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A Green Protocol For The Synthesis Of 5-(2-hydroxyphenyl)-3-Methyl-4- (1-Acetyl-5-Phenyl-Δ^2-Pyrazolin-3-yl) Pyrazoles

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ABSTRACT

A green strategy for the synthesis of 5-(2-hydroxyphenyl)-3-methyl-4-(1-acetyl-5-phenyl-Δ^2-pyrazolin-3-yl) pyrazoles from 3-acetylchromones, aromatic aldehydes and hydrazine hydrate by using two different synthetic route.

Keywords: Microwave, solventfree, condensation, cyclodehydration.

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INTRODUCTION

A large number of compounds having pyrazole nucleus in their structure as a prominent moiety, reported to have wide range of biological activities viz. antioxidants, anti-invasive, antiviral, anti-inflammatory and also used as agrochemicals and dyestuffs[1-6]. Pyrazoles and fused ring pyrazoles constitutes an interesting class of heterocycles due to their synthetic versatility and effective biological activities[7-9]. Considerable attention has been focused on substituted pyrazoles due to their biological activities like antifungal, antidepressant, antibacterial, antitumor and insecticidal properties [10-16]. Some of these compounds have manifested substantial antidibetic and analgesic properties. The use of microwave energy to accelerate the organic reactions is of increasing interest and offers several advantages over conventional heating techniques, like many fold reduction in reaction time, easy workup and so cleaner products. Microwave provide an alternative green approach to environmentally unaccepted procedures using toxic and expensive reagents leading to higher atom economy. A large number of condensation reactions had been carried out by microwave irradiation. In the last few years there has been a growing interest in the use of microwave heating in organic synthesis.This prompted us to synthesize the title pyrazole compounds of a potent medicinal value carrying a pyrazoline moiety at position 4 using two different routes under microwave irradiation.

MATERIALS AND METHODS

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on Perkin Elmer 517 spectrophotometer in KBr pellets. The PMR were recorded in Perkin Elmer-R 32 and varian XL-100A high NMR spectrophotometer. Purity of the samples was checked by TLC on silica gel g plates and schimadzu HPLC system. The reaction was carried out in scientific microwave oven RG31L1, 700W, 2450MHz. Two routes for synthesis of title compound are as follows–

Route-I

3-cinnamoylchromones (IIa-f)

Conventional mode

A mixture of 3-acetyl-2-methylchromones (I a-c, 0.01 mol) and aromatic aldehydes (0.01mol) in ethanol (20ml) containing 3-4 drops of piperidine was refluxed for 1 hr. After cooling and dilution reaction mixture was crystallized from ethanol to get compounds II a-f.

Microwave mode

A mixture of 3-acetyl chromone (Ia-c, 0.01 mol) and aromatic aldehydes (0.01 mol) containing 3-4 drops of piperidine, was irradiated under microwave at medium power 450 W for one minute with intermittent cooling, in borosil container. On cooling the reaction mixture was processed as in conventional mode to get the product IIa in 90% yield.

IIa- IR (KBr,cm^{-1}): 1650-1640 (C=O aroyl),1620 (C=O cyclic), 1570 (C=C),1390-1360 (pyrone oxide of γ pyrone). PMR (in δ ppm):2.42 (s, 3H, Ar-CH_3), 2.49 (s,3H, -CH_3), 7.18 (d, 1H, CH=CH), 7.51 (d,1H, CH=CH), 7.20-7.65 (m,8H, Ar-H).

5-(2-hydroxyphenyl)-3-methyl-4-(1-acetyl-5-aryl)-Δ^2-pyrazolin-3-yl)pyrazoles (IIIa-f)

Conventional mode

A thoroughly stirred solution of 3-cinnamoyl-2-methylchromone (IIa-f,0.005mole) and hydrazine hydrate (0.02 mol) in acetic acid (20ml) was refluxed for one hr. product thus obtained on cooling and dilution was filtered in 70% yield.

Microwave mode

A mixture of 3-cinnamoyl-2-methylchromone (IIa-f, 0.005 mole) and hydrazine hydrate (0.02mol) acetic acid (10ml) was refluxed for 1 minute under microwave in medium power level with intermittent heating and reaction mixture was processed as above to get better yield.

