Indian Journal of Chemistry
Vol. 44B, February 2006, pp. 456-460

Iodine (III) mediated synthesis of new 5-aryl-3-(4-hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenylpyrazoles from dehydrogenation of 5-aryl-3-(4-hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenylpyrazolines

Om Prakash*, Ajay Kumar, Mayank Kinger & Shiv P Singh

Department of Chemistry, Kurukshetra University, Kurukshetra 136 119, Haryana, India

E-mail: dromprakash50@rediffmail.com

Received 02 June 2004; accepted (revised) 13 June 2005

3-Cinnamoyl-4-hydroxy-6-methyl-2-pyrones (chalcone analogs of DHA) on condensation with phenylhydrazine in ethanol, yield 5-aryl-3-(4-hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenylpyrazolines which undergo smooth dehydrogenation to the corresponding pyrazoles in good yield upon treatment with iodobenzene diacetate (IBD).

Keywords: Iodine, phenylpyrazoles, dehydrogenation, phenylpyrazolines

IPC: **Int.Cl.[7] C 07 D**

Pyrazoles have emerged as a group of compounds possessing a broad spectrum of useful medicinal properties such as analgesic, antipyretic, antiinflammatory, germicidal and antifungal activities[1,2]. Among the new pyrazole derivatives, the synthesis of 5-aryl-3-(4-hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenylpyrazoles is of particular interest.

Thus, 3-cinnamoyl-4-hydroxy-6-methylpyran-2-ones (**2**) obtained by the reaction[3] of dehydroacetic acid (DHA, **1**) with various aryl/hetaryl aldehydes were treated with phenylhydrazine to give the corresponding pyrazoline derivatives **3** (ref. 4). Oxidation of pyrazolines **3** was initially attempted by using $Br_2/CHCl_3$. However, repeated efforts ended up with the recovery of starting material **3** and not the desired product **4** (**Scheme I**).

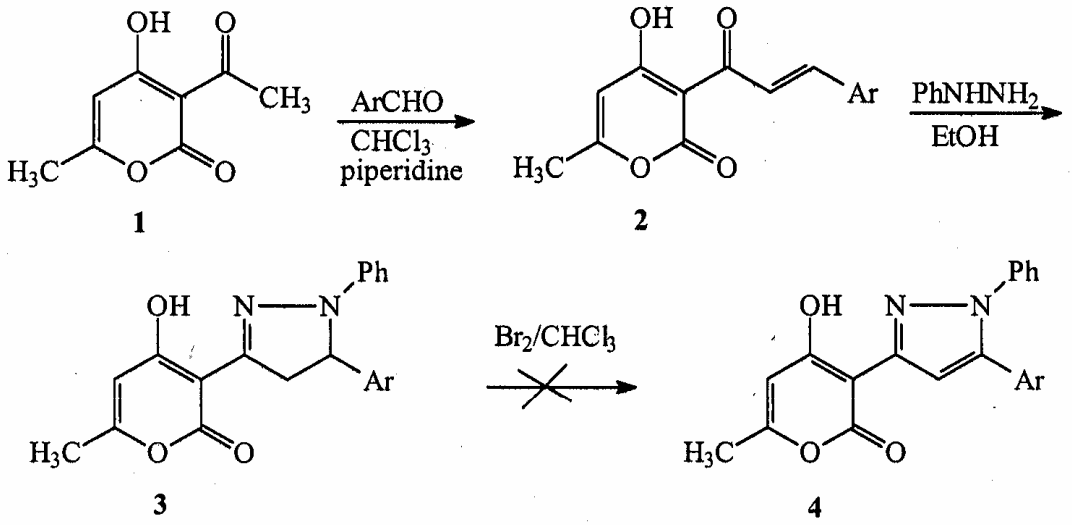
This failure led us to attempt an alternative existing route involving the cyclization of dibromochalcones with hydrazines[5]. Surprisingly, in most of the cases, there was no success in converting dibromo derivatives of the chalcones to the corresponding pyrazole derivatives. The only exception where the desired product could be isolated, was in the case of **4** (when Ar = *p*-tolualdehyde). In this example, the reaction of dibromo derivative of DHA chalcone **5** with phenylhydrazine afforded **4** in 25% yield together with 60% unreacted starting material **5** (**Scheme II**).

In view of the difficulties encountered in the foregoing efforts and encouraged by previous results[6] in the successful conversion of pyrazolines to pyrazoles using IBD, the transformation using this reagent was now attempted.

