–129. (b) Riva, R.; Banfi, L. *Org. React.* **2005**, *65*, 1–140.

(5) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(6) (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (b) Akritopoulou-Zanze, I.; Djuric, S. W. *Heterocycles* **2007**, *73*, 125–147.

(7) (a) Giovenzana, G. B.; Tron, G. C.; Di Paola, S.; Menegotto, I. G.; Pirali, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1099–1102. For recent applications of the *N*-split Ugi reaction see:(b) Pirali, T.; Callipari, G.; Ercolano, E.; Genazzani, A. A.; Giovenzana, G. B.; Tron, G. C. *Org. Lett.* **2008**, *10*, 4199–4202. (c) Piersanti, G.; Remi, F.; Fusi, V.; Formica, M.; Giorgi, L.; Zappia, G. *Org. Lett.* **2009**, *11*, 417–420.

(8) McFarland, J. W. *J. Org. Chem.* **1963**, *28*, 2179–2181.

(9) Ugi, I.; Steinbrückner, C. *Ber. Dtsch. Chem. Ges.* **1961**, *94*, 2802–2814.

(10) (a) Mumm, O. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 886–893. A similar mechanism has been proposed by Danishefsky et al. in the reaction between isocyanides and carboxylic acids: (b) Li, X.; Danishefsky, S. *J. Am. Chem. Soc.* **2008**, *130*, 5446–5448. (c) Jones, G. O.; Li, X.; Hayden, A. E.; Houk, K. N.; Danishefsky, S. J *Org. Lett.* **2008**, *10*, 4093–4096.

(11) For the synthesis of *N*-acyloxyethylamino acid amides obtained by reacting *N*-alkyloxazolidines, isocyanides, and carboxylic acids, see: Diorazio, L. J.; Motherwell, W. B.; Sheppard, T. D.; Waller, R. W. *Synlett* **2006**, *14*, 2281–2283.

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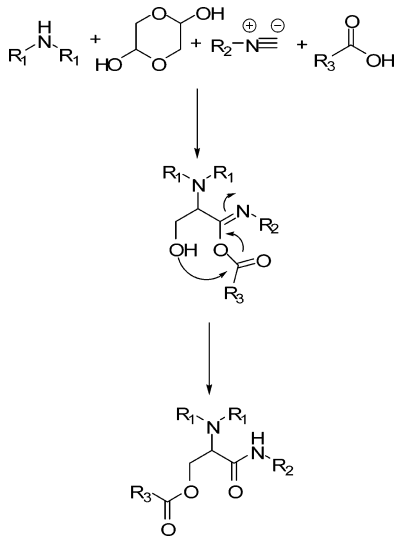
SCHEME 2. Mechanism of the Novel Four-Component Reaction



scaffold that, in this case, contains the typical signature both of the Ugi and of the Passerini products. The underlying principle is shown in Scheme 2.

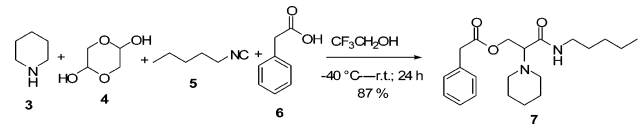
It should be noted that the intercept of the imino anhydride intermediate by means of a hydroxyl group has been reported by the Kim group in two different three-component reactions using α-amino acids, isocyanides, and glycolaldehyde dimer to give morpholinone derivatives[12] and in the reaction between homoserine, aldehydes, and isocyanides to give α-amino-γ-lactams.[13]

In these cases, the use of an α-amino acid favors the nucleophilic attack of the hydroxyl group to the iminoanhydride intermediate to give, respectively, the more stables six- and five-membered rings instead of a nitrogen-mediated transacylation to give the quite strained three-membered ring. On the other hand, when glycoladehyde dimer has been used in a classical Ugi reaction in the presence of a *primary amine*, the more nucleophilic nitrogen atom transacylates as was demonstrated by the Banfi's group.[14] For this reason, we would like to emphasize the novelty of using a *secondary amine*, which allows the hydroxyl group of the glycolaldehyde dimer to transacylate to give a new linear scaffold.

To demonstrate the feasibility of this idea, initial experiments were performed using 1 equiv of piperidine (**3**), 1 equiv of glycolaldeyde dimer (**4**), 1 equiv of pentyl isocyanide (**5**), and 1 equiv of phenylacetic acid (**6**) as test substrates.

When the reaction was carried out using methanol as solvent at room temperature, we did obtain the desired product, but in low yield (45%) without detecting the product deriving from the attack of the solvent on the imino anhydride intermediate. Next we tried a different experimental procedure[12] using 2,2,2-trifluoroethanol as solvent and adding a premixed solution of isocyanide and glycolaldehyde dimer to a cooled (−40 °C) solution of carboxylic acid and a secondary amine. To our delight, the reaction was clean, and we were able to isolate the desired product (**7**) in high yield (87%) (Scheme 3) after column chromatography.[15]

SCHEME 3. Reaction between Piperidine, Glicolaldehyde Dimer, Pentyl Isocyanide, and Phenylacetic Acid



A similar attempt using methanol under the same conditions gave again the desired product but with a lower yield (44%). It is interesting to note that when the reaction was performed using 2,2,2-trifluoroethanol as solvent at room temperature, we isolated only the Passerini adduct in very low yield (20%).

To generalize the scope and the limitation of this new multicomponent reaction, different isocyanides, carboxylic acids, and secondary amines were used as substrates (Figure 1).

The reaction appears to be versatile and a library of analogues (13 examples) has been prepared with good to excellent yields. In particular primary, secondary, and tertiary isocyanides react efficiently, as well as aliphatic, aromatic, and α,β-unsaturated carboxylic acids.

