From *N*-Nitroacetylproline to Leucylproline

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The potential of the nitroacetyl group in peptide synthesis has been demonstrated by converting *N*-nitroacetylproline ethyl ester into *cyclo*(L-Leu-L-Pro).

We previously reported[1] a simple and mild synthesis of nitroacetamides, including *N*-nitroacetyl-L-proline esters. We also indicated that these could serve as useful precursors for modified peptides. We now report the Pd^0-catalysed allylation of such a substrate, leading to moderate diastereoselectivity. We have also established the absolute configuration of the two diastereoisomers thus obtained. In the process, we have demonstrated for the first time the potential use of the nitroacetyl group as a synthetic equivalent of the glycyl anion synthon, since the nitro group could be easily converted in the final step to an amino group.

Pd^0 complexes are known to catalyse allylation of soft nucleophiles.[2] Allylation of nitroalkanes[3] and ethyl nitroacetate[4] by this procedure has been reported to give high yields under mild conditions. We have found that nitroacetylproline esters are equally good substrates for this reaction. The electrophile could be allyl acetate or a substituted allyl acetate, carbonate or even allyl chloride. Thus treatment of **1a** (10 mmol) in degassed MeCN with DBU† (10 mmol), $Pd(dba)_2$ (3 mol%) and dppe (6 mol%) under argon at 25 °C with cinnamyl acetate **2b** (10 mmol) for 10 h, followed by quenching at −20 °C with 5% aqueous HCl gave the product **3b** as a mixture of two diastereoisomers (Scheme 1). The diastereoisomeric excess (d.e.) was estimated by both ^1H and ^{13}C NMR spectroscopy (see Table 1). In view of the very high acidity of the methine proton in **3b** it seemed likely that the ratio of diastereoisomers was thermodynamically controlled. In order to check this, the pure major diastereoisomer‡ was isolated by chromatography (silica gel 60–120 mesh; light petroleum–ethyl acetate) and subjected to equilibration in ethanol in the presence of a catalytic amount of DBU (25 °C; 48 h). The final product, obtained after acidification, had a d.e. of 20 (as compared to a d.e. of 29 for the product obtained directly from the allylation reaction).

The effect of varying the ester group of proline on the diastereoselectivity of this reaction is shown in Table 1. Proline benzyl ester led to the best result with about 45% d.e.

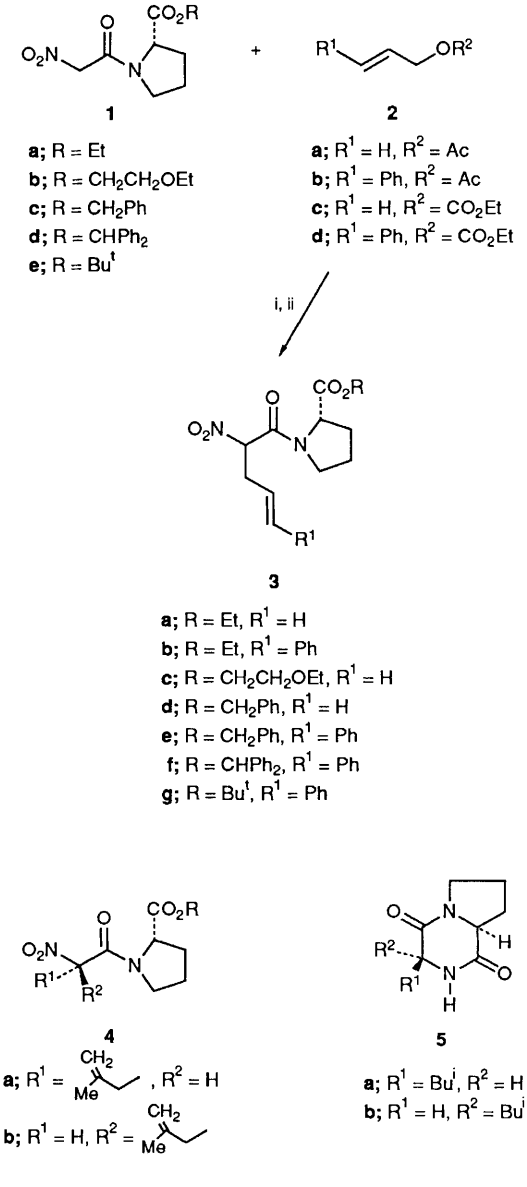
Table 1 Yield and diastereomeric excess of product **3**

