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RESEARCH ARTICLE

Synthesis of Ethyl (2-Aryl-3-oxo-2, 3, 4, 5-tetrahydrobenzo [f][1,4]Oxazepin-7-yl) thiazole-5-carboxylate

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ABSTRACT

Oxazepines, which were synthesized by different methods shown in literature also Oxazepines are great importance in heterocyclic chemistry and more importance in biology and pharmacology. Oxazepines are very biological active molecules. In this work we can synthesize Ethyl 2-(Aryl-3-oxo-2, 3, 4, 5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)thiazole-5-carboxylate by using a different Schiff bases, which were synthesized from ethyl 2-(3-formyl-4-hydroxyphenyl)—methylthiazole-5-carboxylate and Benzyl Amines. During performing reaction get a 60-70% yield. The identification of product by 1H NMR, 13C NMR, IR, elemental analysis.

KEYWORDS

Schiff Bases, Reduction, Chloroacetyl Chloride, Ring Closure, Benzoxazepines

INTRODUCTION

Benzoxazepines and their derivatives have biological activity[1] and pharmacological activities[2]. Also acts on central nervous system as enzyme inhibitor[3], analgesic[2], and antipsychotics[4]. Benzo [1, 4] Oxazepines are crucial moieties in psychoactive drugs[7,8]. It was found that dibenzo [*b, f*][1,4]oxazepin-11(10*H*)-ones to be selective inhibitors of human immunodefiency virus (HIV) type 1 reverse transcriptase[9]. Known synthesis of benzoxazepines includes condensations of 2-aryloxyethylamines with 2-formylbenzoic acid[10], rearrangement of methyl 2-(8-methoxy-2,3-dihydro-1,4-benzoxazepin-5-yl)benzoate using Bischler-Napieralski conditions[11] and scandium or copper triflate catalyzed acylaminoalkylation of α-methoxyisoindolones with the formation of 1,4-benzoxazepines in moderate yields.[12] Some Oxazepines and benzoxazepines were synthesized from amides,[13-15] aminoacids,[16-19] esters,[20] acid chlorides,[21] flavones.[22,23] amines[24] and Mannich base.[25] Working on Schiff bases **3a-c** and biological interest of benzoxazepines impelled us to synthesize different benzoxazepines **6a-c** in our laboratory.

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EXPERIMENTAL SECTION

General

All melting points were taken in open capillaries and uncorrected. IR spectra in KBr were recorded on Mattson 1000 FTR spectrometer and JASCO ST / IR-420 machine and UV spectra were recorded on Unicam UV2-100/Visible spectrometer and 150-20 Hitachi spectrometer.^{1}H-NMR and ^{13}C-NMR spectra were determined at Bruker AC 200L and Bruker 500 MHz spectrometer using DMSO. Mass spectra were obtained in a (LS/MS-APCl) Agilent 1100 MSD Instrument. Elemental

analyses were obtained LECO CHNS 932 Machine. Merck Kieselgel HF_{254} type-60 and Kieselgel 40-60 µm type were used for TLC. For analytical work 0.25 mm, for preparative work 0.75 mm plates were used. All solvents and reagents used were analytical reagent grade.

Synthesis of Schiff bases 3a-c

Schiff bases **3a-c** were synthesized according to the method of Sawich and his coworkers.[26] The structures of the Schiff bases **3a-c** substrates prepared were determined by IR, UV, ^{1}H-NMR, ^{13}C-NMR and mass spectra and compared with literature data.

Reductions of Schiff bases with $NaBH_4$

Schiff base **3a-c** (4mmol) were dissolved in methanol (20 ml) and then $NaBH_4$ (20 mmol) was added slowly until the evolution of H_2 gases ceases and yellow colour disappears. Ice water was added to the reaction mixture. Crude product was crystallized after preparative TLC (SiO_2/toluene) purification.

Reactions of Reduced Schiff bases 4a-c with Chloroacetyl chloride

Chloroacetyl chloride (0.02 moles) was added to a vigorously stirred solution of **4a-c** (0.01 moles) in toluene (15 ml). The reaction mixture was refluxed for 2 hours. The solvent was removed in vacuo and the gummy residue was crystallized from dry ethyl alcohol yielding white crystals **5a-c**.

