

SYNTHESIS AND CHARACTERISATION OF SOME 2-[2(1-PHENYL-3-THIOPHEN-2-YL-1H-PYRAZOL-4-YL)]-VINYL CHROMENE-4-ONES

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Abstract: β -Diketone **5** is prepared by BakerVenkatraman transformation of the ester **4**, which is obtained by esterification of the acrylic acid **2** with 2-hydroxyacetophenone **3**. The acid catalyzed cyclization of **5** yielded 2-[2(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)]-vinyl chromene-4-one **6**.

Introduction

4-Oxo-4H-[1]benzopyran i.e. chromone received early attention of chemists because of its natural abundance in the flavonoid family and the chemistry of this benz-annulated γ -pyrone itself has been extensively studied in the past¹⁻³. The resurgent interest in the chemistry of chromones is, however, due largely to their pharmaceutical activity⁴. The success of disodium chromoglycate in the treatment of certain types of bronchial asthma⁵ and recognition of the $-\text{O}-\text{C}=\text{C}-(\text{CO})-$ grouping as the structural requirement for activity in this compound⁶ have led to a spate of investigations into chromones bearing a reactive functionality on the pyran ring⁷⁻¹⁰.

Chromones containing styryl moiety on pyran ring are associated with a large number of important physiological and biological activities¹¹. Hormothamnione is the first naturally occurring styrylchromone isolated from the blue green algae *Hormothamnion enteromorphoides*¹². It has potent cytotoxicity to P388 lymphocytic leukemia and HL-60 human promyelocytic leukemia cells.

Chromone derivatives are associated with important physiological activities¹³. Different biological activities associated with this nucleus are antibacterial¹⁴, antifungal¹⁴, anticholesterinic¹⁵, antidiabetics¹⁵, antiallergic¹⁶, diuretics, etc.

Chromones having heterocyclic substituents at 2- and 3-position have been reported to possess coronary dilatory¹⁸⁻²¹ activity, muscular relaxation effect²² and antimicrobial activities²²⁻²⁴.

Pyrazoles exhibit a wide range of biological activities²⁵ like antioxidant, antiinvasive, antiviral, antipyretic, anti-inflammatory, antidepressant, blood pressure lowering, etc. Pyrazoles are also used as agrochemicals^{26,27}, dyestuff²⁸, in sunscreen materials²⁹ etc. Thiophene containing molecules are associated with important biological activities.

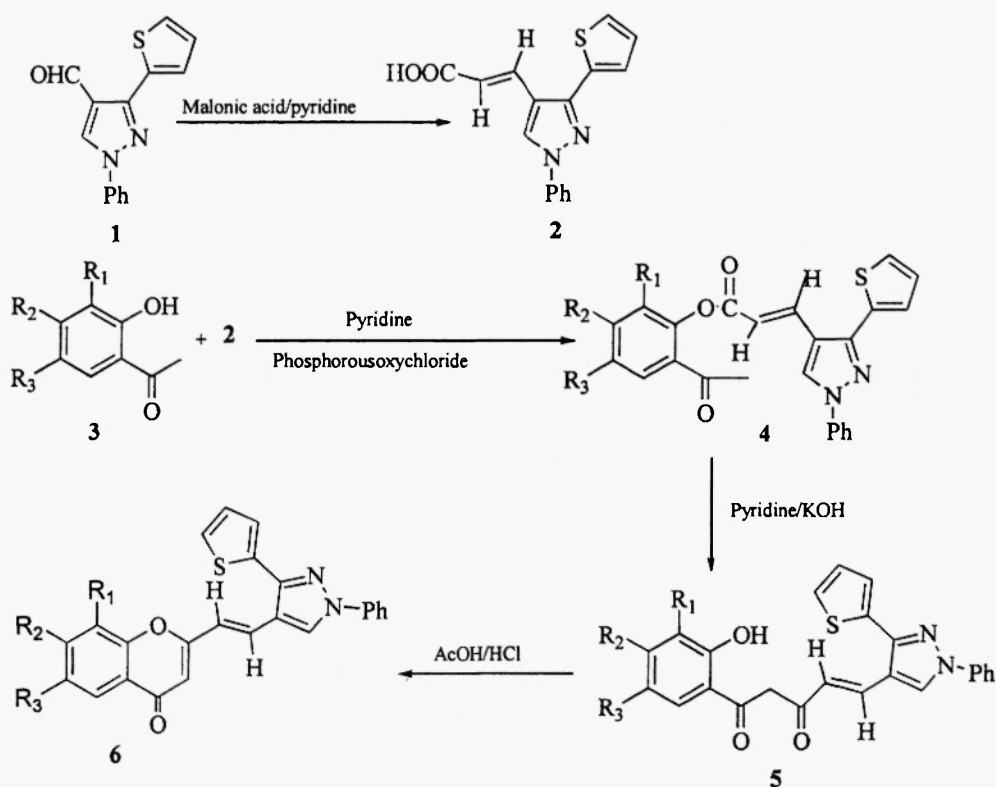
Owing to widespread applications of chromones, styrylchromones, thiophene, pyrazoles and their derivatives, also in continuation of our work on the synthesis of new chromones it was thought worthwhile to prepare some 2-vinyl chromones with pyrazole containing thiophene moiety.

