SYNTHESIS OF NEW HETERO AROYL CHROMEN-4-ONES

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Abstract: Synthesis of 5-methyl-4-[3-(4-oxo-4*H*-chromene-3-yl)-acryloyl)-1,2-dihydro-pyrazol-3-ones **3a-f**, synthesis of 5-methyl-4-[5-(4-oxo-4*H*-chromene-3-yl)-4,5-dihydro-isoxazol-3-yl]-1,2-dihydro-pyrazol-3-ones **4a-f** and 5′-methyl-5-(4-oxo-4*H*-chromen-3-yl)-4,5,1′,2′-tetrahydro-1*H*-[3,4′]bipyrazole-3′-ones **5a-f** in good yields is described under microwave irradiation conditions.

Introduction

Derivatives of pyrazolin-5-ones possess important pharmacological properties including analgesic, antipyretic and anti-inflammatory properties.[1] They are also useful intermediates for many industrial products, e.g. color photography[2] and liquid crystals.[3] Several benzopyran derivatives have been reported as potential pharmaceutical agents.[4-5] In our laboratory isoxazolines[6], benzofurans[7], quinolines[8] have been synthesized based on microwave assistance. Short response time, highly accelerated reaction rate, simple, inexpensive instrument, lesser quantities of solvents are the main advantages of more chemistry (Microwave induced organic reaction enhancement). There were no reports on the synthesis of 5-methyl-4-[3-(4-oxo-4*H*-chromene-3-yl)-acryloyl)-1,2-dihydro-pyrazol-3-ones **3a-f**, 5-methyl-4-[5-(4-oxo-4*H*-chromene-3-yl)-4,5-dihydro-isoxazol-3-yl]-1,2-dihydro-pyrazol-3-ones **4a-f** and 5′-methyl-5-(4-oxo-4*H*-chromen-3-yl)-4,5,1′,2′-tetrahydro-1*H*-[3,4′]bipyrazole-3′ ones **5a-f** in the literature. So we attempted to apply this strategy to the facile synthesis of above titled compounds.

4-Acetyl-5-methyl 1,2-dihydropyrazol-3-one[9] and simple and substituted 4-oxo-4*H*-chromen-3-carbaldehyde[10] were condensed in 4% alcoholic KOH to get the 5-methyl-4-[3-(4-oxo-4*H*-chromene-3-yl)-acryloyl)-1,2-dihydro-pyrazol-3-ones **3a-f** which on reaction with hydroxyl amine hydrochloride in pyridine for 2.5-4 min at 300 watt power level gives 5-methyl-4-[5- (4-oxo-4*H*-chromene-3-yl)-4,5-dihydro-isoxazol-3-yl]-1,2-dihydro-pyrazol-3-ones **4a-f**. **3a-f** on reaction with hydrazine hydrate in ethyl alcohol and few drops of glacial acetic acid for 3 min at 300 watt

power level furnished 5′-methyl-5-(4-oxo-4*H*-chromen-3-yl)4,5,1′,2′-tetrahydro-1*H*-[3,4′] bipyrazole-3′-ones (**5a-f**).

The compounds **3a-f, 4a-f** and **5a-f** were characterized by IR, ^{1}H NMR and mass spectral data. The IR spectra of **3a-f** showed three bands in the region 1670 cm^{-1} (–CH=CH-CO str.), 1595-1630 (-CH=CH- str., belongs to acryloyl group) and 1240-1260 cm^{-1} (-C-O-C- str.). Band around 1750 cm^{-1} is attributed to the -N- C=O group in all the compounds. Band around 1650 cm^{-1} is attributed to the pyrone group in all the compounds. A distinct band around 3100-3400 cm^{-1} is attributed to the N-H group. The ^{1}H NMR (DMSO-d_6) spectra of compounds **3a-f** and **4a-f, 5a-f** confirmed the formation of titled compounds.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra on a Shimadzu FT IR model 8010 spectrophotometer; ^{1}H NMR spectra in DMSO-d_6 on a Varian C_{17}-20-ZM-390-20 MHz spectrometer using TMS as an internal standard; and mass spectra on EIMS at 70eV. The C, H, N analysis of compounds were done on a Carlo Erba model EA1108 CHNS elemental analyzer.

