REACTION OF *rel*-(4*R*,5*R*)-4-BENZOYLAMINO-5-PHENYL-3-PYRAZOLIDINONE WITH ALIPHATIC 1,3-DICARBONYL COMPOUNDS. A 'RING SWITCH' SYNTHESIS OF *rel*-(2*R*,3*R*)-3-PHENYL-3-(PYRAZOLYL-1)ALANINE ESTERS

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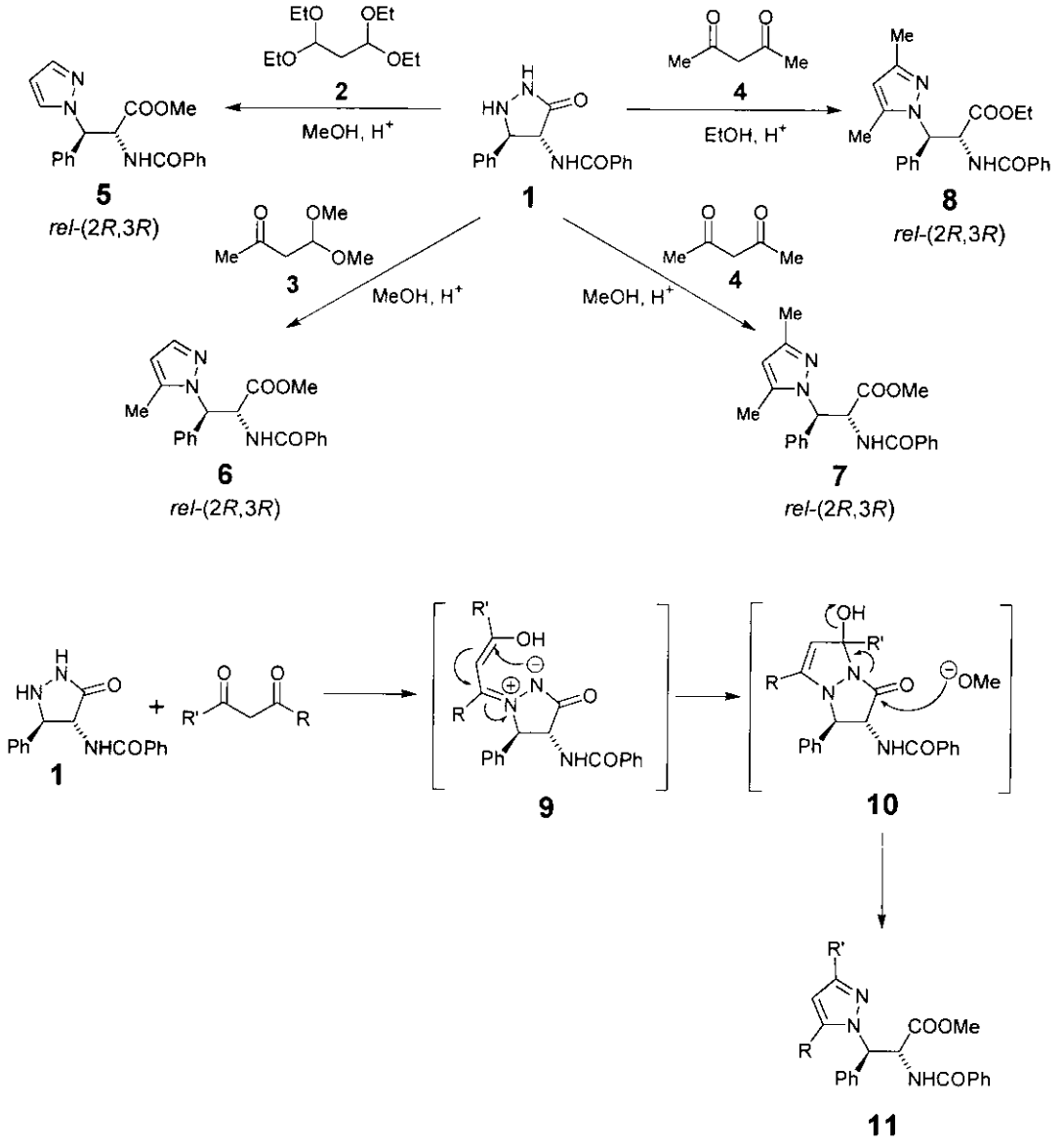
Abstract - *rel*-(2*R*,3*R*)-*N*-Benzoyl-3-phenyl-3-(pyrazolyl-1)alanine esters (**5-8**) were prepared by acid-catalysed treatment of *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**) with various aliphatic 1,3-dicarbonyl compounds (**2-4**).

