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GRAPHICAL ABSTRACT

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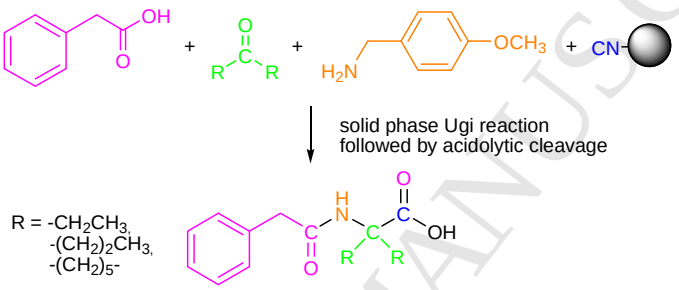

α,α-Dialkylglycines obtained by solid phase Ugi reaction performed over isocyanide functionalized resins

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Abstract: The multicomponent Ugi reaction is a straightforward method that can be used for the synthesis of highly hindered *C*-tetrasubstituted amino acids by reacting an amine, a ketone, an acid and an isocyanide. In the present work, the synthesis of several α,α-dialkylglycines (α,α-diethylglycine, Deg; α,α-dipropylglycine, Dpg; 1-amino-1-cyclohexanecarboxylic acid, Ac6c) was achieved by solid phase Ugi reaction using resins functionalized with the isocyanide group. Since no resins with these features were available commercially, the functionalization of an aminomethylated resin started by the use of glycine (Gly), β-alanine (β-Ala) and γ-aminobutyric acid (GABA) as spacers. After spacer *N*-formylation, followed by dehydration, isocyanide functionalised resins were obtained. The resins were then used in solid phase Ugi reaction, using phenylacetic acid as the acid component, *p*-methoxybenzylamine as the amine component and different ketones, to afford the desired *N*-acylated α,α-dialkylglycines in good yields (60-80%), after acidolytic cleavage from the resin, thus proving the feasibility of this approach.

Keywords: α,α-dialkylglycines, Ugi reaction, isocyanide resin, solid phase synthesis

1. Introduction

α,α-Dialkylglycines are amino acids sterically constrained around the central carbon atom and, for this reason, are useful building blocks in the assembly of peptides with

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specific conformations.[1–3] Additionally, these non-coded amino acids are not recognized by proteolytic enzymes, increasing the resistance of the peptides to physiological biodegradation. However, due to steric hindrance, most of these amino acids are difficult to synthesize[4,5] and to use in peptide synthesis by conventional methods.[6] In fact, the same structural features that make these amino acids interesting and unique for the development of peptide pharmaceuticals, are also responsible for the challenge associated with their synthesis and application. Therefore there is an interest in developing straightforward methodologies for the preparation and incorporation of these amino acids into peptides.

In 1971 Ivar Ugi proposed a condensation reaction of four components as an alternative to the classical methods of amino acid synthesis based on isocyanide chemistry, by reacting an amine, a carbonyl compound, an acid and an isocyanide.[7–9] Our group has been involved in the application of this reaction to the synthesis of symmetrical α,α-dialkylglycines and model di- to pentapeptides containing these highly constrained amino acids. By taking advantage of an unusual acid lability of the C-terminal amide bond, it was possible to overcome drawbacks that prevented a broad application of this multicomponent reaction to the synthesis of α,α-dialkylglycines bearing peptides.[10–12] Despite this innovative contribution, the synthetic protocols used were carried out in solution, with the usual problems associated with purification procedures. Therefore, bearing the above facts in mind, it was envisaged to adapt this synthetic methodology to solid phase synthesis to simplify purification processes. Moreover, in the case of peptide synthesis, it would allow the in situ assembly of α,α-dialkylglycines, to overcome the remarkably low reactivity of the α-amino and carboxyl groups in α,α-dialkylglycines, associated to steric hindrance, which difficult classical coupling methods. There have been reports in the literature on solid phase Ugi reaction with amide resins as the amine component,[13–15] but only few relating to isocyanide functionalized resins as examples for the synthesis of other types of molecules such as heterocycles,[16–18] or involving coupling of isocyanocarboxylic acids prior conducting the Ugi reaction.[19]

