An Unequivocal Synthesis of 7-Oxopyrazolo[1,5-*a*]pyrimidines

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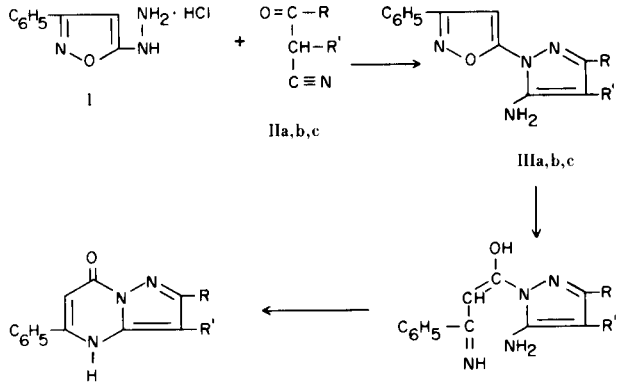
A new improved method of synthesis of 7-oxopyrazole-[1,5-*a*]pyrimidines (Va,b,c) from 3-phenyl-5-(5-amino-3,4-R,R′-1-pyrazolyl) isoxazoles (IIIa,b,c) is reported. Compounds IIIa,b,c were obtained by the action of 5-(3-phenylisoxazolyl)hydrazine hydrochloride (I) on β-ketonitriles. Catalytic hydrogenation of the pyrazolylisoxazoles with W_2 Raney-Nickel caused isoxazole ring opening (1) to give intermediates IVa,b,c (2) which undergo intramolecular acid-catalyzed cyclization leading in high yield to compounds Va,b,c (Scheme I). The structures of the products Va,b,c were confirmed by analytical and spectroscopic data (ir, uv, nmr). The uv spectra were very similar to that of other 7-oxoderivatives (3,4).

SCHEME I

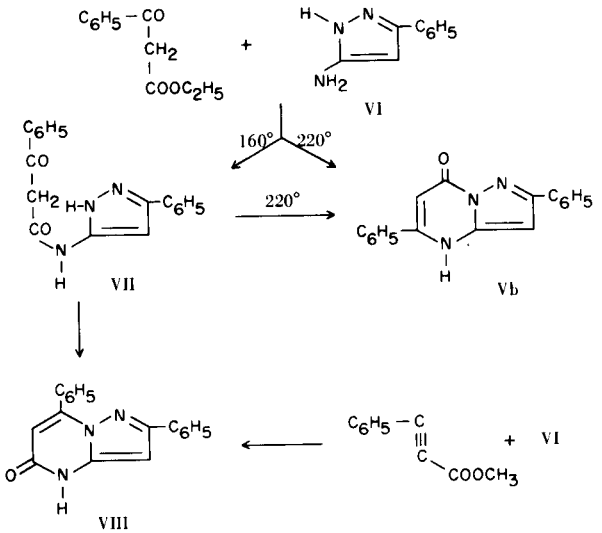


a, R = R′ = CH_3
b, R = C_6H_5, R′ = H
c, R = CH_3, R′ = C_6H_5

Furthermore, compound Vb prepared by the above method was found to be identical with a sample synthesized by an independent route by fusion of 5(3)-amino-3(5)-phenylpyrazole (VI) with ethyl benzoylacetate at 160° for 2 hours, as reported by Checchi and Ridi (5). In addition to Vb, another product melting at 207-210° [lit. (5) m.p. 205-208°] was obtained which was assigned structure VII based upon ir and nmr spectra. Further, by maintaining fusion at 160° for 10 minutes, VII was the main product (yield 76%); however, fusion at 220° for 10 minutes gave only Vb and fusion of VII at 220° for a few minutes also gave Vb.

These results led to the conclusion that cyclization of VII into Vb occurred due to thermal rearrangement of the benzoylacetyl group. This is supported by the fact that VII in ethanol in the presence of hydrochloric acid was converted into VIII. Moreover VIII, whose structure was confirmed by analytical data, ir and nmr spectra, could be obtained by fusion of VI with phenylpropiolic acid methyl ester (Scheme II). The uv spectrum was quite similar to that of 5-oxoderivatives (3,4) with the expected modification due to the substituents.

