Indian Journal of Heterocyclic Chemistry
Vol. 23, April-June, 2014, pp. 335-338

MICROWAVE ASSISTED ONE-POT SYNTHESIS OF 2,3-DIHYDRO-6-ALKYL-2-(1-PHENYL-3-ARYL-1*H*-PYRAZOL-4-YL) CHROMEN-4-ONES

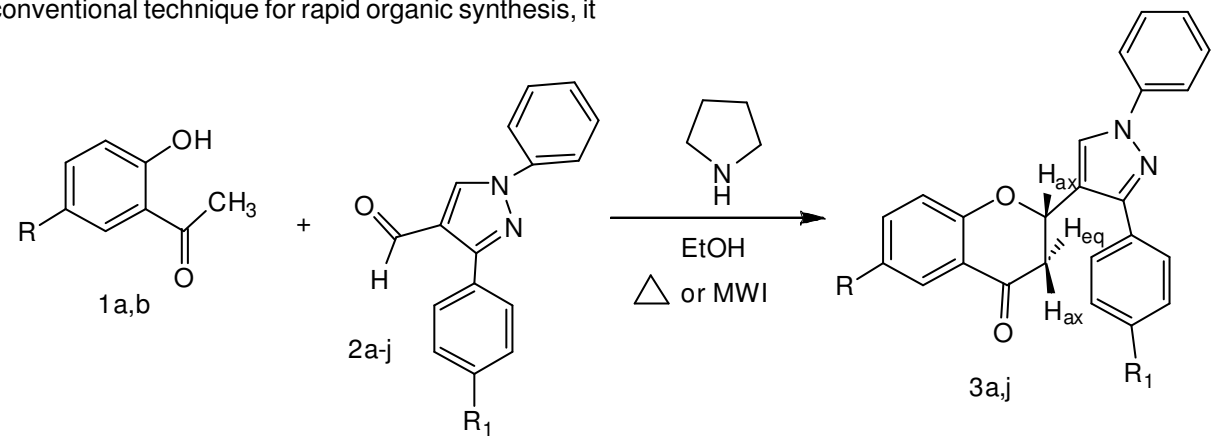
D. Ashok*, K. Padmavathi and P. Sreenivas
Department of Chemistry, Osmania University, Hyderabad-500 007
E-mail : ashokdou@gmail.com

Received 14 Oct. 2013; Accepted 26 March 2014

A series of 2,3-dihydro-6-alkyl-2-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl) chromen-4-ones have been synthesized in one-pot by reacting 2-hydroxyacetophenones and substituted 3-aryl-1-phenylpyrazole-4-carbaldehydes, in the presence of pyrrolidine as an efficient organic base. All the compounds synthesized have been characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

Flavanones play a pivotal role in the field of heterocyclic chemistry. They have been used as radical scavenging agents[1], inhibitors of nitric oxide production[2], antiproliferative agents[3], apoptosis-inducing agents[4], inhibitors of aromatase[5], inhibitors of trypsin[6], antitumor, anti-inflammatory and antioxidant agents[7]. Dioclein, a flavanone of plant origin was found to be biologically active for the treatment of kidney stones and prostate gland disorders[8]. Furthermore pyrazole derivatives are widely used as pharmaceuticals, inhibitors of protein kinases[9], analgesics[19], anti aggregating agents[11] and agrochemicals[12-13]. Microwave induced organic reaction enhancement has gained popularity as a non conventional technique for rapid organic synthesis, it is ecofriendly, economical and is believed to be a step toward green chemistry[14,15].

Flavanones are generally synthesized by cyclization of 2-hydroxychalcones in acetic acid or ethanol in the presence of an acid catalyst such as sulphuric acid[16], polyphosphoric acid[17] or basic catalyst such as pyridine[18], DBU[19] and TEA[20] under conventional heating or microwave irradiation. In continuation of our earlier work on green synthesis[21,22], we wish to report a simple and one-pot microwave assisted synthesis of 2,3-dihydro-6-alkyl-2-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl) chromen-4-ones (**3**a-j) from 2-hydroxyacetophenones (**1**a,b) and a variety of substituted 3-aryl-1-phenylpyrazole-4-carbaldehydes



3a-j	a	b	c	d	e	f	g	h	i	j
R	H	H	H	H	H	H	CH_3	CH_3	CH_3	CH_3
R_1	H	Cl	CH_3	OCH_3	F	Br	H	Cl	OCH_3	F

SCHEME-1

Table-1
Analytical data of 2,3-dihydro-6-alkyl-2-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl) chromen-4-ones (**3**a-j)

Compd	M.P. (^{0}C)	Conventional heating		MW Irradiation	
		Time (hr)	Yield (%)	Time (min)	Yield (%)
3a	170	10	69	5	81
3b	198	10	65	5	84
3c	175	11	65	4	87
3d	160	12	71	5	80
3e	185	10	65	5	81
3f	203	10	61	6	85
3g	190	11	71	4	81
3h	194	12	69	5	84
3i	173	11	70	6	86
3j	186	12	73	6	89

(**2**a-j) in presence of pyrrolidine as an efficient basic organic catalyst. The synthesis of **3**a-j was also carried out under conventional heating method. The advantage of microwave irradiation method in relation to a conventional method was demonstrated.

