SIMPLE AND EFFICIENT SYNTHESIS OF IMINO PYRIMIDO OXAZINE AND THEIR DERIVATIVES.

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Abstract : In this review we report simple and efficient synthesis of novel fused tricyclic heterocyclic compounds by heating 2-(4-chlorophenyl)-6-imino-8-(methylthio)-4-phenyl-9,9a-dihydro-2H,6H-pyrimido[2,1-b][1,3]oxazine-7-carbonitrile with hydrazine, substituted phenyl hydrazine and substituted benzothiazole using potassium carbonate in DMF as solvent under reflux condition to give 8-(4-chlorophenyl)-4-imino-2-substituted-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo [3',4':4,5] pyrimido [2,1-b][1,3]oxazin-3-amine.

Keywords: Addition elimination reaction, pyrimido oxazine, hydrazine, substituted phenyl hydrazine, substituted benzothiazoles

I. INTRODUCTION

Oxazines are an important type of heterocyclic compounds. Heterocyclic compounds are basic for many pharmaceutical, veterinary and agrochemical products1. Synthesis of oxazine was main interest as it is one of the important compounds of heterocycle encompassing nitrogen and oxygen atom in six membered aromatic ring. Oxazine derivatives are an important class of heterocycles, which are useful in the field of medicinal and pharmaceutical chemistry and have been reported to exhibit variety of biological activities like anti-hyperglycemic2, anti-microbial3, anti-ulcer4, anti-inflammatory5, anti-malarial6, analgesic7, anti-cancer8, anti-tuberculosis9, anti-oxidant10, anti-leishmanial11, anti-coagulant activities11-12. Oxazine derivatives have played very important role in the improvement of heterocyclic chemistry and ordinarily used in organic synthesis13. Oxazine derivatives have been reported to possess anti-fungal14-18 antibacterial19-21. Due to its numerous biological activities reported. The structures of the various synthesized compounds were assigned on the basis of IR, 1H NMR, 13C NMR and Mass spectral data. In the view of this observation and extension of earlier work, we have synthesized 2-(4-chlorophenyl)-6-imino-8-(methylthio)-4-phenyl-9,9a-dihydro-2H,6H-pyrimido [2,1-b] [1,3] oxazine-7-carbonitrile by using 6-(4-chlorophenyl)-4-phenyl-6H-1,3Oxazin-2-amine22,23 and 2-bis(methylthio)methylene)malononitrile. Aminooxazines with amino group occupying the position in between two hetero atoms are important synthetic target as well as building block of various heterocycles. The amino Oxazine were prepared by the reaction of chalcone24,25 with urea in the presence of ethanol and Potassium hydroxide under reflux condition.

II. EXPERIMENTAL:

Melting points were determined in open capillary tubes and are uncorrected. The silica gel F254 plates were used for thin layer chromatography (TLC); the spots were examined under UV light and then developed in 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 as follows: IR, KBr pellets, a Perkin-Elmer RX1 FT-IR spectrophotometer; 1H NMR, CDCl3, 200 MHz, a Varian Gemini 200 instrument. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

2-(4-chlorophenyl)-6-imino-8-(methylthio)-4-phenyl-9,9a-dihydro-2H,6H-pyrimido[2,1-b][1,3]oxazin-7-carbonitrile.

Step – I

A solution of KOH 50 % is added to an equimolar solution of acetophenone (0.01mole) and 4-chlorobenzaldehyde (0.01 mole) in ethanol 95 %; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. They are crystallized by ethanol compound.

Step – II

A mixture of chalcone i.e. 3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (2.42 gm, 0.01mole) and urea (0.60 gm 0.01 mole) were dissolved in ethanolic potassium hydroxide solution (10 ml). It was heated for 4 hrs, then it was poured into cold ice obtain 6-(4-chlorophenyl)-4-phenyl-6H-1, 3-Oxazin-2-amine (2).