Result and Discussion

The β -diketones **5** have been prepared by BV transformation of the esters **4** which were obtained by esterification of 3-pyrazolyl propenoic acid **2** with 2-hydroxy acetophenones **3**. The required propenoic acid is prepared by Knoevenagel condensation of 1-phenyl-3-thiopen-2-yl-1H-pyrazol-4-carboxaldehyde³⁰ **1** with malonic acid. The β -diketones **5** were converted into vinyl chromenes **6** by acid catalyzed cyclization. Structures of these compounds **4**, **5** and **6** have been elucidated from elemental analysis, IR, proton NMR and mass spectral data.

A O-C=O ester group band which is characteristic for compounds **4** has been observed between 1720 to 1734 cm^{-1} . For esters ^1H NMR shows common peak at around 2.50 δ for acetyl group. The structures of compound **4** are also confirmed by the mass spectra. For the β -diketones **5** IR shows absorption bands at 3400 to 3435 cm^{-1} due to -OH functionality, which might be due to phenolic and enolic -OH groups. For these compounds carbonyl absorption is observed at lower frequency i.e. in between 1625 to 1630 cm^{-1} that is characteristic of β -diketones. In ^1H NMR these compounds shows presence of two D_2O exchangeable protons indicating enol form for these compounds. The structures of compound **5** are also confirmed by the mass spectra. These β -diketones **5** are cyclized into chromones **6** by acid catalysis. Cyclization is conformed by IR spectra as the bands at 3400 cm^{-1} gets disappeared. This is also confirmed by ^1H NMR as compound **6** do not show any D_2O exchangeable protons. These compounds also shows a characteristic signal at around 6.30 to 6.40 δ due to $\text{C}_3\text{-H}$. The structures of compound **6** are also confirmed by the mass spectra. All the synthesized compounds shows satisfactory elemental analysis.

SCHEME:-



Experimental:- All the recorded melting points were determined in open capillary tubes and are uncorrected. I.R. spectra were recorded on Perkin-Elmer FTIR spectrophotometer in KBr disc. ^1H NMR spectra were recorded on Varian 300 MHz spectrophotometer in DMSO as a solvent and TMS as an internal standard. Peak values are shown in δ ppm and J values are in Hertz. Elemental analyses were quite comparable with their structures. Purity of the compounds was checked by TLC on silica gel G plates.

3-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-acrylic acid 2-acetyl-phenyl ester (4a-j): Equimolar amount (0.05 mole) of compounds **2** and **3** were dissolved in 15 ml dry pyridine. The reaction mixture was then cooled to 0°C . To this reaction mixture phosphorousoxychloride (0.06 mole) was added drop wise maintaining temperature below 10°C . Then reaction mixture was kept over night at room temperature. It was then poured over crushed ice with vigorous stirring. Product was separated by filtration, washed with ice-cold water and then with 2% ice-cold solution of NaOH followed by ice-cold water again. Purification by crystallization after drying with alcohol afforded **4a-j**.

1-(2-Hydroxy-phenyl)-5-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-pent-4-ene-1,3-dione 5a-j: Compound **4** (0.03 mole) was dissolved in 15 ml of dry pyridine. To this mixture powdered KOH (1 g) was added and the reaction mixture was stirred on the magnetic stirrer for 3 hours. Then it was poured over crushed ice and acidified with acetic acid. The product was then separated by filtration, washed with water, dried and crystallized with acetic acid to afford **5a-j**.

2-[2(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)]-vinyl chromene-4-ones 6a-i: Compound **5** (0.01mole) was dissolved in 15 ml glacial acetic acid in RBF. To this reaction mixture 1 ml conc. HCl was added and contents were refluxed for 2 hours. Then it was cooled and poured over crushed ice. The product was then separated by filtration, washed with water, dried and crystallized with acetic acid to afford **6a-j**.

Table 1: Physical and spectral data of the synthesized compounds.

