Indian Journal of Chemistry
Vol. 46B, July 2007, pp. 1174-1178

Environmentally benign synthesis of fluorinated pyrazolone derivatives and their antimicrobial activity

S N Shelke[a], N R Dalvi[a], S B Kale[a], M S More[a], C H Gill[b] & B K Karale[a]*

[a] P.G. Department of Chemistry, S. S. G. M. College, Kopargaon, Dist Ahmednagar 423 601, India

[b] Department of Chemistry, Dr. B. A. M. University, Aurangabad 431 004, India

E-mail: snshelke@yahoo.co.in

Received 27 June 2006; accepted (revised) 6 March 2007

Various fluorine containing 4-[-3-(4-aryl)-1-phenyl-1*H*-pyrazol-4-yl)methylene]-3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one **3a-g** and 3-(trifluoromethyl)-4-(4-oxo-4*H*-chromon-3-yl)methylene-1-phenyl-1*H*-pyrazol-5(4*H*)-one **5a-k** have been synthesized by conventional and non-conventional method. The synthesis **3** and **5** highlights a comparative study of conventional, ultrasonication and microwave techniques. All products have been characterized by IR, ^{1}H NMR, MS study and screened for their antimicrobial activity.

Keywords: Fluorinated compound, 4-formyl pyrazole, 3-formylchromone, pyrazolone, microwave, ultrasound

In recent years design of environmentally benign reactions is an important goal in organic synthesis. Day by day hazardous chemicals and byproducts of various reactions increase the pollution in the environment. Keeping in view the need for avoiding hazardous chemicals and solvents in chemical reactions, ultrasonication and microwave technique was found to be accelerating a wide variety of transformations[1,2].

Commercial microwave assisted organic reactions occur more rapidly, safely and with higher chemical yields[3-5], render the microwave method superior to conventional method. The growing number of publications in the area of microwave-assisted synthesis includes virtually all types of synthesis like Knoevenagel condensation[6].

Ultrasound has increasingly been used in organic synthesis[7,8]. Sonochemistry is also becoming more and more important for a variety of synthetic organic reactions utilizing ultrasound as an energy source to generate radicals and initiate the electron transfer process, *e.g.* Knoevenagel condensation[9].

Fluorinated organic compounds are associated with antimicrobial[10], antitumour[11], antibacterial[12], anti-lung cancer[13] and act as selective inhibitors of biosynthesis of aminergic neurotransmmitters[14].

Pyrazole as well as pyrazole containing compounds have been reported to show a broad spectrum of biological activities such as antimicrobial[15], anti-tumor[16], anti-HCV[17] and antiinflammatory[18] agents. Due to bioactivity associated with pyrazole and pyrazole containing compounds, researchers and chemist are very much interested in pyrazole chemistry[19,20]. Pyrazolone are associated with broad spectrum of biological activities[21,22]. Pyrazolone exhibit analgesic[23], antiinflammatoty[24] and anaesthetic activity[25] and act as potential antidiabetic agents in rats[26].

The ultrasonicated as well as microwave-assisted methods are more convenient as they require shorter time for completion of reaction and higher yields are obtained as compared to conventional method.

Results and Discussion

In the present work various 3-substituted-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** are treated with 3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one **2** by conventional method and non-conventional methods like ultrasonication and microwave irradiation to gave 4-((3-(4-aryl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one **3**.

Equivalent mole of 3-formylchromone **4** and 3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one **2** by conventional method and non-conventional methods gave 3-(trifluoromethyl)-4-(4-oxo-4*H*-

chromon-3-yl)-methylene-1-phenyl-1*H*-pyrazol-(4*H*)-one **5** (**Scheme I**).

In general, the reactions using ultrasonication as well as microwave technique are very clean and required shorter time for completion.

Compounds **3** and **5** were obtained in good yield within 5-10 min under ultrasonication and 2-3 min under microwave irradiation. Each experiment using both methods was repeated three times to confirm the consistency of the results. Comparative results obtained are tabulated in the **Table I** and **II**

The efficiency of non-conventional method was evaluated by comparison with the same reaction in refluxing acetic acid. The later method required 20-25 min for completion of the reaction and yields are found to be comparatively poor.