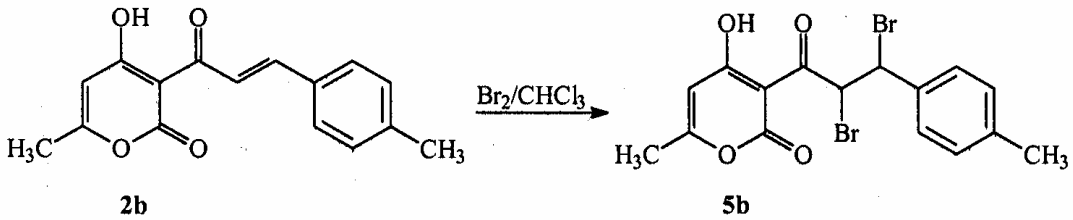
The pyrazolines **3** were treated with 1 equivalent of IBD in CH_2Cl_2 at rt for 2 hr. Interestingly, the reaction smoothly afforded the desired pyrazole derivatives **4** in 80-85% yield (**Scheme III**).

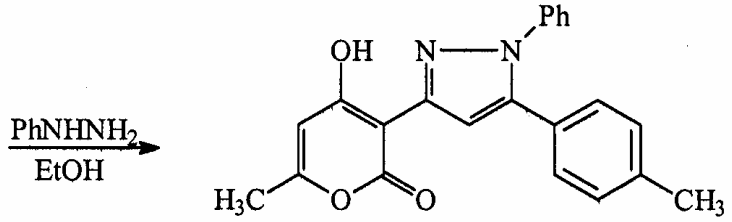
It is to be mentioned here that many conventional oxidizing agents namely potassium ferricyanide, silver nitrate, mercuric nitrate, colloidal platinum, mercuric acetate and lead oxide have also been used for the dehydrogenation of pyrazolines. A careful examination reveals that most of these methods suffer from some serious drawback or the other. To illustrate, catalytic dehydrogenation using colloidal platinum results in the formation of a mixture containing the corresponding pyrazoles and pyrazolidines[7]. Similarly, the oxidation of pyrazolines involving manganese dioxide results in the formation of biphenyl in addition to the desired pyrazoles[8]. Moreover, toxicity associated with reagents such as mercuric acetate, mercuric oxide, lead tetraacetate and lead oxide make their use rather undesirable.

It is amply clear from these results that the use of IBD not only gives a clean product, but the reaction can be carried out under mild conditions with easy isolation of products.

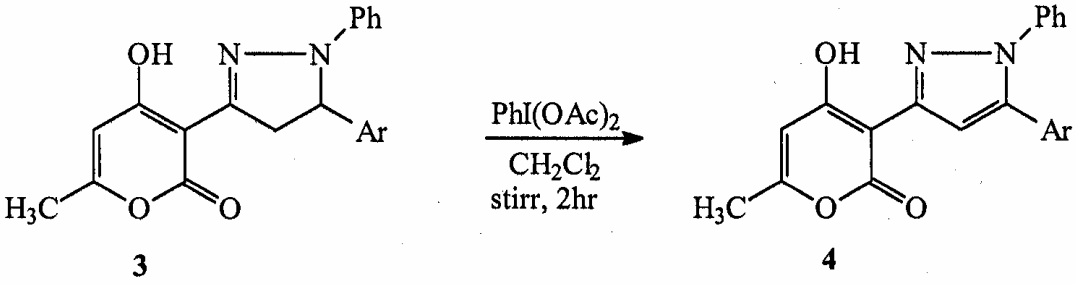


Scheme I





Scheme II



2, 3, 4	Ar	2, 3, 4	Ar
a	C_6H_5	d	2-furyl
b	4-$CH_3C_6H_4$	e	2-thienyl
c	4- ClC_6H_4	f	4-pyridyl

Scheme III

Characterization of the products **4a-f** was based on a careful comparison of ^{1}H NMR spectra with those of **3a-f**. The spectra of pyrazolines **3** showed signals around δ 3.03-3.12 (dd, 1H, C_4-H_A of pyrazoline), 4.01-4.12 (dd, 1H, C_4-H_B of pyrazoline), 5.07-5.12 (dd, 1H, C_3-H of pyrazoline), whereas the spectra of the corresponding oxidized products **4** were devoid of all these signals. While analyzing the ^{1}H NMR spectra of **4**, an interesting observation was made. The C_4-H signal which usually appears at about δ 6.5-6.6 in such pyrazole derivatives, appeared at δ 7.2-7.4 in **4**. An attempt was made to explain the downfield shift of C_4-H using semiempirical calculations, *i.e.*, AM1 calculations using MOPAC Program[9].

