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A Facile Synthesis of 7-Hydroxy-4-methyl-8-heteryl-2*H*-2-chromenones

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7-Hydroxy-4-methyl-8-(1*H*-3-pyrazolyl)-2*H*-2-chromenones and 7-hydroxy-8-(3-isoxazolyl-4-methyl-2*H*-2-chromenones were prepared by a two step synthetic sequence starting from 8-acetyl-7-hydroxyl-4-methyl-2*H*-2-chromenones. Reaction of 8-acetyl chromenone derivatives with dimethylformamide-dimethylacetal (DMF-DMA) and subsequent condensation of the resulted enaminones with hydrazines and hydroxylamine hydrochloride furnished the desired products in high yields.

Key Words: 8-Acetyl-7-hydroxy-4-methyl-2*H*-chromenones, Hydroxylamine hydrochloride, Hydrazine derivatives, Oxazoles, Pyrazoles.

INTRODUCTION

Enaminones are readily obtainable versatile reagents and their chemistry in the synthesis of various heterocyclics has received considerable progress in recent years[1-6].

The synthesis of pyrazole derivatives[6] assumed immense significance in heterocyclic chemistry because of their pharmaceutical and biological importance[7,8] as antibacterial, antiinflammatory, neuroprotective, antioxidant agents and anticoagulant agents. Isoxazoles[6] are another class of important heterocyclic molecules showing antimicrobial, antiinflammatory and sedative activities[9-12]. In the light of these observations, we have planned to synthezise chromenones having pyrazoles and isoxazole moieties and study of their activities.

EXPERIMENTAL

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 in KBr pellets, ^{1}H NMR spectra

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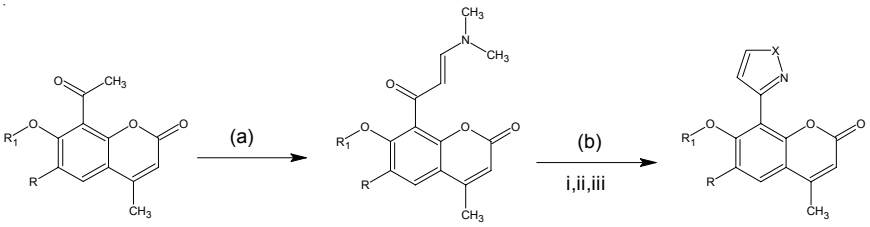
were recorded on a Varian 200 MHz instrument with TMS as internal standard and chemical shifts expressed in δ ppm. Mass spectra were measured on MS 30 and MS 9 (AEI) 70 eV.



1a R = H, R_1 = H
1b R = Cl, R_1 = H

2a R = H, R_1 = H
2b R = Cl, R_1 = H

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Reagents and conditions

(a) DMF-DMA/ Xylene; (b) i. H_2N-OH.HCl/AcOH; ii. Ph-$NHNH_2$/AcOH; iii. H_2N- NH_2. H_2O/AcOH

3a R = H, R_1 = H, X = O
3b R = Cl, R_1 = H, X = O
3c R = H, R_1 = H, X = N-Ph
3d R = Cl, R_1 = H, X = N-Ph
3e R = H, R_1 = H, X = NH
3f R = Cl, R_1 = H, X = NH
3g R = H, R_1 = Me, X = O
3h R = Cl, R_1 = Me, X= O
3i R = H, R_1 = Me, X = N-Ph
3j R = Cl, R_1 = Me, X = N-Ph
3k R = H, R_1 = Me, X = NH
3l R = Cl, R_1 = Me, X = NH

Scheme

Preparation of 2a and 2b: Dimethylformamide-dimethylacetal (DMF-DMA) (0.95 mL, 0.01 mol) was added to 8-acetyl-7-hydroxy-4-methyl-2*H*-2-chromenone (**1a/1b**, 0.01 mol) in xylene (10 mL) and the reaction mixture was refluxed for 4 h. Xylene was distilled off under reduced pressure and resulted crude product was crystallized from benzene to provide 8-[(E)-3-(dimethylamino)-2-propenyl]-7-hyroxy-4-methyl-2H-2-chromenones (**2a/2b**) as yellow crystals.

Preparation of 3a and 3b: A mixture of the enaminone (**2a/2b**, 0.01 mol) and hydroxylamine hydrochloride (0.7 g, 0.01 mol) in acetic acid (8 mL) was refluxed for 4 h. Reaction mixture was cooled to room temperature, the crude product was poured into ice water, separated solid was filtered and further washed with cold water. The solid so obtained was crystallized from methanol to get the corresponding oxazoles.

