

Novel Preparation of 1-Aryl-3-(2-hydroxyphenyl)-2-pyrazolin-5-ones and their Conversion into 2-Aryl-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-ones†

J. Chem. Research (S),
1997, 30–31†

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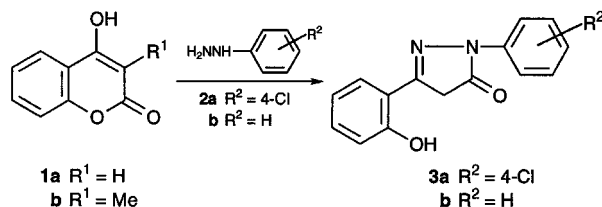
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1-Aryl-3-(2-hydroxyphenyl)-2-pyrazolin-5-ones are prepared from 4-hydroxycoumarin and arylhydrazines and then cyclised with triethyl orthoacetate to give 2-aryl-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-ones.

In the search for routes to 1-aryl-3-(2-hydroxyphenyl)-2-pyrazolin-5-ones it was found that one possibility, the reaction of 4-hydroxycoumarin with arylhydrazines, was not well documented.

Whereas Chantegrel and Gelin¹ described the synthesis of 3-(2-hydroxyaryl)-1-methyl-2-pyrazolin-5-ones by the regioselective reaction of methylhydrazine with 4-hydroxycoumarin **1a**, Heubner and Link² reported, and we have confirmed, that phenylhydrazine **2b** on reaction with **1a** at 120 °C gave 3-(2-hydroxyphenyl)-1-phenyl-4-phenylazo-3-pyrazolin-5-one **4**. In contrast to this we now report a simple one-pot preparation of 1-aryl-3-(2-hydroxyphenyl)-2-pyrazolin-5-ones **3a,b** from the reaction of 4-chlorophenylhydrazine **2a** or phenylhydrazine **2b** with 4-hydroxycoumarin **1a**. This avoids the only other, lengthier, route to **3** published by Colotta *et al.*,³ which involves reaction of the β -ketoester **5** with arylhydrazines followed by debenzylolation.

Thus reaction of 4-hydroxycoumarin **1a** with a 1.5 molar excess of arylhydrazines **2a,b** in toluene under reflux, with azeotropic removal of water, gave the 1-aryl-3-(2-hydroxyphenyl)-2-pyrazolin-5-ones **3a,b** (Scheme 1) in 60–70% yield.⁴ The melting points and ¹H NMR data for **3a,b** are in agreement with those reported by Colotta *et al.*³



Scheme 1

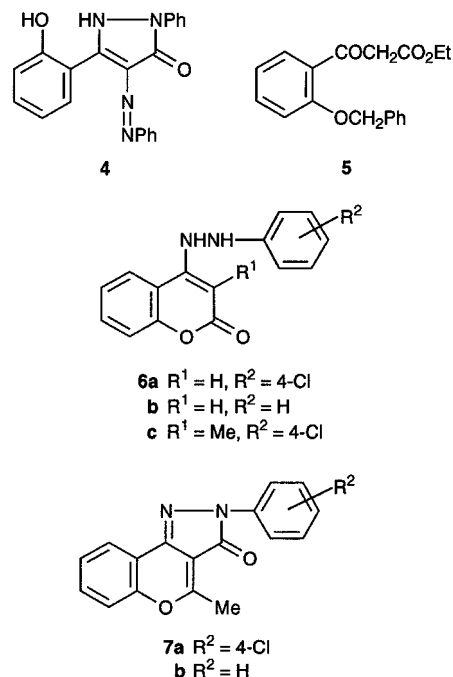
Arylhydrazinocoumarins **6a,b** are intermediates in the one-pot reaction and, as by products, can be removed by virtue of their insolubility in dichloromethane. Coumarin **6a** was isolated as a major reaction product when 1 equiv. of the arylhydrazine was used in the reaction.

In contrast, the reaction of 4-hydroxy-3-methylcoumarin **1b** with 4-chlorophenylhydrazine **2a** gave the arylhydrazinocoumarin **6c** as the sole product. Rearrangement to the pyrazolinone is presumably prevented due to steric hindrance by the methyl group.

Heating the pyrazolin-5-ones **3a,b** with triethyl orthoacetate¹ at 140–150 °C gave cyclisation to 4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-ones **7a,b**.^{3,4} Compound **7a** is a potent immunosuppressant.⁵

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were



carried out on a Carlo-Erba 1106/1 elemental analyser. IR spectra were recorded on a Unicam FTIR 3020 spectrometer and ¹H NMR spectra on a Bruker AC 250 spectrometer using tetramethylsilane as internal standard. Mass spectra were recorded on a Finnegan MAT 8200 mass spectrometer.

