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Simple and Efficient Synthesis of Novel Fused Bicyclic Heterocycles Pyrimido-Thiazine and Their Derivatives

Sirsat Shivraj B and Vartale Sambhaji P*

P.G. Research centre, Department of Chemistry, Yeshwant Mahavidyalaya, Nanded 431602 (MS), India

Abstract

We report simple and efficient synthesis of novel fused bicyclic heterocyclic compounds 3 using bis (methylthio) methylene malononitrile 1 and thiourea 2 with potassium carbonate in DMF at reflux condition. The molar ratios of these substrates are 2:1 for the preparation of 2,6-dihydro-2,6-diimino-4,8-bis(methylthio) pyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile. This newly synthesized pyrimido thiazine acts as bis-electrophilic species reacting with various nucleophiles yielding 2,6-dihydro-2,6-diimino-4,8-(disubstituted)-pyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile in good yields.

Keywords: Thiourea; Bis (methylthio) methylene malononitrile; Bis-electrophilic species; Various nucleophiles

Introduction

In recent years, the synthesis of fused bicyclic heterocyclic compounds possessing pyrimido-thiazine central core has been the focus of great interest. This type of compounds shows various biological properties such as antibacterial, antiallergic, anti-inflammatory, antitumor, phsphodiesterase inhibition and antiparkinsonism [1-6], many workers have synthesized different 1, 3-thiazines [7,8]. Thiazines are very useful units in the fields of medicinal and pharmaceutical chemistry and have been reported to exhibit a variety of biological activities [9,10]. Recently, substituted thiazine are prepared using α, β- unsaturated carbonyl system and that are very versatile substrates for the evolution of various reactions [11] and physiologically active compounds [12]. The reaction of thiourea with α,β- unsaturated system (Michael acceptor) results in 1,3 thiazine [13,14]. It has been well focused that the presence of pyrimido-thiazine with various chemically reactive moieties is an important structural feature and also substituted imino group present in thiazine ring, and the resulting molecule would exhibit promising biological activities in continuation of our work [15-21]. In the present study, we synthesize pyrimido-thiazine containing more reactive functional groups using thiourea and bis methylthio methylene malanonitrile which is used for further cyclisation and derivatization. The synthesized compounds act as bis-electrophilic species reacting with various nucleophiles such as substituted aromatic amines, aromatic phenol, various active methylene compound and alicyclic heterocyclic compound construct 2,6-dihydro-2,6-diimino-4,8-disubstitutedpyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile in good yields.

Experimental Section

Melting points were determined by open capillary tubes and were uncorrected. The silica gel F_{254} plates were used for thin layer chromatography (TLC) in which the spots were examined under UV light and then developed by an iodine vapor. Column chromatography was performed with silica gel (BDH 100-200 mesh). Solvents were purified according to standard procedures. The spectra were recorded with the following instruments; IR: Perkin-Elmer RX1 FT-IR spectrophotometer; NMR: Varian Gemini 200 MHz (^{1}H) and 50 MHz (^{13}C) spectrometer; ESIMS: VG-Autospec micromass. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

General procedure for the synthesis 2,6-dihydro-2,6-diimino-4,8-bis(methylthio)pyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (3)

A mixture of (methylthio) methylene malanonitrile (1) (2 mmol) and thiourea (2) (1 mmol) in DMF and anhydrous potassium carbonate (10 mg) was refluxed for 12 hours on oil bath. The reaction was monitored by TLC. After completion, the reaction mixture was cooled at room temperature then washed with water (3×10 mL) and subsequently extracted with ethyl acetate (3×10 mL). The extract was concentrated and the residue was subjected to column chromatography (silica gel, n-hexane- ethyl acetate 8:2) to obtain pure solid compound 3. The compound 3 confirmed by IR, ^{1}H and ^{13}C NMR and MS analytical data compound is given below.

Yellow solid (yield 76%). Mp: 145-147°C. IR (KBr): 3380 (=NH), 2250(-CN) cm^{-1}.

^{1}H NMR (CDCl3) δ 3.15 (s, 6H, SCH_3), 9.17 (s, 1H, =NH), 9.81 (s, 1H, =NH), ^{13}C NMR ($CDCl_3$) δ 180 (2), 145.1 (2), 131.9, 136.6, 45(2) MS *m/z*: 343(M^+Na 100%) 240,212, 198, 140 Anal. Calcd for $C_{11}H_8N_6S_3$: C-41.23, H-2.52, N-26.23, S-30.02. Found: C- 41.01, H-2.91, N-26.15, S-30.0.

