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Research Article

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An efficient One pot Synthesis of 1, 4-Dihydropyridine Derivatives under Solvent free Condition

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ABSTRACT

Synthesis of 1, 4 – Dihydropyridines were accomplished by the condensation of Acetoacetnilide, Aromatic aldehydes and Ammonium acetate in the presence of Bismuth trichloride as catalyst under solvent free condition. Excellent yields (83% to 96%) with less reaction time (15 to 20 min.) and easy workup are the novelty of this reaction. These compounds were colourless, pale yellow and reddish brown crystalline solids. These compounds structures were elucidated with the help of spectral studies -- IR, ^{1}H NMR, ^{13} C NMR, Mass and Elemental analysis.

Keywords: 1,4 – Dihydropyridenes, Acetoacetanilide, Aldehydes, Ammonium acetate, Bismuth trichloride, Solvent free condition.

INTRODUCTION

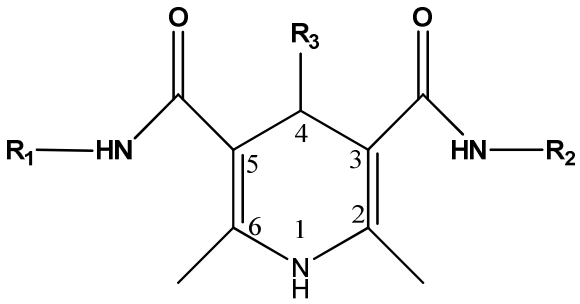
In chemical sciences there emerges a need to carve benign synthetic pathways with high yields which are safe and simple exhibiting high atom efficiency there by abridging the steps with no waste [1]. 1,4 dihydropyridines such as nefedipine and other related compounds are the most important calcium antagonists calcium channel blockers [2] calcium channel modulators [3] and exhibiting attractive pharmacological profiles such as antihypertensive agents alpha-la-antagonists [3a] and neuronpeptide Y(NPY) antagonists [4] and also in the treatment of cardiovascular disorders such as angina and hypertension [5].

Hantzsch reported a process for the synthesis of 1, 4-dihydropyridines (1,4-DHP) [6]. 4 substituted 1, 4-dihydropyridines exhibit a variety of biological activities such as cardiovascular, vasodilator, bronchodilator, antitheroselerotic, antitumor, antidiabatic, hepatoprotective, geroprotective, antituberclosis [7-12]. Dihydropyridine bases drugs such as nifedipine nicoridipine, amlodipine and many others are used in the treatment of hypertension and cerbrocrast. Dihydropyridine derivatives have been used as a Neuroprotective agent [13-14].

Recently microwave heating was widely used for the synthesis of heterocyclic compounds such as 1, 4-dihydropyridine derivatives under solvent free condition shows different biological properties [15, 16].

It is well known in the protocol of green chemistry this main objective of performing reactions under solvent free conditions using heterogeneous catalysts to generate environmentally friendly chemical transformation [17]. In addition it is important to note that an ideal synthesis is considered as one in which a target molecule is produced quantitatively in one step from available and inexpensive raw materials.

4-Aryl 2, 6 dimethyl 1, 4 dihydro pyridine 3, 5 dicarboxylate derivatives are widely used for the treatment of cardiovascular disease (hypertension angina pectoris infraction) [18-19]. 1, 4 dihydro pyridines have different ester groups at 3,5 positions and posses a sterogenic carbon at the 4 position in the 1, 4 DHP nucleus and their enantiomers often shows different biological activity [20].



In addition much attention has been paid to the development of synthesis of mono functional 1,4 DHP'S derivatives and the bi functional 1,4 DHP'S are seldom investigated. It is well established that the calcium antagonistic activity of member family is influenced by the presence of (a)1,4 DHP moiety (b)alkyl groups(preferably methyl groups)attached at C_2,C_6 positions (c)and an aromatic substitute at position at C_4 (d)amide or ester groups at C_3 and C_5 positions (e) an hydrogen atom on N1 [6,21,22]. And also 1,4-dihydropyridine-based calcium channel blockers are oxidatively converted to pyridine derivatives. Then there is biological action of cytochrome P-450 in the liver of human [23,24]. Shasikant et al. reported the synthesis of 1,4-dihydropyridene derivatives and tested for their anti-convulsant activity and found that they are promising anticonvulsant agents [25].