Step – III

A mixture of 6-(4-chlorophenyl)-4-phenyl-6H-1, 3-Oxazin-2-amine (2) and 2-(bis (methylthio) methylene) malononitrile in the presence of catalytic amount of potassium carbonate (10 mg) in DMF was refluxed for 4 hrs. The reaction was monitored by TLC. After completion, the reaction mixture was set to cool at room temperature and washe with water the extracted with ethyl acetate. The extract was concentrated and the residue was subjected to column chromatography (silicagel, n-hexane-ethyl acetate 8:2) to obtain pure solid compound 2-(4-chlorophenyl)-6-imino-8-(methylthio)-4-phenyl-9,9a-dihydro-2H,6H-pyrimido[2,1-b][1,3]oxazin-7-carbo- nitrile (3). The compound (3) confirmed by IR, 1H, C13 NMR and MS analytical data.
3) 2-(4-chlorophenyl)-6-imino-8-(methylthio)-4-phenyl-2H,6H-pyrimido[2,1-b][1,3]oxazine-7-carbonitrile.

1H NMR: δ 3.23 (s, 3H, SCh), 5.89 (s, 1H N-H), 8.32 (s, 1H =NH), 5.36 (s, 1H =CH, 5.62 (s, 1H CH), 4.48 (s, 1H CH), 7.10 (s, 5H Ar-H), 7.28 (dd, 2H Ar-H), 7.36 (dd, 2H Ar-H).

IR (KBr, cm⁻¹): 3350, 2240, 1650, 760 cm⁻¹;

ESI-MS: m/z (M⁺) 408 (M+2) 410.

Anal. Calcd for C₂₂H₁₇ClN₄O₃S: C, 61.68; H, 4.19; Cl, 8.67 ; N, 13.70; O, 3.91; S, 7.84;

Found : C, 61.40; H, 3.91; Cl, 8.67; N, 13.38; O, 4.81; S, 7.83.


**Synthesis of Derivatives**

A mixture of (3) (1mmol) and independently, various hydrazine, substituted hydrazine, substituted benzothiazole (1mmol) in DMF (10 ml) and anhydrous potassium carbonate (10 mg) was reflux for 4 to 6 hrs. The reaction mixture cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water and recrystallized using ethyl alcohol.

3-a) 8-(4-chlorophenyl)-4-imino-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrrozolo[3',4':4,5]pyrimido[2,1-b][1,3]oxazin-3-amine.

1H NMR : δ 7.60 (s, 5H Ar-H), 7.18 (dd, 2H Ar-H), 7.34 (dd, 2H Ar-H), 12.36 (s, 1H N-H), 7.06 (s, 1H =NH), 6.20 (s, 2H NH₂), 6.68 (d, 1H =CH), 5.15 (d, 1H CH), 5.45 (s, 1H CH).

IR (KBr, cm⁻¹): 3310, 1650, 1290, 1190, 740 cm⁻¹;

ESI-MS: m/z (M⁺) 390 (M+2) 392.

Anal. Calcd for C₂₂H₁₇ClN₄O: C, 61.15; H, 4.36; Cl, 9.02; N, 21.39; O, 4.07;

Found : C, 61.10; H, 4.31; Cl, 9.05; N, 21.43; O, 4.11.


3-b) 8-(4-chlorophenyl)-4-imino-2-diphenyl-2,4,9a,10-tetrahydro-8H-pyrrozolo[3',4':4,5]pyrimido[2,1-b][1,3]oxazin-3-amine.

1H NMR : δ 7.64 (s, 5H Ar-H), 7.17 (dd, 2H Ar-H), 7.31 (dd, 2H Ar-H), 6.67 (s, 1H N-H), 10.61 (s, 1H =NH), 6.40 (s, 2H NH₂), 6.64 (d, 1H =CH), 5.19 (d, 1H CH), 5.52 (s, 1H CH), 7.52 (s, 5H Ar-H).

IR (KBr, cm⁻¹): 3320, 1670, 1600, 1310, 1230, 755, cm⁻¹;

ESI-MS: m/z (M⁺) 468 (M+2) 470.