IIIa- IR (KBr,cm^{-1}): 3060-3140 (NH,-OH, phenolic), 1620 (-C=O), 1520 (C=N). PMR (in δ ppm): 2.1 (s, 3H, Ar-CH_3), 2.27 (s, 3H, CH_3), 2.5 (s, 3H, N-$COCH_3$), 2.63 (dd, 1H-C<u>H</u>H,J_{BX}=4Hz, J_{AB}=20Hz), 5.27 (dd, 1H, CH<u>H</u>, J_{AX} = 12Hz, J_{AB}=20 Hz), 5.27 (dd, 1H,-CH, J_{BX}=4Hz, J_{AX}=12Hz), 6.65-7.4 (m, 8H, Ar-H), 9.1 (br, 1H, NH), 7.9 (s, 1H, $CHCl_3$ solvent).

Route-II

5-(2-hydroxy-5-methylphenyl)-4-acetyl-3-methyl-pyrazoles(IVa-c)

Conventional mode

Suspension of 3-acetylchromone (Ia-c 0.01 mol) and hydrazine hydrate (0.02 mol) in ethanol (20ml) was refluxed for 1 hr. Reaction mixture was cooled diluted and crude product thus obtained was crystallized in dil. ethanol.

Microwave mode

A mixture of 3-acetylchromones (Ia-c, 0.01mol) and hydrazine hydrate (0.02 mol) was refluxed for 1 minute under microwave in solvent free condition in medium power level with intermittent cooling and reaction mixture was processed as above to get better yield.

IVa - IR(KBr,cm^{-1}): 3360(-OH), 3000-3040(NH), 1720(C=O), 1570-1590(C=N), PMR (KBr,cm^{-1}): 2.15 (s, 3H, Ar-CH_3), 2.16 (s, 3H, hetro Ar-CH_3), 2.10 (s, 3H, CO-CH_3), 6.85-7.25 (m, Ar-H), 9.5-11.5 (s, br, 1H, –OH), 5.35 (s, br, 1H, NH).

5(2-hydroxy-5-methylphenyl)-4-cinnamoyl-3-methylpyrazoles(Va-f)

Conventional mode

A mixture of 5-(2-hydroxy-5-methylphenyl)-4-acetyl-3-methyl-pyrazoles (IVa-c, 0.01 mole) and benzaldehyde (0.01mole) in ethanol 20ml and few drops of piperidine (0.05 mole) was refluxed for 1 hr. on cooling and diluting the crude product was filtered and crystallized in ethanol.

Microwave mode

A mixture of 5-(2-hydroxy-5-methylphenyl)-4-acetyl-3-methyl-pyrazoles (IVa-c, 0.01 mol) and aromatic aldehydes (0.01 mol) containing 3-4 drops of piperidine, was irradiated under microwave in solvent free condition at medium power 450 W for one minute with intermittent cooling, in borosil container. On cooling the reaction mixture was processed as in conventional mode to get the product IIa in 90% yield.

Va- IR(KBr,cm^{-1}): 3360(-OH), 000-3040(NH) 1720(C=O), 1570-1590(C=N), PMR (KBr,cm^{-1}): 2.18(s, 3H, Ar-CH_3), 2.2(s, 3H, hetroaromatic–CH_3), 6.4-7.39 (m, Ar-H and -CH=CH), 9.8-9.9 (br-s, OH).

5-(2-hydroxy-5-methylphenyl)-3-methyl-4-(1-acetyl-5-phenyl-2-Δ^2-pyrazolin-3-yl) pyrazoles (IIIa-f)

Conventional mode

A solution of 5(2-hydroxy-5-methylphenyl)-4-cinnamoyl-3-methyl pyrazole(Va–f, 0.01 mol) and hydrazine hydrate (0.02 mol) in acetic acid (25ml) was refluxed for 1 hr. Reaction mixture was worked out as above method and product thus obtained was crystallized in ethanol to get the some product IIIa in 70 percent yield.

Microwave mode

A mixture of 5(2-hydroxy-5-methylphenyl)-4-cinnamoyl-3-methylpyrazole (Va–f,0.01 mol) and hydrazine hydrate (0.02 mol) acetic acid (10ml) was refluxed for 1 minute under microwave in medium power level with intermittent cooling and reaction mixture was processed as above to get better yield.

Physical and spectral properties of compound IIIa-f obtained from both the samples have been observed to be the same.

RESULTS AND DISCUSSION

In the present work the title compound have been synthesized by two alternative routes (Scheme-1).

Route-I

3-cinnamoylchromones (IIa-f) have been prepared by the reaction of 3-acetylchromones 1 with aromatic aldehydes in ethanol in presence of piperidine under microwave irradiation for 1 minute.

