Publications

Available Online

J. Sci. Res. **1** (2), 317-325 (2009)

JOURNAL OF SCIENTIFIC RESEARCH

www.banglajol.info/index.php/JSR

Synthesis and Antimicrobial Activities of Some New Thieno and Furopyrimidine Derivatives

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Received 6 January 2009, accepted in final revised form 14 April 2009

Abstract

Fused pyrimidines, 8,9-dimethyl[1,2,4]triazolo[4,3-c]thieno[3,2-e]pyrimidine **5**, 3,8,9-trimethyl[1,2,4]triazolo[4,3-c]thieno[3,2-e]pyrimidine **6**, 4-benzylidinehydrazono-5,6 dimethylthieno[2,3-d]pyrimidine **7**, 4-[4′-hydroxybenzylidine]hydrazono-5,6-dimethylthieno[2,3-d]pyrimidine **8**, 4-[4′-tolylidin]hydrazono-5,6-dimethylthieno[2,3-d]pyrimidine **9**, 4-[4′-nitrobenzylidine]hydrazono-5-ethyl-6-methylthieno[2,3-d]pyrimidine **10** and 4-[4′-chlorobenzylidine]hydrazono-5-ethyl-6-methylthieno[2,3-d]pyrimidine **11** are prepared in good yield by an initial treatment of 2-amino-4,5-dimethylthiophene-3-carbonitrile **1** with formic acid, affording 5,6-dimethylthieno[2,3-d]pyrimidin-4(3*H*)-one **2**, which is chlorinated with thionyl chloride and then hydrazinated with hydrazine hydrate. Finally hydrazino compound **4** is reacted with formic acid, acetic anhydrate, benzaldehyde, p-hydroxybenzaldehyde, p-toluayldehyde, p-nitrobenzaldehyde and p-chlorobenzaldehyde to give thienotriazolopyrimidines **5-6** and thienopyrimidines **7-11** respectively. All the compounds have been screened for their antimicrobial activity.

Keywords: Fused pyrimidines; Hydrazino compound; Thienotriazolopyrmidines; Thienopyrimidines; Antimicrobial activity.

DOI: 10.3329/jsr.v1i2.2299

1. Introduction

The formation of novel fused heterocycles is an important task for heterocyclic chemists from various points of view for the development of living things. Further more, many condensed heterocyclic systems, especially when linked to a pyrimidine ring as thienopyrimidine play an important role as potent analgesic [1], anti-inflammatory [1-5], antipyretic [6-8], antimicrobial [9-10], anticonvulsant [11], fungicidal [12], antiplatelet activities [13-15], and other central nervous system (CNS) affecting activities [16]. In addition, pyrimidine nucleus can be found in a broad variety of antibacterial, anticancer and anti-tumor agents as well as in agrochemicals and veterinary products [17-18]. In continuation of our interest in the development of new and simple methods for the synthesis of polyfunctional substituted heterocycles, furopyrimidines and thieno-

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pyrimidines, with anticipated biological activity [19-27], the present work describes the syntheses and antimicrobial activities of some furopyrimidines and thienopyrimidnes.

2. Materials and Methods

2.1. *Physical measurements*

Melting points were recorded with Electrothermal melting point apparatus and are uncorrected. Evaporation of solvents were performed under reduced pressure on a Buchi rotary evaporator. Thin layer chromatography was performed on Kieselgel GF_{254} and visualization was accomplished by Iodine Flask or UV Lamp. Column chromatography was carried out with silica gel G_{60} (100-200 mesh). ^{1}H-NMR (400 MHz) and ^{13}C-NMR (400 MHz) spectra were recorded for solutions in deuterio chloroform $CDCl_3$, deuterio methanol CD_3OD and deuterio dimethylsulphoxide (DMSO-d_6) $(CD_3)_2SO$ as solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard. The substrate *o*-aminonitrile, 2-amino-4,5-dimethylthiophene-3-carbonitrile **1** was prepared from 2-butanone by reacting with malononitrile and sulphur according to literature procedure [28].

