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Synthesis of *N*-acyl-*N*,α,α-trialkyl and *N*-acyl-α,α-dialkyl glycines by selective cleavage of Ugi–Passerini adducts. Qualitative assessment of the effect of substituents on the path and yield of reaction †

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Several symmetric *N*-acyl-*N*,α,α-trialkyl glycine amides were synthesised by the Ugi–Passerini four-component reaction and subjected to selective cleavage with trifluoroacetic acid. In almost all cases it was possible to obtain the corresponding *N*-acyl-*N*,α,α-trialkyl and *N*-acyl-α,α-dialkyl glycines in fair to good yields directly from the reaction adducts. With some of the bulkier compounds our results show that the selectivity of cleavage is concentration dependent with respect to the acid, which suggests kinetically controlled processes. The isolation of a stable oxazolone as the product of some of the reactions seems to confirm that amide cleavage involves in all cases formation of an oxazolone-type derivative.

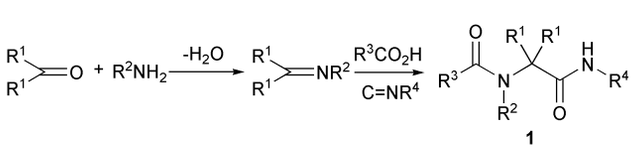
Introduction

During the last decades several authors have been concerned with the investigation of the conformational preferences imparted to peptides by the inclusion of one or more residues of α,α-dialkyl glycines in the peptide chain.[1] Such preferences are related to the hindrance of rotation within the α,α-dialkyl glycine residues due to steric crowding, which makes these residues good candidates for incorporation in peptides in order to grant them special conformational features. Thus, with the aim of developing antagonists or preventing or retarding recognition by enzymes, various important applications of the above amino acids have been devised in connection with the modification of natural peptides or in molecules mimicking them, usually when restriction of backbone flexibility is required.[2] Owing to steric crowding, the synthesis of these uncommon amino acids and reactions with them and their derivatives are slow, thus almost always allowing competitive undesired reactions leading to low yields; usually, this results from difficulties in isolating and purifying the desired products and discourages the use of this class of compounds.[3,4] As a consequence, most of the work found in the literature with α,α-dialkyl glycines deals with the simplest of them, *i.e.* α,α-dimethyl glycine, or with those compounds where the "two side chains" are tied up together in a ring and thus kept sufficiently far from the reaction centres to avoid too strong an interaction with the peptide backbone; this is the case with 1-aminocyclopentyl- and 1-aminocyclohexyl-carboxylic acid and their structural derivatives.[5] By taking advantage of the fact that *N*-acyl-*N*,α,α-trialkyl glycine amides undergo selective amide cleavage with trifluoroacetic acid (TFA)[6] and also of the possibility of cleaving the 4-methoxybenzyl group from amides on boiling with TFA,[7] recently we have been able to solve some difficulties related to the use of the Ugi–Passerini four-component reaction[8] to synthesise α,α-dialkyl glycine derivatives.[9] This allowed us to propose our approach as a general, efficient, and possibly the best, strategy available for the synthesis of peptides incorporating residues of these amino acids. However, prior to engaging in peptide synthesis with these bulky amino acids, we decided (i) to explore the possibility of carrying out the above two cleavages selectively in order to isolate the intermediate *N*-(4-methoxybenzyl)-α,α-dialkyl glycines and (ii) to evaluate the effect of the different substituents on the efficiency of the syntheses. Now, we report the preparation of a series of the above compounds with which we were able to establish cleavage patterns and conditions required for selectivity. The isolation of an oxazolone derivative confirmed that amide cleavage proceeds through a cyclic intermediate and allowed evaluation of the difficulties one can expect when dealing with the bulkier compounds.

Results and discussion

Synthesis of Ugi–Passerini adducts 1

A series of eight compounds was developed by combination of two different groups for each of the substituents R^1, R^3 and R^4 (Scheme 1); R^2 was kept as 4-methoxybenzyl in order to make its cleavage possible. For R^1 the smaller and the bulkier of those groups reported in our previous paper were chosen,[9] *i.e.* methyl and benzyl. In order to ensure a good crystallinity of the compounds and thus facilitate their isolation, R^3 was phenyl and benzyl, which would be generated by the use of benzoic and phenylacetic acid, respectively, as the acid component in Ugi–Passerini reactions. Finally, for R^4 we chose methoxybenzyl and cyclohexyl, which are groups of different bulkiness that would be generated by isonitriles with which we were already familiar and which had shown good behaviour. The required Ugi–Passerini adducts were thus obtained in yields varying within the range 45–83% (Table 1) in reactions taking two to three weeks to completion at room temperature; no attempts were made to carry out the reactions at a higher temperature in order to avoid isonitrile polymerisation that would then increase the difficulty in isolating the reaction product.



