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PYRAZOLOPYRIMIDINES BASED ON 5-AMINOPYRAZOLES UNSUBSTITUTED AT THE POSITION 1

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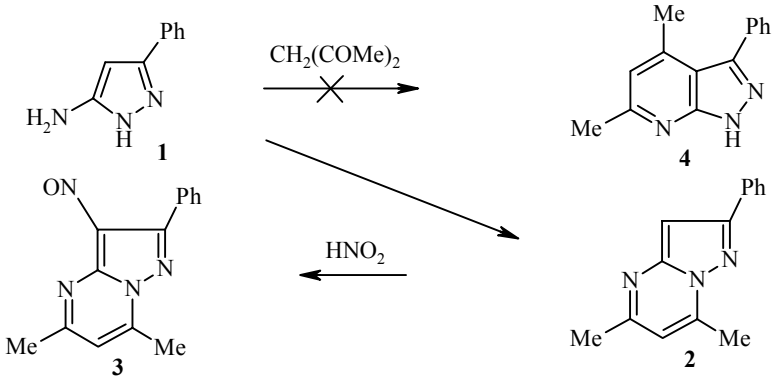
By condensation of various symmetric β-diketones with a series of 5-aminopyrazoles that are unsubstituted at the position 1, we have obtained a series of pyrazolo[1,5-a]pyrimidines that are of interest as physiologically active compounds. Hexafluoroacetylacetone reacts in another direction, forming pyrazolo[4,5-b]pyridine.

Keywords: aminopyrazoles, β-diketones, pyrazolopyrimidines.

It was shown earlier [1] that 5-amino-3-phenylpyrazole (**1**), when heated up to 140°C with acetylacetone, forms 5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (**2**). Unfortunately, that paper did not indicate the yield and other characteristics, except for C, H, N analyses.



Proof that condensation occurred at the position 1 (and not at the position 4) of the pyrazole ring was the facile nitrosation of compound **2** to form nitroso derivative **3**. The nitrosation reaction would be less likely if structure **4** were formed.

We decided to extend the scope of this condensation by using a series of other 5-aminopyrazoles and symmetric β-diketones (asymmetric diketones, of course, would give a mixture of isomers).

We should note that condensation with acetylacetone **6a**, methylacetylacetone **6b**, and hexafluoroacetylacetone **6c** is an exothermic reaction (when the components are mixed, we observe appreciable heating), but for high yield they must be heated for 2 h with bath temperature up to 140°C. With dibenzoylmethane, the reaction proceeds significantly more slowly and the bath temperature must be maintained at a level of 160 to 170°C.

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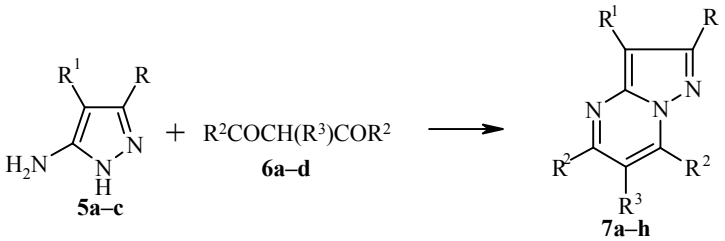
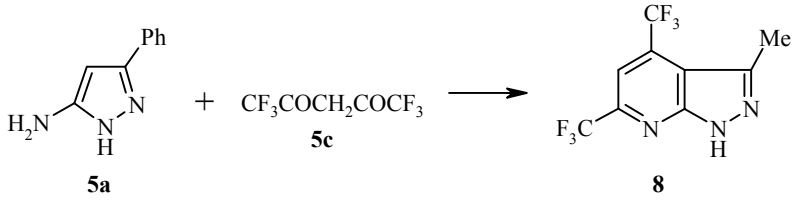