Ring Closure Reactions of Diacetyl Derivatives 5a-c

Compound **5a-c** (0.001 moles) was added to 5% NaOH solution (15 ml) and the mixture was stirred on water bath for 1 hour. The white solid obtained on cooling was filtered, washed with water and crystallized from alcohol to give the compounds **6a-c**.

(E)-Ethyl2-(3-((benzylimino) methyl)-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate **(3a)**

Take ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate (1.0 mole) and phenylmethanamine (1 mole) in methanol. Stir for 1 hrs at room temperature get yellow solid as a product. Filter the solid and wash with methanol and get pure product (E)-ethyl 2-(3-((benzylimino)methyl)-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate Subtracts prepared were determined by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra.

Yield: 90%, mp: 150^{o}C, IR(KBr) ν_{max}: 3415-3205, 3100-3055,3020-2950,1735, 1635, 1595-1585,1425, 925, 725-720 cm^{-1}, ^{1}HNMR(500MHz, DMSO): 1.28-1.31(3H,t), 2.51-2.65(3H,s), 4.24-4.28(2H,s), 4.83(2H,m), 6.91-6.93(2H,m), 7.41(2H,m), 7.87-7.89(2H,m), 8.10-8.12(2H,m), 8.80(1H,s), ^{13}C NMR(125MHz, DMSO): CH_3: 14.06, 17.14, CH_2: 60.77, 60.93, CH: 118.19, 119.81, 127.81, 127.81, 128.62, 128.62, 130.51, 130.90, 160.10, C: 118.36, 122.23, 127.36, 137.92, 161.37, 165.31, 166.13, 168.54, MS: m/z: 380.12 (100.0%), Anal. Calcd. For $C_{21}H_{20}N_2O_3S$ (380.12): C-66.29; H-5.30; N-7.36; O-12.62; S-8.43

(E)-Ethyl 2-(4-hydroxy-3-((3-methylbenzylimino) methyl) phenyl)-4-methylthiazole-5 carboxylate **(3b)**

Take ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate (1.0 mole) and m-tolylmethanamine (1 mole) in methanol. Stir for 1 hrs at room temperature get yellow solid as a product. Filter the solid and wash with methanol and get pure product (E)-ethyl 2-(4-hydroxy-3-((3-methylbenzylimino)methyl)phenyl)-4-methylthiazole-5-carboxylate Subtracts prepared were determined by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra.

Yield: 93%, mp: 132^{o}C, IR (KBr) ν_{max}: 3445-3195, 3065-3005, 2995, 1750-1735, 1700-1635, 1600-1585,, 1465,1430-1425, 930, 725-720 cm^{-1}, ^{1}H NMR(500MHz, DMSO) : 1.28-1.31(3H,t), 2.51-2.65(3H,s), 3.89(3H,s), 4.24-4.28(2H,s), 4.83(2H,m), 7.01-7.05(2H, m), 7.14-7.18(2H, m), 7.21(1H,m), 8.10-8.12(2H,m), 8.80(1H,s), ^{13}C NMR (125MHz, DMSO): CH_3: 14.06, 17.14, 22.0, CH_2: 60.77, 60.93, CH: 118.19, 120.1, 122.0, 128.62, 130.51, 130.70, 130.90, 160.10, C: 118.36, 122.23, 127.36, 136.92, 137.92, 161.37, 165.31, 166.13, 168.54, MS:

m/z: 394.14 (100.0%), Anal. Calcd. For $C_{22}H_{22}N_2O_3S$ (394.14): C-66.98; H-5.62; N-7.10; O-12.17; S-8.13

(E)-Ethyl 2-(4-hydroxy-3-((3-methoxybenzylimino) methyl) phenyl)-4-methylthiazole-5-carbo xylate **(3c)**

Take ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate (1.0 mole) and (3-methoxyphenyl) methanamine (1 mole) in methanol. Stir for 1 hrs at room temperature get yellow solid as a product. Filter the solid and wash with methanol and get pure product (E)-ethyl-2-(4-hydroxy-3-((3-methoxybenzylimino)methyl)phenyl)-4-methylthiazole-5-carboxylate Subtracts prepared were determined by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra.

