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CONDENSATION OF 5-AMINOPYRAZOLES UNSUBSTITUTED IN POSITION 1 WITH β-KETO ESTERS

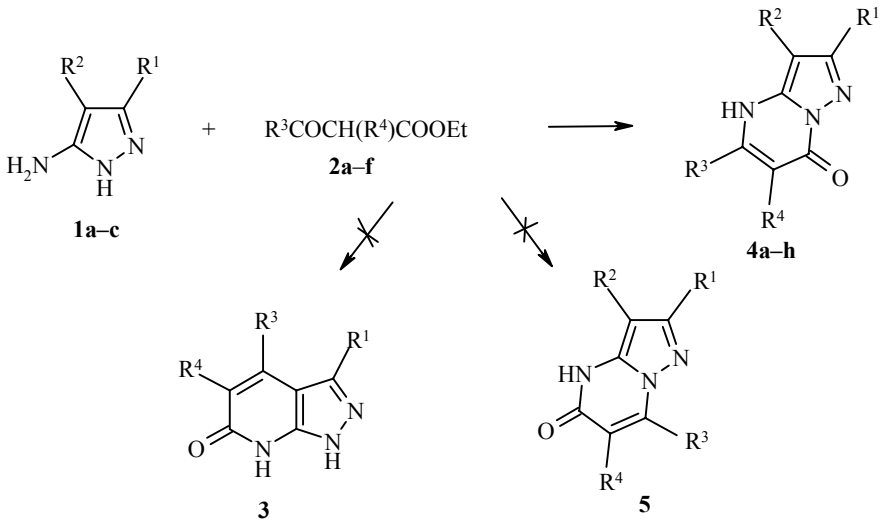
N. L. Nam, I. I. Grandberg, and V. I. Sorokin

Condensation of β-keto esters with 5-aminopyrazoles unsubstituted in position 1 gives 7-oxopyrazolo[1,5-a]pyrimidines.

Keywords: 5-aminopyrazoles, β-keto esters, pyrazolopyrimidones.

S. Checchi and coworkers investigated in 1955 [1] the condensation of 5-amino-3-phenylpyrazole with acetoacetic ester and, without evidence, assigned the structure of the product as 7-oxopyrazolo[1,5-*a*]pyrimidine (see below, structure type **5**).

We have previously reported [2] that the condensation of 5-aminopyrazoles **1** (unsubstituted in position 1) with symmetrical β-diketones gives pyrazolo[1,5-*a*]pyrimidines **4**. Only in the case of hexafluoroacetylacetone did the condensation occur *via* another route to give the pyrazolo[4,5-*b*]pyridine **3**.



1 a R^1 = Me, R^2 = H; **b** R^1 = Et, R^2 = Me; **c** R^1 = Ph, R^2 = H; **2 a** R^3 = Me, R^4 = H; **b** R^3 = Me, R^4 = Et; **c** R^3 = Me, R^4 = CH_2COOEt; **d** R^3 = CF_3, R^4 = H; **e** R^3 = Ph, R^4 = H; **f** R^3 = Me, R^4 = $HOCH_2CH_2$. **4 a** R^1 = R^3 = Me, R^2 = R^4 = H; **b** R^1 = Et, R^2 = R^3 = Me, R^4 = H; **c** R^1 = Ph, R^2 = R^4 = H, R^3 = Me; **d** R^1 = R^3 = Me, R^2 = H, R^4 = CH_2COOEt; **e** R^1 = Me, R^2 = R^4 = H, R^3 = Ph; **f** R^1 = R^3 = Me, R^2 = H, R^4 = Et; **g** R^1 = R^3 = Me, R^2 = H, R^4 = $HOCH_2CH_2$; **h** R^1 = Et, R^2 = Me, R^3 = CF_3, R^4 = H

K. A. Timiryazev Agricultural Academy, Moscow 127550, Russia; e-mail: interbioscan@mtu-net.ru.
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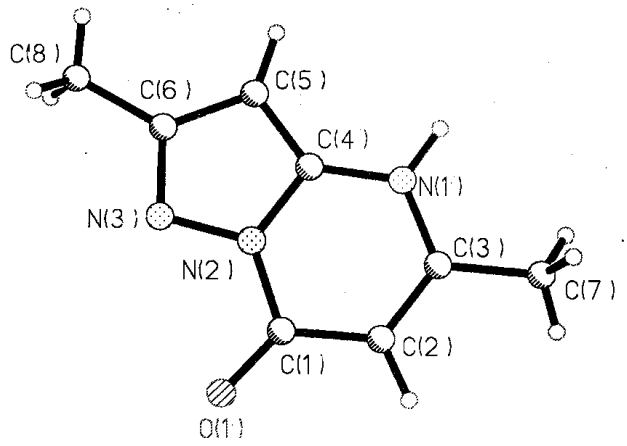

Fig. 1. Structure of compound **4a**.