Experimental Section

All experiments under ultrasonication were carried out in bath type ultrasonicator model EN-20U-S manufactured by Enertech Electronica Pvt., Ltd., Mumbai, India having maximum power output of 100W and 33 KHz operating frequency.

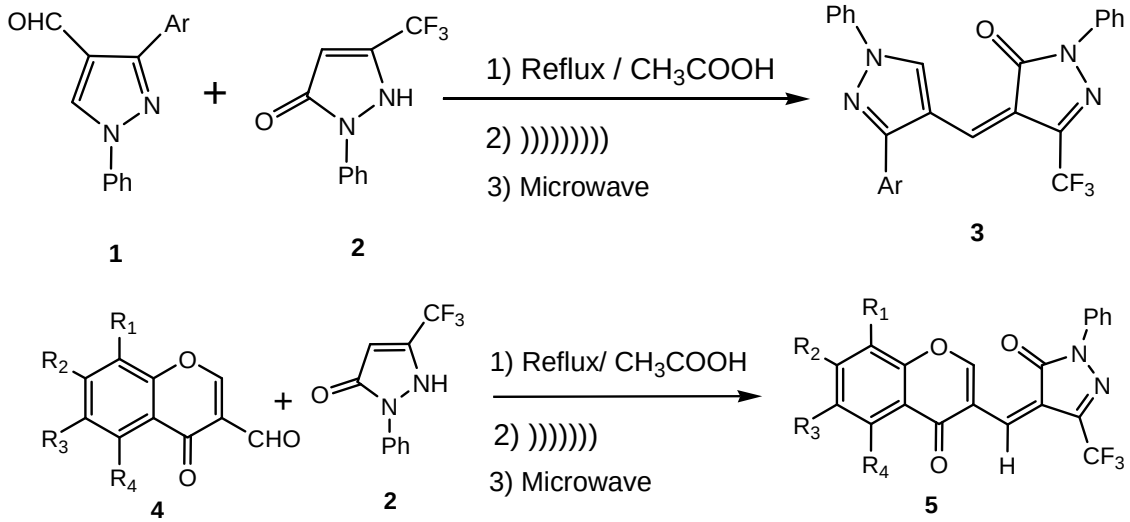
All experiments under microwave irradiation were carried out in unmodified domestic microwave oven model 800T manufactured by BPL Appliances and Utilities Ltd, Bangalore, India having maximum power output of 800W and 2450 MHz frequency.

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr disc on a FT-IR spectrometer. ^{1}H NMR spectra were recorded on 300 MHz instrument with $CDCl_3$ as solvent using TMS as internal standard, while mass spectra were recorded on Finnigan mass spectrometer.

4-[4-Aryl-1-phenyl-1*H*-pyrazol-4-yl)methylene]-3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5 (4*H*)-one 3

Method (A): By conventional method. 3-Aryl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** (0.001 mole) and 3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one **2** (0.001 mole) were taken in 100 mL RBF with 5 mL acetic acid. Reaction mixture was heated under reflux for 20-25 min. Progress of reaction was monitored with the help of TLC. After completion of heating, reaction mixture was cooled to RT and product obtained was separated by filtration. The product was purified by recrystallization from acetic acid. This typical experimental procedure was followed to prepare other analogs of this series. The compounds synthesized by above procedures are listed in **Table I** with their characterization data. IR, NMR and MS data have confirmed their structures. IR, NMR and MS data are in agreement with those obtained for the products synthesized by other methods. Formation of compounds are confirmed by m.p. and mixed m.p.

