Synthesis of new series of 7-methyl-4-(5-aryl-[1,3,4]oxadiazol-2-yl methyl)-chromen-2-one and its derivatives

Sudugu Ramakrishna Reddy¹, Ch. Venkata Ramana Reddy² and B. Satyanarayana*¹

¹Department of Chemistry, University College of Engineering, Osmania University, Hyderabad (Telangana)
²Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad College of Engineering, Kukatpally, Hyderabad (Telangana)

ABSTRACT

A new series of 7-methyl-4-(5-aryl-[1,3,4]oxadiazol-2-ylmethyl)-chromen-2-one and its derivatives have been synthesized in good yields from three intermediates, such as (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid ethyl ester, (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid hydrazide and (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid benzylidene-hydrazides by using commercially available (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid as raw material.

Keywords: Coumarins, Oxadiazoles, Heterocyclic Compounds.

INTRODUCTION

The chemistry of heterocyclic compounds has been an interesting field of study for a long time. Five membered heterocyclic compounds show various types of biological activities. 1, 3, 4-Oxadiazoles are biologically active, synthetically useful and important heterocyclic compounds. The synthesis of novel oxadiazole derivatives and investigation of their chemical and biological behavior have gained more importance in recent decades for biological, medicinal and agricultural reasons. Different classes of oxadiazole compounds possess an extensive spectrum of pharmacological activities. Differently substituted oxadiazole moiety has also been found to have other important activities such as antibacterial [1], antimalarial [2], anti-inflammatory [3], antifungal [4], anticonvulsant [5], analgesic [6] antimicrobial [7], antymycobacterial [8], anticonvulsant [9], antitumor [10], antimalarial [11], ant-hepatitis B viral activities [12], herbicidal [13], vasodialatory [14], cytotoxic [15], hypolipidemic [16], ulcerogenic [17] and antiedema [18].

Coumarins are nowadays an important group of organic compounds that are used as additives to food and cosmetics [19], optical brightening agents [20], and dispersed fluorescent and laser dyes [21]. The derivatives of coumarin usually occur as secondary metabolites present in seeds, root, and leaves of many plant species. Their function is far from clear, though suggestions include waste products, plant growth regulators, fungistats and bacteriostats [22]. It is therefore importance of the synthesis of coumarin and its derivatives should be achieved by a simple and effective method. Coumarins can be synthesised by one of such methods as the Claisen rearrangement, Perkin reaction, Pechmann reaction as well as the Knoevenagel condensation [23]. Some of the industrially important coumarins are the 4-methylsubstituted group (7-hydroxy-4-methylcoumarin) and 7-diethylamino-4-methylcoumarin.
Different classes of oxadiazole possess an extensive spectrum of pharmacological activities. These initial reports stimulated us to integrate 1,3,4-oxadiazole ring into coumarin framework, since these systems possess well documented biological activity. Thus, we have designed and synthesized a new series of 7-methyl-4-(5-aryl-[1,3,4]oxadiazol-2-ylmethyl)-chromen-2-one.

MATERIALS AND METHODS

All reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were obtained on a Varian 300 MHz spectrometer for KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for on silica gel of 60–120 mesh. IR spectra were obtained on a Perkin-Elmer BX series FTIR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer operating at 70 eV.

Synthesis of (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid ethyl ester (2)

A solution of (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid (1) (0.01 mol) in ethyl alcohol (10 ml) was added con. H2SO4 (0.3 ml) drop wise and the reaction mixture was refluxed with uniform stirring on oil-bath for 3 h. After completion of the reaction (monitored by the TLC), the reaction mixture is poured in ice-cold water (20 ml) to get crude product and it is collected by filtration, washed with cold water, dried and recrystallized from ethyl acetate to achieve (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid ethyl ester (2) in pure form.

