

# An improved approach for the synthesis of $\alpha,\alpha$ -dialkyl glycine derivatives by the Ugi–Passerini reaction†

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A general and simple strategy for routine peptide synthesis with  $\alpha,\alpha$ -dialkyl glycines taking advantage of the four-component Ugi–Passerini reaction is presented. The isonitrile required for the reaction can be relatively simple and its selection based on cost, as the group it generates is easily removed under acidic conditions; in addition, this removal is not visibly affected by the bulkiness of the  $\alpha$ -alkyl groups. Being a good leaving group from the N-terminal amino group of the amino acid, 4-methoxybenzyl was the choice for the amine component of the reaction. The method is illustrated with the synthesis of a series of acyl derivatives of several  $\alpha,\alpha$ -dialkyl glycines. The preparation of the latter compounds is also reported.

## Introduction

The synthesis of peptides containing residues of  $\alpha,\alpha$ -dialkyl glycines was pioneered during the 1960s by various authors such as Faust and Lange,<sup>1</sup> Diehl and Young,<sup>2</sup> and McGahren and Goodman;<sup>3</sup> however, the most representative work was carried out by Kenner and his co-workers,<sup>4</sup> who concentrated mainly on developing methodologies to deal with these “sterically hindered” amino acids. In the following decades peptides containing residues of such amino acids were investigated from the point of view of their conformation and, especially, with regard to the ability they have to induce special conformational features in peptides.<sup>5</sup> Lately, various important applications of these amino acids have been devised in connection with modification of natural peptides in order to enhance their properties or to prevent their recognition by enzymes.<sup>6</sup> Nevertheless, most of the reports found in the literature refer to the simplest representative of this class of compounds, *i.e.*  $\alpha,\alpha$ -dimethylglycine (Aib, for  $\alpha$ -aminoisobutyric acid), which is certainly due to the discouraging difficulties usually encountered during syntheses.<sup>4</sup> In fact, apart from a few exceptions,  $\alpha,\alpha$ -dialkyl glycines are not readily available compounds, their synthesis being most commonly carried out by hydrolysis of specially prepared hydantoins or Schiff bases.<sup>7</sup> Owing to steric crowding, reactions involving these compounds and their derivatives are slow and lead almost always to low yields.

As early as 1971, Ugi proposed<sup>8</sup> the use of a four-component reaction as a complement or even an alternative to classical peptide synthesis with common amino acids (Scheme 1;  $R^4 = H$ ), but one can hardly find any such application in the literature. This may be due to the fact that the synthetic simplifications offered by this reaction are overcome by two inherent drawbacks: (i) the high tendency to racemise above  $-20\text{ }^\circ\text{C}$  shown by amino acid and peptide isonitriles required for the reaction and (ii) the need for cleavage of the *N*-alkyl group formed during the reaction. Having it in mind to over-

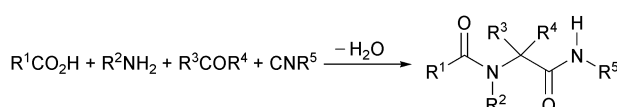
come the above difficulties related to  $\alpha,\alpha$ -dialkyl glycines, we were able to take advantage of the crowding typical of these compounds to develop an improved approach to the synthesis of  $\alpha,\alpha$ -dibenzyl<sup>9</sup> and other symmetric sterically hindered  $\alpha,\alpha$ -dialkyl glycines.<sup>10</sup> Although Ugi has given little attention to this class of compounds (Scheme 1;  $R^3, R^4 \neq H$ ), we speculated that if the above drawbacks could be easily overcome, the Ugi four-component reaction might also turn into a useful and possibly the most efficient approach to synthesise peptides containing residues of  $\alpha,\alpha$ -dialkyl glycines.

As the Ugi reactions involving formation of  $\alpha,\alpha$ -dialkyl glycines are already too slow at room temperature, it is not practical to perform them at temperatures below  $-20\text{ }^\circ\text{C}$  to avoid isonitrile racemisation. Armstrong and co-workers<sup>11</sup> have devised the concept of “convertible” isonitrile, a reagent that would allow mild cleavage of the C-terminal amide of the amino acid residue generated in the Ugi–Passerini reaction. They found that cyclohexenyl isonitrile fulfils this requirement and were able to convert this amide into an acid, an ester or a thioester. However, this isonitrile is difficult to prepare and to handle and also fairly unstable and, thus, Linderman and co-workers<sup>12</sup> developed a new “convertible” isonitrile, a silyl derivative of phenyl isonitrile, that although being stable involves a three-step preparation.