This synthesis promoted us to extend those procedures to the synthesis of compounds containing bi functional compounds of 1, 4 DHP'S. Hence we synthesized 1,4-dihydropyridine derivatives in high yield 90-95% under solvent free condition and it was a neat reaction.

EXPERIMENTAL SECTION

Acetoacetanilide and aldehydes were procured from Aldrich Chemical Co. and were used without further purification. Ammonium acetate, bismuth (III) chloride, ethyl acetate and ether were purchased from Sd. Fine chemicals. Analytical Thin Layer Chromatography (TLC) was performed on Silica Gel 60F 254 plates purchased from Merck. Melting points were determined in open capillary tubes and were uncorrected. The I R spectra were recorded on KBr pellets on a JASCO FT/IR 5300 Spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on an advanced Brucker (BKR at 300MHz) spectrophotometer with TMS as an internal standard using $CDCl_3$ as solvent. The chemical shift values were given δ ppm relative to TMS and compared with literature values. Elemental analysis was done by Flash EA112 Series CHN report Thermo Finigan. Mass Spectra were measured on LCMS/ SMTM at 70 eV.

General procedure for the synthesis of compound 4a

A mixture of 3.54 g (20 m moles) acetoacetanilide, 1.41 g (10 m moles), 4-chlorobenzaldehyde, 1.55 g (15 m moles) ammonium acetate and a minute quantity of bismuth(III)chloride were taken in a 250 ml round bottom flask fitted with condenser with $CaCl_2$ guard tube. The mixture was heated to 60-70^oC while stirring for 15 to 20 min. The progress of the reaction was monitored with TLC using ethyl acetate as an eluent. After the completion of the reaction mixture, the reaction mixture was added with ethyl acetate (10 mi) solution. The organic layer was washed with $NaHCO_3$ and then with brain solution. The organic layer was separated from the solution and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. A pale yellow coloured crystalline solid was formed. The solid was recrystalised from ethyl acetate and ether mixture.

The same procedure was adopted for the remaining compounds **4b** to **4j** by using different aldehydes.

4-(4-chloro phenyl) - 2,6 - dimethyl- N^3,N^5- diphenyl - 1,4- dihydro pyridine - 3,5 dicarboxamide (4a) - pale yellow solid, m.p:171-173^{0}C IR (KBr ν cm^{-1}): 3252(N-H endo), 3136(N-H exo), 3069.2(Ar-H), 1541(C=C), 1660.8 (CO-NH), ^{1}HNMR ($CDCl_3$ TMS): δ 2.324(s 3H), 4.131(s 1H), 8.56(s NH), 9.2(s NH), 7,119-7.302(m 5H), 7.324-7.549(m 4H). ^{13}C NMR ($CDCl_3$-TMS):δ 14.198 (-CH_3),143.9 (C_2&C_6),120.6 (C_3&C_5) ,49.8(C_4), 120.23, 120.66, 120.77 ,124.2, 124.6, 137.4, 129.9, 128.9, 139.2, 171.2. Elemental analysis: $C_{27}H_{24}N_3O_2Cl$: Molecular weight: 457.5. Calculated C: 70.69 H: 5.47 N: 9.79%. Found: C: 70.82 H: 5.25 N: 9.18%. Mass m/z 460.11 (40%), 458.02 (`100%), 456.37 (30%), 365.26(20%), 272.13 (15%), 246.09 (10%), MS-MS of m/z : 458 : 458.24 (40%), 365.11 (100%), 272.13 (20%). MS-MS of m/z : 365 : 365.18 (100%), 272.13 (100%), 246.09 (30%)

4-(4-fluoro phenyl) - 2,6 - dimethyl – N^3, N^5-diphenyl - 1,4 dihydro pyridine - 3,5 dicarboxamide (4b) - pale yellow solid , m.p:170-173^{0}C; IR (KBr ν cm^{-1}) : 3256 (N-H endo), 3136 (N-H exo), 3061 (Ar-H), 1541(C=C), 1660.8 (CO-NH), ^{1}H NMR($CDCl_3$ TMS): δ 2.344 (s 3H), 4.131 (s 1H), 8.60 (s NH), 9.96 (s NH), 7.109-7.302 (m 5H), 7.324-7.549 (m 4H). ^{13}C NMR ($CDCl_3$-TMS): δ 18.54 (-CH_3), 139.286 (C_2&C_6), 120.6 (C_3&C_5), 60.43 (C_4), 120.23, 120.66, 120.77, 124.2, 124.6, 137.4, 137.4, 137.9, 143.9, 166.93. Molecular weight: 441. $C_{27}H_{24}N_3O_2Cl$ Mass m/z 441.19 (10%), 431.19 (100%), 399.17 (25%), 371.82 (10%), 302.27 (15%), 283.67 (0%). MS-MS of m/z 431 : 431.39 (30%), 413.19 (100%), 399.06 (20%), 371.41 (0%), 320.36 (5%), 294.26 (10%), 159.02 (15%).