Synthesis of (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid hydrazide (3)

To the solution of (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid ethyl ester (2) (0.01 mol) in ethyl alcohol (15 ml) was added hydrazine hydrate (10 ml). The reaction mixture was constantly stirred at ambient temperature for 6 h. After accomplishment of the reaction (watched by the TLC), the mixture was poured into ice-cold water (25 ml) to form crude product. It is collected by filtration, washed with cold water, dried and recrystallized from ethyl acetate to get pure (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid hydrazide (3).

Synthesis of (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid benzylidene-hydrazides (4a-f)

To a suspension of (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid hydrazide (3) (0.01 mol) in ethyl alcohol (10 ml) and acetic acid (5 ml) was added a suitable aromatic aldehyde (0.01 mol) at room temperature. Then the reaction mixture was heated at reflux temperature on uniform stirring for 4-5 h. After achievement of the reaction (scanned by the TLC), the excess ethyl alcohol and acetic acid are distilled off and resulted mixture is precipitated after poured in ice-cold water. The crude product was filtered off and washed with hexane, dried and recrystallized with ethyl acetate to get the corresponding pure (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid benzylidene-hydrazides (4a-f). Same procedure is maintained to get compounds 4b-f.

Synthesis of 7-methyl-4-(5-aryl-[1,3,4]oxadiazol-2-ylmethyl)-chromen-2-one and its derivatives (5a-f)

To a solution of (7-methyl-2-oxo-2H-chromen-4-yl)-acetic acid benzylidene-hydrazides (4a-f) (0.01 mol) in bromine-acetic acid (10 ml) was added a solution of sodium acetate (0.01 mol) and acetic acid (5 ml) at room temperature. Then the reaction mixture is stirred uniformly for 7-8 h at reflux temperature. After fulfilment of the reaction (examined by the TLC), the mixture was poured in ice-cold water and is collected by filtration by washed ice-cold water, dried and recrystallized from ethyl acetate to obtain 7-methyl-4-(5-aryl-[1,3,4]oxadiazol-2-ylmethyl)-chromen-2-one and its derivatives (5a-f). Similar procedure is followed to prepare compounds 5b-f.

Spectral and Physical data:

(7-Methyl-2-oxo-2H-chromen-4-yl)-acetic acid ethyl ester (2)

Yield: 69 %, mp: 180-182 °C, IR (KBr): 3052 (C=H, Ar), 2960 (C-H, CH3), 1740 (C=O), 1738 (C=O), 1640 (C=C, Ar), 1085 (C-O) cm⁻¹; 1H NMR (300 MHz, DMSO-d6): δ ppm 7.75 (s, 1H, Ar-H), 7.65 (s, 1H, =CH), 7.43 (d, 1H, J = 7.1 Hz, Ar-H), 7.30 (d, 1H, J = 7.1 Hz, Ar-H), 3.89 (s, 2H, OCH2), 3.68 (q, 2H, J = 5.4 Hz, OCH2), 2.26 (s, 3H, CH3). MS: 246 m/z (M⁺). Elemental analysis: Calculated for C14H14O2: C-68.28, H-5.45, O-24.98.

(7-Methyl-2-oxo-2H-chromen-4-yl)-acetic acid hydrazide (3)

Yield: 66 %, mp: 174-176 °C, IR (KBr): 3358 (N-H), 3245 (N-H), 3048 (C-H, Ar), 2954 (C-H, CH3), 1744 (C=O), 1684 (C=O), 1648 (C=C, Ar), 1092 (C-O) cm⁻¹; 1H NMR (300 MHz, DMSO-d6): δ ppm 12.36 (s, 1H, NH), 7.74 (s, 2H,芳香族-H), 7.65 (s, 1H, =CH), 7.43 (d, 1H, J = 7.1 Hz, Ar-H), 3.89 (s, 2H, OCH2), 2.26 (s, 3H, CH3). MS: 246 m/z (M⁺). Elemental analysis: Calculated for C15H14N2O2: C-66.98, H-5.45, N-12.00, O-22.48.
(7-Methyl-2-oxo-2H-chromen-4-yl)-acetic acid benzylidene-hydrazide (4a)
Yield: 71 %, mp: 144-146 °C, IR (KBr): 3362 (N-H), 3056 (C-H, Ar), 2966 (C-H, CH₃), 1784 (C=O), 1679 (C≡O), 1656 (C≡C, Ar), 1588 (C≡N), 1105 (C-O) cm⁻¹; ᵃIH NMR (300 MHz, DMSO-d₆): δ ppm 12.42 (s, 1H, NH), 7.82 (s, 1H, N=CH), 7.74 (s, 1H, Ar-H), 7.68 (s, 1H, =CH), 7.65 (d, 1H, J = 7.2 Hz, Ar-H), 7.60-7.48 (m, 5H, Ar-H), 7.47 (d, 1H, J = 7.2 Hz, Ar-H), 3.66 (s, 2H, CH₂). MS: 320 m/z (M⁺). Elemental analysis: Calculated for C₁₉H₁₈N₂O₄: C-62.06, H-5.21, N-12.06, O-21.90. Found: C-61.95, H-5.18, N-12.04, O-21.92.

