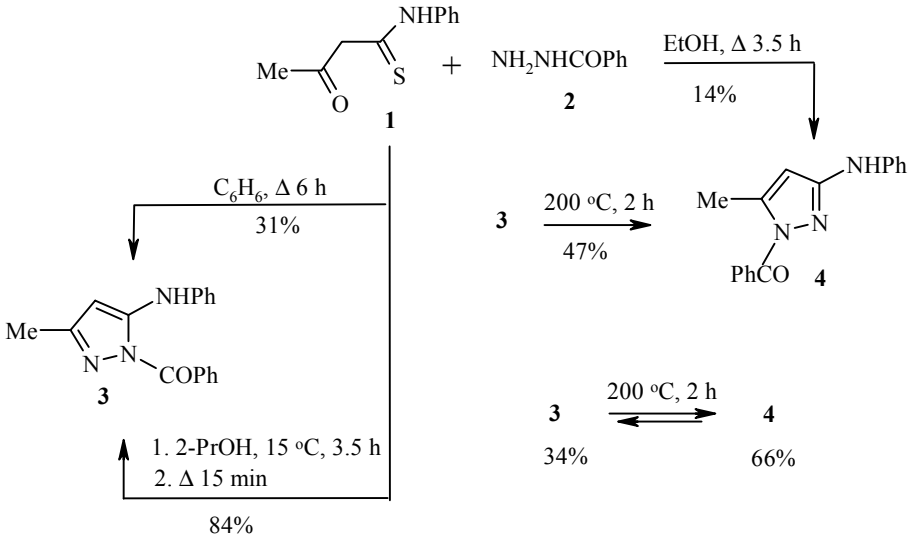
Chemistry of Heterocyclic Compounds, Vol. 38, No. 5, 2002

ACYLOTROPY IN THE CYCLOCONDENSATION OF ACETOTHIOACETANILIDE WITH BENZHYDRAZIDE

I. B. Dzvinchuk, S. A. Kartashov, A. V. Vypirailenko, and M. O. Lozinskii

Keywords: pyrazoles, acylotropy, isomerization, selectivity, cyclocondensation.

Borisevich and Pel'kis [1] found that acetothioacetanilide (**1**) reacts selectively with phenylhydrazine to give 5-anilino-3-methyl-1-phenylpyrazole. On the other hand, this reaction with benzoylhydrazine (**2**) gives a mixture of the expected 5-anilino-1-benzoyl-3-methylpyrazole (**3**) and its isomer, 3-anilino-1-benzoyl-5-methylpyrazole (**4**). Upon prolonged heating of the reagents in benzene at reflux, pyrazole **3** was isolated in low yield. Upon prolonged heating of the reagents in ethanol at reflux, pyrazole **4** was isolated in low yield [2].



The reasons for the nonselective reaction of reagents **1** and **2** according to Borisevich et al. [2] have not been examined. We offer the following explanation. Firstly, pyrazole **3** tends to rearrange to **4** due to migration of the benzoyl group between the nitrogen atoms of the pyrazole ring. Stabilization of **3** by intramolecular hydrogen bonding between the benzoyl group oxygen atom and the aniline fragment hydrogen atom does not hinder the acylotropic isomerization upon prolonged heating. Secondly, the benzoylhydrazone of acetothioacetanilide, which is initially formed in this reaction, has poor solubility. Hence, the cyclization of this

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 02094 Kiev, Ukraine; e-mail: iochkiev@ukrpack.net. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 703-705, May, 2002. Original article submitted November 19, 2001.

 0009-3122/02/3805-0618$27.00

initial product in benzene proceeds slowly. This behavior does not facilitate stopping of the reaction at the step involving formation of **3**. Thirdly, the formation of N-acylpyrazoles is complicated by their hydrazinolysis and, in ethanol, also by their alcoholysis.