In last few decades, several synthetic approaches for the preparation of heteroarylalanines have been developed.[1] Considerable attention has been paid to the synthesis of 3-(pyrazolyl-1)alanine (**1**), which was isolated from the semen of *Citrullus vulgaris* and was also used as constituent of highly potent renine inhibitors.[2,3] A 'ring switch' strategy, introduced by Young and coworkers, is a versatile synthetic method, since it enables the preparation of alanines with various heteroaryl residues.[4,5] Previously, we reported a preparation of various 3-heteroarylalanine esters and their homologs starting from aspartic acid, pyroglutamic acid, and substituted pyrazolo[1,2-*a*]pyrazolones.[5-10]

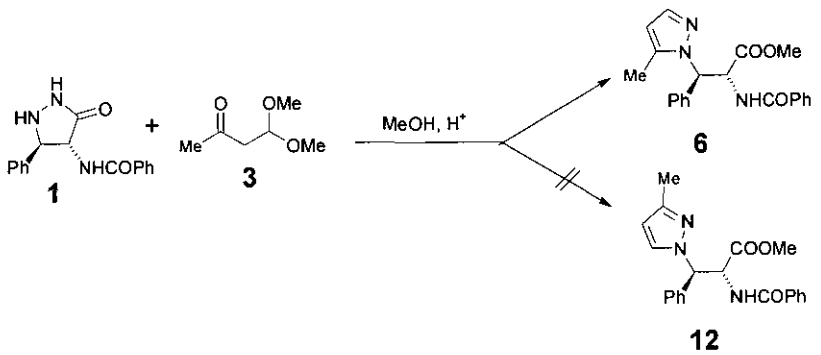
In continuation of our work in this field, we now report a novel one-step 'ring switch' preparation of *rel*-(2*R*,3*R*)-*N*-benzoyl-3-phenyl-3-(substituted pyrazolyl-1)alanine esters (**5-8**) from *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**). Thus, treatment of **1**, accessible in two steps from *N*-benzoylglycine,[11] with the following 1,3-dicarbonyl compounds: 1,1,3,3-tetraethoxypropane (**2**), 3-oxobutyraldehyde dimethyl acetal (**3**), and pentane-2,4-dione (**4**) in methanol in the presence of trifluoroacetic acid gave the corresponding *rel*-(2*R*,3*R*)-*N*-benzoyl-3-phenyl-3-(substituted pyrazolyl-1)alanine esters (**5-7**). Similar treatment of **1** with pentane-2,4-dione (**4**) in ethanol afforded the corresponding pyrazolylalanine ethyl ester (**8**). Reaction mechanism can be explained by initial formation of the corresponding azomethine imine (**9**) which is in equilibrium with non-dipolar bicyclic isomer (**10**). Intermediate (**10**) then undergoes nucleophilic attack of alcohol followed by elimination of water giving pyrazolylalanine derivative (**11**) as product. However, this proposed mechanism is only hypothetical, since we were so far not able to isolate any of the intermediates (**9**, **10**) (Scheme 1).

Scheme 1

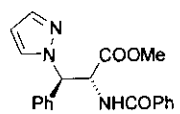
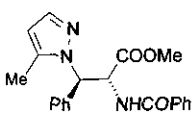
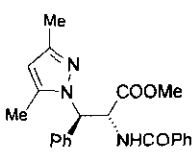


Structures of compounds (**5-8**) were confirmed by spectral characterisations and elemental analyses. Theoretically, the reaction of pyrazolidinone (**1**) with 3-oxobutyraldehyde dimethyl acetal (**3**) could give two isomeric products (**6**) or (**12**) with methyl group attached to the position 5 or 3 in the pyrazole residue, respectively. However, only *N*-benzoyl-3-(5-methyl-1-pyrazolyl)alanine methyl ester (**6**) was formed under these reaction conditions. The structure of the pyrazole residue in compound (**6**) was determined by ^{13}C NMR spectroscopy. The ^{13}C NMR chemical shifts for 3'-CH_3, 5'-CH_3, 3'-C, and 5'-C are in agreement with the literature data for parent pyrazole systems.[12,13] (Scheme 2).

Scheme 2



^{13}C NMR chemical shifts. δ (ppm)

Compound	3'-CH_3	5'-CH_3	3'-C	5'-C	Lit.
1-methylpyrazole	-	-	139.6	130.6	12a
1,3-dimethylpyrazole	13.9	-	148.8	131.0	12a
1,5-dimethylpyrazole	-	11.9	138.7	139.1	12a
1,3,5-trimethylpyrazole	14.0	11.7	147.5	139.8	12a
 **5**	-	-	140.3	130.4	this paper
 **6**	-	11.3	139.2	139.7	this paper
 **7**	14.2	11.2	148.0	140.4	this paper

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H NMR spectra and ^{13}C NMR spectra were obtained by Varian E-360 (60 MHz) and Bruker Avance DPX 300 (300 MHz) spectrometers with $CDCl_3$

as solvent and Me_4Si as internal standard. The microanalyses for C, H, and N were obtained on a Perkin-Elmer CHN *Anal*yser 2400. *rel*-(2*R*,3*R*)-4-Benzoylamino-5-phenyl-3-pyrazolidinone (**1**) was prepared according to the procedure described in the literature.[11]