Meanwhile, Goodman and co-workers<sup>13</sup> reported that the amide bond at the C-terminus of *N*, $\alpha,\alpha$ -trimethylglycine, Aib(Me), is labile to acid; recently they proposed<sup>14</sup> that this is due to intramolecular attack by the carbonyl oxygen atom of the N-terminus of this residue, leading to an oxazolinium intermediate; we had also found a similar behaviour<sup>15</sup> with various *N*, $\alpha,\alpha$ -trialkyl glycines. This result suggests that no special isonitrile is required to ensure selective cleavage at the C-terminus of the generated amino acid. Thus, we decided to test this hypothesis, by using different isonitriles in the synthesis of *N*-acyl- $\alpha,\alpha$ -dialkyl glycines, together with the use of the 4-methoxybenzyl group, which is known to cleave from amides with trifluoroacetic acid (TFA).<sup>16</sup> Now we report a general and simple strategy for routine peptide synthesis with these amino acids taking advantage of the four-component Ugi–Passerini reaction.

## Results and discussion

Schiff bases **1** were prepared by azeotropic reflux of 4-methoxybenzylamine and diethyl, dipropyl, diisobutyl or dibenzyl ketone in toluene and the product distilled in all cases but the



Scheme 1

† Electronic supplementary information (ESI) available: spectroscopic data for compounds **1–5**. See <http://www.rsc.org/suppdata/ob/b2/b212473b/>

**Table 1** Synthesis of  $\text{CH}_3\text{CON}(4\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2)\text{CR}_2\text{CONHR}'$  (**3**)

Compound no.	R	R'	Yield (%)
<b>3a</b>	$\text{CH}_3\text{CH}_2$	$\text{CH}_3\text{CH}_2\text{OCOCH}_2$	60
<b>3b</b>	$\text{CH}_3\text{CH}_2$	$4\text{-CH}_3\text{OC}_6\text{H}_4$	80
<b>3c</b>	$\text{CH}_3\text{CH}_2$	$2,4\text{-(CH}_3\text{O)}_2\text{C}_6\text{H}_3$	80
<b>3d</b>	$\text{CH}_3\text{CH}_2$	$4\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2$	87
<b>3e</b>	$\text{CH}_3(\text{CH}_2)_2$	$\text{CH}_3\text{CH}_2\text{OCOCH}_2$	51
<b>3f</b>	$\text{CH}_3(\text{CH}_2)_2$	$4\text{-CH}_3\text{OC}_6\text{H}_4$	88
<b>3g</b>	$\text{CH}_3(\text{CH}_2)_2$	$2,4\text{-(CH}_3\text{O)}_2\text{C}_6\text{H}_3$	85
<b>3h</b>	$\text{CH}_3(\text{CH}_2)_2$	$4\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2$	84
<b>3i</b>	$(\text{CH}_3)_2\text{CHCH}_2$	$\text{CH}_3\text{CH}_2\text{OCOCH}_2$	49
<b>3j</b>	$\text{C}_6\text{H}_5\text{CH}_2$	$\text{CH}_3\text{CH}_2\text{OCOCH}_2$	41
<b>3k</b>	$\text{C}_6\text{H}_5\text{CH}_2$	$4\text{-CH}_3\text{OC}_6\text{H}_4$	61
<b>3l</b>	$\text{C}_6\text{H}_5\text{CH}_2$	$2,4\text{-(CH}_3\text{O)}_2\text{C}_6\text{H}_3$	68
<b>3m</b>	$\text{C}_6\text{H}_5\text{CH}_2$	$4\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2$	69
<b>3n</b>	$\text{C}_6\text{H}_5\text{CH}_2$	$2,4\text{-(CH}_3\text{O)}_2\text{C}_6\text{H}_3\text{CH}_2$	59

**Table 2** Synthesis of  $\text{CH}_3\text{CONHCR}_2\text{CO}_2\text{H}$  (**4**) by cleavage of  $\text{CH}_3\text{CON}(4\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2)\text{CR}_2\text{CONHR}'$  (**3**)

