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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 4-SUBSTITUTED-5,6,7,8-TETRAHYDRO[1] BENZOTHIENO[2,3-D] PYRIMIDINES (STBP) UNDER COMPARATIVE METHODS

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ABSTRACT

Two convenient methods for synthesis of 4-substituted-5,6,7,8-tetrahydro[1] benzotheino [2,3-d] pyrimidines derivatives (4a-f) were prepared by the displacement reaction between various amines and 4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d] pyrimidine (3). The relative advantage of greener pathway, which use MW, irradiation and eco-friendly aqueous reaction method, for the synthesis of various heterocyclic compounds. All the synthesized compounds have been carried out under conventional and microwave irradiation methods.

KEYWORD : Green chemistry; comparative method , Benzothienopyrimidines derivative

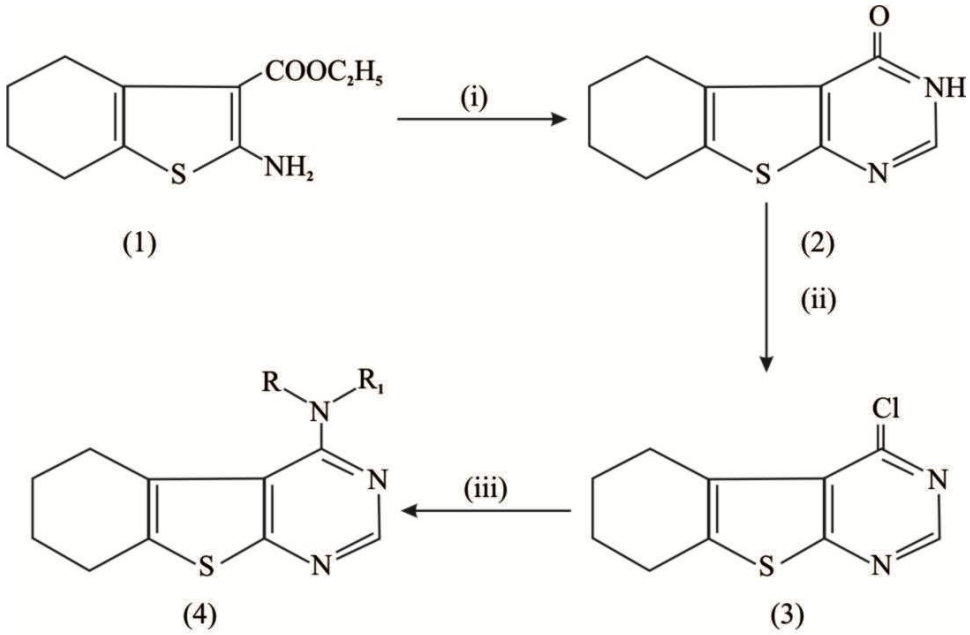
INTRODUCTION

Microwave – assisted organic synthesis is a fast developing area in synthetic organic chemistry[1-3]. The use such non-conventional reaction reveals several features like a short reaction time compounds to conventional heating.[4]

The biological activities of condensed pyrimidines as sedatives antibacterials are well documentd.[5-8] In practice, many Benzothienopyrimidines have been evaluated pharmacologically for their anticaner[9], antiviral[10-11], antihyperlipidemic[12], antimicrobial[13,14] and gastric antisecretary activities.[15]

A series of 4-substituted-5,6,7,8-tetrahydro [1] benzothieno [2,3-d] pyrimidine derivatives (41-d) were prepared by the displacement reaction between various amines, acid 4-chloro-5,6,7,8-tetrahydro [1] benzothieno methanol [2,3-d] pyrimidine(3), which was obtained by refluxing the 5,6,7,8-tetrahydro [1] benzothieno [2,3-d] pyrimidines-4(3H)-one (2) with phosphorus oxychloride, compound 2 was obtained by cydization of ethyl 2-amino-4,5,6,7-tetrahydro-1-benzothieophene-3-carboxylate(1) with dimethyl formamide compound 1 was prepared by gewald thiophere ring synthesis.[16]

All the heterocydic compound were prepared under conventional method-'A' which was refluxing for 1.5 – 6 h, and microwave irradiation method-'B' for 3 – 6 min, rapid reactions, less time and high yields.



