Indian Journal of Chemistry
Vol. 48B, October 2009, pp. 1431-1434

Note

Microwave assisted synthesis of some novel pyrimidinones/thiones

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Received 25 July 2007; accepted (revised) 5 June 2009

A novel series of 1-substituted-4-aryl-5-ethoxycarbonyl-6-methylpyrimidine-2-ones/thiones are prepared in the one pot condensation of appropriate aldehyde, ethylacetoacetate and substituted urea in ethanol medium under microwave irradiation. The new compounds are well characterized by IR, ^{1}H NMR, mass spectra, C,H,N-analysis and in a typical example the structure was further confirmed by X-ray crystallographic data.

Keywords: Microwave synthesis, pyrimidinones, thiones, biological activity

Dihydropyrimidinones are an important class of compounds and gaining increasingly importance due to their therapeutic and pharmacological properties[1]. They have emerged as the integral backbones of several calcium channel blockers, anti-hypertensive agents and alpha-1α-antagonists. Recently several isolated marine alkaloids with interesting biological activities were also found to contain the dihydropyrimidinone-5-carboxylate core. Most notable among them are the batzelladine alkaloids, which have been found to be potent human immunodeficiency virus (HIV) gp-120-CD4 inhibitors[2].

In modern laboratories organic transformations must be rapidly executed and products readily purified. Clearly there will be a continuing need for the definition of novel reaction routes to both multifunctional scaffolds for lead generation and to unique drug like heterocyclic structures. In this field controlled microwave irradiation has proved to be a powerful tool for both speeding up chemical optimizations and for efficient preparation of new target compounds[3-6]. The recent development in highly chemoselective metal catalyzed coupling reactions has further enabled direct incorporation of wide variety of chemical functionalities that previously were difficult to accomplish[7,8].

Keeping in view of these observations it was planned to synthesize a novel series of pyrimidinones/thiones in the one pot reaction of appropriate aldehydes, ethylacetoacteate and substituted urea/thiourea under microwave irradiation technique.

Results and Discussion

The reaction between substituted aldehyde **1**, substituted urea **2** and ethylacetoacetate **3** in ethanol medium in the presence of an acid catalyst under microwave irradiation resulted in the formation of 1-substituted-4-aryl-5-ethoxycarbonyl-6-methyl-pyrimidine-2-one/ thiones **4a-i (Scheme I)**. The generality of this method with respect to various precursors is summarized in **Table I**. The starting materials except phenyl thiourea obtained commercially and were used after purification. Phenylthiourea was prepared by refluxing aniline and ammonium thiocyanate in presence of hydrochloric acid. The structure of the newly synthesized compounds was established on the basis of analytical data IR, ^{1}H NMR and mass spectra. Further in a representative example for compound **4c** the structure was confirmed by recording its single crystal X-ray **Figure 1**.

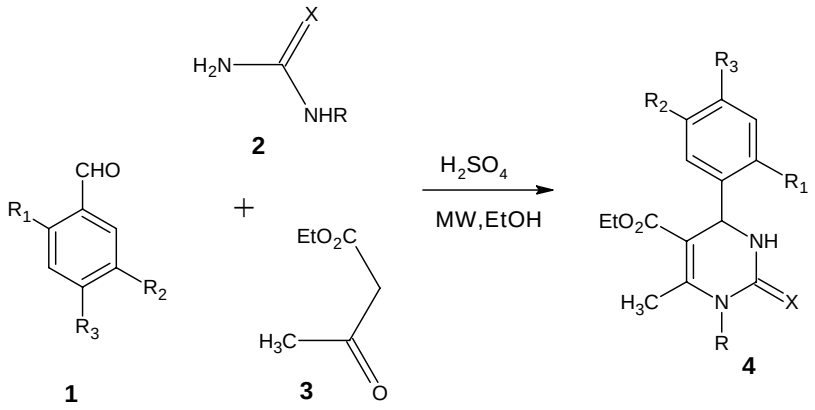
Biological activities

The newly synthesized compounds **4a-i** were screened for their antibacterial and antifungal activity. The bacteria employed were *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* and the antifungal activity was tested against the fungus *Candida albicans*. The screening results indicated that among the compounds tested **4a-c** showed significant activity against all the microorganisms tested and were active at a very low concentration compared to the standards employed Furacin and Flucanazole **(Table II)**.