Product	Starting material	R	R'	Yield (%)
<b>4a</b>	<b>3a</b>	$\text{CH}_3\text{CH}_2$	$\text{CH}_3\text{CH}_2\text{OCOCH}_2$	87
<b>4a</b>	<b>3b</b>	$\text{CH}_3\text{CH}_2$	$4\text{-CH}_3\text{OC}_6\text{H}_4$	94
<b>4a</b>	<b>3c</b>	$\text{CH}_3\text{CH}_2$	$2,4\text{-(CH}_3\text{O)}_2\text{C}_6\text{H}_3$	74
<b>4a</b>	<b>3d</b>	$\text{CH}_3\text{CH}_2$	$4\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2$	77
<b>4b</b>	<b>3e</b>	$\text{CH}_3(\text{CH}_2)_2$	$\text{CH}_3\text{CH}_2\text{OCOCH}_2$	91
<b>4b</b>	<b>3f</b>	$\text{CH}_3(\text{CH}_2)_2$	$4\text{-CH}_3\text{OC}_6\text{H}_4$	81
<b>4b</b>	<b>3g</b>	$\text{CH}_3(\text{CH}_2)_2$	$2,4\text{-(CH}_3\text{O)}_2\text{C}_6\text{H}_3$	78
<b>4b</b>	<b>3h</b>	$\text{CH}_3(\text{CH}_2)_2$	$4\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2$	98
<b>4c</b>	<b>3i</b>	$(\text{CH}_3)_2\text{CHCH}_2$	$\text{CH}_3\text{CH}_2\text{OCOCH}_2$	78
<b>4d</b>	<b>3j</b>	$\text{C}_6\text{H}_5\text{CH}_2$	$\text{CH}_3\text{CH}_2\text{OCOCH}_2$	81
<b>4d</b>	<b>3k</b>	$\text{C}_6\text{H}_5\text{CH}_2$	$4\text{-CH}_3\text{OC}_6\text{H}_4$	89
<b>4d</b>	<b>3l</b>	$\text{C}_6\text{H}_5\text{CH}_2$	$2,4\text{-(CH}_3\text{O)}_2\text{C}_6\text{H}_3$	78
<b>4d</b>	<b>3m</b>	$\text{C}_6\text{H}_5\text{CH}_2$	$4\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2$	99
<b>4d</b>	<b>3n</b>	$\text{C}_6\text{H}_5\text{CH}_2$	$2,4\text{-(CH}_3\text{O)}_2\text{C}_6\text{H}_3\text{CH}_2$	63

last one in the series owing to its high boiling point. The required isonitriles **2** were prepared from the corresponding formamides by treating them with triphosgene in the presence of triethylamine, as usual, and the reaction products purified by flash chromatography. Then, with a few exceptions, each of the Schiff bases was combined with each of the isonitriles and acetic acid in dry methanol and allowed to react at room temperature for one to two weeks to give the expected Ugi–Passerini adducts **3**, usually in high yields independently of the bulkiness of the reagents or that of the reaction products (Scheme 2, Table 1). The lower yields obtained in the case of the dibenzyl derivatives may have resulted from the use of the Schiff base as a crude material. The low stability of the glycine ester isonitrile is reflected in the lower yields found in the case of these dipeptide derivatives.

The Ugi–Passerini adducts were reacted with neat trifluoroacetic acid (TFA) under reflux; as shown by TLC, the reactions were complete after a few minutes. The residue obtained by evaporating the acid was treated with aqueous sodium hydroxide, followed by washing and precipitation at low pH to allow separation of the required *N*-acetylamino acids **4** (Scheme 3, Table 2). As shown in the Table, neither the bulkiness of the dialkyl glycine side chains nor the nature of the isonitrile moiety seems to affect the lability of the amide bond at their C-terminus, thus allowing good cleavage selectivity and yields in all cases. Thus, the choice of the isonitrile should be based only on the availability and price of the starting material. In addition, the use of 4-methoxybenzylamine seems to be a good choice to allow the easy removal of the *N*-alkyl group present in the Ugi–Passerini adduct (**3**).

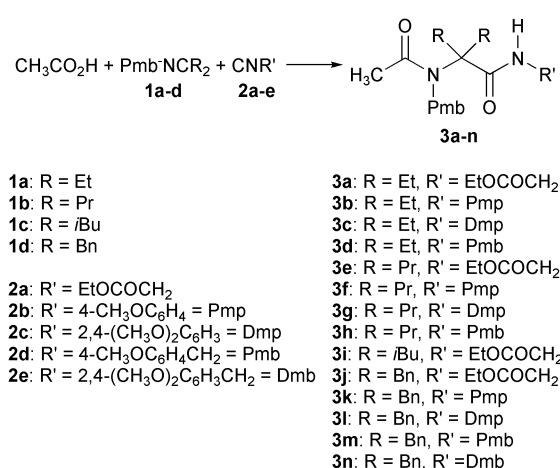
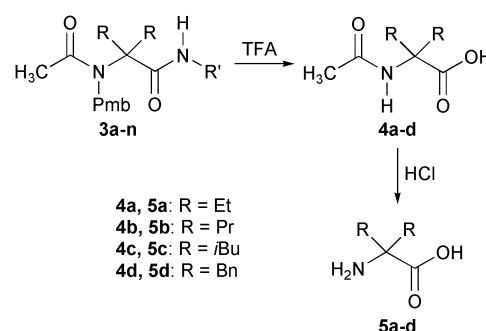
**Scheme 2****Scheme 3**

