Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2016, 7(3):38-42

Pelagia Research Library

ISSN: 0976-8505
CODEN (USA) CSHIA5

Solvent free microwave-assisted synthesis of some novel pyrimidinones/ thiones and their biological studies

Jyothi N. Rao and Balakrishna Kalluraya

Department of PG Studies in Chemistry, Mangalore University, Mangalagangothri

---

ABSTRACT

Microwave assisted as well as conventional synthesis of 1-substituted - (5-chloro-3-methyl-1- phenyl- pyrazol -4-yl) -5- carboxyethy1 /methyl-6- methyl- pyrimidine -2- ones / thiones is carried out and their antibacterial and antifungal activity is reported.

Keywords: Microwave synthesis, biological activity, spectroscopic characterization, pyrimidine- 2- one/thiones.

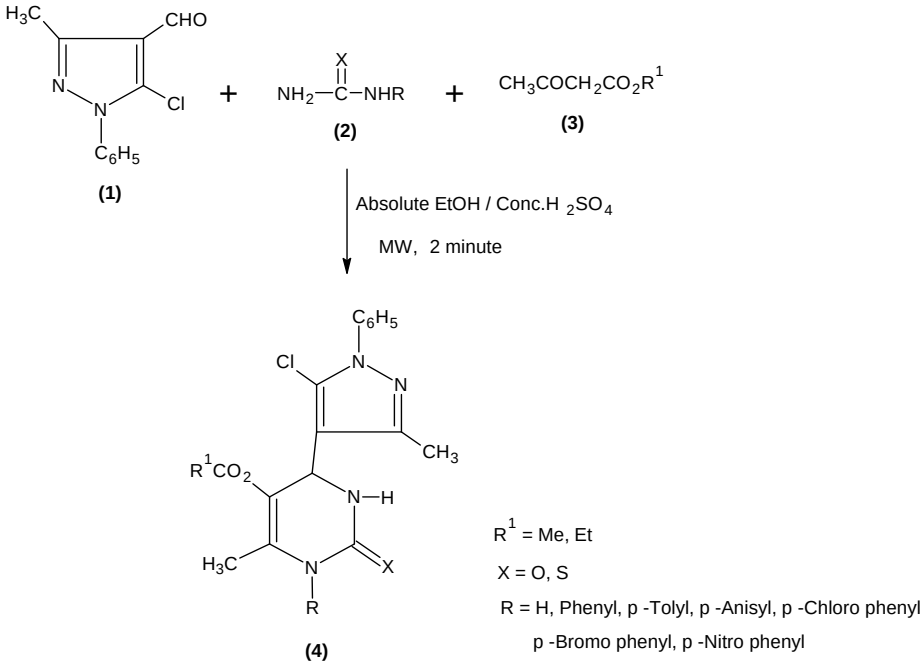
INTRODUCTION

Use of microwave technology in organic and inorganic reaction is repeated in a number of publications and reviews [1-3]. In the last few years, there has been increasing in the use of environmentally benign reagents and conditions[4-6] particularly in solvent free procedures[7]in dry media, reactions occur rapidly and the methods avoid hazards associated with solvent especially in sealed vessels. The absence of solvent reduces reaction time and always improves yield. Using microwaves with proper control of power and reaction temperature is more efficient than conventional heating.

In this context, we planned to prepare pyrimidinones derivatives and ecofriendly and environmentally benign solvent free conditions, wherein several disadvantages like long reaction time and tedious work up can be overcome. Dihydropyrimidinones are compound that have drawn widespread attention due to their medical applications[7]. A variety of dihydropyrimidinone derivatives have been screened for antihypertension[8] antibacterial[9] anti-inflammatory[10] and anticarcinogenic[11]activities or as sedative and adrenergicreceptorantagonists[12]. The common synthetic routes to these compound generally involve multi step transformation that are essentially based on Biginelle condensation methodology[13-14].

MATERIALS AND METHODS

The starting material 1- pheny1 -3- methy1 -5- chloro – pyrazolo -4- aldehyde **1** employed in the preparation of pyrimidinone is obtained by Vilsmeir Haack formylation reaction and is used after purification by recrystallization. Ethyl acetoacetate **2** was procured from Ranbaxy and was purified by distillation.



