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Three component one pot synthesis of 1-N, 7-*N*-bisethoxyphthalimido-4-(3,5-dimethyl-4-substitutedphenyl-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e]pyridin-8-yl)-benzothiazole

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Abstract: In the three component one pot synthesis 5-methyl-2,4-dihydro-3H-pyrazole-3-one reacted with substituted aldehydes and 2-Aminobenzothiazole to produce 4-{3,5-dimethyl-4-(substitutedphenyl)-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-*e*]pyridin-8-yl}-benzothiazole (**4a-e).** Condensation of (**4a-e)** with two mole of Bromoethoxyphthalimide in ethanol using NaH as a base give 1-N,7-N-bisethoxyphthalimido-4-(3,5-dimethyl-4-substitutedphenyl-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-*e*]pyridine-8-yl)-aminobenzo thiazole (**5a-e).** Structure of the synthesized compounds was confirmed on the basis of elemental analyses and spectral studies.

Keywords: Substituted aldehydes, Bromoethoxyphthalimide, NaH, Pyrazole, Benzothiazole

Introduction

Heterocyclic compounds are important class of biologically active molecules. Specifically the pyrazole moiety has various biological activities [1] as herbicides, fungicides, analgesics, etc. Many pyrazole derivatives are known to exhibit a wide range of biological properties such as analgesic, antipyretic, anti-inflammatory, antidiabetics[2-4], insecticidal, matricidal and hypoglycemic activities [5-7]. Nasir Hussain [8] has reported medicinal importance of pyrazole derivatives. Many of the work have been directed toward the design and synthesis of fused-pyrazole derivatives [9–14]. Substituted 1,4-dihydropyridines (1,4-DHPs) are well known as Ca^{2+} channel blockers and emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases including hypertension[15].

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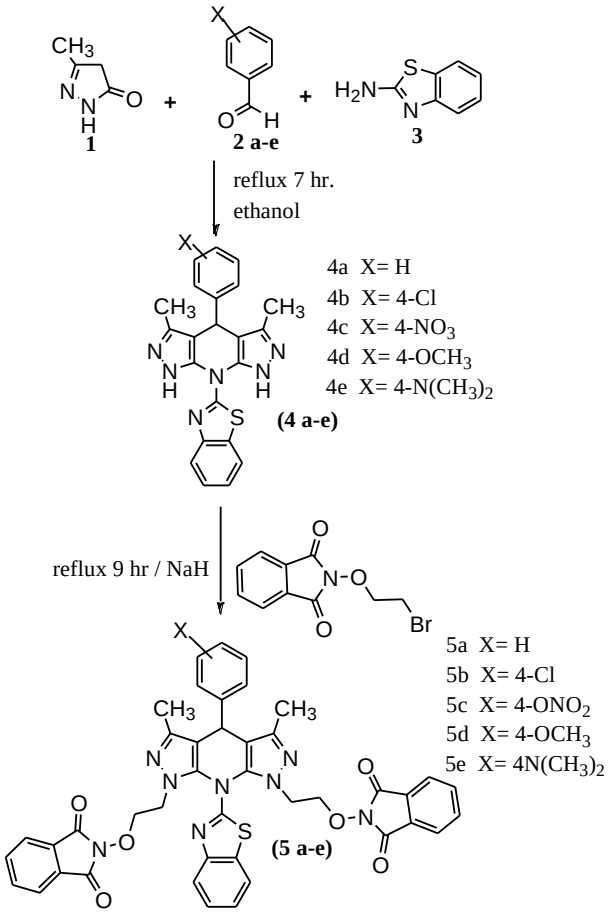
1,4-Dihydropyridines possess a variety of biological activities such as, geroprotective, hepatoprotective and antidiabetic agent[16,17]. Recent studies have revealed that 1,4-DHPs exhibit several medicinal applications which include neuroprotectant [18] and platelet anti-aggregatory activity[19], alzheimer's disease[20] and as chemo-sensitizer in tumor therapy [21-22]. These examples clearly demonstrate the remarkable potential of DHP derivatives as a source of valuable drug candidates. Various combination of heterocyclic rings attached to aminothiazole group have been synthesized [23] and tested for antimicrobial [24] and antimalarial [25] activities.