Yield:82%, mp: 140^{o}C, IR (KBr) ν_{max}: 3445-3195, 3100-2900, 2985-2980,1750-1735, 1700-1635,1600-1585, 1465,1430-1425, 1330, 950, 735-720 cm^{-1}, ^{1}H NMR (500MHz, DMSO): 1.28-1.31(3H,t), 2.51-2.65(3H,s), 3.89(3H,s), 4.24-4.28(2H,s), 4.83(2H,m), 6.91-6.93(2H,m), 7.01-7.05(2H, m), 7.21(1H,m), 8.10-8.12(2H,m), 8.80(1H,s), ^{13}C NMR (125MHz, DMSO): CH_3: 14.06, 17.14, 54.2, CH_2: 60.77, 60.93, CH: 110.9, 112.4, 118.0, 118.19, 128.30, 130.51, 130.90, 160.10, C: 118.36, 122.23, 127.36, 138.92, 160.10, 161.37, 165.31, 166.13, 168.54, MS: m/z: 410.13 (100.0%), Anal. Calcd. For $C_{22}H_{22}N_2O_4S$ (410.13): C- 64.37; H-5.40; N- 6.82; O-15.59; S-7.81

Ethyl 2-(4-benzyl-3-oxo-2, 3, 4, 5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)-4-methylthiazole-5-carboxylate **(6a)**

(E)-Ethyl-2-(3-((benzylimino)-methyl)-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate (4mmol) were dissolved in methanol (20 ml) and then $NaBH_4$ (20 mmol) was added slowly until the evolution of H_2 gases ceases and yellow colour disappears. Ice water was added to the reaction mixture. Get an ethyl 2-(3-((benzylamino) methyl)-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate as Crude product. It was crystallized after preparative TLC (SiO_2/toluene) purification. Chloroacetyl chloride (0.02 mole) was added to a vigorously stirred solution of ethyl 2-(3-((benzylamino) methyl)-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate (0.01 mole) in toluene (15 ml). The reaction mixture was refluxed for 2 hours. The solvent was removed *in vacuo* and the gummy residue was crystallized from dry ethyl alcohol yielding white crystals ethyl 2-(3-((N-benzyl-2-chloroacetamido)methyl)-4-(2-chloroacetoxy)phenyl)-4-methylthiazole-5-carboxylate.Take ethyl 2-(3-((N-benzyl-2-chloroacetamido)methyl)-4-(2-chloroacetoxy)phenyl)-4-methylthiazole-5-carboxylate (0.001 mole) was added to 5% NaOH solution (15 ml) and the mixture was stirred on water bath for 1 hour. The white solid obtained on cooling was filtered, washed with water and crystallized from alcohol to give the compounds ethyl 2-(4-benzyl-3-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)-4-methylthiazole-5-carboxylate.

Yield:90%, mp:185^{o}C, IR (KBr) ν_{max}: 3325-3245, 3100-3050, 1755-1735, 1745, 1715, 1670-1665, 1600-1595, 1275-1270 cm^{-1}, ^{1}H NMR(500MHz, DMSO) : 1.28-1.31(3H,s), 2.51-2.65(3H,d), 4.27-4.28(2H,s), 4.66(2H,s), 4.80(2H,s), 4.97(2H,s), 6.99-7.00(1H,m), 7.25-7.31(5H,m), 7.80(2H,s), ^{13}C NMR(125MHz, DMSO): CH_3: 14.07, 17.12, CH_2: 48.79, 49.93, 61.06, 70.02, CH: 119.58, 125.58, 127.16, 127.63, 127.63, 128.34, 128.34, 128.48, C: 120.49, 124.59, 127.49, 137.29, 158.81, 160.16, 161.36, 168.13, 168.30, MS: m/z: 422.13 (100.0%), Anal. Calcd. For $C_{23}H_{22}N_2O_4S$ (422.13): C- 65.38; H- 5.25; N- 6.63; O- 15.15; S- 7.59