Table 3 shows the excellent yields obtained in the hydrolysis of the *N*-acetylamino acids to the corresponding free derivatives or their hydrochlorides (**5**). Our results suggest that this is the best route to the synthesis of bulky  $\alpha,\alpha$ -dialkyl glycines, as it

**Table 3** Synthesis of  $\text{NH}_2\text{CR}_2\text{CO}_2\text{H}$  (**5**) by cleavage of  $\text{CH}_3\text{-CONHCR}_2\text{CO}_2\text{H}$  (**4**)

Product	Starting material	R	Yield (%)
<b>5a</b>	<b>4a</b>	$\text{CH}_3\text{CH}_2$	97
<b>5b</b>	<b>4b</b>	$\text{CH}_3(\text{CH}_2)_2$	92
<b>5c</b>	<b>4c</b>	$(\text{CH}_3)_2\text{CHCH}_2$	90
<b>5d</b>	<b>4d</b>	$\text{C}_6\text{H}_5\text{CH}_2$	96

involves simple procedures in clean reactions leading to high overall yields, usually above 60%.

## Experimental

All ketones except dibenzyl ketone were freshly distilled. Methanol and toluene were dried by standard procedures. All other solvents and reagents were used as obtained from commercial sources. The formamides required for the synthesis of isonitriles were prepared from the corresponding amines by the usual methods. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel 60F<sub>254</sub>) and spots were visualised under UV light or by exposure to vapourised iodine. Preparative chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected.  $^1\text{H}$  NMR spectra were recorded at 25 °C in ~5%  $\text{CDCl}_3$  solution on a Varian 300 Unity Plus spectrometer; all shifts are given in  $\delta$  ppm using  $\delta_{\text{H}}$   $\text{Me}_4\text{Si} = 0$  and  $J$ -values are given in Hz. Assignments were made by comparison of chemical shifts, peak multiplicity and  $J$ -values.  $^{13}\text{C}$  NMR spectra were recorded with the same instrument at 75.4 MHz and using the solvent peak as internal reference; assignments were carried out by the DEPT 135, HMQC and HMBC techniques. IR spectra were run on an FTIR Perkin-Elmer 1600 spectrophotometer. Elemental analyses were carried out on a Leco CHNS 932 instrument.

### General procedure for the synthesis of Schiff bases 1

The required ketone (0.36 mol) was dissolved in dry toluene (60 ml) and 45.27 g (0.33 mol) of 4-methoxybenzylamine added. This solution was refluxed overnight under nitrogen and the condensate collected in a Dean–Stark device to separate the water. Except for compound **1d**, after evaporation of the solvent, the residue was distilled under reduced pressure and kept in the cold under nitrogen.

#### *N*-(4-Methoxybenzyl)-3-pentanamine **1a**

The crude product was distilled under reduced pressure to yield imine **1a** (53.90 g, 80%) as a colourless oil, bp 126–130 °C (2 mmHg). Anal. Found: C, 75.8; H, 9.4; N, 6.7. Calc. for  $\text{C}_{13}\text{H}_{19}\text{NO}$ : C, 76.1; H, 9.3; N, 6.8%.

#### *N*-(4-Methoxybenzyl)-4-heptanamine **1b**

The crude product was distilled under reduced pressure to yield imine **1b** (61.84 g, 80%) as a colourless oil, bp 140–142 °C (2 mmHg). Anal. Found: C, 77.3; H, 10.2; N, 6.0. Calc. for  $\text{C}_{15}\text{H}_{23}\text{NO}$ : C, 77.2; H, 9.9; N, 6.0%.

#### *N*-(4-Methoxybenzyl)-2,6-dimethyl-4-heptanamine **1c**

The crude product was distilled under reduced pressure to yield imine **1c** (65.39 g, 76%) as a colourless oil, bp 162–166 °C (2 mmHg). Anal. Found: C, 77.9; H, 10.4; N, 5.4. Calc. for  $\text{C}_{17}\text{H}_{27}\text{NO}$ : C, 78.1; H, 10.4; N, 5.4%.