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Scheme 1

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/ob/b3/b307111c/

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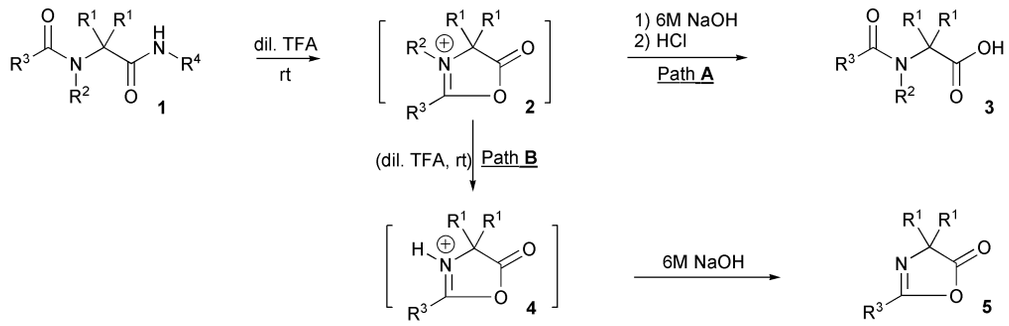


2a, **3a**: R^1 = Me, R^2 = Pmb, R^3 = $PhCH_2$
2b, **3b**: R^1 = Me, R^2 = Pmb, R^3 = Ph
2e, **3e**: R^1 = $PhCH_2$, R^2 = Pmb, R^3 = $PhCH_2$
2f, **3f**: R^1 = $PhCH_2$, R^2 = Pmb, R^3 = Ph
4f, **5f**: R^1 = $PhCH_2$, R^3 = Ph

Scheme 2

Table 1 Synthesis of Ugi–Passerini adducts **1**

Product	R^1	R^2	R^3	R^4	Yield (%)
1a	Me	Pmb[a]	CH_2Ph	Pmb	48
1b	Me	Pmb	Ph	Pmb	77
1c	Me	Pmb	CH_2Ph	C_6H_{11}	76
1d	Me	Pmb	Ph	C_6H_{11}	83
1e	CH_2Ph	Pmb	CH_2Ph	Pmb	45
1f	CH_2Ph	Pmb	Ph	Pmb	59
1g	CH_2Ph	Pmb	CH_2Ph	C_6H_{11}	80
1h	CH_2Ph	Pmb	Ph	C_6H_{11}	48

[a] Pmb = 4-Methoxybenzyl.

Cleavage of 1 with diluted TFA: synthesis of *N*-acyl-*N*-(4-methoxybenzyl)-α,α-dialkyl glycines 3

Adducts **1a**–**1h** were reacted at room temperature with 2% TFA in acetonitrile until the presence of starting material could no more be observed by thin layer chromatography. The reactions with α,α-dibenzyl glycine derivatives **1e**–**1h** required longer times to completion (9–36 hours) than those with the α,α-dimethyl analogues **1a**–**1d** (1.5–24 hours), the same applying to the cyclohexylamides **1c**,**1d**,**1g** and **1h** (4.5–36 hours) as compared to the corresponding 4-methoxybenzylamides **1a**,**1b**,**1e** and **1f** (1.5–9 hours). The differences correlate well with the bulkiness of the substituents at R^1 and R^4, respectively. The residue obtained by evaporation of the reaction solvent was taken up in aqueous sodium hydroxide and the pH adjusted to 1 to convert the sodium salt into the required acid. Work-up and purification by column chromatography in silica-gel afforded the *N*-acyl-*N*-alkylamino acids **3a**,**3b** and **3e** (from **1a** and **1c**,**1b** and **1d**, and **1e** and **1g**, respectively) in yields falling within the range 60–88% (Scheme 2, Table 2). In the case of **1f** the expected *N*,α,α-trialkyl glycine **3f** and the dibenzyl oxazolone **5f** were obtained in almost equal amounts, *i.e.* 47 and 44%, respectively, the latter being obtained by extracting the above sodium hydroxide solution with dichloromethane (DCM). With adduct **1h** the above two compounds were also obtained but the oxazolone was the major product (76%). This behaviour reveals the occurrence of two competitive reactions according to paths A and B of Scheme 2. While the reaction with **1f** required 7.5 hours to completion, that with **1h** needed as much as 36 hours; hence, when the reaction mixture was treated with base, in the latter case already a much larger amount of oxazolonium **2f** had decomposed into **4f** than it had in the former case. The positive charge at the nitrogen atom of cyclic intermediates **2** must facilitate the nucleophilic attack at the carbonyl group when they are treated with aqueous base and thus give the linear products **3**. This is not the case with compounds **4**, which are readily converted into the stable oxazolone **5f** by deprotonation with the base. The phenyl group at position 2 of the ring may stabilise the cyclic derivatives **4** and **5** by conjugation (Scheme 2) but help in destabilising intermediates **2** in which the bulky benzyl groups at the α-carbon atom already tend to assist elimination of the substituent at the nitrogen atom. Such assistance becomes obvious if one compares the behaviour of **1h** with its analogue **1d**, which has methyl instead of benzyl groups at the α-carbon atom; although cleavage of the latter requires as much as 24 hours for completion, in this case no oxazolone could be isolated and the expected open chain compound **3b** where the *N*-alkyl group is still present was obtained with a yield of 81% (path A of Scheme 2). To our knowledge, this was the first time an oxazolone was isolated by acidic cleavage of an amino acid amide bond, its structure being fully supported by IR and NMR spectroscopy, and also by mass spectrometry. It is noteworthy that this cyclic compound is stable in aqueous 6 M NaOH and that to hydrolyse it requires

