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

N.S. Joshi, B.K. Karale and C.H. Gill*
P.G. Dept. of chemistry, S.S.G.M. College, Kopargaon, Dist. Ahmednagar-423 601, India
E-Mail- chgill 50 @yahoo.com; narenjoshi_be@yahoo.com

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-1*H*-pyrazol-4-yl)]-vinyl chromene-4-one **6**.

Introduction

4-Oxo-4*H*-[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 past[1-3]. The resurgent interest in the chemistry of chromones is, however, due largely to their pharmaceutical activity[4]. The success of disodium chromoglycate in the treatment of certain types of bronchial asthma[5] and recognition of the –O-C=C-(CO)- grouping as the structural requirement for activity in this compound[6] have led to a spate of investigations into chromones bearing a reactive functionality on the pyran ring[7-10].

Chromones containing styryl moiety on pyran ring are associated with a large number of important physiological and biological activities[11]. Hormothamnione is the first naturally occurring styrylchromone isolated from the blue green algae *Hormothamnion enteromorpholides*[12]. It has potent cytotoxicity to P388 lymphocytic leukemia and HL-60 human promyelocytic leukemia cells.

Chromone derivatives are associated with important physiological activities[13]. Different biological activities associated with this nucleus are antibacterial[14], antifungal[14], anticholesternic[15], antidiabetics[15], antiallergic[16], diuretics, etc.

Chromones having heterocyclic substituents at 2- and 3-position have been reported to posses coronary dilatory[18-21] activity, muscular relaxation effect[22] and antimicrobial activities[22-24].

Pyrazoles exhibit a wide range of biological activities[25] like antioxidant, antiinvassive, antiviral, antipyretic, anti-inflammatory, antidepressant, blood pressure lowering, etc. Pyrazoles are also used as agrochemicals[26,27], dyestuff[28], in sunscreen meterials[29] 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-thiophen-2-yl-1*H*-pyrazol-4-carboxaldehyde[30] **1** with malonic acid. The β-diketones **5** were converted into vinyl chromones **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=0 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 2.50δ 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 from 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 3400cm^{-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 6.40δ due to C_3-H. The structures of compound **6** are also confirmed by the mass spectra. All the synthesized compounds shows satisfactory elemental analysis.

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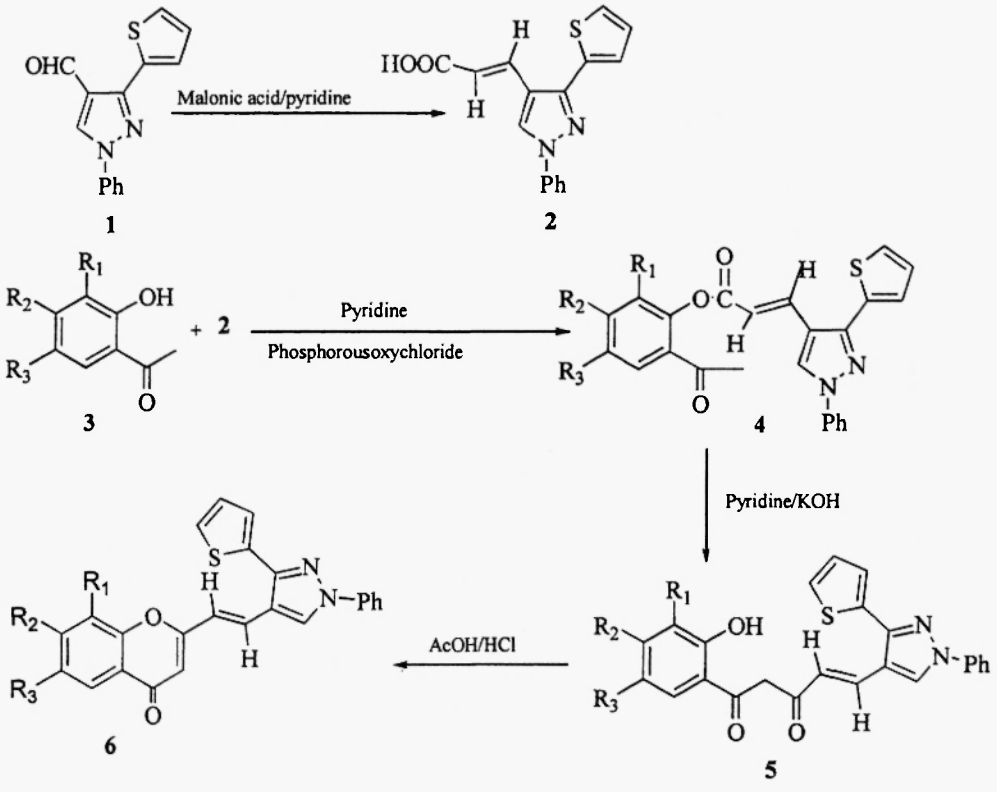

Experimental:- All the recorded melting points were determined in open capillary tubes and are uncorrected. I.R. spectra were recorded on Perkin-Elmer FTIR spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on Varian 300 MHz spectrophotometer in DMSO as a solvent and TMS as an internal standard. 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-1*H*-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 0^0C. To this reaction mixture phosphorousoxychloride (0.06 mole) was added drop wise maintaining temperature below 10^0 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-1*H*-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-1*H*-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. (^{0}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.