Method (B) By ultrasound method. 3-Aryl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** (0.001 mole) and 3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one **2** (0.001 mole) were taken in 100 mL RBF with 5 mL acetic acid. Reaction mixture was subjected to ultrasonication for 5-10 min. Progress of reaction was monitored with the help of TLC. After completion of reaction, the product obtained was separated by filtration. The product was purified by recrystallization from acetic acid. The same experimental procedure was followed to prepare other analogs of this series. The compounds synthesized by the above



Scheme I

Table I — Characterization data of synthesized compounds* **3a-g** and **5a-k** by conventional and non-conventional methods

Compd	Ar group	m.p. °C	Conventional Method		Ultrasonication Method		Microwave Method	
			Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
3a	Phenyl	220	21	68	07	83	2	74
3b	Naphthyl	196	20	69	09	86	3	72
3c	4-Methyl phenyl	160	23	65	05	87	2	71
3d	4-Chloro phenyl	162	24	68	08	81	2.5	73
3e	4-Bromo phenyl	180	24	71	09	88	2.5	75
3f	2,4 Dichloro, 5 flurophenyl	165	25	70	10	86	3	76
3g	Thiophene	202	22	59	07	82	2	70
5a	R_1= R_2= R_3= R_4= H	192	20	56	06	72	2	68
5b	R_1= R_2= R_4= H, R_3=Cl	233	21	60	08	78	3	76
5c	R_1= R_3= Cl, R_2= R_4= H	228	20	71	10	88	2.5	81
5d	R_1= R_3= CH_3, R_2= R_4= H	249	24	72	07	87	2.5	80
5e	R_1= R_2= R_4= H, R_3=C_2H_5	180	23	68	09	82	3	76
5f	R_1= R_2= R_4= H, R_3=F	210	21	69	09	85	2	75
5g	R_1= R_3= R_4= H, R_2= CH_3	198	22	70	08	87	2.5	77
5h	R_1= R_3= H, R_2= R_4= CH_3	210	24	74	07	89	2	73
5i	R_1= R_2= R_4= H, R_3= CH_3	224	24	72	08	88	3	80
5j	R_1= R_4= H, R_2=CH_3,R_3= Cl	244	25	59	09	84	2.5	71
5k	R_1= R_3= R_4= H, R_2= Br	220	23	68	05	82	2	72

*All compounds showed satisfactory elemental analysis.

Table II — Antibacterial and antifungal activity of compounds **3a-g** and **5a-k**

Compd	Zone of inhibition in mm		
	E. coli	*S. albus*	*A. niger*
3a	12	10	6
3b	10	08	6
3c	10	10	4
3d	12	10	6
3e	10	12	4
3f	12	08	4
3g	12	08	6
5a	8	08	-
5b	6	04	4
5c	-	-	4
5d	6	-	-
5e	8	04	4
5f	10	06	6
5g	6	04	4
5h	-	04	-
5i	-	06	04
5j	6	-	-
Streptomycin sulphate	18	20	Not tested
Greseofulvin	Not tested	Not tested	12

procedures are listed in **Table I** along with their characterization data.

Method (C) By microwave method. 3-Aryl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** (0.001 mole) and 3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one **2** (0.001 mole) were taken in 100 mL beaker provided with a watch glass to function as a lid in the absence of any solvent. Reaction mixture was subjected to microwave irradiation at an output of 450 W for 2-3 min. Progress of reaction was monitored with the help of TLC. After completion of reaction, the product was purified by recrystallization from acetic acid. IR, NMR and MS data are in agreement with those obtained for the products synthesized by other methods. Formation of compounds are confirmed by m.p. and mixed m.p.

3c: IR (KBr): 3049, 1695, 1595, 1533, 1501, 1050 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.4 (s, 3H-CH_3), 7.2-8.0 (m, 15H aromatic and olefinic proton) 10.2 (s, 1H); MS: *m/z* 472 (M+), 403, 375, 285, 91, 77, 44. **3f**: IR (KBr): 3051, 1693, 1599, 1530, 1503, 1051, 735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.1-8.2 (m, 13H aromatic and olefinic proton) 9.98 (s, 1H); MS: *m/z* 544 (M+), 546 (M+2), 548 (M+4), 509, 475, 411, 321, 273, 104, 91,

77. **3g**: IR (KBr): 3043, 1692, 1591, 1535, 1508, 1049 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.1-8.2 (m, 14H aromatic and olefinic proton) 10.4 (s, 1H); MS: *m/z* 464 (M+), 395, 367, 277, 104, 91, 77.

