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SYNTHESIS OF PYRAZOLO[1,5-*a*]-PYRIMIDINES BY REACTION OF 3,5-DIAMINO-4-NITROPYRAZOLE WITH ACETOACETIC ESTER IN THE PRESENCE OF ALKALINE AGENTS

V. A. Makarov, N. P. Solov'eva, O. B. Ryabova, and V. G. Granik

Two major compounds are formed in the reaction of 3,5-diamino-4-nitropyrazole with acetoacetic ester: 2-amino-5-methyl-3-nitro-4,7-dihydropyrazolo[1,5-a]pyrimidin-7-one and 3-amino-5-(β-hydroxycrotonyl)amino-4-nitropyrazole. The latter is converted to bicyclic dihydropyrazolo[1,5-a]-pyrimidinone in solutions with heating.

Keywords: nitropyrazole, acetoacetic ester, pyrazolopyrimidine, diketene.

Under acid catalysis conditions, 3,5-diamino-4-nitropyrazole (**1**) reacts smoothly with acetoacetic ester to form 2-amino-5-methyl-3-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-one (**2**) [1]. This paper is devoted to the study of this reaction in the presence of alkaline agents, since according to our data [2], for starting compound **1**, p*K*a = 8.48 and under these conditions it acts considerably like an anion, which might change the orientation and course of the condensation reaction. As the starting reagents, we used triethylamine in ethanol, sodium methoxide–MeOH (pyrazole **1**:MeONa ratio equal to 1:1, 1:3, and 1:5), potassium carbonate in DMF, and sodium hydride in DMF. Furthermore, the reaction was carried out with heating and without catalysts or solvent. The obtained reaction mixtures were studied by NMR spectroscopy. In all cases, after the process is complete, the mixture contains two major components in different ratios (see below for discussion of other minor reaction products). One of the reaction products is a bicyclic compound **2**, which spectral data and other physicochemical properties (after isolation) are identical to the substance obtained by using of acid catalysis [1, 2]. Generally, this compound predominates in the reaction mixture (an exception is the process using sodium methoxide in methanol). The ratio of bicyclic compound **2** to the second major component **3**, determined from ^{1}H NMR spectra, is presented in Table 1 for different reaction conditions.

At heating at 60-80°C or storage at 20°C of the solution of the analyte mixture (**2+3**) for a long time (7 days or more), an appreciable decrease in the content of component **3** with a simultaneous and corresponding increase in the amount of the bicyclic compound **2** was observed in the ^{1}H NMR spectra, i.e., compound **3** converts to bicycle **2**. At storage for more than a month at 20°C, only pyrazolo[1,5-*a*]pyrimidine **2** remains in solution. This process is considerably accelerated by heating of the analyte mixture. So in attempt to crystallize from DMF (160°C), exclusively pyrazolopyrimidine **2** was isolated; a similar effect was observed in the course of drying of the analyte mixture at 105°C for 6 h. Compound **3** could not be isolated in pure state, so its structure was analyzed in a mixture with pyrazolopyrimidine **2** using NMR spectroscopy (see Experimental). Some scatter in the values in the spectra for this compound is connected with different compositions of the analyte reaction mixtures **2** and **3**. In the ^{13}C NMR spectrum of the mixture (33% compound **2** and 67% compound **3**), along with signals of

State Science Center of the Russian Federation NIOPIK (Scientific Research Institute of Organic Intermediates and Dyes), Moscow 103787; e-mail: makar-cl@ropnet.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 73-77, January, 2000. Original article submitted November 17, 1998.

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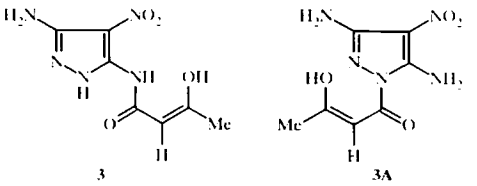
TABLE 1. Reaction Conditions and Ratio of Reaction Products **2/3** According to ^{1}H NMR Spectral Data