Preparation of 3c and 3d: A mixture of the enaminone (**2a/2b**, 0.01 mol) and hydrazine hydrate (0.05 mL, 0.01 mol) in acetic acid (10 mL) was refluxed for 3 h. Reaction mixture was cooled to room temperature, the crude product was poured into ice water and separated solid was filtered and washed with cold water. The solid so obtained was crystallized from methanol to get the corresponding pyrazoles.

Preparation of 3e and 3f: A mixture of the enaminone (**2a/2b**, 0.01 mol) and phenyl hydrazine (1.0 mL, 0.01 mol) in acetiacid (10 mL) was refluxed for 3 h. Reaction mixture was cooled to room temperature, the

crude product was poured into ice water, separated solid was filtered and washed with cold water. The solid so obtained was crystallized from methanol to get the corresponding pyrazoles.

Preparation of 3g-l: A mixture of 8-heteryl chromenone derivative (**3a-f**, 0.01 mol) dimethyl sulphate (0.01 mol) and K_2CO_3 (5 mol) in acetone (20 mL) refluxed with for 6 h. After completion of reaction, reaction mixture was concentrated under reduced pressure. The reaction solution was diluted with water (40 mL) and acidified with dil. HCl and extracted with ethyl acetate (3 × 25 mL). The organic extracts were combined, dried (Na_2SO_4) and evaporated *in vacuo* to provide compound **3** as white solid. Compounds **3g-l** were recrystallized from ethyl acetate and *n*-hexane mixtures.

RESULTS AND DISCUSSION

Enaminone derivatives were earlier used as starting materials for the synthesis of pyrazoles and isoxazole derivatives[13,14]. We have employed a similar strategy in construction of pyrazole and isoxazole moieties on Chromenone skeleton. 7-Hydroxy-8-acetyl-4-methyl-2*H*-2-chromenones (**1a**) and its 6-chloro derivative (**1b**) were used as starting materials.

Thus, condensation of **1a** with dimethylformamide-dimethylacetal (DMF-DMA) in refluxing xylene provided a crystalline compound, characterized as 8-[(E)-3-(dimethylamino)-2-propenyl]-7-hyroxy-4-methyl-2*H*-2-chromenone (**2a**), based on its spectral data, [IR (KBr, cm^{-1}): 3443, 2922, 1731, 1601; ^{1}H NMR (DMSO-d_6) δ (ppm), 2.4 (s, 3H, CH_3), 3.1 (s, 3H, NCH_3), 3.2 (s, 3H, NCH_3), 6.1 (s, 1H, H-3), 6.6 (d, 1H, H-6), 6.8 (d, 1H, *J* = 11.88 Hz, olefinic-H), 7.5 (d, 1H, H-5), 8.0 (d, 1H, *J* = 12.72 Hz, olefinic-H), 15.8 (s, 1H, OH-7); MS m/z: 274 (M+1)].

The enamino ketone (**2a**) on treatment with hydroxylamine hydrochloride in glacial acetic acid yielded 7-hydroxy-8-isoxazole-3-yl-4-methyl-2*H*-chromen-2-one (**3a**). Presence of molecular ion peak at 243 (M^+) in the mass spectrum, carbonyl absorption (1726 cm^{-1}) in the IR spectrum and signals at δ 2.4 (s, 3H, CH_3), 6.1 (s, 1H, H-3), 6.7 (d, 1H, oxazole), 7.0 (d, 1H, H-6), 7.6 (d, 1H, *J* = 8 Hz, H-5), 8.4 (d, 1H, oxazole), 11.0 (s, 1H, OH-7) in the ^{1}H NMR spectrum of **3a** fully confirmed its assigned structure.

Compound **2a** was also reacted with hydrazine derivatives in refluxing glacial acetic acid to provide 7-hydroxy-4-methyl-8-(1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one (**3c**). Other oxazole (**3b**) and pyrazole derivatives **3d-f** were obtained in good yields (Table-1) by a similar synthetic sequence through enaminones **2a** and **2b**.

Compounds **3a-f** was further converted into their alkoxy derivatives **3g-l**.

