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RESEARCH ARTICLE

Multicomponent synthesis of 2, 6-dihydro-2, 6-diimino-4, 8-bis (methylthio) pyrimido [2, 1-b] [1, 3] thiazine-3, 7-dicarbonitrile and its derivatives

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ABSTRACT:
Substituted derivatives of 2,6-dihydro-2,6-diimino-4,8-bis (methylthio) pyrimido[2,1-b] [1,3] thiazine-3,7-dicarbonitrile have been prepared through One Step Multicomponent reaction by heating a mixture of bis methylthio methylene malononitrile (I), thiourea (II) independently with different heteryl amines respectively in the presence of dimethyl formamide and catalytic amount of anhydrous potassium carbonate. All these newly synthesized compounds were screened for antibacterial activity and characterized by elemental analysis and spectral data.

KEYWORDS: Bis methylthio methylene malononitrile, thiourea, heteryl amines, dimethyl formamide, K_2CO_3.

INTRODUCTION:
Nitrogen-containing five or six membered heterocyclic compounds such as oxazolines, thiazolines and thiazines are of great interest to organic chemists, because they are present in various natural compounds having interesting bioactivities [1-3]. Furthermore, the optically active heterocyclic compounds have been successfully used in asymmetric synthesis as chiral templates [4, 5] or ligands [6-9] reported the synthesis of thioethers and thioesters in acetonitrile. Thiazines represent an important class of heterocyclic compounds due to their valuable biological properties. For example, some derivatives of thiazine are cannabinoid receptor agonists [10] also they can act as an antihypotensive [11] antitubercular [12] and antibacterial [13] agents. Moreover, thiazine derivatives can be used for gastrointestinal disorders [14] or diabetes [15] prevention. Condensed heterocyclic systems possessing thiazine ring have been reported as antioxidants [16] analgesic, anti-inflammatory agents [17] or calcium channel modulators [18].

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Also it should be noted that thiazines are useful intermediates in synthetic organic chemistry. The synthetic ways for the preparation of 4H-thiazine ring can be classified into several groups: intramolecular cyclizations; reactions between thioureas or thioamides and Michael acceptors; reactions between thioureas and malonic acid derivatives; reactions between 3-mercaptoacrylamides and carbonyl compounds or Michael acceptors, and heteroDiels–Alder reactions. There are also some reports about biosynthetic pathways to thiazine rings.

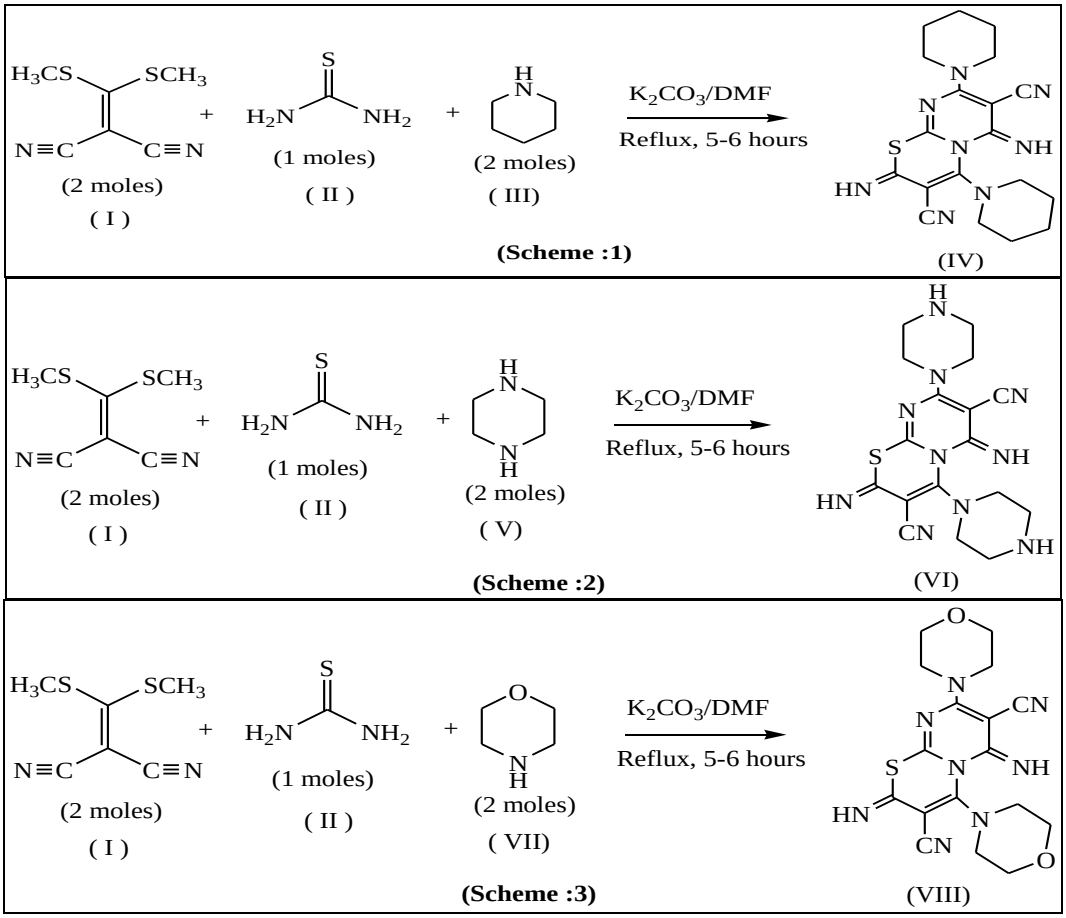
In recent years, the synthesis of fused bicyclic heterocyclic compounds possessing pyrimido-thiazine central core has been the focus of great interest. This type of compounds have been reported to exhibit a variety of biological activities [19,20]. Recently, substituted thiazine are prepared using α, β- unsaturated carbonyl system and that are very versatile substrates for the evolution of various reactions [21] and physiologically active compounds [22]. 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 heteryl amines.