Table 2 Cleavage of Ugi–Passerini adducts with diluted acid

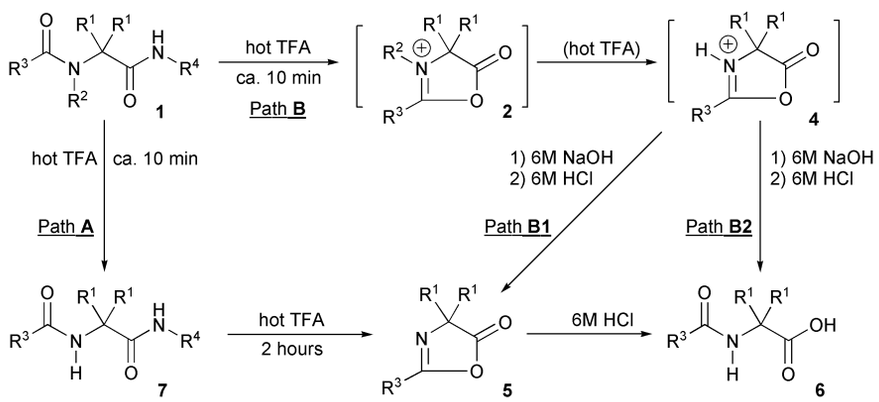
Reagent[a]	R^1	R^2	R^3	R^4	Reaction time/h[b]	Product	Yield (%)
1a	Me	Pmb	CH_2Ph	Pmb	1	**3a**	88
1b	Me	Pmb	Ph	Pmb	5	**3b**	84
1c	Me	Pmb	CH_2Ph	C_6H_{11}	2	**3a**	75
1d	Me	Pmb	Ph	C_6H_{11}	11	**3b**	81
1e	CH_2Ph	Pmb	CH_2Ph	Pmb	7	**3e**	60
1f	CH_2Ph	Pmb	Ph	Pmb	8	**3f**	47
						5f	44
1g	CH_2Ph	Pmb	CH_2Ph	C_6H_{11}	12	**3e**	70
1h	CH_2Ph	Pmb	Ph	C_6H_{11}	12	**3f**	15
						5f	76

[a] Reactions with TFA at a concentration of 2% and work-up with NaOH followed by acidification. [b] Measured when at least 95% of the reagent had been consumed as estimated by TLC.

Table 3 Cleavage of Ugi–Passerini adducts with neat TFA

Reagent	R^1	R^2	R^3	R^4	Product[a]	Yield (%)
1a	Me	Pmb	CH_2Ph	Pmb	**6a**	66
1b	Me	Pmb	Ph	Pmb	**6b**	59
1c	Me	Pmb	CH_2Ph	C_6H_{11}	**6a**	72
1d	Me	Pmb	Ph	C_6H_{11}	**6b**	70
1e	CH_2Ph	Pmb	CH_2Ph	Pmb	**6e**	95
1f	CH_2Ph	Pmb	Ph	Pmb	**5f**	79
					6f	9
1g	CH_2Ph	Pmb	CH_2Ph	C_6H_{11}	**6e**	80
1h[b]	CH_2Ph	Pmb	Ph	C_6H_{11}	**5f**	40
					6f	12
					7h	44
5f	CH_2Ph	—	Ph	—	**6f**	94
7h	CH_2Ph	H	Ph	C_6H_{11}	**5f**	72

[a] All reactions but that with **5f** were carried out with neat TFA followed by work-up with NaOH and acidification; the reaction with **5f** was carried out by boiling the substrate with 6 M HCl for 4 hours. [b] The results are for 10 minute reactions; in a 5 minute reaction the yields of **5f**, **6f** and **7h** were 42, 0 and 52%, respectively.



5f: $R^1 = PhCH_2$, $R^3 =$ Ph
6a: $R^1 =$ Me, $R^3 = PhCH_2$
6b: $R^1 =$ Me, $R^3 =$ Ph
6e: $R^1 = PhCH_2$, $R^3 = PhCH_2$
6f: $R^1 = PhCH_2$, $R^3 =$ Ph
7h: $R^1 = PhCH_2$, $R^3 =$ Ph, $R^4 = C_6H_{11}$

Scheme 3

boiling with semi-concentrated hydrochloric acid for 4 hours (Table 3). This seems to differ from what was found by Goodman and co-workers[6] when cleaving α,α-dimethyl glycine derivatives. In fact, although having postulated formation of an intermediate oxazolonium, these authors did not report having isolated either such an intermediate or its deprotonated derivative, suggesting that it would be readily converted into the corresponding acid by trace water. In the case of the α,α-dimethyl compounds **1a**–**1d** we were also unable to isolate an oxazolone, but our results with compounds **1f** and **1h** confirm Goodman's proposal and show that in these two compounds, the cyclic intermediate does not undergo ring opening even when treated with strong base.