Experimental

Melting points were determined in open capillaries and are uncorrected. Purity of the compounds was checked by TLC on silica gel 60 F_{254} (Merck). Microwave reactions were carried out in a multi SYNTH series microwave system (Milestone). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II 400 spectrometer using TMS as an internal standard. IR spectra were recorded in KBr on a Shimadzu FTIR 8400S spectrophotometer. Mass spectra were recorded on a GCMS-QP 1000 mass spectrometer. Elemental analysis was performed by using EA1112 Thermo Finnigan CHNS analyzer.

Synthesis of 2,3-dihydro-6-alkyl-2-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl) chromen-4-ones (3a-j) : General procedure

Conventional method

A mixture of 5-substituted-2-hydroxyacetophenones (0.01 mol), 3-aryl-1-phenylpyrazole-4-carbaldehydes (0.01 mol) and pyrrolidine (0.01 mol) in ethanol (20 ml) was refluxed for appropriate time (Table-1). Progress of the reaction was monitored by TLC. After completion of the reaction, it was cooled to room temp and diluted with cold water. The precipitate formed was filtered, washed with water and recrystallized from methanol to obtain the pure compounds as pale yellow solid.

Microwave irradiation method

A mixture of 5-substituted-2-hydroxyacetophenones (0.01 mol), 3-aryl-1-phenylpyrazole-4-carbaldehydes (0.001 mol) and pyrrolidine (0.001 mol) in ethanol (5 ml) was taken in a quartz tube and inserted into Teflon vial with screw capped and subjected to microwave irradiation at 180W for appropriate time (Table-1). Progress of the reaction was monitored by TLC. After completion of the reaction, it was cooled to room temp and diluted with cold water. The precipitate formed was filtered, washed with water and recrystallized from methanol to obtain the pure compounds as pale yellow solid.

Spectral data

3a: IR (KBr, cm^{-1}): 1682 (>C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H, pyrazole-H), 7.96-7.99 (dd, 1H, J=8.2, 1.7Hz, H-5), 7.81 (m, 4H, ArH), 7.40-7.58 (m, 6H, ArH), 7.28-7.35 (m, 1H, H-7), 7.08-7.12 (m, 2H, H-6,8), 5.66-5.70 (dd, 1H, J=12.7, 3.1 Hz, H-2), 3.20-3.27 (dd, 1H, J=17.0, 3.1 Hz, $3H_{eq}$), 3.00-3.05 (dd, 1H, *J*=17.0, 12.7 Hz, 3, H_{ax}). ^{13}C NMR (100 MHz, $CDCl_3$): 191.3, 161.1, 151.9, 139.9, 135.9, 132.8, 129.3, 128.6, 128.5, 128.3, 128.2, 127.0, 126.7, 121.6, 121.2, 119.5, 119.3, 72.0, 43.5. Mass 367 (100% $[M+H]^+$). [Found : C, 78.67, H, 4.95 $C_{24}H_{18}N_2O_2$ requires C, 78.73, H, 4.91, N, 7.63%].

3b: IR (KBr), 1678 (>C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 8.12 (s, 1H, pyrazole-H), 7.96-7.99 (dd, 1H, J=8.2, 1.7 Hz, H-5, ArH), 7.75-7.79 (m, 4H, ArH), 7.43-7.58 (m, 5H, ArH), 7.34-7.38 (m,1H, H-7), 7.05-7.13 (m, 2H, H-6,8), 5.62-5.66 (dd, 1H, J=12.7, 3.1Hz, H-

2), 3.19-3.27 (dd, 1H, J=17.0, 3.1 Hz, 3-H_{eq}), 3.00-3.05 (dd, 1H, J=17.0, 12.7Hz, C_3-H_{ax}). ^{13}C NMR (100 MHz, $CDCl_3$): 191.1, 160.9, 150.8, 139.8, 136.1, 134.5, 131.2, 129.5, 129.4, 128.8, 127.1, 126.9, 121.7, 121.2, 119.4, 119.3, 117.9, 71.8 and 43.2. Mass: 401 (100%) $[M+H]^+$). [Found : C, 71.91, H, 4.27, N, 6.99 $C_{24}H_{17}ClN_2O_2$ requires C, 71.87, H, 4.31, N, 6.96%].