General procedure for the preparation of 5-methyl-4-[3-(4-oxo-4*H*-chromene-3-yl)-acryloyl)-1,2-dihydro-pyrazol-3-ones by microwave irradiation method 3a-f: 4-Acetyl-5-methyl-1,2-dihydro-pyrazol-3-one (0.001mole) 4-oxo-4*H*-chromen-3-carbaldehydes (0.001mole) in dry acetone and 4% KOH (5 mL) were irradiated at 300 W power level for about 3-4.5 min. The reaction mixture was allowed to cool and then poured over crushed ice, extracted with ether to remove the unreacted aldehyde. The aqueous layer was neutralized with dilute HCl. The crude product was recrystallized from ethanol (**Scheme-I**).

3a: Yield: 0.23 g, (80%) m.p: 120-123°, M.F: $C_{16}H_{12}N_2O_4$, MS: m/z 296 (25% M^++1), 146 (100%) 281 (40%), 118 (10%), Required (%): C, 64.86; H, 4.08; N, 9.45, Found (%): C, 64.88; H, 4.10; N, 9.47; ^{1}H NMR, 4.50 (s, 1H, NH), 11.2 (s, 1H, CONH), 6.40 (d, 1H, 16Hz, C=C- α H), 7.8 (d, 1H, J=16Hz, C=C-βH), 7.45 (s, 1H, C_2-H), 7.30-7.70 (m, 4H, Ar-H), 2.4 (s, 3H, CH_3).

3b: Yield: 0.23 g, (75%) m.p: 142-143°, M.F: $C_{17}H_{14}N_2O_4$, Required (%): C, 65.80; H, 4.55; N, 9.03, Found (%): C, 65.82; H, 4.58; N, 9.04. ^{1}H NMR, 4.50 (s, 1H, NH), 11.23 (s, 1H, CONH), 6.40 (d, 1H, 16Hz, C=C- α H), 7.75 (d, 1H, J=16Hz, C=C-βH), 7.40 (s, 1H, C_2-H), 7.12-7.20 (m, 2H, Ar-H), 6.80 (s, 1H, C_5-H), 2.6 (s, 3H, C_6-CH_3), 2.4 (s, 3H, CH_3). Carry out D_2O exchange.

3c: Yield: 0.25 g, (73%), m.p: 158-159°C; M.F: $C_{16}H_{11}ClN_2O_4$; Required (%): C, 58.11; H, 3.35; N, 8.47; Cl, 10.72; Found (%): C, 58.13; H, 3.38; N, 8.49, Cl, 10.69; ^{1}H NMR, 4.40 (s, 1H, NH), 11.34 (s, 1H, CONH), 6.40 (d, 1H, 16Hz, C=C- α H), 7.75 (d, 1H, J=16Hz, C=C-βH), 7.85 (s, 1H, C_2-H), 7.12-7.20 (m, 2H, Ar-H), 6.80 (s, 1H, C_5-H), 2.4 (s, 3H, CH_3).

3d: Yield: 0.27 g, (69%), m.p: 182-184°C; M.F: $C_{16}H_{11}BrN_2O_4$, Required (%): C, 51.22; H, 2.96; N, 7.47; Br, 21.30; Found (%): C, 51.24; H, 2.95; N, 7.49, Br, 21.33; ^{1}H NMR, 4.42 (s, 1H, NH), 11.22 (s, 1H, CONH), 6.40 (d, 1H, 16Hz, C=C- α H), 7.75 (d, 1H, J=16Hz, C=C-βH), 7.80 (s, 1H, C_2-H), 7.12-7.20 (m, 2H, Ar-H), 6.90 (s, 1H, C_5-H), 2.40 (s, 3H, CH_3).