NMR spectra of compound (IIa) shows appearance of deshielded doublets at δ 7.18 (d) and δ7.3 (d) due to cinnamoyl O=C-CH=CH group, whereas methyl protons of $COCH_3$ (reactant 3-acetylchromone) gets disappeared. This conversion has also been confirmed by a multiplate of eight aromatic protons at δ 7.31 – 7.65. IR spectrum shows prominent signals (cm^{-1})1650-1640 (>C=O aroyl), 1620 (>C=O cyclic), 1570 (ethylenic double bond) and 1390-1360 (γ- pyrone). These compounds (IIa-f) were subjected with excess of hydrazine hydrate/EtOH in medium high power in microwave for 1 minute to get the title compounds. In IR spectra of the compound (IIIa) a broad band at 3060-3140 appears for -NH and phenolic –OH which was absent in its substrate.^{1}H NMR spectra show three methyl group signals i.e. one new N-$COCH_3$ appears at δ2.5 which was absent in chromones. Similarly characteristic pattern of pyrazoline appears at 2.63 (dd) (C<u>H</u>H) J_{BX}-4 Hz, J_{AB}-20 Hz, δ3.35 (dd) (CH<u>H</u>)) J_{ax}- 12 Hz, J_{AB}-20 Hz and 5.2 Hz(dd) , 1 H (CH) J_{BX} – 4 Hz, J_{AX}-12 Hz and a (br) NH signal at δ 9.1. The formation of pyrazoline from α-β unsaturated ketones and hydrazine hydrate involves 1,2-addition leading to the formation of intermediate hydrazone which undergoes cyclisation giving pyrazoline, N-acetyl derivative of pyrazoline obtatined in acidic medium. This N-acetyl derivative further reacts with a second molecule of hydrazine hydrate through the formation of an intermediate which undergoes cydodehydration giving pyrazole.

Table-1:Physical data of synthesised compounds

Compounds	R	R_1	R_2	M.P.^{0}C
IIa	CH_3	H	C_6H_5	166
IIb	CH_3	H	MeO.C_6H_4	146
IIc	H	H	C_6H_5	166
IId	H	H	MeO.C_6H_4	155
IIe	H	CH_3	C_6H_5	140
IIf	H	CH_3	MeO.C_6H_4	164
IIIa	CH_3	H	C_6H_5	226
IIIb	CH3	H	MeO.C_6H_4	201
IIIc	H	H	C_6H_5	200
IIId	H	H	MeO.C_6H_4	240
IIIe	H	CH_3	C_6H_5	255
IIIf	H	CH_3	MeO.C_6H_4	250
IVa	CH_3	H	-	180
IVb	H	H	-	65
IVc	H	CH3	-	60
Va	CH_3	H	C_6H_5	101
Vb	CH_3	H	MeO.C_6H_4	120
Vc	H	H	C_6H_5	102
Vd	H	H	MeO.C_6H_4	110
Ve	H	CH_3	C_6H_5	125
Vf	H	CH_3	MeO.C_6H_4	121

Route-II

The synthesis of 5-(2-hydroxyphenyl)-4-(1-acetyl-5-aryl-Δ^2-pyrazolin-3-yl) methylpyrazoles involves the following steps.

Step I

3-Acetylchromones (Ia-c) were treated with NH_2NH_2/ EtOH under microwave for 1 minute to get 5-(2-hydroxyphenyl)-4-acetyl-3-methylpyrazoles (IVa-c). Spectral analysis confirm its structure. In IR spectra a broad band at 3360 cm^{-1} confirms phenolic –OH group, 3000-3040 (br) NH group. ^{1}H NMR shows a broad singlet at δ 5.35 for NH, a br peak at δ 9.1-11.5 for phenolic –OH confirm the above structure.

Step II

4-acetyl group of above pyrazoles on condensation with aromatic aldehydes / EtOH ,piperidine gave 5-(2-hydroxyphenyl)-4-cinnamoyl-3-methylpyrazoles (Va-f) under microwave in 1 minute. In PMR spectra two doublets

at δ6.4 and 7.0 deshielded confirms O=C-CH=CH- group, δ10-10.8 (br) –OH and also δ 9.8 - 9.9 (br) singlet for NH groups.