5a R = Me, **b** R = Ph, **c** R = Et, **a**, **b** R^1 = H, **c** R^1 = Me; **6 a**, **b** R^2 = Me, **c** R^2 = CF_3, **d** R^2 = Ph, **a**, **c**, **d** R^3 = H, **b** R^3 = Me; **7 a**, **b**, **d** R = Me, **c**, **e** R = Et, **f-h** R = Ph, **a**, **b**, **d**, **f-h** R^1 = H, **c**, **e**, R^1 = Me, **a**, **c-g** R^2 = Me, **b**, **h** R^2 = Ph, **a-c**, **f**, **h** R^3 = H, **d**, **e**, **g** R^3 = Me

Additional although indirect evidence for the reaction occurring at the position 1 is the fact that the process also easily occurs for 4-substituted 5-aminopyrazole **5c**, forming derivatives **7c** and **7e**. Conclusive confirmation of structure **7** came from analysis of the ^{1}H NMR spectra. The signal for the proton at the position 4 of the pyrazole ring is registered in the 5.8-7 ppm region and can be easily distinguished. Furthermore, if structures of type **8** were formed, then a signal for the NH proton should be present in the spectrum in the 9.5-14 ppm region. The ^{1}H NMR spectra (see experimental section) suggest that in all cases of condensation, except when hexafluoroacetylacetone is used, the reaction proceeds to form pyrazolo[1,5-*a*]-pyrimidines. But in the case of reaction between hexafluoroacetylacetone and 3-methylaminopyrazole **5a**, 3-methyl-4,6-ditrifluoromethylpyrazolo[4,5-*b*]pyridine (**8**) was formed. We observed such condensation earlier for N-substituted 5-aminopyrazoles [2].



The structure of compound **8** is confirmed by ^{1}H NMR spectral data, which showed a singlet for the Me group in the 2.65 ppm region, only one singlet in the aromatic proton region 7.75 ppm (5-H), and a broadened singlet for the NH proton in the 14.3 ppm region. Such a change in direction of cyclization may be due to the higher electronegativity of the carbon atom for the C=O group in **6c**, which is sufficient for electrophilic attack at the reactive 4 position of the aminopyrazole ring.

EXPERIMENTAL

The IR spectra were taken on a Perkin-Elmer in KBr tablets; the UV spectra were taken on a Specord M-40 spectrometer in alcohol; the NMR spectra were recorded on a Bruker AM-300 (300 MHz) in DMSO-d_6. TLC was performed on Silufol plates.

5-Amino-3-methylpyrazole (5a). A mixture of β-aminocrotononitrile (24.6 g, 0.3 mol) and hydrazine hydrate (50 ml), containing 0.8 mol of hydrazine, was heated to boiling under reflux. Then the excess hydrazine hydrate was distilled off from the reaction mass under vacuum, and the residue was distilled. Obtained 22.6 g (77.7%) of aminopyrazole **5a**; bp 152-153°C (6 torr); crystallizes on standing; mp 48-49°C. R_f 0.52 (methanol–acetone, 1:1), visualized by iodine. IR spectrum, ν, cm^{-1}: 1490, 1580, 3250. UV spectrum, λ_{max}: 232 nm, log ε 3.84. Found, %: C 49.2; H 7.4; N 43.6. $C_4H_7N_3$. Calculated, %: C 49.48; H 7.72; N 43.30.

5-Amino-3-phenylpyrazole (5b). A mixture of benzoylacetonitrile (8.7 g, 0.06 mol), methylcellosolv (15 ml), and 85% hydrazine hydrate (4 ml) was heated under reflux to boiling. The reaction mixture was evaporated down on a rotary evaporator to dryness and the residue was recrystallized from a 1:2 benzene–hexane mixture. Obtained 7.4 g (77.6%) of aminopyrazole **5b**; mp 123°C (mp 123°C [3]). R_f 0.13 (benzene–acetone, 2.5:1), visualization by iodine. IR spectrum, ν, cm^{-1}: 1500, 1560, 1610, 3240. UV spectrum, λ_{max} 254 nm, log ε 3.84. Found, %: C 49.2; H 5.7; N 26.3. $C_9H_9N_3$. Calculated, %: C 67.92; H 5.66; N 26.42.

