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Research Article

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Synthesis and Characterization of 3-Cyano-6,9-dimethyl-4-oxo-2-methylthio-4*H*-Pyrimido[2,1-*b*][1,3] Benzothiazole and its 2-Substituted derivatives

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Abstract A compound 3-cyano-6, 9-dimethyl- 4-oxo 2-methylthio-4H-Pyrimido[2,1-*b*][1,3] benzothiazole 3 has been prepared by the reaction of 2-amino- 4,7- dimethyl [1, 3] benzothiazole 1 with Ethyl -2-cyano-3,3'-bis-methylthio acrylate 2 in presence of anhydrous K_2CO_3 in DMF. The compound pyrimido benzothiazole 3 has methylthio functional group at 2- position which was substituted by using selected nucleophiles like substituted phenols, anilines, heteryl amine and active methylene compounds to yield 4a-d. All the synthesised compounds were characterised by spectral analysis.

Keywords Benzothiazoles, Pyrimido Benzothiazole, K_2CO_3, DMF

Introduction

Heterocyclic compounds containing hetero atom like sulphur, nitrogen, and oxygen have been received much more attention during the recent years. The compounds like Thiazole, Triazine, Tetrazole, Oxazole, Imidazole, and Pyrazole have been reported to possess a wide range of biological activities [1-4]. Some fused heterocyclic rings like pyrimidine, pyrazole, benzothiazole, benzoxazole benzimidazole, pyrimidotriazipine have been also reported an effective pharmacophores. Such fused heterocyclic compounds with their important pharmacophores would exhibit better pharmacological activities. The important and pharmacological properties of benzothiazole derivatives along with their improved synthetic methods widely used in the development of new heterocyclic compounds. Manoj N Bhoi *et al* [5] reported the one pot solvent-free microwave assisted synthesis and their biological evaluation of novel benzothiazole containing 4*H*-pyrimido[2,1-*b*]benzothiazoles derivatives and reported as reported as antioxidant and antimicrobial activities. Maruthamuthu et al [6] reported the chemistry and various biological significance of imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone nucleus . Abdel-Mohsen H T et al [7] prepared fused pyrimido benzothiazole derivatives from catechols and 6-substituted 1, 2, 3, 4-tetrahydro-4-oxo-2-thioxo-5-pyrimidinecarbonitriles using aerial O_2 as the oxidant. Kamal et al [8] synthesised a series of benzothiazole linked to the pyrrolodiazepine and reported their anticancer activity, DNA thermal denaturation studies, restriction endonuclease digestion assay, and flow cytometric analysis in human melanoma cell line (A375). N D Amnerkar et al [9] reported a series benzothiazole derivatives and evaluated for neurotoxicity and hepatotoxicity and behavioural study. Vijay N. Bhosale et al [10] reported antibacterial activity of Aryl / Heteryl fused pyrazolo [3¢,4¢: 4,5] pyrimido[2,1-*b*][1,3]benzothiazoles and 2- substituted derivatives. P. Ravi Prasad et al [11] reported the synthesis and biological activity evaluation of some fused imino pyrimido benzothiazole derivatives.

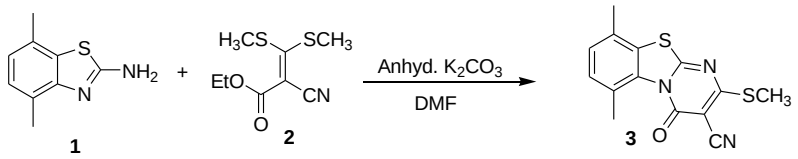
In the present work, reported the synthesise of 3-cyano-6, 9-dimethyl- 4-**o**xo 2-methylthio-4H-pyrimido[2,1-*b*][1,3] benzothiazole **3**, by the reaction of 2-amino- 4,7- dimethyl [1, 3] benzothiazole **1** with Ethyl -2-cyano-3,3'-bis-methylthio acrylate **2** in presence of anhydrous K_2CO_3 in DMF. Finally its 2-substituted derivatives **4 a-d** have been prepared by using selected nucleophiles like P-nitro phenol, P-chloro aniline, Pyrrolidine and active methylene compound malononitrile.

