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Synthesis of 2-substituted 3-cyano-8-ethyl carboxylate-2-methylthio-4-oxo-4H-pyrimido[2,1-*b*] benzothiazole

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ABSTRACT

Novel series of 3-cyano-8-ethyl carboxylate-2-methylthio-4H-pyrimido[2,1-b]benzothiazole ***(III)*** *& its 2-substituted derivatives* ***[IV(a-d),V(a-c),VI(a-c),VII(a-d)]*** *synthesized by the reactions of 2-amino benzothiazole* ***(I)*** *and ethyl-2-cyano-3, 3-bismethyl thioacrylate* ***(II).*** *3-cyano-8-ethyl carboxylate-2-methylthio-4H-pyrimido[2,1-b]benzothiazole* ***(III)*** *possesses replaceable active methylthio group at 2-position, the susceptibility of it towards condensation with different reagents like aryl amines, heteryl amines, phenols and compounds containing active methylene group has been investigated. These reactions resulted in the formation of 2-substituted derivatives of 3-cyano-8-ethylcarboxylate-2-methylthio-4H-pyrimido[2,1-b]benzothiazole* ***(III)*** *in DMF and catalytic amount of potassium carbonate. All the synthesized compounds are confirmed by their spectral data and elemental analysis.*

Keywords: 3-cyano-8-ethylcarboxylate-2-methylthio-4H-pyrimido[2,1-*b*]benzothiazole, ethyl-2-cyano-3, 3-bismethyl thioacrylate, 2-amino benzothiazole, DMF, K_2CO_3.

INTRODUCTION

Heterocycles are the important class of organic chemistry. Synthesis of pyrimido benzothiazole system condensed with other heterocyclic rings such as pyridine, benzene, pyrazole, etc. is challenging work, because of complex structure. Azoles have played a crucial part in the history of heterocyclic chemistry and also been used extensively as important synthons in organic synthesis. Owing to the versatile chemotherapeutical activities of azoles especially imidazole and benzimidazole, a significant amount of research activity and efforts has been directed towards this class of compounds.

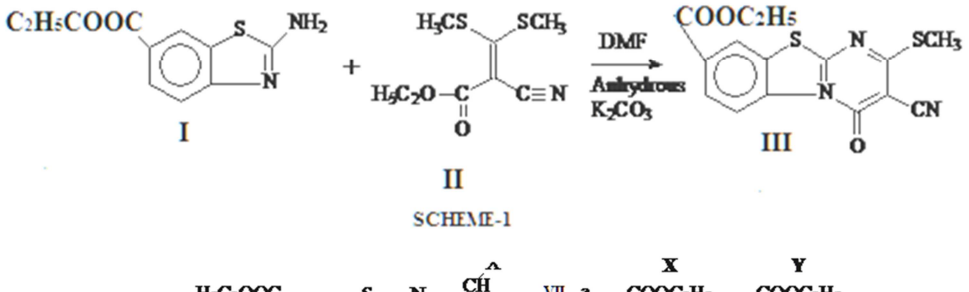
One pot synthesis of new heterocyclic compound, 4H-pyrimido[2, 1-*b*]benzothiazole-2-methylthio-3-cyano-4-one **(III)** by the reaction of 2-amino benzothiazole **(I)** with ethyl-2-cyano-3, 3-bismethyl thioacrylate **(II)** in the presence of dimethyl formamide and anhydrous potassium carbonate. They also reported[16] 2, 3-disubstituted derivatives of compound **(III)** by condensing compound **(III)** with different reagents like aryl amines, heteryl amines, phenols and compounds containing active methylene group. We report herein one pot synthesis of 3-cyano-8-ethylcarboxylate-2-methylthio-4-oxo-4H-pyrimido[2,1-*b*]benzothiazole **(III)** and preparation of its 2-substituted derivatives. The parent compound **(III)** was prepared by the reaction of 2-amino-6-ethylcarboxylate benzothiazole **(I)** with ethyl-2-cyano-3, 3-bismethyl thioacrylate[17-19] in the presence of dimethyl formamide and anhydrous potassium carbonate.