StepIII

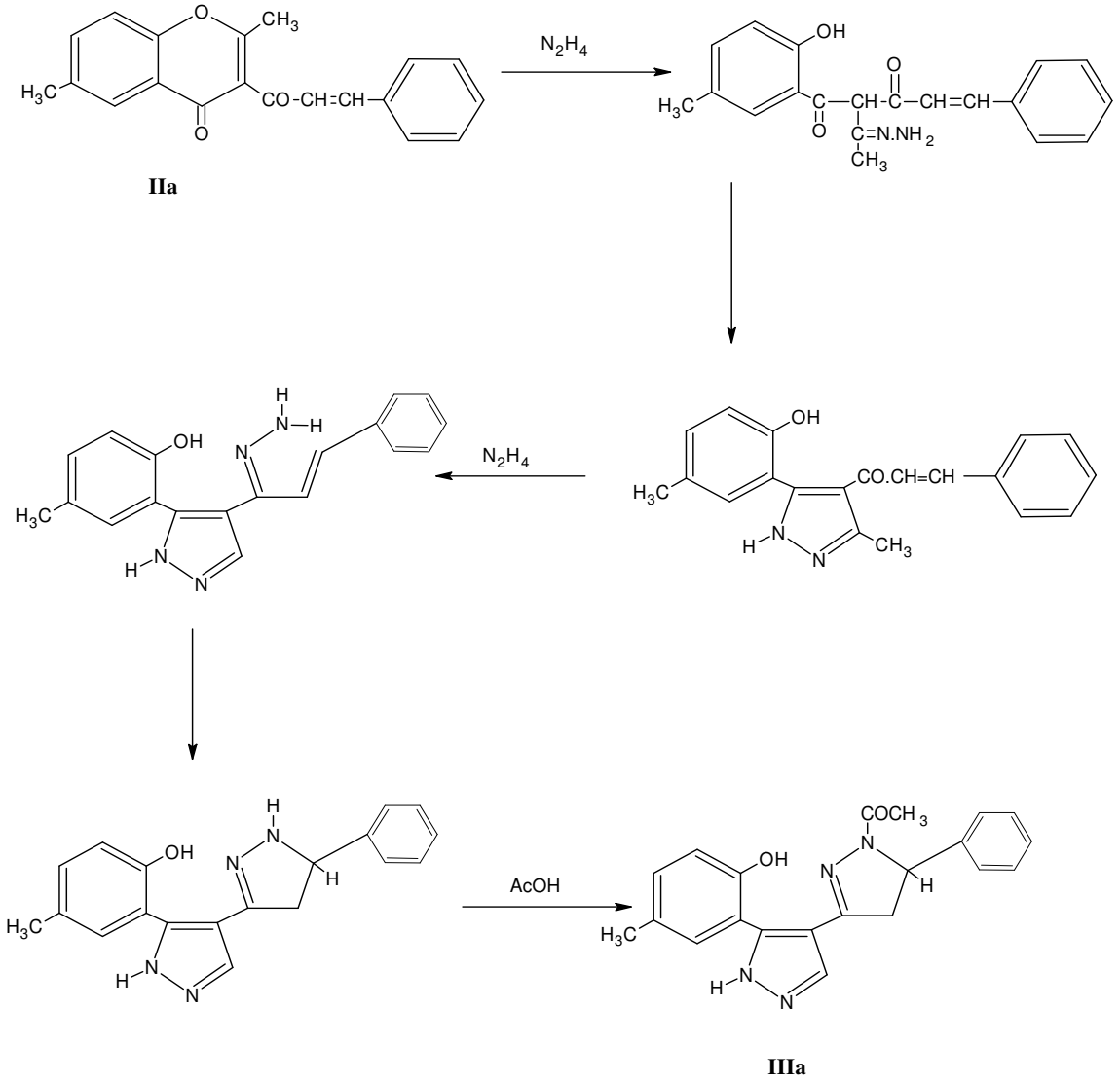
5-(2-hydroxyphenyl)-4-cinnamoyl-3-methylpyrazoles (Va-f) and hydrazine hydrate/ EtOH was refluxed under microwave for 1 minute gave the title compound (IIIa-f).

All the properties, melting points, elemental and spectral analysis of compounds (IIIa-f) have been same as the compounds obtained by the Route-I.