Semiempirical AM1 Calculations

All semiempirical calculations were done using AM1 method incorporated in MOPAC Package[10]. AM1 is a re-parameterization of semiempirical MNDO method (MNDO = Modified Neglect of Diatomic Overlap), which is based on NDDO (NDDO = Neglect of Diatomic Differential Overlap) approximation. The optimized geometry of pyrazole derivative obtained from AM1 calculations is as given below. It reveals that all the rings are planar in geometry as they lie in the same plane.

It was found from the calculations that the electron density at 4th carbon of 3-substituted-1,5-diphenylpyrazole was 4.2062 when the substituent was H, CH_3 or Ph at position 3. However, when 4-hydroxy-6-methyl-2-oxopyran-3-yl (ring of DHA) was placed as the substituent at position 3, the electron density at 4th carbon of pyrazole was reduced to 4.1829. It can thus be concluded that electron density is one of the factors for the deshielding of C_4H of pyrazole derivative **4**.

Experimental Section

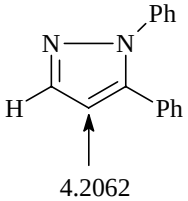
Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker 300 MHz instrument using TMS as an internal standard. IR spectra were recorded on a Buck Scientific IR M-500 spectrophotometer. Elemental analysis were carried out in a Perkin Elmer-2400 instrument and mass spectra were recorded on Kratos MS-50 mass spectrometer. Most of the common chemicals such as dehydroacetic acid, aldehydes, phenylhydrazine, *etc*. were obtained from commercial suppliers. 3-Cinnamoyl-4-hydroxy-6-methyl-2-pyrones (chalcone analogs of DHA, **2a-f**) were prepared according to literature procedure[3].

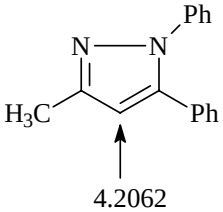
General procedure for the synthesis of 5-aryl- 3-(4-hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenyl-pyrazoline 3.

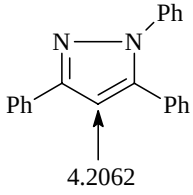
A solution of 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrones (**2**, 0.002 mole) and phenyl hydrazine (0.2 mL, 0.002 mole) in ethanol (25 mL) containing 6-8 drops of acetic acid was heated under reflux for 2 hr. Excess of ethanol was distilled off under reduced pressure. After cooling the reaction mixture, the product which separated out was filtered, washed with a little ethanol and purified by recrystallization from ethanol to afford **3**.

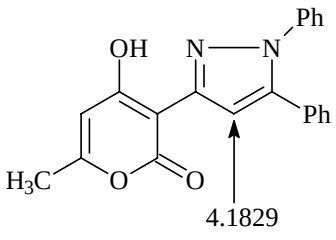
3-(4-Hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1,5-diphenylpyrazoline 3a: Yield 85%; m.p. 158-59 °C, (Lit.[4] 160 °C); ^{1}H NMR ($CDCl_3$): δ 2.4 (s, 3H, CH_3), 3.63-3.65 (dd, 1H, C_4-H_A), 4.11-4.12 (dd, 1H, C_4-H_B), 5.37-5.39 (dd, 1H, C_3-H), 6.04 (s, 1H, $C_{5'}$-H, DHA), 7.0-7.5 (m, 10H, Ar), 13.5 (s, 1H, OH); IR (KBr): 1728 cm^{-1} (C=O).

5-(4-Methylphenyl)-3-(4-hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenylpyrazoline 3b: Yield 83%; m.p. 182-83 °C, (Lit.[4] 184 °C); ^{1}H NMR









($CDCl_3$): δ 2.3 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.65-3.68 (dd, 1H, C_4-H_A), 4.12-4.15 (dd, 1H, C_4-H_B), 5.40-5.42 (dd, 1H, C_3-H), 6.08 (s, 1H, $C_{5'}$-H, DHA), 7.0-7.5 (m, 9H, Ar), 13.5 (s, 1H, OH); IR (KBr): 1725 cm^{-1} (C=O).

5-(4-Chlorophenyl)-3-(4-hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenylpyrazoline 3c: Yield 84%; m.p. 208-10 °C; ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H, CH_3), 3.64-3.65 (dd, 1H, C_4-H_A), 4.11-4.13 (dd, 1H, C_4-H_B), 5.41-5.42 (dd, 1H, C_3-H), 6.02 (s, 1H, $C_{5'}$-H, DHA), 7.2-7.7 (m, 9H, Ar), 13.5 (s, 1H, OH); IR (KBr): 1723 cm^{-1} (C=O). Anal. Found: C, 73.08; H, 4.95; N, 8.14; $C_{21}H_{17}ClN_2O_3$ requires: C, 73.04; H, 4.93; N, 8.12 %.

