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Phenylhydrazine or hydrazine react with 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**) to give 4-acetoacetyl-3-methylpyrazolin-5-ones **4**. The synthesis of bipyrazoles and pyrazoloisoxazoles from **4** are reported.

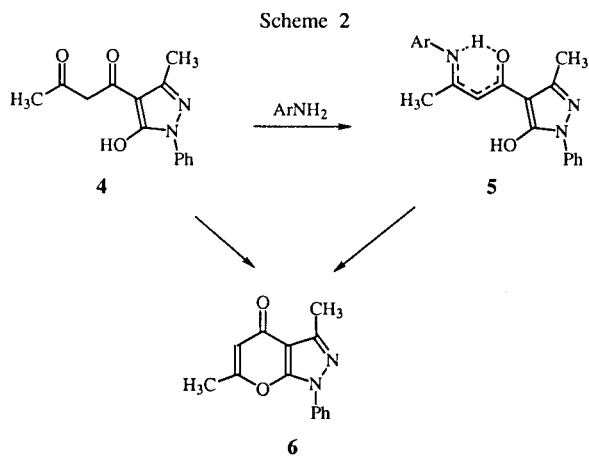
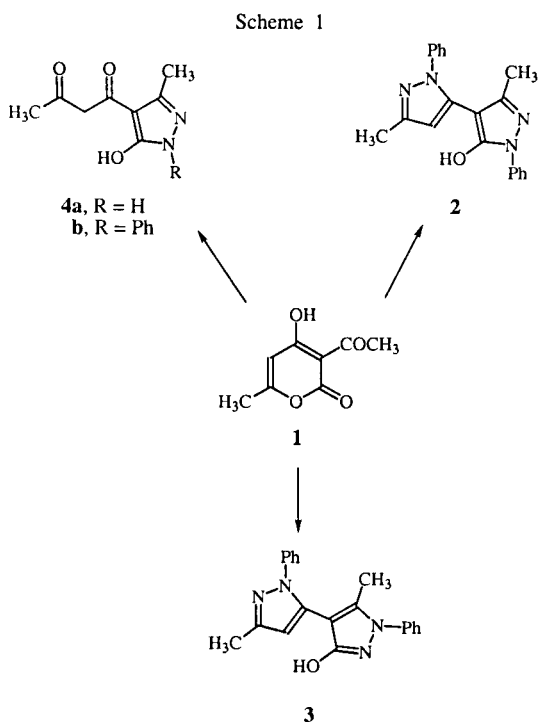
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Dehydroacetic acid, 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**) has been reported to generate a number of heterocyclic compounds through ring opening and cyclization upon treatment with a variety of binucleophiles [1-5]. One such significant reaction was the synthesis of 5-hydroxy-3-methyl-1-phenyl-4-(3-methyl-1-phenylpyrazol-5-yl)pyrazole (**2**) by Gelin *et al.* [6] in 1983. This transformation was used to reestablish the bipyrazole structure of the product obtained by treatment of **1** and phenylhydrazine, correcting an erroneous literature report in 1973 [7].

In 1991 we reported the synthesis 4-acetyl-3-phenyl(substituted)-1-phenylpyrazoles [8]. Surprisingly, in a more recent work of Djerrari *et al.* [9], 3-hydroxy-5-methyl-4-[3-methyl-1-phenylpyrazol-5-yl]-1-phenylpyrazole (**3**), was described from the reaction of

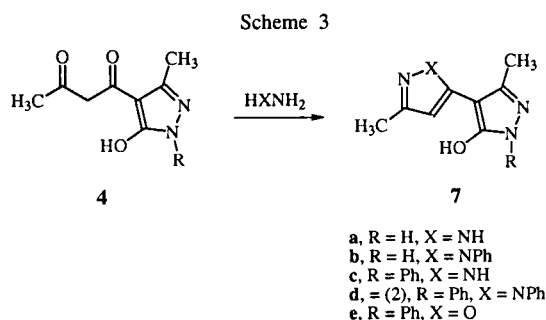
**1** and phenylhydrazine. On the basis of the results, we investigated the action hydrazine and phenylhydrazine on **1** following the literature method. We have found that the hydrazinolysis reaction of **1** affords 4-acetoacetyl-3-methylpyrazolin-5-one (**4**). To our knowledge, this product has never been described by Djerrari [9] (Scheme 1).