SCHEME II



EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. Infrared spectra were determined in nujol mull (unless otherwise specified) with a Perkin-Elmer Infracord 137 spectrophotometer; ultraviolet spectra were determined in methanol solution with a Beckman DB recording spectrophotometer. The nmr spectra (DMSO-d_6) were obtained with a Jeol C-60H spectrometer (TMS as internal reference).

3-Phenyl-5-(5-amino-3,4-dimethyl-1-pyrazolyl)isoxazole (IIIa).

Equimolar amounts of 5-(3-phenylisoxazolyl)hydrazine hydrochloride (6) [m.p. 168° dec. (ethanol-ether)] (I) (7 mmoles) and α-acetylpropionitrile (IIIa) (7) (7 mmoles) in ethanol (25 ml.) were refluxed for 1 hour. After cooling IIIa, yield 75%, was obtained. The product melted at 203-206° (benzene); ir: 3480, 3340, 3160 cm^{-1}(NH_2); nmr: 1.80 δ (s, 3H, -CH_3), 2.02 δ (s, 3H, -CH_3), 5.54 δ (s, 2H, NH_2), 6.78 δ (s, isoxazole H), 7.30-8.00 δ (m, 5H, C_6H_5).

Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.12; H, 5.55; N, 22.04. Found: C, 66.39; H, 5.50; N, 22.29.

3-Phenyl-5-(5-amino-3-phenyl-1-pyrazolyl)isoxazole (IIIb).

Equimolar amounts of 5-(3-phenylisoxazolyl)hydrazine hydrochloride (I) (7 mmoles) and of α-cyanoacetophenone (IIb) (8) (7 mmoles) in ethanol (25 ml.) were refluxed for 1 hour. The precipitate was collected and recrystallized from benzene, m.p. 196-198° (yield 75%); ir: 3420, 3300, 3160 cm^{-1} (NH_2); nmr: 5.90 δ (s, pyrazole H), 6.08 δ (s, 2H, NH_2), 7.00 δ (s, isoxazole H), 7.20-8.00 δ (m, 10H, 2 x C_6H_5).

Anal. Calcd. for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.85; H, 4.95; N, 18.83.

3-Phenyl-5-(5-amino-3-methyl-4-phenyl-1-pyrazolyl)isoxazole (IIIc).

Equimolar amounts of 5-(3-phenylisoxazolyl)hydrazine hydrochloride (I) (7 mmoles) and α acetylbenzyl cyanide (IIc) (9) (7 mmoles) in ethanol (25 ml.) were refluxed for 1 hour. The precipitate was collected and recrystallized from benzene, m.p. 190-193° (yield 75%); ir: 3480, 3340, 3160 cm^{-1} (NH_2); nmr: 2.20 δ (s, 3H, CH_3), 5.88 δ (s, 2H, NH_2), 7.10 δ (s, isoxazole H), 7.40-8.20 δ (m, 10H, 2 x C_6H_5).

Anal. Calcd. for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.53; H, 5.07; N, 17.61.

Hydrogenation of the Pyrazolylisoxazoles. General Procedure.

A mixture of 3 mmoles of IIIa,b,c, 300 ml. of ethanol and *ca.* 2 g. of W_2 Raney-Nickel (10) was hydrogenated in a Parr apparatus at 45-50 psi for 3 hours at room temperature. Removal of the catalyst and evaporation of ethanol left the reduced products, yield 80-85% after recrystallization.

Hydrogenation of IIIa: 5-Amino-α-(benzimidoylmethylene)-3,4-dimethylpyrazole-1-methanol (IVa).

The product melted at 152-155° (ethanol); ir: 3400, 3380, 3200 (broad) cm^{-1} (NH, NH_2); nmr: 1.74 δ (s, 3H, CH_3), 1.88 δ (s, 3H, CH_3), 6.00 δ (s, 1H, CH), 6.10 δ (s, 2H, NH_2), 7.28-8.00 δ (m, 6H, C_6H_5 and O*H*), 8.80 δ (broad, 1H, NH).