Ethyl 4-methyl-2-(4-(3-methylbenzyl)-3-oxo-2, 3, 4, 5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)thiazole-5-carboxylate **(6b)**

(E)-ethyl2-(4-hydroxy-3-((3-methylbenzylimino)-methyl)-phenyl)-4-methylthiazole-5-carboxylate (4mmol) were dissolved in methanol (20 ml) and then $NaBH_4$ (20 mmol) was added slowly until the evolution of H_2 gases ceases and yellow colour disappears. Ice water was added to the reaction mixture. Get an ethyl 2-(4-hydroxy-3-((3-

methylbenzylamino) methyl) phenyl)-4-methylthiazole-5-carboxylate as Crude product. It was crystallized after preparative TLC (SiO_2/toluene) purification. Chloroacetyl chloride (0.02 mole) was added to a vigorously stirred solution of ethyl 2-(4-hydroxy-3-((3-methylbenzylamino) methyl) phenyl)-4-methylthiazole-5-carboxylate (0.01 mole) in toluene (15 ml). The reaction mixture was refluxed for 2 hours. The solvent was removed *in vacuo* and the gummy residue was crystallized from dry ethyl alcohol yielding white crystals ethyl 2-(3-((2-chloro-N-(3-methylbenzyl) acetamido) methyl)-4-(2-chloroacetoxy) phenyl)-4-methylthiazole-5-carboxylate. Take ethyl 2-(3-((2-chloro-N-(3-methylbenzyl)acetamido)methyl)-4-(2-chloroacetoxy)phenyl)-4-methylthiazole-5-carboxylate (0.001 mole) was added to 5% NaOH solution (15 ml) and the mixture was stirred on water bath for 1 hour. The white solid obtained on cooling was filtered, washed with water and crystallized from alcohol to give the compound ethyl-4-methyl-2-(4-(3-methylbenzyl)-3-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7yl)thiazole-5-carboxylate.

Yield:86%, mp: 200°C, IR(KBr) ν_{max}: 3320-3240, 3100-3045,1750-1730, 1740, 1710, 1670-1665, 1600-1590, 1275-1270, 725-720 cm^{-1}, ^1H NMR(500MHz, DMSO) : 1.28-1.31(3H,s), 2.34 (3H,s), 2.51-2.65(3H,d), 4.27-4.28(2H,s), 4.66(2H,s), 4.80(2H,s), 4.97(2H,s), 6.99-7.00(1H,m), 7.25-7.31(4H,m), 7.80(2H,s), ^{13}C NMR(125MHz, DMSO): CH_3: 14.07, 17.12, 21.6, CH_2: 48.79, 49.93, 61.06, 70.02, CH: 119.58, 125.58, 127.16, 127.63, 127.63, 128.34, 128.48, C: 120.49, 124.59, 127.49, 137.29, 138.5, 158.81, 160.16, 161.36, 168.13, 168.30, MS: m/z: 436.15 (100.0%), Anal. Calcd. For $C_{24}H_{24}N_2O_4S$ (436.15): C-66.03; H-5.54; N-6.42; O-14.66; S-7.35

Ethyl 2-(4-(3-methoxybenzyl)-3-oxo-2, 3, 4, 5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)-4-methyl thiazole-5-carboxylate **(6c)**

