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Isolation of Ugi Four-Component Condensation Primary Adducts: A Straightforward Route to Isocoumarins

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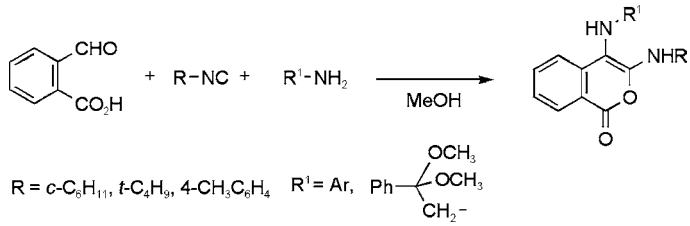
ABSTRACT

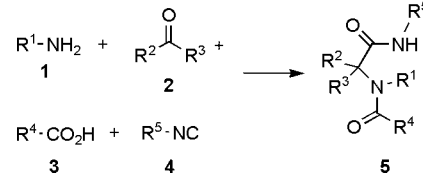


Ugi four-component condensation (Ugi-4CC) between 2-formylbenzoic acid, phenacylamine dimethyl acetal, and isocyanides afforded 1*H*-isochromen-1-ones (isocoumarins). These products, where structure corresponds to the tautomeric enediamine form of the Ugi-4CC primary adducts, were stable enough to allow their isolation and characterization. Stable isocoumarins were also obtained by employing anilines as the amino component in the Ugi four-component condensation.

In the well-known Ugi four-component condensation (Ugi-4CC), amines **1**, carbonyl compounds **2**, carboxylic acids **3**, and isocyanides **4** react to afford α-acylamino amides **5** (Scheme 1).[1,2]

According to the commonly accepted mechanism proposed by Ugi,[3] the amine, the carbonyl compound, and the acid

Scheme 1. Ugi Four-Component Condensation



are in equilibrium with the iminium carboxylate **6** in the reaction medium. The α-addition of the iminium carboxylate onto the carbenoid carbon of the isocyanide leads to the formation of the primary four-component adduct **7**, which undergoes an intramolecular acylation known as Mumm rearrangement to give the stable Ugi adduct **5** (Scheme 2). Other reaction mechanisms have been proposed to account for the stereochemical features of the Ugi-4CC.[4] However,

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(1) Reviews: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (b) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187–191. (c) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306–313. (d) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53–66. (e) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144. (f) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321–3329. (g) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(2) The term Ugi four-component condensation usually refers to the reaction between amines, carbonyl compounds, carboxylic acids, and isocyanides. Really, there are many kinds of Ugi reactions since large variations of the nature of the components are possible. See for example refs 1a,g and Marcaccini, S.; Torroba, T. *Nature Protocols* **2007**, *2*, 632–639.

(3) Ugi, I. *Angew. Chem., Int. Ed.* **1962**, *1*, 8–21.

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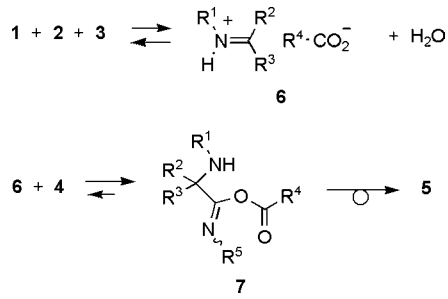
Scheme 2. Mechanism of Ugi-4CC



in all of the mechanisms the final step consists of the Mumm rearrangement of the primary α-adduct.

Although an impressive number of Ugi-4CCs have been performed, mainly because of the widespread application of combinatorial techniques,[5] to the best of our knowledge, only the successful isolation of the primary adducts **8** and **9** has been reported as unpublished results,[6] half a century after the discovery of this fundamental reaction (Figure 1).

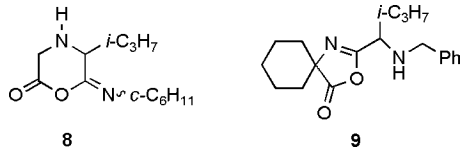


Figure 1. Previously isolated Ugi-4CC primary adducts.