Anal. Calcd. for $C_{14}H_{16}N_4O$: C, 65.60; H, 6.29; N, 21.86. Found: C, 65.84; H, 6.38; N, 22.13.

Hydrogenation of IIIb: 5-Amino-α-(benzimidoylmethylene)-3-phenylpyrazole-1-methanol (IVb).

The product melted at 136-139° (ethanol); ir: 3420, 3460, 3300 cm^{-1} (NH, NH_2); nmr: 5.80 δ (s, pyrazolo H), 6.28 δ (s, 1H, -*CH*=C-OH), 6.62 δ (s, 2H, NH_2), 7.20-8.10 δ (m, 11H, 2 x C_6H_5 and *OH*), 9.00 δ (broad, 1H, NH).

Anal. Calcd. for $C_{18}H_{16}N_4O$: C, 71.03; H, 5.30; N, 18.41. Found: C, 70.90; H, 5.18; N, 18.12.

Hydrogenation of IIIc: 5-Amino-α-(benzimidoylmethylene)-3-methyl-4-phenylpyrazole-1-methanol (IVc).

The product melted at 133-136° (ethanol): ir: 3400, 3320, 3200 (broad) cm^{-1} (NH, NH_2); nmr: 2.18 δ (s, 3H, CH_3), 6.28 δ (s, 1H, CH) 6.60 δ (s, 2H, NH_2), 7.20-8.00 δ (m, 11H, 2 x C_6H_5 and *OH*), 8.20 δ (broad 1H, NH).

Anal. Calcd. for $C_{19}H_{18}N_4O$: C, 71.67; H, 5.70; N, 17.60. Found: C, 71.60; H, 5.77; N, 17.82.

General Procedure for the Pyrazolepyrimidines.

To a solution of 4 mmoles of IVa,b,c in 30 ml. of ethanol was added 2 ml. of ethanol saturated with hydrochloric acid. After refluxing 1 hour the solution was cooled, and the solid was collected and recrystallized. In some cases, it was necessary to concentrate the reaction mixture to obtain the product, yield 80-85% after recrystallization.

7-Oxo-2,3-dimethyl-5-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine (Va).

The product melted at 285-287° (ethanol); uv λ max nm log ε: 248 (4.45), 274 (3.87) shoulder, 330 (3.52); ir (potassium bromide): 3100 (NH), 1680 (CO) cm^{-1}; nmr: 2.08 δ (s, 3H, CH_3), 2.20 δ (s, 3H, CH_3), 5.78 δ (s, 1H, CH), 7.30-7.90 δ (m, 5H, C_6H_5), 11.90 δ (broad 1H, NH).

Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.48; N, 17.56. Found: C, 70.43; H, 5.46; N, 17.65.

7-Oxo-2,5-diphenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine (Vb).

The product melted at 339-340° (ethanol): uv λ max nm log ε 266 (4.44), 294 (3.92) shoulder; ir (potassium bromide): 3100 (NH), 1680 (CO) cm^{-1}; nmr: 6.00 δ (s, 1H, CH), 6.58 δ (s, 1H, CH); 7.20-8.10 δ (m, 10H, 2 x C_6H_5), 12.20 δ (broad 1H, NH).

Anal. Calcd. for $C_{18}H_{13}N_3O$: C, 75.24; H, 4.56; N, 14.63. Found: C, 74.93; H, 4.44; N, 14.27.

7-Oxo-2-methyl-3,5-diphenyl-4,7-dihydropyrazole[1,5-*a*]pyrimidine (Vc).

The product melted at 287-290° (ethanol): uv λ max nm log ε 258 (4.36) 348 (3.71); ir (potassium bromide); 3100 (NH) 1680 (CO) cm^{-1}; nmr: 2.42 δ (s, 3H, CH_3), 6.02 δ (s, 1H, CH), 7.20-8.00 δ (m, 10H, 2 x C_6H_5), 11.70 δ (broad 1H, NH).

Anal. Calcd. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.95. Found: C, 75.93; H, 5.22; N, 13.87.

5-Oxo-2,7-diphenyl-4,5-dihydropyrazole[1,5-*a*]pyrimidine (VIII).