3c: IR (KBr): 1683 (>C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 8.13 (s, 1H, pyrazole-H), 7.96-7.98 (dd, 1H, J=8.2, 1.7Hz, H-5), 7.68-7.79 (m, 4H, ArH), 7.47-7.56 (m, 4H, ArH), 7.32-7.36 (m, 1H, H-7), 7.26-7.31 (m, 1H, ArH), 7.08-7.12 (m, 2H, H-6,8), 5.65-5.69 (dd, 1H, J=12.7, 3.1Hz, H-2), 3.18-3.26 (dd, 1H, J=17.0,3.1Hz, 3-H_{eq}), 2.98-3.03 (dd, 1H, J=17.0, 12.7Hz, 3-H_{ax}), 2.41 (s, 3H, -CH_3), ^{13}C NMR (100 MHz, $CDCl_3$): 191.4, 161.3, 152.1, 140.1, 138.2, 135.9, 130.0, 129.3, 139.3, 128.3, 127.1, 126.7, 126.6, 121.6, 121.4, 119.6, 119.3, 118.1, 72.3, 43.6, 21.6. Mass : 381 (100%($[M+H]^+$). [Found : C, 78.93, H, 5.30, N, 7.36 $C_{25}H_{20}N_2O_2$ requires C, 78.97, H, 5.28, N, 7.32%].

3d:IR (KBr): 1683 (>C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 8.12 (s, 1H, pyrazole-H), 7.96-7.99 (dd, 1H, J=8.2, 1.7 Hz, H-5), 7.73-7.78 (m, 4H, ArH), 7.47-7.58 (m, 3H, ArH), 7.32-7.36 (m, 1H, H-7), 7.08-7.12 (m, 2H, H-6,8), 6.99-7.01 (m, 2H, ArH), 5.63-5.67 (dd, 1H, J=12.7, 3.1Hz, H-2), 3.86 (s, 3H, -OCH_3), 3.20-3.27 (dd, 1H, J=17.0, 3.1Hz, 3-H_{eq}), 2.99-3.04 (dd, 1H, J=17.0, 12.7Hz, 3-H_{ax}). ^{13}C NMR (100 MHz, $CDCl_3$): 191.4, 161.3, 161.1, 160.3, 151.9, 140.2, 136.0, 129.7, 129.6, 129.2, 127.2, 127.0, 126.7, 126.5, 125.6, 121.7, 119.4, 119.2, 118.2, 114.2, 72.4, 55.4, 43.6. Mass : 397 (100% $[M+H]^+$). [Found : C, 75.74. J. 5.08, N, 7.07 $C_{25}H_{20}N_2O_3$ requires C, 75.78, H, 5.11, N, 7.05%].

3e: IR (KBr): 1685 (>C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 8.12 (s, 1H, pyrazole-H), 7.96-7.99 (dd, 1H, J=8.2, 1.7Hz, H-5), 7.76-7.82 (m, 4H, ArH), 7.48-7.58 (m, 3H, ArH), 7.34-7.37 (m, 1H, H-7), 7.06-7.18 (m, 4H, ArH), 5.62-5.66 (dd, 1H, J=12.7, 3.1Hz, H-2), 3.20-3.27 (dd, 1H, J=17.0, 3.1 Hz, 3-H_{eq}), 3.00-3.05 (dd, 1H, J=17.0, 12.7Hz, 3-H_{ax}). ^{13}C NMR (100 MHz, $CDCl_3$): 191.0, 164.3, 160.9, 151.0, 139.9, 135.9, 130.1, 130.1, 129.3, 128.9, 127.0, 126.8, 121.6, 121.3, 119.3, 117.9, 115.5. 115.3, 71.9, 43.3. Mass : 385 (100% $[M+H]^+$). [Found : C, 74.99, H, 4.46, N, 7.29 $C_{24}H_{17}FN_2O_2$ requires C, 74.96, H, 4.50, N, 7.32%].