In this work we have studied the condensation of 5-aminopyrazoles unsubstituted in position 1 with various β-keto esters by heating both components without solvent at 150°C. 5-Amino-3-methylpyrazole (**1a**), 5-amino-3-ethyl-4-methylpyrazole (**1b**), and 5-amino-3-phenylpyrazole (**1c**) were used in the reactions.

The question regarding the direction of condensation at the C or N atoms of the pyrazole ring to give compounds of type **3** or of type **4,5** respectively was readily resolved using ^{1}H NMR spectroscopy. Since a distinction between the structures **4** and **5** was practically impossible using ^{1}H NMR we have used X-ray structural analysis*. In the example of the condensation of acetoacetic ester with 5-amino-3-methylpyrazole the product was 3,5-dimethyl-7-oxopyrazolo[1,5-*a*]pyrimidine (**4a**) without an admixture of the isomeric compound **5** (see Fig. 1).

Because the spectroscopic data and the physical characteristics for the compounds obtained are similar (see Experimental) we propose that in the other examples the reaction occurs with the formation of the 7-oxopyrazolo[1,5-*a*]pyrimidines **4a-h**. The ^{1}H NMR spectra and the TLC data point to the absence of isomeric products. The yields are 65-99%.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 577 instrument (using KBr). UV spectra were taken on a Specord M-40 spectrophotometer using alcohol and ^{1}H NMR spectra on a Bruker AM-300 instrument (300 MHz) using DMSO-d_6. TLC was carried out on Silufol plates in methanol and revealed using iodine vapor or an alcoholic solution of $FeCl_3$ with subsequent heating. The synthesis of the aminopyrazoles used in the reaction has previously been reported by us [2].

General Condensation Method. A mixture of the corresponding 5-aminopyrazole (50 mmol) and the β-dicarbonyl compound (55 mmol) in a flask (30 ml) was heated on a metal bath at 140-150°C for 3 h, allowing elimination of the water and alcohol evolved (in the case of the benzoylacetic ester the bath temperature was held at 165-170°C). The crystallized mixture was recrystallized from 80% alcohol.

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* X-ray analysis was carried out at Institute of Organoelement Compounds of the Russian Academy of Sciences by O. Ya. Burbulevich. A crystal was grown from 80% acetic acid. Detailed X-ray analytical data will be the subject of a separate communication.

Compounds **4a-h** were prepared using this method.

2,5-Dimethyl-7-oxopyrazolo[1,5-*a*]pyrimidine (4a). Yield 99%; mp 245-246°C. R_f 0.59. UV spectrum, λ_{max}, nm (log ε): 249 (4.42); 255 (3.92); 294 (4.02). IR spectrum, ν, cm^{-1}: 1630, 1680. ^{1}H NMR spectrum, δ, ppm: 2.26 (3H, s, 2-CH_3); 2.28 (3H, s, 5-CH_3); 5.85 (s, 3H); 5.40 (s, 6-H); 11.85 (s, NH). Found, %: C 58.5; H 5.7; N 25.8. $C_8H_{10}N_3O$. Calculated, %: C 58.5; H 6.1; N 25.6.

2-Ethyl-3,5-dimethyl-7-oxopyrazolo[1,5-*a*]pyrimidine (4b). Yield 73%; mp 243-244°C. R_f 0.70. UV spectrum, λ_{max}, nm (log ε): 220 (4.48); 253 (4.11); 261 (4.15); 288 (3.95). IR spectrum, ν, cm^{-1}: 1630, 1670. ^{1}H NMR spectrum, δ, ppm: 1.23 (3H, t, 2-$CH_2\underline{CH_3}$); 2.61 (2H, q, 2-$\underline{CH_2}CH_3$); 2.09 (3H, s, 3-CH_3); 2.29 (3H, s, 5-CH_3); 5.36 (s, 6-H); 11.50 (s, NH). Found, %: C 62.6; H 6.8; N 22.0. $C_{10}H_{13}N_3O$. Calculated, %: C 62.8; H 6.8; N 22.0.

5-Methyl-7-oxo-2-phenylpyrazolo[1,5-*a*]pyrimidine (4c). Yield 64%; mp 308-310°C (with decomp.). R_f 0.72. UV spectrum, λ_{max}, nm (log ε): 258 (4.47); 299 (3.90). IR spectrum, ν, cm^{-1}: 1630, 1685. ^{1}H NMR spectrum, δ, ppm: 2.31 (3H, s, 5-CH_3); 6.42 (s, 3-H); 5.50 (s, 6-H); 12.10 (s, NH); 7.35-7.96 (m, H_{arom}). Found, %: C 68.9; H 4.9; N 18.6. $C_{13}H_{11}N_3O$. Calculated, C 69.3; H 4.9; N 18.7.

