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Synthesis of diverse phenylglycine derivatives via transformation of Ugi four-component condensation primary adducts

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ABSTRACT

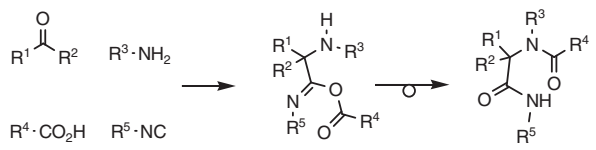
3-(N-Substituted)amino-4-arylamino-1*H*-isochromenones (isocoumarins) which can be regarded as the enediamine tautomers of the Ugi four-component condensation primary adducts between 2-formylbenzoic acids, arylamines, and isocyanides undergo a facile ring cleavage with amines to give a series of phenylglycine derivatives. Thus, a synthetically useful post-condensation transformation of Ugi four-component condensation primary adducts is described for the first time.

The Ugi four-component condensation (Ugi-4CC) between carbonyl compounds, amines, carboxylic acids, and isocyanides affords α-acylamino amides via rearrangement of the initially formed primary adducts[1,2] (Scheme 1).

Because of elusive nature of the Ugi-4CC primary adducts, until recently only two examples of the successful isolation of these products were reported.[3]

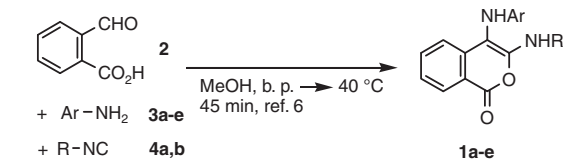
An examination of the literature showed that the Ugi-4CC accompanied by post-condensation transformations (spontaneous or upon addition of suitable reagents) is a powerful synthetic tool for the preparation of a plethora of very interesting compounds which appear to be not easily obtainable by other synthetic routes.[4]

The general unavailability of the Ugi-4CC primary adducts has prevented their use as starting materials for further transformations.[5] In a very recent Letter, we reported a general method that allowed the preparation of Ugi primary adducts, namely 3-(N-substituted)amino-4-arylamino-1*H*-isochromenones (isocoumarins) **1**, by reacting 2-formylbenzoic acid (**2**), anilines **3**, and isocyanides **4**[6] (Scheme 2).



Scheme 1. The Ugi four-component condensation (Ugi-4CC).

The presence of a cyclic enol ester moiety in the isochromenones **1** prompted us to attempt the ring cleavage of these compounds with a series of amines **5**. Because of the inherent instability of isochromenones **1** in solution[6] we performed the reactions in solventless conditions by employing an excess of the amine. The reaction took place smoothly at room temperature to afford the desired pure phenylglycine derivatives **6** in almost quantitative yields after removal of the unreacted amine. The low boiling point isobutylamine was easily removed by evaporation under diminished pressure, whereas high boiling point amines were removed upon



1	Ar	R
a	4-ClC$_6$H$_4$	*c*-C$_6$H$_{11}$
b	4-FC$_6$H$_4$	4-CH$_3$C$_6$H$_4$
c	C$_6$H$_5$	*c*-C$_6$H$_{11}$
d	4-CH$_3$C$_6$H$_4$	*c*-C$_6$H$_{11}$
e	3-ClC$_6$H$_4$	*c*-C$_6$H$_{11}$

3	Ar
a	4-ClC$_6$H$_4$
b	4-FC$_6$H$_4$
c	C$_6$H$_5$
d	4-CH$_3$C$_6$H$_4$
e	3-ClC$_6$H$_4$

4	R
a	*c*-C$_6$H$_{11}$
b	4-CH$_3$C$_6$H$_4$

Scheme 2. Synthesis of isochromenones **1a**–**e**.