MATERIALS AND METHODS

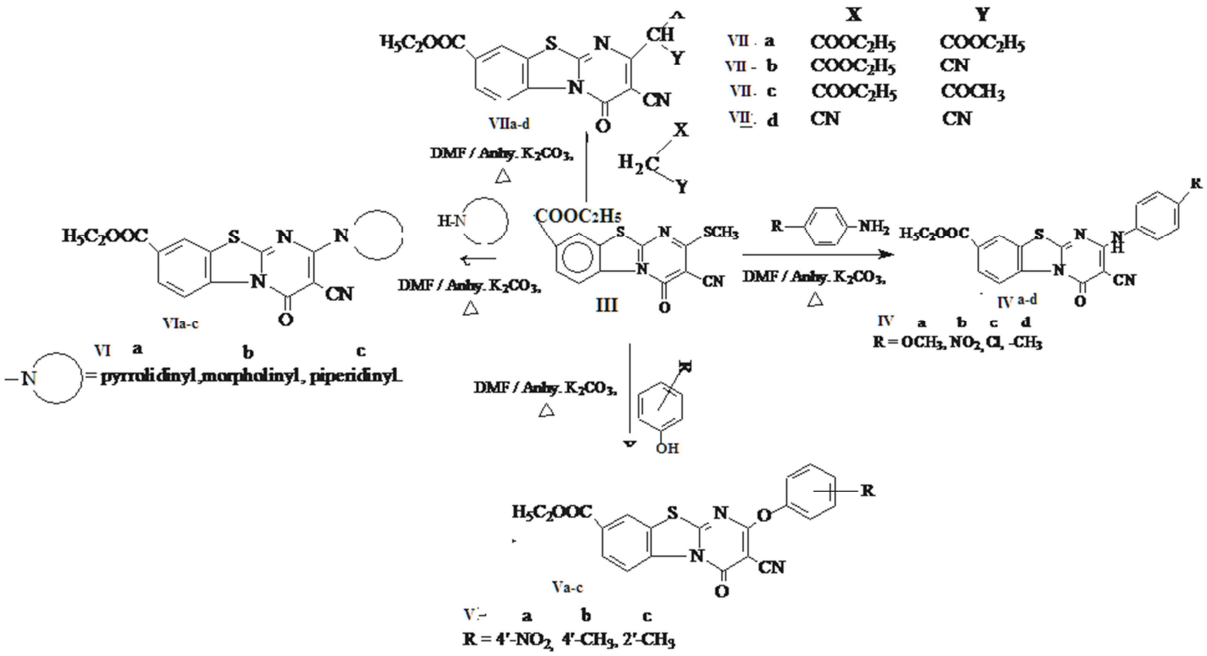
General procedure:
A mixture of 0.01mole of 2-amino-6-ethyl carboxylate benzothiazole and ethyl-2-cyano-3, 3- bismethyl thio acrylate 2.12g (0.01 mole) was refluxed in the presence of 15-20 ml of dimethyl formamide and pinch of anhydrous potassium carbonate for 4 hour. The reaction mixture was cooled to 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 1.50g of crystalline solid of **(III,IV,V,VI,VII).**

Reaction:



SCHEME-1



SCHEME-2 (Synthesis of IV, V, VI, VII)

Following table no.-1 shows reaction data for the schemes (I,II)

Table-1: Reaction Data

Sr. No.	Comp. No.	Mol. Formula	Mol. Wt	Yield (%)	M.P ^{0}C	Reaction Time	Elemental analysis					
							Calculated %			Found %		
							C	H	N	C	H	N
1	**III**	$C_{15}H_{11}N_3O_3S_2$	345	44	165	4	55.17	3.18	12.17	52.17	3.14	12.15
2	**IVa**	$C_{21}H_{16}N_4O_4S_1$	420	57	230	6	60.0	3.80	13.33	59.96	3.77	13.30
3	**IVb**	$C_{20}H_{13}N_5O_5S_1$	150	64	435	7	55.17	2.98	16.09	55.14	2.94	16.6
4	**IVc**	$C_{20}H_{13}N_4O_3S_1Cl_1$	220	70	424	8	56.60	3.06	13.20	56.56	3.02	13.17
5	**IVd**	$C_{21}H_{16}N_4O_3S_1$	404	61	217	8	62.37	3.96	13.86	62.33	3.94	13.83
6	**Va**	$C_{20}H_{12}N_4O_6S_1$	436	34	215	3	55.04	2.75	12.84	55.01	2.73	12.82
7	**Vb**	$C_{21}H_{15}N_3O_4S_1$	405	41	220	4.5	62.22	3.70	10.37	62.20	3.67	10.34
8	**Vc**	$C_{21}H_{15}N_3O_4S_1$	405	42	120	4.5	62.22	3.70	10.37	62.20	3.67	1034
9	**VIa**	$C_{18}H_{16}N_4O_3S_1$	368	69	188	4	58.69	4.34	15.21	58.67	4.31	15.18
10	**VIb**	$C_{18}H_{16}N_4O_4S_1$	384	73	198	2.5	56.25	4.16	14.58	56.21	4.13	14.54
11	**VIc**	$C_{19}H_{18}N_4O_3S_1$	382	68	202	4	59.68	4.71	14.65	59.64	4.69	14.62
12	**VIIa**	$C_{21}H_{19}N_3O_7S_1$	457	56	198	1.5	55.14	4.15	9.19	55.11	4.12	9.15
13	**VIIb**	$C_{19}H_{14}N_4O_5S_1$	410	61	132	2.0	55.60	3.41	13.65	55.57	3.39	13.61
14	**VIIc**	$C_{20}H_{17}N_3O_6S_1$	427	56	110	1.5	56.20	3.98	9.83	56.16	5.96	9.80
16	**VIId**	$C_{17}H_9N_5O_3S_1$	363	55	260	3.0	56.19	2.47	2.47	19.28	56.17	2.44