2,6-dihydro-2,6-diimino-4,8-bis (substituted) pyrimido [2,1b][1,3]thiazine-3,7- dicarbonitrile (4a-e), (5a-e)

A mixture of 3 (1 mmol) and, independently, various substituted aromatic amines, and substituted aromatic phenol (0.002 mol) in N, N'- dimethyl formamide (10 mL) and anhydrous potassium carbonate (10 mg) was refluxed for 4 to 6 hours. The reaction mixture was cooled to room temperature and poured into ice cold water. The separated

***Corresponding author:** Vartale Sambhaji P, P.G. Research Centre, Department of Chemistry, Yeshwant Mahavidyalaya, Nanded-431602 (MS), India, E-mail: spvartale@gmail.com

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solid product was filtered, washed with water and recrystallized using ethyl alcohol.

2,6-dihydro-2,6-diimino-4,8-bis(phenylamino) pyrimido [2,1-b][1,3]thiazine-3,7-dicarbonitrile (4a)

Colourless solid (yield 65%). Mp: 155-156°C. IR (KBr): 3450 (=NH), 2220 (-CN) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.15 (s, 2H,-NH), 9.27 (s, 1H,=NH), 9.61 (s, 1H,=NH), 7.26.-7.5 (s, 10H Ar-H). MS *m/z*: 411(M^+ 100%) 323, 240, 212, 198, 140 Anal. Calcd for $C_{21}H_{14}N_8S$: C-61.23, H-3.52, N-27.23, S-7.82. Found: C- 61.01, H-3.91, N-27.15, S-8.0.

4,8-bis(4-bromophenylamino)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (4b)

Yellow solid (yield 70%). Mp: 185-186°C. IR (KBr): 3435 (=NH), 2255 (-CN) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.0 (s, 2H,-NH), 9.37 (s, 1H, =NH), 9.71 (s, 1H, NH), 7.2-7.5 (dd, 8H J=7.5-8HzAr-H).MS *m/z*: 568(M^+ 2 80%) 411, 323, 240, 212, 198, 140 Anal. Calcd for $C_{21}H_{12}N_8SBr_2$: C-44.40, H-2.12, N-19.70, S-5.5, Br-28.12. Found: C- 44.12, H-2.15, N-20.00, S-5.9, Br-28.00.

4,8-bis(4-methoxyphenylamino)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (4c)

Brown solid (yield 60%). Mp: 150-152°C. IR (KBr): 3350 (=NH), 2240 (-CN) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.8 (s, 2H, -NH-Ar), 9.47 (s, 1H,=NH), 9.81 (s, 1H,=NH), 7.2-7.5 (dd, 8H J=7.5-8Hz Ar-H) , 3.5 (s 6H-OCH_3). MS *m/z*: 471(M^+ 100%) 411, 323, 212, 190, 140 Anal. Calcd for $C_{23}H_{18}N_8SO_2$: C-58.80, H-3.86, N-23.82, S-6.5. Found: C- 58.50, H-3.90, N-24.00, S-6.4.

4,8-bis(4-methylphenylamino)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (4d)

White solid (yield 65%). Mp: 145-148°C. IR (KBr): 3380 (-NH), 3400 (=NH), 2255 (-CN) cm^{-1}. ^1H NMR (CDCl3) δ 5.0 (s, 2H, -NH-Ar), 9.23 (s, 1H,=NH), 9.71 (s, 1H,=NH), 7.0-7.3 (dd, 8H J=7.5-8Hz, Ar-H), 1.8 (s 6H, CH_3). MS *m/z*: 439(M^+ 60, 323, 212, 190, 140 Anal. Calcd for $C_{23}H_{18}N_8S$: C-63.00, H-4.15, N-25.55 S-7.1 Found: C- 62.5, H-4.10, N-25.00, S-7.5.

