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STEREOSELECTIVE METHOD OF SYNTHESIS OF SUBSTITUTED trans-4,5-DIHYDRO-2-AMINOTHIOPHENES

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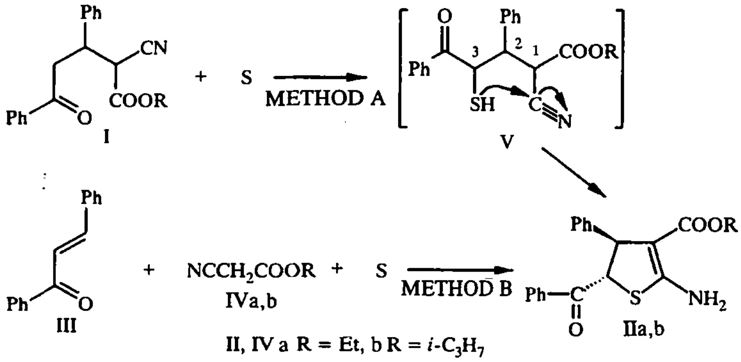
It is known that reaction of 2-aryl-3-aroyl-1,1-dicyanopropanes with elemental sulfur in the presence of base gives 4,6-diaryl-3-cyanopyridine-2(1H)-thiones [1].

We have shown, for the first time, that 1-alkoxycarbonyl-3-benzoyl-1-cyano-2-phenylpropane (I) reacts with elemental sulfur upon short refluxing in ethanol in the presence of triethylamine to form substituted trans-4,5-dihydro-2-aminothiophenes (II) (method A). The same compounds are obtained by a three component condensation of chalcone III, cyanoacetic ester IV, and sulfur without preliminary separation of compound I (method B).



The probable course of this reaction is an initial thiolation of the carbon atom C_3, and not C_1 as seen in the case of the corresponding dicyanopropanes [1]. Subsequent cyclization of the intermediate (V) gives compound II. The discovered reaction differs from the known Gewald reaction [2] in that the activator of CH acidity is the electron accepting PhCO group which is directly connected to the thiolated carbon atom C_3 and not the nitrile which is bound to the thiolating carbon through the two carbon atom. This makes possible the preparation of the hydrogenated thiophenes.

Trans-2-amino-5-benzoyl-4-phenyl-3-ethoxycarbonyl-4,5-dihydrothiophene (IIa). A. A mixture of compound I (1.6 g, 0.005 mole), sulfur (0.26 g, 0.008 mole) and piperidine (0.3 ml) in ethanol (10 ml) was refluxed for 1.5 h. The reaction mixture was filtered though a fluted filter, cooled to 20°C, and diluted with hydrochloric acid (5%, 5 ml). The precipitate was recrystallized from ethanol. Yield 1.2 g (68%), mp 183-185°C.

B. A mixture of chalcone III (1.04 g, 0.005 mole), compound IVa (0.57 g, 0.005 mole), and sodium ethylate (0.1 g) in ethanol (10 ml) was stirred at 20°C for 0.5 h. Sulfur (0.26 g, 0.008 mole) and piperidine (0.3 ml) were added and the work up continued as in method A. Yield 0.9 g (52%). IR spectrum (KBr): 3285, 3197 (ν NH_2), 1688 (C=O), 1645 (δ NH_2). PMR spectrum (DMSO-D_6): 1.02 (3H, t, CH_3 ^3J = 7.9 Hz); 3.93 (2H, q, CH_2, ^3J = 7.9 Hz); 4.84 (1H, d, 4-$H_{thiophene}$, ^3J = 0.8 Hz); 4.96 (1H, d, 5-$H_{thiophene}$, ^3J = 0.8 Hz); 7.24-7.92 ppm (12H, m, $(C_6H_5)_2$, NH_2). Found, %: C 67.74; H 5.18; N 3.48; S 9.45. $C_{20}H_{19}NO_3S$. Calculated, %: C 67.97; H 5.42; N 3.96; S 9.07.

Trans-2-amino-5-benzoyl-3-isopropyloxycarbonyl-4-phenyl-4,5-dihydrothiophene (IIb). Obtained similarly in propan-2-ol. Yield by method A 63% and by B 57%, mp 166-168°C. IR spectrum (KBr): 3274, 3185 (ν NH_2), 1685 (C=O), 1642 cm^{-1} (δ NH_2). PMR spectrum (DMSO-D_6): 1.02 (3H, d, CH_3, ^3J = 8.2 Hz); 1.08 (3H, d, CH_3, ^3J = 8.2 Hz); 3.95 (1H, m, CH); 4.85 (1H, d, 4-$H_{thiophene}$, ^3J = 1.1 Hz); 4.92 (1H, d, 5-$H_{thiophene}$, ^3J = 1.1 Hz); 7.22-7.95 ppm (12H, m, $(C_6H_5)_2$, NH_2); Found, %: C 68.32; H 5.44; N 3.46; S 8.97. $C_{21}H_{21}NO_3S$. Calculated, %: C 68.32; H 5.76; N 3.81; S 8.73.

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