RESULTS AND DISCUSSION

The structure of this compound was assigned on the basis of analytical and spectral data. Its IR spectrums all cpmpounds exhibits absorption bands at 2212, 1712, 1679 and 1279 cm^{-1} which can be assigned to CN, C=O of ester, cyclic C=O and C-O stretching respectively.

The ^{1}H-NMR spectrum of the compounds were recorded in DMSO because of its poor solubility in other solvents, shows triplet at σ1.41, singlet at σ 2.5 and quartet at σ 2.92 assignable to $-CH_3$, SCH_3 and $-CH_2$ groups respectively and multiplet at σ 7.8 - 8.4 due to aromatic protons. Mass spectrum exhibit molecular ion peak at m/e 345 which corresponds to its molecular weight.

Since compound 3-cyano-8-ethyl carboxylate-2-methylthio-4H-pyrimido[2,1-*b*]benzothiazole **(III)** possesses replaceable active methylthio group at 2-position, the susceptibility of it towards condensation with different reagents like aryl amines, heteryl amines, phenols and compounds containing active methylene group has been investigated. These reactions resulted in the formation of 2-substituted derivatives of 3-cyano-8-ethylcarboxylate-2-methylthio-4H-pyrimido[2,1-*b*]benzothiazole **(III)**. Similarly all the derivatives of (III) gives exacts expected spectral data, thus the designed compounds prepared successively having following spectral data.

Spectral Data(IR, H^1-NMR,MASS):

1) 3-Cyano-8-ethyl carboxylate-2-methylthio-4-oxo-4H-pyrimido[2,1-*b*] benzothiazole (III): IR(KBr): 2212 cm^{-1} (-CN), 1712 cm^{-1} (C=O, ester), 1673 cm^{-1} (cyclic C=O), ^{1}H-NMR in DMSO : σ 1.41(t, 3H, CH), σ 2.50(s, 3H, SCH_3), σ 2.92(q, 2H, CH_2), σ 7.2-8.3 (m, 3H, Ar-H) MS(m/e) : 345(M^+, 92%), 317, 300, 272, 225, 197, 171.

2) 3-Cyano-8-ethyl carboxylate-2-(p-anisidino)-4-oxo-4H-pyrimido[2,1-*b*] benzothiazole (IVa): IR(KBr): 3313 cm^{-1} (-NH), 2216 cm^{-1} (-CN), 1716 cm^{-1} (C=O of ester), 1668 cm^{-1} (cyclic C=O) M S(m/e) : 420(M^+)

3) 3-Cyano-8-ethyl carboxylate-2-(p-nitroanilino)-4-oxo-4H-pyrimido[2,1-*b*] benzothiazole (IV): IR(KBr): 3363 cm^{-1} (-NH), 2215 cm^{-1} (-CN), 1710 cm^{-1} (C=O of ester), 1550 cm^{-1} (NO_2 asymmetric), 1330 cm^{-1} (NO_2 symmetric) MS(m/e) : 435(M^+)

4) 3-Cyano-8-ethyl carboxylate-2-(p-chloroanilino)-4-oxo-4H-pyrimido [2,1-*b*]benzothiazole (IVc): IR(KBr): 3240 cm^{-1} (NH), 2220 cm^{-1} (CN), 1710 cm^{-1} (C=O of ester), 1660 cm^{-1} (cyclic C=O) MS(m/e) : 424(M+, 30%)

5) 3-Cyano-8-ethyl carboxylate-2-(p-toluidino)-4-oxo-4H-pyrimido[2,1-*b*] benzothiazole (IVd): IR(KBr): 3320cm^{-1} (-NH), 2215 cm^{-1} (CN), 1740 cm^{-1} (C=O of ester), 1680 cm^{-1} (cyclic C=O) MS(m/e) : 404 (M^+)