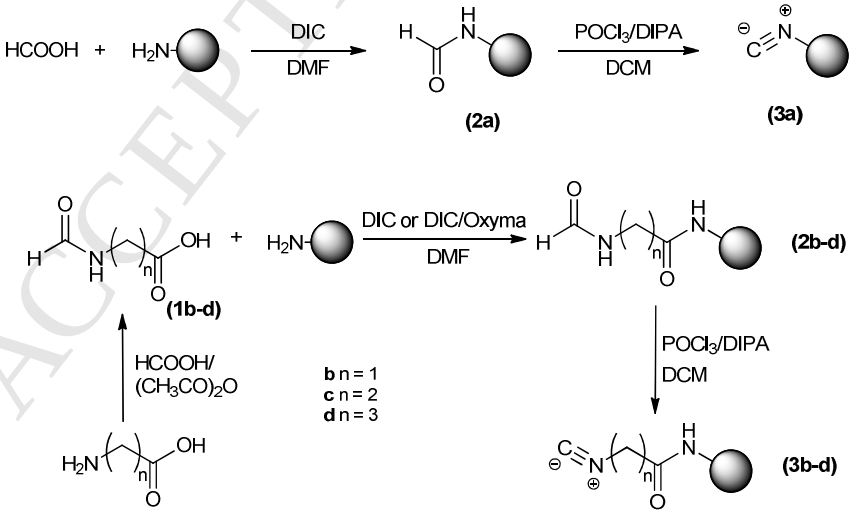
As a result, we now report the preparation of resins bearing an isocyanide functionalized spacer unit, to decrease steric hindrance at the functional group in order to facilitate the multicomponent reaction. After unsuccessful preliminary results with a directly functionalized isocyanide resin, it was decided to use variable length unbranched amino acids as spacers (glycine, β-alanine and γ-aminobutyric acid) in order to maintain

chemical identity without increasing steric hindrance. The isocyanide resins were used in Ugi reactions involving symmetrical ketones and appropriate acid and amine components, to evaluate the efficacy of this approach to the straightforward synthesis of α,α-dialkylglycine derivatives.

2. Results and Discussion

Having in mind the aim of obtaining highly hindered amino acids using a solid phase Ugi reaction with an isocyanide functionalized resin in conditions that would represent a reduction of the processing time of the previously developed strategy[11,12,20] without a severe increase in costs, a simple and inexpensive resin was chosen as the subject of our study, an aminomethylated polystyrene resin.

Taking into account previous reports,[16,18] the resin was formylated with formic acid in the presence of *N*,*N*'-diisopropylcarbodiimide (DIC) (scheme 1). The reactions proceeded as expected yielding a resin **2a** where the presence of the carbonyl group could be detected by IR spectroscopy performed on KBr disc at 1694 cm^{-1}(figure 1). The resin was then dehydrated in the presence of $POCl_3$ (scheme 1) affording the desired resin **3a**, as could be verified by the disappearance of the carbonyl band and the appearance of the isocyanide band in the IR spectra at 2147 cm^{-1} (figure 1).



Scheme 1 Preparation of the isocyanide functionalized resins **3a-d**.

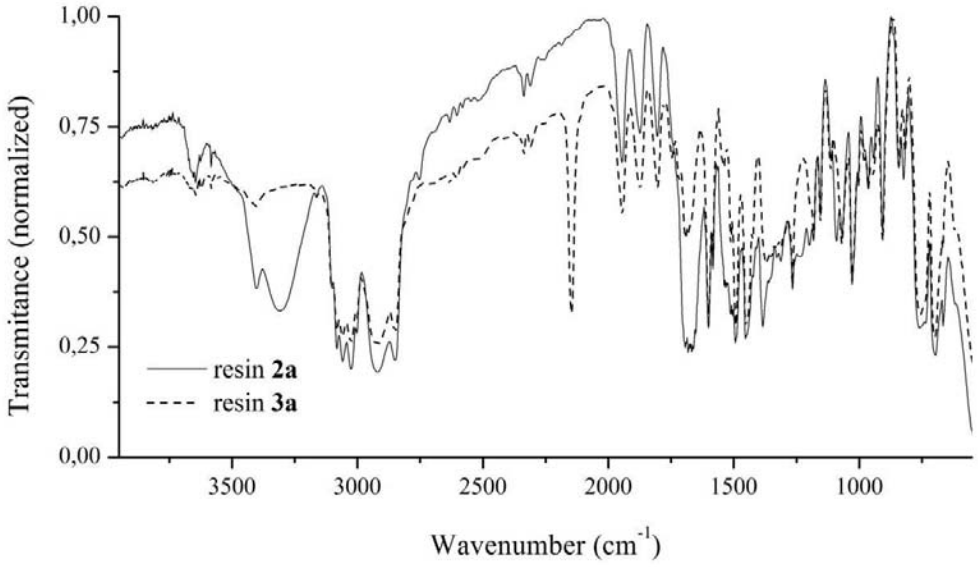
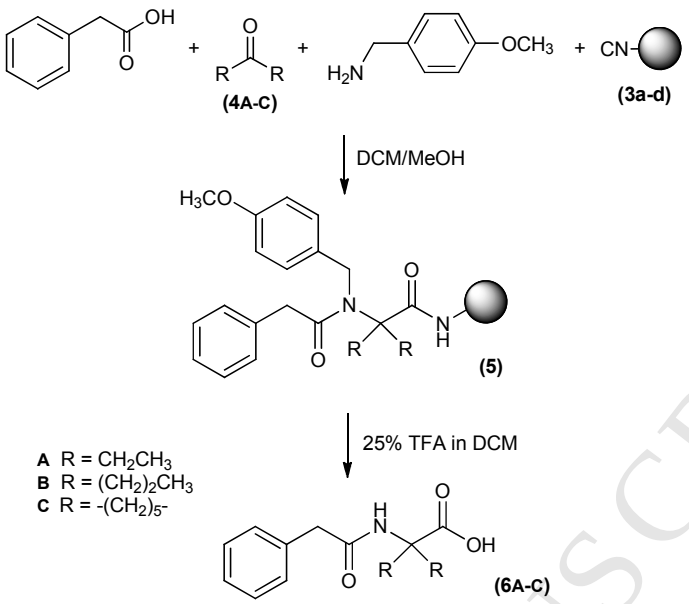