Anal. Calcd for C₂₂H₂₀ClN₄O: C, 66.59; H, 4.51; Cl, 7.56; N, 17.92; O, 3.41;

Found : C, 66.55; H, 4.45; Cl, 7.60; N, 17.97; O, 3.43.


3-c) 8-(4-chlorophenyl)-2-(4-nitrophenyl)-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrrozolo[3',4':4,5]pyrimido[2,1-b][1,3]oxazin-3-amine.

1H NMR : δ 7.62 (s, 5H Ar-H), 7.20 (dd, 2H Ar-H), 7.30 (dd, 2H Ar-H), 6.62 (s, 1H N-H), 10.62 (s, 1H =NH), 6.33 (s, 2H NH₂), 6.70 (d, 1H =CH), 5.18 (d, 1H CH), 5.48 (s, 1H CH), 8.06 (dd, 2H Ar-H), 8.38 (dd, 2H Ar-H).

IR (KBr, cm⁻¹): 3330, 1660, 1590, 1320, 1210, 810, cm⁻¹;

ESI-MS: m/z (M⁺) 513 (M+2) 515.

Anal. Calcd for C₂₂H₂₁N₄O₃: C, 60.76; H, 3.92; Cl, 6.90; N, 19.08; O, 9.34;

Found : C, 60.72; H, 3.86; Cl, 6.94; N, 19.11; O, 9.37.


3-d) 8-(4-chlorophenyl)-2-(2,4-dinitrophenyl)-4-imino-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrrozolo[3',4':4,5]pyrimido[2,1-b][1,3]oxazin-3-amine.

1H NMR : δ 7.68 (s, 5H Ar-H), 7.16 (dd, 2H Ar-H), 7.32 (dd, 2H Ar-H), 6.72 (s, 1H N-H), 7.08 (s, 1H =NH), 6.36 (s, 2H NH₂), 6.64 (d, 1H =CH), 5.16 (d, 1H CH), 5.52 (s, 1H CH), 8.11 (d, 1H Ar-H), 8.68 (d, 1H Ar-H), 8.76 (s, 1H Ar-H).

IR (KBr, cm⁻¹): 3340, 1650, 1580, 1310, 1220, 880, cm⁻¹;

ESI-MS: m/z (M⁺) 558 (M+2) 560.

Anal. Calcd for C₂₂H₁₉ClN₄O₃: C, 55.87; H, 3.43; Cl, 6.34; N, 20.05; O, 14.31;

Found : C, 55.92; H, 3.48; Cl, 6.32; N, 20.01; O, 14.27.


3-e) 2-(benzo[d][thiazol-2-yl]-8-(4-chlorophenyl)-4-imino-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrrozolo[3',4':4,5]pyrimido[2,1-b][1,3]oxazin-3-amine.

1H NMR : δ 7.64 (s, 5H Ar-H), 7.18 (dd, 2H Ar-H), 7.32 (dd, 2H Ar-H), 6.69 (s, 1H N-H), 7.08 (s, 1H =NH), 6.37 (s, 2H NH₂), 5.69 (d, 1H =CH), 5.19 (d, 1H CH), 5.47 (s, 1H CH), 7.98 (d, 1H Ar-H), 7.48 (dd, 1H Ar-H), 7.51 (dd, 1H Ar-H), 8.10 (d, 1H Ar-H).

IR (KBr, cm⁻¹): 3330, 1630, 1590, 1330, 1230, 660 , 1620 cm⁻¹;

ESI-MS: m/z (M⁺) 526 (M+2) 528.

Anal. Calcd for C₂₃H₁₈ClN₅OS: C, 61.65; H, 3.83; Cl, 6.74; N, 18.64; O, 3.04; S, 6.09;

Found : C, 61.63; H, 3.80; Cl, 6.72; N, 18.68; O, 3.06; S, 6.11.
3-f) 8-(4-chlorophenyl)-4-imino-2-(6-methylbenzo[d]thiazol-2-yl)-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo[3′,4′:4,5]pyrimido[2,1-b][1,3]oxazin-3-amine

Mol. Formula: C_{27}H_{22}ClN_{5}O_{5}Mol. Wt : 526 & 528.