5-(2-Furyl)-3-(4-hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenylpyrazoline 3d: Yield 80%; m.p. 210-11 °C; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 3.63-3.65 (dd, 1H, C_4-H_A), 4.15-4.17 (dd, 1H, C_4-H_B), 5.40-5.42 (dd, 1H, C_3-H), 6.02 (s, 1H, $C_{5'}$-H, DHA), 7.2-7.6 (m, 8H, Ar), 13.5 (s, 1H, OH); IR (KBr): 1720 cm^{-1} (C=O). Anal. Found: C, 67.88; H, 4.79; N, 8.30; $C_{19}H_{16}N_2O_4$ requires: C, 67.86; H, 4.76; N, 8.33 %.

3-(4-Hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenyl-5-(2-thienyl)-pyrazoline 3e: Yield 81%; m.p. 218-19 °C; ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 3.63-3.65 (dd, 1H, C_4-H_A), 4.14-4.16 (dd, 1H, C_4-H_B), 5.38-5.40 (dd, 1H, C_3-H), 6.08 (s, 1H, $C_{5'}$-H, DHA), 6.9-7.2 (m, 8H, Ar), 13.5 (s, 1H, OH); IR (KBr): 1722 cm^{-1} (C=O). Anal. Found: C, 64.79; H, 4.57; N, 7.92; $C_{19}H_{16}N_2O_3S$ requires: C, 64.77; H, 4.55; N, 7.95 %.

3-(4-Hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenyl-5-(4-pyridyl)-pyrazoline 3f: Yield 80%; m.p. 138-39 °C; ^{1}H NMR ($CDCl_3$): δ 2.4 (s, 3H, CH_3), 3.03-3.12 (dd, 1H, C_4-H_A), 4.01-4.12 (dd, 1H, C_4-H_B), 5.07-5.12 (dd, 1H, C_3-H), 6.0 (s, 1H, $C_{5'}$-H, DHA), 7.0-7.7 (m, 9H, Ar), 13.5 (s, 1H, OH); IR (KBr): 1726 cm^{-1} (C=O). Anal. Found: C, 69.18; H, 4.87; N, 12.04; $C_{20}H_{17}N_3O_3$ requires: C, 69.16; H, 4.89; N, 12.01 %.

General procedure for the synthesis of 5-aryl-3-(4-hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenylpyrazole 4.

To a stirred solution of **3** (0.001 mole) in dichloromethane (15 mL) was added IBD (0.386 g, 0.0012 mole) at rt. The reaction mixture was stirred for 5 hr. Dichloromethane was distilled off on a steam bath and the residual gummy mass was triturated with pet-ether to remove iodobenzene and was purified by recrystallization from ethanol to afford the title compound **4** in excellent yield (80-85%).

3-(4-Hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1,5-diphenylpyrazole 4a: Yield 85%; m.p. 148-49°C; ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H, CH_3), 6.0 (s, 1H, $C_{5'}$-H, DHA), 7.1 (s, 1H, C_4-H), 7.0-7.5 (m, 10H, Ar), 13.5 (s, 1H, OH); IR (KBr): 1728 cm^{-1} (C=O). Anal. Found: C, 73.28; H, 4.69; N, 8.09; $C_{21}H_{16}N_2O_3$ requires: C, 73.26; H, 4.65; N, 8.14 %.

5-(4-Methylphenyl)-3-(4-hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenylpyrazole 4b: Yield 81%; m.p. 158-59 °C; ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 6.02 (s, 1H, $C_{5'}$-H, DHA), 7.3 (s, 1H, C_4-H), 7.0-7.5 (m, 9H, Ar), 13.5 (s, 1H, OH); IR (KBr): 1725 cm^{-1} (C=O). Anal. Found: C, 73.79; H, 5.09; N, 7.77; $C_{22}H_{18}N_2O_3$ requires: C, 73.74; H, 5.03; N, 8.16 %.

5-(4-Chlorophenyl)-3-(4-hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenylpyrazole 4c: Yield 82%; m.p. 178-79 °C; ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3), 6.0 (s, 1H, $C_{5'}$-H, DHA), 7.4 (s, 1H, C_4-H), 7.0-7.7 (m, 9H, Ar), 13.5 (s, 1H, OH); IR (KBr): 1723 cm^{-1} (C=O). Anal. Found: C, 73.42; H, 4.39; N, 8.14; $C_{21}H_{15}N_2O_4$ requires: C, 73.47; H, 4.37; N, 8.16 %.