The physical constant , yield and analytical data of 1- substituted -4- (-5- chloro -3- methyl -1- pheny1 -1H-pyrazol -4- y1) -5-carboxyethy1 / methy1 -6- methy1 pyrimidine -2- oneare given in table 1

Table1: Characterization data of 1-substituted-4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-carboxyethyl/methyl–6-methyl–pyrimidine-2-ones/thiones 4a-i

Compd. No.	R	X	R^1	Mol. Form. Mol. Wt.	m.p.^{0}C	Crystal nature	Yield[a] (%)	% Analysis Found (Calculated)		
								C	H	N
4a	H	O	C_2H_5	$C_{18}H_{19}N_4O_3Cl$ 374	160-63	Yellow crystals	56 (51)	57.71 (57.75)	5.03 (5.08)	14.92 (14.97)
4b	H	S	C_2H_5	$C_{18}H_{19}N_4O_2SCl$ 390	201-03	White crystals	58 (55)	55.30 (55.38)	4.83 (4.87)	14.37 (14.35)
4c	Phenyl	S	C_2H_5	$C_{24}H_{23}N_4O_2SCl$ 466	135-37	Orange crystals	64 (59)	61.86 (61.80)	4.95 (4.93)	12.09 (12.07)
4d	p-Anisyl	S	C_2H_5	$C_{25}H_{25}N_4O_3SCl$ 497	188-90	Pale yellow crystals	54 (49)	60.38 (60.36)	5.09 (5.03)	11.29 (11.26)
4e	p-Tolyl	S	C_2H_5	$C_{25}H_{25}N_4O_2SCl$ 480	156-58	Brown crystals	57 (53)	62.31 (62.37)	5.12 (5.19)	11.68 (11.64)
4f	p-Chloro phenyl	S	C_2H_5	$C_{24}H_{22}N_4O_2SCl_2$ 502	132-35	White crystals	69 (66)	57.42 (57.48)	4.36 (4.39)	11.11 (11.17)
4g	p-Bromo phenyl	S	C_2H_5	$C_{24}H_{22}N_4O_4SClBr$ 544	121-23	Orange crystals	61 (58)	52.87 (52.84)	4.09 (4.03)	10.23 (10.27)
4h	p-Nitro phenyl	S	C_2H_5	$C_{24}H_{22}N_4O_2SCl_2$ 510	198-20	White crystals	63 (59)	56.31 (56.36)	4.34 (4.30)	13.64 (13.69)
4i	H	O	CH_3	$C_{17}H_{17}N_4O_3Cl$ 360	178-90	White crystals	69 (64)	56.68 (56.66)	4.74 (4.72)	15.59 (15.55)

Biological activity

Antibacterial activity

Studies on the antibacterial activity of synthesized compounds **4**have been carried out against four pathogenic organisms' viz., *Staphylococcus aureus* (G^+), *Klebsiella pneumonias* (G^-), *Escherichia coli* (G^-). The anti-bacterial activity of the newly synthesized in the present investigation was assessed by the cup-plate method[15]. The results of the antibacterial studies are share in table2. Among the compounds tested. **4e** and **4l** showed good activity against the bacteria. *E, coli, P. aeruginosa, K. pnenomoniae* and moderate activity against S. aureus. Compound **4h** showed good activity against *E.coli,* and *P.aeruginosa* and moderate against. *K. pneumonias* and moderate activity against *S. aureus.*

The pyrimidine chemistry has been developed extensively and is still developing. Presently there are a number of drugs used clinically with comprise pyrimidanone moiety in association with various heterocyclic rings.

In view of them, a project was undertaken is synthesis a new series of pyrimidanones by microwave irradiation and to evaluates pharmacological activity.

Antifungal activity

The antifungal activity studies of the newly synthesized pyrimidinone derivatives have been carried out against the fungi *Aspergillus flavus, A. fumigatus, penicillium* and trichophyton by the cup plate method. The results of the antifungal studies are shown in table 4. Among the compounds tested, **7d** shows good activity against all the fungi. Compound tested **7b** and **7c**showed good activity against the fungi *A flavos* and pencillium compounds 7b and 7c showed good activity against *pencillium*. Compound 7j showed good activity against the fungus A fumigator and moderate activity against Trichophyton respectively.

Table 2: Antibacterial and antifungal activity data of compounds 4a-i

Compd. No.	Antibacterial activity (MIC in µg / mL)				Antifungal activity (MIC in µg/mL)
	S.aureus	*P.aeruginosa*	*E.coli*	*B.subtilis*	*C. albicans*
4a	**0.125**	**0.125**	**0.125**	**0.125**	**0.125**
4b	0.25	0.25	0.25	0.25	0.25
4c	0.25	0.25	0.25	0.25	0.25
4d	**0.125**	**0.125**	**0.125**	**0.125**	**0.125**
4e	0.25	0.25	0.25	0.25	0.25
4f	0.25	0.25	0.25	0.25	0.25
4g	**0.125**	**0.125**	**0.125**	**0.125**	**0.125**
4h	**0.125**	**0.125**	**0.125**	**0.125**	**0.125**
4i	0. 25	0.25	0. 25	0.25	0.25
Standard Furacin	0.25	0.25	0.25	0.5	_
Standard Flucanazol	-	-	-	-	0.25
Control DMF	-	-	-	-	-

Index for antibacterial and antifungal activity
Disc size : 5.5 mm
S. aureus **:** *Staphy1ococcus aureus*
P. aeruginosa : *Pseudomonas aeruginosa*
E. coli : *Escherichia coli*
B. subtilis : *Bacillus subtilis*
C. albicans : *Candida albicans*

MATERIALS AND METHODS

General

All reagents and solvent were procured from Ranbaxy. The reactions were carried out under microwave irradiation at 160 W. TLC was used to monitor the progress of the reaction. The melting points of the newly synthesis compounds were determined in open capillaries and are uncorrected.

