# SYNTHESIS OF 3-[3-(ARYL)-1-(1,3-DIARYLPYRAZOL-4-YL)-3-OXOPROPYL]-4-HYDROXY-2*H*-1-BENZOPYRAN-2-ONES AS POSSIBLE ANTICOAGULANT AGENTS

D. Ashok and K. Pallavi
Department of Chemistry, P.G. College of Science, Saifabad, Osmania University, Hyderabad-500 004, India
and
G. Jagath Reddy * and K. Srinivasa Rao
R & D Laboratories, Dr. Jagath Reddy's Heterocyclics, 81, S.V.Co-op Industrial Estate, Balanagar, Hyderabad – 500 037, India. E-mail-jagathreddy@usa.net; Fax # 91-40-23773487

**Abstract**: A series of 3-[3-(aryl)-1-(1,3-diarylpyrazol-4-yl)-3-oxopropyl]-4-hydroxy-2H-1-benzopyran-2-ones (4 and 5) have been synthesized as possible anticoagulant agents under classical heating and microwave irradiation conditions.

## Introduction

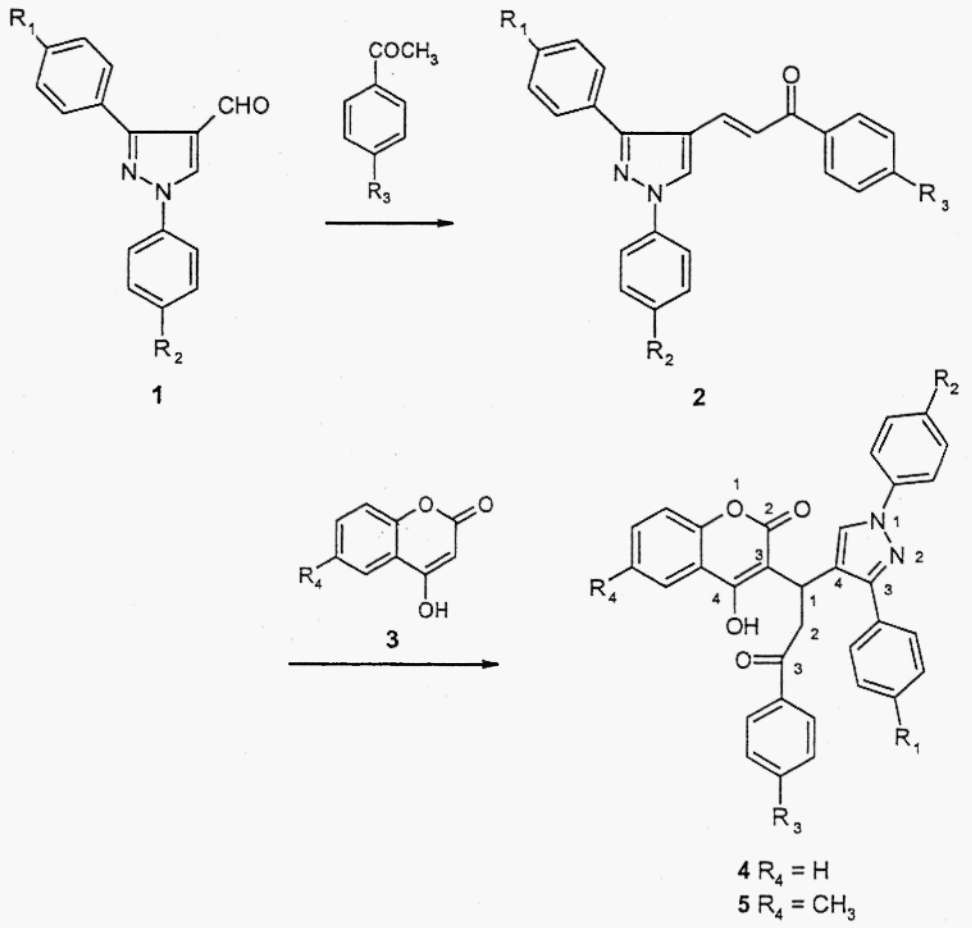
Benzopyrans exhibit a variety of biological activities such as antifungal, antibacterial and insecticidal[1]. The biological importance of 3-substituted 4-hydroxybenzopyrans is evidenced by the widely marketed oral anticoagulant agent *Warfarin*[2]. It is known to exert its potent anticoagulant effect by inhibiting the biosynthesis of vitamin K dependent coagulation factor[3]. However the drug has certain limitations like narrow therapeutic index, long duration of therapy and adverse effect of severe bleeding. This emphasizes the need for the development of new orally active coagulant agents that are safer. Several pyrazole derivatives have been reported as antibacterial, antiinflammatory neuro protective and antioxidant agents[4]. Furthermore, pyrazoles with anticoagulant properties have been disclosed recently[5]. In view of this and in continuation of our work on benzopyrans[6] and pyrazoles[7], it was considered of interest to synthesize some new propiophenones having the hydroxycoumarin and pyrazole pharmacophores in a single molecular framework as possible anticoagulant agents.