Compd	R ₁	R ₂	R ₃	R ₄	M.P. ($^\circ\text{C}$)	Yield (%)	Spectral data (NMR in δ ppm, IR values in cm^{-1} and mass given as M^+)
4a	H	Me	Cl	H	157	48	IR-3075, 1731, 1686, 1635, 757. NMR-2.39(s, 3H, CH_3), 2.50 (s, 3H, CH_3), 6.80(d, 1H, J=15 Hz), 7.56(d, 1H, J=15 Hz), 7.23 to 9.40(m, 11H, Ar-H) Mass (m/e)= 463.5
4b	H	H	Cl	H	155	44	IR-3070, 1721, 1686, 1624, 752. NMR-2.54(s, 3H, CH_3), 6.79(d, 1H, J=15 Hz), 7.56(d, 1H, J=15 Hz), 7.23 to 9.40(m, 12H, Ar-H) Mass (m/e)=449.5
4c	H	H	Br	H	162	49	IR-3068, 1722, 1685, 1625, 686. NMR-2.54(s, 3H, CH_3), 6.79(d, 1H, J=15 Hz), 7.56(d, 1H, J=15 Hz), 7.23 to 9.40(m, 12H, Ar-H) Mass (m/e)=495
4d	H	H	Me	H	101	45	IR-3070, 1733, 1684, 1637.

4e	Cl	H	Cl	H	165	44	NMR-2.39(s, 3H, CH ₃), 2.52 (s, 3H, CH ₃), 6.82(d, 1H, J=15 Hz), 7.55(d, 1H, J=15 Hz), 7.23 to 9.40(m, 12H, Ar-H) IR-3072, 1725, 1688, 1626, 755.
4f	H	Me	H	Me	112	40	NMR-2.50(s, 3H, CH ₃), 6.76(d, 1H, J=15 Hz), 7.55(d, 1H, J=15 Hz), 7.25 to 9.46(m, 11H, Ar-H) IR-3070, 1733, 1684, 1637.
4g	Me	H	Me	H	129	45	NMR-2.38(s, 3H, CH ₃), 2.41(s, 3H, CH ₃), 2.50 (s, 3H, CH ₃), 6.80(d, 1H, J=15 Hz), 7.52(d, 1H, J=15 Hz), 7.20 to 9.30(m, 11H, Ar-H) IR-3072, 1732, 1687, 1635.
4h	H	Me	H	H	105	40	NMR-2.37(s, 3H, CH ₃), 2.42(s, 3H, CH ₃), 2.51 (s, 3H, CH ₃), 6.78(d, 1H, J=15 Hz), 7.48(d, 1H, J=15 Hz), 7.24 to 9.36(m, 11H, Ar-H) IR-3068, 1730, 1682, 1635.
4i	H	H	Et	H	98	39	NMR-2.39(s, 3H, CH ₃), 2.52(s, 3H, CH ₃), 6.82(d, 1H, J=15 Hz), 7.50(d, 1H, J=15 Hz), 7.28 to 9.18(m, 12H, Ar-H) IR-3077, 1731, 1683, 1634.
4j	H	H	F	H	121	48	NMR-1.18(t, 3H, CH ₃), 2.54(q, 2H, CH ₂), 2.49 (s, 3H, CH ₃), 6.82(d, 1H, J=15 Hz), 7.50(d, 1H, J=15 Hz), 7.24 to 9.37(m, 12H, Ar-H) IR-3070, 1721, 1686, 1624, 1020.
5a	H	Me	Cl	H	254	80	NMR-2.55(s, 3H, CH ₃), 6.84(d, 1H, J=15 Hz), 7.58(d, 1H, J=15 Hz), 7.28 to 9.49(m, 12H, Ar-H) IR-3409, 3075, 1625, 1596, 1576, 753.
5b	H	H	Cl	H	237	85	NMR-2.40(s, 3H, CH ₃), 6.83 to 9.25(m, 13H, vinylic and Ar-H), 11.00(s, 1H, D ₂ O exchangeable) 15.90(s, 1H, D ₂ O exchangeable). IR-3409, 3075, 1625, 1596, 1576, 753.
5c	H	H	Br	H	230	81	NMR-6.83 to 9.30(m, 14H, vinylic and Ar-H), 11.80(s, 1H, D ₂ O exchangeable) 16.00(s, 1H, D ₂ O exchangeable). IR-3432, 3074, 1629, 1596, 1573, 687
5d	H	H	Me	H	250	78	NMR-6.94 to 9.26(m, 14H, vinylic and Ar-H), 12.00(s, 1H, D ₂ O exchangeable) 16.00(s, 1H, D ₂ O exchangeable). IR-3435, 3070, 1628, 1595, 1570.
5e	Cl	H	Cl	H	208	75	NMR-2.39(s, 3H, CH ₃), 6.90 to 9.28(m, 14H, vinylic and Ar-H), 12.02(s, 1H, D ₂ O exchangeable) 15.95(s, 1H, D ₂ O exchangeable) IR-3438, 3070, 1628, 1596, 1575, 755.
5f	H	Me	H	Me	276	85	NMR-6.85 to 9.35(m, 13H, vinylic and Ar-H), 11.85(s, 1H, D ₂ O exchangeable) 16.05(s, 1H, D ₂ O exchangeable). IR-3430, 3070, 1627, 1596, 1571.
5g	Me	H	Me	H	312	87	NMR-2.39(s, 3H, CH ₃), 2.41(s, 3H, CH ₃), 6.89 to 9.25(m, 13H, vinylic and Ar-H), 12.05(s, 1H, D ₂ O exchangeable) 15.90(s, 1H, D ₂ O exchangeable) IR-3435, 3072, 1625, 1595, 1570.
5h	H	Me	H	H	202	78	NMR-2.38(s, 3H, CH ₃), 2.45(s, 3H, CH ₃), 6.85 to 9.15(m, 13H, vinylic and Ar-H), 12.00(s, 1H, D ₂ O exchangeable) 15.85(s, 1H, D ₂ O exchangeable) IR-3434, 3072, 1625, 1596, 1572.