The IR spectra were records on a perkin-Elmer 983 in spectrophotometer as KBr pellet. The ^{1}H-NMR spectra were recorded on a Bruker Ac 300F (300MHz) NMR spectrometer using DMSO-d_6 or $CDCl_3$as solvent and TMS as internal standard. All chemical shift values are expressed in the δ scale down field from TMS and proton signals are indicated as s= singlet d=double t=triple m= multiple mass spectra of the compounds were records on a Jeol JMS -D300 mass spectrometer by operating at 70eV.

1- pheny1 -3- methy1 -5-chloropyrazole -4- aldehyde (1)

N, N – Dimethylform amide (14.6ml, 0.2 ml) was taken in a round -bottom flask, filter with a dropping funnel and a thermometer and cooled in ice -salt mixture to 0^0C. Then phosphorousoxychloride was added to it. The above solution mixture so prepared heated at 50-55^{0}C for 3 hours. Then phosphorusoxychloride was added to it. The above solution mixture so prepared heated at 50-55^{0}C for 3 hours. Then contents were refluxed at 100^{0}C for 10 hours , cooled to room temperature and to excess of ice with vigorous stirring and neutralized with sodium acetatetrihydrate. The solid separated was filtered, washed with water dried and recrystallized from ethanol.m.p.144^{0}C (lit [16]m.p. 144-45^{0}C) yield 80%.

1-Substituted -4-(5-chloro-3- methyl-1- pheny1 -14- pyrazol -4- yl) -5-carbohyethyl- 1- methy1 -6- methyl – pyrimidine -2- ones /thiones

Method I

A mixture of 1-pheny1 -3- methyl-5- chloropyrazole -4- aldehyde (0.01mol) **(1)**, ethylacetoacetate/ methylacetoacetate**(2)** (0.015), Urea /thiourea / thiourea derivatives **(3)** (0.01ml) and conc.H_2SO_4 (2drops) in absolute ethanol (10ml) taken in a borosil beaker (100ml) and was zapped inside a microwave over for a duration of

2 minute (at 160W). The reaction mixture was then allowed to stand at room temp and the product formedwas filtered, washed with ethanol, dried and recognized from ethanol

Method II

A mixture of 1-phenyl -3- methyl-5- chloro- pyrazole -4- aldehyde**(1)** (0.01mol), ethylacetoacetate/ methylacetoacetate**(2)** (0.015mol), Urea /thiourea / thiourea derivatives **(3)** (0.01ml) in ethyl alcohol(25ml) containing 2 drops of conc. H_2SO_4 was refluxed for 8 hrs on a water bath. After cooling the reaction mixture to room temperature the content were poured into 100ml of ice cold water taken in a beaker. The solid mass was collected by filtration, dried and recrystallized from ethanol to give 4a-l.

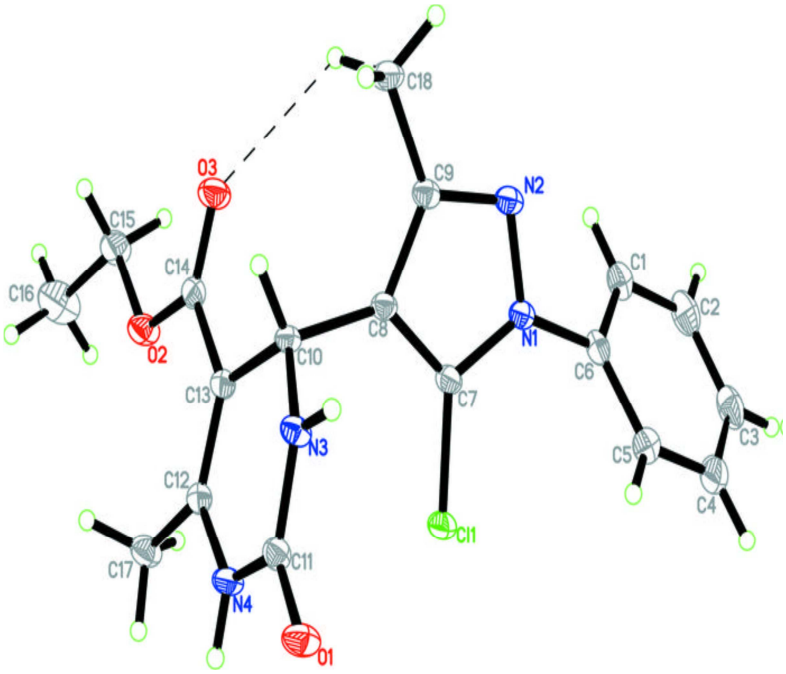
A few typical compounds are described below:

4a: 1894cm^{-1}- amide carbonyl stretching, ester carbonyl was observed at1624cm^{-1}. NH stretching is observed at 3402cm^{-1}. ^{1}HNMR-***δ***1.06 (t, CH_3), 2.18 (pyrazole methy1 & pyrimidine methy1 protons***δ*** 4.01 (q),***δ*** 5.30 (s, CH protons) Two NH proton- two separate broad singlet ***δ***7.56 &8.29. phenyl protons (m, 7.43-7.53) mass: M+1 peak375.2(374)

4 c: ***δ***.1.06 (t, 3H, $CH_3$of ethy1 group) ,2.45(s,3H,CH_3 group of pyrazole), 2.50 (s,3H, CH_3group of pyrimidine), 4.01 (q,2H,CH_2 of ethy1 group), 5.29 (s,1H,CH) , 7.53-7.63 (m, 10H,Ar-H), 8.48(br, 1H, NH) mass: M+1 (466)

4d: ***δ***1.06 (t,3H, CH_3 of ethy1 group) 2.17 (s,3H, CH_3 of pyrazole group) , 2.53(s,3H,CH_3 of phenyl),2.59(s,3H,CH_3 of pyrimidine group), 4.01 (q,2H,CH_2 of ethyl group), 5.40(s,1H,CH), 7.36-7.55 (m, 9H, Ar-H), 8.49 (br, 1H , NH), IR: 1685cm^{-1} for C=O group, NH stretching 3318 cm^{-1}, Mass: (M+1) 481.0

Further the structure is confirmed by XRD-data. The XRD structure for the compound **4a** is given below



Structure of 4a based on the X–ray diffraction study

CONCLUSION

1-substituted - (5-chloro-3-methyl-1- phenyl- pyrazol -4- yl) -5- carboxyethy1 /methyl-6- methyl- pyrimidine -2- ones / thiones were synthesized and screened for their antibacterial antifungal activity. The antimicrobial study revealed that compounds 4a, 4d, 4g and 4h showed excellent antibacterial and antifungal activity against all the tested organisms. This enhanced activity could be attributed to the presence of potential pyrimidine functionality along with anisyl, bromophenyl and chloro phenyl group.

Acknowledgement
The authors thank the authorities of the Regional Sophisticated Instrumentation centre, Indian institute of Technology, Chennai and Sophisticated instrumentation facility Indian institute of Science, Bangalore for spectral and analytical data.

REFERENCES

[1] G.C Rovnyak, K.S Atwal, A.Hedberg,S.D.Kimball, S.Moreland J.Z Goughoutas, B.C ReillySchwartaz and MF Malley*J Med chem***1992**, 35, 3254.
[2] K.S Atwal *J.MedChem.,* **1990**,33, 1510
[3] 3. T. Matsuda and I. Hirao*Nippon kagakuzashi* **1965,** 86,1965
[4] Y.S Sadanandam,M.M Shetty and P.V Diwar*Eur J Med Chem*.,**1992,** 27, 87
[5] T. Kato *Jpn.KokaiTokkyoKoho*Jp, **1984**,59,190
[6] B. Lagu*Bioorg.Med chem. Let*, **2000**,101,75
[7] T,G Steel, C.A Goburn, M.A Patane and Book MG *TetrahedronLett***1998,** 39,9315
[8] R.A Abramovitch*Org.Prep.Proc.Int***1991,** 23, 685
[9] D.R Baghurst and D.M Mingos*Chem .Soc.Rev***1991,**201
[10] A. Loupy*Spect Anal***1993,**175, 33
[11] J.H Clark, S.R Culer, S.J Barlow and T.W Bastock*J.Chem .Soc,Perkin Trans* **1994,**1117.
[12] D. Villemine and Hammadi*Synth. Commun.*,**1996,** 26, 4337
[13] R.S Varma, R. Dahiya and R.K Saini*TetraheranLett***1997,**386, 7029
[14] G. Loupy Bram and J. Sansoulel*NewJ.Chem.*,**1992,**16,233
[15] B. K Kaur andJ.Kaur *Indian J.Chem.*,**2002,**41B,1526
[16] AghayanBaourtchain and Hossein*Synthetic communications***2004,**34 1, 3335