#### *N*-(4-Methoxybenzyl)-1,3-diphenyl-2-propanamine **1d**

A slight excess of ketone was used to prepare imine **1d** (95.62 g, 88%), which was utilised without purification immediately after

evaporation of the reaction solvent, once it decomposed before distilling. Anal. Found: C, 84.0; H, 7.0; N, 3.9. Calc. for  $\text{C}_{23}\text{H}_{23}\text{NO}$ : C, 83.9; H, 7.0; N, 4.2%.

### General procedure for the synthesis of isonitriles 2

The required formamide (0.05 mol) was dissolved in dichloromethane (125 ml) and 16.0 ml (0.12 mol) of triethylamine added. The mixture was cooled in an ice bath and a solution of 5.44 g (0.06 mol) of triphosgene in dichloromethane (50 ml) added dropwise under vigorous stirring. When the addition was finished, the reaction mixture was set aside at room temperature under stirring and samples collected for TLC; when the formamide had been consumed (usually an hour was enough), distilled water (75 ml) was added and the organic layer separated and dried over anhydrous  $\text{MgSO}_4$ . The residue from evaporation of the solvent was chromatographed through a silica gel column using dichloromethane as the eluent. The fractions containing the isonitrile were collected and the solvent evaporated under reduced pressure without heating, the residue being used without delay.

#### Ethyl isocyanoacetate **2a**

The reaction was carried out on a 0.1-molar scale to yield isonitrile **2a** (8.08 g, 72%) (lit.,<sup>8</sup> 77%) as a light yellow oil.

#### 4-Methoxyphenyl isonitrile **2b**

The reaction was carried out on a 0.05-molar scale to yield isonitrile **2b** (6.35 g, 95%) (lit.,<sup>8</sup> 63%) as a light yellow solid.

#### 2,4-Dimethoxyphenyl isonitrile **2c**

The reaction was carried out on a 0.05-molar scale and the crude product recrystallised from dichloromethane–petroleum ether (40–60 °C) to yield isonitrile **2c** (7.07 g, 87%) (lit.,<sup>8</sup> 41%) as a pink solid, mp 70–71 °C. Anal. Found: C, 66.2; H, 5.7; N, 8.6. Calc. for  $\text{C}_9\text{H}_9\text{NO}_2$ : C, 66.2; H, 5.6; N, 8.6%.

#### 4-Methoxybenzyl isonitrile **2d**

The reaction was carried out on a 0.05-molar scale to yield isonitrile **2d** (6.97 g, 95%) (lit.,<sup>8</sup> 25%) as a light yellow oil.

#### 2,4-Dimethoxybenzyl isonitrile **2e**

The reaction was carried out on a 0.015-molar scale and the crude product recrystallised from dichloromethane–petroleum ether (40–60 °C) to yield isonitrile **2e** (2.30 g, 87%) as a light yellow solid, mp 66–67 °C. Anal. Found: C, 67.6; H, 6.4; N, 8.2. Calc. for  $\text{C}_{10}\text{H}_{11}\text{NO}_2$ : C, 67.8; H, 6.3; N, 7.9%.

### General procedure for the Ugi–Passerini reaction (preparation of **3**)

Acetic acid (0.6 g, 0.01 mol) was added to dry methanol (5 ml) containing the Schiff base (**1**, 0.01 mol). The mixture was stirred for 15 minutes and then 0.01 mol of isonitrile (**2**) was added and the mixture left at room temperature under nitrogen in the dark. The reaction was followed by IR spectroscopy, by monitoring the isonitrile peak fading within the range 2100–2200  $\text{cm}^{-1}$ . If a precipitate formed either in the course of the reaction or by concentration at the end, it was filtered off and recrystallised; otherwise, the residue from evaporation was chromatographed through a silica gel column that was eluted with dichloromethane–hexane (1 : 1), followed by neat dichloromethane and then by dichloromethane–methanol (50 : 1). The fractions containing the product (**3**) were collected and the solvent evaporated under reduced pressure. The solid residue was recrystallised.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -diethylglycylglycine ethyl ester **3a****

The reaction was carried out on a 0.025-molar scale and the crude product recrystallised from diethyl ether to yield adduct **3a** (5.57 g, 60%) as a white solid, mp 95–96 °C. Anal. Found: C, 63.2; H, 8.0; N, 7.5. Calc. for  $C_{20}H_{30}N_2O_5$ : C, 63.5; H, 8.0; N, 7.4%.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -diethylglycine 4-methoxyphenyl amide **3b****

The reaction was carried out on a 0.02-molar scale and the crude product recrystallised from ethyl acetate to yield adduct **3b** (6.38 g, 80%) as a white solid, mp 139–140 °C. Anal. Found: C, 69.1; H, 7.5; N, 7.1. Calc. for  $C_{23}H_{30}N_2O_4$ : C, 69.3; H, 7.6; N, 7.0%.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -diethylglycine 2,4-dimethoxyphenyl amide **3c****

