A one-pot three-component synthesis of β-nitro-α-amino acids and their *N*-alkyl derivatives

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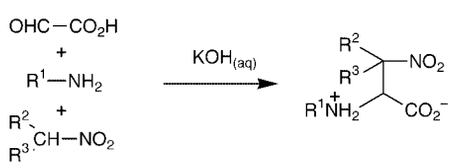
A water-based condensation of glyoxylic acid, nitroalkanes and amines is described, offering a straightforward synthesis of β-nitro-α-amino acids and their *N*-alkyl derivatives.

Multi-component reactions offer a number of advantages over other methods since they afford rapid syntheses of often complex compounds from relatively simple building blocks, frequently in one pot.[1] Syntheses *via* multi-component couplings, such as the Strecker and Ugi reactions,[2] provide access to a wide variety of amino acids. However, the initial products are generally protected amino acids and the methods require the use of undesirable or exotic reagents such as cyanide or alkylboronic acids.

β-Nitro amino acids have been studied as enzyme inhibitors[3] and as precursors in the synthesis of other classes of α-amino acids, such as β-amino and α,β-dehydro amino acids.[4,5] Some time ago we reported the multi-step synthesis of β-nitro amino acid derivatives through reaction of *N*-acyl-2-bromoglycine ester derivatives with the anions of nitroalkanes.[4,5] We now report a new procedure for the preparation of β-nitro amino acids and their *N*-alkyl derivatives, *via* a three-component condensation of glyoxylic acid, nitroalkanes and amines, in water [eqn. (1)]. This offers straightforward access to amino acids,

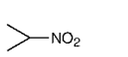
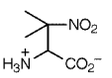
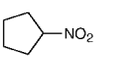
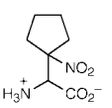
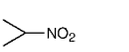
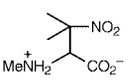
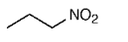
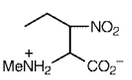
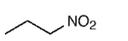
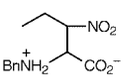
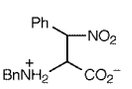


(1)

some of which are not available using methods previously reported.

The method involves separate addition of an aqueous ammonia solution, or an amine, and aqueous glyoxylic acid to a solution of a nitroalkane and potassium hydroxide in water, with stirring at room temperature, followed by acidification with aqueous hydrochloric acid to pH 2–4. Table 1 shows the generality of the method in the range of β-nitro amino acids and their *N*-alkyl derivatives prepared from four different nitroalkanes and three different amine components. The free amino acids **1** and **2** were obtained after a short work-up whilst products **3**–**6** containing *N*-alkyl groups precipitated from the reaction mixtures upon acidification and were isolated by filtration. Significantly, no chromatography was necessary, with analytically pure products being obtained directly from the reaction mixtures for products **3** and **4**, after re-crystallization for **2**, **5** and **6**, and after a short work-up and purification for **1**. Products **4** and **5** were isolated as *ca.* 1:6 and 1:2 diastereomeric mixtures, respectively, whilst **6** was isolated as a single diastereomer. Of particular significance are the *N*-alkyl derivatives **3**–**6** which are not attainable using the previously reported multi-step methodology.[4,5]

Table 1 Condensation of glyoxylic acid, nitroalkanes and amines in basic aqueous solution at room temperature

Nitroalkane	Amine (equivalents)	*t*/h	Product	Yield (%)
	NH_3 (10)	1	 **1**	50
	NH_3 (10)	1	 **2**	38
	$MeNH_2$ (5)	2	 **3**	54
	$MeNH_2$ (5)	1	 **4**	57
	$BnNH_2$ (1)	20	 **5**	41
$BnNO_2$	$BnNH_2$ (1)	2	 **6**	42