4,8-bis(3-nitrophenylamino)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (4e)

Yellow solid (yield 70%). Mp: 190-192°C. IR (KBr): 3370 (-NH), 3410 (=NH), 2220 (-CN) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.5 (s, 2H -NH-Ar), 9.12 (s, 1H, =NH), 9.67 (s, 1H,=NH), 7.0-7.2 (s, 2H Ar-H) , 7.5-7.8 (m 6H Ar-H). MS *m/z*: 501(M^+ 1), 315, 212, 166, 140 Anal. Calcd for $C_{21}H_{12}N_{10}SO_4$: C-50.35, H-2.42, N-27.99, S-6.41 Found: C- 50.50, H-2.5, N-28.00, S-6.5.

2,6-dihydro-2,6-diimino-4,8-diphenoxypyrimido[2,1-b][1,3] thiazine-3,7-dicarbonitrile (5a)

White solid (yield 75%). Mp: 145-146°C. IR (KBr): 3410 (=NH), 2240 (-CN) cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.27 (s, 1H, =NH), 9.61 (s, 1H, =NH), 7.1-7.5 (s, 10H, Ar-H). MS *m/z*: 413(M^+1 60%) 306 , 220, 212, 198, Anal. Calcd for $C_{21}H_{12}N_6SO_2$: C-61.16, H- 2.94, N-20.23, S-7.82. Found: C-61.01, H-3.00, N-27.15, S-8.0.

4,8-bis(4-bromophenoxy)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (5b)

Yellow (yield 70%). Mp: 190-193°C. IR (KBr): 3410 (=NH), 2240 (-CN) cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.14 (s, 1H, =NH), 9.32 (s, 1H, =NH), 7.4-7.7 (dd, 8H J=7-7.5Hz, Ar-H). MS *m/z*: 570(M+ 2 67%) 405, 305, 212, 125, 140 Anal. Calcd for $C_{21}H_{10}N_6S0_2Br_2$: C-44.30, H-1.77, N-14.70, S-5.5, Br-28.23. Found: C- 44.12, H-2.15, N-20.00, S-5.9, Br-28.00.

4,8-bis(4-methoxyphenoxy)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (5c)

Brown (yield 60%). Mp: 145-152°C. IR (KBr): 3412 (=NH), 2222 (-CN) cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.33 (s, 1H,=NH), 9.67 (s, 1H,=NH), 7.4-7.8 (dd, 8H J=7.5-8Hz, Ar-H), 3.1 (s 6H,-OCH_3). MS *m/z*: 472(M^+ 70%) 411, 397, 381, 212, 190, Anal. Calcd for $C_{23}H_{16}N_6SO_4$: C-58.47, H-3.46, N-17.82, S-6.79. Found: C- 58.50, H-3.50, N-17.50, S-6.4.

4,8-bis(4-chlorophenoxy)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (5d)

Solid (yield 65%). Mp: 145-148°C. IR (KBr): 3420 (=NH), 2240 (-CN) cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.24(s, 1H,=NH), 9.32 (s, 1H,=NH), 7.1-7.5 (dd, 8H J=7.5-8HzAr-H). MS *m/z*: 482(M^+ 2 67%) 405, 307, 212, 140 Anal. Calcd for $C_{21}H_{10}N_6S0_2Cl_2$: C-52.40, H-2.09, N-17.70, S-6.66, Cl-28.23. Found: C-52.30, H-2.00, N-17.90, S-6.76, Cl-28.00.

4,8-bis(3-nitrophenoxy)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (5e)

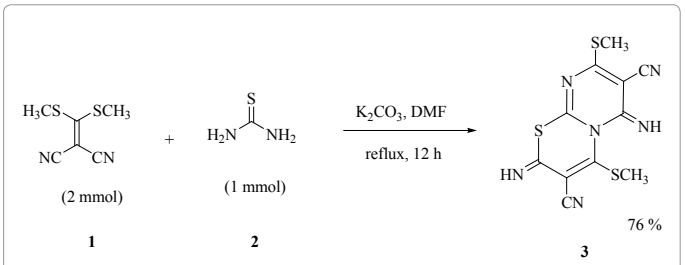
Yellow (yield 70%). Mp: 180-183°C. IR (KBr): 3410 (=NH), 2245(-CN) cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.45 (s, 1H, =NH), 9.87 (s, 1H, =NH), 7.3-7.5 (s, 2H, Ar-H), 7.5-7.8 (m 6H, Ar-H). MS *m/z*: 477(M^+), 318, 212, 166, 140 Anal. Calcd for $C_{21}H_{10}N_8SO_6$: C-50.20, H-2.02, N-22.30, S-6.41 Found: C- 50.50, H-2.0, N-22.00, S-6.5.