Cleavage of 1 with neat TFA: synthesis of *N*-acyl-α,α-dialkyl glycines 6

Having been able to convert six of the above eight adducts **1** into the corresponding *N*-acyl-*N*,α,α-trialkyl glycines in good yields, we set out to obtain all corresponding *N*-acyl-α,α-dialkyl derivatives **6** by refluxing the above adducts with neat TFA (Scheme 3). By working up the reaction mixture with aqueous base the *N*-acylamino acids **6a**,**6b** and **6e** were obtained (from **1a** and **1c**,**1b** and **1d**, and **1e** and **1g**, respectively) in yields falling within the range 59–95% (Table 3). Compound **1f** gave the expected product **6f** in only very low yield (9%), the major product being oxazolone **5f** (79%); paths B2 and B1 of Scheme 3 depict these two competitive processes, respectively. With **1h** also only a small amount of **6f** (12%) was obtained, but two major products were isolated both exhibiting no alkyl group at the nitrogen atom, *viz*. oxazolone **5f** (40%) and the amino acid amide **7h** (45%); these two major products suggest the competitive cleavages depicted by paths A and B of Scheme 3. On boiling **7h** with neat TFA until no more starting material could be observed by TLC, which required 2 hours, and purifying the product solely by chromatography on silica gel, oxazolone **5f** was obtained with a yield of 72% instead of the expected oxazolonium trifluoroacetate. In order to confirm that this salt was decomposed in the chromatographic column, a genuine sample of oxazolone was treated with excess TFA and chromatographed through a silica gel column; the first fractions collected from the column contained the deprotonated compound, which was proved by a mixed melting point of the original material with the residue obtained from evaporation of the solvent. Goodman's results seem to indicate that scission of the amide bond *via* an oxazolonium intermediate would require an alkyl group at the nitrogen atom, whatever its role might be in inducing the conformation required for internal nucleophilic attack (by the N-terminal carbonyl oxygen atom to the carbonyl group at the C-terminus). However, conversion of amide **7h** into the oxazolone **5f** in high yield without any visible cleavage of the *N*-acyl group shows that with α,α-dibenzyl glycine derivatives (i) not only does such a requirement not apply any more but (ii) also the C-terminal amide bond is more labile than

that at the N-terminus, possibly because the bulky benzyl groups at the α-carbon atom induce the conformation that provides the proximity required for internal nucleophilic attack. This finding also corroborates the above mentioned competition, as the oxazolone obtained in 5 minute reactions with a yield of about 42% (Table 3, footnote to entry 1h) could not result solely from cleavage of amide **7h** (Path A, Scheme 3), which requires a much longer reaction time, but would be the product of cleavage of the *N*-alkyl group of oxazolonium **2** (Path B). Comparing with what was observed in the case of reactions in diluted TFA, in neat TFA the *N*-alkyl group of the bulkier *N*-benzoyl derivatives cleaves faster than their amide bond, which seems to indicate that the composition of the products of these reactions is kinetically controlled by the bulkiness of the substituents at R^1 and R^4, and by the concentration of acid.

Spectroscopic characterisation of oxazolone 5f and other α,α-dibenzyl glycine derivatives.

The α-carbon atom of symmetrical α,α-dialkyl glycines and their derivatives is always prochiral[10] and, thus, the two hydrogen atoms of each of the benzyl methylene groups are non-equivalent; as a result, separate absorption peaks for each of the two protons of either methylene group should be expected to be observed in the ^{1}H NMR spectra of these compounds. In practice, this results in two distorted doublets, one for each proton, with a pattern resembling an AB quartet. In DMSO-d_6 the two doublets are separated by 0.31 to 0.40 ppm in all *N*-(4-methoxybenzyl)-α,α-dibenzyl glycine derivatives **1e**–**1h**, close to 0.5 ppm in the *N*-acyl-α,α-dibenzyl glycines **6e** and **6f** and as much as 0.80 ppm in the *N*-benzoyl-α,α-dibenzylglycine cyclohexylamide **7h** (Fig. 1). However, the ^{1}H NMR spectrum of oxazolone **5f** shows the methylene proton absorptions as 4 peaks shaped as a very narrow AB-type pattern in which the absorption lines are separated by only as little as 0.02 ppm (Fig. 1). This almost isochronous behaviour seems to be typical of α,α-dibenzylglycine oxazolones, was reported for the first time thirty years ago[4] and is a reliable means of identifying these cyclic species. In all compounds, including **5f**, the coupling constant lay within −11.0 and −13.5 Hz, which is typical of a vicinal coupling. The IR spectrum of oxazolone **5f** showed typical stretching peaks for C=O and C=N bonds at 1815 and 1655 cm^{-1}, respectively; in addition, a high resolution electron impact mass spectrum showed a good agreement with the molecular weight expected for this compound. In the ^{1}H NMR spectra of some of the above α,α-dibenzylglycine derivatives recorded at 25 °C, the AB-type pattern for the methylene groups bonded to the α-carbon atom was not symmetrical as one would expect, but distorted with the doublet at higher field well resolved and the other very broad; nevertheless, when these spectra were inspected at 50 °C the broad doublet sharpened and the AB-type pattern became almost symmetrical (Fig. 2). This was observed with all *N*-acyl-*N*-(4-methoxybenzyl)-α,α-dibenzyl glycine amides **1e**–**1h** both in $CDCl_3$ and DMSO-d_6 but not with the oxazolone **5f** or the amide **7h** (Fig. 1), which showed always a symmetric pattern; the fully cleaved *N*-acyl-amino acids **6e** and **6f** also showed well resolved symmetric patterns in both solvents. However, for **3e** and **3f**, which are the partially cleaved analogues of compounds **6** above having a 4-methybenzyl group bonded to the nitrogen atom, the AB-type pattern was asymmetric in $CDCl_3$ and symmetric in the more polar DMSO-d_6 (Fig. 2), the separation of the two doublets falling within the range indicated above for compounds **1e**–**1h**. These effects suggest slow rotamer interconversion and the compounds where they were observed were those and only those having a substituent at the nitrogen atom of the α,α-dibenzyl glycine residue; somehow this correlates with the deviating behaviour towards acidic cleavage found with some of these compounds.