IR (KBr, cm⁻¹): 3320, 1660, 1590, 1330, 1230, 670, 1621 cm⁻¹;
ESI-MS: m/z (M⁺) 540 (M+2) 542.

Found: C, 62.32; H, 4.14; Cl, 6.59; N, 18.16; O, 2.96; S, 5.94.

Mol. Formula: C_{28}H_{22}ClN_{5}OS. Mol. Wt: 540 & 542.

3-g) 8-(4-chlorophenyl)-4-imino-2-(6-methoxybenzo[d]thiazol-2-yl)-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo[3′,4′:4,5]pyrimido[2,1-b][1,3]oxazin-3-amine

Mol. Formula: C_{28}H_{22}ClN_{5}O_{5}S: Mol. Wt: 556 & 558.

Found: C, 60.52; H, 3.95; Cl, 6.35; N, 17.60; O, 5.76; S, 5.82.

3-h) 2-(6-chlorobenz[d]thiazol-2-yl)-8-(4-chlorophenyl)-4-imino-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo[3′,4′:4,5]pyrimido[2,1-b][1,3]oxazin-3-amine

Mol. Formula: C_{27}H_{19}ClN_{5}O_{5}S. Mol. Wt: 560 & 562.

Found: C, 57.82; H, 3.40; Cl, 12.61; N, 17.49; O, 2.85; S, 5.72.

III. RESULT AND DISCUSSION:

The compound 2-(4-chlorophenyl)-6-imino-8-(methylthio)-4-phenyl-9,9a-dihydro-2H,6H-pyrimido [2,1-b] [1,3] oxazine-7-carbonitrile (3) are synthesized by dissolving 6-(4-chlorophenyl)-4-phenyl-6H-1,3-Oxazin-2-amine and 2-(bis(methylthio) methylene) malononitrile in presence of K_{2}CO_{3} in DMF under reflux condition. The synthesized compound acts as electrophilic species due to leaving nature reacting with various hydrazine, substituted phenyl hydrazine and substituted benzothiazole give 8-(4-chlorophenyl)-4-imino-2-substituted-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo [3′,4′:4,5] pyrimido [2,1-b][1,3] oxazin-3-amine in good yield.

IV. CONCLUSION:

A new different 8-(4-chlorophenyl)-4-imino-2-substituted-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo [3′,4′:4,5] pyrimido [2,1-b][1,3] oxazin-3-amine are synthesized by using simple and efficient chemistry and this synthesized compounds possess methylthio group at 8-position which is best leaving group therefore synthesized compound act as an electrophilic species and reacting with various nucleophiles. In compound (3) cyano and thiomethyl groups are at adjacent position it also undergo cyclization to give polycyclic heterocyclic compound.
\[
\text{CHO} + \text{O} + \text{NH}_2\text{CONH}_2 \xrightarrow{\text{Alc. KOH}} 3-(4\text{-chlorophenyl})-1\text{-phenylprop-2-en-1-one}
\]

\[
\text{NH}_2\text{CONH}_2 \xrightarrow{\text{Alc. KOH}} 6-(4\text{-chlorophenyl})-4\text{-phenyl}6\text{-H,1,3-oxazin-2-amine}
\]

\[
\text{K}_2\text{CO}_3/\text{DMF} \rightarrow (\text{bis(methylthio)methylene})\text{malononitrile}
\]

\[
2-(4\text{-chlorophenyl})-6\text{-imino}-8\text{-methylthio}-4\text{-phenyl}9,9\text{a-dihydro}-2\text{H,6H-pyrimido}[2,1-b][1,3]oxazine-7\text{-carbonitrile}
\]
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