Figure 1. IR spectra of resins **2a** and **3a** obtained in KBr disc.

This resin was used as the isocyanide component in a Ugi reaction where the carbonyl component chosen was 3-pentanone **4A**, to achieve the synthesis of a α,α-diethylglycine derivative, and the amine was 4-methoxybenzylamine, since the resulting 4-methoxybenzyl group in the Ugi adduct **5Aa** (scheme 2) is cleavable with trifluoroacetic acid (TFA).[21] The chosen acid was phenylacetic acid, because we have used it previously in Ugi reactions and it afforded the desired products in good yields. Moreover, the corresponding NMR signals in the Ugi adduct are distinctive from the signals of the remaining molecule.[20,21] The reaction was carried out using a 10 equivalent excess of the reactants relatively to the initial degree of functionalization of the resin. Ugi reactions performed over this resin didn't afford the desired products **5Aa**, as the intensity of the isocyanide IR band didn't decrease significantly after 2 weeks reacting. Despite the unpromising result, the resin was treated with 25 % TFA affording an oily trace of compound **6A** as suggested by the NMR of the obtained residue.



Scheme 2. Preparation of *N*-phenylacetyl-α,α-dialkylglycines **6A-C**.

Given this result, it was decided to introduce a spacer between the site of the multicomponent reaction and the polymer chains of the resin. Amino acids of variable carbon chain length were chosen as spacers, namely glycine (Gly), β-alanine (β-Ala) and γ-aminoisobutyric acid (GABA), as with these unbranched compounds the distancing from the polymer chain could be achieved without increasing the stereochemical hindrance, while maintaining chemical character.

The amino acids were formylated prior to their attachment to the resin, by reaction with formic acid in the presence of acetic anhydride. The reaction with Gly and β-Ala proceeded smoothly affording the desired compounds **1b-c** in good yields (table 1). The reaction with GABA yielded the desired compound **1d** in lower yields due to a side reaction of internal cyclisation under the reaction conditions, affording pyrrolidin-2-one, proven by the appearance of the corresponding signals in the ^{1}H-NMR spectra of the crude reaction mixture.

Table 1. Synthesis and characterization data of amino acids **1b-d** bearing a formyl group (For).

	Compound	n	Yield (%)	δ_C (C=O) (ppm)	ν (C=O, NH) (cm^{-1})
1b	For-Gly-OH	1	74	161.47	1631, 3373
1c	For-β-Ala-OH	2	93	161.40	1634, 3370
1d	For-GABA-OH	3	58	164.27	1633, 3385

The formyl-amino acids **1b-d** were coupled to the resin (scheme 1) using DIC as coupling reagent. In order to assure that all the amine groups of the resin had reacted and no loss of functionalization had occurred, 2,4,6-trinitrobenzenesulphonic acid (TNBS) tests were performed and, whenever any coloured beads were detected, the coupling procedure was repeated. The coupling of For-Gly-OH **1b** proceeded well under these conditions; however, coupling of For-β-Ala-OH **1c** and For-GABA-OH **1d** did not proceed as smoothly, requiring a second coupling reaction cycle. The two latter compounds were successfully coupled to the resin in only one coupling cycle when Oxyma was added to the coupling reaction cocktail.

Dehydration of the obtained resin formamides **2b-d** to the corresponding isocyanide was achieved with $POCl_3$ in the presence of *N,N*-diisopropylamine (DIPA) (Scheme 1). The modification of the functional group present was confirmed by IR spectroscopy by following the appearance of the characteristic band of the isocyanide at 2145-2155 cm^{-1} (Figure 2- **2b** and **3b**).