The reaction was carried out on a 0.015-molar scale and the crude product recrystallised from diethyl ether to yield adduct **3c** (5.11 g, 80%) as a white solid, mp 131–132 °C. Anal. Found: C, 67.1; H, 7.6; N, 6.7. Calc. for  $C_{24}H_{32}N_2O_5$ : C, 67.3; H, 7.5; N, 6.5%.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -diethylglycine 4-methoxybenzyl amide **3d****

The reaction was carried out on a 0.015-molar scale and the crude product recrystallised from diethyl ether to yield adduct **3d** (5.40 g, 87%) as a white solid, mp 96–97 °C. Anal. Found: C, 69.8; H, 7.8; N, 7.0. Calc. for  $C_{24}H_{32}N_2O_4$ : C, 69.9; H, 7.8; N, 6.8%.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -dipropylglycylglycine ethyl ester **3e****

The reaction was carried out on a 0.015-molar scale and the crude product recrystallised from diethyl ether–petroleum ether (40–60 °C) to yield adduct **3e** (3.10 g, 51%) as a white solid, mp 121–122 °C. Anal. Found: C, 64.9; H, 8.3; N, 7.0. Calc. for  $C_{22}H_{34}N_2O_5$ : C, 65.0; H, 8.4; N, 6.9%.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -dipropylglycine 4-methoxyphenyl amide **3f****

The reaction was carried out on a 0.01-molar scale and the crude product recrystallised from ethyl acetate–petroleum ether (40–60 °C) to yield adduct **3f** (3.73 g, 88%) as a white solid, mp 134–135 °C. Anal. Found: C, 70.1; H, 7.9; N, 6.7. Calc. for  $C_{25}H_{34}N_2O_4$ : C, 70.4; H, 8.0; N, 6.6%.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -dipropylglycine 2,4-dimethoxyphenyl amide **3g****

The reaction was carried out on a 0.015-molar scale and the crude product recrystallised from methanol–diethyl ether to yield adduct **3g** (5.81 g, 85%) as a white solid, mp 154–155 °C. Anal. Found: C, 68.3; H, 8.1; N, 6.1. Calc. for  $C_{26}H_{36}N_2O_5$ : C, 68.4; H, 8.0; N, 6.1%.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -dipropylglycine 4-methoxybenzyl amide **3h****

The reaction was carried out on a 0.03-molar scale and the crude product recrystallised from ethyl acetate–diethyl ether to yield adduct **3h** (11.12 g, 84%) as a white solid, mp 114–115 °C. Anal. Found: C, 71.1; H, 8.4; N, 6.6. Calc. for  $C_{26}H_{36}N_2O_4$ : C, 70.9; H, 8.2; N, 6.4%.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -diisobutylglycylglycine ethyl ester **3i****

The reaction was carried out on a 0.015-molar scale to yield adduct **3i** (3.08 g, 49%) as a light yellow oil.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -dibenzylglycylglycine ethyl ester **3j****

The reaction was carried out on a 0.015-molar scale and the crude product recrystallised from dichloromethane–diethyl ether to yield adduct **3j** (3.08 g, 41%) as a white solid, mp 156–158 °C. Anal. Found: C, 71.4; H, 6.7; N, 5.7. Calc. for  $C_{30}H_{34}N_2O_5$ : C, 71.7; H, 6.8; N, 5.6%.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -dibenzylglycine 4-methoxyphenyl amide **3k****

The reaction was carried out on a 0.0165-molar scale and the crude product recrystallised from ethyl acetate–diethyl ether to yield adduct **3k** (4.79 g, 61%) as a light yellow solid, mp 192–194 °C. Anal. Found: C, 75.9; H, 6.5; N, 5.4. Calc. for  $C_{33}H_{34}N_2O_4$ : C, 75.8; H, 6.6; N, 5.4%.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -dibenzylglycine 2,4-dimethoxyphenyl amide **3l****

The reaction was carried out on a 0.02-molar scale and the crude product recrystallised from dichloromethane–diethyl ether to yield adduct **3l** (7.51 g, 68%) as a white solid, mp 200–201 °C. Anal. Found: C, 73.7; H, 6.6; N, 5.1. Calc. for  $C_{34}H_{36}N_2O_5$ : C, 73.9; H, 6.6; N, 5.1%.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -dibenzylglycine 4-methoxybenzyl amide **3m****

The reaction was carried out on a 0.01-molar scale and the crude product recrystallised from ethyl acetate–diethyl ether to yield adduct **3m** (3.71 g, 69%) as a white solid, mp 163–165 °C. Anal. Found: C, 75.9; H, 6.8; N, 5.5. Calc. for  $C_{34}H_{36}N_2O_4$ : C, 76.1; H, 6.8; N, 5.2%.