Experimental Section

General

Melting points were determined by open capillary method and are uncorrected. All compounds were analyzed satisfactorily for C, H, and N. ^{1}H NMR spectra were recorded on a Bruker AC 300F (400 MHz) NMR spectrometer using $CDCl_3$ as



R=H/Ph

X=O/S

R_1=H/NO_2

R_2=H/OMe

R_3=OMe/N,N$(Et)_2$/SMe

Scheme I

Table I — Characterization data of pyrimidinones/thiones **4a-i**

Compd	R	X	R_1	R_2	R_3	Mol.Fomula. M.W.	Irrdn Time (Min)	Yield (%)	m.p. (°C)	Nature of the solid	Found (Calcd)% C	H	N
4a	H	O	NO_2	OMe	OMe	$C_{16}H_{19}N_3O_7$ 365	3	52	195-97	Yellow Crystals	52.50 (52.6	5.16 5.20	11.46 11.50)
4b	H	S	NO_2	OMe	OMe	$C_{16}H_{19}N_3O_6S$ 381	3.5	58	160-63	Yellow Crystals	50.51 (50.39	5.09 4.98	10.91 11.02)
4c	Ph	S	NO_2	OMe	OMe	$C_{22}H_{23}N_3O_6S$ 457	4	56	185-87	Orange Crystals	57.78 (57.76	5.07 5.03	9.10 9.19)
4d	H	O	H	H	SMe	$C_{15}H_{18}N_2O_3S$ 306	2.5	63	160-62	Yellow Crystals	58.88 (58.82	5.80 5.88	9.11 9.15)
4e	H	S	H	H	SMe	$C_{15}H_{18}N_2O_2S_2$ 322	3	65	150-53	Yellow Crystals	55.84 (55.90	5.50 5.59	8.62 8.69)
4f	Ph	S	H	H	SMe	$C_{21}H_{22}N_2O_2S_2$ 398	4	68	140-42	Yellow Crystals	63.25 (63.31	5.56 5.52	7.14 7.03)
4g	H	O	H	H	N-$(Et)_2$	$C_{18}H_{25}N_3O_3$ 331	3.5	59	180-82	Orange Crystals	65.20 (65.25	7.46 7.55	12.57 12.68)
4h	H	S	H	H	N-$(Et)_2$	$C_{18}H_{25}N_3O_2S$ 347	3.5	60	197-199	Brown Powder	62.20 (62.24	7.11 7.20	12.21 12.10)
4i	Ph	S	H	H	N-$(Et)_2$	$C_{24}H_{29}N_3O_2S$ 423	4	58	135-37	Orange Crystals	68.00 (68.08	6.81 6.85	9.96 9.92)

Solvent for recrystalization: Ethanol +DMF (2:1)

solvent and TMS as internal standard. Mass spectra were recorded either on a Jeol JMS-D 300 mass spectrometer or API 3000 LCMS instrument operating at 70 eV.

Procedure for the preparation of phenylthiourea

Aniline (0.1 mole) was dissolved in minimum amount of dilute hydrochloric acid in a round bottomed flask. Ammonium thiocyanate (0.2 mole)

was then added and the mixture was refluxed for 5-6 hr. After cooling, the product separated was filtered and washed several times with cold water and recrystallized from ethanol.

General procedure for the synthesis of 1-substituted-4-aryl-5-carboxyethyl-6-methyl-pyrimidine-2-one/thiones 4a-i

A mixture of substituted aldehyde (0.01 mole), ethylacetoacetate (0.015 mole), urea/thiourea/phenylthiourea (0.01mole) and Conc.H_2SO_4 (1-2 drops) in absolute ethanol (10mL) were taken in a borosil beaker (100 mL) was zapped[9] inside the microwave oven for a period of 3-4 minutes (at 160 W i.e. 25% microwave power). The reaction- mixture was then allowed to stand at RT and the product formed was filtered, washed with ethanol, water, dried and recrystallized from ethanol to afford **4a-i** in 52-68% yield (microwave oven: LG-Little Chef MS-192W). The characterization data of the compounds **4a-i** is given in **Table I**.

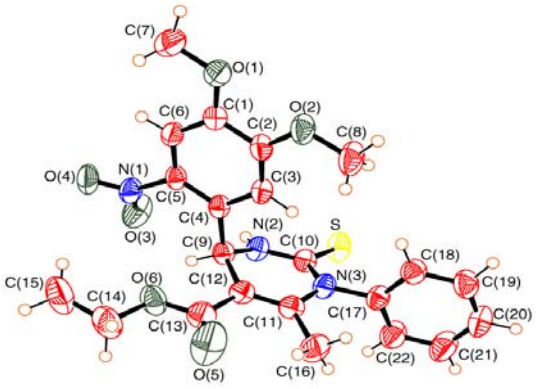


Figure 1 — X-ray Crystallographic structure of compound **4c**

Spectral data for compounds 4a-i

4a: Ethyl 4-(4,5-dimethoxy-2-nitrophenyl)-6-methyl-2 – oxo -1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate ^{1}H NMR (400 MHz), Solvent $CDCl_3$: δ 1.01 (t, 3H, CH_3 of ethyl group), 2.49 (s, 3H, Me), 3.95 (s, 3H, OCH_3) and 3.98 (s, 3H, OCH_3), 4.04 (q, 2H, CH_2 of ethyl group), 5.99 (s, 1H, CH), 6.78 (s, 1H, NH), 7.27 (s, 1H, Ar-H), 7.63 (s, 1H, ArH), 8.40 (s, 1H, NH); .MS: *m/z* 365 for $C_{16}H_{19}N_3O_7$.