We selected the reaction with 4-acetoacetyl-3-methyl-1-phenyl-2-pyrazolin-5-one (**4b**). The reactivity of this latter compound *vis-à-vis* the aromatic amines (alkylamino-deoxy-bisubstitution) has not been reported in the literature. The reaction mixture was heated in ethanol and was followed by thin layer chromatography (eluent: dichloromethane/methanol, 10/1, v/v), which indicated the formation of a single product. After purification and recrystallization, elemental analysis and a pmr study confirm the following structure: 4-(1-oxo-3-arylamino-2-butenyl)-5-hydroxy-3-methyl-1-phenyl-2-pyrazoline (**5**). The ring closure of **4** to **6** was easily accomplished by refluxing in acetic acid in the presence of sulfuric acid [6]. Under similar conditions treatment of **5** afforded the simple pyrazoloisoxazole **6**. The structure of product **6** was confirmed of physico-chemical parameters and literature data [6]. (Scheme 2).



Condensation of binucleophiles (hydrazines, *o*-phenylenediamine, and hydroxylamine) with  $\beta$ -dicarbonyl compounds has been the most widely used method for synthesis of the heterocyclic compounds (pyrazoles, pyrazolones, benzodiazepines, and oxazoles). We report here results on the reactivity of **4** with hydrazine, phenylhydrazine, and hydroxylamine in equal volumes of ethanol and acetic acid.

The structure of compounds **7a-e** was confirmed by elemental analysis,  $^1\text{H}$  and  $^{13}\text{C}$  nmr. The  $^1\text{H}$  and/or  $^{13}\text{C}$  spectra obtained for **7b** and **7d** are in agreement with those of structural analogues reported in the literature [6-9]. The spectra of compounds **7c** and **7e** suggest a pyrazoles structure type **7b** and **7d**. A common fragmentation mode is obtained by mass spectroscopy for compounds **7a**, **7c**, **7d** and **7e**; it corresponds to a proton loss by  $\text{C}_3\text{C}_4$  and  $\text{C}_5\text{N}_1$  bonds breaking. This lends further support to our proposed structures. Compound **7e** has been examined by X-ray crystallography [10] (Scheme 3).



These results indicated a two stage reaction for the formation **7d**: a) intramolecular cyclization of the phenylhydrazone **1** formed by nucleophilic attack of the NH group on position 2 with opening of the pyrone ring and formation of **4b**; b) condensation of binucleophile with the acetoacetyl group of **4b** [8].

This method of preparation is noteworthy from the synthetic point of view as it affords access to a new series of substituted pyrazoles [8] in a simple and rapid reaction. Studies are in progress on their chemical reactivity and potential biological activity.

## EXPERIMENTAL

Melting points were determined in an Electrothermal apparatus. The  $^1\text{H}$  nmr and  $^{13}\text{C}$  nmr were recorded on a Bruker AC 80, ARX 400 MHz and Bruker WM 300 Instruments. Mass spectra were recorded on a Nermag R10-10c quadrupole mass spectrometer.

### 4-Acetoacetyl-3-methyl-2-pyrazolin-5-one (**4a**).

To a solution of **1** (16.8 g, 0.1 mole) in ethanol (60 ml) and water (5 ml) was added hydrazine hydrate (5 ml, 0.1 mole). The

mixture was refluxed while stirring. A precipitate was observed after 20 minutes. First a yellow product separated. The filtrate was allowed to stand at room temperature for two hours, the second precipitate which formed was collected by filtration and the filtrate was allowed to stand in the refrigerator for 12 hours. The precipitate, obtained from the cooled mixture was filtered to give the compound in the crude state, 6 g, mp 200-202°. This crude compound (5 g) was dissolved in 30 ml of acetic acid and refluxed while stirring for two hours. The mixture was poured in the ice-water (100 ml), the precipitate was collected and recrystallized from aqueous ethanol to yield 2.5 g of **4a**, mp 244-245°;  $^1\text{H}$  nmr: (dimethyl- $d_6$  sulfoxide):  $\delta$  keto and enolic forms 2.13 (s, 3H,  $\text{CH}_3$ ), 2.35 (s, 3H,  $\text{CH}_3$ ), 2.51 (s, 3H,  $\text{CH}_3$ ), 2.47 (s, 3H,  $\text{CH}_3$ ), 3.85 (s, 2H,  $\text{CH}_2$ ), 5.72 (s, 1H, CH), 8.32 (s, 1H, NH);  $^{13}\text{C}$ :  $\delta$  ketonic form 145.2 ( $\text{C}_3$ ), 106.8 ( $\text{C}_4$ ), 161.8 ( $\text{C}_5$ ), 190.7 ( $\text{C}_6$ ), 51.1 ( $\text{C}_7$ ), 187.8 ( $\text{C}_8$ ), 25.1 ( $\text{C}_9$ ), 12.8 ( $\text{C}_{10}$ ); ms: (m/z, %), 182 (10), 164 (25), 140 (15), 125 (30), 124 (25), 98 (20), 85 (45), 83 (40), 43 (100).