Result and Discussion

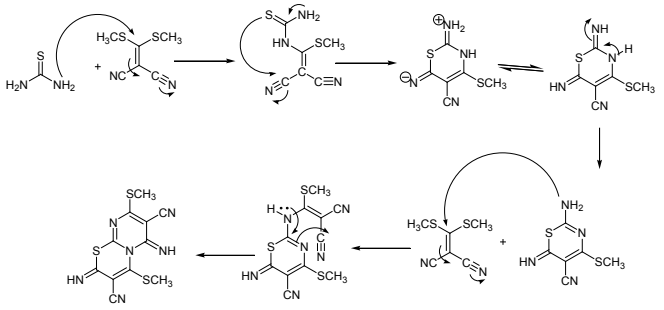
The fused heterocyclic compounds 2,6-dihydro-2,6-diimino-4,8-bis(methylthio) pyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (3) was prepared from bis (methylthio) methylene malononitrile 1 and thiourea 2 with catalytic amount of potassium bicarbonate (1 mmol) in DMF at reflux condition and the molar ratios of these substrates are 2:1 (Scheme 1).

Proposed pathway for formation of 2,6-dihydro-2,6-diimino-4,8-bis(methylthio) pyrimido [2,1-b][1,3]thiazine-3,7-dicarbonitrile (Scheme 2).

The compound 3 posses a replaceable active methylthio group (-SCH_3) at 4, 8- position which is activated by nitrogen atom and electron withdrawing cyano group. Compound 3 reacted with selected various nucleophilles like substituted aryl amines hetryl amines, substituted phenols and activated methylene compound in DMF and catalytic amount of anhydrous potassium carbonate, to afford 2,6-dihydro-2,6-diimino-4,8-bis(substituted) pyrimido[2,1-b] [1,3]thiazine-3,7-dicarbonitrile (4a-e) and (5a-d) Table 1 (Scheme 3) respectively.



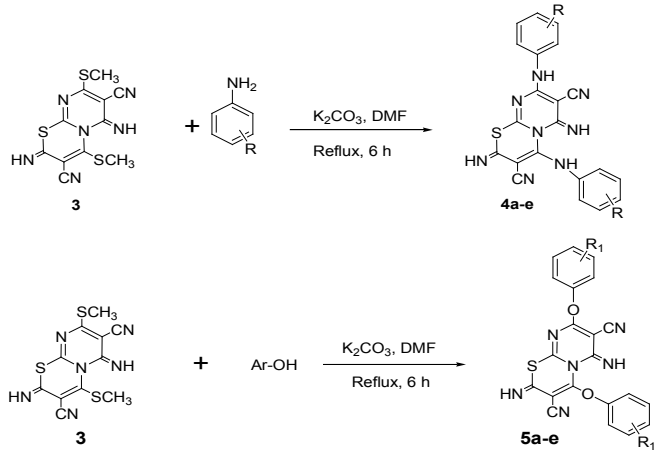
Scheme 1: General procedure for the synthesis 2,6-dihydro-2,6-diimino-4,8-bis(methylthio)pyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile.



Scheme 2: Proposed pathway for formation of 2,6-dihydro-2,6-diimino-4,8-bis(methylthio) pyrimido [2,1-b][1,3]thiazine-3,7-dicarbonitrile.

Compound	4a	4b	4c	4d	4e
-R	-H	P-Br	P-OCH_3	P-CH_3	P-NO_2
Compound	5a	5b	5c	5d	5e
-R^1	-H	P-Br	P-OCH_3	P-Cl	M-NO_2

Table 1: 2,6-dihydro-2,6-diimino-4,8-bis (substituted) pyrimido [2,1b][1,3] thiazine-3,7- dicarbonitrile.



Scheme 3: 2,6-dihydro-2,6-diimino-4,8-bis (substituted) pyrimido [2,1b][1,3] thiazine-3,7- dicarbonitrile.

Conclusion

In conclusion, we have synthesised simple and efficent novel fused bicyclic heterocycles pyrimido-thiazine having bis-electrophilic species reacting with various nucleophiles.

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