A stepwise procedure for these reactions was found to be necessary for the selective synthesis of pyrazoles **3** and **4**. The reaction of **1** and **2** in 2-propanol without heating leads to the predominant formation of the benzoylhydrazone of **1**. Subsequent brief heating at reflux leads selectively to pyrazole **3**. At 200°C, **3** isomerizes to give **4**. This isomerization is an equilibrium process. ^{1}H NMR spectroscopy indicates that the equilibrium mixture contains about 66% of **4**. The same result was obtained in a separate experiment upon heating **4**. Isomer **4** was isolated predominantly upon crystallization of the melt from toluene. The yield can probably be increased if the solvent is removed from the filtrate by distillation and the residue is again brought to the equilibrium state by heating. Borisevich et al. [2] obtained **3** and **4** in yields of 31% and 14%, respectively. Our procedure permitted an increase in the yields of these products to 84 and 47%, respectively.

These results hold significance for optimizing the conditions for the synthesis of 3- and 5-arylamino-N-acylpyrazoles, which have been difficult to obtain.

5-Anilino-1-benzoyl-3-methylpyrazole (3). Samples of up to 5 mmoles of **1** and **2** in 2-propanol (5 ml) were stirred until the solution was homogeneous and then maintained for 3.5 h at 15°C. The suspension obtained was treated according to one of the procedures below.

A. The mixture was heated at reflux with shaking for about 15 min until homogeneous and then stirred until the onset of crystallization. The mixture was slowly cooled to 5°C. The precipitate was filtered off and washed with 2-propanol to give 1.17 g **3** (84%) as yellow crystals with mp 89-90.5°C (89-90°C [2]). IR spectrum in KBr pellet, ν, cm^{-1}: 1680 (C=O), 3370 (N–H). ^{1}H NMR spectrum (300 MHz, DMSO-d_6, TMS as the internal standard), δ, ppm: 2.14 (3H, s, CH_3); 6.08 (1H, s, 4-H); 7.00-7.38 (5H, m, C_6H_5N); 7.52-7.97 (5H, m, C_6H_5C=O); 9.33 (1H, s, NH).

B. The precipitate was removed from the suspension by filtration and the benzoylhydrazone of acetothioacetanilide (**5**) was obtained in 77% yield; mp 133-135°C (dec.). IR spectrum in KBr pellet, δ, cm^{-1}: 1670 (C=O), 3205, 3250 (N–H). Found, %: C 65.66; H 5.55; N 13.39; S 10.32. $C_{17}H_{17}N_3OS$. Calculated, %: C 65.57; H 5.50; N 13.49; S 10.30. Fusion of hydrazone **5** led to its decomposition with the release of H_2S and cyclization to pyrazole **3**, which was identical in melting point and thin-layer chromatographic behavior to the sample obtained using procedure A.

3-Anilino-1-benzoyl-5-methylpyrazole (4). A sample of **3** or **4** (5 mmol) was maintained for 2 h at 200°C. The melt was dissolved in toluene (5 ml). After cooling, the mixture was maintained for 10 min at 0°C. The precipitate was filtered off and washed with toluene to give 0.65 g **4** (47%) as yellow crystals with mp 124-126°C (118-119°C [2]). IR spectrum in KBr pellet, δ, cm^{-1}: 1670, 1680 (C=O), 3380 (N–H). ^{1}H NMR spectrum (300 MHz, DMSO-d_6, TMS as the internal standard), δ, ppm: 2.61 (3H, s, CH_3); 6.12 (1H, s, 4-H); 6.77-7.42 (5H, m, C_6H_5N); 7.52-7.99 (5H, m, C_6H_5C=O); 9.05 (1H, s, NH).

The authors express their gratitude to Aventis CropScience for financial support.

REFERENCES

1. A. N. Borisevich and P. S. Pel'kis, *Khim. Geterotsikl. Soedin.*, 312 (1969).
2. A. N. Borisevich, A. Sh. Bragina, V. P. Forsyuk, and V. I. Dombrovskaya, *Physiologically Active Compounds* [in Russian], Vol. 9, Naukova Dumka, Kiev (1977), p. 47.