Synthesis of 5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (**2**):

A solution of *o*-aminonitrile **1** (2.0 g, 13.15 mmol) and formic acid (2 ml) was refluxed for 3 hours at 100°C with continuous stirring. The progress of the reaction was monitored by TLC (ethylacetate: *n*-hexane, 1:4, *v/v*, R_f = 0.39) on silica gel and showed complete conversion of the reactant to the product. After completing the reaction, the mixture was cooled to room temperature and ethanol was added whereby a yellow precipitate was obtained. The precipitate was collected by filtration and recrystallized from ethanol to afford thienopyrimidinone **2** (2.05 g, 85 %) as yellowish crystals, m.p. 136-138°C. ^{1}H-NMR (DMSO-d_6): δ_H 2.14 (s, 6H, 2×CH_3), 7.60 (s, 1H, CH), 9.60 (s, 1H, NH).

Synthesis of 4-chloro-5,6-dimethylthieno[2,3-d]pyrimidine (**3**):

A mixture of pyrimidinone **2** (2.05 g, 11.5 mmol) and thionyl chloride (20 ml) was refluxed for 2 hours at 90°C bath temperature with stirring. After the completion of the reaction, the mixture was standing to cool. Then the mixture was poured onto ice-water and stirred for another 30 minutes. The precipitate was collected by filtration and recrystallized from ethanol to give chloropyrimidine **3** (1.44g, 63.88%) as yellow crystals, m.p. 150-155°C. ^{1}H-NMR (DMSO-d_6): δ_H 2.14 (s, 6H, 2×CH_3), 7.60 (s, 1H, CH).

Synthesis of 4-hydrazino-5,6-dimethylthieno[2,3-d]pyrimidine (**4**):

A mixture of chloro compound **3** (1.44g, 7.28 mmol) and hydrazine hydrate (8 ml) in dioxane (20 ml) was refluxed at 120°C for one hour whereby a solid was separated. It was then filtered and recrystallized from dioxane to afford hydrazinopyrimidine **4** (1.01g, 78%) as yellowish crystals, m.p. 161-163°C. ^{1}H-NMR (DMSO-d_6): δ_H 2.14 (s, 6H, 2×CH_3), 3.60 (s, 1H, NH), 4.10 (s, 2H, -NH_2), 8.10 (s, 1H, CH).

Synthesis of 8,9-dimethyl[1,2,4]triazolo[4,3-c]thieno[3,2-e]pyrimidine (**5**):

An equimolar amount of hydrazino compound **4** (0.89g, 5 mmol) and formic acid (5 mmol) in dioxane (20 ml) was refluxed at 120°C for about 3 hours with continuous stirring. The reaction mixture was then concentrated and left to cool overnight to room temperature for complete precipitation. The obtained solid was then filtered off, dried and recrystallized from ethanol to give compound **5** (0.87g, 85.2%) as brown crystals, m.p. 140-142°C. ^{1}H-NMR (DMSO-d_6): δ_H 2.14 (s, 6H, 2×CH_3), 7.90 (s, 1H, 5-CH), 8.50 (s, 1H, 3-CH). ^{13}C-NMR (DMSO-d_6): δ_C 158.0 (C-5), 147.9 (C-3), 135.8 (C-9), 135.1 (C-8), 129.2 (C-9a), 123.9 (C-6a), 8.0, 5.6.

