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Novel synthesis and antibacterial activity of 10-Chloro-15-imino-14-oxo-14(H)benzothiazolo[2,3-*b*]pyrimido[5,6-*e*]pyrimido[2,3-*b*]benzothiazole and its 3-disubstituted derivatives

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ABSTRACT

Novel heterocyclic compound 10-Chloro-15-imino-14-oxo-14(H) benzothiazolo[2,3-*b*]pyrimido[5,6-*e*] pyrimido[2,3-*b*]benzothiazole and its 3-substituted derivatives were synthesized by reaction of 8-chloro-3-cyno-2-methylthio-4-oxo-[4H]-pyrimido-(2,1-*b*) benzothiazole (1a) with 2-amino-6- substituted benzothiazoles(2a-e). © 2009 Trade Science Inc. - INDIA

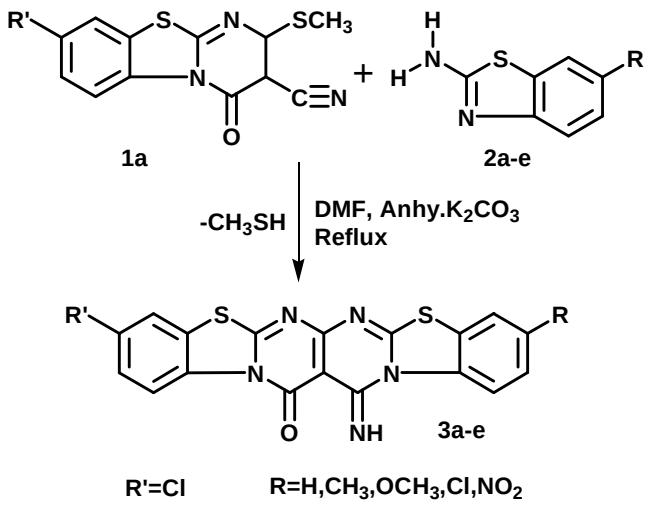
KEYWORDS

Ethyl 2- cyano -3,3-bismethyl thioacrylate; 10-Chloro-15-imino-14-oxo-14(H) benzothiazolo [2,3-*b*] pyrimido [5,6-*e*]pyrimido[2,3-*b*]benzothiazole.