3e: Yield: 0.23g, (67%), m.p: 173-175°C; M.F: $C_{17}H_{14}N_2O_5$; Required: C, 62.58; H, 4.32; N, 8.58; ^{1}H NMR, 4.40 (s, 1H, NH), 11.23 (s, 1H, CONH), 6.40 (d, 1H, 16Hz, C=C- α H), 7.75 (d, 1H, J=16Hz, C=C-βH), 7.85 (s, 1H, C_2-H), 7.12-7.20 (m, 2H, Ar-H), 6.80 (s, 1H, C_5-H), 3.8 (s, 3H, OCH_3), 2.4 (s, 3H, CH_3).

3f: Yield: 0.24 g, (71%), m.p: 210-212°C; M.F: $C_{16}H_{11}N_3O_6$; Required (%): C, 56.31; H, 3.25; N, 12.31; Found (%): C, 56.34; H, 3.23; N, 12.35; ^{1}H NMR, 4.40 (s, 1H, NH), 11.24 (s, 1H, CONH), 6.40 (d, 1H, 16Hz, C=C- α H), 7.75 (d, 1H, J=16Hz, C=C-βH), 7.85 (s, 1H, C_2-H), 7.12-7.20 (m, 2H, Ar-H), 6.90 (s, 1H, C_5-H), 2.4 (s, 3H, CH_3).

General procedure for the preparation of 5-methyl-4-[5-(4-oxo-4*H*-chromene-3-yl)-4,5-dihydro-isoxazol-3-yl]-1,2-dihydro-pyrazol-3-ones 4a-f: Simple and substituted 5-methyl-4-[3-(4-oxo-4*H*-chromene-3-yl)-acryloyl)-1,2-dihydro-pyrazol-3-one (0.001mole) and hydroxyl amine hydrochloride (0.0695g, 0.001mole) were mixed and irradiated in microwave oven at 300 Watt power level for about 2.5-4 min in presence of pyridine to get the product. The reaction mixture was poured into cold water, filtered, dried and recrystallized from methanol (**Scheme-I**).

4a: Yield: 0.19 g, (63%) m.p: 135-137°, M.F: $C_{16}H_{13}N_3O_4$, MS: 312 (12% M^++1), 146 (100%) 118 (90%), Required (%): C, 61.73; H, 4.21; N, 13.50, Found (%): C, 61.75; H, 4.23; N, 13.54. ^{1}H NMR, 11.41 (s, 1H, CONH), 4.42 (s, 1H, NH), 7.45 (s, 1H, C_2-H), 6.60-6.90 (m, 4H, Ar-H), 4.2 (t, 1H, J=9Hz, -CH), 3.30 (d, 2H, $-CH_2$), 2.3 (s, 3H, CH_3).

4b: Yield: 0.24 g, (76.5%) m.p: 142-144°C; M.F: $C_{17}H_{15}N_3O_4$; Required (%): C, 62.76; H, 4.65; N, 12.92; Found (%): C, 62.79; H, 4.68; N, 12.91; ^{1}H NMR, 11.54 (s, 1H, CONH), 4.42 (s, 1H, NH), 7.82 (s, 1H, C_2-H), 6.60-6.90 (m, 3H, Ar-H), 4.7 (t, 1H, J=9Hz, -CH), 3.30 (d, 2H, $-CH_2$), 2.4 (s, 3H, CH_3), 2.3 (s, 3H, CH_3).

4c: Yield: 0.27 g, (81%), m.p: 193-195°C; M.F: $C_{16}H_{12}ClN_3O_4$; Required (%): C, 55.58; H, 3.50; N, 12.15; Cl, 10.25; Found (%): C, 55.57; H, 3.52; N, 12.17, Cl, 1.26;