Typical Procedure.—1-(4-Chlorophenyl)-3-(2-hydroxyphenyl)-2-pyrazolin-5-one **3a**. 5 M Sodium hydroxide (50 cm³) was added to a suspension of 4-chlorophenylhydrazine hydrochloride (22.7 g, 0.138 mol) in water (600 cm³), maintaining the temperature at 20 °C. The mixture was extracted with diethyl ether (3 × 200 cm³) and the extracts were washed with water (200 cm³), dried (MgSO₄) and evaporated under reduced pressure below 40 °C. To the thus isolated 4-chlorophenylhydrazine (18.90 g, 0.133 mol) was added immediately 4-hydroxycoumarin (14.25 g, 0.088 mol) and dry toluene (150 cm³) and the resultant mixture was stirred under reflux with a Dean–Stark trap. After 2 h, water separated (1.6 cm³, 0.088 mol) and the solution was allowed to cool to yield the *title compound* **3a** as orange crystals, mp 190–191 °C (19.8 g, 72.5%) (Found: C, 63.1; H, 4.0; Cl, 12.8; N, 10.1%; M⁺, 286.0494. C₁₅H₁₁ClN₂O₂ requires C, 63.1; H, 4.0; Cl, 12.8; N, 10.1%; M, 286.0509); δ_{H} (CDCl₃) 3.9 (2 H, s, CH₂), 6.9–7.8 (8 H, m, aromatic protons), 10.0 (1 H, s, OH).

1-Phenyl-3-(2-hydroxyphenyl)-2-pyrazolin-5-one **3b**. Mp 129–131 °C (56% yield) (Found: C, 71.8; H, 4.9; N, 11.35; M⁺, 252.0900. C₁₅H₁₂N₂O₂ requires C, 71.4; H, 4.8; N, 11.1%; M, 252.0899); δ_{H} (CDCl₃) 3.9 (2 H, s, CH₂), 6.9–7.8 (8 H, m, aromatic protons), 10.1 (1 H, s, OH).

4-(4-Chlorophenylhydrazino)coumarin **6a**. Repetition of the procedure for **3a** but with only an equimolar amount of 4-chlorophenylhydrazine (12.5 g, 0.088 mol) gave a mixture of **3a** and **6a** on filtration of the cooled reaction mixture. Digestion of the solid with boiling dichloromethane (250 cm³), followed by recrystallisation from industrial methylated spirits, gave **6a** as a colourless solid (2.1 g, 8% yield) (Found: C, 63.0; H, 3.9; Cl, 12.7; N, 8.9%; M⁺, 286.0494. C₁₅H₁₁ClN₂O₂ requires C, 63.1; H, 4.0; Cl, 12.8; N, 10.1%;

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M, 286.0509); δ_{H} [(CD₃)₂SO] 5.4 (1 H, s, CH), 6.8–8.3 (8 H, m, aromatic protons), 8.45 (1 H, s, NH), 9.85 (1 H, s, NH).

4-(4-Chlorophenylhydrazino)-3-methylcoumarin **6c**. Repetition of the procedure for **3a** but starting from 4-hydroxy-3-methylcoumarin gave **6c**, mp 218–220 °C (85% yield) (Found: C, 63.7; H, 4.1; Cl, 11.5; N, 9.1%; M⁺, 300.0662. C₁₆H₁₃ClN₂O₂ requires C, 63.9; H, 4.3; N, 9.3; Cl, 11.8%; M, 300.0665); δ_{H} [(CD₃)₂SO] 2.0 (3 H, s, Me), 3.35 (1 H, brs, NH), 6.9–7.9 (8 H, m, aromatic protons), 10.7 (1 H, brs, NH).

2-(4-Chlorophenyl)-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one **7a**. A mixture of **3a** (60 g, 0.21 mol) and triethyl orthoacetate (115 cm³, 101.8 g, 0.63 mol) was stirred and heated at 140–150 °C for 30 min. The reaction mixture was allowed to cool to room temperature and was then diluted with diethyl ether (20 cm³). The product was filtered to afford the *title compound* **7a** as yellow crystals (62.4 g, 96%), mp 204–206 °C (Found: C, 65.8; H, 3.55; Cl, 11.6; N, 8.9%; M⁺, 310.0513. C₁₇H₁₁ClN₂O₂ requires C, 65.7; H, 3.5; Cl, 11.1; N, 9.0%; M, 310.0509); δ_{H} [(CD₃)₂SO] 2.83 (3 H, s, Me), 7.5–8.3 (8 H, m, aromatic protons).

2-Phenyl-4-methyl[1]benzopyrano[4,3-c]pyrazol-3(2H)-one **7b**. Mp 163–165 °C (57% yield) (Found: C, 73.9; H, 4.5; N, 10.2%; M⁺, 276.0899. C₁₇H₁₂N₂O₂ requires C, 73.9; H, 4.35; N, 10.1%; M,

276.0899); δ_{H} [(CD₃)₂SO] 2.8 (3 H, s, Me), 7.2–8.1 (9 H, m, aromatic protons).

We thank Dr R. V. Davies for helpful discussions.

Received, 5th August 1996; Accepted, 18th October 1996

Paper E/6/05456K

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