Proline ester	Electrophile	Product	Yield (%)	D.e. (%)
1a	**2a**	**3a**	81	20
1a	**2b**	**3b**	63	29
1a	**2c**	**3a**	82	26
1a	**2d**	**3b**	62	22
1b	**2a**	**3c**	48	22
1c	**2a**	**3d**	55	35
1c	**2b**	**3e**	40	45
1d	**2b**	**3f**	40	26
1e	**2b**	**3g**	48	8

† DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; dba = dibenzylideneacetone; dppe = 1,2-bisdiphenylphosphinoethane.

‡ NMR data of **3b**: major diastereoisomer; ^1H: δ 1.27 (t, 3H, Me), 2.0–2.3 (m, 4H, $[CH_2]_2$), 3.0–3.25 (m, 2H, =C–CH_2), 3.7 (t, 2H, N–CH_2), 4.15–4.26 (qq, 2H, OCH_2), 4.56–4.6 (q, 1H, N–CH), 5.33 (dd, 1H, NO_2–CH), 6.13–6.23 (m, 1H, –CH), 6.58 (d, 1H, Ph–CH=) and 7.2–7.5 (m, 5H, ArH); ^{13}C: 13.89, 24.46, 28.83, 33.59, 47.36, 59.39, 61.15, 85.74, 121.57, 126.20, 127.57, 128.35, 134.84, 136.30, 161.77 and 170.97.

Allylation of **1a** with methylallyl chloride [DBU, 1 equiv.; $Pd(dba)_2$, 3 mol%; dppe, 6 mol%] gave the product **4** (yield 65%) as a mixture of two diastereoisomers (25% d.e.). The two diastereoisomers were separated by column chromatography (silica 60–120 mesh; light petroleum–ethyl acetate). The major isomer **4a** (TLC, light petroleum–ethyl acetate, 30 : 70; R_f 0.4) was subjected to catalytic hydrogenation (10% Pd on charcoal; amount of catalyst: 20% w/w of the substrate, 60 psi, MeOH). Under these conditions, the NO_2 group was reduced to NH_2, the terminal alkene was saturated, and the resultant dipeptide ester cyclised to the diketopiperazine, *cyclo*(Leu-Pro) **5**. The product corresponded to authentic *cyclo*(L-Leu-L-Pro) **5a** (m.p. 158–165 °C, HPLC: RCM C-18,



Scheme 1 *Reagents and conditions*: i, DBU, MeCN, $Pd(dba)_2$, dppe; ii, aq. HCl (5%), −20 °C

MeCN–H_2O, t_R 6.37 min)§ thus establishing the absolute configuration of the major diastereoisomer of **4** as *S,S*. Similarly, the pure minor diastereoisomer **4b** was subjected to catalytic hydrogenation to obtain *cyclo*(D-Leu-L-Pro) **5b** identical (m.p. 138–143 °C. HPLC: RCM C-18, MeCN–H_2O, t_R 6.17 min) with an authentic sample prepared by conventional methods from D-leucine and L-proline. An artificial mixture of the two diastereoisomeric diketopiperazines **5a** and **5b** was easily resolved under the above HPLC conditions. **4b** therefore has the *R,S* configuration.

§ Waters M6000A pumps with system controller Det. H-P 1050 MWD at 230 nm connected to H-P 3396A integrator. Col, RCM-C-18, 8 mm, 10 × 100 cm length, Solvent system (v/v): A: MeCN–H_2O (20 : 80), B: MeCN–H_2O (50 : 50), A to B in 10 min (linear); at B 10 min, flow rate 2 ml min^{-1}.

By extrapolation, one can expect that in all the mono-allyl derivatives **3** the major diastereoisomer would have the *S,S* stereochemistry (as in **4** R^1 = allyl, R^2 = H).

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