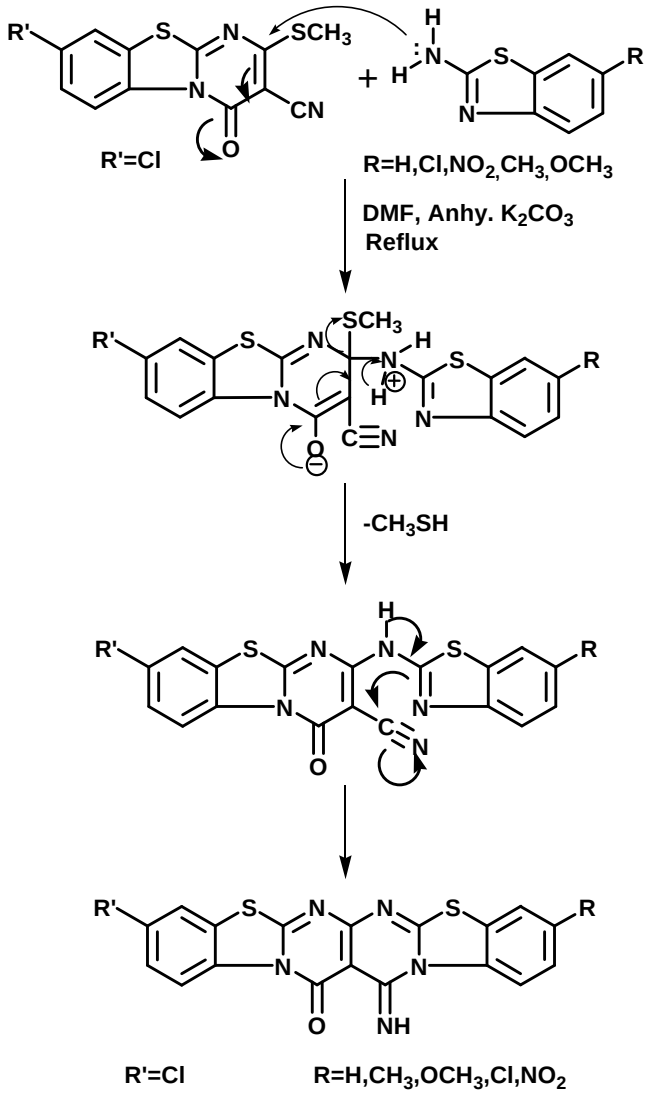
INTRODUCTION

A survey of literature made it evident that very little work has been carried out on the synthesis of fused pyrimido benzothiazole possessing three to four rings[1,2] which exhibit a wide spectrum of activities like antitumor[3], phosphodiesterase inhibition[4], antiallergic[5], anti-inflammatory[6], antiparkinsonism[7]. In view of the reported biological activities of this system, synthesis of such condensed system has attracted much attention in recent years.

In this communication, we report synthesis of a novel heterocyclic system possessing six rings. Compound 10-Chloro-15-imino-14-oxo-14(H)benzothiazolo[2,3-*b*]pyrimido[5,6-e]pyrimido[2,3-*b*]benzothiazole **(3a)** and its 3- substiuted derivatives **(3a-e)**. 2-Amino-6-chloro- benzothiazole in dimethyl formamide on refluxing in the presence of anhydrous potassium carbonate with ethyl-2-cyano-3,3-bismethylthioacrylate afforded 8-chloro-3-cyno-2-methylthio-4-oxo-[4H]-pyrimido-(2,1-*b*)benzothiazole **(1a)** which possesses reactive thiomethyl group at 2-position and cyano group at 3-position. Compounds **(3a-e)** were prepared by reaction of **(1a)** with 2-amino-6- substituted benzothiazole[9] **(2a-e)** in the presence of dimethyl formamide and catalytic amount of anhydrous potassium carbonate in 40-70% yield Scheme 1. The reaction proceeds with initial attack of amino group of benzothiazole **(2a-e)** on carbon attached to SCH_3 group resulting in loss of thiomethyl group in the form of methyl mercaptan. The resulting secondary amine polarize on to nitrile carbon to give cyclized product Scheme 2. Similarly other 3-substituted derivatives of **(3a)** were prepared by heating **(1a)** independently with 2-amino-6-substituted benzothiazoles **(2a-e)** in the presence of anhydrous potassium carbonate. The structures of these newly synthesized cyclized compounds **(3a-e)** were confirmed on the basis of elemental analysis and IR, ^{1}H-NMR



Scheme 1



Scheme 2

and mass spectral data. The IR spectra of compounds **(3a-e)** showed the absence of CN stretching absorption band in the region of 2260-2220cm^{-1}and showed the presence of absorption bands in the region 3400-3050cm^{-1} and 1685-1645cm^{-1} which can be assigned to =NH and α, β-unsaturated cyclic C=O stretching respectively. The NMR spectra exhibited singlet peak in the region of δ 8.3-9, exchangeable with D_2O, which can be assigned to =NH proton. Mass spectra of compounds exhibited the molecular ion peaks which correspond to molecular weights.

EXPERIMENTAL

All melting points were determined in capillary tube and are uncorrected. IR spectra were recorded in potassium bromide pellets on Bomen MB 104 FT Infrared Spectrophotometer, ^{1}H-NMR spectra were scanned on a FT Gemini 60 (200MHz) Spectrometer with Tetramethyl silane as an internal standard. Mass spectra were recorded on a FT VG – 7070 H Mass Spectrophotometer using the EI technique at 70 ev. Micro analysis were performed on a Heraeus CHN-O rapid analyzer. All the reactions were monitored by Thin layer chromatography, carried out on 0.25 mm thick silica gel-G plate using iodine vapour for detection.