Result and Discussion

The synthesis of ethoxyphthalimide derivatives of some amino dipyrazolopyridine through a three component one pot synthetic process. 4-{3,5-Dimethyl-4-(substitutedphenyl)-4,7-dihydro-1H-

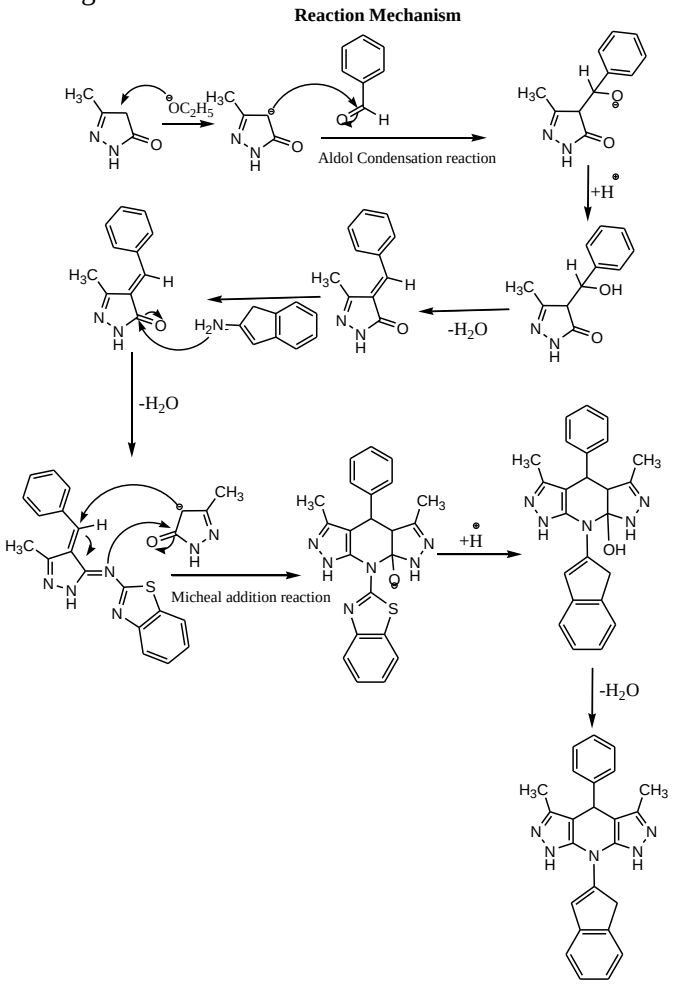
dipyrazolo[3,4-b;4',3'-*e*]pyridin-8-yl}aminothiazole (**4a-e)** were prepared by one pot three components reaction of 5-methyl-2,4-dihydro-3H-pyrazole-3-one, with substituted aldehydes and 1-aminothiazole using ethanol as a solvent.



Scheme 1: Scheme of reaction.

Formation of the product (**4a)** was confirmed by a sharp peak at 3245 cm^{-1} for NH group and get singlet signal of NH group at δ 8.10, disappear of NH_2 group IR. Spectra. Treatment of **(4a-e)** with two mole of Bromoethoxyphthalimide using NaH as a base give 1-N,7-N-bisethoxy phthalimido-4-(3,5-dimethyl-4-substituted phenyl-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e]pyridine-8-yl)-benzothiazole (**5a-e).**

Formation of **(5a)** was confirmed by appearance of two triplets at δ 4.8 (t, O-CH_2), and 3.7 (t, N-CH_2) in the ^{1}HNMR spectra and disappearance of a singlet at 8.10 (NH of pyrazole ring,) indicated that the reaction at the ring NH.



Scheme 2: Mechanism of reaction.

Experimental

Melting points were taken in open capillary tubes and are therefore uncorrected. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using n-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine chamber. The IR spectra were recorded on Perkin-Elmer spectrometer. The ^{1}H NMR spectra were scanned on a Bruker DRX-300 MHz. spectrometer (300 MHz) in (DMSO-d_6) using TMS as internal standard and chemical shifts are expressed in δ ppm. The mass spectra were recorded on a Joel SX-102 (FAB) spectrometer. Phthalimidoxyethyl bromide was synthesized by the reported method[22] and 5-methyl-2,4-dihyro-3H-pyrazol-3-one (**1)** as synthesized by literature method.

Synthesis of 4-{3,5-dimethyl-4-(phenyl)-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e] pyridin-8-yl}-benzothiazole (4a):

A mixture of 5-methyl-2,4-dihydro-3H-pyrazol-3-one (0.02 mol) benzaldehyde, (0.01 mol), p-phenylenediamine (0.01 mol) and C_2H_5ONa (0.02 mol) in ethanol (30 ml) was heated under reflux for 7 hr. The mixture was cooled and the separated solid was filtered, washed with methanol and recrystallized from ethanol m.p. 160 ºC. Similarly, compounds **4b-e** was also synthesized by minor change in reflux times.