6-Carbethoxymethyl-2,5-dimethyl-7-oxopyrazolo[1,5-*a*]pyrimidine (4d). Yield 76% (acetosuccinate ester was used as the β-keto ester); mp 233-234°C. R_f 0.80. IR spectrum, ν, cm^{-1}: 1615, 1665, 1730. UV spectrum, λ_{max}, nm (log ε): 252 (3.95); 257 (3.96); 266 (3.68); 297 (3.85). ^{1}H NMR spectrum, δ, ppm: 1.27 (3H, t, O–$CH_2\underline{CH_3}$); 4.10 (2H, q, O–$\underline{CH_2}CH_3$); 2.26 (3H, s, 2-CH_3); 2.30 (3H, s, 5-CH_3); 3.82 (2H, s, 6-CH_2); 5.82 (s, 3-H). Found, %: C 57.7; H 6.2; N 17.0. $C_{12}H_{15}N_3O_3$. Calculated, %: C 57.8; H 6.2; N 16.9.

2-Methyl-7-oxo-5-phenylpyrazolo[1,5-*a*]pyrimidine (4e). Yield 67%; mp 261-263°C. R_f 0.70. UV spectrum, λ_{max}, nm (log ε): 248 (4.72); 297 (4.11); 319 (3.86). IR spectrum, ν, cm^{-1}: 1630, 1680. ^{1}H NMR spectrum, δ, ppm: 2.36 (3H, s, 2-CH_3); 5.90 (3-H); 5.99 (s, 6-H); 12.60 (s, NH); 7.56-7.84 (m, H_{arom}). Found, %: C 69.2; H 5.1;N 18.3. $C_{13}H_{13}N_3O$. Calculated, %: C 69.3; H 4.9; N 18.7.

6-Ethyl-2,5-dimethyl-7-oxopyrazolo[1,5-*a*]pyrimidine (4f). Yield 73%; mp 220-222°C. R_f 0.68. UV spectrum, λ_{max}, nm (log ε): 254 (3.93); 260 (3.94); 301 (2.91). IR spectrum, ν, cm^{-1}: 1630, 1675. ^{1}H NMR spectrum, δ, ppm: 2.28 (3H, s, 2-CH_3); 2.29 (3H, s, 5-CH_3); 1.06 (3H, t, 6-$CH_2\underline{CH_3}$); 2.48 (2H, q, 6-$\underline{CH_2}CH_3$); 5.76 (s, 3-H); 11.68 (s, NH). Found, %: C 62.7; H 6.8; N 22.00. $C_{10}H_{13}N_3O$. Calculated, %: C 62.8; H 6.8; N 22.00.

6-β-Hydroxyethyl-2,5-dimethyl-6-oxopyrazolo[1,5-*a*]pyrimidine (4g). Yield 92% (α-acetylbutyrolactone was used as the β-keto ester); mp 219-221°C. R_f 0.66. IR spectrum, ν, cm^{-1}: 1600, 1670. UV spectrum, λ_{max}, nm (log ε): 256 (4.38); 260 (4.40); 298 (4.31). ^{1}H NMR spectrum, δ, ppm: 2.28 (3H, s, 2-CH_3); 2.32 (3H, s, 5-CH_3); 2.61 (2H, t, 6-α-CH_2); 3.48 (2H, t, 6-β-CH_2); 5.78 (s, 3-H); 11.68 (s, NH). Found, %: C 58.00; H 6.3; N 20.0. $C_{10}H_{13}N_3O_2$. Calculated, %: C 58.0; H 6.3; N 20.3.

2-Ethyl-3-methyl-7-oxo-5-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (4h). Yield 73%; mp 202-203°C. R_f 0.71. IR spectrum, ν, cm^{-1}: 1640, 1675. UV spectrum, λ_{max}, nm (log ε): 223 (4.29); 269 (3.79); 279 (3.90); 299 (3.85); 314 (3.80); 327 (3.77). ^{1}H NMR spectrum, δ, ppm: 1.28 (3H, t, 2-$CH_2\underline{CH_3}$); 2.78 (2H, q, 2-$\underline{CH_2}CH_3$); 2.18 (3H, s, 3-CH_3); 6.09 (s, 6-H); 10.35 (s, NH). Found, %: C 49.0; H 4.2; N 17.5. $C_{10}H_{10}F_3N_3O$. Calculated, %: C 49.0; H 4.1; N 17.1.

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