5-(2-Furyl)-3-(4-hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenylpyrazole 4d: Yield 80%; m.p. 121-22 °C; ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H, CH_3), 6.05 (s, 1H, $C_{5'}$-H, DHA), 7.2 (s, 1H, C_4-H), 7.0-7.4 (m, 8H, Ar), 13.5 (s, 1H, OH); IR (KBr): 1720 cm^{-1} (C=O); MS: m/z 334. Anal. Found: C, 68.29; H, 4.23; N, 8.44; $C_{19}H_{14}N_2O_4$ requires: C, 68.26; H, 4.19; N, 8.38 %.

3-(4-Hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenyl-5-(2-thienyl)pyrazole 4e: Yield 85%; m.p. 135-36 °C; ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H, CH_3), 6.0 (s, 1H, $C_{5'}$-H, DHA), 7.3 (s, 1H, C_4-H), 6.9-7.3 (m, 8H, Ar), 13.5 (s, 1H, OH); IR (KBr): 1722 cm^{-1} (C=O). Anal. Found: C, 65.18; H, 4.05; N, 7.94; $C_{19}H_{14}N_2O_3S$ requires: C, 65.14; H, 4.00; N, 8.00 %.

3-(4-Hydroxy-6-methyl-2*H*-pyran-2-oxo-3-yl)-1-phenyl-5-(4-pyridyl)pyrazole 4f: Yield 85%; m.p. 158-59 °C; ^{1}H NMR ($CDCl_3$): δ 2.4 (s, 3H, CH_3), 6.05 (s, 1H, $C_{5'}$-H, DHA), 7.3 (s, 1H, C_4-H), 7.2-7.7 (m, 9H, Ar), 13.5 (s, 1H, OH); IR (KBr): 1726 cm^{-1} (C=O). Anal. Found: C, 69.64; H, 4.39; N, 12.09; $C_{20}H_{15}N_3O_3$ requires: C, 69.57; H, 4.35; N, 12.17 %.

Acknowledgement

The authors are thankful to DRDO (ERIP/ER/0103294/M/01), New Delhi for financial assistance. The authors are also grateful to Prof. R.K. Bansal, Department of Chemistry, University of Rajsthan,

Jaipur, for providing help related to molecular modeling and also to UCSF mass spectrometry facility, USA for providing mass spectra.

References

1 (a) Goodman L S & Gilman A in *The Pharmacological Basis of Therapeutics*, (Macmillan, New York) **1980**; (b) Wachter M & Ferro M, *US Patent*, **1989**, 4826868, *Chem Abstr* 108, **1988**, 186735v; (c) Argentieri D, Ritchie D, Tolman E, Ferro M, Watcher M, Mezick J & Capetola R, *The FASEB J Antiinflammatory Agents*, 4 (2), **1988**, A369.

2 (a) Secor H V & De Bardelaben J F, *J Med Chem*, 14, **1971**, 997; (b) Bauer V J, Fanshawe W J, Dalalian H P, Safir S R, Tocus E C & Boshart C R, *J Med Chem*, 11, **1968**, 981; (c) Corsi G, Germani C, Palazzo G, Silvest Rini B & Barcellone P S, *J Med Chem*, 19, **1976**, 778; (d) Durham N N, Chesnut R W, Hashen M M & Berlin K D, *J Med Chem*, 19, **1976**, 229.

3 Wiley R H, Jarboe C H & Ellert H G, *J Am Chem Soc*, 77, **1955**, 5102.

4 Mahesh V K & Gupta R S, *Indian J Chem*, 12B, **1974**, 956.

5 Sharma T C, Saxena M K & Bokadia M M, *Indian J Chem*, 9, **1971**, 794.

6 Singh S P, Kumar D, Prakash O & Kapoor R P, *Synth Commun*, 27(45), **1997**, 2683.

7 Golubeva G A, *Hydrogenation and the Catalytic Cleavage of Nitrogen-Nitrogen links in Pyrazolines*, Ph D Thesis, Moscow University, **1962**.

8 Bhatnagar I & George M V, *Tetrahedron*, 24, **1968**, 1293.

9 Stewart J J P, *Comp Chem*, 10, **1989**, 209.

10 MOPAC 6.0, Stewart J J P, QCPE, **1990**.