IR (KBr, cm^{-1}): 3245 (N-H str.), 3025 (C-H str., Ar-H), 2910, 2850 (CH_3), 1620 (C=N str.), 1220 (C-N); ^{1}H NMR (DMSO-d_6) δ : δ 8.10 (s, NH), 6.80-7.60 (m, 9H, Ar-H), 2.90 (s, CH_3), 5.60 (s, CH); ^{13}CNMR δ :30.8, 92.5, 116.7, 118.6, 121.9, 124.4, 138.8, 139.7, 140.5, 141.5, 152.2, 158.7; $[M]^{+\cdot}$ = 396, m.p. 122º C, Mol. Formula $C_{22}H_{18}N_6S$, Analysis of N % Calc. 21.09, Found 20.72.

4-{3,5-dimethyl-4-(4-chlorophenyl)-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e] pyridin-8-yl}- benzothiazole (4b):

IR (KBr) cm^{-1}: 3252 (N-H str.), 3025 (C-H str., Ar-H), 1630 (C=N str.), 1225 (C-N), 885 (C-Cl); ^{1}H NMR (DMSO-d_6) δ : 8.35 (s, NH), 6.95-8.10 (m, Ar-H, 8H), 3.10 (s, CH_3), 5.68 (s, CH); ^{13}CNMR δ : 38, 108, 116.7, 119.0, 128.4, 131.7, 133.5, 135.7, 137.0, 139.4, 157.6, 163.5; $[M]^{+\cdot}$ =432, m.p. 148 ºC Formula $C_{22}H_{17}ClN_6S$, Analysis of N % Calc. 19.41, Found 21.12.

4-{3,5-dimethyl-4-(4-nitrophenyl)-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e]pyridin-8-yl}- benzothiazole (4c):

IR (KBr) cm^{-1}: 3280 (N-H str.), 3096 (C-H str., Ar-H), 1638 (C=N str.), 1540-1320 (NO_2), 1227 (C-N), ^{1}H NMR (DMSO-d_6) δ : 8.90 (s, NH), 7.22-8.60 (m, , Ar-H), 3.10 (s, CH_3), 5.20 (s, 1H ,CH); ^{13}CNMR δ : 38.8, 111.5, 119.9, 122.5, 130.1, 137.5, 139.9, 142.3, 143.7, 140.2, 149.7, 157.2; $[M]^{+\cdot}$ = 442, m.p. 157ºC Mol. Formula $C_{22}H_{17}N_2O_2$ S Analysis of N % Calc. 22.10, Found 24.01.

4-{3,5-dimethyl-4-(4-methoxyphenyl)-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e] pyridin-8-yl}-benzothiazole (4d):

IR (KBr) cm^{-1}: 3272 (N-H str.), 3092 (C-H str., Ar-H), 1634 (C=N str.), (1228) C-N,(1232) C-O-C; ^{1}H NMR (DMSO-d_6) δ : 8.72 (s, NH), 7.26-8.45 (m, Ar-H), 3.22 (s, CH_3), 5.27 (s, 1H ,CH), 3.42 (O-CH_3); ^{13}CNMR δ : 39.8, 78.2, 113.4, 127.6, 127.8, 133.0, 134.5, 136.8, 139.8, 141.5, 147.4, 158.6, 162.7; $[M]^{+\cdot}$ = 428 m.p. 162 ºC Mol. Formula $C_{23}H_{20}N_6OS$ Analysis of N % Calc. 19.61, Found 21.29.

4-{3,5-dimethyl-4-(4-N,N-Dimethylamino)-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e] pyridin-8-yl}-benzothiazole (4e):

IR (KBr) cm^{-1}: 3265 (N-H str.), 3088 (C-H str., Ar-H), 1617 (C=N str.), 1242 (C-N), ^{1}H NMR (DMSO-d_6) δ: 8.61 (s, NH), 7.32-8.55 (m, Ar-H), 5.42 (s, CH), 4.2 (s, $N(CH_3)_2$), 3.44 (s, CH_3); ^{13}CNMR δ : 12.8, 42.5, 103.5, 115.3, 119.3, 126.4, 130.5, 134.2, 137.6, 137.9, 138.5, 143.5, 155.9; $[M]^{+\cdot}$ = 441, m.p. 174ºC Mol. Formula $C_{24}H_{23}N_7S$ Analysis of N % Calc. 22.21, Found 23.32.

Synthesis of 1-N,7-N-bisethoxyphthalimido-4-{3,5-dimethyl-4-phenyl-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e]pyridin-8-yl}- benzothiazole (5a):

Compound (**4a**, 0.01 mol) was dissolved in ethanol were added phthalimidoxyethylbromide (0.02 mol) and NaH (0.02 mol). The mixture was heated at refluxed for 9 h. It was filtered and poured into crushed ice. The solid thus separated, was filtered, dried and recrystallized from ethanol to yield needle shaped shining white crystals. Other darivative **5(b-e)** were also prepared by similar method.

