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Ugi four-component condensation with two cleavable components: the easiest synthesis of 2,*N*-diarylglycines

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Dedicated to the memory of Professor Ivar Ugi

Abstract

The Ugi four-component condensation between anilines, aromatic aldehydes, isocyanides, and α-oxoacids afforded the expected adducts which were cleaved in mild conditions to give 2,*N*-diarylglycines in high yields.

The use of cleavable components in the Ugi four-component condensation is of great importance since it allows to broaden the scope of this important reaction.[1] Although the best known cleavable reagent is 1-isocyanocyclohex-1-ene, reported more than 40 years ago by Ugi and Rosendahl as a synthetic equivalent of the unknown 'hydrogen isocyanide'[2] and then exploited by Keating and Armstrong,[3] other cleavable isocyanides, acids, amines, and carbonyl compounds are known.[1,4]

This Letter deals with a post-condensation transformation of Ugi-4CC adducts in which two components behave, at the same time, as cleavable reagents.

The reaction between cyclohexyl isocyanide (**1a**), 4-chlorobenzaldehyde (**2a**), 4-chloroaniline (**3a**), and benzoylformic acid (**4a**) afforded the expected Ugi-4CC adduct, namely 2-[*N*-benzoylformyl-*N*-(4-chloro)phenyl]amino-2-(4-chlorophenyl)-*N*-cyclohexyl acetamide (**5a**). Upon treatment of **5a** with methanolic potassium hydroxide, the potassium salt of 2,*N*-di-(4-chlorophenyl)glycine (**6a**) was isolated in high yield and purity from the reaction mixture and converted into the corresponding α-amino acid **7a**. The same product **7a** was obtained upon alkaline treatment of the Ugi-4CC adducts **5b**, prepared by employing benzyl isocyanide (**1b**) in the place of cyclohexyl isocyanide, and **5c** obtained by employing pyruvic acid (**4b**) in the place of benzoylformic acid (**4a**). Thus, the basic cleavage of the Ugi adducts appeared to be feasible, regardless of the kind of the isocyanide and the α-ketoacid.

The general interest of α-amino acids[5] and certain 2,*N*-diarylglycines[6] besides our interest in the post-condensation modifications of the isocyanide-based multicomponent reactions[1b] prompted us to perform further studies on this cleavage.

At first sight the transformations **5a**,**b**,**c**→**6a** appeared as a double amide bond hydrolysis, but we were doubtful, since the reaction took place smoothly in mild conditions, whereas the hydrolysis of amides requires, as it is well-known, drastic conditions. A careful examination of the basic cleavage of **5a** showed that only one equivalent of potassium hydroxide was consumed. In addition we were able to isolate a product from the reaction mixture, which was identified as *N*-cyclohexyl benzoylformamide (**8a**) by comparison with an authentic specimen obtained by a known method.[7]