4b: Ethyl 4-(4,5-dimethoxy-2-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ^{1}H NMR (400 MHz), $CDCl_3$: δ 1.02 (t, 3H, CH_3 of ethyl group), 2.50 (s, 3H, Me), 3.96 (s, 3H, OCH_3) and 3.98 (s, 3H, OCH_3), 4.02 (q, 2H, CH_2 of ethyl group), 5.99 (s, 1H, CH), 6.78 (s, 1H, NH), 7.27 (s, 1H, Ar-H), 7.61(s, 1H, ArH), 8.09(s, 1H, NH); MS: *m/z* 381 for $C_{16}H_{19}N_3O_6S$.

4c: Ethyl-4-(4,5-dimethoxy-2-nitrophenyl)-6-methyl-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ^{1}H NMR (400 MHz), $CDCl_3$: δ 1.03 (t, 3H, CH_3 of ethyl group), 2.28 (s, 3H, Me), 4.01(s, 6H, 2xOMe), 4.04 (q, 2H, CH_2 of ethyl group), 6.05 (s, 1H, CH), 6.98(s, 1H, NH) 7.27 -7.61(m, 7H, ArH); MS: *m/z* 457 for $C_{22}H_{23}N_3O_6S$.

4d: Ethyl-4-[4-(methylthio)phenyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ^{1}H NMR (400 MHz), $CDCl_3$: δ 1.16 (t, 3H, CH_3 of ethyl group), 2.35 (s, 3H, Me), 2.45 (s, 3H, SMe), 4.08 (q,

Table II— Antibacterial and antifungal activity data of compounds **4a-i**

Compd.	Antibacterial activity (MIC in μg/mL)				Antifungal activity (MIC in μg/mL)
	S. aureus	*E. coli*	*P. aeruginosa*	*B. subtilis*	*C. albicans*
4a	0.125	0.125	0.125	0.125	0.125
4b	0.125	0.125	0.125	0.125	0.125
4c	0.125	0.125	0.125	0.125	0.125
4d	0.25	0.25	0.25	0.25	0.25
4e	0.5	0.25	0.25	0.25	0.25
4f	0.25	0.25	0.25	0.25	0.25
4g	0.25	0.25	0.25	0.25	0.25
4h	0.25	0.25	0.25	0.25	0.25
4i	0.25	0.25	0.25	0.25	0.25
Standard:Furacin	0.5	0.5	0.25	0.5	-
Standard:flucanazol	-	-	-	-	0.25
DMF	-	-	-	-	-

2H, CH_2 of ethyl group), 5.34 (s, 1H, CH), 7.16-7.27 (m, 4H, ArH), 7.94 (s, 1H, NH) 8.51(s, 1H, NH).

4e: Ethyl-4-[4-(methylthio)phenyl]- 6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ^{1}H NMR (400 MHz), $CDCl_3$: δ 1.18 (t, 3H, CH_3 of ethyl group), 2.36 (s, 3H, Me), 2.46 (s, 3H, SMe), 4.09 (q, 2H, CH_2 of ethyl group), 5.35 (s, 1H, CH), 7.16 -7.27 (m, 4H, ArH) 7.94 (s, 1H, NH) 8.51 (s, 1H, NH); MS:*m/z* 322 for $C_{15}H_{18}N_2O_2S_2$.

4f: Ethyl-4-[4-(methylthio)-phenyl]-6-methyl -1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ^{1}H NMR (400 MHz), $CDCl_3$: δ 1.22 (t, 3H, CH_3 of ethyl group), 2.15 (s, 3H, Me), 2.53 (s, 3H, SMe), 4.14 (q, 2H, CH_2 of ethyl group), 5.43 (s, 1H, CH), 7.23 -7.48 (m, 9H, ArH) 8.08 (s, 1H, NH); MS: *m/z* 398 for $C_{21}H_{22}N_2O_2S_2$.

4h: Ethyl 4-[4-(dimethylamino) phenyl]-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. MS: *m/z* 347 for $C_{18}H_{25}N_3O_2S$.

Acknowledgements

The authors thank Head, RSIC, Chandigarh, for spectral and analytical data. The authors are also thankful to UGC, New Delhi for the financial assistance in the form of a Major Research Project.

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