The presence of electron-withdrawing or -releasing groups on benzoic acid maintain high yields, with a decrease only when a nitro group is present. This is probably due to the highly electrophilic character of the imino anhydride intermediate, which can be intercepted intermolecularly by the solvent.

Finally, both alicylic and linear secondary amines are suitable for this type of reaction (Figure 2). An attempt to use a *N*-methyl aniline did not give the desired product but only the adduct deriving from Passerini reaction. This behavior is probably due to both to the hindered nature of the nitrogen atom and the low concentration of the iminium ion in the reaction medium.

Except glycolaldeyde dimer, α-hydroxy aldehydes are not stable and tend to isomerize to α-hydroxy ketones. When we carried out this reaction using 2-hydroxyacetophenone, we were not able to obtain the desired product.

In conclusion, we have reported a fast and flexibile new MCR that allowed the generation of a new scaffold difficult to obtain with the classical multistep chemistry.[16] This scaffold can be considered as a hybrid derived from a homo-Passerini[17] and an Ugi adduct.

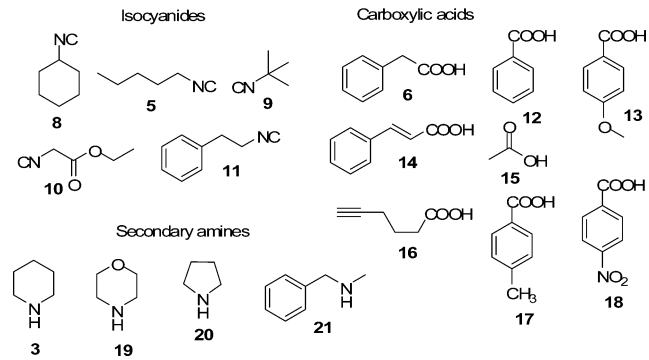


FIGURE 1. Isocyanide, carboxylic acid, and secondary amine building blocks.

(12) Kim, Y. B.; Choi, E. H.; Keum, G.; Kang, S. B.; Lee, D. H.; Koh, H. Y.; Kim, Y. *Org. Lett.* **2001**, *3*, 4149–4152.

(13) Park, S. J.; Keum, G.; Kang, S. B.; Koh, H. Y.; Kim, Y. *Tetrahedron Lett.* **1998**, *39*, 7109–7113.

(14) Banfi, L.; Basso, A.; Guanti, G.; Lecinska, P.; Riva, R. *Mol. Diversity* **2008**, *12*, 187–190.

(15) When 0.5 equiv of glycolaldehyde dimer was used, the yield dropped to 57%.

(16) A survey on Sci-Finder Scholar revealed the presence of only one example of a similar scaffold using a five-step procedure. See: (a) Hollowood, J.; Jansen, A. B. A.; Southgate, P. J. *J. Med. Chem.* **1967**, *10*, 863–867. (b) Jansen, A. B. A.; Hollowood, J. U.S. Patent 3543850, 1970.

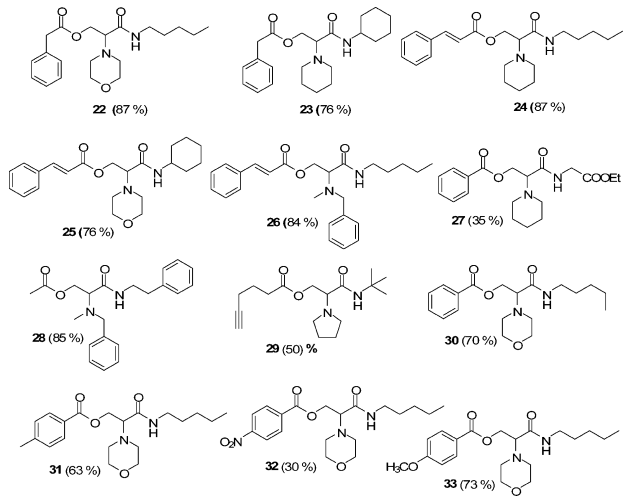


FIGURE 2. Synthesized compounds.

As we have demonstrated in a previous manuscript,[7a] the imino anhydride intermediate, generated using a secondary amine in the Ugi reaction, can be intramolecularly attacked by other nucleophiles before the well-known synthetic fates can take place,[9,10] allowing the formation of new scaffolds.

The use of molecules in which the hydroxyl group is grafted on isocyanide and secondary amine building blocks is under investigation, and the results will be reported in due course.

Experimental Section

General Procedure for the Preparation of 9, 24−35. To a solution of amine (1 equiv) in trifluoroethanol (1 M) was added carboxylic acid (1 equiv) under a nitrogen atmosphere. The resulting mixture was cooled to −40 °C, and then a solution of glycolaldehyde dimer (1 equiv) and isocyanide (1 equiv) in trifluoroethanol (1 M) was added. The cooling bath was removed, and the solution was stirred at room temperature for 24 h. The organic layer was washed with saturated $NaHCO_3$ (×1) and brine (×1), dried over sodium sulfate, and evaporated. The crude material was purified by column chromatography.

Acknowledgment. Financial support from Università del Piemonte Orientale, Italy is gratefully acknowledged.

Supporting Information Available: Characterization data for all new compounds and copies of the ^1H and ^{13}C spectra. This material is available free of charge via the Internet http://pubs.acs.org.

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(17) A homo-Passerini adduct generated by a MCR has never been reported in the literature. For an incorrect assignment, see: (a) Kern, O. T.; Motherwell, W. B. *Chem. Commun.* **2003**, 2988–2989. (b) Kern, O. T.; Motherwell, W. B. *Chem. Commun.* **2005**, 1787.