(7-Methyl-2-oxo-2H-chromen-4-yl)-acetic acid (4-bromo-benzylidene)-hydrazide (4e)
Yield: 71%, mp: 144-146 °C, IR (KBr): 3362 (N-H), 3056 (C-H, Ar), 2966 (C-H, CH₃), 1784 (C=O), 1679 (C≡O), 1656 (C≡C, Ar), 1588 (C≡N), 1105 (C-O) cm⁻¹; ᵃIH NMR (300 MHz, DMSO-d₆): δ ppm 12.42 (s, 1H, NH), 7.82 (s, 1H, N=CH), 7.74 (s, 1H, Ar-H), 7.68 (s, 1H, =CH), 7.65 (d, 1H, J = 7.2 Hz, Ar-H), 7.60-7.48 (m, 5H, Ar-H), 7.47 (d, 1H, J = 7.2 Hz, Ar-H), 3.66 (s, 2H, CH₂). MS: 320 m/z (M⁺). Elemental analysis: Calculated for C₁₉H₁₈N₂O₄: C-62.06, H-5.21, N-12.06, O-21.90. Found: C-61.95, H-5.18, N-12.04, O-21.92.
7-Methyl-4-[(5-p-tolyl)[1,3,4]oxadiazol-2-ylmethyl]-chromen-2-one (5b)
Yield: 72%, mp: 149-151°C, IR (KBr): 3048 (C-H, Ar), 2963 (C-H, CH₃), 1749 (C=O), 1645 (C=C, Ar), 1520 (C=N), 1132 (C-O) cm⁻¹: ¹H NMR (300 MHz, DMSO-d₆): δ ppm 7.72 (s, 1H, Ar-H), 7.67 (s, 1H, =CH), 7.70 (d, 2H, J = 7.4 Hz, Ar-H), 7.50 (d, 2H, J = 7.3 Hz, Ar-H), 7.41 (d, 1H, J = 7.3 Hz, Ar-H), 3.58 (s, 2H, CH₂), 3.13 (s, 3H, CH₃). MS: 397 m/z (M⁺). Elemental analysis: Calculated for C₁₉H₁₃BrN₂O₂: C-57.45, H-3.11, Br-19.85, N-7.05, O-11.88. Found: C-57.39, H-3.15, Br-19.98, N-7.03, O-11.83.

4-[4-Methoxyphenyl]-[1,3,4]oxadiazol-2-ylmethyl]-7-methyl-chromen-2-one (5c)
Yield: 67%, mp: 133-135°C, IR (KBr): 3046 (C-H, Ar), 2952 (C-H, CH₃), 1746 (C=O), 1645 (C=C, Ar), 1518 (C=N), 1124 (C-O) cm⁻¹: ¹H NMR (300 MHz, DMSO-d₆): δ ppm 7.65 (s, 1H, Ar-H), 7.62 (s, 1H, =CH), 7.56 (d, 2H, J = 7.4 Hz, Ar-H), 7.49 (d, 2H, J = 7.4 Hz, Ar-H), 7.45 (d, 1H, J = 7.7 Hz, Ar-H), 3.58 (s, 2H, CH₂), 3.13 (s, 3H, CH₃). MS: 352 m/z (M⁺). Elemental analysis: Calculated for C₁₆H₁₅NO₂: C-71.85, H-5.00, N-9.55, O-15.55. Found: C-71.81, H-4.97, N-9.52, O-15.53.