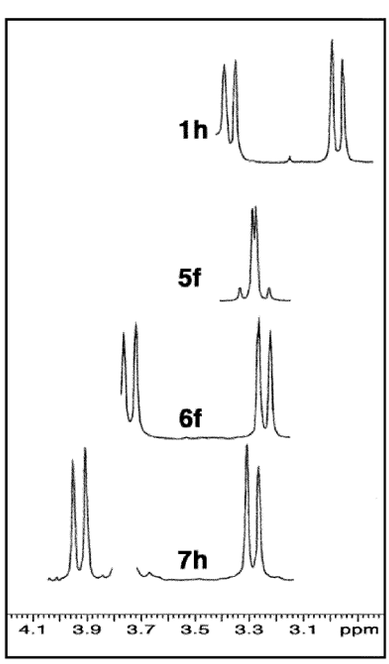


Fig. 1 Partial ^{1}H NMR spectra of **1h**,**5f**,**6f** and **7h** showing typical AB-type patterns for the benzyl methylene protons. The spectrum of **1h** was recorded at 50 °C, while the others were run at 25 °C.

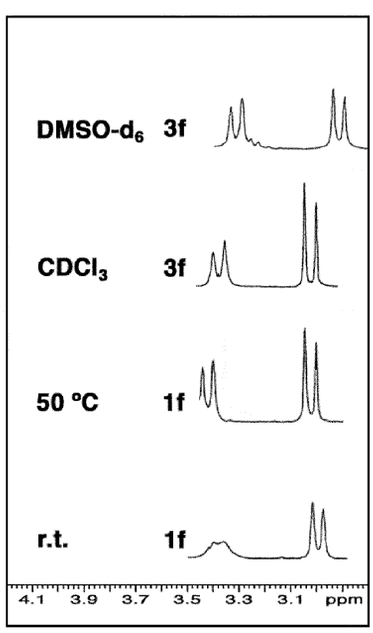


Fig. 2 Partial ^{1}H NMR spectrum of **1f** run in DMSO-d_6 at 25 °C showing an asymmetric AB-type pattern for the benzyl methylene protons, which sharpens and becomes almost symmetric at 50 °C, together with that of **3f** in $CDCl_3$ at 25 °C showing an also asymmetric AB-type pattern, which is almost symmetric in DMSO-d_6.

Conclusions

All α,α-dimethyl glycine Ugi–Passerini adducts exhibited a consistent pattern of behaviour according to which treatment with diluted TFA for several hours only cleaves their C-terminal amide bond, while boiling with neat TFA for 5 to 10 minutes cleaves the amide bond and also the *N*-alkyl group. A similar behaviour was observed with the *N*-phenylacetyl derivatives of α,α-dibenzyl glycine, but the *N*-benzoyl analogues behaved differently; with diluted TFA selective amide cleavage with regard to the *N*-alkyl group could not be fully accomplished, as the major product was a very stable oxazolone. To our knowledge such cyclic compound had never been obtained under these

circumstances and conditions; its formation supports Goodman's proposal[6] that amide cleavage is preceded by a cyclic intermediate. With neat TFA the same compounds behaved again differently, the bulkier yielding two major products, *viz*, oxazolone and *N*-acylamino acid amide, both of them exhibiting no 4-methoxybenzyl group at the nitrogen atom of the of α,α-dibenzyl glycine residue. The fact that the latter compound could also undergo amide cleavage on boiling with neat TFA under forcing conditions to give the oxazolone as the only product leads us to conclude also that (i) no *N*-alkyl group is necessary to assist selective amide cleavage within this compound, although for such purpose long reaction times are required, (ii) the oxazolone formed in the 5 minute reactions did not arise from the above amide but must have resulted directly from the Ugi–Passerini adduct, which indicates the occurrence of two competitive reactions, (iii) the apparently facilitated loss of the *N*-alkyl group from both above products suggests assistance by the two bulky benzyl groups at the α-carbon atom and (iv) formation of oxazolone under these circumstances also suggests assistance by the same groups in generating the conformation required for internal nucleophilic attack, which in the α,α-dimethyl glycine series seemed to require assistance also by the *N*-alkyl group. This was corroborated by the evidence of slow conformational interconversion observed in the NMR spectra of the *N*,α,α-tribenzyl glycine derivatives, which seems to be related to the presence of the methoxybenzyl group at the amino acid nitrogen atom.