***N*-Acetyl-*N*-(4-methoxybenzyl)- $\alpha,\alpha$ -dibenzylglycine 2,4-dimethoxybenzyl amide **3n****

The reaction was carried out on a 0.013-molar scale and the crude product recrystallised from ethyl acetate–diethyl ether to yield adduct **3n** (3.25 g, 59%) as a white solid, mp 170–171 °C. Anal. Found: C, 74.0; H, 6.8; N, 4.9. Calc. for  $C_{35}H_{38}N_2O_5$ : C, 74.2; H, 6.8; N, 4.9%.

**General procedure for the synthesis of the *N*-acetyl- $\alpha,\alpha$ -dialkyl glycines **4****

The Ugi–Passerini adduct (**3**, 1 g) was dissolved in 5 ml of TFA and refluxed for 5–10 minutes, during which the solution became purple. The residue from evaporation of the solvent was taken up in a 2 M aqueous solution of sodium hydroxide and the pH adjusted to 12. After leaving for 2 hours under stirring, the solid residue formed was removed by filtration and the solution acidified to pH 1 with 6 M aqueous HCl solution. The precipitate (**4**) was filtered off, washed with petroleum ether (40–60 °C) and dried in a vacuum oven.

***N*-Acetyl- $\alpha,\alpha$ -diethylglycine **4a****

The reaction was carried out on a 0.006-molar scale from **3b** to yield the *N*-acetylamino acid **4a** (0.98 g, 94%) as a white solid, mp 209–211 °C. Anal. Found: C, 55.2; H, 8.5; N, 8.1. Calc. for  $C_8H_{15}NO_3$ : C, 55.5; H, 8.7; N, 8.0%.

***N*-Acetyl- $\alpha,\alpha$ -dipropylglycine **4b****

The reaction was carried out on a 0.005-molar scale from **3h** to yield the *N*-acetylamino acid **4b** (1.02 g, 98%) as a white solid,



mp 196–197 °C. Anal. Found: C, 58.7; H, 9.5; N, 7.0. Calc. for  $C_{10}H_{19}NO_3$ : C, 58.7; H, 9.5; N, 7.0%.

#### *N*-Acetyl- $\alpha,\alpha$ -diisobutylglycine **4c**

The reaction was carried out on a 0.002-molar scale from **3i** to yield the *N*-acetylamino acid **4c** (1.79 g, 78%) as a white solid, mp 216–218 °C. Anal. Found: C, 62.5; H, 9.8; N, 6.2. Calc. for  $C_{12}H_{23}NO_3$ : C, 62.8; H, 10.1; N, 6.1%.

#### *N*-Acetyl- $\alpha,\alpha$ -dibenzylglycine **4d**

The reaction was carried out on a 0.006-molar scale from **3m** to yield the *N*-acetylamino acid **4d** (1.47 g, 99%) as a white solid, mp 233–235 °C. Anal. Found: C, 72.4; H, 6.5; N, 4.7. Calc. for  $C_{18}H_{19}NO_3$ : C, 72.7; H, 6.4; N, 4.7%.

#### General procedure for the synthesis of $\alpha,\alpha$ -dialkyl glycine hydrochlorides **5**

The required *N*-acetyl- $\alpha,\alpha$ -dialkyl glycine (**4**, 0.01 mol) was refluxed for 2 hours in a 6 M aqueous HCl solution (50 ml). The solvent was then evaporated to dryness and the residue (**5**) dried in a vacuum oven. In the case of the dibenzyl derivative aqueous HBr (48%) was used, as the compound resisted dissolution in HCl.

#### $\alpha,\alpha$ -Diethylglycine hydrochloride **5a**

The reaction was carried out on a 0.0058-molar scale to yield amino acid **5a** (0.94 g, 97%) as a white solid, mp > 288 °C (dec.). Anal. Found: C, 42.8; H, 8.3; N, 8.3. Calc. for  $C_6ClH_{14}NO_2$ : C, 43.0; H, 8.4; N, 8.4%.

#### $\alpha,\alpha$ -Dipropylglycine hydrochloride **5b**

The reaction was carried out on a 0.01-molar scale to yield amino acid **5b** (1.80 g, 92%) as a white solid, mp > 290 °C (dec.). Anal. Found: C, 49.1; H, 9.1; N, 7.4. Calc. for  $C_8ClH_{18}NO_2$ : C, 49.1; H, 9.3; N, 7.2%.