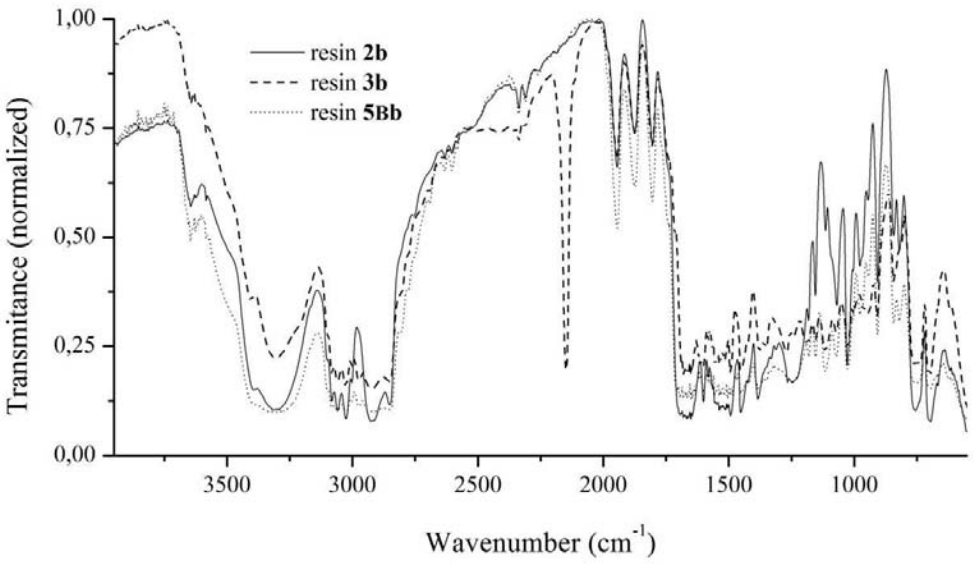


Figure 2. Example of the resin IR spectra obtained in KBr disc after spacer coupling (resin **2b)**, dehydration reaction (resin **3b)** and Ugi reaction (resin **5Bb)**.

Resins **3b-d** were then subjected to Ugi reaction using phenylacetic acid as acid component and 4-methoxybenzylamine as amine component, in the same way as the

Ugi reaction performed over the **3a** resin. Three different ketones (**4A-C**) were used in order to achieve the synthesis of phenylacetyl-α,α-dialkylglycines with different side chain length, namely phenylacetyl-α,α-diethylglycine **6A**, phenylacetyl-α,α-dipropylglycine **6B** and 1-*N*-phenylacetylamino-1-cyclohexenecarboxylic acid **6C**. A 10 equivalent excess of the different components with respect to the initial degree of functionalization of the resin was used and the reaction followed by IR spectroscopy until disappearance of the isocyanide band (Figure 2 – **5Bb**). The desired phenylacetylamino acids (**6A-C**) were obtained after separation of the product from the resin, by acidolysis with 25% TFA in DCM at room temperature for 4 hours (Scheme 2).

Compound **6A** was obtained in yields ranging from 58 to 69%, **6B** from 70 to 77% and **6C** from 77 to 82%. These values were considered quite satisfactory, as they refer to the initial degree of functionalization of the resin after a process of four sequential reactions and they are better than the results obtained when similar compounds bearing a *N*-acetyl group were synthesized in solution phase in two sequential reactions, with overall yields between 52-67% for Deg and 46-71% for Dpg.[11] The obtained *N*-phenylaceyl-amino acids **6A-C** can be converted to the corresponding free amino acids, suitable for peptide synthesis, by a straightforward acid hydrolysis.[11,21] Resin **3d** afforded the best results although Ugi reaction on this resin required a longer reaction time.

Resins **2b-d** proved to be resistant to degradation during the period of this study, as they were prepared in large scale and used frequently several months later without significant decrease in the overall yields observed. Dehydrated resins **3b-d** were not as resistant, since some colouring of the resins beads was observed after a few weeks from preparation.

Table 2. Conditions used in the Ugi reactions performed

Solid phase Ugi reaction*				TFA acidolysis		
Ketone	Resin	Reaction time (d)	Resin adduct	Isolated product	m (g)	Yield** (%)
4A	3a	15	5Aa	**6A**	-	traces
	3b	3	5Ab		0.3211	58
	3c	4	5Ac		0.3712	67
	3d	5	5Ad		0.3852	69
4B	3b	4	5Bb	**6B**	0.4366	70

	3c	5	5Bc		0.4612	74
	3d	6	5Bd		0.4748	77
	3b	3	5Cb		0.4521	77
4C	3c	4	5Cc	**6C**	0.4587	79
	3d	5	5Cd		0.4810	82

* All reactions were performed with 2 g of resin and a 10 equiv excess of reactants relative to the isocyanide resin.