5-Amino-3-ethyl-4-methylpyrazole (5c) was obtained analogously to 5-amino-3-methylpyrazole from α-methyl-β-iminobutyronitrile (0.1 mol) and 85% hydrazine hydrate (0.4 mol) in 79% yield; bp 141-143°C (2 torr) in the form of a thick yellow oil. R_f 0.50 (methanol–acetone, 1:1), visualization by iodine. IR spectrum, ν, cm^{-1}: 1500, 1590, 3300. UV spectrum, λ_{max}: 231 nm, log ε (3.77). Found, %: C 57.4; H 8.8; N 32.9. $C_6H_{11}N_3$. Calculated, %: C 57.60; H 8.81; N 33.60.

General Condensation Procedure. A mixture of the corresponding aminopyrazole (0.05 mol) and β-dicarbonyl compound (0.051 mol) was heated in an open flask on a metallic bath with a bath temperature of 140-150°C, making it possible to distill off the cleaved water (in the case of dibenzoylmethane, the bath temperature was 160-170°C). After this, the crystallized mixture was recrystallized from 80% alcohol and again as needed from a benzene–hexane mixture.

2,5,7-Trimethylpyrazolo[1,5-*a*]pyrimidine (7a). Yield 92%; mp 69-70°C. *R*f 0.51 (benzene–acetone, 5:1), visualization by iodine. IR spectrum, ν, cm^{-1}: 1450, 1560, 1620. UV spectrum, λ_{max}, nm (log ε): 234 (4.73); 265 (3.43); 267 (3.48); 282 (3.64); 312 (3.43). ^{1}H NMR spectrum, δ, ppm: 2.44 (3H, s, 2-CH_3); 2.47 (3H, s, 5-CH_3); 2.66 (3H, s, 7-CH_3); 6.22 (s, 3-H); 6.66 (s, 6-H). Found, %: C 66.9; H 6.9; N 25.8. $C_9H_{11}N_3$. Calculated, %: C 67.08; H 6.83; N 26.09.

2-Methyl-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (7b). Yield 98%; mp 112-113°C. R_f 0.31 (benzene), visualization by iodine. IR spectrum, ν, cm^{-1}: 1495, 1560, 1610. UV spectrum, λ_{max}, nm (log ε): 236 (4.23); 267 (4.60); 321 (3.83); 367 (3.53). ^{1}H NMR spectrum, δ, ppm: 2.47 (3H, s, 2-CH_3); 7.50 (s, 6-H); 7.47-8.25 (m, aromatic protons); 6.52 (s, 3-H). Found, %: C 79.6; H 5.2; N 15.1. $C_{19}H_{15}N_3$. Calculated, %: C 80.00; H 5.26; N 14.74.

2-Ethyl-3,5,7-trimethylpyrazolo[1,5-*a*]pyrimidine (7c). Yield 85%; mp 50-51°C, R_f 0.62 (benzene–acetone, 5:1), visualization by iodine. IR spectrum, ν, cm^{-1}: 1510, 1545, 1590, 1630, 1670 (weak). UV spectrum, λ_{max}, nm (log ε): 238 (4.35), 278 (3.27), 289 (3.25). ^{1}H NMR spectrum, δ, ppm: 1.28 (3H, t, 2-CH_3); 2.74 (2H, q, 2-CH_2); 2.20 (3H, s, 3-CH_3); 2.46 (5H, s, 5-CH_3); 2.63 (3H, s, 7-CH_3); 6.75 (s, 6-H). Found, %: C 70.0; H 8.2; N 22.4. $C_{11}H_{15}N_3$. Calculated, %: C 69.84; H 7.94; N 22.22.

