

# Four-component Condensation (Ugi Reaction) at High Pressure: Novel Synthesis of Peptides containing Very Bulky $\alpha,\alpha$ -Disubstituted Glycines

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Peptides, Z-Val-X-Gly-OMe, containing a very bulky  $\alpha,\alpha$ -disubstituted glycine, such as *N*-benzyl- $\alpha,\alpha$ -diisopropylglycine or *N*-benzyl- $\alpha,\alpha$ -diphenylglycine, as the residue X can be synthesized in moderate yields by four-component condensation (Ugi reaction) at high pressure (9 kbar, 0.9 GPa).

There has been increasing interest in the incorporation of  $\alpha,\alpha$ -disubstituted glycines (DSGs) into peptides, because of their particular role for the restriction of the conformational mobility of peptide backbones.<sup>1</sup> Synthesis of DSGs and their peptides provides challenging problems since steric hindrance associated with the quaternary  $\alpha$ -carbon atom of the DSG gives rise to difficulty in the conventional synthesis of their peptides.

The four-component condensation (Ugi reaction)<sup>2</sup> is relatively insensitive to steric hindrance<sup>3†</sup> and, thus, constitutes one of the most convenient methods for synthesis of DSGs and their peptides; indeed, several derivatives<sup>4</sup> and peptides<sup>5,6</sup> containing DSGs, such as  $\alpha,\alpha$ -dibenzyl- (Dbz), diethyl- (Deg), di-*n*-propyl- (Dpg), di-*n*-butyl- (Dbu) and diisobutylglycine (Dib) have been successfully prepared by this strategy. However, attempts to synthesize tripeptides possessing  $\alpha,\alpha$ -diisopropylglycine (Dip) and  $\alpha,\alpha$ -diphenylglycine (Dph) failed, probably because of extreme steric hindrance.<sup>5</sup> No attempt to prepare Dip itself has so far been successful,<sup>4,7</sup> although Dph is commercially available.<sup>‡</sup>

The application of high pressure offers the possibility of solving some problems in organic synthesis, particularly when the reactions are sluggish or do not occur at all under conventional conditions on account of steric hindrance.<sup>8</sup> We previously reported that sluggish peptide-forming reactions on sterically crowded derivatives of *N*-(carboxymethyl)amino acids were significantly accelerated by using high pressure.<sup>9</sup>

We now report the surprising results that yields of up to about 60% of the highly congested tripeptides **5** having Dip and Dph components were achieved when the modified Ugi reaction was performed at a high pressure of 0.9 GPa (9 kbar).

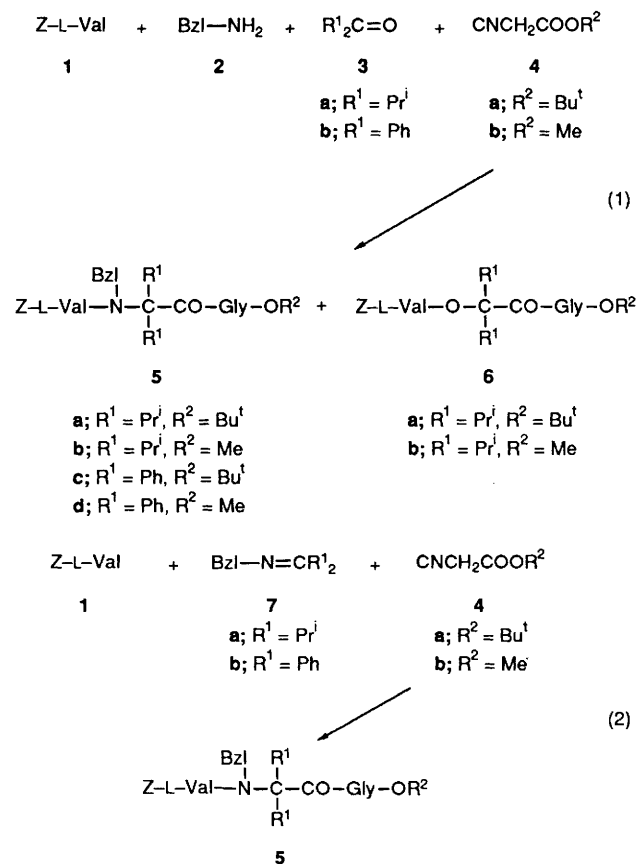
The reactions at high pressure were carried out in a Teflon capsule (4.5 ml capacity) containing Z-L-Val **1** (4.4 mmol), benzylamine **2** (4.4 mmol), ketone **3** (4.4 mmol), isocyanoacetate **4** (4.0 mmol) and dry methanol (4 ml) (Method A, eqn. 1), or **1**, Schiff's base **7**, **4**, and dry methanol or dichloromethane (Method B, eqn. 2), compressed in a stainless steel apparatus<sup>8a</sup> at ambient temperature for 14 days. After depressurisation, the reaction mixture was concentrated *in vacuo* to afford a crude product, which was chromatographically purified after usual washing and, if possible, was recrystallized. The results are summarized in Table 1.