Result and Discussion

The work related to fused pyrimido benzothiazoles were reported by our research group and focused on the synthesis of 3-cyano-6, 9-dimethyl- 4-imino 2-methylthio-4H-pyrimido[2,1-*b*][1,3] benzothiazole from 2-amino 4,7 –dimethyl [1,3] benzothiazole with 3,3' bis-methylthio methylene malononitrile [12]. In continuation to our previous work, planned to synthesize novel heterocyclic compound containing oxo functionality at 4-position in target molecule. A new heterocyclic compound 3-cyano-6, 9-dimethyl- 4-oxo 2-methylthio-4H-pyrimido[2,1-*b*][1,3] benzothiazole synthesized by the reaction of 2-amino 4,7 –dimethyl [1,3] benzothiazole **1** with Ethyl- 2-cyano-3,3' bis-methylthio acrylate **2** in presence of anhydrous K_2CO_3 in DMF as solvent **(Reaction Scheme-I).** Anhydrous K_2CO_3 play an important role to maintain basic condition which favour to the cyclization reaction.

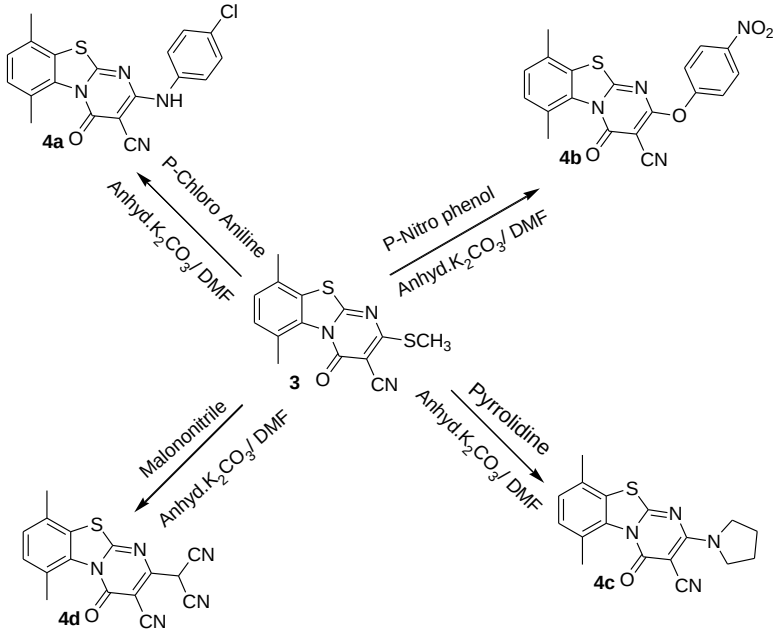
Compound 3 has fused substituted pyrimido benzothiazole possesses best leaving group at. 2- Position. The thiomethly functionality at 2- position in compound 3 favours for the nucleophilic substitution reaction in basic condition. The thiomethyl functionality at 2- position was get substituted by using different selected nucleophiles like p-nitro phenols, p-chloro anilines, pyrrolidine and active methylene compound malononitrile to yield corresponding 2-substituted derivatives (4a-d) of compound 3 (Reaction Scheme-II). The compound 3 and its 2-substituted derivatives were characterized on the basis of spectral analysis technique like IR, NMR and Mass spectroscopy.

Reaction Scheme-I:



1 **2** **3**

Reaction Scheme-II:



Experimental Section

The melting points of synthesized compounds were determined in open capillary tubes and were uncorrected. Infrared (IR) spectra compounds were recorded in KBr pallet on SHIMADZ-FTIR Spectrophotometer in cm^{-1}. The PMR spectra of compounds were recorded on FT Gemini 300MHz Spectrometer using DMSO-d^6/$CDCl_3$ and TMS as an internal reference. Chemical shift values are expressed in δ (ppm). Mass spectra were recorded on SCHIMADZU- GCMS Spectrometer using EI technique.

General Method

Synthesis of 3-cyano-6, 9-dimethyl- 4-oxo 2-methylthio-4H-pyrimido[2,1-*b*][1,3] benzothiazole (3):

The equimolar mixture of 2-amino 4,7-dimethyl [1,3]benzothiazole (0.01 mole) and Ethyl 2-cyano 3,3' bis-methylthio acrylate (0.01 mole) was refluxed for 4-5 hours in presence of anhydrous K_2CO_3 in DMF as solvent **(Reaction Scheme-I)**. The reaction mixture was monitored with TLC,cooled at room temperature and poured in ice cold water. The solid product was separate out by filtration and recrystallized from ethanol. Yield:70% , M.P=240^{0}C, IR(KBr / cm^{-1}):3025, 2950 cm^{-1}(=C-H), 2202 cm^{-1} (CN), 1624 cm^1 (C=N). ^{1}HNMR:(DMSO-d^6): δ2.2 (s 3H -SCH_3), δ 2.3 (s 3H Ar-CH_3), δ 2.35 (s 3H Ar-CH_3), δ 6.6 (d 1H Ar-H), δ 7.1 (d 1H Ar-H). Mass : (m/z): 301 (50%), M.F: $C_{14}H_{11}N_3OS_2$ Found 301, Calculated (%):C 55.79, H 3.68, N 13.94,O 5.31 and S 21.28.