(E)-Ethyl 2-(4-hydroxy-3-((3-methoxybenzylimino) methyl) phenyl)-4-methylthiazole-5-carboxylate (4mmol) were dissolved in methanol (20 ml) and then $NaBH_4$ (20 mmol) was added slowly until the evolution of H_2 gases ceases and yellow colour disappears. Ice water was added to the reaction mixture. Get an ethyl 2-(4-hydroxy-3-((3-methoxybenzylamino) methyl) phenyl)-4-methylthiazole-5-carboxylate as Crude product. It was crystallized after preparative TLC (SiO_2/toluene) purification. Chloroacetyl chloride (0.02 mole) was added to a vigorously stirred solution of ethyl 2-(4-hydroxy-3-((3-methoxybenzylamino) methyl) phenyl)-4-methylthiazole-5-carboxylate (0.01 mole) in toluene (15 ml). The reaction mixture was refluxed for 2 hours. The solvent was removed *in vacuo* and the gummy residue was crystallized from dry ethyl alcohol yielding white crystals ethyl 2-(3-((2-chloro-N-(3-methoxybenzyl) acetamido) methyl)-4-(2-chloroacetoxy) phenyl)-4-methylthiazole-5-carboxylate. Take ethyl 2-(3-((2-chloro-N-(3-methoxybenzyl)acetamido)methyl)-4-(2-chloroacetoxy)phenyl)-4-methylthiazole-5-carboxylate (0.001 mole) was added to 5% NaOH solution (15 ml) and the mixture was stirred on water bath for 1 hour. The white solid obtained on cooling was filtered, washed with water and crystallized from alcohol to give the compounds ethyl 2-(4-(3-methoxybenzyl)-3-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)-4-methylthiazole-5-carboxylate**.**

Yield:82%, mp:205°C, IR (KBr) ν_{max}: 3420-3320, 3125-3040,1740-1735, 1755, 1695, 1670-1665, 1600-1590, 1275-1270, 1320-1000, 725-720 cm^{-1}, ^1H NMR (500MHz, DMSO) : 1.28-1.31(3H,s), 3.86 (3H,s), 2.51-2.65(3H,d), 4.27-4.28(2H,s), 4.66(2H,s), 4.80(2H,s), 4.97(2H,s), 6.99-7.00(1H,m), 7.25-7.31(4H,m), 7.80(2H,s), ^{13}C NMR (125MHz, DMSO): CH_3: 14.07, 17.12, 56.2, CH_2: 48.79, 49.93, 61.06, 70.02, CH: 119.58, 125.58, 127.16, 127.63, 127.63, 128.34, 128.48, C: 120.49, 124.59, 127.49, 137.29, 158.81, 160.0, 160.16, 161.36, 168.13, 168.30, MS: m/z: 452.14 (100.0%). Anal. Calcd. For $C_{24}H_{24}N_2O_5S$ (452.14): C-63.70; H-5.35; N-6.19; O-17.68; S-7.09

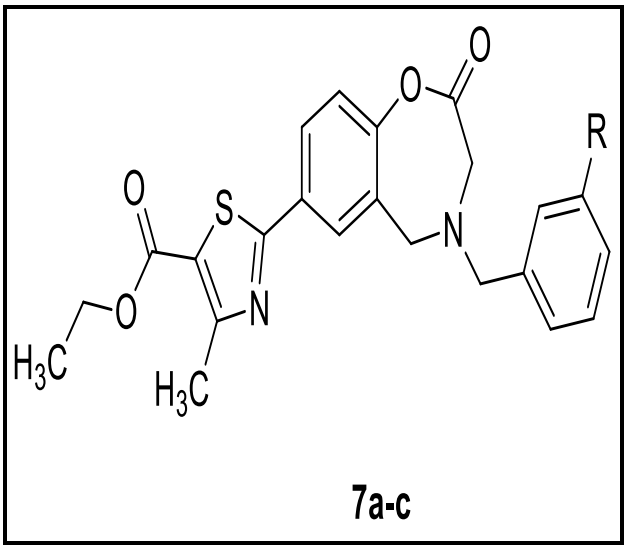
RESULTS AND DISCUSSION

Benzoic Schiff bases **3a-c** were obtained from ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5carboxylate **1** and substituted Benzyl anilines **2** in ethyl alcohol according to the method of Sawich and his coworkers.[26] The synthesized Schiff bases were reduced.[27,28] in a Methyl Alcohol with $NaBH_4$ until no CH=N group was seen in IR spectra at 1625 cm^{-1}. **4a-c** was obtained in good yields. The isolated and purified amines **4a-c** was refluxed in toluene with chloroacetyl chloride to give **5a-c** .^{1}H-NMR spectra of diacetylated products gave three singlets at 5.35, 4.22 and 3.65 ppm. The singlet at 5.35, 4.22 and 3.65 ppm were assigned to (Ar-CH_2-N-Ar), O-acyl (CH_2-Cl) and N-acyl (CH_2-Cl) methylene protons respectively. Since we saw three methylene protons in ^{1}H-NMR we thought that the acetylation occurred on both phenolic oxygen and amines nitrogen atoms.