The mechanism of the three-component condensation presumably involves the *in situ* formation of imine intermediates[6] (from glyoxylic acid and ammonia and the amines) followed by Mannich-type addition of the alkyl nitronates.[7] Grieco and co-workers[8] have shown that a similar imine undergoes a Diels–Alder cycloaddition when methylamine, glyoxylic acid and cyclopentadiene are mixed in aqueous media. Confirmation that imines are intermediates in the present three-component condensation was obtained by exploiting the chemistry of Santaballa and co-workers.[9] They showed that under basic aqueous conditions *N*-chloroglycine decomposes *via* the corresponding imine. In the present work, treatment of glycine in base with sodium hypochlorite, to produce *N*-chloroglycine, in the presence of 2-nitropropane afforded β-nitrovaline **1**.

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The synthetic utility of both multi-component and aqueous reactions is generally well recognized[1,10] and is now further demonstrated by the synthesis of β-nitro amino acids and their *N*-alkyl derivatives on a multi-gram scale. The nitro group is a versatile functional group in synthetic organic chemistry as exemplified by the Henry, Michael and Nef reactions.[11] Therefore a wide range of other amino acids should also be accessible using this methodology.

Experimental

Synthesis of the β-nitro amino acids 1 and 2

For the synthesis of β-nitrovaline **1**, ammonia (25% in water, 75 ml, 1.1 mol) and glyoxylic acid (25% in water, 17 ml, 0.057 mol) were added to a solution of 2-nitropropane (9.8 g, 0.11 mol) and KOH (7.4 g, 0.13 mol) in water (140 ml). After stirring at room temperature for 1 h, the mixture was carefully adjusted to pH 1 with conc. 2 M HCl, washed with $CHCl_3$ (2 × 50 ml) and freeze dried. The solid residue was suspended in dry EtOH, the suspension was filtered and the filtrate was concentrated under reduced pressure. Et_2O was added and the resulting insoluble salts were removed by filtration. To the filtrate was added aniline (5 ml) and the mixture was allowed to stand at room temperature for 30 min. The solid was collected by filtration and washed with 1 : 1 EtOH–Et_2O to give β-nitrovaline **1** (4.66 g, 50%) as a white solid; mp 143–144 °C (lit.[4] 145–147 °C); δ_H(D_2O, 300 MHz) 4.23 (1H, s, C*H*), 1.68 (3H, s, CH_3), 1.63 (3H, s, CH_3). Compound **2** was obtained using a similar procedure, except that in this case concentrating the reaction mixture under reduced pressure and acidifying with 2 M HCl to approximately pH 4.5 resulted in the product precipitating from solution. It was isolated by filtration as a white solid and washed with 1 : 5 H_2O–EtOH; mp 128–129.5 °C; δ_H(D_2O, 300 MHz) 4.14 (1H, s, C*H*CO_2), 2.57–2.69 (1H, m), 2.25–2.37 (1H, m), 2.00–2.15 (2H, m), 1.60–1.85 (4H, m); δ_C(D_2O, 75.5 MHz) 172.9, 101.5, 63.1, 40.4, 39.1, 26.9, 26.6.