In the reaction of **1**, **2**, diisopropyl ketone **3a** and *t*-butyl isocyanoacetate<sup>10</sup> **4a** (eqn. 1), three main products (*t<sub>R</sub>* in

**Table 1** Synthesis of tripeptides **5** containing  $\alpha,\alpha$ -disubstituted glycines (DSGs) by Ugi reaction at high pressure [equations (1) and (2)]<sup>a</sup>

Entry	<b>5</b>	DSG in <b>5</b>	Method <sup>b</sup>	Solvent	Isolated yield of <b>5</b> <sup>c</sup> (%)
1	<b>5a</b>	Dip	A	MeOH	4
2	<b>5b</b>	Dip	A	MeOH	6
3	<b>5b</b>	Dip	B	MeOH	37
4	<b>5b</b>	Dip	B	CH <sub>2</sub> Cl <sub>2</sub>	61
5	<b>5c</b>	Dph	A	MeOH	9
6	<b>5d</b>	Dph	B	MeOH	19
7	<b>5d</b>	Dph	B	CH <sub>2</sub> Cl <sub>2</sub>	63

<sup>a</sup> Conditions are not optimized. <sup>b</sup> Methods A and B are according to the reactions shown in eqn. 1 and 2, respectively. <sup>c</sup> **5a**, oil,  $[\alpha]_{\text{D}}^{27} -20.6^\circ$  (c 1.0, MeOH); **5b**, oil,  $[\alpha]_{\text{D}}^{25} -20.8^\circ$  (c 1.0, MeOH); **5c**, m.p. 184–185 °C,  $[\alpha]_{\text{D}}^{27} +0.8^\circ$  (c 1.0, CHCl<sub>3</sub>); **5d**, m.p. 126–127 °C,  $[\alpha]_{\text{D}}^{25} -16.0^\circ$  (c 1.0, CHCl<sub>3</sub>). All new compounds were characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and elemental analyses.



† For example, we have successfully prepared peptides containing  $\alpha,\alpha'$ -iminodicarboxylic acids by the Ugi reaction.<sup>3</sup>

‡ Note added in proof: Toniolo *et al.* have recently reported a conformational study of the Dph residue. They synthesized two dipeptides with the sequence Dph-Gly in low yields. See M. Crisma, G. Valle, G. M. Bonora, E. De Menego, C. Toniolo, F. Lelj, V. Barone and F. Fraternali, *Biopolymers*, 1990, **30**, 1.

HPLC§ 4.68, 8.27 and 10.68 min) were obtained in isolated yields of 15, 12 and 4%, respectively (entry 1). The products were determined to be **6b**, **6a** and **5a**, respectively, by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, elemental analyses and mass spectra. Compounds **6a** and **6b** are by-products formed by the Passerini reaction<sup>11</sup> in which benzylamine does not participate. Ugi *et al.* have mentioned that steric bulk in the components might lead to the Passerini reaction as a side reaction.<sup>12</sup> Interestingly, **6b** seems to be formed through the transesterification of the t-butyl ester **4a** or **6a** with methanol, although t-butyl esters are scarcely transesterified at atmospheric pressure. When **3a** and methyl isocyanoacetate **4b** were used, **5b** was obtained in a yield of 6%, **6b** predominating (46%) (entry 2). The corresponding Passerini products **6** could not be isolated in the reaction using benzophenone **3b** (entry 5).

Next, in order to suppress the Passerini reaction, Schiff's bases **7** prepared from **2** and **3** were used for the Ugi reaction in methanol (eqn. 2). As expected, no Passerini product was formed and yields of **5** improved (entries 3 and 6). However, when **7b** was treated with **1** and **4b** in methanol, the yield of **5d** was unexpectedly lower than that of **5b** (compare entry 6 with 3). This seems to be attributed to the low solubility in methanol of **7b**, which might crystallize out from the reaction mixture at high pressure.

Astonishingly, the yield of **5d** was improved up to 63% when a mixture of **1**, **7b** and **4b** was compressed in dichloromethane (entry 7). The reaction of **1**, **7a** and **4b** in dichloromethane also produced **5b** in markedly improved yield (61%) (entry 4). This is presumably due to a solvent effect related to the low polarity of dichloromethane. This suggests that charge separation may occur in the transition state of the Ugi reaction.<sup>13</sup>

§ HPLC conditions: column, Cosmosil 5C<sub>18</sub> (4.6 I.D. × 150 mm); mobile phase, 80% aq. MeOH; flow rate, 1.0 ml min<sup>-1</sup>; column temperature, 30 °C; detection, 254 nm.

In conclusion, the Ugi reaction at high pressure enables some peptides containing very bulky DSG units such as Dip and Dph, to be formed in significantly high yields.

We thank Dr. K. Saiki (Kobe Women's College of Pharmacy, Japan) for recording mass spectra.

Received, 14th August 1990; Com. 0/03742G

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