** yields were calculated relatively to resin initial degree of functionalization (1.12 mmol/g).

3. Conclusions

The results herein presented prove that it is possible to synthetize α,α-dialkylglycines by solid phase Ugi reaction performed over isocyanide functionalized resins, when a spacer is placed between the polymer support and the reaction site. The yields presented are all above 58% which was considered very satisfactory, as they represent the overall procedure, including the coupling of the *N*-formylamino acid, the dehydration, the Ugi reaction and the separation from the resin.

The comparison of the different results obtained when different spacers where used led us to conclude that, the grater the distance from the polymer chain, the better de resulting overall yield and thus *N*-formyl-GABA **1d** was considered the best spacer in our study. However, the differences were not very substantial and *N*-formyl-Gly **1b**, considerably less expensive, can also be used satisfactorily.

As expected, the yields for the synthesis of products **6A-C** were different due to the different nature of the α,α-dialkylglycines side chains. This effect proved to be as significant as the spacer size in the overall process.

For further incorporation into peptides, a straightforward acid hydrolysis of the obtained *N*-phenylaceyl-amino acids **6A-C** will afford the corresponding fully deprotected amino acids. Although this methodology was tested for symmetrical α,α-dialkylglycines, it can easily be extended to chiral amino acids of this family (with formation of the corresponding racemates).

4. Experimental Section

4.1 General

All melting points were measured on a Stuart SMP3 melting point apparatus. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel $60F_{254}$) and spots were visualised under UV light. Chromatography on silica gel was carried out on Merck Kieselgel (230-240 mesh). IR spectra were determined on a BOMEM MB 104 spectrophotometer and the samples prepared in KBr discs. NMR spectra were obtained on a Varian Unity Plus Spectrometer at an operating frequency of 300 MHz for ^{1}H and 75.4 MHz for ^{13}C or a Bruker Avance III 400 at an operating frequency of 400 MHz for ^{1}H and 100.6 MHz for ^{13}C using the solvent peak as internal reference at 25 ºC. All chemical shifts are given in ppm using δ_H Me_4Si = 0 ppm as reference and *J* values are given in Hz. Assignments were supported by spin decoupling-double resonance and bidimensional heteronuclear correlation techniques. Mass spectrometry analyses were performed at the "C.A.C.T.I. - Unidad de Espectrometria de Masas", at University of Vigo, Spain. All commercial reagents were used as received, except methanol, dichloromethane and *N*,*N*-dimethylformamide, that were dried as described in the literature.[22] The aminomethylated polystyrene resin used was purchased from AAPPTec with a degree of functionalization of 1.12 mmol/g. All glass and metallic material used in Ugi reactions was dried in an incubator at 60ºC.

4.2 Synthesis of formylated resins 2a-d

4.2.1. ***N*-formyl-aminomethylated polystyrene resin (2a**). Aminomethylated polystyrene resin (2 g, 1.12 mmol/g of resin) was swollen in dry dimethylformamide (DMF, 10 mL) for 10 min. The solvent was removed and a mixture of formic acid (5 equiv, 0.17 mL) and *N*,*N*'-diisopropylcarbodiimide (DIC) (5 equiv, 0.69 mL) in DMF (20 mL) was added. The mixture was left stirring for 24 h. After washing the resin with DMF (3×5 mL) the 2,4,6-trinitrobenzenesulphonic acid (TNBS) test was performed to evaluate if there were still some free NH_2 groups in the resin. If the resin turned red the above procedure was repeated until no free NH_2 groups were detected. IR (KBr): ν = 509, 537, 697, 755, 822, 841, 906, 942, 964, 1004, 1028, 1069, 1114, 1154, 1182, 1384, 1451, 1493, 1583, 1601, 1694, 1745, 1803, 1873, 1943, 2337, 2852, 2921, 3025, 3081, 3323, 3406, 3646, 3851 cm^{-1}.

4.2.2. ***N*-formylglycyl-aminomethylated polystyrene resin (2b).** This compound was prepared by the procedure described for **2a**, using *N*-formylglycine **1b** (5 equiv, 0.58 g)

in the place of the formic acid. IR (KBr): ν = 504, 519, 529, 695, 755, 819, 841, 907, 944, 977, 1028, 1069, 1114, 1155, 1182, 1245, 1384, 1453, 1494, 1538, 1582, 1601, 1651, 1667, 1804, 1874, 1945, 2311, 2336, 2603, 2852, 2925, 3025, 3059, 3082, 3293, 3645 cm^{-1}.

