SYNTHESIS AND STRUCTURAL STUDY OF SOME 4-(α -ARYLETHYLIDENE)-1-PYRIMIDINYL-2-PYRAZOLIN-5-ONES.

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Abstract. 4-(α -Phenylethylidene)-1-pyrimidinyl-2-pyrazolin-5-ones **4-9** were synthesised by Knoevenagel condensation of the corresponding 3-methyl-1-pyrimidinylpyrazolin-5-ones **1-3** with some aromatic ketones. The structural assignments and the stereochemistry of these compounds were confirmed by UV and NMR methods.

INTRODUCTION

It is of interest to note that 2-pyrazolin-5-ones have wide applications in industrial photographic colour couplers (1). This class of compounds is also known as filter dyes and electron acceptors (2). As these compounds are used in the preparation of cyanine dyes, they may be used as photosensitizers (3). It is known that the 4-position of 2-pyrazolin-5-ones is very reactive and undergoes a characteristic condensation of the active methylene group. The most Knoevenagel condensations have been performed on 1-phenylpyrazolin-5-one derivatives, with aromatic or heterocyclic aldehydes and ketones (4-7). In previous papers (8,9), we extended these reactions to 5-pyrazolones, substituted with the pyrimidine ring in the 1-position. 1-Pyrimidinylpyrazolin-5-ones represent a new class of heterocycles, relatively recently discovered (10-12). Thus, 3-methyl-1-pyrimidinyl-2-pyrazolin-5-ones reacted easily with aromatic aldehydes, to give 4-arylidene-pyrazolinone methinic dyes (A) (9).

These compounds are also very useful intermediates in organic syntheses, by their reactive conjugated system $C=C-C=O$, in Michael additions with various nucleophiles (13), or in syntheses of new heterocyclic spirooxiranes (4,14). In this paper, we have performed the Knoevenagel condensation of 3-methyl-1-pyrimidinyl-2-pyrazolin-5-ones **1-3** with aromatic ketones (benzophenone and various acetophenones), and developed a study concerning the stereochemistry of the new compounds, by NMR spectroscopy.

RESULTS AND DISCUSSION

Treatment of 3-methyl-1-pyrimidinyl-2-pyrazolin-5-ones **1-3** (obtained from aminoguanidine salts and ethylacetoacetate) (12), with aromatic ketones, using Et_3N as catalyst, gave in good yield 4-(α -phenylethylidene)-1-pyrimidinyl-2-pyrazolin-5-ones **4-9**. The condensation of **1** with acetone led to 4-isopropylidene-1-pyrimidinyl-2-pyrazolin-5-one **10** (Scheme 1).

Scheme 1

The ketones are less reactive than the aldehydes, and required vigorous conditions. Thus, the compounds **1-3** reacted with acetone and acetophenone, in refluxing EtOH for 6 hours, under basic catalysis (Et_3N). The products **7**, **8** and **9** were obtained in good yield by reacting **1** with substituted acetophenones, in melt at 160°C for 2 hours. The reactions were monitored by TLC using "Merck" silicagel 60 F 254 plates, and acetone: $CHCl_3$: AcOH 5:5:1 as eluent. In the UV spectra recorded in ethanol a characteristic band at 340-380 nm was observed. The structural assignments and the stereochemistry of the exocyclic double bond were

performed by $^1\text{H-NMR}$ spectroscopy. We have compared the chemical shifts of the methyl protons located in position 3 of the pyrazolone ring, for the compounds **4**, **9** and **10**, respectively. For the compounds **4** and **10**, the methyl signals have appeared at the same chemical shifts ($\delta = 2.25$ ppm for **4**; $\delta = 2.30$ ppm for **10**). For the compound **9**, the methyl signal is significantly shielded ($\delta = 1.65$ ppm) due to the anisotropy caused by the phenyl ring (4). These results demonstrate that for all the compounds prepared **4-8** ($\delta = 2.25\text{-}2.40$ ppm), the phenyl ring is in “syn” position towards carbonyl group. This observation provides additional confirmation for the *Z-configuration* of the exocyclic double bond in arylidene compounds.

It can be observed that in the Knoevenagel condensation, the aromatic benzaldehydes (**4,9**), and the ketones give only one stereoisomer (*Z-isomer*), which is more stable energetically, because the phenyl ring is “*anti*” to the methyl group from the position 3 of the pyrazolone ring. In basic-catalysed condensation, the pyrazolone reacts in the enolate form with the aromatic ketones, which is probably oriented with phenyl ring “*anti*” to methyl group, thus affording the *Z-isomer* by an E_2 elimination (Scheme 2).

Scheme 2

EXPERIMENTAL

Melting points were determined with Electrothermal melting apparatus and are uncorrected. $^1\text{H-NMR}$ spectra were recorded with 300 MHz Varian spectrometer using TMS as an internal standard in CDCl_3 . Electronic spectra were recorded in EtOH on a "Specord" spectrophotometer.

General procedure (for compounds **4**, **5**, **6** and **10**). A mixture of 1-pyrimidinyl-5-pyrazolone (0.01 mol), the appropriate ketones (0.012 mol) in 15 ml EtOH and a few drops of Et_3N , was heated under reflux for 6 hours. The reaction mixture was concentrated and triturated with ethyl ether. The solid that separated was recrystallized from the proper solvent.