(a) A mixture of 0.477 g. (3.00 mmoles) of 3(5)-phenyl-5(3)-aminopyrazole (VI) and 0.600 g. (3.75 mmoles) of phenylpropiolic acid methyl ester was heated at 100° for 30 minutes. After cooling, trituration with ethanol gave a crystalline product. Recrystallization from ethanol (with charcoal) gave white needles of 5-oxo-2,7-diphenyl-4,5-dihydropyrazole[1,5-*a*]pyrimidine, m.p. 273-275° (yield 42%); uv λ max nm log ε 254 (4.16), 300 (4.01); ir (potassium bromide): 3100 (NH), 1680 (CO) cm^{-1}; nmr: 6.10 δ (s, 1H, CH), 6.40 δ (s, 1H, CH), 7.40-8.00 δ (m, 10H, 2 x C_6H_5), 12.10 δ (broad 1H, NH).

Anal. Calcd. for $C_{18}H_{13}N_3O$: C, 75.24; H, 4.56; N, 14.63. Found: C, 74.97; H, 4.40; N, 14.87.

(b) To a solution of 3 g. (10 mmoles) of 5(3)-benzoylacetamido-3(5)-phenylpyrazole (VII) (see below) in ethanol (40 ml.) was added 15 ml. of ethanol saturated with hydrochloric acid. After refluxing 2 hours, a crystalline product separated, m.p. 273-275° (ethanol).

Anal. Calcd. for $C_{18}H_{13}N_3O$: C, 75.24; H, 4.56; N, 14.63. Found: C, 75.38; H, 4.59; N, 14.29.

Fusion of 5(3)-Amino-3(5)-phenylpyrazole with Ethyl Benzoylacetate.

(a) Fusion at 160°: 5(3)-Benzoylacetamido-3(5)-phenylpyrazole (VII).

A mixture of 2 g. (12.5 mmoles) of 5(3)-amino-3(5)-phenylpyrazole (VI) and 3 g. (15.6 mmoles) of ethyl benzoylacetate was heated at 160° for 10 minutes. After cooling, the crude reaction product was purified by column chromatography on 150 g. of silica gel (Kieselgel 0.05-0.2 mm). The benzene-ethyl acetate (8:2) eluate (F_{1-10}, each 60 ml.) afforded 500 mg. of unreacted VI. The successive eluate with benzene-ethyl acetate (1:1) (F_{11-30}, each 60 ml.) gave VII (yield 76%) m.p. 207-210° (ethanol). The ir spectrum showed broad bands in the NH stretching region and at 1670, 1680 cm^{-1} (2 x CO); the nmr spectrum determined in dimethylsulfoxide-d_6 exhibited proton signals consistent with a keto-enol tautomerism of a phenacyl group on a side chain and two signals at 12.84 δ and 10.72 δ for pyrazole NH and amidic NH respectively.

(b) Fusion at 220°: 7-Oxo-2,5-diphenyl-4,7-dihydropyrazole-[1,5-*a*]pyrimidine (Vb).

A mixture of 1 g. (6.2 mmoles) of 5(3)-amino-3(5)-phenylpyrazole and 1.5 g. (7.8 mmoles) of ethyl benzoylacetate was heated at 220° for 10 minutes. After cooling, trituration with ethanol gave a crystalline product (yield 72%). Recrystallization from ethanol gave white scales of 7-oxo-2,5-diphenyl-4,7-dihydropyrazole[1,5-*a*]pyrimidine, m.p. 339-340°. Fusion at 220° for 10 minutes of 5(3)-benzoylacetamido-3(5)-phenylpyrazole (VII) gave Vb in high yield (80%).

Anal. Calcd. for $C_{18}H_{13}N_3O$: N, 14.63. Found: N, 14.95.

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(2) All three products were assigned the structure with the benzoylacetyl-β-imino group in the enol-form on the basis of spectroscopic evidence (nmr, ir). The nmr spectra determined in dimethylsulfoxide-d_6 exhibited methine proton signals but no methylene signals and an enolic proton downfield exchangeable with deuterium oxide. The ir spectra showed no absorption bands for a carbonyl group.

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