*Anal.* Calcd. for  $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_3$ : C, 52.74; H, 5.53; N, 15.48. Found: C, 52.70; H, 5.48; N, 15.43.

### 4-Acetoacetyl-3-methyl-1-phenyl-2-pyrazolin-5-one (**4b**).

This compound was prepared by the literature method [6]. Characteristic  $^1\text{H}$  nmr and  $^{13}\text{C}$  spectra data and tautomeric composition of (**4b**) is in agreement with the spectral data in the literature [6]; ms: (m/z, %) 258 (40), 201 (25), 200 (65), 175 (20), 174 (25), 91 (25), 85 (55), 77 (100), 43 (85).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_3$ : C, 65.10; H, 5.46; N, 10.85. Found: C, 65.17. H, 5.50; N, 10.90.

### 4-[1-Oxo-3-arylamino-2-butenyl]-5-hydroxy-3-methyl-1-phenylpyrazole (**5**).

#### General Procedure.

A solution of **4b** (5 mmoles) and arylamine (5 mmoles) in the ethanol (25 ml) was refluxed while stirring for two hours. The precipitate, obtained from the hot solution, was collected and washed several times with hot methanol. Recrystallization is generally unnecessary.

### 4-[1-Oxo-3-phenylamino-2-butenyl]-5-hydroxy-3-methyl-1-phenylpyrazole (**5a**).

This compound was sufficiently pure, (yield 75%), mp 169-170°;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  2.12 (s, 3H,  $\text{CH}_3$ ), 2.47 (s, 3H,  $\text{CH}_3$ ) 5.36 (s, 1H, CH), 7.20-7.92 (m, 11H, 2Ar, NH), 11.96 (s, 1H, OH).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_2$ : C, 72.01; H, 5.79; N, 12.62. Found: C, 71.90; H, 5.56; N, 12.55.

### 4-[1-Oxo-3-(2,4-dichlorophenylamino-2-butenyl)-5-hydroxy-3-methyl-1-phenylpyrazole (**5b**).

This compound was sufficiently pure, (yield 70%), mp 169-170°;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  2.06 (s, 3H,  $\text{CH}_3$ ), 2.48 (s, 3H,  $\text{CH}_3$ ), 5.47 (s, 1H, CH), 7.27-7.90 (m, 9H, 2Ar, NH), 11.96 (s, 1H, OH).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{17}\text{N}_3\text{Cl}_2\text{O}_2$ : C, 59.68; H, 4.26; N, 10.48. Found: C, 59.40; H, 4.20; N, 10.38.

### 4-[1-Oxo-3-(3,4-dichlorophenylamino-2-butenyl)-5-hydroxy-3-methyl-1-phenylpyrazole (**5c**).

A precipitate was observed after 20 minutes, (yield 72%), mp 172-173°;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  2.15 (s, 3H,  $\text{CH}_3$ ), 2.47 (s, 3H,  $\text{CH}_3$ ), 5.43 (s, 1H, CH), 7.07-7.90 (m, 9H, 2Ar, NH), 12.12 (s, 1H, OH).

*Anal.* Calcd. for  $C_{20}H_{17}N_3Cl_2O_2$ : C, 59.68; H, 4.26; N, 10.48. Found: C, 59.50; H, 4.30; N, 10.40.

4-[1-Oxo-3-(2,3-dichlorophenylamino-2-butenyl)-5-hydroxy-3-methyl-1-phenylpyrazole (**5d**).

A precipitate was observed after 1.5 hour, (yield 70%), mp 149-150°;  $^1H$  nmr (deuteriochloroform):  $\delta$  2.07 (s, 3H,  $CH_3$ ), 2.48 (s, 3H,  $CH_3$ ), 4.58 (s, 1H, CH), 7.15-7.82 (m, 9H, 2Ar, NH), 12.20 (s, 1H, OH).