In the course of our studies on isocyanide-based multicomponent reactions,[7] we attempted to perform an Ugi-4CC between 2-formylbenzoic acid (**10**), phenacylamine dimethyl acetal (**11**), and cyclohexyl isocyanide (**12a**) in methanol.[8,9] After 18 h stirring at rt a yellow solid **13a**, mp 148.5−150 °C, was isolated by filtration. The analytical and spectral data of **13a** confirmed that this product was the Ugi primary α-adduct in the tautomeric enediamine form, namely, 3-(*N*-cyclohexyl)amino-4-[*N*-(2,2-dimethoxy-2-phenyl)ethyl]amino-1*H*-isochromen-1-one. The assigned structure **13a** was further

(4) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.;Wiley-VCH: Weinheim, 2005; pp 1−32.

(5) Hulme, C. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; pp 311−341.

(6) Gokel, G., Lüdke, G., Ugi, I. In *Isocyanide Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971; pp 158−159.

(7) (a) Marcaccini, S.; Torroba, T. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; pp 33−75. (b) Carrillo, R. M.; Neo, A. G.; López-García, L.; Marcaccini, S.; Marcos, C. F. *Green Chem.* **2006**, *8*, 787–789. (c) Neo, A. G.; Carrillo, R. M.; Barriga, S.; Momán, E.; Marcaccini, S.; Marcos, C. F. *Synlett* **2007**, 327–329. (d) García-Valverde, M.; Macho, S.; Marcaccini, S.; Rodríguez, T.; Rojo, J.; Torroba, T. *Synlett* **2007**, 33–36. (e) Marcos, C. F.; Marcaccini, S.; Menchi, G.; Pepino, R.; Torroba, T. *Tetrahedron Lett.* **2008**, *49*, 149–152. (f) Corres, N.; Delgado, J. J.; García-Valverde, M.; Marcaccini, S.; Rodríguez, T.; Rojo, J.; Torroba, T. *Tetrahedron* **2008**, *64*, 2225–2232. (g) Faggi, C.; Neo, A. G.; Marcaccini, S.; Menchi, G.; Revuelta, J. *Tetrahedron Lett.* **2008**, *49*, 2099–2102. (h) Sañudo, M.; García-Valverde, M.; Marcaccini, S.; Delgado, J. J.; Rojo, J.; Torroba, T. *J. Org. Chem.* **2009**, *74*, 2189–2192.

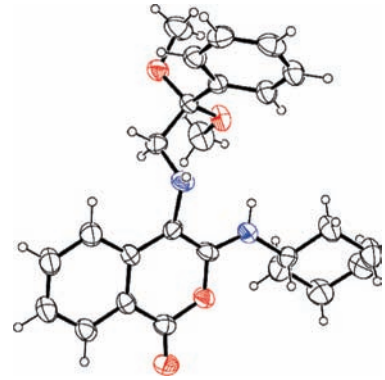
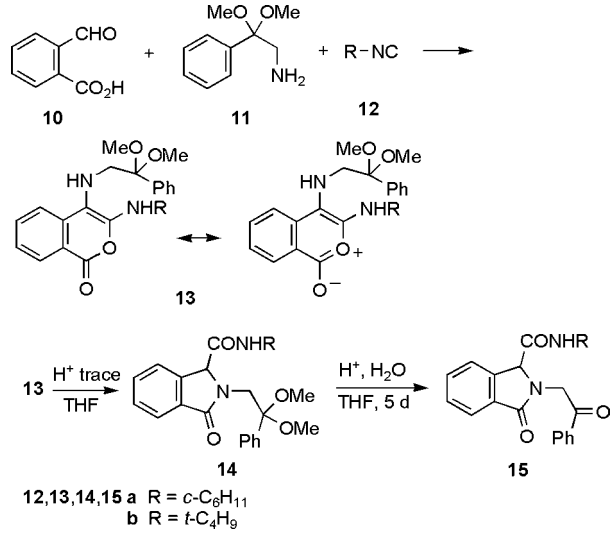


Figure 2. ORTEP drawing of **13a** with 30% probability thermal ellipsoids.