4-[4-Chloro-phenyl]-[1,3,4]oxadiazol-2-ylmethyl]-7-methyl-chromen-2-one (5d)
Yield: 71%, mp: 135-137°C, IR (KBr): 3046 (C-H, Ar), 2952 (C-H, CH₃), 1746 (C=O), 1646 (C=C, Ar), 1506 (C=N), 1132 (C-O) cm⁻¹: ¹H NMR (300 MHz, DMSO-d₆): δ ppm 7.70 (s, 1H, Ar-H), 7.66 (s, 1H, =CH), 7.60 (d, 2H, J = 7.4 Hz, Ar-H), 7.51 (d, 2H, J = 7.4 Hz, Ar-H), 7.46 (d, 1H, J = 7.4 Hz, Ar-H), 3.58 (s, 2H, CH₂), 3.13 (s, 3H, CH₃). MS: 397 m/z (M⁺). Elemental analysis: Calculated for C₁₆H₁₅ClNO₂: C-65.80, H-5.00, Cl-9.98, N-9.56, O-14.43. Found: C-65.73, H-5.07, Cl-10.02, N-9.97, O-14.42.

4-[4-Bromo-phenyl]-[1,3,4]oxadiazol-2-ylmethyl]-7-methyl-chromen-2-one (5e)
Yield: 72%, mp: 149-151°C, IR (KBr): 3048 (C-H, Ar), 2963 (C-H, CH₃), 1746 (C=O), 1641 (C=C, Ar), 1523 (C=N), 1130 (C-O) cm⁻¹: ¹H NMR (300 MHz, DMSO-d₆): δ ppm 7.70 (s, 1H, Ar-H), 7.67 (s, 1H, =CH), 7.56 (d, 2H, J = 7.4 Hz, Ar-H), 7.49 (d, 2H, J = 7.4 Hz, Ar-H), 7.45 (d, 1H, J = 7.7 Hz, Ar-H), 3.58 (s, 2H, CH₂), 3.13 (s, 3H, CH₃). MS: 352 m/z (M⁺). Elemental analysis: Calculated for C₁₆H₁₅BrNO₂: C-69.69, H-3.71, Br-19.85, N-7.94, O-13.61. Found: C-69.60, H-3.52, Br-19.90, N-7.76, O-13.02.

RESULTS AND DISCUSSION

Thus the initial intermediate 2 has been prepared from the raw material 1 on esterification with ethyl alcohol in presence of catalytic amount of concentrated H₂SO₄ under reflux temperature on constant stirring for 3 h. The formation of compound 2 was confirmed by its spectral analysis. The IR spectrum of 2 showed the absorption bands at 3052 (C-H, Ar), 2960 (C-H, CH₃), 1740 (C=O), 1738 (C=O), 1640 (C=C, Ar) and 1085 (C-O) cm⁻¹. The proton NMR spectrum of compound 2 showed signals at δ 7.65 ppm as a singlet for one proton corresponding to =CH group. The chemical shifts appeared at δ 7.55 ppm as singlet for one proton, at δ 7.43 ppm as doublet for one proton and at δ 7.30 ppm as doublet for one proton associated with all aromatic ring. The resonance frequency at δ 3.89 ppm as a singlet for two protons correlates with CH₂ group. The chemical shifts at δ 3.68 ppm as a quartet with J value of 5.4 Hz for two protons and at δ 1.82 ppm as a triplet with same J value for three protons associated with CH₂ and CH₃ groups respectively. The δ-chemical shift at 2.26 ppm as a singlet for three protons corresponding to CH₃ group. Mass spectrum showed peak at m/z 246.