Experimental

N-(4-Methoxybenzyl)-1,3-diphenyl-2-propanimine and 4-methoxybenzyl isonitrile were prepared as described elsewhere.[9] Acetone was freshly distilled after drying over $CaCl_2$. Methanol and toluene were dried by standard procedures. All other solvents and reagents, including cyclohexyl isonitrile, were used as obtained from commercial sources. TLC analyses were carried out on 0.25 mm thick pre-coated silica plates (Merck Fertigplatten Kieselgel $60F^{254}$) and spots were visualised under UV light or by exposure to vaporised 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}H NMR Spectra were recorded at 25 °C in ~5% $CDCl_3$ or DMSO-d_6 solution on a Varian 300 Unity Plus spectrometer; all shifts are given in δ ppm using δ_H Me_4Si = 0 and *J*-values are given in Hz, and assignments were made by comparison of chemical shifts, peak multiplicity and *J*-values. ^{13}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, HMBC and/or HMQC techniques. IR Spectra were run on a FTIR Perkin-Elmer 1600 spectrophotometer. Elemental analyses were carried out on a Leco CHNS 932 instrument. Comparison of compounds with genuine samples was carried out by mixed melting points.

General method 1: synthesis of Ugi–Passerini adducts (for compounds 1a–d)

Freshly distilled acetone (20 ml) was added to a flask, followed by anhydrous sodium sulfate (1 g) and 4-methoxybenzylamine (4.12 g, 0.03 mol). After stirring at room temperature for 15 min, the acid (0.03 mol) was added, which caused a large amount of a white solid to separate. After stirring for 10 min, the isonitrile (0.03 mol) was added. The reaction mixture was stirred in the dark at room temperature under nitrogen and monitored every day by TLC. When no more starting material could be observed, which required two to three weeks depending on the nature of the reagents, the solvent was evaporated and the residue taken up in methanol (200 ml). The mixture was filtered to separate the sodium sulfate and the filtrate concentrated to a small volume (50 ml) and set aside overnight at room temperature. The precipitate thus formed was collected by filtration and recrystallised from methanol-diethyl ether.

***N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dimethylglycine 4-methoxybenzylamide 1a.** The reaction was carried out on a 0.084 molar scale and **1a** (18.5 g, 48%) was isolated as a white solid, mp 119.4–119.6 °C. Anal. Found: C, 72.91; H, 7.07; N, 6.06. Calc. for $C_{28}H_{32}N_2O_4$: C, 73.02; H, 7.00; N, 6.08%.

***N*-Benzoyl-*N*-(4-methoxybenzyl)-α,α-dimethylglycine 4-methoxybenzylamide 1b.** The reaction was carried out on a 0.02 molar scale and **1b** (6.90 g, 77%) was isolated as a white solid, mp 64.4–65 °C. Anal. Found: C, 72.34; H, 6.82; N, 6.23. Calc. for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27%.

***N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dimethylglycine cyclohexylamide 1c.** The reaction was carried out on a 0.06 molar scale and **1c** (19.28 g, 76%) was isolated as a white solid, mp 168.4–169.8 °C. Anal. Found: C, 73.92; H, 7.91; N, 6.70. Calc. for $C_{26}H_{34}N_2O_3$: C, 73.90; H, 8.11; N, 6.63%.

***N*-Benzoyl-*N*-(4-methoxybenzyl)-α,α-dimethylglycine cyclohexylamide 1d.** The reaction was carried out on a 0.03 molar scale and **1d** (10.19 g, 83%) was isolated as a white solid, mp 140.3–140.8 °C. Anal. Found: C, 73.09; H, 7.68; N, 6.81. Calc. for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.89; N, 6.86%.

General method 2: synthesis of Ugi–Passerini adducts (for compounds 1e–h)

Freshly distilled *N*-(4-methoxybenzyl)-1,3-diphenyl-2-propanimine and the acid (0.055 mol) were added to a flask containing dry methanol (20 ml). After stirring at room temperature for 10 min to dissolve the acid, the isonitrile (0.055 mol) was added. The reaction mixture was stirred in the dark at room temperature under nitrogen for two to three weeks, after which the solvent was evaporated and the product chromatographed with silica, using the following eluents: DCM–hexane (1 : 2), DCM–hexane (1 : 1), neat DCM or DCM–methanol (50 : 1). The pure compounds were obtained by evaporation of the combined fractions.

***N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dibenzylglycine 4-methoxybenzyl amide 1e.** The reaction was carried out on a 0.0455 molar scale and **1e** (12.56 g, 45%) was isolated as a white solid, mp 90.4–91.0 °C. Anal. Found: C, 78.18; H, 6.51; N, 4.66. Calc. for $C_{40}H_{40}N_2O_4$: C, 78.41; H, 6.58; N, 4.57%.