4-(4-Nitro phenyl) - 2,6 - dimethyl – N^3,N^5 - diphenyl 1,4 dihydro pyridine - 3,5 dicarboxylic acid phenyl amide (4c) - reddish brown solid
m.p:180-182^{0}C; IR (KBr ν cm^{-1}): 3288 (N-H endo), 3137 (N-H exo), 3055 (Ar-H), 1540 (C=C), 1657.8 (CO-NH), ^{1}H NMR($CDCl_3$ TMS):δ 2.342(s 3H), 4.131 (s 1H), 8.97 (s NH), 10.32 (s NH), 7,119-7.302 (m 5H), 7.324-7.549 (m 4H). ^{13}C NMR ($CDCl_3$-TMS):δ 14.2(-CH_3),140.9 (C_2&C_6), , 120.23 (C2&C_3), 46.8 (C_4), 120.23, 120.7, 120.77, 123.2, 124.2, 137.6, 130, 129.9, 139.2, 169.6. Elemental analysis: $C_7H_{24}N_4O_4$: Molecular weight: 468. Calculated C: 69.23, H: 5.13, N: 11.97%. Found: C: 69.12, H: 5.17, N: 11.48%. Mass m/z 468.19, 408.02 (10%), 375.96 (10%) 374.86 (15%), 360.19 (30%), 336.05 (10%), 328.6 (5%), 253.13 (10%), 243.17 (5%). MS-MS of m/z 468 : 467.84 (20%) 420.98 (15%), 374.87 (25%), 328.57 (20%) 236.96 (100%) 235 (90%).

4-(2-Nitro phenyl) - 2,6 - dimethyl –N^3,N^5 – diphenyl - 1,4 dihydro pyridine - 3,5 dicarboxamide (4d) - reddish brown solid, m.p:179-182^{0}C; IR (KBr ν cm^{-1}) : 3288.9 (N-H endo), 3132 (N-H exo), 3055 (Ar-H), 1545 (C=C), 1657 (CO-NH), 1599 (C-NO_2). ^{1}H NMR ($CDCl_3$ TMS):δ 2.342 (s 3H), 4.134 (s 1H), 8.97(s NH), 10.32(s NH), 7.119-7.302 (m 5H), 7.324-7.549 (m 4H). ^{13}C NMR ($CDCl_3$TMS): δ 14.198(-CH_3), 143.9 (C_2&C_6), 123.5 (C_3&C_5), 46.8 (C_4), 123.5, 120.66, 120.77, 124.2, 124.6, 137.4, 129.9, 128.9, 139.2, 171.2. Elemental analysis: $C_{27}H_{24}N_4O_4$: Molecular weight: 468.calculated C: 69.23, H: 5.13, N: 11.97%. Found: C: 69.12, H: 5.17, N: 11.48%. Mass: m/z 468.1, 408.02 (10%), 375.96 (10%) 374.86 (15%), 360.19(30%), 336.05 (10%), 328.6 (5%), 253.13 (10%), 243.17 (5%).MS-MS of m/z 468 :467.84 (20%) 420.98 (15%), 374.87 (25%), 328.57 (20%) 236.96 (100%) 235 (90%).