Further the compound 2 is turned into the next intermediate 3 when reacts with hydrazine hydrate in refluxing ethanol on stable stirring for 6 h. Formation of the compound 3 was confirmed by its IR. ¹H NMR and Mass spectra. The IR spectrum of 3 showed the absorption bands at 3358 (N-H), 3245 (N-H), 3048 (C-H, Ar), 2954 (C-H, CH₃), 1744 (C=O), 1684 (C=O), 1648 (C=C, Ar), 1092 (C-O) cm⁻¹. The proton NMR spectrum of 3 showed a signal.
at δ 12.36 ppm as a singlet integrating for one proton is assigned to NH group, between δ 7.74-7.58 ppm as singlets and doublets for five aromatic protons, the signal at δ 7.70 ppm integrating for one proton is assigned to the =CH group. The resonance frequency appeared at δ 4.42 ppm as singlet for two protons is allotted to NH₂ group. Two protons of the CH₂ group as singlet are come into view at δ 7.70 ppm. The lowest δ-chemical shift at 2.31 ppm of this compound as singlet for three protons is related to the CH₃ group. The mass spectrum of compound 3 showed molecular ion peak at m/z 232.

The next intermediate 4a-f has been achieved from condensation reaction of a mixture of compound 3 and an aromatic aldehyde in acetic acid and ethanol under reflux on uniform stirring for 4-5. The structure of the compound 4a was confirmed by its IR, ¹H NMR and Mass spectra. The IR spectrum of 4a showed the absorption bands at 3362 (N-H), 3056 (C-H, Ar), 2966 (C-H, CH₃), 1784 (C=O), 1679 (C=O), 1656 (C=C, Ar), 1588 (C=N), 1105 (C-O) cm⁻¹. The proton NMR spectrum of compound 4a showed different signals corresponding to eight aromatic protons between δ 7.74-7.47. The signal performed at δ 12.42 ppm as a singlet for one proton is allocated to NH group. One proton of N=CH group as singlet is come into light at δ 7.82 ppm. The δ-chemical shift at 7.68 ppm as singlet for one proton is belongs to =CH group. Two signals as singlets at δ 3.66 ppm for two protons and 2.38 ppm for three protons are assigned to the CH₂ and CH₃ groups respectively. The mass spectrum of compound 4a showed the peak at m/z 320. The chemical structures of the remaining compounds of this series are also confirmed by IR, ¹H NMR and Mass spectral data.

Finally the target compounds 5a-f were obtained through cyclization of compound 4 on reaction with Br-AcOH in presence of sodium acetate on refluxing with steady stirring for 7-8 h. The structures of these synthesized compounds 5a-f were confirmed by their IR, ¹H NMR and Mass spectra. The IR spectrum of 5a showed the absorption bands at 3052 (C-H, Ar), 2940 (C-H, CH₃), 1771 (C=O), 1643 (C=C, Ar), 1516 (C=N), 1119 (C-O) cm⁻¹. The proton NMR spectrum of compound 5a showed four signals between δ 7.79-7.58 ppm with different multiplicity integrating for eight protons are assigned to the aromatic protons. The singlet signal at δ 7.72 ppm for one proton is assigned to the =CH group. Another signal appeared at δ 3.62 ppm as a singlet integrating for two protons of CH₂ group. The signal at δ 2.44 ppm as singlet for three protons is assigned to the CH₃ group. The mass spectrum of compound 5a showed molecular ion peak at m/z 318. The chemical structures of the rest of compounds of this series are also confirmed by IR, ¹H NMR and Mass spectral data.

Scheme 1: (i) EtOH, H₂SO₄, reflux. 3 h; (ii) NH₃·H₂O, EtOH, RT, 6 h; (iii) ArCHO, EtOH, AcOH, reflux, 4-5 h; (iv) Br₂/AcOH,
AcONa, reflux, 7-8 h. 4/5 R = (a) = H, (b) = 4-CH₃, (c) = 4-CH₃, (d) = 4-Cl, (e) = 4-Br, (f) = 4-NO₂

REFERENCES


www.scholarsresearchlibrary.com