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SYNTHESIS OF ETHYL *cis*- AND *trans*-4-CHLORO-5-OXO-1,2-DIPHENYL-PYRROLIDINE-2-CARBOXYLATE

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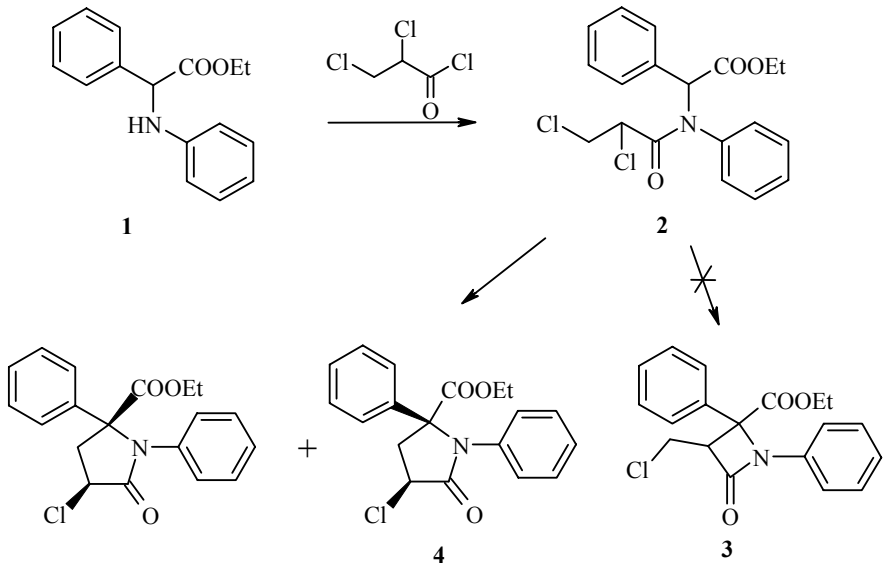
Ethyl cis- and trans-4-chloro-5-oxo-1,2-diphenylpyrrolidine-2-carboxylate have been synthesized by the cyclization of ethyl N-(α,β-dichloropropionyl)-N-phenyl-α-aminophenylacetate.

Keywords: α,β-dichloropropionyl chloride, 4-chloro-5-oxo-1,2-diphenylpyrrolidine-2-carboxylic acid, α-(phenylamino)phenylacetic acid, phenylacetic acid.

We have previously developed a method for the synthesis of 2-phenylproline derivatives involving the cyclization of the corresponding N-(β-chloropropionyl)-α-phenylglycines under phase-transfer catalytic conditions [1].

The 2-phenylproline derivatives prepared using this method can be included in a large group of non-nucleosidic compounds which are inhibitors of the enzyme of the reverse transcriptase virus in immunodeficient individuals (HIV-1) [2].



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With the aim of further functionalizing the pyrrolidine ring we have studied the possible cyclization of ethyl N-phenyl-N-(α,β-dichloropropionyl)-α-aminophenylacetate (**2**), which was prepared by the acylation of ethyl N-phenyl-α-phenylglycinate (**1**) [3] using α,β-dichloropropionyl chloride.

Under phase transfer catalytic conditions the cyclization does not form the β-lactam (**3**) but occurs regioselectively to form a mixture of the two stereoisomers of ethyl *cis*- and *trans*-4-chloro-5-oxo-1,2-diphenyl-pyrrolidine-2-carboxylate (**4**) in almost equal amounts. This is supported by the ^{1}H NMR spectrum which shows two sets of signals.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury-300 instrument (300 MHz) at 31°C and mass spectra on an MX-1321A instrument with an ionization energy of 70 eV. TLC was performed on Silufol UV-254 plates in the system acetone–hexane (1:1).

Ethyl N-(α,β-Dichloropropionyl)-N-phenyl-α-phenylglycinate (2). α,β-Dichloropropionyl chloride (1.6 g, 10 mmol) was added to a mixture of ester **1** [3] (2.55 g, 10 mmol), triethylamine (1.05 g, 10 mmol) and acetone (30 ml) at 0-5°C. Acetone was distilled off and the residue was diluted with ether (100 ml), washed with dilute HCl solution, then water, and dried over sodium sulfate. The ether was distilled off to give the ester **2**; mp 85-86°C (2-propanol). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 7.85-6.35 (10H, m, $2C_6H_5$); 5.99 (1H, s, CHN); 4.31-4.00 (4H, m, OCH_2, CH_2Cl); 3.74-3.57 (1H, m, CHCl); 1.29 (3H, t, CH_3). Found, %: C 59.73; H 5.18; Cl 18.81; N 4.00. $C_{19}H_{19}Cl_2NO_3$. Calculated, %: C 60.00; H 5.00; Cl 18.68; N 3.68. M^+ 379 (determined by mass spectrometry).

Ethyl *cis*- and *trans*-4-Chloro-5-oxo-1,2-diphenylpyrrolidine-2-carboxylate (4). A mixture of the ester **2** (3.8 g, 10 mmol), dry potassium carbonate (4.0 g, 30 mmol), triethylbenzylammonium chloride (0.12 g, 5 mmol), and acetonitrile (20 ml) was stirred for 4 h at 45-50°C. The reaction product was filtered, the filtrate evaporated, and the residue was dissolved in chloroform, washed with water, and dried over sodium sulfate. Chloroform was distilled off to give the ester **4** (2.9 g, 84%); mp 74-76°C (2-propanol), R_f 0.45 and 0.44. ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm (*J*, Hz): 7.36-7.02 (10H, m, $2C_6H_5$); 4.91 (0.5H, dd, *J* = 9.5 and 8.1, CHCl); 4.67 (0.5H, dd, *J* = 7.5 and 4.4 CHCl); 4.36-4.11 (2H, m, OCH_2); 3.43 (0.5H, dd, *J* = 13.5 and 8.3, CH_2); 3.32 (0.5H, dd, *J* = 14.0 and 7.4, CH_2); 3.04 (0.5H, dd, *J* = 14.0 and 4.3, CH_2); 2.82 (0.5H, dd, *J* = 13.5 and 9.6, CH_2); 1.19 (1.5H, t, *J* = 7.1, CH_3); 1.10 (1.5H, t, *J* = 7.1, CH_3). Found, %: C 66.12; H 5.38; Cl 10.52; N 4.12. $C_{19}H_{18}ClNO_3$. Calculated, %: C 66.38; H 5.24; Cl 10.33; N 4.08.

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