***N*-Benzoyl-*N*-(4-methoxybenzyl)-α,α-dibenzylglycine 4-methoxybenzyl amide 1f.** The reaction was carried out on a 0.0455 molar scale and **1f** (16.0 g, 59%) was isolated as a white solid, mp 100.8–101.1 °C. Anal. Found: C, 78.20; H, 6.44; N, 4.77. Calc. for $C_{39}H_{38}N_2O_4$: C, 78.24; H, 6.40; N, 4.68%.

***N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dibenzylglycine cyclohexyl amide 1g.** The reaction was carried out on a 0.039 molar scale and **1g** (17.95 g, 80%) was isolated as a white solid, mp 87.3–87.9 °C. Anal. Found: C, 79.37; H, 7.63; N, 5.04. Calc. for $C_{38}H_{42}N_2O_3$: C, 79.41; H, 7.37; N, 4.87%.

***N*-Benzoyl-*N*-(4-methoxybenzyl)-α,α-dibenzylglycine cyclohexyl amide 1h.** The reaction was carried out on a 0.045 molar scale and **1h** (12.0 g, 48%) was isolated as a white solid, mp 100.9–101.5 °C. Anal. Found: C, 78.85; H, 7.07; N, 4.99. Calc. for $C_{37}H_{40}N_2O_3$: C, 79.25; H, 7.19; N, 5.00%.

General method 3: cleavage of Ugi–Passerini adducts with diluted TFA

The Ugi–Passerini adduct **1** was dissolved in dry acetonitrile, which was followed by addition of the amount of TFA

necessary to give a 0.02 M solution of substrate containing the acid at a concentration of 2%. This was kept at room temperature until TLC (eluent: dichloromethane–MeOH, 9 : 1) showed no more starting material (1.5–36 hours, depending on the substrate). The solvent was then evaporated at 30 °C and the residue taken up in 6 M NaOH (10 ml). In the case of compounds **1a**–**1g** about 30 min later the pH was adjusted to 1. Then, dichloromethane (DCM) (20 ml) was added and the aqueous layer extracted with DCM (2 × 15 ml). The combined organic layers were washed with brine (3 × 10 ml), and dried over anhydrous $MgSO_4$. This was removed by filtration and the filtrate concentrated under vacuum. The residue thus obtained was purified by column chromatography (DCM–MeOH, 50 : 1) to yield *N*-acylamino acids **3** by evaporation of the corresponding fractions. For compounds **1f** and **1h** the pH was first adjusted to 7 and the aqueous phase extracted with DCM; the combined extracts were dried over magnesium sulfate and concentrated to yield oxazolone **5f**. The pH of the aqueous layer was then adjusted to 1 and the work-up continued as described above for the other compounds.

***N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dimethylglycine 3a (from 1a and 1c).** Adduct **1a** (0.92 g, 2.0 mmol) gave compound **3a** (0.60 g, 88%) as a white solid, mp 168.6–169.2 °C. Anal. Found: C, 69.75; H, 6.82; N, 4.06. Calc. for $C_{20}H_{23}NO_4 \cdot ¼H_2O$: C, 69.45; H, 6.85; N, 4.05%. Compound **3a** (0.51 g, 75%) was also obtained from **1c** (0.85 g, 2.0 mmol).

***N*-Benzoyl-*N*-(4-methoxybenzyl)-α,α-dimethylglycine 3b (from 1b and 1d).** Adduct **1b** (0.89 g, 2.0 mmol) gave compound **3b** (0.55 g, 84%) as a white solid, mp 154.9–155.8 °C. HRMS (EI) calcd. for $C_{19}H_{21}NO_4$: 327.1471; found: 327.1460. Compound **3b** (0.53 g, 81%) was also obtained from **1d** (0.92 g, 2.0 mmol).

***N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dibenzylglycine 3e (from 1e and 1g).** Adduct **1e** (1.23 g, 2.0 mmol) gave compound **3e** (0.59 g, 60%) as a white solid, mp 158.2–159.2 °C. Anal. Found: C, 77.43; H, 6.47; N, 2.95. Calc. for $C_{32}H_{31}NO_4$: C, 77.87; H, 6.33; N, 2.84%. Compound **3e** (0.69 g, 70%) was also obtained from **1g** (1.15 g, 2.0 mmol).

***N*-Benzoyl-*N*-(4-methoxybenzyl)-α,α-dibenzylglycine 3f (from 1f and 1h).** Adduct **1f** (120 mg, 0.2 mmol) gave compound **3f** (45 mg, 47%) as a white solid, mp 154.6–155.4 °C. Anal. Found: C, 74.67; H, 6.47; N, 2.75. Calc. for $C_{31}H_{29}NO_4$: C, 74.83; H, 6.28; N, 2.82%. A large amount of oxazolone **5f** (30 mg, 44%) was also obtained, comparing well with a genuine sample as described below. Compound **1h** (112 mg, 0.2 mmol) gave only a small amount of **3f** (14 mg, 15%), the major product being oxazolone **5f** (52 mg, 76%).