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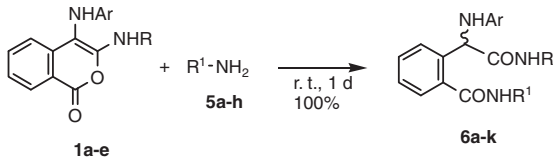
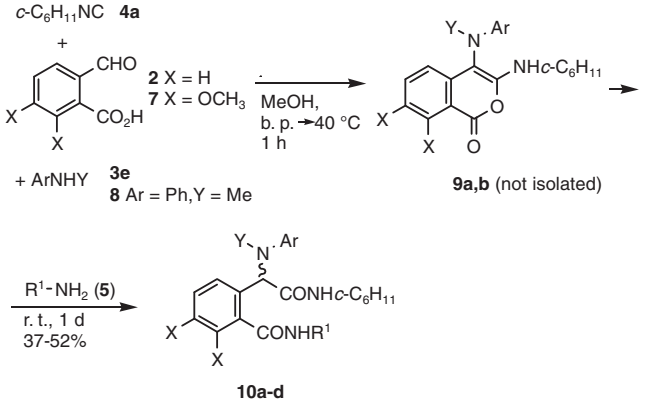


6	Ar	R	R^1
a	4-ClC_6H_4	*c*-C_6H_{11}	*i*-Bu
b	4-FC_6H_4	4-$CH_3C_6H_4$	*i*-Bu
c	C_6H_5	*c*-C_6H_{11}	4-$CH_3C_6H_4CH_2$
d	C_6H_5	*c*-C_6H_{11}	4-$CH_3OC_6H_4CH_2$
e	4-$CH_3C_6H_4$	*c*-C_6H_{11}	2-thienylmethyl
f	4-$CH_3C_6H_4$	*c*-C_6H_{11}	4-$CH_3OC_6H_4CH_2$
g	4-$CH_3C_6H_4$	*c*-C_6H_{11}	$C_6H_5CH_2CH_2$
h	4-$CH_3C_6H_4$	*c*-C_6H_{11}	3,4-$(OCH_2O)C_6H_3CH_2$
i	4-FC_6H_4	*c*-C_6H_{11}	$C_6H_5CH_2$
j	4-FC_6H_4	*c*-C_6H_{11}	$C_6H_5CH_2CH_2$
k	4-ClC_6H_4	*c*-C_6H_{11}	4-$CH_3C_6H_4CH_2$

Scheme 3. Ring cleavage of isochromenones **1a–e** with amines **5a–h** to give phenylglycine derivatives **6a–k**.



10	X	Y	Ar	R^1
a	OCH_3	H	3-ClC_6H_4	4-$CH_3C_6H_4CH_2$
b	OCH_3	H	3-ClC_6H_4	$C_6H_5CH_2CH_2$
c	H	CH_3	C_6H_5	4-$ClC_6H_4CH_2$
d	H	CH_3	C_6H_5	4-$CH_3C_6H_4CH_2$

Scheme 4. Introduction of further diversity points into phenylglycine derivatives **10a–d**.

treatment of the reaction mixture with $H_2PO_4^-/HPO_4^{2-}$ buffer (pH 4.5). In this manner a series of eleven hitherto unknown phenylglycine amides **6** with three diversity points were prepared by employing a set of five isochromenones **1** and eight amines **5** (Scheme 3).

In order to achieve the introduction of a fourth diversity point we attempted the Ugi-4CC between the commercially available opianic acid (**7**), cyclohexyl isocyanide (**4a**), and 3-chloroaniline (**3e**). Unfortunately, the Ugi primary adduct (**9a**) did not precipitate in the reaction medium. Thus, we reacted phenylethylamine (**5e**) and 4-methylbenzylamine (**5b**) with the crude reaction mixture.[7] The desired products **10a** and **10b** were isolated after column chromatography in 47% and 52% yield, respectively (Scheme 4).

A further structural change at the amino group proved to be possible. Thus, the reaction between 2-formylbenzoic acid (**2**), *N*-methylaniline (**8**), and cyclohexyl isocyanide (**4a**) gave the corresponding primary adduct **9b** which was reacted, without previous isolation, with 4-chlorobenzylamine (**5h**) and 4-methylbenzylamine (**5b**) to give the expected phenylglycine derivatives **10c** and **10d** in 42% and 37% yield, respectively (Scheme 4).