confirmed by X-ray diffraction analysis (Figure 2). Upon treatment of a THF solution of **13a** with a trace of acid, a rapid and quantitative isomerization to the "normal" Ugi-4CC adduct **14a**, namely, *N*-cyclohexyl-2-(2,2-dimethoxy-2-phenyl)ethyl-1,3-dihydro-1-oxoisoindol-3-carboxamide, took place. Prolonged exposure of **13a** to higher concentrations of hydrochloric acid afforded quantitatively the deprotected Ugi-4CC adduct **15a**. The same product **15a** was also obtained in the same conditions by employing **14a** as the starting material. Analogously, we obtained compounds **13b**, **14d**, and **15b** by employing *tert*-butyl isocyanide (**12b**) in the place of cyclohexyl isocyanide (**12a**) (Scheme 3).

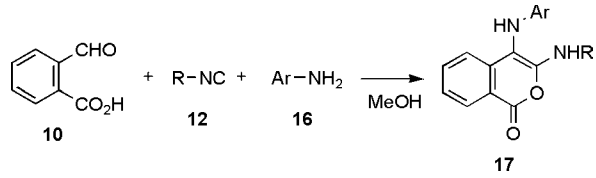
Scheme 3. Formation of the Ugi-4CC Primary Adducts **13** and Their Transformations



The successful isolation of the Ugi primary adducts **13** can surely be ascribed to the rigid nature and to the aromatic character of the isochromenone ring.

Furthermore, the X-ray analysis of **13a** showed that the alkoxy groups had no stabilizing effects such as strong hydrogen bonds. Thus, the sole effect of the alkoxy groups seemed to result in a reduced strength of the nitrogen basicity due to the inductive effect of the oxygen atoms. Keeping in mind that the Ugi-4CC between 2-acylbenzoic acids, isocyanides, and strongly basic amines afforded the secondary adducts,[8c,d] we reasoned that the use of a scarcely basic amine might result in the stabilization of the primary α-adduct. To verify this hypothesis, we reacted 2-formylbenzoic acid (**10**), isocyanides **12**, and anilines **16**. As expected we were able to isolate the Ugi-4CC primary adducts **17** in satisfactory yields (Table 1).

Table 1. Formation of 3-(*N*-Substituted)amino-4-arylamino-1*H*-isochromen-1-ones **17**



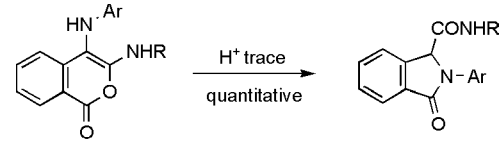
10 12 16 17

entry	R	isocyanide	Ar	amine	product	yield (%)
1	*c*-C_6H_{11}	**12a**	C_6H_5	**16a**	**17a**	57
2	*c*-C_6H_{11}	**12a**	4-FC_6H_5	**16b**	**17b**	58
3	*c*-C_6H_{11}	**12a**	3-ClC_6H_5	**16c**	**17c**	62
4	*c*-C_6H_{11}	**12a**	4-ClC_6H_5	**16d**	**17d**	68
5	4-$CH_3C_6H_4$	**12c**	4-FC_6H_5	**16b**	**17e**	64
6	*c*-C_6H_{11}	**12a**	4-$CH_3C_6H_4$	**16e**	**17f**	82

It must be emphasized that careful control of the reaction conditions was crucial to ensure both good yields and facile workup of compounds **17**. In fact, compounds **17** are stable in the solid state, whereas in solution they show a tendency to rearrange to the secondary Ugi products. Thus, if too high temperatures and/or prolonged reaction periods were employed, mixtures of **17** and secondary adducts were always found. If reaction conditions were too mild, the reactions afforded mixtures of **17** and the Schiff's base arising from the reaction between **10** and **16**. After some experimentation we were able to optimize the reaction conditions to ensure satisfactory yields of pure products by means of an experimentally simple general method.

With regard to the stability of compounds **17** in solution, it must be underlined that their solutions in neutral solvents at room temperatures showed a fair stability. The tendency of compounds **17** to rearrange to the Ugi secondary adducts **18** was accelerated at higher temperatures. In the presence of traces of acid the rearrangement took place almost instantaneously as demonstrated by the quick disappearance of the yellow color (Scheme 4).