Synthesis of 3,8,9-trimethyl[1,2,4]triazolo[4,3-c]thieno[3,2-e]pyrimidine (**6**):

An equimolar amount of hydrazino compound **4** (0.89g, 5 mmol) and acetic anhydrate (5 mmol) in methanol (20 ml) was refluxed at 65°C for about 2 hours with continuous stirring. The reaction mixture was then concentrated and left to cool overnight to room temperature for complete precipitation. The separated solid was then filtered off, dried and recrystallized from methanol to give compound **6** (0.71g, 65.4%) as brown crystals, m.p. 180-184°C. ^{1}H-NMR (DMSO-d_6): δ_H 2.14 (s, 6H, 2×CH_3), 4.10 (s, 3H, -CH_3), 7.26 (s, 1H, CH). ^{13}C-NMR (DMSO-d_6): δ_C 160.4 (C-3), 158.0 (C-5), 147.6 (C-9b), 135.8 (C-9), 135.1 (C-8), 129.2 (C-9a), 123.9 (C-6a), 11.6, 8.0, 5.6.

General procedure for the synthesis of hydrazonothienopyrimidine (**7-11)**:

An equimolar amount of hydrazino compound **4** (0.89g, 5 mmol) and different aldehydes (5 mmol) one by one i.e., benzaldehyde, *p*-hydroxybenzaldehyde, *p*-tolualdehyde, *p*-nitrobenzaldehyde and *p*-chlorobenzaldehyde in ethanol (20 ml) was refluxed at 80°C for about 2-3 hours with continuous stirring. The reaction mixture was then concentrated and left to cool overnight to room temperature for complete precipitation. The precipitated solid was then filtered off, dried and recrystallized from ethanol to give hydrazonothienopyrimidines **7-11**.

4-benzylidinehydrazono-5,6-dimethylthieno[2,3-d]pyrimidine (**7**):

Yield: 0.72g (51.2%), white crystals, m.p. 170-173°C.
^{1}H-NMR (DMSO-d_6): δ_H 2.14 (s, 6H, 2×CH_3), 1.61 (s, 1H, NH), 7.40 (m, 5H, -Ph), 7.80 (s, 1H, 2-CH), 8.60 (s, 1H, CH).
^{13}C-NMR (DMSO-d_6): δ_C 167.7 (C-4), 157.1 (C-2), 154.7 (benzylic carbon), 136.1 (C-5), 135.1 (C-6), 130.8, 129.2, 128.8 (benzene ring carbon), 123.9, 7.7, 5.8.

4-[4′-hydroxybenzylidine]hydrazono-5,6-dimethylthieno[2,3-d]pyrimidine (**8**):

Yield: 1.10g (73.5%), yellowish crystals, m.p. 117-121°C.

^{1}H-NMR (DMSO-d$_6$): δ_H 2.18 (s, 6H, 2×CH$_3$), 1.78 (s, 1H, NH), 6.62 (s, 1H, 2-CH), 7.4-7.6 (dd, 4H, -Ph), 7.70 (s, 1H, CH), 8.10 (s, 1H, -OH).
^{13}C-NMR (DMSO-d$_6$): δ_C 167.7 (C-4), 159.6 (C-4$^{/}$), 157.1 (C-2), 154.7 (benzylic carbon), 135.8 (C-5), 135.1 (C-6), 123.9-123.1 (benzene ring carbon), 7.7, 5.8.

4-[4$^{/}$-tolylidin]hydrazono-5,6-dimethylthieno[2,3-d]pyrimidine (**9**):

Yield: 0.98g (67.0%), brown crystals, m.p. 192-194°C.
^{1}H-NMR (DMSO-d$_6$): δ_H 1.14 (s, 6H, 2×CH$_3$), 2.40 (s, 3H, CH$_3$), 7.20 (s, 1H, NH), 7.7-8.1 (dd, 4H, -Ph), 8.70 (s, 1H, 2-CH), 9.90 (s, 1H, CH).
^{13}C-NMR (DMSO-d$_6$): δ_C 167.7 (C-4), 157.1 (C-2), 154.7 (benzylic carbon), 140.0 (C-4$^{/}$), 135.8 (C-5), 135.1 (C-4), 129.1 (benzene ring carbon), 20.9, 7.7, 5.8.