2,5,6,7-Tetramethylpyrazolo[1,5-*a*]pyrimidine (7d). Yield 86%; mp 126-127°C. R_f 0.67 (benzene–acetone, 5:1), visualization by iodine. IR spectrum, ν, cm^{-1}: 1450, 1490, 1525, 1620. UV spectrum, λ_{max}, nm (log ε): 235 (4.50); 269 (3.38); 284 (3.23); 294 (3.23). ^{1}H NMR spectrum, δ, ppm: 2.42 (3H, s, 2-CH_3); 2.68 (3H, s, 5-CH_3); 2.28 (3H, s, 6-CH_3); 3.08 (3H, s, 7-CH_3); 6.18 (s, 3-H). Found, %: C 68.7; H 7.7; N 24.2. $C_{10}H_{13}N_3$. Calculated, %: C 68.57; H 7.43; N 24.00.

2-Ethyl-3,5,6,7-tetramethylpyrazolo[1,5-*a*]pyrimidine (7e). Yield 79%; mp 72-73°C. R_f 0.51 (benzene–acetone, 4:1), visualization by iodine followed by heating. IR spectrum, ν, cm^{-1}: 1450, 1505, 1530, 1580, 1630, 1675 (weak). UV spectrum, λ_{max}, nm (log ε): 239 (4.78), 281 (3.33), 291 (3.39), 333 (3.59). ^{1}H NMR spectrum, δ, ppm: 1.28 (3H, t, 2-CH_3); 2.74 (2H, q, 2-CH_2); 2.21 (3H, s, CH_3); 2.46 (3H, s, 5-CH_3); 2.25 (3H, s, 6-CH_3); 2.65 (3H, s, 7-CH_3). Found, %: C 70.9; H 8.2; N 21.0. $C_{12}H_{17}N_3$. Calculated, %: C 70.94; H 8.37; N 20.69.

5,7-Dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (7f). Yield 97%; mp 155-156°C. R_f 0.53 (benzene–acetone, 4:1), visualization by iodine followed by heating. IR spectrum, ν, cm^{-1}: 1440, 1470, 1525, 1560, 1625. UV spectrum, λ_{max}, nm (log ε): 239 (4.42), 259 (4.77), 283 (4.04), 299 (3.98). ^{1}H NMR spectrum, δ, ppm: 2.48 (3H, s, 5-CH_3); 2.73 (3H, s, 7-CH_3); 6.76 (s, 3-H); 7.37 (t, *p*-H arom.); 7.47 (dd, *m*-H arom.); 8.00 (d, *o*-H arom.). Found, %: C 75.2; H 5.9; N 19.1. $C_{14}H_{13}N_3$. Calculated, %: C 75.34; H 5.83; N 18.83.

5,6,7-Trimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (7g). Yield 90%; mp 187-188°C. R_f 0.57 (benzene–acetone, 4:1), visualization by iodine followed by heating. IR spectrum, ν, cm^{-1}: 1430, 1465, 1520, 1630. UV spectrum, λ_{max}, nm (log ε): 235 (4.24), 244 (4.37), 254 (4.56), 262 (4.63), 272 (4.54), 299 (3.87), 310 (3.83). ^{1}H NMR spectrum, δ, ppm: 2.47 (3H, s, 5-CH_3); 2.30 (3H, s, 6-CH_3); 2.77 (3H, s, 7-CH_3); 6.81 (s, 3-H); 7.37 (t, *p*-H arom.); 7.48 (dd, *m*-H arom.); 7.98 (d, *o*-H arom.). Found, %: C 76.3; H 6.3; N 18.1. $C_{15}H_{15}N_3$. Calculated, %: C 75.95; H 6.33; N 17.72.

2,5,7-Triphenylpyrazolo[1,5-*a*]pyrimidine (7h). Yield 94%; mp 153-155°C. R_f 0.64 (benzene), visualization by iodine followed by heating. IR spectrum, ν, cm^{-1}: 1450, 1470, 1500, 1560, 1580, 1615. UV spectrum, λ_{max}, nm (log ε): 236 (4.78), 260 (4.96), 342 (4.20). ^{1}H NMR spectrum, δ, ppm: 7.07 (s, 3-H); 7.4-8.3 (m, protons of phenyl rings and 6-H). Found, %: C 83.1; H 4.8; N 12.3. $C_{24}H_{17}N_3$. Calculated, %: C 82.90; H 4.90; N 12.10.

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