General method 4: cleavage of Ugi–Passerini adducts with neat TFA

The Ugi–Passerini products **1** (1 g) were dissolved in neat TFA (5 ml) and refluxed for 10 min, which made the colour of the solution turn red. The acid in excess was evaporated and the residue taken up in 6 M NaOH. After stirring for 30 min, the white solid formed was filtered off and the filtrate extracted twice with Et_2O. In the case of compounds **1a**–**1g** the pH of the aqueous layer was adjusted to 1 to precipitate the corresponding product **6**, which was filtered off, washed with water and dried. For compounds **1f** and **1h** DCM was used instead of Et_2O and the pH first adjusted to 7. The aqueous phase was extracted with DCM, the combined extracts being dried over magnesium sulfate and concentrated. The residue was purified by column chromatography to yield compounds **5** and/or **7**. Then, the pH of the aqueous layer was adjusted to 1 and the work-up continued as described above for the other compounds.

***N*-Phenylacetyl-α,α-dimethylglycine 6a (from 1a and 1c).** Adduct **1a** (1.0 g, 2.2 mmol) gave the N-protected amino acid **6a** (0.32 g, 66%) as a white solid, mp 190.3–191.0 °C. Anal. Found: C, 65.17, H, 6.76, N, 6.45. Calc. for $C_{12}H_{15}NO_3$: C, 65.14, H, 6.83, N, 6.33%. Compound **6a** (0.38 g, 72%) was also obtained from **1c** (1.1 g, 2.4 mmol).

***N*-Benzoyl-α,α-dimethylglycine 6b (from 1b and 1d).** Adduct **1b** (1.0 g, 2.2 mmol) gave the N-protected amino acid **6b** (0.27 g, 59%) as a white solid, mp 197.3–198.0 °C. Anal. Found: C, 63.58; H, 6.29; N, 6.79. Calc. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76%. Compound **6b** (0.35 g, 70%) was also obtained from **1d** (1.0 g, 2.45 mmol).

***N*-Phenylacetyl-α,α-dibenzylglycine 6e (from 1e and 1g).** Adduct **1e** (1.0 g, 1.6 mmol) gave the N-protected amino acid **6e** (0.58 g, 95%) as a white solid, mp 210.6–211.6 °C. HRMS (EI) calcd. for $C_{24}H_{23}NO_3$: 373.1678; found: 373.1676. Compound **6e** (0.517 g, 80%) was also obtained from **1g** (1.0 g, 1.7 mmol).

***N*-Benzoyl-α,α-dibenzylglycine 6f (from 1f).** Adduct **1f** (1.0 g, 1.7 mmol) gave the N-protected amino acid **6f** (0.054 g, 9%) as a white solid, mp 208.6–209.2 °C. HRMS (EI) calcd. for $C_{23}H_{21}NO_3$: 359.1521; found: 359.1506. However, oxazolone **5f** (0.45 g, 79%) was the major product, comparing well with a genuine sample as described below.

***N*-Benzoyl-α,α-dibenzylglycine cyclohexylamide 7h (from 1h).** In a 10 minute reaction adduct **1h** (1.0 g, 1.8 mmol) gave compound **7h** (0.35 g, 44%) as a white solid, mp 205.9–206.8°C. Anal. Found: C, 77.74, H, 7.32, N, 6.33. Calc. for $C_{29}H_{32}N_2O_2 \cdot ½ H_2O$: C, 77.47, H, 7.40, N, 6.23%. Oxazolone **5f** (0.258 g, 40%) was also obtained together with a small amount of compound **6f** (0.077 g, 12%), both comparing well with genuine samples as they are described below. In a 5 minute repeat of this reaction no free acid **6f** was isolated, while compounds **5f** and **7h** were obtained in slightly better yields than above (42 and 52%, respectively).

Other preparations

2-Phenyl-4,4-dibenzyl-1,3(4*H*)-oxazol-5-one 5f

From 7h with neat TFA. Amide **7h** (0.11 g, 0.25 mmol) was refluxed with neat TFA for 2 hours after which the residue from evaporation of the solvent was taken up in 6 M NaOH (10 ml). Then, oxazolone **5f** (0.061 g, 72%) was isolated by the procedure described in general method 4 above as a white solid, mp 118.1–119.1 °C. HRMS (EI) calcd. for $C_{23}H_{19}NO_2$: 341.1416; found: 341.1413.

From 1f and 1h with 2% TFA. *Cf*. preparation of **3f** above by general method 3.

From 1f and 1h with neat TFA. *Cf*. preparation of **6f** above by general method 4.

N-Benzoyl-*N*-α,α-dibenzylglycine 6f (from 5f)

Oxazolone **5f** (100 mg, 0.29 mmol) was suspended in 10 ml of 6 M HCl and stirred at 100 °C for 4 h; the precipitate thus formed was separated by filtration, washed well with water and dried to give the open-chain product **6f** (98 mg, 94%), which compared well with a genuine sample as described above.

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