## Results and Discussions

The required starting materials 1-aryl-3-(1,3-diarylpyrazol-3-yl)propen-1-ones **2** were prepared by condensation of 1,3-diaryl-4-carboxaldehydes **1** with acetophenones in methanol in presence of potassium hydroxide at room temperature. Reaction of **2** with various 4-hydroxycoumarins **3** in refluxing pyridine underwent Michael addition to give the title coumarinyl pyrazolylpropiophenones **4** in moderate yields (Scheme-1). Keeping in view of the advantages by microwave irradiation[8] like simplicity and completion of reaction at lesser times, the reaction was also carried out under microwave irradiation condition and the reaction is completed in 10 min when compared to 6-8 hrs under conventional heating. The structures of compounds **4** were based on their IR and $^1$H NMR spectra. 4-Exhibited typical signals for –C-$CH_2$-CH-pyrazole system in their $^1$H NMR spectra. Thus three sets of double doublets at δ 3.56, 4.54 and 4.84, apart from a pyrazole proton (δ 8.37) and a coumarin hydroxy proton (δ 9.98) were observed.

## Experimental Section

Melting points were determined in open capillaries and are uncorrected. The purity of all the compounds was routinely checked by TLC on silica gel coated plates. IR spectra were recorded on KBr pellets on Perkin-Elmer system 2000 FT IR spectrometer. $^1$H NMR spectra on a Varian 200 MHz instrument with TMS as internal standard and chemical shifts were expressed in δ ppm and mass spectra on a Hewelett Packard mass spectrometer operating at 70 eV.




**2 – 5** a) $R_1 = R_2 = F, R_3 = H$
b) $R_1 = R_2 = F, R_3 = CH_3$
c) $R_1 = F, R_2 = CH_3, R_3 = H$
d) $R_1 = F, R_2 = R_3 = CH_3$
e) $R_1 = Cl, R_2 = F, R_3 = H$
f) $R_1 = Br, R_2 = 2,4\text{-diF}, R_3 = H$

Scheme-1

**General procedure for the preparation of 1,3-diaryl-4-[3-aryl-3-oxopropenyl-1*H*-pyrazole 2**

An equimolar mixture of 1,3-diarylpyrazole-4-carboxaldehyde **1** (0.01 mol) and acetophenone (0.01 mol) in 3 ethanolic KOH (30 ml) was stirred at room temperature for 4 hr. The precipitate formed was filtered washed with ethanol, dried and recrystallized from dichloromethane /hexane (3 :1).

The following **2** were prepared according to the procedure described above (Yield %, m.p °C). **2a** (76%, 189°C); **2b** (74%, 205°C); **2c** (72%, 171°C); **2d** (78%, 177°C); **2e** (71%, 159°C).

**General procedure for the preparation of 3-[3-(aryl)-1-(1,3-diarylpyrazol-4-yl)-3-oxopropyl]-4-hydroxy-2*H*-1-benzopyran-2-ones 4 & 5 under classical heating condition.**

A mixture of 4-hydroxycoumrain (**3**, 0.01 mol) and 1,3-diaryl-4-[3-aryl-3-oxopropenyl]-1*H*-pyrazole (**2**, 0.01 mole) in pyridine (10 ml) was heated to reflux for 6-8 hrs. The progress of the reaction was

monitored by TLC. It was poured onto cold water (100 ml), the separated solid was filtered and washed with water (2 x 50 ml). The product was purified by column chromatography using hexane : ethylacetate (9 : 1) as eluent to give pure **4** & **5** as crystalline solids.

The physical and spectral data of **4** & **5** thus prepared are listed in Table –1.