Mechanism

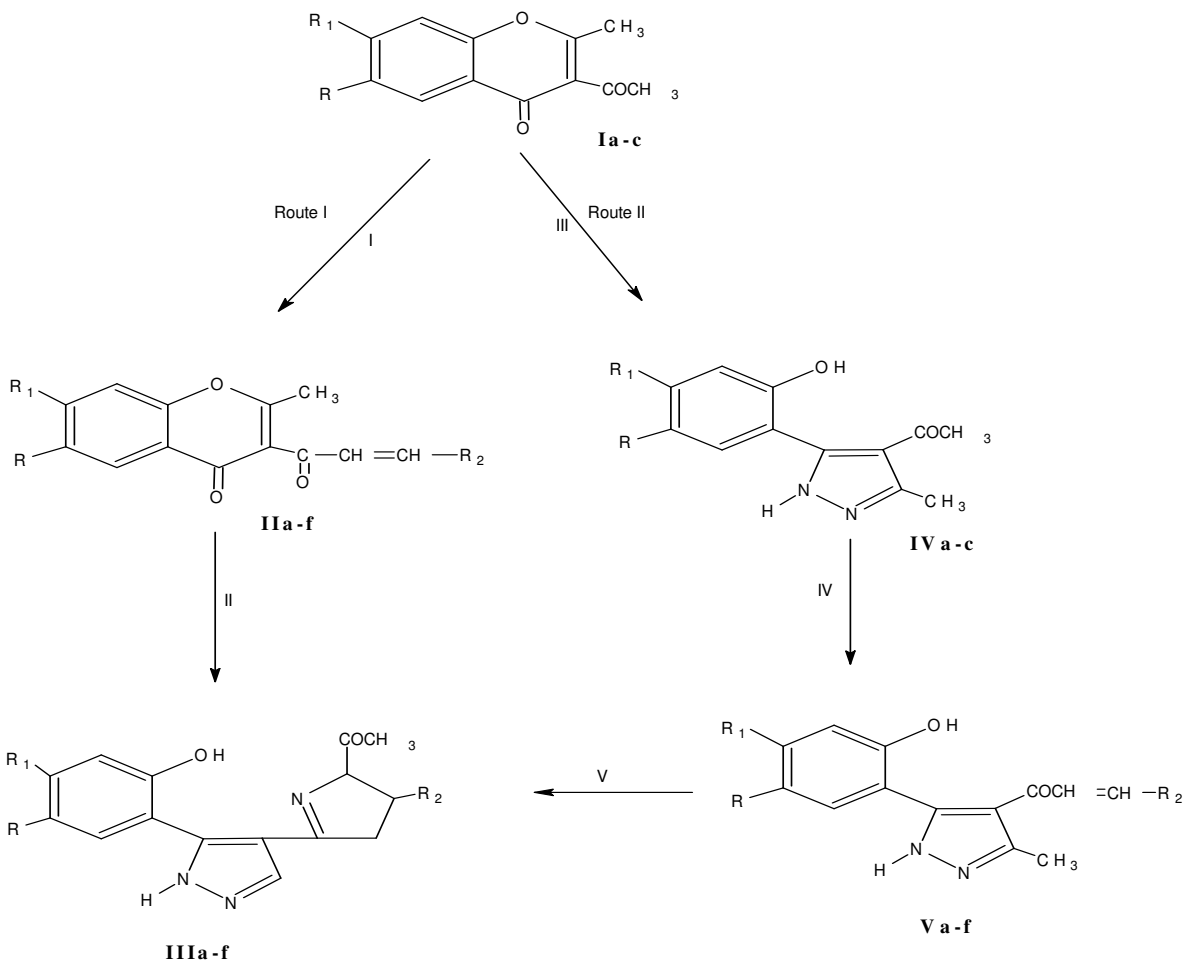
The formation of pyrazoline from α-β-unsaturated ketones and hydrazine takes place in formation of intermediate hydrazone(not isolated). The isolation of intermediate hydrazone is not achieved because under experimental condition it is more proned to cyclisation. The reaction is carried out in moderately acidic medium.

The reaction involves 1,2-addition leading to the formation of intermediate hyrazone which undergoes cyclisation giving pyrazoline. N-acetyl derivative of pyrazoline is obtained in acetic acid medium. This N-acetyl derivative further reacts with a second molecule of hydrazine through the formation of an intermediate which undergoes cyclodehydration giving pyrazole. The reactions may be schematized as under.



IIa

IIIa



I, IV – ArCHO/ Piperdine; II, V – $NH_2NH_2H_2O$/ ACOH; III – $NH_2NH_2H_2O$/ EtOH

Scheme –1

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