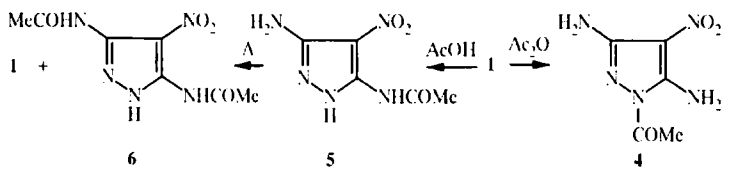
Solvent	Catalyst	Reaction temperature, °C	Reaction time	Ratio of reaction products 2/3	Spectrum recording conditions (T_{soln}/T_{record}, °C)
MeOH	HCl	56	3	1.00/0	[1]
EtOH	1 mol Et_3N	76	3	0.60/0.40	70/70
MeOH	1 mol MeONa	56	3	0.45/0.55	60/60
MeOH	3 mol MeONa	20	3	0.40/0.60	20/20
MeOH	5 mol MeONa	56	3	0.33/0.67	60/20
DMF	1.5 mol K_2CO_3	100	4	0.80/0.20	60/20
DMF	1.5 mol NaH	100	4	0.60/0.40	60/20
AAE		20	24	0.56/0.44	60/20
AAE		156	1	0.66/0.34	60/20

pyrazolo[1,5-*a*]pyrimidine **2** signals belonging to compound **3** were observed (the spectrum was taken with complete proton decoupling): 16.8 (narrow s), 103.7 (strongly broadened s), 108.4 (low-intensity s), 141.2 (broad s), 149.2 (narrow s), 153.1 (s), and 161.9 ppm (strongly broadened s). In the spectrum recorded without proton decoupling, the multiplicity is apparent only for signals at 16.8 ppm (q, CH_3) and 149.2 ppm (m), the signal of the carbon atom bonded to the CH_3 group. The multiplicity of the remaining ^{13}C signals could not be determined because of their strong broadening. Recording the ^{13}C NMR spectrum at 60-70°C, appreciable narrowing of the previously broadened signals occurs. The data presented, in particular the absence of signals from Et- and C=O ketone groups, restrict the discussion of possible structures to the following two alternatives:



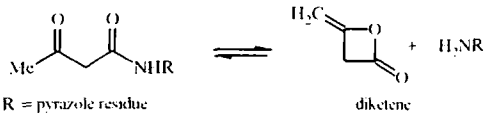
3 **3A**

It would seem that the conversion of compound **3** to **2** discussed above is evidence in favor of structure **3A** for the compound studied, but the spectral data are not consistent with this structure. First of all, a signal from the second NH_2 group (individually or in the form of a general signal of intensity 4H) is not observed in the ^{1}H NMR spectrum of this compound. Secondly, for structure **3A** it is difficult to explain the appreciable broadening of the signals of some carbon atoms observed in the ^{13}C NMR spectrum. At the same time, for structure **3** the broadening of some signals in the ^{13}C NMR spectra may be associated with amide isomerism of the moiety at the exocyclic nitrogen atom 5-NH. To clarify the situation, we needed to study the spectra of model compounds whose structure is similar to compounds **3** and **3A**, i.e., compounds having acyl groups at endo- and exocyclic nitrogen atoms. For this purpose, we studied acylation of 3,5-diamino-4-nitropyrazole **1**, whose reaction with acetic anhydride leads to isolation of the 1-acetyl derivative **4** in high yield, and upon acetylation by acetic acid we obtained a mixture consisting mainly of 5-acetylamino-3-amino-4-nitropyrazole (**5**) and the starting compound **1** (80:20).