Table-1: Characterization data of compounds **4** & **5**

| Compd* | m.p °C | Yield % | Mol. formula | $^1$H NMR (δ ppm) 200 MHz ($CDCl_3$), $M^+$ (70eV) |
|---|---|---|---|---|
| **4a** | 206 | 62 | $C_{33}H_{22}F_2N_2O_4$ | 3.54(d, 1H), 4.53(dd, 1H), 4.83(d, 1H), 6.96(m, 2H), 7.27(m, 3H), 7.46(m, 5H), 7.61(m, 3H), 7.93(m, 4H), 8.36(s, 1H), 9.83(s, 1H), $M^+$ 548 |
| **4b** | 225 | 61 | $C_{34}H_{24}F_2N_2O_4$ | 2.47(s, 3H), 3.44(d, 1H), 4.79(dd, 1H), 4.81(d, 1H), 7.12(m, 6H), 7.53(m, 5H), 7.81(m, 3H), 8.06(m, 2H), 8.41(s, 1H), 7.99(s, 1H), $M^+$ 562 |
| **4d** | 203 | 58 | $C_{35}H_{27}FN_2O_4$ | 2.46(2s, 6H), 3.51(d, 1H), 4.53(dd, 1H), 4.81(d, 1H), 7.16(m, 9H), 7.42(m, 3H), 7.63(d, 1H), 7.91(m, 3H), 8.39(s, 1H), 10.91(s, 1H), $M^+$ 558 |
| **4e** | 201 | 61 | $C_{33}H_{22}ClFN_2O_4$ | 3.44(d, 1H), 4.54(dd, 1H), 4.81(d, 1H), 7.14(m, 2H), 7.34(m, 8H), 7.57(m, 2H), 7.81(m, 3H), 8.02(d, 2H), 8.21(d, 1H), 9.78(s, 1H), $M^+$ 564 |
| **4f** | 190 | 64 | $C_{33}H_{21}BrF_2N_2O_4$ | 3.56(dd, 1H), 4.54(dd, 1H), 4.84(dd, 1H), 6.49(m, 2H), 7.27(m, 3H), 7.47(m, 5H), 7.61(m, 2H), 7.83(m, 4H), 8.37(d, 1H), 9.98(d, 1H) |
| **5a** | 210 | 57 | $C_{34}H_{24}F_2N_2O_4$ | 2.51(s, 3H), 3.45(d, 1H), 4.61(dd, 1H), 4.81(d, 1H), 7.10(m, 6H), 7.51(m, 5H), 7.79(m, 3H), 8.06(m, 2H), 8.43(s, 1H), 9.78(d, 1H), $M^+$ 562 |
| **5c** | 212 | 56 | $C_{35}H_{27}FN_2O_4$ | 2.43(2s, 6H), 3.42(d, 1H), 4.55(dd, 1H), 4.81(d, 1H), 7.08(m, 3H), 7.26(m, 3H), 7.51(m, 4H), 7.59(m, 1H), 7.66(d, 2H), 7.78(s, 1H), 8.01(d, 2H), 8.41(s, 1H), 9.78(s, 1H), $M^+$ 558 |
| **5d** | 208 | 64 | $C_{36}H_{29}FN_2O_4$ | 2.45(3s, 9H), 3.44(d, 1H), 4.53(dd, 1H), 4.81(d, 1H), 7.11(m, 3H), 7.23(m, 5H), 7.43(m, 2H), 7.63(d, 2H), 7.74(s, 1H), 7.97(d, 2H), 8.42(s, 1H), 9.91(s, 1H), $M^+$ 572 |
| **5e** | 200 | 59 | $C_{34}H_{24}ClFN_2O_4$ | 2.46(s, 3H), 3.43(d, 1H), 4.54(dd, 1H), 4.79(d, 1H), 7.12(m, 2H), 7.34(m, 8H), 7.56(m, 1H), 7.78(m, 3H), 8.00(d, 2H), 8.21(s, 1H), 9.75(s, 1H) |

*All the compounds gave satisfactory C, H & N analyses

**General procedure for the preparation of 4 & 5 under microwave irradiation condition**

A mixture of **3** (0.01 mol) and **2** (0.01 mol) in pyridine (10 ml) taken in a 250 ml Erlenmeyer flask was irradiated in a domestic microwave oven for 10 min (5 x 2 min, with 2 min intervals). After completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature and poured onto ice water. The separated solid was filtered and purified by column chromatography as described above.

**References**

1. J. D. Hapwortn, *Comprehensive Heterocyclic Chemistry*, edited by J. A. Boutton and A. Mikillap, Pergaman Press, Oxford, **3**, 737 (1984).
2. *Merck Index*, 10097, 13th edition published by Meck & Co. Inc., New Jersey, (2001).
3. M. D. Taylor, *Comprehensive Medicinal Chemistry*, Pergamon Press, Oxford **2**, 489 (1990).
4. J. V. Greenhill, *Comprehensive Heterocyclic Chemistry*, edited by A. R. Katritzky & C. W. Rees, Pergamon Press, Oxford **5**, 305 (1984).
5. P. Y. S. Lam, C. G. Clark, R Li, D. J. P. Pinto, M. J. Orwat, R. A. Galemmo, J. M. Fevig, C. A. Teleha, R. S. Alexander, A. M. Smallwood, K. A. Rossi, M. R. Wright, S. A. Bai, K. Hc, J. M. Luettgen, P. C. Wong, R. M. Knabb, R. R. Wexler, *J. Med. Chem*, **46**, 4405 (2003).
6. G. Jagath Reddy, R. Shailaja Reddy, K. Pallavi, K. Srinivasa Rao, *Heterocyclic Communication*, **10**, 93 (2004).
7. G. Jagath Reddy, K. Pallavi, R. Shailaja Reddy, K. Srinivasa Rao, *Indian. J. Chem*, (in press) (2004).
8. B. L. Hayes, *Aldrichimica Acta*, **37(2)**, 66 (2004).

Received on September 5, 2005