SCHEME - I

METHOD 'A'

(1) DMF, reflux 160 – 180ºC, 6 h

(2) $POCl_3$, triethylamine, reflux 140ºC, 1.5 h

(3) Methanol, corresponding amine, reflux 2 h

METHOD 'B'

(1) DMF, MWI 5 min.

(2) $POCl_3$, triethylamine, MWI 2 min.

(3) Methanol, corresponding amine, MWI 3 min.

SCHEME - I

MATERIALS AND METHODS

All the synthesized compounds were purified by recrystallization by using DMF water (2:1). The melting points were recorded on melting point apparatus in open capillaries and are uncorrected. All melting points were compared with the authentic samples[3] and are formed to be same. The purity of compounds checked by TLC using silica gel G. All reactions were carried out in a commercially /domestically available Panasonic MW. Oven having a maximum power out put of 80 – 110W. operating at 2450 MHz, IR (KBr) spectra were recorded on JASCO FT/IR-5300 spectrophotometer. ^{1}HNMR ($CDCl_3$ δ ppm) spectra were recorded on Bruker DPX-400 MHz NMR spectrophotometer, chemical shifts (δ) are reported in ppm, with TMS as internal standard. GC mass spectra were recorded on a shimadzu QP 5000, Elemental analysis for C, H and N were performed on a Perkin Elemer-240.

Conventional Method 'A'

Synthesis of 4-substituted-5,6,7,8-tetrahydro [1] benzothieno [2,3-d] pyrimidines (4a-d):

A mixture of 4-chloro-5,6,7,8-tetrahydro [1] benzothieno [2,3-d] pyrimidines (3) (2.24g, 0.01 mol) and appropriate amine (10ml) in methanol (20ml) was refluxed for 2 h. The reaction mixture was concentrated to 1/3 of the initial volume and cooled at room temperature. The crystals formed were filtered and recrystallized from appropriate solvents (DMF).

Yeild : 60%, M.P. 63ºC.

Microwave Irradiation Method 'B'

Synthesis of 4-substituted-5,6,7,8-tetrahydro [1] benzothieno [2,3-d] pyrimidines (4a-d):

A mixture of 4-chloro-5,6,7,8-tetrahydro [1] benzothieno [2,3-d] pyrimidines (3) (2.24g, 0.01 mol) and amine (10ml) in 2 ml distilled water. The contents were thoroughly mixed. The reaction mixture was subjected to microwave irradiation in a commercially or domestically available Panasonic microwave oven having a maximum power out put of 80 – 110W operating at 2450 MHz intermittently at 30 sec. intervals for 3 – 6 min. The reaction mixture was concentrated to 1/3 of the initial volume and cool to room temperature. After completion of the reaction, products were is dated from simple filtration, washed and dried followed by recrystallization from appropriate solvent (DMF). The purity of compounds was checked with TLC (MP RF and yeidls compared with authentic sample).

Yeild : 90%, M.P. 63ºC.

Antimicrobial activity: The antimicrobial activity of the title compounds was evaluated by zone of inhibition method[13] against six bacterial strains viz., Streptococcus pneumoniae (ATCC 49619) (gram positive), Staphylococcus aureus (ATCC 25923) (gram positive), Streptococcus pyogenes (ATCC 23162) (gram positive), Escherichia coli (ATCC 25922) (gram negative), Pseudomonas aeruginosa (ATCC 27853) (gram negative), Shigella dysenteriae (ATCC 49247) (gram negative), and two fungal strains namely candida albicans and Aspergillus fumigates. The compounds were tested at a concentration of (1 mg/ml) (for gram positive bacteria), cefixime (1 mg/mL) (for gram negative bacteria), for antibacterial and ketoconazole (1 mg/mL) for antifungal activity as standard for comprasion of a antibacterial and antifungal activity respectively. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 h for bacteria and 48 h for fungi. Each experimnent was repeated thrice and average of three independent determinations was recorded.