3f: IR (KBr): 1682 (>C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 8.16 (s, 1H, pyrazole-*H*), 7.98-8.00 (d, 1H, J=8.2, 1.7 Hz, H-5), 7.66-7.80 (m, 6H, ArH), 7.32-7.52 (m, 6H, ArH), 7.16-7.18 (d, 1H, ArH), 5.73-5.77 (dd, 1H, J=12.7, 3.1 Hz, H-2), 3.31-3.38 (dd, 1H, J=17.0, 3.1Hz, 3-H_{eq}), 3.09-3.14 (dd, 1H, J=17.0 Hz, 12.7Hz, 3H_{ax}). ^{13}C NMR (100 MHz, $CDCl_3$): 191.7, 160.93, 150.9, 139.5, 136.4, 131.9, 131.4, 129.8, 129.5, 127.2, 127.1, 122.8, 121.9, 121.0, 119.3, 119.1, 118.0, 71.6, 43.1. Mass : 445 (100% [M+H]+). [Found : C, 64.73, H, 3.85, N, 6.29 $C_{24}H_{17}BrN_2O_2$ requires C, 64.77, H, 3.89, N, 6.32%].

3g: IR (KBr): 1680 (>C=O). ^{1}H NMR (400 MHz, $CDCl_3$); 8.14 (s, 1H, pyrazole-*H*), 7.76-7.82 (m, 5H, ArH), 7.33-7.52 (m, 7H, ArH), 6.98-7.00 (d, 1H, H-8), 5.62-5.66 (dd, 1H, J=12.7, 3.1 Hz, H-2), 3.17-3.24 (dd, 1H, J=17.0, 3.1 Hz, 3-H_{eq}), 2.97-3.02 (dd, 1H, J=17.0, 12.7Hz, 3-H_{ax}), 2.36 (s, 3H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 191.4, 159.2, 151.9, 140.0, 139.9, 132.9, 131.1, 129.3, 128.4, 128.3, 126.6, 120.9, 119.7, 119.3, 117.8, 72.1, 43.5, 20.1. Mass : 381 (100% $[M+H]^+$). [Found : C, 78.93, H, 5.30, N, 7.36 $C_{25}H_{20}N_2O_2$ requires C, 78.89, H, 5.35, N, 7.40%].

3h: IR (KBr): 1682 (>C=O). ^{1}H NMR (400 MHz, $CDCl_3$); 8.10 (s, 1H, pyrazole-*H*), 7.74-7.77 (m, 5H, ArH), 7.34-7.51 (m, 6H, ArH), 6.95-6.97 (d, 1H, H-8), 5.57-5.61 (dd, 1H, J=12.7, 3.1Hz, H-2), 3.16-3.24 (dd, 1H, J=17.0, 3.1Hz, 3-H_{eq}), 2.97-3.02 (dd, 1H, J=17.0, 12.7Hz, 3-H_{ax}), 2.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 191.5, 159.1, 151.0, 140.0, 137.3, 134.7, 131.5, 129.7, 129.5, 128.9, 127.0, 126.8, 121.0, 119.7, 119.4, 119.3, 117.9, 71.9, 43.4, 20.3. Mass : 415 (100% $[M+H]^+$). [Found : C, 72.37, H, 4.62, N, 6.75 $C_{25}H_{19}ClN_2O_2$ require C, 72.34, H, 4.66, N, 6.79%]

3i: IR (KBr): 1683 (>C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 8.11 (s, 1H, pyrazole-*H*), 7.73-7.78 (m, 5H, ArH), 7.47-7.51 (m, 2H, ArH), 7.33-7.38 (m, 2H, ArH), 6.98-7.00 (d, 1H, H-8), 5.59-5.63 (dd, 1H, J=12.7, 3.1 Hz, H-2), 3.86 (s, 3H, -OCH_3), 3.17-3.25 (dd, 1H, J=17.0, 3.1 Hz, 3-H_{eq}), 2.96-3.01 (dd, 1H, J=17.0, 12.7Hz, 3-H_{ax}), 2.36 (s, 3H, CH_3). ^{13}H NMR (100 MHz, $CDCl_3$): 191.6, 160.6, 160.0, 159.2, 151.8, 140.0, 137.0, 131.1, 126.9, 129.2, 126.6, 126.5, 125.4, 120.8, 119.3, 119.2, 117.8, 114.2, 72.1, 55.2, 43.5, 20.1. Mass: 411 (100% $[M+H]^+$). [Found : C, 76.08, H, 5.40, N, 6.82 $C_{26}H_{22}N_2O_2$ requires C, 76.12, H, 5.44, N, 6.86%].