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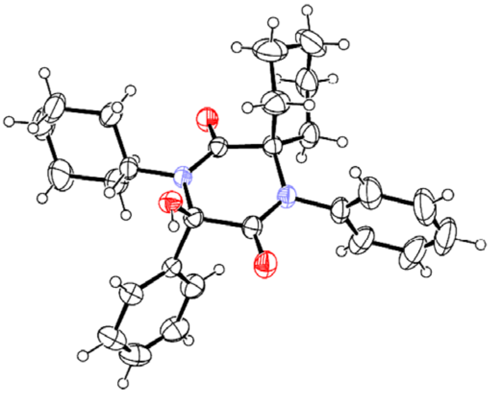
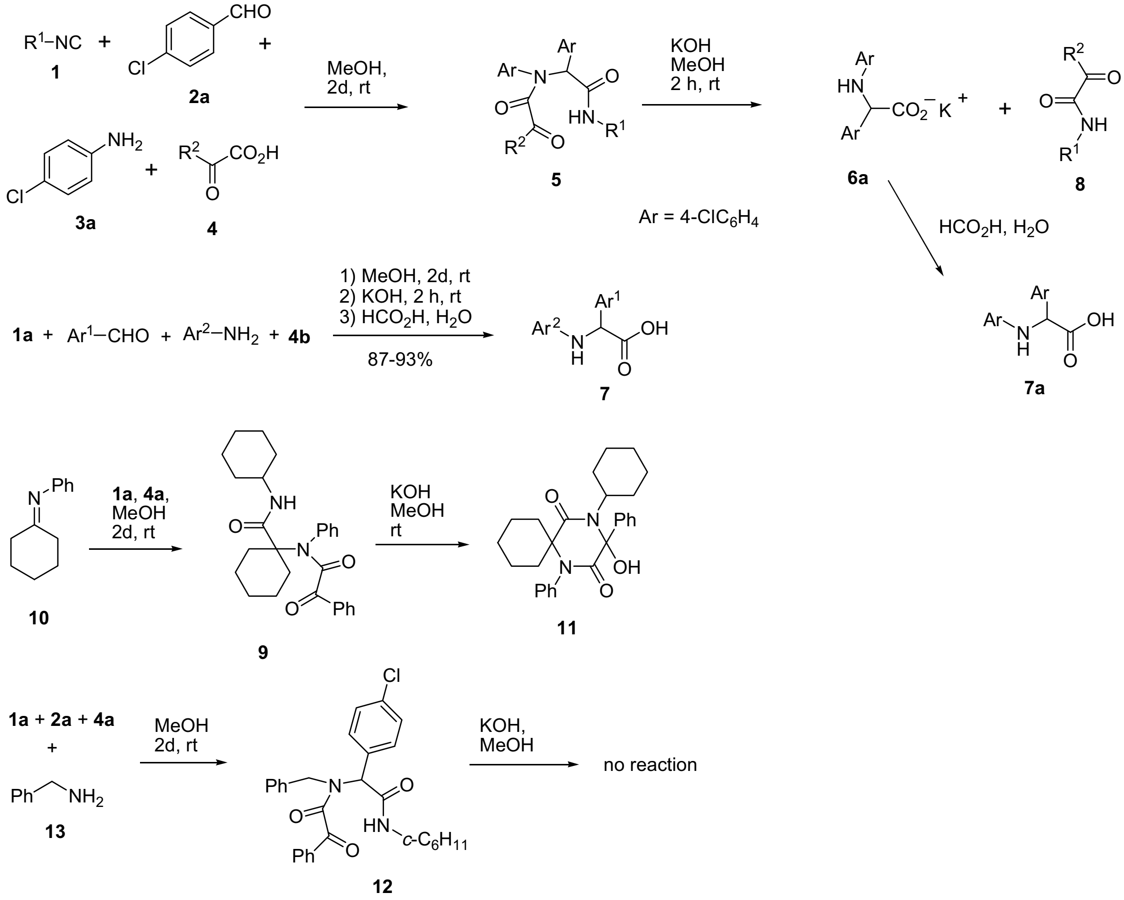


Fig. 1. ORTEP Drawing of compound **11**.

In all of the cases studied, high yields of α-amino acids **7** were obtained from Ugi adducts **5** prepared from aromatic aldehydes and anilines. It must be underlined that the isolation of the Ugi adducts is unnecessary and the synthesis of α-amino acids **7** was carried out in a more satisfactory manner by employing a two-step one-pot procedure. The one-pot procedure allowed us to obtain high yields of **7** by employing the cheap pyruvic acid (**4b**) in the place of the relatively expensive benzoylformic acid (**1a**).[8,9]

Interestingly, the reaction did not afford α-amino acid salts when Ugi-4CC adducts arising from aliphatic aldehydes, ketones, and alkylamines were subjected to methanolic potassium hydroxide. When 1-(*N*-benzoylformyl-*N*-phenyl)amino-*N*-cyclohexyl-1-*cyclo*-hexanecarboxamide (**9**)



1	R^1
a	c-C_6H_{11}
b	$C_6H_5CH_2$

2	Ar^1
a	4-ClC_6H_4
b	4-FC_6H_4
c	4-$CH_3OC_6H_4$
d	C_6H_5

3	Ar^2
a	4-ClC_6H_4
b	4-$CH_3OC_6H_4$
c	4-$CH_3C_6H_4$
d	C_6H_5

4	R^2
a	C_6H_5
b	CH_3

5,8	R^1	R^2
a	c-C_6H_{11}	C_6H_5
b	$C_6H_5CH_2$	C_6H_5
c	c-C_6H_{11}	CH_3

7	Ar^1	Ar^2
a	4-ClC_6H_4	4-ClC_6H_4
b	4-FC_6H_4	4-$CH_3OC_6H_4$
c	4-ClC_6H_4	4-$CH_3OC_6H_4$
d	4-ClC_6H_4	4-$CH_3C_6H_4$
e	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$