General method for the synthesis of compounds (4a-d):

A mixture of compound **3** (0.01 mole) and selected nucleophiles (0.01 mole) (like p-nitro phenol / p- chloro Aniline /pyrrolidine / malononitrile) independently refluxed in presence of a pinch of anhydrous K_2CO_3 in DMF for 4-5 hours (**Reaction Scheme-II)**. The reaction mixtures were monitored by TLC cooled and kept for overnight. Reaction mixture was poured in ice cold water, solid get separated and recrystlized from ethanol to yield compound **4a-d.**

Spectral Discussion:

3-cyano-6, 9-dimethyl- 4-oxo 2- (p-chloro anilino)-4H-pyrimido[2,1-*b*][1,3] benzothiazole (4a): Yield : 50%, M.P: 280^{0}C, IR: (KBr / cm^{-1}): 3313 cm^{-1}(NH); 3031, 2912cm^{-1}(Ar C-H); 2195 cm^{-1}(C≡N); 1626 cm^{-1} (C=N). ^{1}HNMR:(DMSO-d^6): δ 2.3 (s 3H Ar-CH_3), δ 2.35 (s 3H Ar-CH_3), δ 4.5 (s 1H N-H), δ 6.4 (d 2H Ar-H), δ 6.5 (d 1H Ar-H), δ 7.0 (d 1H Ar-H), δ 7.2 (d 2H Ar-H). Mass : (m/z): 380 (60%), M.F: $C_{19}H_{13}N_4OSCl$. Found 380, Calculate (%): C 59.92, H 3.40, N 14.71, O 4.20, S 8.82, Cl 9.31.

3-cyano-6, 9-dimethyl- 4-oxo 2- (p-nitro phenoxy)-4H-pyrimido[2,1-*b*][1,3] benzothiazole (4b): Yield : 54%, M.P: 270^{0}C, IR: (KBr / cm^{-1}): 3027, 2928 cm^{-1}(Ar C-H); 2200 cm^{-1}(C≡N); 1639 cm^{-1} (C=N), 1420,1308 cm^{-1}(NO_2). ^{1}HNMR:(DMSO-d^6): δ 2.3 (s 3H Ar-CH_3), δ 2.35 (s 3H Ar-CH_3), δ 6.5 (d 1H Ar-H), δ 6.6 (d 1H Ar-H), δ 7.0 (d 2H Ar-H), δ 7.3 (d 2H Ar-H). Mass : (m/z): 392 (45%), M.F: $C_{19}H_{12}N_4O_4S$. Found 390, Calculate (%): C 58.16, H 3.08, N 14.28, O 16.31, S 8.17.

3-cyano-6, 9-dimethyl- 4-oxo 2- (pyrrolidino)-4H-pyrimido [2,1-*b*][1,3] benzothiazole (4c): Yield : 40%, M.P: 255^{0}C, IR: (KBr / cm^{-1}): 3031, 2912cm^{-1}(C-H); 2190 cm^{-1}(C≡N); 1623 cm^{-1} (C=N). ^{1}HNMR:(DMSO-d^6): δ 1.6 (t 4H -CH_2), δ 2.3 (s 3H Ar-CH_3), δ 2.35 (s 3H Ar-CH_3), δ 2.7 (t 4H N-CH_2) δ 6.6 (d 1H Ar-H), δ 6.7 (d 1H Ar-H). Mass : (m/z): 324 (65%), M.F: $C_{17}H_{16}N_4OS$. Found 324, Calculate (%): C 62.94, H 4.97, N 17.27, O 4.93, S 9.88.

3-cyano-6, 9-dimethyl- 4-oxo 2- (malononitrile)-4H-pyrimido [2,1-*b*][1,3] benzothiazole (4d): Yield : 40%, M.P: 275^{0}C, IR: (KBr / cm^{-1}): 3029, 2910cm^{-1}(Ar C-H); 2190 cm^{-1}(C≡N); 1630 cm^{-1} (C=N). ^{1}HNMR:(DMSO-d^6): δ 2.3 (s 3H Ar-CH_3), δ 2.35 (s 3H Ar-CH_3), δ 4.1 (s 1H C-H), δ 6.7 (d 1H Ar-H), δ 7.0 (d 1H Ar-H). Mass : (m/z): 319 (50%), M.F: $C_{16}H_9N_5OS$. Found 319, Calculate (%): C 60.18, H 2.84, N 21.93, O 5.01, S 10.04.

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