#### $\alpha,\alpha$ -Diisobutylglycine hydrochloride **5c**

The reaction was carried out on a 0.01-molar scale to yield amino acid **5c** (2.01 g, 90%) as a white solid, mp 271–273 °C. Anal. Found: C, 53.8; H, 9.6; N, 6.4. Calc. for  $C_{10}ClH_{22}NO_2$ : C, 53.7; H, 9.9; N, 6.3%.

#### $\alpha,\alpha$ -Dibenzylglycine **5d**

The reaction was carried out on a 0.01-molar scale. After evaporation of the solvent, the residue was dissolved with a 1 M solution of NaOH, precipitated at pH 5; the precipitate was

filtered off and dried to give amino acid **5d** (2.45 g, 96%) as a white solid, mp 290–297 °C. Anal. Found: C, 74.9; H, 6.7; N, 5.5. Calc. for  $C_{16}H_{17}NO_2$ : C, 75.3; H, 6.7; N, 5.5%.

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#### References

- 1 G. Faust and H. Lange, *J. Prakt. Chem.*, 1960, **11**, 153.
- 2 J. F. Diehl and E. A. Young, *J. Med. Chem.*, 1964, **7**, 820.
- 3 W. J. McGahren and M. Goodman, *Tetrahedron*, 1967, **23**, 2017.
- 4 D. S. Jones, G. W. Kenner, J. Preston and R. C. Sheppard, *J. Chem. Soc.*, 1965, 6227.
- 5 C. Toniolo, *Janssen Chim. Acta*, 1993, **11**, 10 (review article); J.-P. Mazeleyrat, K. Wright, M. Wakselman, F. Fromaggio, M. Crisma and C. Toniolo, *Eur. J. Org. Chem.*, 2001, 1821.
- 6 V. De Filippis, F. De Antoni, M. Frigo, P. P. Laureto and A. Fontana, *Biochemistry*, 1998, **37**, 1686; H. Medzihradszky-Schweiger, K. Medzihradszky, H. Nádasi and H. Suli-Vargha, in *Peptides 1998, Proceedings of the 25th European Peptide Symposium*, eds. S. Bajusz and F. Hudecz, Akadémiai Kiadó, Budapest, 1999, p. 606.
- 7 L. Goodson, I. L. Honigberg, J. J. Lehman and W. H. Burton, *J. Org. Chem.*, 1960, **25**, 1920; B. Lygo, J. Crosby and J. A. Peterson, *Tetrahedron Lett.*, 1999, **40**, 8671.
- 8 G. Gokel, P. Hoffmann, H. Kleimann, H. Klusacek, G. Ludke, D. Marquaerding and I. Ugi, in *Isonitrile Chemistry*, ed. I. Ugi, Academic Press, New York and London, 1971, p. 201.
- 9 H. L. Maia, B. Ridge and H. N. Rydon, *J. Chem. Soc.*, 1973, 98.
- 10 A. M. Freitas and H. L. S. Maia, in *Peptides 1988, Proceedings of the 20th European Peptide Symposium*, eds. G. Jung and E. Bayer, Walter de Gruyter, Berlin and New York, 1989, p. 13.
- 11 R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, *Acc. Chem. Res.*, 1996, **29**, 123 and refs. therein; see also C. Hulme, J. Peng, S.-Y. Tang, C. J. Burns, I. Morize and R. Labaudiniere, *J. Org. Chem.*, 1998, **63**, 8021.
- 12 R. J. Linderman, S. Binet and S. R. Petrich, *J. Org. Chem.*, 1999, **64**, 336.
- 13 J. R. Spencer, N. G. J. Delaet, A. Toy-Palmer, V. V. Antonenko and M. Goodman, *J. Org. Chem.*, 1993, **58**, 1635.
- 14 C. J. Creighton, T. T. Romoff, J. H. Bu and M. Goodman, *J. Am. Chem. Soc.*, 1999, **121**, 6786.
- 15 S. P. G. Costa, H. L. S. Maia and S. M. M. A. Pereira-Lima, communication no. P022 to the 16th American Peptide Symposium, Minneapolis, 1999; S. P. G. Costa, H. L. S. Maia and S. M. M. A. Pereira-Lima, in *Peptides 2000, Proceedings of the 26th European Peptide Symposium*, eds. J. Martinez and J.-A. Fehrentz, EDK, Paris, 2001, p. 367.
- 16 T. Johnson, M. Quibell, D. Owen and R. C. Sheppard, *J. Chem. Soc., Chem. Commun.*, 1992, 1573.