4.2.3. ***N*-formyl-β-alaninyl-aminomethylated polystyrene resin (2c).** Aminomethylated polystyrene resin (2 g, 1.12 mmol/g of resin) was swollen in dry DMF (10 mL) for 10 min. The solvent was removed and a mixture of *N*-formyl-β-alanine **1c** (3 equiv, 0.39 g), DIC (3 equiv, 0.52 mL) and ethyl 2-cyano-2-(hydroxylimino)acetate (Oxyma, 3 equiv, 2.74×10^{-3} mol) in DMF (20 mL) was added. The mixture was left stirring for 24 h. After washing the resin with DMF (3×5 mL) the TNBS test was performed to evaluate if there were still some free NH_2 groups in the resin. If the resin turned red the above procedure was repeated until no free NH_2 groups were detected. IR (KBr): ν = 514, 533, 696, 757, 819, 841, 907, 843, 965, 980, 1028, 1069, 1095, 1114, 1155, 1196, 1240, 1266, 1384, 1451, 1493, 1538, 1582, 1601, 1651, 1805, 1874, 1945, 2311, 2317, 2603, 2632, 2851, 2921, 3002, 3025, 3059, 3081, 3296, 3403, 3645 cm^{-1}.

4.2.4. ***N*-formyl-GABA-aminomethylated polystyrene resin (2d).** This compound was prepared by the procedure described for **2c** using *N*-formyl-γ-aminobutyric acid **1d** (3 equiv, 0.88 mL). IR (KBr): ν = 509, 537, 697, 755, 822, 841, 906, 942, 964, 1004, 1028, 1069, 1114, 1154, 1182, 1384, 1451, 1493, 1583, 1601, 1694, 1745, 1803, 1873, 1943, 2337, 2852, 2921, 3025, 3081, 3323, 3406, 3646, 3851 cm^{-1}.

4.3 General procedure for the preparation of *N*-formyl amino acids 1c-d.

Formic acid (140 mL, 3.71 mol) and acetic anhydride (47 mL, 0.50 mol) were stirred at 45ºC for 1 hour. After the addition of the appropriate amino acid (0.05 mol), the mixture was left stirring at room temperature for 24 h, and evaporated until dryness.

4.3.1. ***N*-formylglycine (1b)**. The compound was obtained as described in the general procedure above using 5 g of glycine, yielding a white solid (5,06 g, 74 %). mp = 128.8 – 130.5 ºC. δ_H (400 MHz, DMSO-d_6) 3.78 (2H, d, *J* 6.0 Hz, CH_2), 8.06 (1H, s, CHO), 8.27 (1H, s, NH).). δ_C (100.6 MHz, DMSO-d_6) 40.46 (CH_2), 161.47 (CHO), 170.92 (COOH). IR (KBr): ν = 515, 623, 656, 684, 786, 889, 931, 947, 993, 1017, 1041, 1065,

1128, 1215, 1236, 1367, 1443, 1631, 1713, 1923, 1944, 2112, 2169, 2198, 2305, 2345, 2471, 2534, 2632, 2926, 3373 cm^{-1}.

***4.3.2. N*-formyl-β-alanine (1c)**. The compound was obtained as described in the general procedure above using 1 g of β-alanine, yielding an yellow oil (1.22 g, 93 %). δ_H (300 MHz, DMSO-d_6) 2.37 (2H, *t*, *J* 6.9 Hz, C$\underline{H_2}$COOH), 3.25 (2H, *q*, *J* 7.5 Hz, NHC$\underline{H_2}$), 7.95 (1H, *s*, CHO), 8,18 (1H, *s*, NH). δ_C (75.4 MHz, DMSO-d_6) 34.72 ($NHCH_2$), 35.22 ($\underline{C}H_2COOH$), 161.40 (CHO), 171.50 (COOH). IR (KBr): ν = 509, 658, 753, 843, 874, 921, 943, 988, 1014, 1031, 1060, 1156, 1220, 1361, 1453, 1554, 1634, 1717, 1934, 1983, 2063, 2081, 2155, 2190, 2312, 2351, 2470, 2509, 2612, 2891, 2930, 3370 cm^{-1}.

***4.3.3. N*-formyl-γ-aminobutyric acid (1d)**. The compound was obtained as described in the general procedure above using 1 g of γ-aminobutyric acid (GABA), yielding a yellow solid (0.742 g, 58 %). mp = 85.1 – 87.0 ºC. δ_H (300 MHz, DMSO-d_6) 1.67-1.76 (2H, *m*, $CH_2C\underline{H_2}CH_2$), 2.30 (2H, *t*, *J* 9 Hz, 6 Hz, C$\underline{H_2}$COOH), 2.76 (2H, *t*, *J* 6 Hz, 6 Hz, NHC$\underline{H_2}$), 8.27 (2H, *s*, CHO and NH). δ_C (75.4 MHz, DMSO-d_6) 22.79 ($CH_2\underline{C}H_2CH_2$), 31.38 ($\underline{C}H_2COOH$), 38.42 ($NHCH_2$), 164.28 (CHO), 174.17 (COOH). IR (KBr): ν = 506, 636, 765, 845, 879, 953, 979, 1064, 1128, 1195, 1281, 1333, 1395, 1411, 1461, 1501, 1603, 1726, 1929, 1954, 2053, 2088, 2159, 2195, 2303, 2340, 2468, 2504, 2622, 3030, 3385 cm^{-1}.