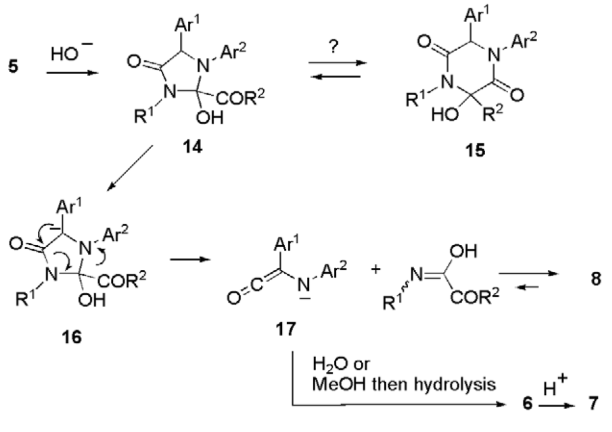
7	Ar^1	Ar^2
f	4-$CH_3OC_6H_4$	C_6H_5
g	C_6H_5	C_6H_5
h	4-ClC_6H_4	C_6H_5
i	4-FC_6H_4	C_6H_5
j	4-FC_6H_4	4-$CH_3C_6H_4$

Scheme 1. Behavior of Ugi-4CC adducts arising from α-oxoacids toward KOH.

obtained from **1**, **4a**, and *N*-phenyl cyclohexanone imine (**10**) was treated with the base, a cyclization to 2,5-dioxo-1,3-diphenyl-3-hydroxy-1,4-diazaspiro[5.5]undecane (**11**) whose structure was confirmed by X-ray analysis[10] (Fig. 1) took place. Ugi adduct **12** arising from benzylamine (**13**), cyclohexyl isocyanide (**1a**), 4-chlorobenzaldehyde (**2a**), and benzoylformic acid (**4a**) was recovered unchanged after 2 days exposure to methanolic KOH (Scheme 1).

On the basis of the above observations we proposed a cleavage mechanism (Scheme 2). The formation of the reaction products can be explained by hypothesizing the base-induced formation of the 5-membered intermediates **14** alone or in equilibrium with the 6-membered intermediates **15** in the reaction medium.[11] The presence of an acid hydrogen in position 5 of the imidazolidinone ring of **14** ensures the prosecution of the reaction. The failure of the reaction with Ugi-4CC adducts arising from ketones can be explained with the absence of acid hydrogens. When aliphatic amines and/or aldehydes are employed the H-5 is not acidic enough to give anions **16**. Rearrangement of anions **16** leads to the formation of **8** and the intermediate ketene anions **17** which give the α-amino acid salts **6** directly, via the addition of water or via the addition of methanol followed by the hydrolysis of the corresponding methyl esters. Thus, both the acid and the isocyanide act as cleavable reagents. In the α-amino acids **7** only the isocyanide carbon is retained and this is a typical feature of convertible isocyanides. It is noteworthy that simple aliphatic isocyanides such as **1**, without multiple bonds or additional functional groups, behave as convertible isocyanides.[12]

In conclusion the present method allows the preparation of 2,*N*-diarylglycines in a very simple manner: all the reagents are commercially available, reagents and solvents are used as supplied, the reactions are performed by simple mixing of the reagents at room temperature, and no special apparatus is required. It must be noted that 2,*N*-diarylglycines are usually prepared via alkaline hydrolysis of the corresponding esters, which are not easily available.[13] Another method consists of the hydrolysis of the corresponding nitriles, in turn obtained via Strecker-type reactions.[14] Since the hydrolysis of α-aminonitriles is generally carried out in strong acidic medium at high temperatures, the survival of sensitive groups cannot be ensured. Thus, the present method appears to be an alternative to the traditional Strecker synthesis and, at the same time, similar. In fact the carbon atom of the carboxylic group arises from the isocyanide and the inorganic cyanide, respectively, whereas the amine and the aldehyde are the same. In addition this route appears to be suitable for the preparation of 2,*N*-diarylglycines in the solid phase by using resin-bound isocyanides, such as polystyrene isocyanide resin.[15]



Scheme 2. Proposed mechanism for the formation of 2,*N*-diarylglycines from Ugi-4CC adducts.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.134.