GENERAL PROCEDURE

A mixture of 8-Chloro-3-cyano-2-methylthio-4-oxo-4H-pyrimido [2, 1-*b*]- benzothiazole (0.307; 0.001 mole) and 2-amino benzothiazole (0.150;0.001 mole) in DMF (5 ml) and pinch of anhydrous potassium carbonate was refluxed for five hrs. The reaction mixture was cooled at room temperature and poured in ice cold water.. The reaction mixture was cooled to room temperature and poured in ice cold water. The separated solid product was filtered, washed with water and recrystallised from DMF-ethanol mixture to give pure **(3a-e)**.

10-Chloro-15-imino-14-oxo-14(H)benzothiazolo [2, 3-*b*] pyrimido [5, 6-*e*] pyrimido [2, 3-*b*] benzothiazole (3a)

A mixture of 8-Chloro-3-cyano-2-methylthio-4-oxo-4H-pyrimido [2, 1-*b*]- benzothiazole (0.307;

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0.001 mole) and 2-amino benzothiazole (0.150, 0.001 mole) in DMF (5 ml) and pinch of anhydrous potassium carbonate was refluxed for five hrs. The reaction mixture was cooled at room temperature and poured in ice cold water. The separated solid product was filtered, washed with water and recrystallized from DMF-ethanol mixture to give pure crystalline product of 0.264 g.Yield 67%,m.p.210°C. IR(KBr)cm^{-1}3120(=NH), 1648(C=O) ^{1}H-NMR(DMSO-d_6) δ2.2(s,3H,CH_3), 7.2-7.8(m,7H,Ar-H),8.6(s,1H,=NH,exch.D_2O)MS: m/e (%) 411(M^{+2},80), (25).Anal.calcd.For $C_{18}H_8N_5OS_2Cl$: C,52.81; H,1.95; N,17.11. Found: C,52.76; H,1.91; N,17.08.

10-Chloro-15-imino-3-methyl-14-oxo-14(H)benzothiazolo[2, 3-*b*]pyrimido[5, 6-*e*] pyrimido[2, 3-*b*]benzothiazole (3b)

A mixture of 8-chloro-3-cyano-2-methylthio-4-oxo-4H-pyrimido [2, 1-*b*]- benzothiazole (0.307; 0.001 mole) and 2-amino-6-methyl-benzothiazole (0.174, 0.001 mole) in DMF (5 ml) and pinch of anhydrous potassium carbonate was refluxed for five hrs. the reaction mixture was cooled in room temperature and poured in ice cold water. The separated solid product was filtered, washed with water and recrystallized from DMF-ethanol mixture to give pure crystalline product of 0.241 gm. Yield 57% m.p.>300°CIR(KBr)cm^{-1}3363(=NH),1670(C=O) ^{1}H-NMR (DMSO-d_6) δ2.5(s,3H,CH_3),7.1-7.9(m,6H,Ar-H),MS: m/e(%)425(M^{+2},4),423(13)Anal.calcd.For $C_{19}H_{10}N_5OS_2Cl$: C,53.90; H,2.36; N,16.54. Found: C,53.86; H,2.32; N,16.53.

10-Chloro-15-imino-3-methyoxy-14-oxo-14(H)benzothiazolo[2, 3-*b*]pyrimido[5, 6-*e*] pyrimido[2, 3-*b*]benzothiazole (3c)

A mixture of 8-chloro-3-cyano-2-methylthio-4-oxo-4H-pyrimido [2, 1-*b*]- benzothiazole (0.307; 0.001 mole) and 2-amino-6-methoxy-benzothiazole (0.180, 0.001 mole) in DMF (5 ml) and pinch of anhydrous potassium carbonate was refluxed for five hrs. the reaction mixture was cooled in room temperature and poured in ice cold water. the separated solid product was filtered, washed with water and recrystallized from DMF-ethanol mixture to give pure crystalline product of 0.212g.Yield 48% m.p.155°C IR(KBr)cm^{-1}3345(=NH),1670(C=O), ^{1}H-NMR(DMSO-d_6) δ2.4(s,3H,CH_3),7.0-7.8 (m,6H, Ar-H) 8.6(s,1H,=NH, exch. D_2O) MS: m/e (%)441(M+2,5)439(M^+,15) Anal.calcd.For $C_{19}H_{10}N_5O_2S_2Cl$:C,51.93; H,2.27; N,15.94. Found: C,51.88; H,2.25; N,15.91.