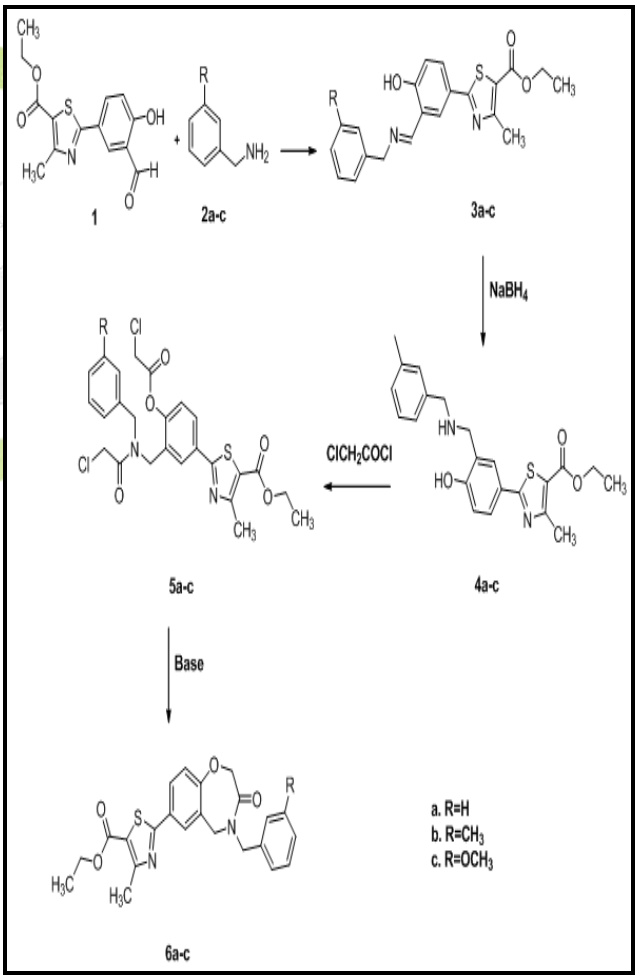
The peaks that were observed in IR at 1804 and 1651 cm^{-1} were due to the absorption of ester and amide carbonyl absorptions, respectively. The diacetyl derivatives structures **5a-c** was confirmed by ^{13}C-NMR spectra. Then we warmed the diacetyl derivatives **5a-c** in 10 % NaOH solution by controlling with IR spectra until the two peaks at 1804 and 1651 cm^{-1} were not observed in IR spectra.

The IR spectra of crude products showed typical peaks at 1656 cm^{-1} for amide carbonyl and at 1242 cm^{-1} for ethers. These peaks confirmed us that Oxazepines rings were formed. The presence of two singlets at 5.24 and 4.83 ppm in ^{1}H-NMR spectra of isolated and purified Oxazepines also confirmed the Oxazepines formation. ^{13}C-NMR spectra of the products also confirmed Oxazepines formation.

After four steps we obtained **6a-c**.In our reaction conditions we isolated only **6a-c**, which were formed from the oxygen attack. The other regioisomer 7**a-c**, which could be formed from the nitrogen attack, was not isolated.



The schematic diagram for Oxazepines synthesize is given in Scheme 1.



Scheme 1: Synthesis of benzoxazepines 6a-c

CONCLUSION

A condensation of aldehyde and different amine to give a Schiff base which is in good yield and then next reduced product and at last final product also give good yield. Products confirmed by ^{1}H NMR and ^{13}C NMR with mass analysis. Also at last step produced regioisomer but not isolated.

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