The isolation of the Ugi primary adducts appeared to be crucial for obtaining the desired amino acid derivatives in high yields and purities. When the Ugi primary adducts were reacted without previous isolation the yields were substantially lowered (derivatives **10a–d**). However, the method again was convenient because of the simple experimental procedure. It is noteworthy that only in two cases (derivatives **10a,b**), column chromatography was necessary to obtain pure products.

Evidence for the assigned structures **6a–k** and **10a–d** was provided by spectral and analytical data. In the ^{13}C NMR spectra of compounds **6a–e**,**g–k** and **10a–d** two well-separated signals were found at 170.6–168.6 and 169.6–167.3 ppm in agreement with the presence of two amide carbonyl groups.

In the ^{13}C NMR spectrum of **6f** a unique signal at 169.6 ppm was detected; its very high intensity accounted for the overlapping of two signals. In all of the ^1H NMR spectra of compounds **6a,c–k** and **10a,b** a doublet signal at 8.56–8.20 ppm was detected, due to the acetamide NH proton coupled with the H-1 of the cyclohexyl group.

In the ^1H NMR spectrum of **6b** the singlet signal of the acetamide NH proton was found at about 11 ppm because of the deshielding effect of the aromatic ring. The ^1H NMR spectra of **10c,d** showed a NH doublet signal at about 6.5 ppm; probably, this value can be ascribed to the absence of hydrogen bonds involving the amino group. In most of the ^1H NMR spectra of phenylglycine amides **6** and **10** the multiplet signal due to the NH proton of the benzamide group was not detected because of the overlapping with the aromatic proton signals. When the substituent at the benzamide nitrogen is *t*-butyl (compounds **6a and 6b**) and 2-phenylethyl (compounds **6g**,**j** and **10b**) the NH proton signal was found at the expected chemical shift (5.38–6.77 ppm).

The mass spectra of compounds **6** and **10a**,**b** showed a common fragmentation pathways. Besides the molecular ion although in a low intensity,[8] the ion $[M–RNHCO–H–R^1NH]^+$ was only detected as the mother peak. The fragmentation pathway of compounds **10c**,**d** was totally different. Thus, the absence of a hydrogen atom linked to the amino nitrogen in position 4 plays a crucial role in the fragmentation. Besides the molecular ion, again in low intensity, the ions $[R^1]^+$ and $[M–c\text{-}C_6H_{11}NHCO]^+$ were found in high intensity.

In summary, we have described for the first time a synthetically useful post-condensation transformation of Ugi-4CC primary adducts. The present method allows the preparation of a hitherto unknown class of diverse phenylglycine derivatives in high yields by means of an experimentally simple two-step procedure.[9] Although nearly quantitative yields are obtained starting from the isolated Ugi primary adducts, this procedure appears to be attractive even if the isolation of the Ugi primary adducts is not possible.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.074.

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2. The rearrangement consists of an *O→N(a)* acyl migration. In many publications on the Ugi reaction such a rearrangement is erroneously referred as Mumm rearrangement. The true Mumm rearrangement consists of the transformation of an *O*-acyl isoamide into an imide. Professor Helmut Quast, University of Würzburg, Germany, private communication.
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6. Faggi, C.; García-Valverde, M.; Marcaccini, S.; Menchi, G. *Org. Lett.* **2010**, *12*, 788–791.
7. Previous experiments performed in our laboratory showed that attempts to isolate the Ugi-4CC primary adducts by column chromatography were unsatisfactory because the rearrangement of the Ugi primary adducts to secondary adducts took place to a large extent.
8. The molecular ion was not detected in the mass spectra of compounds **6c**,**f**.
9. *General procedures for the cleavage of isochromenones **1** and **9**: Procedure A (derivatives **6a**,**b**):* Isobutylamine (**5a**) (351 mg, 0.48 ml, 4.8 mmol) was added under nitrogen to the starting isochromenone **1** (1.2 mmol) and the resulting mixture stirred for 24 h at room temperature. Longer reaction periods (48–72 h) had no detrimental effect. The resulting clear oil was taken up in chloroform and the resulting solution evaporated to dryness under diminished pressure. The last traces of solvent and unreacted amine were removed at 0.1 mm/Hg to give almost pure **6a**,**b** in nearly quantitative yields.