This typical experimental procedure was followed to prepare other analogs of this series. The compounds synthesized by above procedures are listed in **Table I** along with their characterization data.

3-(Trifluoromethyl)-4-(4-oxo-4*H*-chromon-3-yl)-methylene-1-phenyl-1*H* pyrazol-5(4*H*)-one 5.

Method (A) By conventional method. Equimolar amount of 3-formylchromone **4** (0.001 mole) and 3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one **2** (0.001 mole) were taken in 100 mL RBF with 5 mL acetic acid. Reaction mixture was heated under reflux for 20-25 min. Progress of reaction was monitored with the help of TLC. After completion of heating, the reaction mixture was cooled to RT and the product obtained was separated by filtration. The product was purified by recrystallization from acetic acid. The same experimental procedure was followed to prepare other analogs of this series. The compounds synthesized by the above procedures are listed in **Table I** along with their characterization data. IR, NMR and MS data confirmed their structures. IR, NMR and MS data are in agreement with those obtained for the products synthesized by other methods.

Method (B) By ultrasound method. Equimolar amount of 3-formylchromone **4** (0.001 mole) and 3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one **2** (0.001 mole) was taken in 100 mL RBF with 5 mL acetic acid. Reaction mixture was subjected to ultrasonication for 5-10 min. Progress of reaction was monitored with the help of TLC. After completion of reaction, the product obtained was separated by filtration. The product was purified by recrystal-lization from acetic acid. The same experimental procedure was followed to prepare other analogs of this series. The compounds synthesized by the above procedures are listed in **Table I** along with their characterization data. IR, NMR and MS data are in agreement with those obtained for the products synthesized by other methods. Formation of compounds are confirmed by m.p. and mixed m.p.

Method (C) By microwave method. Equimolar amount of 3-formylchromone **4** (0.001 mole) and 3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one **2** (0.001 mole) was taken in 100 mL beaker provided with a watch glass to function as a lid in the absence of any solvent. Reaction mixture was subjected to microwave irradiation at an output of 450W for 2-3 min. Progress of reaction was monitored with the help of TLC. After completion of reaction, the product was purified by recrystallization from acetic acid. IR, NMR and MS data are in agreement with those obtained for the products synthesized by other methods. Formation of compounds are confirmed by m.p. and mixed m.p.

5b: IR (KBr): 3058, 1660, 1134, 1696, 1623, 1482 , 1612, 737 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.9-8.1 (m, 8H aromatic and olefinic proton), 8.6 (s, 1H), 10.5 (s,1H, C_2-H of chromone moiety); MS: *m/z* 418 (M+), 420 (M+2), 389, 236, 154, 77. **5i**: IR (KBr): 1661, 1136, 1698, 1619, 1479 , 1619, 3071 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.5 (s, 3H-CH_3), 7.2-8 (m, 8H aromatic and olefinic proton) 8.2 (s, 1H), 10.5 (s, 1H, C_2-H of chromone moiety); MS: *m/z* 398 (M+), 370, 236, 134, 77. **5j**: IR (KBr): 3072, 1663, 1134, 1692, 1620, 1474 , 1615, 735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.5 (s, 3H-CH_3), 7.2-8 (m, 7H aromatic and olefinic proton) 8.2 (s, 1H), 10.5 (s,1H, C_2-H of chromone moiety); MS: *m/z* 432 (M+), 434 (M+2), 404, 236, 168, 77.

This typical experimental procedure was followed to prepare other analogs of this series. The compounds synthesized by above procedures are listed in **Table I** along with their characterization data.

Antimicrobial Screening

Compounds listed in **Tables I** and **II** were screened (doses of 100 μg) for their antibacterial activity against gram-ve bacteria *E. coli* and gram+ve bacteria *S. albus* using filter paper disc method. Plates inoculated with *E. coli* were incubated for 48 hr and plates inoculated with *S. albus* for 24 hr respectively at RT. Streptomycin sulphate were used as a standard. Inhibition zones were measured in mm and results obtained are shown in **Table II**.