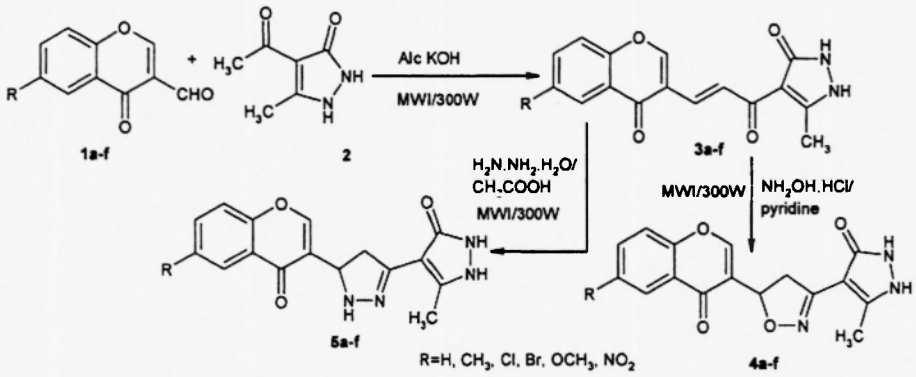
^{1}H NMR, 11.40 (s, 1H, CONH), 4.4 (s, 1H, NH), 7.85 (s, 1H, C_2-H), 6.60-6.90 (m, 3H, Ar-H), 4.7 (t, 1H, J=9Hz, -CH), 3.30 (d, 2H, -CH_2), 2.4 (s, 3H, CH_3).

4d: Yield: 0.30g, (77%), m.p: 202-204°C; M.F: $C_{16}H_{12}BrN_3O_4$; Required (%): C, 49.25; H, 3.10; N, 10.77; Br, 20.48; Found (%): C, 49.22; H, 3.16; N, 10.78, Br, 20.46; ^{1}H NMR, 11.42 (s, 1H, CONH), 4.4 (s, 1H, NH), 7.82 (s, 1H, C_2-H), 6.60-6.90 (m, 3H, Ar-H), 4.7 (t, 1H, J=9Hz, -CH), 3.30 (d, 2H, -CH_2), 2.4 (s, 3H, CH_3).

4e: Yield: 0.21g, (64%) m.p: 217-219°C; M.F: $C_{17}H_{15}N_3O_5$; Required (%): C, 59.82; H, 4.43; N, 13.31; Found (%): C, 59.82; H, 4.44; N, 13.33; ^{1}H NMR, 11.48 (s, 1H, CONH), 4.4 (s, 1H, NH), 7.82 (s, 1H, C_2-H), 6.60-6.90 (m, 3H, Ar-H), 4.7 (t, 1H, J=9Hz, -CH), 3.30 (d, 2H, -CH_2), 3.8 (s, 3H, OCH_3), 2.4 (s, 3H, CH_3).

4f: Yield: 0.21g, (59%) m.p: 198-200°C; M.F: $C_{16}H_{12}N_4O_6$; Required (%): C, 53.94; H, 3.39; N, 15.72; Found (%): C, 53.92; H, 3.37; N, 15.75; ^{1}H NMR, 11.34 (s, 1H, CONH), 4.4 (s, 1H, NH), 7.82 (s, 1H, C_2-H), 6.60-6.90 (m, 3H, Ar-H), 4.7 (t, 1H, J=9Hz, -CH), 3.30 (d, 2H, -CH_2), 2.4 (s, 3H, CH_3).

General procedure for the preparation of 5′-methyl-5-(4-oxo-4*H*-chromen-3-yl)-4,5,1′,2′-tetrahydro-1*H*-[3,4′]bipyrazole-3′-ones 5a-f: 5-Methyl-4-[3-(4-oxo-4*H*-chromene-3-yl)-acryloyl)-1,2-dihydro-pyrazol-3-one (0.001mole) and hydrazine hydrate (0.001mole) were mixed in ethyl alcohol and few drops of glacial acetic acid. The reaction mixture was irradiated in microwave oven at 300 Watt power level for 3 min to get the product. The reaction mixture was poured into cold water, filtered, dried and recrystallized from methanol (**Scheme-I**).