4-[4$^{/}$-nitrobenzylidine]hydrazono-5-ethyl-6-methylthieno[2,3-d]pyrimidine (**10**):

Yield: 0.85g (52.2%), brown crystals, m.p. 175-180°C.
^{1}H-NMR (DMSO-d$_6$): δ_H 1.20 (s, 6H, 2×CH$_3$), 2.20 (s, 1H, NH), 7.30 (s, 1H, 2-CH), 7.4-7.9 (dd, 4H, -Ph), 8.70 (s, 1H, CH).
^{13}C-NMR (DMSO-d$_6$): δ_C 167.7 (C-4), 157.1 (C-2), 154.7 (benzylic carbon), 150.7 (C-4$^{/}$), 137.3, 135.8, 135.1, 129.2, 126.8 (benzene ring carbon), 123.9, 7.7, 5.8.

4-[4$^{/}$-chlorobenzylidine]hydrazono-5-ethyl-6-methylthieno[2,3-d]pyrimidine (**11**):

Yield: 1.14g (72.5%), yellowish crystals, m.p. 182-183°C.
^{1}H-NMR (DMSO-d$_6$): δ_H 1.14 (s, 6H, 2×CH$_3$), 2.20 (s, 1H, NH), 6.80 (s, 1H, 2-CH), 7.3-7.8 (dd, 4H, -Ph), 8.80 (s, 1H, CH).
^{13}C-NMR (DMSO-d$_6$): δ_C 167.7 (C-4), 157.1 (C-2), 154.7 (benzylic carbon), 136.1 (C$^{/}$-4), 135.8, 135.1, 129.7-129.2 (benzene ring carbon), 123.9, 7.7, 5.8.

2.2. *Antibacterial and Antifungal Screenings*

All the synthesized compounds (**2-11**) were screened for their antibacterial activity against three gram-positive bacteria *Bacillus cereus* (BTCC 19), *Bacillus subtilis* and *Staphylococcus aureus* and three Gram-negative bacteria *Shigella dysenteriae* (AE 14396), *Salmonela typhi* (AE 14612) and *Pseudomonous sp.* (Tables 1 and 2). The antifungal activity was tested against the fungi *Macrophomina phaseolina* (Tassi) Goid, *Fusarium equiseti* (Corda) Sacc, *Alternaria alternata* (Fr.) Kedissler, *Colletotrichum corchori* Ikata (Yoshida) and *Curvularia lunata* (see Table 3). For the screening of antibacterial activities, the disc diffusion method [31] was used with solvent methanol. For antifungal test, the poisoned-food technique [32] was frequently used by the solvent methanol. The tested compounds were dissolved in methanol to get a solution of

1mg mL^{-1}. The inhibition zones were measured in millimeters at the end of an incubation period of 48 hours at (35±2)˚C. Methanol alone showed no inhibition. Commercial antibacterial and antifungal brands, respectively, Ampicillin and Nystatin were also tested under similar conditions for comparison. Nutrient agar (NA) and potato dextrose agar (PDA) were used as basal media to test bacteria and fungi respectively.

Table 1. Antibacterial screenings (gram positive) of the test compounds.

Compound No.	Diameter of zone of inhibition in mm (100 µg (dw)/disc)		
	Bacillus Subtilis	*Staphylococcus Aureus*	*Bacillus Cereus*
2	8	-	-
3	-	5	9
4	13	8	13
5	31*	25*	18
6	28*	21*	24*
7	11	16	17
8	19	11	16
9	17	9	12
10	19	22*	17
11	13	10	11
Ampicillin 100µg(dw)/disc	**24**	**19**	**21**

‘ - ’ No inhibition, **‘ * ’** Moderate/ highest inhibition

Table 2. Antibacterial screenings (gram negative) of the test compounds.