IR (KBr) cm^{-1}: 1742 (C=O), 1628 (C=N str.), 1238 (C-N), ^{1}H NMR (DMSO-d_6) δ 6.95-7.79 (m, Ar-H), 2.90 (s, CH_3), 5.61 (s, CH), 4.8 (t, O-CH_2), 3.7 (t, N-CH_2); ^{13}CNMR δ : 39.5, 58.2, 71.3, 111.7, 119.7, 122.3, 124.6, 129.5, 131.6, 133.4, 135.6, 136.3, 138.2, 141.9, 146.8, 152.3, 167.7; $[M]^{+\cdot}$ =762, m.p. 192ºC Mol. Formula; $C_{42}H_{34}N_8O_5S$, Analysis of N % Calc. 14.05, Found 15.18.

1-N,7-N-bisethoxyphthalimido-4-{3,5-dimethyl-4-(4-chlorophenyl)-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e]pyridin-8-yl}- benzothiazole (5b):

IR (KBr) cm^{-1}: 1741 (C=O), 1624 (C=N str.), 1239 (C-N), 772 (C-Cl), ^{1}H NMR (DMSO-d_6) δ : 6.99-8.48 (m, Ar-H), 2.96 (s, CH_3), 5.59 (s, CH), 4.9 (t, O-CH_2), 3.8 (t, N-CH_2); ^{13}CNMR δ : 34.5, 48.5, 69.9, 106.4, 119.4, 128.5, 129.5, 131.0, 132.4, 133.6, 135.2, 135.8, 137.7, 138.9, 140.1, 148.0, 157.3, 162.7; m.p. 205 ºC Mol. Formula; $C_{42}H_{33}ClN_8O_5S$, Analysis of N % Calc. 14.05, Found 14.86.

1-N,7-N-bisethoxyphthalimido-4-{3,5-dimethyl-4-(4-nitrophenyl)-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e]pyridin-8-yl}- benzothiazole (5c):

IR (KBr) cm^{-1}: 1749 (C=O), 1629 (C=N str.), 1243 (C-N),1355-1656 (NO_2), ^1H NMR (DMSO-d_6) δ : 7.05-8.55 (m, Ar-H), 3.21 (s, CH_3), 5.39 (s, CH), 4.82 (t, O-CH_2), 4.21 (t, N-CH_2); ^{13}CNMR δ : 34.6, 49.2, 71.3, 106.6, 117.4, 119.0, 124.5, 127.5, 131.5, 132.6, 133.0, 135.4, 137.1, 138.4, 139.6, 148.3, 153.8, 162.9. $[M]^{+\cdot}$ = 807, m.p. 199ºC Mol. Formula; $C_{42}H_{33}N_9O_7S$, Analysis of N% Calc. 16.17, Found 16.28.

1-N,7-N-bisethoxyphthalimido-4-{3,5-dimethyl-4-(4-methoxyphenyl)-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e]pyridin-8-yl}-benzothiazole (5d):

IR (KBr) cm^{-1}: 1755 (C=O), 1629 (C=N str.), 1239 (C-N), ^1H NMR (DMSO-d_6) δ : 6.95-7.98 (m, Ar-H), 3.41 (s, CH_3), 5.39 (s, CH), 4.9 (t, O-CH_2), 3.6 (t, N-CH_2), 3.87 (s, OCH_3). ^{13}CNMR δ : 34.5, 53.4, 58.3, 69.3, 103.5, 117.5, 118.4, 127.3, 128.7, 131.0, 132.5, 134.5, 135.6, 136.7, 137.8, 138.9, 139.0, 157.6, 165.6; $[M]^{+\cdot}$ =792, m.p. 201 ºC Mol. Formula; $C_{43}H_{36}N_8O_6S$, Analysis of N % Calc. 14.13, Found 14.91.

1-N,7-N-bisethoxyphthalimido-4-{3,5-dimethyl-4-(4-N,N-Dimethylaminophenyl)-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e]pyridin-8-yl}-benzothiazole (5e):

IR (KBr) cm^{-1}: 1743 (C=O), 1663 (C=N str.), 1242 (C-N), ^1H NMR (DMSO-d_6) δ : 6.93-8.25 (m, Ar-H), 2.79 (s, CH_3), 5.39 (s, CH), 4.6 (t, O-CH_2), 3.4 (t, N-CH_2), 3.74 (N-CH_3); ^{13}CNMR δ : 34.5, 43.6, 49.6, 71.0, 105.5, 118.5, 119.3, 126.8, 129.4, 133.6, 134.7, 135.4, 136.8, 138.2, 139.6, 144.7, 145.9, 153.0, 162.5; $[M]^{+\cdot}$ = 805, m.p.194 ºC Mol. Formula; $C_{44}H_{39}N_9O_5S$, Analysis of N % Calc. 15.64, Found 16.71.

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