6) 3-Cyano-8-ethyl carboxylate-2-(p-nitro phenoxy)-4-oxo-4H-pyrimido[2,1-*b*] benzothiazole (II-Va): IR(KBr): 2204 cm^{-1} (CN), 1692 cm^{-1} (C=O of ester), 1660 cm^{-1} (cyclic C=O), 1528 cm^{-1} (NO_2 asymmetric), 1363 cm^{-1} (NO_2 symmetric), 1279 cm^{-1} (C-O-C linkage) MS(m/e) : 436(M^+)

7) 3-Cyano-8-ethyl carboxylate-2-(p-methyl phenoxy)-4-oxo-4H-pyrimido[2,1-*b*] benzothiazole (Vb): IR(KBr): 2210 cm^{-1} (CN), 1708 cm^{-1} (C=O of ester), 1658 cm^{-1} (cyclic C=O), 1278 cm^{-1} (C-O-C linkage) MS(m/e) : 405(M^+)

8) 3-Cyano-8-ethyl carboxylate-2-(o-methyl phenoxy)-4-oxo-4H-pyrimido[2,1-*b*] benzothiazole (Vc): IR(KBr): 2210 cm^{-1} (CN), 1683 cm^{-1} (C=O ofester), 1650 cm^{-1} (cyclic C=O), 1292 cm^{-1} (C-O-C linkage) MS(m/e) : 405(M^+)

9) 3-Cyano-8-ethyl carboxylate-2-(pyrrolidinyl)-4-oxo-4H-pyrimido[2,1-*b*] benzothiazole (VIa): IR(KBr): 2209 cm^{-1} (CN), 1711 cm^{-1} (C=O of ester), 1694 cm^{-1} (cyclic C=O), 1277 cm^{-1} (C-O) MS(m/e) : 368(M^+, 35%).

10) 3-Cyano-8-ethyl carboxylate-2-(morpholinyl)-4-oxo-4H-pyrimido[2,1-*b*] benzothiazole (VIb): IR(KBr): 2220 cm^{-1} (CN), 1709 cm^{-1} (C=O of ester), 1680 cm^{-1} (cyclic C=O), 1260 cm^{-1} (C-O) MS(m/e) : 384(M^+).

11) 3-Cyano-8-ethyl carboxylate-2-(piperidinyl)-4-oxo-4H-pyrimido [2,1-*b*] benzothiazole (VIc): IR(KBr): 2190 cm^{-1} (CN), 1715 cm^{-1} (C=O of ester), 1690cm^{-1} (cyclic C=O), 1270 cm^{-1} (C-O) MS(m/e) : 382(M^+)

12) 3-Cyano-8-ethyl carboxylate-2-(diethyl malonyl)-4-oxo-4H-pyrimido [2, 1-*b*] benzothiazole (VIIa): IR(KBr) : 2216 cm^{-1} (CN), 1708cm^{-1} (C=O of ester), 1683 cm^{-1} (cyclic C=O) MS(m/e) : 457(M^+)

13)3-Cyano-8-ethyl carboxylate-2-(α-ethyl cyano acetyl)-4-oxo-4H-pyrimido [2, 1-*b*] benzothiazole (VIIb): IR(KBr): 2227cm^{-1} (CN), 1744cm^{-1} (C=O of ester), 1248cm^{-1} (C-O) MS(m/e) : 410(M^+)

14) 3-Cyano-8-ethyl carboxylate-2-(α-ethyl aceto acetyl)-4-oxo-4H-pyrimido [2, 1-*b*] benzothiazole (VIIc): : IR(KBr): 2199 cm^{-1} (CN), 1714 cm^{-1} (C=O of ester), 1698 cm^{-1} (cyclic C=O), 1235 cm^{-1} (C-O) MS(m/e) : 427(M^+)

15) 2-(α-Malono nitrilyl)-4H-pyrimido [2, 1-*b*] benzothiazole-8-methyl-3-cyano-4-one (VIId): IR(KBr): 2210 cm^{-1} (CN), 1715cm^{-1} (C=O of ester), 1680cm^{-1} (cyclic C=O) MS(m/e) : 363(M^+, 50%)

CONCLUSION

On the basis of structural information, it can be concluded that the anti-convulsant, anti-asthmatic and neuroprotector activities might be due to the presence of basic skeleton of the molecule. The presence of benzothiazolyl signature renders free radical scavenging activity to the molecule.

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