Compound No.	Diameter of zone of inhibition in mm (100 µg (dw)/disc)		
	Shigella dysenteriae	*Salmonela typhi*	*Pseudomonous sp.*
2	6	-	-
3	-	7	10
4	11	8	9
5	29*	22*	18*
6	35*	25*	13
7	25	16	11
8	22	20	16*
9	19	12	10
10	26*	21*	12
11	20	17	9
Ampicillin 100µg(dw)/disc	**30**	**24**	**15**

‘ - ’ No inhibition, **‘ * ’** Moderate/ highest inhibition

Table 3. Inhibitory activity of different synthesized compounds (2-11) against various fungi.

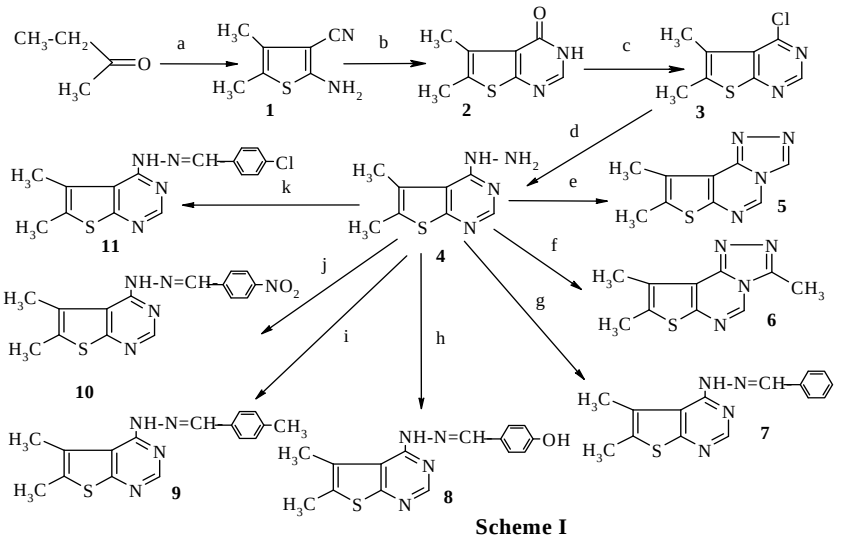
Compd. No.	Percent (%) Inhibitions of mycelial growth (100 μg(dw)/ml PDA)				
	Macrophomina phaseolina	*Fusarium equiseti*	*Alternaria alternata*	*Colletotrichum corchori*	*Curvularia lunata*
2	26	12	23	16	57
3	17	31	20	21	50
4	24	21	29	13	28
5	72*	43*	55*	42*	77*
6	70*	47*	60*	40*	74*
7	37	22	41	33	46
8	40	25	39	17	56
9	50	44*	35	25	67*
10	62*	32	40	32	65*
11	53	45*	26	21	55
Nystatin 100μg (dw)/PDA	**71.78**	**44.70**	**51.55**	**40.51**	**75.00**

‘ - ’ No inhibition, **‘ * ’** Moderate/ highest inhibition.

3. Results and Discussion

When 2-amino-4,5-dimethylthiophene-3-carbonitrile **1** was prepared by usual Gewald procedure [28], it was refluxed with formic acid for cyclization to form thienopyrimidinone 2, which was confirmed by ^{1}H-NMR and ^{13}C-NMR spectra. The thienopyrimidinone **2** was then chlorinated with thionyl chloride to form 4-chloro-5,6-dimethylthieno[2,3-d]pyrimidine **3**. Hydrazinopyrimidine **4** was obtained upon treatment of chloro derivative **3** with hydrazine hydrate in dioxane under reflux condition. Hydrazonopyrimidine **4** was then readily cyclized to the corresponding two cyclized compounds, 8,9-dimethyl[1,2,4]triazolo[4,3-c]thieno[3,2-e]pyrimidine **5**, 3,8,9-trimethyl [1,2,4]-triazolo[4,3-c]thieno[3,2-e]pyrimidine **6** with formic acid and acetic anhydride, respectively. The ^{1}H-NMR spectrum of **5** exhibited one-proton singlets at δ 7.90 for 5-CH proton and δ 8.50 for 3-CH proton and the disappearance of NH and NH_2 peaks clearly demonstrated the existence of molecule **5**. Similarly the spectral data proved the formation of thieno[3,2-e]pyrimidine **6**.