*Anal.* Calcd. for  $C_{20}H_{17}N_3Cl_2O_2$ : C, 59.68; H, 4.26; N, 10.48. Found: C, 59.60; H, 4.25; N, 10.50.

3,6-Dimethyl-1-phenylpyrano[2,3-c]pyrazole-4(1H)-one (**6**).

To a solution of **5a-d** (5 mmoles) in 30 ml of acetic acid was added concentrated sulfuric acid (1 ml). The mixture was allowed to stand at room temperature for two hours, then poured into ice-water. The precipitate was filtered, washed several times with cold water and dried to give crude product **6**, recrystallized from acetonitrile, yield 70%, mp 150-152° (lit [6] 150°).

5-Hydroxy-3-methyl-4-(3-methyl-1-phenylpyrazol-5-yl)pyrazole (**7a**).

To a solution **4a** (1.8 g, 0.01 mole) in a mixture of ethanol (40 ml) and acetic acid (40 ml) a solution of phenylhydrazine (1 ml, 98%) in ethanol (5 ml) was gradually added and refluxed for three hours. The solvent was removed under reduced pressure and the viscous residue was washed with hot ether then hot ethanol. The solid thus formed was collected by filtration, yield (45%), mp 285° dec;  $^1H$  nmr (dimethyl- $d_6$  sulfoxide):  $\delta$  1.75 (s, 3H,  $CH_3$ ), 2.10 (s, 3H,  $CH_3$ ), 6.30 (s, 1H, CH) 7.30-7.60 (m, 5H, Ph), 9.50 (broad s, 2H, deuterium oxide-exchangeable); ms: m/z 254 ( $M^+$ , 100), 334 (15), 236 (10), 223 (10), 212 (20), 211 (15), 197 (50), 169 (10), 77 (15), 51 (10).

*Anal.* Calcd. for  $C_{14}H_{14}N_4O$ : C, 66.12; H, 5.55; N, 22.03. Found: C, 66.08; H, 5.60; N, 22.10.

5-Hydroxy-3-methyl-4-(3-methylpyrazol-5-yl)pyrazole (**7b**).

Dehydroacetic acid (**1**) (8.4 g, 0.05 mole) and hydrazine monohydrate (98%, 0.05 mole) were refluxed in ethanol (50 ml) for 20 minutes and then allowed to stand in the refrigerator for three hours. The solid that separated was recrystallized from ethanol to afford yellow crystals, yield (55%), mp 260-261°;  $^1H$  nmr (dimethyl- $d_6$  sulfoxide):  $\delta$  2.18 (s, 3H,  $CH_3$ ), 2.37 (s, 3H,  $CH_3$ ), 6.35 (s, 1H, CH), 10 (broad, 3H, deuterium oxide-exchangeable); ms: m/z 178 ( $M^+$ , 30), 164 (15), 150 (20), 149 (20), 139 (25), 125 (10), 124 (5), 121 (10), 83 (10), 43 (15).

*Anal.* Calcd. for  $C_8H_{10}N_4O$ : C, 53.92; H, 5.65; N, 31.44. Found: C, 53.94; H, 5.65; N, 31.47.

5-Hydroxy-3-methyl-1-phenyl-4-(3-methylpyrazol-5-yl)pyrazole (**7c**).

To a solution of 2.6 g (0.01 mole) of **4b** in 40 ml of ethanol, a solution of hydrazine monohydrate in ethanol (5 ml) was added over a period of 10 minutes. After the addition was complete, the solution was refluxed for 1.5 hours. The mixture was cooled and then allowed to stand in the refrigerator for 24 hours. The solid was collected by filtration and recrystallized from methanol, yield (50%), mp 123-124°;  $^1H$  nmr (dimethyl- $d_6$  sulfoxide):  $\delta$  2.28 (s, 3H,  $CH_3$ ), 2.42 (s,

3H,  $CH_3$ ), 6.35 (s, 1H, CH), 7.21 (m, 5H, Ph), 9.25 (broad, 2H, deuterium oxide-exchangeable);  $^{13}C$  nmr (dimethyl- $d_6$  sulfoxide): 10.4 ( $C_3$ - $CH_3$ ), 11.3 ( $C_3$ - $CH_3$ ), 97.4 ( $C_4$ ), 101.6 ( $C_4$ ), 121.0, 126.3, 128.7, 136.2, (C-Phenyl), 140.4 ( $C_4$ ), 143.7 ( $C_3$ ), 159.3 ( $C_5$ ); ms: m/z 254 ( $M^+$ , 55), 225 (5), 211 (11), 184 (10), 162 (5), 148 (5), 134 (5), 121 (50), 106 (10), 94 (10), 91 (15), 77 (100), 65 (25), 53 (20), 52 (20), 51 (50), 43 (40).

