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

Jurij Svete and Branko Stanovnik

Faculty of Chemistry and Chemical Technology, University of Ljubljana,
Aškerčeva 5, 1000 Ljubljana, Slovenia

Abstract - rel-(2R,3R)-N-Benzoyl-3-phenyl-3-(pyrazolyl-1)alanine esters (5-8) were prepared by acid-catalysed treatment of rel-(4R,5R)-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. 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. 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. 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. In continuation of our work in this field, we now report a novel one-step 'ring switch' preparation of rel-(2R,3R)-N-benzoyl-3-phenyl-3-(substituted pyrazolyl-1)alanine esters (5-8) from rel-(4R,5R)-4-benzoylamino-5-phenyl-3-pyrazolidinone (1). Thus, treatment of 1, accessible in two steps from N-benzoylglycine, 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 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).
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

![Chemical structure diagram](image)

<table>
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<th>Compound</th>
<th>3'-CH₃</th>
<th>5'-CH₃</th>
<th>3'-C</th>
<th>5'-C</th>
<th>Lit.</th>
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<td>-</td>
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<tr>
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<td>-</td>
<td>-</td>
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<td>130.4</td>
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**EXPERIMENTAL**

Melting points were taken on a Kofler micro hot stage. The ¹H NMR spectra and ¹³C NMR spectra were obtained by Varian E-360 (60 MHz) and Bruker Avance DPX 300 (300 MHz) spectrometers with CDCl₃.
as solvent and Me$_4$Si as internal standard. The microanalyses for C, H, and N were obtained on a Perkin-Elmer CHN Analyser 2400. _rel-(2R,3R)-4-Benzoylamino-5-phenyl-3-pyrazolidinone_ (1) was prepared according to the procedure described in the literature.$^{11}$

**rel-(2R,3R)-N-Benzoyl-3-phenyl-3-(pyrazolyl-1)alanine methyl ester** (5). A mixture of _rel-(2R,3R)-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°C for 7 days, and the precipitate collected by filtration to give 5; yield 1.081 g (62%); mp 159-160°C (from methanol). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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$_{23}$H$_{21}$N$_3$O$_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.38; H, 5.47; N, 11.83.

**rel-(2R,3R)-N-Benzoyl-3-(5-methylpyrazolyl-1)-3-phenylalanine methyl ester** (6). A mixture of _rel-(2R,3R)-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°C 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$_3$): $\delta$ 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 (12H, m, 10H-Ph, 3'-H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 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, 167.6, 170.8. Anal. Calcd for C$_{21}$H$_{21}$N$_3$O$_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.09; H, 5.62; N, 11.44.

**rel-(2R,3R)-N-Benzoyl-3-(3,5-dimethylpyrazolyl-1)-3-phenylalanine methyl ester** (7). A mixture of _rel-(2R,3R)-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°C 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$_3$): $\delta$ 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$_3$): $\delta$ 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_{3}O_{3}: C, 70.01; H, 6.14; N, 11.13. Found: C, 70.00; H, 6.13; N, 11.49.

**rel-(2R,3R)-N-Benzoyl-3-(3,5-dimethylpyrazolyl-1)-3-phenylalanine ethyl ester (8).** A mixture of *rel-(2R,3R)-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 0.189 g (48%); mp 142-143°C (from *n*-heptane). "H NMR (60 MHz, CDCl₃): δ 1.08 (3H, t, J = 7.1 Hz, CH₃CH₂), 2.09 (3H, s, 5'-Me), 2.23 (3H, s, 3'-Me), 4.28 (2H, q, J = 7.2 Hz, CH₂CH₂), 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_{3}O_{3}: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.26; H, 6.55; N, 10.62.

**ACKNOWLEDGEMENT**

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**REFERENCES AND NOTES**


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