***rel*-(2*R*,3*R*)-*N*-Benzoyl-3-phenyl-3-(pyrazolyl-1)alanine methyl ester (5).** A mixture of *rel*-(2*R*,3*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**) (1.405 g, 5 mmol), 1,1,3,3-tetraethoxypropane (**2**) (1.320 g, 6 mmol), methanol (20 mL), and trifluoroacetic acid (0.5 mL) was heated at reflux temperature for 2 h. The resulting solution was cooled, left to stand at 20° for 7 days, and the precipitate collected by filtration to give **5**; yield 1.081g (62%); mp 159-160°C (from methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (3H, s, OMe), 5.61 (1H, dd, *J* = 6.0, 7.9 Hz, 2-H), 6.03 (1H, d, *J* = 6.0 Hz, 3-H), 6.27 (1H, t, *J* = 2.1 Hz, 4'-H), 6.90 (1H, br d, *J* = 7.5 Hz, NH), 7.28-7.70 (12H, m, 10H-Ph, 3'-H, 5'-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 53.1, 56.8, 66.8, 106.34, 127.5, 127.9, 128.9, 129.0, 129.1, 130.4, 132.3, 133.9, 137.1, 140.3, 167.5, 170.8. *Anal*. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.38; H, 5.47; N, 11.83.

***rel*-(2*R*,3*R*)-*N*-Benzoyl-3-(5-methylpyrazolyl-1)-3-phenylalanine methyl ester (6).** A mixture of *rel*-(2*R*,3*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**) (1.405 g, 5 mmol), 3-oxobutyraldehyde dimethyl acetal (**3**) (0.792 g, 6 mmol), methanol (20 mL), and trifluoroacetic acid (1 mL) was stirred at 20° for 5 days. Volatile components were evaporated *in vacuo*, the residue triturated with ether (20 mL), and the precipitate collected by filtration to give **6**; yield 1.131 g (62%); mp 141-142°C (from *n*-heptane/benzene, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (3H, s, 5'-Me), 3.64 (3H, s, OMe), 5.52 (1H, dd, *J* = 6.0, 7.2 Hz, 2-H), 6.01 (1H, d, *J* = 6.0 Hz, 3-H), 6.03 (1H, m, 4'-H), 6.97 (1H, br d, *J* = 7.2 Hz, NH), 7.22-7.68 (11H, m, 10H-Ph, 3'-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.3, 52.9, 57.2, 62.6, 106.1, 127.4, 127.7, 128.4, 128.9, 129.0, 132.3, 134.0, 137.9, 139.2, 139.7, 167.6, 170.8. *Anal*. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.09; H, 5.62; N, 11.44.

***rel*-(2*R*,3*R*)-*N*-Benzoyl-3-(3,5-dimethylpyrazolyl-1)-3-phenylalanine methyl ester (7).** A mixture of *rel*-(2*R*,3*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**) (1.405 g, 5 mmol), pentane-2,4-dione (**4**) (0.600 g, 6 mmol), methanol (20 mL), and trifluoroacetic acid (1 mL) was stirred at 20° for 2 h. Volatile components were evaporated *in vacuo*, the residue triturated with ether (20 mL), and the precipitate collected by filtration to give **7**; yield 1.656 g (88%); mp 140-141°C (from methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08 (3H, s, 5'-Me), 2.25 (3H, s, 3'-Me), 3.65 (3H, s, OMe), 5.45 (1H, dd, *J* = 6.0, 7.0 Hz, 2-H), 5.80 (1H, br s, 4'-H), 5.90 (1H, d, *J* = 5.7 Hz, 3-H), 7.03 (1H, br d, *J* = 6.8 Hz, NH), 7.02-7.68 (10H, m, 10H-Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.2, 14.2, 52.8, 57.5, 62.4, 105.8, 127.4, 127.7,

128.2, 128.8, 129.0, 132.2, 134.2, 138.2, 140.4, 148.0, 167.6, 170.7. *Anal.* Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 70.00; H, 6.13; N, 11.49.

***rel*-(2*R*,3*R*)-*N*-Benzoyl-3-(3,5-dimethylpyrazolyl-1)-3-phenylalanine ethyl ester (8).** A mixture of *rel*-(2*R*,3*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**) (0.281 g, 1 mmol), pentane-2,4-dione (**4**) (0.600 g, 1.2 mmol), anhydrous ethanol (3 mL), and trifluoroacetic acid (0.2 mL) was heated at reflux temperature for 30 min. Volatile components were evaporated *in vacuo*, the residue triturated with ether (3 mL), and the precipitate collected by filtration to give **8**; yield 0.189g (48%); mp 142-143°C (from *n*-heptane). ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.08 (3H, t, J = 7.1 Hz, CH_3CH_2), 2.09 (3H, s, 5'-Me), 2.23 (3H, s, 3'-Me), 4.28 (2H, q, J = 7.2 Hz, CH_2CH_3), 5.52 (1H, t, J = 6.6 Hz, 2-H), 5.87 (1H, s, 4'-H), 5.99 (1H, d, J = 6.2 Hz, 3-H), 7.08-7.91 (11H, m, 10H-Ph, NH). *Anal.* Calcd for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.26; H, 6.55; N, 10.62.

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