3j: IR (KBr): 1682 (>C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 8.09 (s, 1H, pyrazole-*H*), 7.71-7.77 (m, 5H, ArH), 7.51-7.55 (m, 2H, ArH), 7.36-7.38 (m, 2H, ArH),

7.00-7.03 (d, 1H, H-8), 5.55-5.58 (dd, 1H, J=12.7, 3.1 Hz, H-2), 3.15-3.23 (dd, 1H, J=17.0, 3.1Hz, 3-H_{eq}), 2.95-3.00 (dd, 1H, J=17.0, 12.7Hz, 3-H_{ax}), 2.38 (s, 3H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 192.0, 164.2, 161.7, 159.0, 151.2, 139.6, 137.5, 131.4, 130.1, 129.5, 128.6, 128.64, 127.0, 127.03, 126.7, 119.3, 119.1, 117.8, 115.8, 115.6, 71.8, 43.2, 20.5. Mass : 399 (100% $[M+H]^+$). [Found : C, 75.36, H, 4.81, N, 7.03 $C_{25}H_{19}FN_2O_2$ requires C, 75.40, H, 4.83, N, 6.99%].

Acknowledgement

The authors are thankful to UGC (SERO) for financial support. Authors are also grateful to Head, Department of Chemistry and Director, CFRD, Osmania University, Hyderabad for providing laboratory and instrumental facilities.

References

1. H. Matsuda, T. Wang, H. Managi and M. Yoshikawa, *Bioorg. Med. Chem.,* **11** (2003), 5317.
2. H. Matsuda, T. Morikawa, S. Ando, I. Toguchida and M. Yoshikawa, *Bioorg. Med. Chem.,* **11** (2003), 1995.
3. C. Pouget, F. Lauthier, A. Simon, C. Fagnere, J.P. Basly, C. Delage and A.J. Chulia, *Bioorg. Med. Chem. Lett.,* **11** (2001), 3095.
4. C.H. Ko, S.C. Shen and Y.C. Chen, F*ree Radical Bio. Med.,* **36** (2004), 897.
5. C. Pouget, C. Fagnere, J.P. Basly, G. Habrioux and A.J. Chulia, *Bioorg. Med. Chem. Lett.,* **12** (2002), 1059.
6. T. Maliar, A. Jedinak, J. Kadrabova and E. Sturdik, *Eur. J. Med. Chem.,* **39** (2004), 241.
7. (a) J.B. Harbone and C.A. Williams, *Nat. Prod. Res.,* **12** (1995), 639.
   (b) D. Ashok and P.N. Sharma, *Curr. Sci.*, **56** (1987), 234.
8. P. Spearring, G. Majetich and J. Bhattacharya, *J. Nat. Prod.,* **60** (1997), 399.
9. *Chem. Abstr.*, **125(9)** (1996), 135, 105089.
10. F. Bondavalli, O. Bruno, A. Ranise, P. Schenone, D. Donnoli, M.L. Cenicola, C. Matera, S. Russo and E. Marmo, *Farmaco,* **44(7-8)** (1989), 655.
11. O. Bruno, A. Ranise, F. Bondavalli, S. Schenone, M.D. Amico, M. Falciani, C. Vacca and A. Filipplli, *Farmaco,* **49(9)** (1994), 533.
12. U. Hanefeld, C.W. Rees, A.J.P. White and D.J. Williams, *J. Chem. Soc. Perkin Trans,* **1** (1996), 1545.
13. *Chem. Abstr.*, 110 75390a, **110** (1989), 641.
14. J.P. Bazureau and F.T. Boullet, *'Microwaves in Organic Synthesis'*, Chapter **8**, Ed. By. A. Loupy, Wiley (2002).
15. L. Pale, T. Jason, W. Bernard and W. Jacob, *Tetrahedron*, **57** (2001), 9225.
16. S. Babber, S. Chandra and A.K. Aggarwal, *Indian J. Chem.*, **26B** (1987), 797.
17. G. Sagrera, V. Lopez, E. Pandolfi, G. Seoane and T. Eicher, *Informacion Tecnologica,* **9** (1998), 11.
18. Om, V. Singh, M. Muthukrishnan and M. Sunderavadivelu, *Indian J. Chem.,* **44B (12)** (2005), 2575.
19. T. Patonay, R.S. Varma, A. Vass, A. Levai and J. Dudas, *Tetrahedron Lett.,* **42** (2001), 1403.
20. R.C. Kamboj, G. Sharma, D. Kumar, R. Arora, C. Sharma and K.R. Aneja, *Int. J. Chem. Tech. Res.,* **3(2)** (2011), 901.
21. D. Ashok, K. Sudershan and M. Khalilullah, *Green Chem. Lett. Rev.*, **5(2)** (2012), 121.
22. D. Ashok and D. Shravani, *Tetrahedron Lett.,* **49** (2008), 7227.

3234/2013