5i	H	H	Et	H	231	80	NMR-2.35(s, 3H, CH ₃), 6.85 to 9.25(m, 14H, vinylic and Ar-H), 12.08(s, 1H, D ₂ O exchangeable) 15.85(s, 1H, D ₂ O exchangeable) IR-3435, 3070, 1628, 1595, 1570.
5j	H	H	F	H	232	84	NMR-1.18(t, 3H, CH ₃), 2.54(q, 2H, CH ₂), 6.95 to 9.28(m, 14H, vinylic and Ar-H), 12.04(s, 1H, D ₂ O exchangeable) 15.98(s, 1H, D ₂ O exchangeable) IR-3435, 3075, 1630, 1596, 1575, 1012.
6a	H	Me	Cl	H	274	68	NMR-6.95 to 9.30(m, 14H, vinylic and Ar-H), 12.00(s, 1H, D ₂ O exchangeable) 16.00(s, 1H, D ₂ O exchangeable). IR-3070, 1629, 1596, 1573, 754.
6b	H	H	Cl	H	238	71	NMR-2.42(s, 3H, CH ₃), 6.33(s, 1H, C ₃ -H), 7.07 to 9.25(m, 13H, Ar-H & vinylic). Mass (m/e)= 444.0
6c	H	H	Br	H	297	74	IR-3074, 1628, 1585, 1565, 755. NMR-6.42(s, 1H, C ₃ -H), 7.07 to 9.25(m, 14H, Ar-H & vinylic). Mass (m/e)= 431.0
6d	H	H	Me	H	288	69	IR-3076, 1630, 1586, 1567, 686. NMR-6.42(s, 1H, C ₃ -H), 7.07 to 9.25(m, 14H, Ar-H & vinylic).
6e	Cl	H	Cl	H	290	76	IR-3071, 1625, 1586, 1575. NMR-2.40(s, 3H, CH ₃), 6.30(s, 1H, C ₃ -H), 7.05 to 9.28(m, 14H, Ar-H & vinylic).
6f	H	Me	H	Me	225	70	IR-3072, 1621, 1580, 1559, 749. NMR-6.42(s, 1H, C ₃ -H), 7.05 to 9.29(m, 13H, Ar-H & vinylic).
6g	Me	H	Me	H	301	69	IR-3071, 1625, 1575, 1554. NMR-2.38(s, 3H, CH ₃), 2.45(s, 3H, CH ₃), 6.30(s, 1H, C ₃ -H), 7.05 to 9.28(m, 13H, Ar-H & vinylic).
6h	H	Me	H	H	256	68	IR-3074, 1629, 1573, 1556. NMR-2.38(s, 3H, CH ₃), 2.45(s, 3H, CH ₃), 6.34(s, 1H, C ₃ -H), 7.08 to 9.24(m, 13H, Ar-H & vinylic).
6i	H	H	Et	H	277	60	IR-3072, 1623, 1579, 1565. NMR-2.40(s, 3H, CH ₃), 6.29(s, 1H, C ₃ -H), 7.09 to 9.23(m, 14H, Ar-H & vinylic).
6j	H	H	F	H	264	64	IR-3071, 1629, 1596, 1573, 1524. NMR-1.23(t, 3H, CH ₃), 2.75(q, 2H, CH ₂), 6.38(s, 1H, C ₃ -H), 7.07 to 9.21(m, 14H, Ar-H & vinylic).
							IR-3074, 1629, 1596, 1573, 1556, 1020. NMR-6.42(s, 1H, C ₃ -H), 7.07 to 9.23(m, 15H, Ar-H & vinylic). Mass (m/e)=414.

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