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STUDY OF THE ORIENTATION OF THE THORPE–ZIEGLER REACTION

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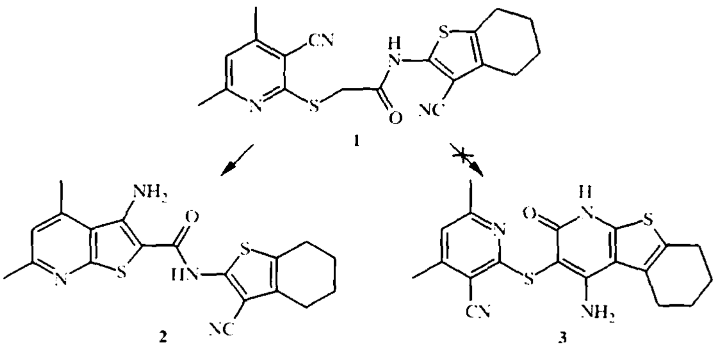
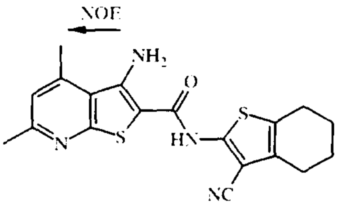
The Thorpe–Ziegler reaction is widely used in synthesis of heterocyclic compounds [1]. In particular, substituted amides of 3-aminothieno[2,3-*b*]pyridine-2-carboxylic acids [2] have been obtained by cyclization of amides of S-(3-cyanopyrid-2-yl)thioglycolic acid.

The objective of this work was to study the Thorpe–Ziegler reaction for the example of the model N-(3-cyano-4,5,6,7-tetrahydrobenzothiophen-2-yl)amide of S-(3-cyanopyrid-2-yl)thioglycolic acid (**1**), which contains two cyano groups and, in principle, may undergo ring closure with formation of five-membered or six-membered heterocycles (**2**,**3**).



We established that when the compound is boiled with an equivalent amount of KOH in ethanol, the reaction proceeds with formation of an annelated five-membered heterocycle. The structure of product **2** is confirmed by IR, ^{1}H NMR, and mass spectra. We decided between structures **2** and **3** on the basis of measurement of the nuclear Overhauser effect [3]. The intense water signal was saturated; as a result of rapid deuterium exchange, the saturation was transferred to the amino group [4]. As a result, we observed a change in the intensity of the signal from protons of the 4-CH_3 group. The appearance of such an effect is possible only for amide **2**.



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The rate of the Thorpe–Ziegler reaction is determined by the nucleophilicity of the CH groups and the electrophilicity of the CN group [1]. In the molecule of amide **1**, the CN group bonded to the pyridine ring probably is more electrophilic than the cyano group bonded to the thiophene ring, which probably also has the dominant effect on the orientation of the reaction.

Amide **1** is obtained by a procedure similar to that in [2]: mp 205-206°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.7 (4H, m, $2CH_2$); 2.4 (6H, d, $2CH_3$); 2.6 (4H, m, $2CH_2$); 4.3 (2H, s, CH_2–S); 7.1 (1H, s, CH); 11.9 (1H, br. s, NH). IR spectrum (KBr, ν, cm^{-1}): 3250, 3220, 3080, 2950, 2225, 1685, 1580, 1550, 1440, 1320, 1300, 1275, 1175. Found, %: C 59.57; H 4.77; N 14.59. $C_{19}H_{18}N_4OS_2$. Calculated, %: C 59.69; H 4.71; N 14.66.

3-Amino-4,6-dimethyl-2-[N-(4,5-tetramethylene-3-cyanothien-2-yl)carbamoyl]thieno[2,3-*b*]pyridine (2). A solution of compound **1** (0.76 g, 0.002 mol) and KOH (12 mg) was boiled in ethanol (40 ml) for 4 h, then the mixture was cooled; water (60 ml) was added and the precipitate was filtered off and then washed successively with water, alcohol, and hexane. Yield 0.72 g (95%); mp 286°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.75 (4H, m, $2CH_2$); 2.45 (3H, s, CH_3); 2.6 (4H, m, $2CH_2$); 2.75 (3H, s, CH_3); 7.1 (1H, s, CH). Mass spectrum (EI, *m/z*): 382 (M^+), 205, 177, 150. IR spectrum (KBr, ν, cm^{-1}): 3500, 3375, 3150, 2950, 2225, 1650, 1600, 1540, 1490, 1450, 1410, 1370, 1320, 1290, 1260. Found, %: C 59.60; H 4.75; N 14.61. $C_{19}H_{18}N_4OS_2$. Calculated, %: C 59.69; H 4.71; N 14.66.

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