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An expeditious ,eco-friendly synthesis and Antimicrobial activity of Pyrimidine-2-thione derivatives

Medical Science

KEYWORDS : One pot condentation , Pyrimidine-2-thione derivative , CdCl2 , solvent-free and Anti microbial Activity.

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ABSTRACT

Conventional method of organic synthesis usually need longer heating time, tedious apparatus setup, which result in higher cost of process and the excessive use of solvents reagents lead to environmental pollution. In the recent year microwave assisted organic reaction has emerged as new tool in organic synthesis and this is considered as an important approach toward green chemistry. This growth of green chemistry holds significant potential for a reduction of the by product & waste production and a lowering of the energy costs.

The one pot condentation of phenyl thio-urea 1 with ethyl acetoacetate 2 and different aromatic aldehyde 3 using CdCl2 as a catalyst in solvent-free condition under microwave irradiation (2-4 min) gave Pyrimidine-2-thione derivative 4(a-f) with excellent yield is described here.

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The use of microwave assisted organic reaction has gained much attention In the recent year because it offers several advantages such as simple, clean, fast[1,2], efficient, economic and higher yield of purified products[3] as a consequences of selective absorption of microwave energy by polar molecule or polar intermediate formed in due course of reaction .

Pyrimidine ring system having substituted six –membered ring and mercapto group occupy unique position in medicinal chemistry[4] , moreover some new Pyrimidine-2-thione with certain structural modification containing cyano or N-arylcarbamoyl moiety at the 5-position have diverse range of therapeutic effects[5].

A perusal literature on pyrimidine has revealed that these compound play a vital role on many biologicalactivities such as a anti-malarial [6], anti-tumor[7], anti-inflammatory[8], anti-thyroid , and anti-viral activity[9]. Some series of pyrimido-[1,3]-thiazine derivatives exhibited modest activity against gram-positive bacterial strains. Some thiazolo-[3,2-a]-pyrimidine were tested for their anti-inflammatory activities, and exerted moderate anti-inflammatory activity

The first synthesis of this heterocycle nucleus was carried out by Biginelli[10] involving one-pot condensation of , ethyl acetoacetate , benzaldehyde and urea under strong acidic condition. However serious drawback of Biginelli's reaction strong acid which decomposes some of acid sensitive reactants as well as low yield in case of substituted aromatic and aliphatic aldehyde.

In the view of these observation and in continuation of our work on eco-friendly synthetic protocol for biologically active compounds[11] , we have developed a much improve modification Biginelli synthesis of Pyrimidine using $CdCl_2$ as a catalyst without using protic acid and organic solvent with increase yield.

Experimental section

Melting point were determined in open capillaries and were uncorrected. The progress of the reaction was monitored by TLC. The solvent system used for TLC was a 8:2 mixture of chloroform:methanol. An unmodified domestic household microwave oven (Kenstar OM-34 ECR) operating at 2450 MHz was used at a power output of 300 W for all experiments. IR spectra were recorded in KBr as a Perkin-Elmer BX series FT-IR spectrophotometer.. 1HNMR ($CDCl_3$) spectra were recorded on Bruker AMX 500 MHz and AC 200 MHz spectrometer using TMS as internal reference . Mass spectra were recorded on a Shimadzu-GCMS 50508. All the solvents used were of analytical grade. The yield and melting point are given in Phenyl tiourea 1 (0.003 mol) , ethylacetate 2 (0.002 mol), aromatic aldehyde 3 (0.002 mol) and catalytic amount of $CdCl_2$ were thoroughly in a beaker and it was placed in alumina bath inside the microwave oven oprating at medium power (570 W) for specidied time (2-3 min) . After the completion of recation , the reaction mixture was poured onto crushed ice and stirred for several time. The solid product Pyrimidine-2-thione 4(a-f) was filtered , washed with cold water and crystallized from absolute ethanol.

Anti microbial Activity :

The activity was determined using cup plate agar diffusion method by measuring the inhibition zone in mm. All the compounds exhibited siginificant antibacterial activity against E.coli and P.fluorescence in various consentrations.

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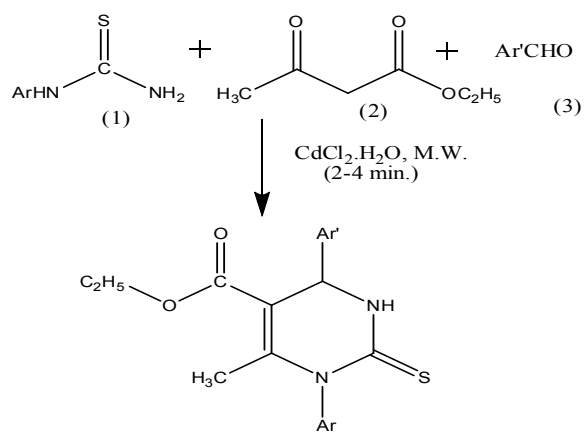

4(a-f)

Compd.	Ar	Ar'
4a	$-C_6H_5$	$-C_6H_5$
4b	$-C_6H_5$	p-ClC_6H_4
4c	$-C_6H_5$	p-NO_2 C_6H_4
4d	$-C_6H_5$	p-OH C_6H_4
4e	$-C_6H_5$	p-OCH_3 C_6H_4
4f	$-C_6H_5$	3,4-$(OCH_3)_2$ C_6H_3

Table-1 Physical and Spectral data of Compound 4(a-f)

Compd.	Mol. Formula	M.P (^{0}C)	MS M/z(M^+)	1HNMR (S ppm)
4a	$C_{20}H_{19}N_2O_2S$	120	319	1.5 (s,3H,CH_3),1.80 (t,3H,$COOCH_2CH_3$) 2.50(q,2H, $COOCH_2CH_3$),3.41(s,1H,C-NH),6.45-7.16(m,9H,ArH)
4b	$C_{20}H_{18}N_2O_2S$	105	353	1.62 (s,3H,CH_3),1.89 (t,3H,$COOCH_2CH_3$) 2.58 (q,2H, $COOCH_2CH_3$),3.46(s,1H,C-NH),6.45-7.16(m,9H,ArH)
4c	$C_{20}H_{18}N_3O_4S$	98	364	1.5 (s,3H,CH_3),1.80 (t,3H,$COOCH_2CH_3$) 2.50(q,2H, $COOCH_2CH_3$),3.41(s,1H,C-NH),6.45-7.16(m,9H,ArH)
4d	$C_{20}H_{19}N_2O_3S$	90	335	1.52 (s,3H,CH_3),1.83 (t,3H,$COOCH_2CH_3$) 2.50(q,2H, $COOCH_2CH_3$),3.42(s,1H,C-NH),6.42-7.10(m,9H,ArH)
4e	$C_{21}H_{21}N_2O_3S$	95	349	1.53 (s,3H,CH_3),1.84 (t,3H,$COOCH_2CH_3$) 2.53(q,2H, $COOCH_2CH_3$),3.43(s,1H,C-NH),6.43-7.10(m,9H,ArH),4.10(s,3H,OCH_3
4f	$C_{22}H_{23}N_2O_4S$	130	379	1.55 (s,3H,CH_3),1.85 (t,3H,$COOCH_2CH_3$) 2.55 (q,2H, $COOCH_2CH_3$),3.44 (s,1H,C-NH),6.43-7.13 (m,9H,ArH),4.09 (s,1H,C-NH-CO), 4.13 (s,3H,-OCH_3)

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