Synthesis of some Thienopyrimidines from *o*-Aminonitrile (**5-11**) shown in scheme 1.



Scheme I

Reagents

a) Malononitrile, S, Et_2NH, EtOH, b) HCOOH, reflux, 110°C, 4 hours, c) $SOCl_2$, reflux, 4 hours, d) NH_2-NH_2.H_2O, reflux, 1 hour, e) Formic acid, reflux, 2 hours, f) Acetic anhydride, reflux, 3 hours, g) Benzaldehyde, ethanol, reflux, 2 hours, h) p-Hydroxybenzaldehyde, ethanol, reflux, 3 hours, i) p-Tolualdehyde, ethanol, reflux, 3 hours, j) p-Nitrobenzaldehyde, ethanol, reflux, 3 hours, k) p-Chlorobenzaldehyde, ethanol, reflux, 4 hours.

Compound **4** also condensed to 4-benzylidinehydrazono-5,6-dimethyl-thieno[2,3-d] pyrimidine **7**, 4-[4′-hydroxybenzylidine]hydrazono-5,6-dimethylthieno[2,3-d]pyrimidine **8**, 4-[4′-tolylidin]hydrazono-5,6-dimethylthieno[2,3-d]pyrimidine **9**, 4-[4′-nitrobenzylidine]hydrazono-5-ethyl-6-methylthieno[2,3-d]pyrimidine **10** and 4-[4′-chlorobenzylidine]hydrazono-5-ethyl-6-methylthieno[2,3-d]pyrimidine **11** upon treatment with benzaldehyde, *p*-hydroxybenzaldehyde, *p*-tolualdehyde, *p*-nitrobenzaldehyde and *p*-chlorobenzaldehyde respectively. ^{1}H-NMR spectrum showed the appearance of one proton singlet for benzylic proton at δ 8.60 and disappearance of $-NH_2$ peak indicated the formation of Hydrazonothienopyrimidine **7** and its ^{13}C-NMR spectra displayed signals at δ 154.7 for benzylic carbon and δ 128.8 as multiplet for phenyl group. The rest of the spectrum also in good agreement with the structure **7**. Similarly, the corresponding thieno[2,3-d]pyrimidines **8-11** were ascertained by their spectral data (see experiment).

Antimicrobial activity

The inhibition zone of the micro-organisms due to the treatment of different synthesized compounds are mentioned in Tables 1 to 3. It was found that the inhibition zone of the

compounds **5**, **6** and **10** were more effective than that of other chemicals for all bacterial strain. They exhibited stronger activity than ampicillin also towards *Bacillus Subtilis and Shigella dysenteriae.* Other compounds were either inactive or moderately to fairly active against the tested bacterial strain.

As far as antifungal activity is concerned, all compounds showed good to excellent activity against all the fungi. Especially, it could be stressed that the test chamicals **5** and **6** exhibited even stronger activity than nystatin against *Macrophomina phaseolina* and *Alternaria alternata.* From the observation of inhibitions of the tested compounds, it was ascertained that, generally triazolothienopyrimidine derivatives **5-6** exhibited higher activities against human pathogenic bacteria and phytopathogenic fungi.

4. Conclusion

In this work, we have demonstrated that cyclisation with pyrimidine ring from *o*-aminonitirile afforded thienopyrimidines and furopyrimidines with promising antibacterial and antifungal activity. The activity data obtained during the study will be certainly useful to go for further research for drug designing and synthesizing new fused pyrimidines.

Acknowledgements

The authors wish to thank Chittagong University Research Cell for providing financial assistance to carry out this research and Mr. M. K. Hossain for helping with the spectral data when he was in Japan as doctoral research fellow.

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