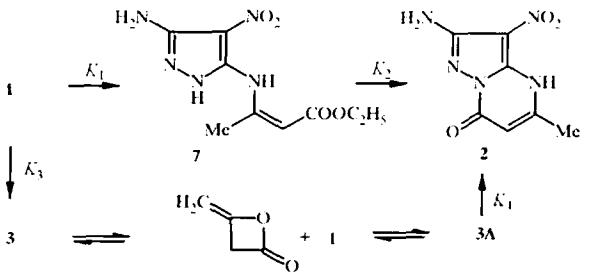
6 **5** **4**

The NMR spectroscopy data (see Experimental) suggests that upon 1-acylation, the unshared electron pair of the endocyclic nitrogen atom is included in the aromatic system, practically unconjugated with the C=O group, while amide isomerism is not realized and accordingly we do not see broadening of signals from the carbon atoms. We note an important point for further discussion. On heating of a mixture of compounds **5** and **1** with a predominance of **5** at ~100°C for 6 h, formation of 3,5-diacetylamino-4-nitropyrazole (**6**) (disproportionation) was observed, as established by ^{1}H NMR spectroscopy (δ $COCH_3$ = 2.14 ppm) and ^{13}C NMR spectra: 23.49 ($CO\underline{C}H_3$); 110 (strongly broadened s, $C_{(4)}$); 140 ppm (strongly broadened s, $C_{(3)}$, $C_{(5)}$). As follows from the spectral data for compounds **4** and **5**, compound **5** is very similar to pyrazole **3**; similarly to compound **5**, the latter typically exhibits amide isomerism and the related broadening of some signals of carbon atoms in the ^{13}C NMR spectrum. We also note the closeness of the signals of the $C_{(5)}$ carbon atoms for pyrazoles **3** and **5**: 141.2 and 139.8 ppm respectively, while for compound **4** the chemical shift of the $C_{(5)}$ atom is 149 ppm. So we have an unambiguous assignment of the carbon atom signals in compound **3** (see Experimental) and we can exclude the alternative structure **3A** as a possible second component of the mixture formed during reaction of diaminopyrazole **1** with acetoacetic ester. Obviously identification of the second component of the mixture as **3** creates a new problem: how does this compound convert to pyrazolopyrimidine **2**? This question can be answered to some extent by the disproportionation of compound **5** to **6** described above. In other words, in a similar system, cleavage of the acyl group from the exocyclic NH group is possible with its transfer to another position. A likely interpretation of the observed phenomenon involves the existence of an equilibrium of the type



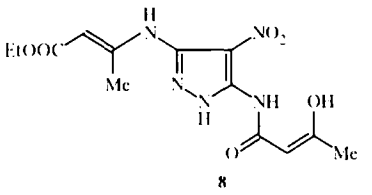
followed by addition of the diketene at the other position of the moiety R and a further irreversible cyclization step, which shifts the equilibrium toward the end product of the reaction. In the literature, data are available on the dissociation of acetoacetamides to the corresponding amines and ketenes (or diketenes) [3], but such decomposition was observed at 160°C or above. In our case, the process was observed even at room temperature, which possibly was promoted by the unusual amide component, the diaminonitropyrazole residue. As follows from the data presented, the process of conversion of compound **3** to **2** is sharply accelerated even by brief heating (for example, in an attempt at recrystallization of this mixture from DMF). We can suppose that this type of rearrangement occurs at a slower rate than the reaction of the acetoacetic ester condensation with compound **1** followed by cyclization, as we discussed for the case of acid catalysis in [1].

The most likely proposed scheme for the process under study, in our opinion, includes two parallel directions for reaction of diaminopyrazole **1** with acetoacetic ester, leading ultimately to the same result – bicyclic pyrazolopyrimidine **2**.



In this case, $K_2 \gg K_1$, which is the reason for the absence of intermediate **7** in the reaction mixture. At the same time, K_3 is somewhat smaller than K_1, and the formation of compound **2** is predominant, but $K_3 > K_4$, and consequently compound **3** can be identified in the mixture.

In conclusion, we turn to the question of the mixture obtained in the reaction of compound **1** with acetoacetic ester in the presence of sodium hydride. In this case, in addition to the signals of compound **2** (50%) and **3** (30%), in the ^{1}H NMR spectrum of the reaction mixture there are signals of compounds **8** (9%) and **9** (11%). As follows from the spectral data, these compounds are formed upon further condensation of acetoacetic ester at the second amino group of compounds **3** and **2**.



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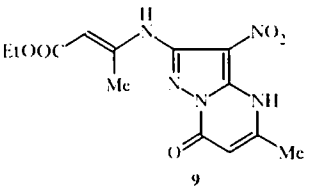

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Evidence in favor of this hypothesis comes first of all from the fact that such a compound was isolated earlier [1] and secondly, signals of additional CH_3 and =CH groups: 2.47 (3H, br. s, CH_3); 6.36 (1H, br. s, =CH) for **8** and 2.39 (3H, d, CH_3); 6.04 ppm (1H, q, =CH) for **9** and signals of O-ethyl groups: 1.10 (3H, t, CH_3) and 4.10 ppm (2H, q, CH_2) are observed in the ^{1}H NMR spectra. At keeping of the solution, the enamine moieties are hydrolyzed with formation of compounds **3** and **2** and acetoacetic ester, and then a correspondence between the spectra of the solution and the bicycle **2** is observed, i.e., sequential conversion of compound **8** to **3** and then to **2** occurs, and then conversion of **9** to **2**, which is quite consistent with the data presented above.

EXPERIMENTAL

The NMR spectra were recorded on an Oxford Unity-400 spectrometer, internal standard TMS. The mass spectra were obtained on a Finnigan SSQ-700 spectrometer with direct injection of the material into the ion source. The purity of the materials and the course of the reactions were monitored by TLC using Fluka TLC-Cards Silicagel 60778 plates.