*Anal.* Calcd. for  $C_{14}H_{14}N_4O$ : C, 66.12; H, 5.55; N, 22.03. Found: C, 66.10; H, 5.50; N, 22.06.

5-Hydroxy-3-methyl-1-phenyl-4-(3-methyl-1-phenylpyrazol-5-yl)pyrazole (**7d**).

Dehydroacetic acid **1** (8.4 g, 0.05 mole) and phenylhydrazine (5.4 g, 0.05 mole) were refluxed in a mixture of ethanol (50 ml) and acetic acid (50 ml) for two hours. The reaction mixture was allowed to stand at room temperature. The precipitate was separated and recrystallized from dimethylformamide-ethanol, yield (50%), mp 260-261°. The same product was obtained when the mixture of **4b** and phenylhydrazine was refluxed in ethanol for two hours yield (60%), mp 261-263°;  $^1H$  nmr 1.77 (s, 3H,  $CH_3$ ), 2.29 (s, 3H,  $CH_3$ ), 6.31 (s, 1H, CH), 7.24-7.66 (m, 10H, Ar), 11.50 (broad, 1H, deuterium oxide-exchangeable);  $^{13}C$  nmr (dimethyl- $d_6$  sulfoxide):  $\delta$  12.9 ( $C_3$ - $CH_3$ ), 13.8 ( $C_3$ - $CH_3$ ), 97.2 ( $C_4$ ), 109.8 ( $C_4$ ), 123.8, 127.0, 129.2, 129.3, 134.6, (C-Ar), 140.7 ( $C_5$ ), 147.3 ( $C_3$ ), 148.6 ( $C_3$ ), 159.0 ( $C_5$ ); ms: m/z 330 ( $M^+$ , 100), 313 (5), 287 (5), 260 (10), 225 (10), 210 (10), 197 (50), 182 (10), 169 (15), 154 (10), 132 (5), 128 (10), 105 (10), 91 (15), 77 (60), 51 (20), 43 (10).

*Anal.* Calcd. for  $C_{20}H_{18}N_4O$ : C, 72.71; H, 5.49; N, 16.96. Found: C, 72.80; H, 5.58; N, 16.80.

5-Hydroxy-3-methyl-1-phenyl-4-(3-methylisoxazol-5-yl)pyrazole (**7e**).

A solution of 2.6 g (0.01 mole) of **4b** and 0.7 g (0.01 mole) of hydroxylamine hydrochloride in 50 ml of ethanol and 50 ml of acetic acid was heated at reflux for two hours. The reaction mixture was cooled and then allowed to stand in the refrigerator for 12 hours. The solid was collected and recrystallized from ethanol, yield (65%), mp 125-126°;  $^1H$  nmr:  $\delta$  2.31 (s, 3H,  $CH_3$ ), 2.56 (s, 3H,  $CH_3$ ), 6.52 (s, 1H, CH), 7.34-7.66 (m, 5H, Ph);  $^{13}C$  nmr: 12.5 ( $C_3$ - $CH_3$ ), 11.3 ( $C_3$ - $CH_3$ ), 94.9 ( $C_4$ ), 99.2 ( $C_4$ ), 120.7, 126.1, 129.4, 138.0, (C-Ar), 146.3 (C-3), 158.6 (C-3'), 159.5 (C-5), 164.2 (C-5'); ms: m/z 255 ( $M^+$ , 100), 213 (20), 200 (25), 185 (20), 157 (5), 144 (20), 132 (25), 130 (15), 122 (10), 118 (20), 105 (10), 91 (30), 82 (25), 77 (80), 67 (40), 51 (45), 39 (25).

*Anal.* Calcd. for  $C_{14}H_{13}N_3O_2$ : C, 65.87; H, 5.13; N, 16.46. Found: C, 65.80; H, 5.10; N, 16.37.

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