Experimental Section:

All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded with potassium bromide pellets technique, ^{1}H NMR spectra were recorded on AVANCE 300 MHz Spectrometer in DMSO using TMS as internal standard. Mass spectra were recorded on a FT VG-7070 H Mass Spectrometer using EI technique at 70 eV. All the reactions were monitored by Thin layer chromatography.

MATERIALS AND METHOD:



Experimental:

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

A mixture of BMMM (2 moles) and thiourea (1 mole) on reflux with dimethyl formamide solvent in presence of K_2CO_3 for 5-6 hours gives 2,6-dihydro-2,6-diimino-4,8-bis (methylthio) pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile. The product was filtered, washed with water and then dried. The product recrystallized from ethyl alcohol.

Yield: 67 %, M.P.: 175 ^{0}C.

2. Synthesis of 2, 6-dihydro-2,6-diimino-4,8-di (piperidin-1-yl) pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile (IV):

A mixture of bis methylthio methylene malononitrile (I), thiourea (II) and piperidine (III) on reflux with dimethyl formamide solvent in presence of K_2CO_3 for 5-6 hours gives 2,6-dihydro-2,6-diimino-4,8-di (piperidin-1-yl) pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile (IV). The product was filtered, washed with water and then dried. The product recrystallized from ethyl alcohol.

Yield : 61 %, M.P. : 180°C, IR:(KBr/cm^{-1}) : 2251 (-CN), 3441 (=NH), ^{1}H-NMR: (DMSO): δ 1.5 (m 12H CH_2), δ 2.7 (t 8H $–CH_2$), δ 8.10 (s 2H =NH), EI-MS: (m/z:RA%): 395 (M+1), Elemental analysis : $C_{19}H_{22}N_8S$, Calculated: (%) C 57.85, H 5.62, N 28.40, S 8.13 Found (%) : C 57.80, H 5.60, N 28.35, S 8.11

3. Synthesis of 2, 6-dihydro-2,6-diimino-4,8-di (piperazin-1-yl) pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile (VI):

A mixture of bis methylthio methylene malononitrile (I), thiourea (II) and piperazine (V) on reflux with dimethyl

formamide solvent in presence of K_2CO_3 for 5-6 hours gives 2,6-dihydro-2,6-diimino-4,8-di (piperazin-1-yl) pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile (VI). The product was filtered, washed with water and then dried. The product recrystallized from ethyl alcohol.

Yield : 65 %, M.P. : 167 ^{0}C, IR:(KBr/cm^{-1}) : 2235 (-CN), 3435 (=NH), ^{1}H-NMR: (DMSO): δ 2.0 (s 2H -NH), δ 2.67 (t 16H $-CH_2$), δ 7.75 (s 2H =NH), EI-MS:(m/z:RA%): 397 (M+1), Elemental analysis : $C_{17}H_{20}N_{10}S$, Calculated: (%) C 51.50, H 5.08, N 35.33, S 8.09 Found (%) : C 51.44, H 5.05, N 35.30, S 8.07

4) Synthesis of 2,6-dihydro-2,6-diimino-4,8-dimorpholino pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile (VIII):

A mixture of bis methylthio methylene malononitrile (I), thiourea (II) and morpholine (VII) on reflux with dimethyl formamide solvent in presence of K_2CO_3 for 5-6 hours gives 2,6-dihydro-2,6-diimino-4,8-dimorpholino pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile (VIII). The product was filtered, washed with water and then dried. The product recrystallized from ethyl alcohol.

Yield : 55 %, M.P. : 189 ^{0}C, IR:(KBr/cm^{-1}) : 2240 (-CN), 3447 (=NH), ^{1}H-NMR: (DMSO): δ 2.9 (t 8H CH_2), δ 3.67 (t 8H $-CH_2$), δ 8.12 (s 2H =NH), EI-MS: (m/z:RA%): 399 (M+1), Elemental analysis: $C_{17}H_{18}N_8O_2S$, Calculated: (%) C 51.25, H 4.55, N 28.12, O 8.03, S 8.05 Found (%) : C 51.22, H 4.51, N 28.10, O 8.00, S 8.03

RESULT AND DISCUSSION:

The objectives of the present work are to synthesize substituted pyrimido oxazine derivatives and study their biological properties. Thus an attempt has been made in this direction. As expected substituted pyrimido oxazine exhibited antibacterial, anti allergic, anti inflammatory, antitumor activities.

CONCLUSION:

In conclusion a facile multicomponent and one pot synthesis has been developed for the title compounds using readily available starting materials. We have synthesized simple and efficient novel fused bicyclic heterocycles pyrimido-oxazine having bis-electrophilic species reacting with various nucleophiles.

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