3,10-Dichloro-15-imino-14-oxo-14(H)benzothiazolo[2,3-*b*]pyrimido[5,6-e]pyrimido [2, 3-*b*]benzothiazole (3d)

A mixture of 8-chloro-3-cyano-2-methylthio-4-oxo-4H-pyrimido[2,1-*b*]- benzothiazole (0.307; 0.001 mole) and 2-amino-6-chloro-benzothiazole (0.185, 0.001 mole) in DMF (5 ml) and pinch of anhydrous potassium carbonate was refluxed for five hrs. the reaction mixture was cooled in room temperature and poured in ice cold water. the separated solid product was filtered, washed with water and recrystallized from DMF-ethanol mixture to give pure crystalline product of 0.235 g.Yield 53% m.p.244°C IR(KBr) cm^{-1}3358 (=NH) 1680 (C=O) ^{1}H-NMR (DMSO-d_6) δ1.9 (s,3H,CH_3), 3.5 (s,3H,OCH_3), 7.1-7.7 (m,6H,Ar-H), 8.8 (s,1H,=NH, exch. D_2O) MS: m/e (%) 445(M^{+2},15),443(45) Anal.calcd.For $C_{18}H_7N_5OS_2Cl_2$:C,48.75; H,1.58; N,15.80. Found: C,48.71; H,1.55; N,15.77.

10-Chloro-15-imino-3-nitro-14-oxo-14(H)benzothiazole [2, 3-*b*] pyrimido [5, 6-*e*]pyrimido[2, 3-*b*]benzothiazole (3e)

A mixture of 8-chloro-3-cyano-2-methylthio-4-oxo-4H-pyrimido [2, 1-*b*]- benzothiazole (0.307; 0.001 mole) and 2-amino-6-nitro-benzothiazole (0.195, 0.001 mole) in DMF (5 ml) and pinch of anhydrous potassium carbonate was refluxed for five hrs. the reaction mixture was cooled in room temperature and poured in ice cold water. The separated solid product was filtered, washed with water and recrystallized from DMF-ethanol mixture to give pure crystalline product of 0.242 gm. Yield 53% m.p.230°C.IR(KBr)cm^{-1} 3348(=NH)1682(C=O) ^{1}H-NMR(DMSO-d_6) δ3.6(s,3H,OCH_3), 7.2-7.8 (m,7H,Ar-H), 9.0(s,1H,=NH,exch. D_2O) MS: m/e(%) 405(M^+,40), 390(20), 362(30), 335(20), 257(50), 149(100), 122(60). Anal.calcd.For $C_{18}H_7N_6O_3S_2Cl_2$: C,47.57; H,1.54; N,18.50. Found: C,47.53; H,1.51; N,18.48.

ANTIBACTERIALACTIVITY

The synthesized compounds were evaluated for their antibacterial activity against gram positive species S. aureus and B. substilis and gram negative species E. coli and S. typhi by paper disc diffusion method[10]. All the synthesized compounds were dissolved in dimethyl sulphoxide. The synthesized compounds exhibited zone of inhibition of 09-13mm in diameter whereas standard streptomycin exhibited zone of inhibition of 18 and 22mm in diameter against S. aureus and B. substilis and penicillin inhibited zone of inhibition of 15 and 16mm in diameter against E. coli and S. typhi respectively. Amongst the synthesized compounds, some compounds showed higher zone of inhibition against S. aureus, B. substilis, E. coli and S. typhi respectively.

TABLE 1 : Antibacterial activity by disc diffusion method of compound (3a-e)

Compd.	Diameter in mm of zone of inhibition at 25 µg / disc			
	S. aureus	B. substilis	E. coli	S. typhi
3a	08	07	12	09
3b	09	08	10	09
3c	09	08	11	10
3d	07	08	11	09
3e	07	08	11	10
Streptomycin	18	22	-	-
Penicillin	-	-	15	16

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