*Procedure B (derivatives **6c–k**):* The starting isochromenone **1** (1.2 mmol) and the appropriate amine **5** (4.8 mmol) were reacted as described above. The reaction mixture was taken up in chloroform (10 mL) and the resulting solution stirred for 15 min with satd aqueous buffer NaH_2PO_4/Na_2HPO_4, pH 4.5 (7.5 mL). If a precipitation occurred, water was gradually added until all the salts dissolved. The organic layer was separated, washed with water (5 mL), and dried ($MgSO_4$). Removal of the solvent under diminished pressure left almost pure **6c–k** in nearly quantitative yields. Analytical samples were obtained from EtOH/*i*-Pr_2O.
*Procedure C (derivatives **10a**,**b**):* A small flask containing a solution of opianic acid (**7**) (364 mg, 1.73 mmol) in MeOH (4 mL) was poured into an oil bath (bath temperature 80 °C). When the solution began to boil a solution of cyclohexyl isocyanide (**4a**) (197 mg, 1.8 mmol) and 3-chloroaniline (**3a**) (243 mg, 1.9 mmol) in MeOH (1 mL) was added and the flask lifted and maintained at such a distance from the oil surface that the temperature dropped to 40 °C during 15 min. The flask was then transferred to another bath and maintained at 40 °C (reaction mixture temperature) for 45 min. The flask was removed from the bath and allowed to cool at room temperature. A small magnetic bar was poured into the flask and stirring was started. After 15 min stirring at room temperature the reaction mixture was cooled with an ice–salt bath and freed from a small amount of insoluble matter by filtration. The filtrate was evaporated to dryness under diminished pressure to give a glass-like residue, which was stirred with the appropriate amine **5** (5.2 mmol) under a nitrogen atmosphere for 24 h at room temperature. The reaction mixture was taken up in chloroform (10 mL) and the resulting solution stirred for 15 min. with satd aqueous buffer NaH_2PO_4/Na_2HPO_4, pH 4.5 (7.5 mL). The organic layer was separated, washed with water (5 mL), and dried ($MgSO_4$). Removal of the solvent under diminished pressure left a glass-like residue which was chromatographed on a silica gel column (petroleum ether bp 40–70 °C/ethyl acetate 60:40 v/v) to give **10a**,**b**. Analytical samples were obtained by triturating the crude products with *i*-Pr_2O/*i*-PrOH 9:1.
*Procedure D (derivatives **10c**,**d**):* A small flask containing a solution of phthalaldehydic acid (**2**) (226 mg, 1.5 mmol) in MeOH (3 mL) was poured into an oil bath (bath temperature 80 °C). When the solution began to boil a solution of cyclohexyl isocyanide (**4a**) (186 mg, 1.7 mmol) and *N*-methylaniline (**8**) (193 mg, 1.8 mmol) in MeOH (1 mL) was added and the flask lifted and maintained at such a distance from the oil surface that the temperature dropped to 40 °C during 15 min. The flask was then transferred to another bath and maintained at 40 °C (reaction mixture temperature) for 1 h. The flask was removed from the bath and allowed to cool at room temperature. A small magnetic bar was poured into the flask and stirring was started. After 15 min stirring the reaction mixture was evaporated to dryness under diminished pressure to give a glass-like residue which was stirred with the appropriate amine **5** (4.5 mmol) under a nitrogen atmosphere for 24 h at room temperature. The reaction mixture was taken up in chloroform (10 mL) and the resulting solution stirred for 15 min. with satd. aqueous buffer NaH_2PO_4/Na_2HPO_4, pH 4.5 (7.5 mL). The organic layer was separated, washed with water (5 mL), and dried ($MgSO_4$). Removal of the solvent under diminished pressure left a semisolid residue which was stirred overnight with a little *i*-Pr_2O/*i*-PrOH 9:1 and filtered to give **10c**,**d**. Analytical samples were obtained from EtOH/*i*-Pr_2O.