							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)
4e	Cl	H	Cl	H	165	44	IR-3072, 1725, 1688, 1626, 755. 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)
4f	H	Me	H	Me	112	40	IR-3070, 1733, 1684, 1637. 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)
4g	Me	H	Me	H	129	45	IR-3072, 1732, 1687, 1635. 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)
4h	H	Me	H	H	105	40	IR-3068, 1730, 1682, 1635. 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),7.28to 9.18(m, 12H, Ar-H).
4i	H	H	Et	H	98	39	IR-3077, 1731, 1683, 1634. 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)
4j	H	H	F	H	121	48	IR-3070, 1721, 1686, 1624, 1020. 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)
5a	H	Me	Cl	H	254	80	IR-3409, 3075, 1625,1596, 1576, 753. NMR-2.40(s, 3H, CH_3),6.83 to 9.25(m, 13H, vinylic and Ar-H), 11.00(s, 1H, D_2O exchangeable) 15.90(s, 1H, D_2O exchangeable).
5b	H	H	Cl	H	237	85	IR-3409, 3075, 1625,1596, 1576, 753. NMR-6.83 to 9.30(m, 14H, vinylic and Ar-H), 11.80(s, 1H, D_2O exchangeable) 16.00(s, 1H, D_2O exchangeable).
5c	H	H	Br	H	230	81	IR-3432, 3074, 1629,1596, 1573, 687 NMR-6.94 to 9.26(m, 14H, vinylic and Ar-H), 12.00(s, 1H, D_2O exchangeable) 16.00(s, 1H, D_2O exchangeable).
5d	H	H	Me	H	250	78	IR-3435, 3070, 1628,1595, 1570. NMR-2.39(s, 3H, CH_3), 6.90 to 9.28(m, 14H, vinylic and Ar-H), 12.02(s, 1H, D_2O exchangeable) 15.95(s, 1H, D_2O exchangeable)
5e	Cl	H	Cl	H	208	75	IR-3438, 3070, 1628,1596, 1575, 755. NMR-6.85 to 9.35(m, 13H, vinylic and Ar-H), 11.85(s, 1H, D_2O exchangeable) 16.05(s, 1H, D_2O exchangeable).
5f	H	Me	H	Me	276	85	IR-3430, 3070, 1627,1596, 1571. 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_2O exchangeable) 15.90(s, 1H, D_2O exchangeable)
5g	Me	H	Me	H	312	87	IR-3435, 3072, 1625,1595, 1570. 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_2O exchangeable) 15.85(s, 1H, D_2O exchangeable)
5h	H	Me	H	H	202	78	IR-3434, 3072, 1625,1596, 1572.

							NMR-2.35(s, 3H, CH_3), 6.85 to 9.25(m, 14H, vinylic and Ar-H), 12.08(s, 1H, D_2O exchangeable) 15.85(s, 1H, D_2O exchangeable)
5i	H	H	Et	H	231	80	IR-3435, 3070, 1628,1595, 1570. NMR-1.18(t, 3H, CH_3), 2.54(q, 2H, CH_2), 6.95to 9.28(m, 14H, vinylic and Ar-H), 12.04(s, 1H, D_2O exchangeable) 15.98(s, 1H, D_2O exchangeable)
5j	H	H	F	H	232	84	IR-3435, 3075, 1630,1596, 1575, 1012. NMR-6.95 to 9.30(m, 14H, vinylic and Ar-H), 12.00(s, 1H, D_2O exchangeable) 16.00(s, 1H, D_2O exchangeable).
6a	H	Me	Cl	H	274	68	IR-3070, 1629, 1596,1573, 754. 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
6b	H	H	Cl	H	238	71	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
6c	H	H	Br	H	297	74	IR-3076, 1630, 1586, 1567, 686. NMR-6.42(s, 1H, C_3-H), 7.07 to 9.25(m,14H,Ar-H & vinylic).
6d	H	H	Me	H	288	69	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).
6e	Cl	H	Cl	H	290	76	IR-3072, 1621, 1580,1559, 749. NMR-6.42(s, 1H, C_3-H), 7.05 to 9.29(m,13H,Ar-H & vinylic).
6f	H	Me	H	Me	225	70	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).
6g	Me	H	Me	H	301	69	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).
6h	H	Me	H	H	256	68	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).
6i	H	H	Et	H	277	60	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).
6j	H	H	F	H	264	64	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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