Synthesis of the *N*-alkyl β-nitro amino acids 3–6

The procedure employed for the synthesis of the *N*-alkyl amino acids **3**–**6** is illustrated by the synthesis of *N*-methyl-3-nitrovaline **3**. To a solution of 2-nitropropane (0.98 g, 0.011 mol) and KOH (0.74 g, 0.013 mol) in water (15 ml) was added methylamine (33% in EtOH, 5.0 ml, 0.055 mol) and glyoxylic acid (50% in water, 1.6 ml, 0.011 mol). After stirring at room temperature for 2 h the mixture was carefully adjusted to pH 3 with 2 M HCl and the resultant precipitate was collected by filtration to give *N*-methyl-3-nitrovaline **3** (1.06 g, 54%) as a white solid; mp 146–147 °C; δ_H(d_6-DMSO, 300 MHz) 3.61 (1H, s, C*H*CO_2), 2.31 (3H, s, NCH_3), 1.55 (3H, s, CH_3), 1.51 (3H, s, CH_3); δ_C(D_2O, 75.5 MHz) 170.8, 90.8, 71.2, 36.6, 27.9, 24.3. For *N*-methyl-2-amino-3-nitropentanoic acid **4**: *ca*. 1 : 6 mixture of diastereomers, mp 159–160 °C; the major diastereomer had δ_H(CD_3OD–DCl, 300 MHz) 5.15 (1H, ddd, *J* 2, 6 and 8.5 Hz, C*H*NO_2), 4.62 (1H, d, *J* 2 Hz, C*H*CO_2), 2.86 (3H, s, NCH_3), 2.40 (1H, ddq, *J* 8.5, 14.5 and 7.5 Hz, CH*H*CH_3), 2.10 (1H, ddq, *J* 6, 14.5 and 7.5 Hz, C*H*HCH_3), 1.12 (3H, t, *J* 7.5 Hz, CH_2CH_3); δ_C(CD_3OD–DCl, 75.5 MHz) 167.1, 87.6, 62.8, 33.9, 25.3, 11.0; separate resonances were detected for the minor isomer at δ_H(CD_3OD–DCl, 300 MHz) 2.88 (3H, s, NCH_3), 1.10 (3H, t, *J* 7 Hz, CH_2CH_3); δ_C(CD_3OD–DCl, 75.5 MHz) 167.4, 87.8, 62.6, 34.1, 25.4, 11.1. For *N*-benzyl-2-amino-3-nitropentanoic acid **5**: *ca*. 1 : 2 mixture of diastereomers, mp 129–131 °C; the major diastereomer had δ_H(CD_3OD–DCl, 300 MHz) 7.40–7.62 (5H, m, br, Ar), 5.29 (1H, ddd, *J* 2.5, 6 and 8.5 Hz, C*H*NO_2), 4.63 (1H, d, *J* 2.5 Hz, C*H*CO_2), 4.43 (2H, s, PhCH_2), 2.36 (1H, ddq, *J* 8.5, 14.5 and 7.5 Hz, C*H*HCH_3), 2.11 (1H, ddq, *J* 6, 14.5 and 7.5 Hz, CH*H*CH_3), 1.03 (3H, t, *J* 7.5 Hz, CH_3); δ_C(CD_3OD–DCl, 75.5 MHz) 167.1, 132–130, 88.0, 61.2, 60.3, 25.5, 11.2; separate resonances were detected for the minor diastereomer at δ_H(CD_3OD–DCl, 300 MHz) 5.20 (1H, ddd, *J* 4, 5 and 9 Hz, C*H*NO_2), 4.51 (1H, d, *J* 4 Hz, C*H*CO_2), 2.36 (1H, ddq, *J* 9, 15 and 7.5 Hz, C*H*HCH_3), 2.11 (1H, ddq, *J* 5, 15 and 7.5 Hz, CH*H*CH_3), 0.89 (3H, t, *J* 7.5 Hz, CH_3); δ_C(CD_3OD–DCl, 75.5 MHz) 167.4, 87.3, 61.0, 60.0, 24.0, 11.1. For *N*-benzyl-3-nitrophenylalanine **6**: mp 123–125 °C; δ_H(CD_3OD–DCl, 300 MHz) 7.38–7.51 (10H, m, br, 2 × Ar), 6.56 (1H, d, *J* 5 Hz, C*H*NO_2), 5.03 (1H, d, *J* 5 Hz, C*H*CO_2), 4.45 (1H, d, *J* 13 Hz, PhC*H*H), 4.37 (1H, d, *J* 13 Hz, PhCH*H*); δ_C(CD_3OD–DCl, 75.5 MHz) 166.9, 131.9, 131.8, 131.0, 131.0, 130.5, 130.2, 130.1, 129.7, 88.3, 61.3, 52.8. All new compounds were fully characterized.

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