4.4. Dehydration of resins 2a-d.

Dry dichloromethane (DCM) (40 mL) and 2 g of the appropriate resin **2**, previously swollen in dry DCM, were placed into a 2 neck 200 mL round bottom flask, under nitrogen atmosphere. After the addition of *N*,*N*-diisopropylamine (DIPA) (15 equiv, 4.74 mL), the mixture was placed in an ice bath and $POCl_3$ (5 equiv, 1.04 mL) were added dropwise. The mixture was stirred for 2 h in an ice bath followed by 2 h at room temperature. $NaHCO_3$ 1M (20 mL) was added and the mixture stirred for 1 hour. The resin was separated from the reaction mixture by filtration and washed successively with DCM (10 mL), MeOH (10 mL), DCM (10 mL), MeOH (10 mL) and diethyl ether (10 mL). The resin was stored under vacuum and the presence of the isocyanide group confirmed by IR spectroscopy.

Isocyanide resin 3a. IR (KBr): ν = 501, 511, 538, 619, 659, 697, 752, 818, 843, 907, 940, 963, 1028, 1089, 1114, 1153, 1180, 1247, 1302, 1349, 1383, 1452, 1493, 1512, 1583, 1601, 1681, 1716, 1745, 1784, 1874, 1946, 2147(NC), 2237, 2603, 2691, 2850, 2926, 2973, 3025, 3059, 3082, 3102, 3337, 3646 cm^{-1}.

Isocyanide resin 3b. IR (KBr): ν = 504, 526, 538, 638, 666, 697, 754, 817, 836, 907, 942, 965, 1003, 1028, 1070, 1115, 1154, 1181, 1218, 1277, 1317, 1360, 1422, 1451, 1492, 1513, 1526, 1583, 1601, 1674, 1802, 1873, 1944, 2148 (NC), 2312, 2337, 2631, 2850, 2923, 3003, 3025, 3060, 3082, 3101, 3323, 3583, 3644 cm^{-1}.

Isocyanide resin 3c. IR (KBr): ν = 510, 517, 532, 696, 759, 842, 907, 942, 1028, 1071, 1115, 1154, 1182, 1267, 1350, 1380, 1454, 1494, 1556, 1602, 1681, 1715, 1805, 1874, 1945, 2148 (NC), 2337, 2853, 2915, 2973, 3026, 3060, 3082, 3307, 3403, 3645 cm^{-1}.

Isocyanide resin 3d. IR (KBr): ν = 508, 528, 692, 754, 816, 841, 907, 944, 963, 1003, 1028, 1069, 1114, 1155, 1181, 1266, 1372, 1424, 1452, 1593, 1512, 1538, 1583, 1601, 1693, 1747, 1804, 1873, 1944, 2147 (NC), 2337, 2850, 2915, 3026, 3082, 3405 cm^{-1}

4.5 General procedure for solid phase Ugi reaction and separation of the Ugi adducts (6A-C) from the solid support

The appropriate ketone (10 equiv) and 4-methoxybenzylamine (10 equiv) were dissolved in a mixture of dry DCM (12 mL) and dry MeOH (5 mL) and stirred for 30 minutes. Phenylacetic acid (10 equiv) was dissolved in dry MeOH (2 mL), added to the mixture and stirred for 30 minutes. This mixture was poured into a reaction vessel containing the appropriate resin **3** (2 g) previously swollen and suspended in dry DCM (6 mL). The mixture was left stirring for 1-3 days at room temperature. After separation from the reaction mixture by filtration, the resin was washed with DMF (2×10 mL), DCM (2×10 mL) and MeOH (2×10 mL) and dried in vacuum. The nonexistence of the isocyanide group in the resin was proven by the disappearance of the isocyanide signal from the IR spectrum. If the signal was still present the previous procedure was repeated.

The resin obtained after Ugi reaction (2.50 g) was swollen in DCM and suspended in 25 % trifluoroacetic acid (TFA) in DCM (5 mL). The mixture was stirred for 4 hours and the resin removed by filtration. The filtrate was concentrated till dryness under reduced pressure, the crude suspended in 2 mL of water and the pH raised till 12 by the addition of NaOH 6M. The suspension was stirred overnight and the solid removed by filtration. The filtrate pH reduced to 2 with HCl 6M and the solid that separated isolated by

filtration and washed with water and light petroleum. The exact reaction conditions and yields obtained using the different isocyanide functionalized resins **3** are summarized in table 1.