TABLE-1
CHARACTERIZATION DATA OF THE VARIOUS COMPOUNDS PREPARED

Compd.	m.p. (ºC)	Yield (%)	^{1}H NMR (δ ppm)	Mass
2a	218-219	78	2.4 (s, 3H, CH_3), 3.1 (s, 3H, NCH_3), 3.2 (s, 3H, NCH_3), 6.1 (s, 1H, H-3), 6.6 (d, 1H, H-6), 6.8 (d, 1H, *J* = 11.88 Hz, olefinic-H), 7.5 (d, 1H, H-5), 8.0 (d, 1H, *J* = 12.72 Hz, olefinic-H), 15.8 (s, 1H, OH-7)	274 (M+1)
2b	225-226	75	2.4 (s, 3H, CH_3), 3.1 (s, 3H, NCH_3), 3.2 (s, 3H, NCH_3), 6.1 (s, 1H, H-3), 6.6 (d, 1H, *J* = 11.86 Hz, olefinic-H), 7.6 (s, 1H, H-5), 8.2 (d, 1H, *J* = 12.61 Hz, olefinic-H)	308 (M+1)
3a	211	79	δ 2.4 (s, 3H, CH_3), 6.1 (s, 1H, H-3), 6.7 (d, 1H, oxazole), 7.0 (d, 1H, H-6), 7.6 (d, 1H, H-5), 8.4 (d, 1H, oxazole), 11.0 (s, 1H, OH-7)	243 (M^+)
3b	300 (+)	72	δ 2.5 (s, 3H, CH_3), 6.1 (s, 1H, H-3), 6.8 (d, 1H, oxazole), 7.8 (d, 1H, H-5), 8.5 (d, 1H, oxazole)	278 (M+1)
3c	277-278	82	δ 2.4 (s, 3H, CH_3), 6.0 (s, 1H, H-3), 6.4 (d, 1H, pyrazole), 6.8 (d, 1H, H-6), 7.2-7.4 (m, 5H, Ar-H), 7.5 (d, 1H, H-5), 7.8 (d, 1H, pyrazole), 12.0 (s, 1H, OH-7)	318 (M^+)
3d	300 (+)	76	δ 2.4 (s, 3H, CH_3), 6.0 (s, 1H, H-3), 6.5 (d, 1H, pyrazole), 7.2-7.4 (m, 5H, Ar-H), 7.6 (d, 1H, H-5), 7.8 (d, 1H, pyrazole), 10.2 (s, 1H, OH-7)	352 (M^+)
3e	289	69	δ 2.4 (s, 3H, CH_3),6.1 (s, 1H, H-3), 6.8 (d, 1H, pyrazole), 7.2 (d, 1H, H-6), 7.6 (d, 1H, H-5), 7.8 (d, 1H, pyrazole), 12.8 (s, 1H, OH-7),13.4 (s, 1H, N-H)	242 (M^+)
3f	300 (+)	65	δ 2.4 (s, 3H, CH_3), 6.1 (s, 1H, H-3), 6.8 (d, 1H, pyrazole), 6.9 (d, 1H, H-5), 7.8 (d, 1H, pyrazole), 12.9 (s, 1H, OH-7), 13.2 (s, 1H, N-H)	276 (M^+)
3g	195-196	78	δ 2.5 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 6.1 (s, 1H, H-3), 6.6 (d, 1H, oxazole), 7.0 (d, 1H, H-6), 7.6 (d, 1H, H-5), 8.4 (d, 1H, oxazole)	258 (M+1)
3h	211-212	72	δ 2.4 (s, 3H, CH_3), 6.1 (s, 1H, H-3), 6.8 (d, 1H, oxazole), 7.8 (d, 1H, H-5), 8.6 (d, 1H, oxazole)	291 (M^+)
3i	181-182	85	δ 2.4 (s, 3H, CH_3), 3.6 (s, 3H, OCH_3), 6.1 (s, 1H, H-3), 6.5 (d, 1H, pyrazole), 6.7 (d, 1H, H-6), 7.1-7.4 (m, 5H, Ar-H), 7.5 (d, 1H, H-5), 7.8 (d, 1H, pyrazole)	333 (M+1)
3j	197-198	80	δ 2.4 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 6.1 (s, 1H, H-3), 6.5 (d, 1H, pyrazole), 7.2-7.4 (m, 5H, Ar-H), 7.6 (d, 1H, H-5), 7.8 (d, 1H, pyrazole)	366 (M^+)
3k	172-173	71	δ 2.4 (s, 3H, CH_3), 4.0 (s, 3H, OCH_3), 6.1 (s, 1H, H-3), 6.8 (d, 1H, pyrazole), 7.0 (d, 1H, H-6), 7.6 (d, 1H, H-5), 7.8 (d, 1H, pyrazole), 13.2 (s, 1H, N-H)	256 (M^+)
3l	206-207	66	δ 2.4 (s, 3H, CH_3), 6.1 (s, 1H, H-3), 6.8 (d, 1H, pyrazole), 6.9 (d, 1H, H-5), 7.8 (d, 1H, pyrazole), 13.6 (s, 1H, N-H)	290 (M^+)

All these compounds **3a-l** are new and are fully characterized based on their IR, ^{1}H NMR, mass spectral data. They will be screened for their activity and results will be reported in due course.

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