RESULTS AND DISCUSSION

The synthesis of 4-chloro-5,6,7,8-tetrahydro [1] benzothieno [2,3-d] pyrimidines (4a-d) were synthesized by condensing substituted 4-chloro-5,6,7,8-tetrahydro [1] benzothieno [2,3-d] pyrimidines (3) were dissolved in appropriate distilled water. Under N, N-dimethyl formamide (DMF) was heated under reflux for 3 min under microwave oven and reflux for 2 h under conventional method heating.

Compd	R^1	R^2	Mol. Formula	Mol.	M.P. ºC	Method-A yield/T %/h	Rf value
4a	Me	Me	$C_{12}H_{15}N_3S$	233	63	69/2	0.56
4b	Et	Et	$C_{14}H_{19}N_3S$	261	60	71/2	0.63
4c	Ph	Ph	$C_{22}H_{19}N_3S$	357	40	71/2	0.58
4d	$-(CH_2)_5$		$C_{15}H_{19}N_3S$	273	115	74/2	0.64

TABLE 1 : CHARACTERISTICS DATA FOR 4-CHLORO-5,6,7,8-TETRAHYDRO [1] BENZOTHIENO [2,3-D] PYRIMIDINES (STBP) OF CONVENTIONAL METHOD 'A' (4a-d)

RF values : was determined in

Compd	R^1	R^2	Mol. Formula	Mol.	M.P. ºC	Method-B yield/T %/min	Rf value
4a	Me	Me	$C_{12}H_{15}N_3S$	233	63	90/3	0.56
4b	Et	Et	$C_{14}H_{19}N_3S$	261	60	94/3	0.63
4c	Ph	Ph	$C_{22}H_{19}N_3S$	357	40	94/3	0.58
4d	$-(CH_2)_5$		$C_{15}H_{19}N_3S$	273	115	96/3	0.64

TABLE 2: CHARACTERISTICS DATA FOR 4-CHLORO-5,6,7,8-TETRAHYDRO [1] BENZOTHIENO [2,3-D] PYRIMIDINES (STBP) OF MICROWAVE IRRADIATION METHOD 'B' (4a-d)

Spectral and Elemental Analysis of Synthesized Compounds (4a-d)

Synthesis of 4-substituted-5,6,78-tetrahydro[1] benzothieno[2,3-d] pyrimidines (4a-d): A mixture of 4-choloro-5,6,7,8-tetrahydro[1] benzothieno[2,3-d] pyrimidine (3) (2.24g, 0.01 mol) and appropriate amine (10 mL) in methanol (20 mL) was refluxed for 2 h. The reaction mixture was concentrated to 1/3 of the initial volume and cooled to room temperature. The crystal formed were filtered off and recrystallized from appropriate solvent.

N,N-Dimethy1-5,7-8tetrahydro[1]benzothieno[2,3-d]pyrimidine-4-amine(4a):

IR (KBr,cm^{-1}) 2854 v(aliphatic C-H str), 1568 v(C=N) and 1365 v(C-N); The ^1H NMR ($CDCl_3$, δppm); δ:8.04(s,1H, 2-pyrimidinyl-H), 3.21(s,6H, -NCH_3)3.02-3.05 (t, 2H, -CH_2-), 2.79-2.80 (t,2H,-CH_2-) and 1.85-1.90 (m,4m,-$(CH_2)_2$-); m/z:233(M+); Anal. ($C_{12}H_{15}N_3S$) Found (%): C,61053; H,6.80; N,17.79. Calculated (%): C, 61.77; H, 6.48; N, 18.01.

N,N-Diethyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-d] pyrimidine-4-amine (4b):

IR (KBr, cm^{-1}) 2937 v(aliphatic C-H str), 1558 v(C=N) and 1365c(C-N); The ^1H NMR ($CDCl_3$, δ ppm): δ:8.71 (s,1H,2-pyrimidinyl-H), 3.10 (q,4H, -CH_2CH_3), 2.89 (m, 4H, $0CH_2)_2$-) Anal. ($C_{14}H_{19}N_3S$) Found (%): C,64.67; H,7.64; N,16.32. Calculated (%): C, 64.33; H, 7.33; N, 16.08.