All these compounds were also screened (doses of 100 μg) for their antifungal activity against *A. niger* using greseofulvin as a standard. The results are shown in **Table II**.

Acknowledgement

Authors are thankful to the Principal G. T. Sangle, S.S.G.M. College, Kopargaon, Ahmednagar for

providing necessary facilities and constant encouragement. One of the authors (SNS) thanks UGC, New Delhi for the award of Teacher Fellowship.

References

1 Novikov S S, Khmel'nitskii L I, Lebedev O V, Sevast'yanova V V, Epishina L V, *Khim Geterotsikl Soedin*, 4, **1970,** 503; *Chem Abstr*, 73, **1970,** 66491z.

2 Mackie & Cartney M, *Practical Medicinial Microbiology*, edited by J G Collee, Duguid J P, Fraser A G and Marmion, **1989,** p87.

3 Maruthikumar T V, Reddy V P & Rao P H, *Indian J Chem*, 44B, **2005,** 1931.

4 Dalvi N R, Karale B K & Gill C H, *Chemistry an Indian J*, 1(8), **2004,** 582.

5 Chornous V O, Bratenko M K & Vovk M V, *Synth Commn*, 34(1), **2004,** 79.

6 (a) Yakaiah T, Reddy G V & Lingaiah B P V, Rao P S & Narsaiah B, *Indian J Chem*, 44B, **2005,** 1301; (b) Wang G & Cheng B, *ARKIVOC*, (ix), **2004,** 4.

7 Dalvi N R, Karale B K & Gill C H, *Indian J Chem*, 44B, **2005,** 1522.

8 Naik R & Pasha M A, *Indian J Chem*, 44B, **2005,** 778.

9 Shindalkar S S, Madje B K & Shingare M S, *Indian J Chem*, 44B, **2005,** 1519.

10 Joshi N S, Shaikh A A, Deshpande A P, Karale B K, Bhirud & Gill C H, *Indian J Chem*, 44B, **2005,** 422.

11 Lucey N M & McElhinney R S, *J Chem Research*, **1985,** 240.

12 Patel V M & Desai K R, *Indian J Chem*, 44B, **2005,** 1084.

13 Hammam A E G, El-Salam O I A, Mohamed A M & Hafez N A, *Indian J Chem*, 44B, **2005,** 1887.

14 Kollonitsch J, Patchett A A, Marburg S, Maycock A L, Perkins L M, Doldouras G A, Duggan D E & Aster S D, *Nature*, 274, **1978,** 906.

15 (a) Karale B K, Chavan V P, Mane A S, Hangarge R V, Gill C H & Shingare M S, *Korean J Med Chem*, 10(2), **2000,** 84; (b) Chornous V A, Bratenko M K, Vovk M V & Sidorchuk I I, *Pharm Chem J*, 35(4), **2001,** 203.

16 Rostom S A F, Shalaby M A & El-Demellawy M A, *Euro J Med Chem*, 38, **2003,** 959.

17 Goal A & Madan A K, *J Chem Inf Comput Sci*, 35, **1995,** 510.

18 Ren X L, Li H B, Wu C & Yang H Z, *ARKIVOC*, (xv), **2005,** 59.

19 Turk C, Golic L, Selic L, Svete J & Stanovnik B, *ARKIVOC*, (v), **2001,** 87.

20 Abrovt A A, Abella W A & Sokka I A E I, *J Drug Res*, 7, **1975**, 1.

21 Ahluwalia V K & Bina M, *Indian J Chem*, 24B, **1989**, 150.

22 Wiley J, *Burger's Medicinal Chem*, 4, **1980**, 291.

23 Lubs H A, *The Chemistry of Synthesic Drugs and Pigments*, 290, **1970**, 298.

24 Mulwad V V & Choudhari B P, *Indian J Chem*, 43B, **2004**, 1544.

25 Garg H G & Prakash C, *J Indian Chem Soc*, 53, **1976**, 1168.

26 Frankle S, Reitman S & Sonnenwirth A C, *Gradwol's Clinical Laboratory Methods and Diagnosis* Voll. II, 7th edn, **1970**, p.1406.