***4.5.1. N*-Phenylacetyl-α,α-diethylglycine (6A).** Obtained by using 3-pentanone (**4A**) and the above general procedure. mp = 220.1 – 221.6 ºC. δ_H (400 MHz, DMSO-d_6) 0.65 (6H, *t, J* 7.3 Hz, 2×CH_3), 1.69-1.74 (2H, *m*, β-CH_2), 1.89-1.94 (2H, *m*, β-CH_2), 3.47 (2H, *s*, CH_2CO), 7.19-7.30 (5H, *m*, Ph), 7.60 (1H, *s*, NH), 12.56 (1H, *br s*, COOH). δ_C (100.6 MHz, DMSO-d_6) 7.89 (2×CH_3), 25.90 (2×β-CH_2), 42.46 ($\underline{C}H_2CO$), 63.00 (α-C), 126.29 (Ph-C4), 128.17 (Ph-C3,5), 129.00 (Ph-C2,6), 136.56 (Ph-C1), 169.23 (CONH), 174.47 (COOH). HRMS (ESI): *m/z* [M^++H] calc. for $C_{14}H_{20}NO_3$ 250.14440, found 250.14452.

***4.5.2. N*-Phenylacetyl-α,α-dipropylglycine (6B).** Obtained by using 4-heptanone (**4B**) and the above general procedure. mp = 156.3 – 157.4 ºC. δ_H (400 MHz, DMSO-d_6) 0.78 (6H, *t, J* 7.2 Hz, 2×CH_3), 1.02-1.10 (4H, *m*, 2×γ-CH_2), 1.65-1.68 (2H, *m*, β-CH_2), 1.87-1.90 (2H, *m*, β-CH_2), 3.46 (2H, *s*, CH_2CO), 7.20-7.30 (5H, *m*, Ph), 7.60 (1H, *s*, NH), 12.56 (1H, *br s*, COOH). δ_C (100.6 MHz, DMSO-d_6) 14.09 (2×CH_3), 16.57 (2×β-CH_2), 35.95 (2×γ-CH_2) 42.49 ($\underline{C}H_2CO$), 62.14 (α-C), 126.31 (Ph-C4), 128.17 (Ph-C3,5), 128.98 (Ph-C2,6), 136,52 (Ph-C1), 169.23 (CONH), 174.70 (COOH). HRMS (ESI): *m/z* [M^++H] calc. for $C_{16}H_{24}NO_3$ 278.17572, found 278.17587.

***4.5.3.* 1-(*N*-Phenylacetyl)amino-1-cyclohexanecarboxylic acid (6C).** Obtained by using cyclohexanone (**4C**) and the above general procedure. mp = 155.6 – 156.4 ºC. δ_H (400 MHz, DMSO-d_6) 1.14-1.23 (1H, *m*, δ-CH_2), 1.29-1.51 (5H, *m*, 2×γ-CH_2 and δ-CH_2), 1.61 (2H, *dt*, *J* 13.4 and 2.4 Hz, β-CH_2), 1.92 (2H, *dt*, *J* 13.2 and 2.4 Hz, β-CH_2), 3.45 (2H, *s*, CH_2CO), 7.18-7.29 (5H, *m*, Ph), 8.01 (1H, *s*, NH), 12.04 (1H, *br s*, COOH). δ_C (100.6 MHz, DMSO-d_6) 21.01 (2×γ-CH_2), 24.96 (δ-CH_2), 31.64 (2×β-CH_2), 42.00 ($\underline{C}H_2CO$), 57.68 (α-C), 126.16 (Ph-C4), 128.07 (Ph-C3,5), 128.93 (Ph-C2,6), 136.65 (Ph-C1), 169.75 (CONH), 175.53 (COOH). HRMS (ESI): *m/z* [M^++H] calc. for $C_{15}H_{20}NO_3$ 262.14440, found 262.14423.

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CAPTIONS

Scheme 1. Preparation of the isocyanide functionalized resins **3a-d**.

Scheme 2. Preparation of *N*-phenylacetyl-α,α-dialkylglycines **6A-C**.

Figure 1 IR spectra of resins **2a** and **3a** obtained in KBr disc.

Figure 2. Example of the resin IR spectra obtained in KBr disc after spacer coupling (resin **2b)**, dehydration reaction (resin **3b)** and Ugi reaction (resin **5Bb)**.

Table 1. Synthesis and characterization data of formyl-amino acids **1b-d**.

Table 2. Conditions used in the Ugi reactions performed