General procedure (for compounds **7**, **8** and **9**). A mixture of 1-pyrimidinyl-5-pyrazolone (0.01 mol), the appropriate ketones (0.01 mol) and a few drops of Et_3N , was heated in an oil bath at 150-160°C for 2 hours using two boiling sticks to assist in the evolution of water. The reaction mixture was left to cool, and the product was triturated with ethyl ether, then recrystallized from the proper solvent.

(Z)-3-Methyl-4-(α -phenylethylidene)-1-(4-hydroxy-6-methyl-2-pyrimidinyl)-pyrazolin-5-one **4.** Reddish, m.p. 119-120°C. Yield 75% (AcOEt). Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_2$: C 66.16, H 5.19, N 18.16, Found: C 65.92, H 5.30, N 17.91, $^1\text{H-NMR}$ δ (CDCl_3): 2.25 (3H, s, 3- CH_3), 2.15 (3H, s, 6- CH_3), pyrim. ring 6.05 (1H, s, 5-H), 2.40 (3H, s, 6- CH_3), 7.55-7.98 (5H, m, arom.), UV λ_{max} =330nm (EtOH).

(Z)-3-Methyl-4-(α -phenylethylidene)-1-(4-chloro-5,6-dimethyl-2-pyrimidinyl)-pyrazolin-5-one **5.** Yellow, m.p. 101-102°C. Yield 85% (MeOH). Anal. Calcd. for $\text{C}_{18}\text{H}_{17}\text{N}_4\text{OCl}$: C 63.37, H 4.98, N 16.43, Found: C 63.12, H 4.85, N 16.27, $^1\text{H-NMR}$ δ (CDCl_3): 2.28 (3H, s, 3- CH_3), 2.13 (3H, s, 6- CH_3), pyrim. ring 2.02 (3H, s, 5- CH_3), 2.45 (3H, s, 6- CH_3), 7.45-7.80 (5H, m, arom.), UV λ_{max} =340nm (EtOH).

(Z)-3-Methyl-4-(α -phenylethylidene)-1-(4-methoxy-5,6-dimethyl-2-pyrimidinyl)-pyrazolin-5-one **6.** Yellow, m.p. 110-111°C. Yield 60% (AcOEt). Anal. Calcd. for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_2$: C 67.77, H 5.94, N 16.64, Found: C 67.69, H 6.10, N 16.52, $^1\text{H-NMR}$ δ (CDCl_3): 2.37 (3H, s, 3- CH_3), 2.20 (3H, s, 6- CH_3), pyrim. ring 2.10 (3H, s, 5- CH_3), 2.43 (3H, s, 6- CH_3), 4.05 (3H, s, OCH_3), 7.40-7.89 (5H, m, arom.), UV λ_{max} =345nm (EtOH).

(Z)-3-Methyl-4-(α -m-nitrophenylethylidene)-1-(4-hydroxy-6-methyl-2-pyrimidinyl)-pyrazolin-5-one **7.** Reddish, m.p. 95-96°C. Yield 65% (Benzene). Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{N}_5\text{O}_4$: C 57.73, H 4.24, N 19.81, Found: C 57.86, H 4.39, N 19.70, $^1\text{H-NMR}$ δ (CDCl_3): 2.32 (3H, s, 3- CH_3), 2.21 (3H, s, 6- CH_3), pyrim. ring 6.10 (1H, s, 5-H), 2.46 (3H, s, 6- CH_3), 8.58 (1H, s, arom.), 7.79-8.38 (3H, m, arom.), UV λ_{max} =325nm (EtOH).

(Z)-3-Methyl-4(α -p-methoxyphenylethylidene)-1-(4-hydroxy-6-methyl-2-pyrimidinyl)-pyrazolin-5-one 8. Red, m.p. 134-135°C. Yield 70% (MeOH). Anal. Calcd. for $C_{18}H_{18}N_4O_3$: C 63.84, H 5.31, N 16.55. Found: C 63.97, H 5.42, N 16.47. $^1\text{H-NMR}$ δ (CDCl_3): 2.33(3H, s, 3- CH_3), 2.20(3H, s, 6- CH_3), pyrim. ring 6.14(1H, s, 5-H), 2.41(3H, s, 6- CH_3), 7.04(2H, d, arom.), 8.42(2H, d, arom.). UV λ_{max} =385nm (EtOH).

4-diphenylmethylene-3-methyl-1-(4-hydroxy-6-methyl-2-pyrimidinyl)-pyrazolin-5-one 9. Reddish, m.p. 179-180°C. Yield 50% (MeOH-AcOEt). Anal. Calcd. for $C_{22}H_{18}N_4O_2$: C 71.27, H 4.85, N 15.11. Found: C 71.36, H 4.70, N 15.23. $^1\text{H-NMR}$ δ (CDCl_3): 1.65(3H, s, 3- CH_3), pyrim. ring 6.12(1H, s, 5-H), 2.38(3H, s, 6- CH_3), 7.45-8.10(10H, m, arom.), UV λ_{max} =355nm (EtOH).

4-Isopropylidene-3-methyl-1-(4-hydroxy-6-methyl-2-pyrimidinyl)-pyrazolin-5-one 10. Yellow, m.p. 148-149°C. Yield 75% (Benzene-Ether). Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C 58.47, H 5.68, N 22.74. Found: C 58.32, H 5.76, N 22.63. $^1\text{H-NMR}$ δ (CDCl_3): 2.30(3H, s, 3- CH_3), 2.33(3H, s, 6- CH_3), 2.56(3H, s, 6- CH_3), pyrim. ring 6.14(1H, s, 5-H), 2.47(3H, s, 6- CH_3), UV λ_{max} =290nm (EtOH).

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