2-Amino-5-methyl-3-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-one (2) and 3-Amino-5-(β-hydroxycrotonyl)amino-4-nitropyrazole (3). A. (In the presence of a basic catalyst). The calculated amount of the alkaline agent (see Table 1) was added to a suspension of 3,5-diamino-4-nitropyrazole **1** (1.0 g, 7 mmol) in the appropriate solvent (30 ml), and, after dissolving, acetoacetic ester (6.2 ml, 21 mmol) was added. The reaction mass was boiled (see Table 1) until disappearance of the bright red color typical for 3,5-diamino-4-nitropyrazole **1**. Then the mixture was cooled down to room temperature and neutralized with 10% aqueous hydrochloric acid. The bright yellow precipitate (a mixture of compounds **2** and **3**) was filtered and washed with water and ether.

B. (Without catalyst). A suspension of 3,5-diamino-4-nitropyrazole **1** (1.0 g, 7 mmol) in acetoacetic ester (20 ml) was held under the conditions indicated in Table 1. The reaction mass was cooled and diluted with methanol. The bright yellow precipitate (a mixture of compounds **2** and **3**) was filtered out. The yields, calculated on the basis of 2-amino-5-methyl-3-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-one **2**, were 90-95%. The mother liquors in some cases were evaporated and studied by ^{1}H NMR spectroscopy. In this case, the ratio of compounds **2** (the physicochemical characteristics and spectral data of pyrazolopyrimidine **2** completely match those described in [1]) and **3** did not differ from their ratio in the isolated dry mixture. M^+: 209 and 227. ^{1}H NMR spectrum for compound **3** (DMSO-d_6): 2.43-2.47 (3H, s, CH_3); 6.22-6.30 (1H, s, =CH); 6.60-6.83 ppm (2H, br. s, NH_2). ^{13}C NMR spectrum for compound **3** (DMSO-d_6): 16.8 (CH_3); 103.7 (CH); 108.4 ($C_{(4)}$); 141.2 and 149.2 ($C_{(3)}$ and $C_{(5)}$); 153.1 (C–OH); 161.9 ppm (C=O).

1-Acetamido-3,5-diamino-4-nitropyrazole (4). A suspension of pyrazole **1** (1.0 g, 7 mmol) in acetic anhydride (10 m) was stirred at ~20°C for 20 min and then a yellow crystalline material (1.0 g, 78%) was filtered out; mp 176-78°C (DMF–water). M^+ 185. ^{1}H NMR spectrum (DMSO-d_6): 2.41 (3H, s, $COCH_3$); 8.40 and 8.50 (two equal intensity 1H, br. s, 5-NH_2); 6.39 ppm (2H, s, 3-NH_2). ^{13}C NMR spectrum (DMSO-d_6): 23.55 (CH_3); 108.5 ($C_{(4)}$); 148.8 and 149.8 ($C_{(3)}$ and $C_{(5)}$); 173.5 ppm (C=O). Found, %: C 32.54; H 3.78; N 37.54. $C_5H_7N_5O_3$. Calculated, %: C 32.43; H 3.78; N 37.83.

3-Acetamido-5-amino-4-nitropyrazole (5) and 3,5-Diacetamido-4-nitropyrazole (6). A suspension of pyrazole **1** (1.0 g, 7 mmol) in acetic acid (20 ml) was boiled for 2 days; after evaporation of the reaction mass, a mixture of pyrazoles **1**, **5**, and **6** was obtained. The mixture was studied by NMR spectroscopy. M^+ 185 and 227. ^1H NMR spectrum for compound **5** (a mixture of compounds **5** and **1** with predominance of **5**) (DMSO-d_6): 2.06 (3H, s, $COCH_3$); 7.05 (2H, s, $3NH_2$); 8.06 (1H, br. s, NHCO), 11.60 ppm (1H, strongly br. s, ring NH). ^{13}C NMR spectrum for compound **5** (DMSO-d_6): 23.6 (CH_3); 111.2 (strongly broadened low-intensity s, $C_{(4)}$); 139.8 (strongly broadened, $C_{(5)}$); 148.1 ($C_{(3)}$), 169.5 ppm (strongly broadened, CON). ^1H NMR spectrum for pyrazole **6** (DMSO-d_6): 2.14 ppm (3H, s, $COCH_3$) and ^{13}C NMR spectrum (DMSO-d_6): 23.49 (s, $CO\underline{C}H_3$); 110 (strongly broadened s, $C_{(4)}$); 140 ppm (strongly broadened s, $C_{(3)}$ and $C_{(5)}$).

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