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8. The Ugi 4-CC adducts prepared from pyruvic acid are more soluble in methanol than the corresponding adducts arising from benzoylformic acid. Thus, lower overall yields of α-amino acids were obtained when the cleavage was performed on the isolated Ugi adducts.
9. General procedure for one-pot synthesis of 2,*N*-diarylglycines **8**: A solution of the amine **3** (5.0 mmol) in MeOH (10 ml) was treated under stirring with aldehyde **2** (finely powdered if solid) (5.0 mmol). The resulting mixture was stirred for 10 min at room temperature and then treated with pyruvic acid (**4a**) (440 mg, 5.0 mmol) and cyclohexyl isocyanide (**1a**) (546 mg, 5.0 mmol). The resulting mixture was stirred for 48 h at rt and then treated with a solution of KOH (337 mg, 6.0 mmol) in MeOH (4 ml). After 2 h stirring at room temperature (a prolonged time has no detrimental effect on the yield and purity of the reaction product) the solvent was removed under diminished pressure, and the residue partitioned between H_2O (30 ml) and $CHCl_3$ (30 ml). The layers were separated and the aqueous phase was acidified with formic acid until pH 4. The resulting suspension was filtered and the collected solid product washed with water and dried to give almost pure **7** in 87–93% yield.
10. Crystal data for compound **11**: $C_{27}H_{32}N_2O_3$, $M = 432.55$, triclinic, space group $P\bar{1}$, $a = 9.814(2)$, $b = 10.705(2)$, $c = 11.603(2)$ Å, $\alpha = 79.17(1)$, $\beta = 83.14(2)$, $\gamma = 88.94(1)$, $V = 1188.7(4)$ Å^3, $Z = 2$, $D_c = 1.208$, $\mu = 0.079$ mm^{-1}, $F(000) = 464$. In total 8157 reflections

were collected with a $4.40 < \theta < 31.92°$ range; 6123 were independent; the parameters were 298 and the final R index was 0.0571 for reflections having $I > 2\sigma(I)$ and 0.0967 for all data. RX-analysis was carried out with a Goniometer Oxford Diffraction KM4 Xcalibur2 at room temperature. Graphite-monochromated Mo/Kα radiation (40 mA/−40 kV) and a KM4 CCD/SAPPHIRE detector were used for cell parameter determination and data collection. The integrated intensities, measured using the ω scan mode, were corrected for Lorentz and polarization effects [Walker, N.; Stuart, D. *Acta Crystallogr., Sect. A* **1983**, *39*, 158–166]. The substantial redundancy in data allows empirical absorption corrections (SADABS) [Sheldrick, G. M. SADABS *version 2.03, a Program for Empirical Absorption Correction*; Universität Göttingen, 1997–2001] to be applied using multiple measurements of symmetry-equivalent reflections. The structure was solved by direct methods of SIR97 [Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119] and refined using the full-matrix least squares on F^2 provided by SHELXL97 [Sheldrick, G. M. SHELXL*97: Program for Crystal Structure Refinement*; Institut für Anorganische Chemie der Universität Göttingen: Göttingen, Germany]. The non-hydrogen atoms were refined anisotropically; aromatic and methylenic hydrogens were assigned in calculated positions, whereas hydrogens on C(22) and O(3) were found in the Fourier synthesis; all of them were refined as isotropic. The X-ray CIF file for this structure has been deposited at the Cambridge Crystallographic Data Center with the deposition number CCDC 616531. Copies of the data can be obtained, free of charge, from CCDC, 12 Union Road, Cambridge, CB2 1EZ UK (e-mail: deposit@ccdc.cam.ac.uk, internet: www.ccdc.cam.ac.uk).

11. Both carbonyl groups are reactive enough to undergo base-promoted nucleophilic attacks by the amide nitrogen. The formation of orthoamides from Ugi-4CC adducts has been reported: Marcaccini, S.; Miguel, D.; Torroba, T.; García-Valverde, M. *J. Org. Chem.* **2003**, *68*, 3315–3318; For another example of the reactivity of Ugi-4CC adducts with additional carbonyl groups: García-Valverde, M.; Macho, S.; Marcaccini, S.; Rodríguez, T.; Rojo, J.; Torroba, T. *Synlett* **2008**, 33–36.
12. To our knowledge only an example has been reported in which a saturated, unfunctionalized isocyanide behaves as a C1 synthon: Henkel, B.; Weber, L. *Synlett* **2002**, 1877–1879.
13. Recently a simple solution-phase access to these compounds based on the method of Henkel and Weber has been reported. See Ref. 6.
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