5a: Yield: .20g, (66%) m.p: 160°, M.F: $C_{16}H_{14}N_4O_3$, MS: m/z 310 (16% M^+), 295 (20%), 214 (35%), 146 (100%), Required (%): C, 61.93; H, 4.55; N, 18.05, Found (%): C, 61.95; H, 4.58; N, 18.09. ^{1}H NMR, 11.12(s, 1H, CONH), 4.8 (s, 1H, NH), 4.4

(s, 1H, N-NH), 8.20-8.30 (m, 4H, Ar-H), 7.35 (s, 1H, C_2-H), 4.70 (t, 1H, J=9Hz, -CH), 3.4 (d, 2H, $-CH_2$), 2.2 (s, 3H, CH_3).

5b: Yield: 0.22 g, (69%) m.p: 172-175°C; M.F: $C_{17}H_{16}N_4O_3$; Required (%): C, 62.95; H, 4.97; N, 17.27; Found (%): C, 62.96; H, 4.99; N, 17.31; ^{1}H NMR, 11.21 (s, 1H, CONH), 4.8 (s, 1H, NH), 4.4 (s, 1H, N-NH), 8.20-8.30 (m, 3H, Ar-H), 7.35 (s, 1H, C_2-H), 4.70 (t, 1H, J=9Hz, -CH), 3.4 (d, 2H, $-CH_2$), 2.4 (s, 3H, CH_3), 2.2 (s, 3H, CH_3).

5c: Yield: 0.25g, (75%) m.p: 155-157°C; M.F: $C_{16}H_{13}ClN_4O_3$; Required (%): C, 55.74; H, 3.80; N, 16.25; Cl, 10.28; Found (%): C, 55.73; H, 3.81; N, 16.24, Cl, 10.26; ^{1}H NMR, 11.24 (s, 1H, CONH), 4.8 (s, 1H, NH), 4.4 (s, 1H, N-NH), 8.20-8.30 (m, 3H, Ar-H), 7.35 (s, 1H, C_2-H), 4.70 (t, 1H, J=9Hz, -CH), 3.4 (d, 2H, $-CH_2$), 2.4 (s, 3H, CH_3).

5d: Yield: 0.31g, (82%) m.p: 159-161°C; M.F: $C_{16}H_{13}BrN_4O_3$; Required (%): C, 49.38; H, 3.37; N, 14.39; Br, 20.53; Found (%): C, 49.39; H, 3.35; N, 14.42, Br, 20.55; ^{1}H NMR, 11.36 (s, 1H, CONH), 4.8 (s, 1H, NH), 4.4 (s, 1H, N-NH), 8.20-8.30 (m, 3H, Ar-H), 7.35 (s, 1H, C_2-H), 4.70 (t, 1H, J=9Hz, -CH), 3.4 (d, 2H, $-CH_2$), 2.4 (s, 3H, CH_3),

5e: Yield:0.22 g, (67%) m.p: 184-186°C; M.F: $C_{17}H_{16}N_4O_4$; Required (%): C, 60.00; H, 4.74; N, 16.46; Found (%): C, 60.01; H, 4.75; N, 16.48; ^{1}H NMR, 11.22 (s, 1H, CONH), 4.8 (s, 1H, NH), 4.4 (s, 1H, N-NH), 8.20-8.30 (m, 3H, Ar-H), 7.35 (s, 1H, C_2-H), 4.70 (t, 1H, J=9Hz, -CH), 3.4 (d, 2H, $-CH_2$), 3.80 (s, 3H, OCH_3), 2.4 (s, 3H, CH_3).

5f: Yield: 0.24 g, (70%), m.p: 234-236°C; M.F: $C_{16}H_{13}N_5O_5$; Required: C, 54.09; H, 3.69; N, 19.71; Found: C, 54.07; H, 3.68; N, 19.75; ^{1}H NMR, 11.20 (s, 1H, CONH), 4.8 (s, 1H, NH), 4.4 (s, 1H, N-NH), 8.20-8.30 (m, 3H, Ar-H), 7.35 (s, 1H, C_2-H), 4.70 (t, 1H, J=9Hz, -CH), 3.4 (d, 2H, $-CH_2$), 2.4 (s, 3H, CH_3).

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