N, N-Diphenly1-5, 7-8-tetrahydro [1] benzothieno [2,3-d] pyrimidine-4-amine(4c):

IR (KBr, cm^{-1}) 3042 v(aromatic C-H str), 1593 v(C=N) and 1315 v(C-N); The ^1H NMR ($CDCl_3$, δ ppm): δ:8.71 (s,1H,2-pyrimidinyl-H), 7.06-7.08 (m,10H, Ar-H), 3.09-.3.10 (t, 2H, - CH2-), 2.88-2.89 (t, 2H-CH2-) and 1.91-1.93 (m,4H,-$(CH_2)_2$-); m/z:357(M+); Anal. ($C_{22}H_{19}N_3S$) Found (%): C,73.76; H,5.10; N,11.54. Calculated (%): C, 73.92; H, 5.36; N, 11.75.

4-Piperidin-1-5, 7-8-tetrahydro [1] benzothieno [2,3-d] pyrimidine-4-amine(4d):

IR (KBr, cm^{-1}) 2937 v(aliphatic C-H str), 1556 v(C=N) and 1365c(C-N); The ^1H NMR ($CDCl_3$, δ ppm): δ:8.50 (s,1H,2-pyrimidinyl-H), 3.31-3.33(m,4H,-$(CH_2)_3$-); m/z:273(M+); Anal. ($C_{15}H_{19}N_3S$) Found (%): C,66.02; H,7.23; N,15.71. Calculated (%): C, 65.90; H, 7.00; N, 15.37.

All the compounds have been screened for antimicrobial activity against six bacterial strains viz., Streptococcus pneumonia (ATCC 49619) (gram negative), Staphylococcus aureus (ATCC 25923) (gram negative), Streptococcus pyogenes (ATCC 25922) (gram positive), Pseudomonas aeruginosa (ATCC 27853) (gram negative), Shigella dysenteriae (ATCC 49247) (gram negative), and two fungal strains namely candida albicans and Aspergillus fumigates. From the table -2the reduction of total serum cholesterol by compounds 4c and 4d is comparable to the standard gemfibrozil. From the Table – 3, it is clear that compounds 4a and 4d have excellent antimicrobial activity against Staphylococcus aureus and Streptococcus pneumonia when compared with standard. Compound 4b have good activity against

Streptococcus pneumonia and Escherichia coli when compared with standard. Compound 4e has excellent activity against Staphylococcus aureus when compared with standard.

Micro-organism	**Diameter of zone (mm) Compounds (amg/mL)**				
	4a	**4b**	**4c**	**4d**	**STD**
	Antibacterial activity				
S.pyogenes	4	2	NA	NA	14*
S.aureus	12	6	2	18	8*
S.pneumoniae	16	10	NA	10	10*
S.dysenteriae	8	6	NA	10	12*
E.coli	14	12	NA	4	13*
P.aeruginosa	NA	NA	NA	6	15*
	Antifungal activity				
C.albicans	6	4	2	2	18**
A.fumigatus	10	NA	NA	6	16**
	LD_{50} values				
LD_{50}	1585	1380	1380	1445	-----

NA: No activity;* Standard drugs: Amoxicillin – clavulanic acid (for gram positive bacteria); Cefixime (for gram negative bacteria);** Standard drug Ketoconazole.

CONCLUSION

A convenient method for the synthesis i.e. 4-substituted-5,6,7,8-tetrahydro [1] benzothieno [2,3-d] pyrimidines were prepared under mild and environmentally benign reactions conditions using green chemistry methodology has been reported. The reactions can be carried out in the blask within the least possible time in contract with the literatures multistep methods. Considering the easy availability of the starting materials, the speed of the reactions and simplicity of the work up the present method appears to be useful.

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