Scheme 4. Acid-Induced Rearrangement of Isocoumarins **17** to Isoindolinones **18**



17c,f 18c,f

This behavior was taken into account when preparing the deuterochloroform solutions for recording the NMR spectra. Since hydrogen chloride is known to be a common contaminant of chloroform, commercial deuterochloroform was stirred with potassium carbonate in D_2O and dried prior to use.

Naturally occurring and synthetic products containing the isocoumarin ring display a wide variety of interesting biological activities such as protease inhibitory,[10] antiviral,[11] anti histamine release,[12] cytotoxic,[13] phytotoxic,[14] antifungal, antibacterial, antialgal,[15] anticoagulant,[16] and antitumor[17] properties.

Although a large number of isocoumarins are known,[18] those bearing amino groups in the heterocyclic portion of the ring are rare, and to the best of our knowledge, only a few synthetic routes have been reported.[19,20]

Interestingly, 3-amino-4-arylamino-1*H*-isochromen-1-ones were recently prepared by Opatz and Ferenc via a Strecker

(8) The use of 2-formylbenzoic acids and 2-acylbenzoic acids in isocyanide-based multicomponent reactions is well-known. Passerini reactions: (a) Passerini, M.; Ragni, G. *Gazz. Chim. Ital.* **1931**, *61*, 964–969. (b) Falck, J. R.; Manna, S. *Tetrahedron Lett.* **1981**, *22*, 619–620. Ugi reactions: (c) Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett.* **1998**, *39*, 2725–2728. (d) Zhang, J.; Jacobson, A.; Rusche, J. R.; Herlihy, W. *J. Org. Chem.* **1999**, *64*, 1074–1076. (e) Marcaccini, S.; Pepino, R.; Polo, C.; Pozo, M. C. *Synthesis* **2001**, 85–88. Groebcke reaction: (f) Mert-Balci, F.; Conrad, J.; Meindl, K.; Schulz, T.; Stalke, D.; Beifuss, U. *Synthesis* **2008**, 3649–3656.

(9) Some authors regard this kind of reactions as Ugi-3C-4CR or Ugi-3CR: Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634. According to the definition given by Ugi himself (Ugi, I.; Dömling, A.; Hörl, W. *Endeavour, New Series* **1994**, *18*, 115−122), "The reagents may be different individual molecules or they may be different functional groups of the same reagent", this reaction must be regarded as a true Ugi four-component condensation.

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(12) Qadeer, G.; Rama, N. H.; Shah, S. J. H. *Arkivoc* **2007**, *14*, 12–19.

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(14) (a) Tabacchi, R. *Pure Appl. Chem.* **1994**, *66*, 2299–2302. (b) Okuno, T.; Oikawa, S.; Goto, T.; Sawai, K.; Shirahama, H.; Matsumoto, T. *Agric. Biol. Chem.* **1986**, *50*, 997–1001.

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(19) Wells, J. N.; Wheeler, W. J.; Davisson, L. M. *J. Org. Chem.* **1971**, *36*, 1503–1506.

(20) Boyd, G. V.; Monteil, R. L. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1338–1350.

reaction between 2-formylbenzoic acid, anilines, and potassium cyanide in the presence of acetic acid.[21] In a successive paper the same authors described the facile rearrangement of these products to dihydroisoindolinones.[22] The method of Opatz and Ferenc and the present one are closely related, both being based on multicomponent reactions. However, it must be underlined that our method allows the introduction of another diversity point in the isocoumarin ring.

(21) Opatz, T.; Ferenc, D. *Eur. J. Org. Chem.* **2005**, 817–821.
(22) Opatz, T.; Ferenc, D. *Eur. J. Org. Chem.* **2006**, 121–126.

In conclusion, we have described a procedure that consistently allows the isolation of the usually elusive Ugi-4CC primary adducts. Furthermore, the synthetic route described in this Letter allows a facile access to the isocoumarin ring.

Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds and X-ray analysis of the isocoumarin **13a**, including CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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