4-(4-Hydroxy phenyl) - 2,6 – dimethyl – N^3,N^5 – diphenyl - 1,4 dihydro pyridine - 3,5 dicarboxamide (4e) – pale yellow solid, m.p:122-125^{0}C; IR (KBr ν cm^{-1}) : 3271 (N-H endo), 3132 (N-H exo), 3055(Ar-H), 1539 (C=C), 1662 (CO-NH), 3359 (C-OH), ^{1}HNMR ($CDCl_3$ TMS):δ 2.183 (s 3H), 4.083 (s 1H), 9.2 (s NH), 10.12 (s NH), 7.119-7.229 (m 5H) 7.324-7.549 (m 4H). ^{13}C NMR ($CDCl_3$-TMS): δ 14.3(-CH_3), 140.8(C_2&C_6), 119.8(C_3&C_5), 43.2(C_4), 120.23, 120.66, 120.77, 123.2, 124.2, 139.2, 137.5, 129.2, 143.5, 166.9. Elemental analysis: $C_{27}H_{25}N_3O_3$ Molecular weight: 438. Calculated C: 73.95, H: 5.58, N: 9.68%. Found: C: 73.95, H: 5.58, N: 9.61%. Mass: m/z 439.19 (100%), 302.56(10%), 399.65(23%), MS-MS of m/z 439 : 423.32 (100%), 399 (14%), 294(5%), 159 (11%).

4-(2,6-dimethyl-3,5-bis(phenylcarbamoyl)-1,4-dihydropyridin-4-yl)benzoic acid (4f) - pale yellow solid
m.p:138-142^{0}C;IR (KBr ν cm^{-1}): 3256 (N-H endo), 3136 (N-H exo), 3069.2 (Ar-H), 1541 (C=C), 1660.8 (CO-NH), 1722 (CO-OH). ^{1}H NMR ($CDCl_3$ TMS): δ 2.183 (s 3H), 4.134 (s 1H), 8.97 (s NH), 10.32 (s NH), 7.119-7.302 (m 5H), 7.324-7.549 (m 4H). ^{13}C NMR ($CDCl_3$TMS): δ 14.5 (-CH_3), 141.8 (C_2&C_6), 120.23 (C_3&C_5), 60.4(C_4), 128.23, 124.2, 124.77, 124.2, 143.6, 137.4, 129.9, 128.9, 139.2, 171.2, 166.9. Molecular weight 467. $C_{28}H_{25}N_3O_4$ Mass: m/z 466.14 (80%), 472.01 (90%), 467 (30%), 360.03 (100%), 335.96 (10%), 319.13 (10%), 253.13 (30%), 200.01 (15%), 177.94 (80%), 160.11 (30%), 119.99 (20%). MS-MS of m/z 360 : 377.02 (0%), 360.03 (20%), 342.40 (10%), 267.04 (100%), 240.99 (10%), 222.19 (0%), 174.00 (5%).

4-(benzo[d][1,3] dioxol - 5-yl) - 2,6 dimethyl – N^3,N^5 - 1,4 dihydro pyridine - 3,5 dicarboxamide (4g) – pale yellow solid, m.p:170-173^{0}C; IR (KBr ν cm^{-1}): 3254 (N-H endo), 3136 (N-H exo), 3070 (Ar-H), 1541 (C=C), 1662(CO-NH), 1236(C-O-C), ^{1}H NMR($CDCl_3$ TMS): δ 2.324 (s 3H), 4.131 (s 1H), 8.56 (s NH), 9.2 (s NH), 7.119-7.302 (m 5H), 7.324-7.549 (m 4H). ^{13}C NMR($CDCl_3$-TMS): δ 14.198 (-CH_3), 143.9 (C_2&C_6), 120.6 (C_3&C_5), 49.8 (C_4), 120.23, 120.66, 120.77, 124.2, 124.6, 137.4, 129.9, 128.9, 139.2, 171.2. Molecular weight 467 $C_{28}H_{25}N_3O_4$ Mass: m/z 468.01(100%), 467.94(87%), 359.31(26%), 267.14(10%), 204.77(32%), 176.42(11%), 93.93(18%).
MS-MS of m/z 468: 374.85(100%), 467.94(40%), 281.79(20%), 251.96(21%)

2,6-dimethyl-N^3,N^5-diphenyl-4-*p*-tolyl-1,4-dihydropyridine-3,5-dicarboxamide (4h) – pale yellow solid**,** m.p.:135-138^{0}C IR (KBr ν cm^{-1}): 3257 (N-H endo), 3251 (N-H exo), 3036.2 (Ar-H) 1541 (C=C), 1660.8 (CO-NH), 2957 (C-H), ^{1}H NMR($CDCl_3$ TMS): δ 2.342 (s 3H), 3.578 (s 1H), 8.97 (s NH), 10.32 (s NH), 7.119-7.302 (m 5H), 7.324-7.549 (m 4H). ^{13}C NMR($CDCl_3$-TMS): δ 14.4 (-CH_3), 139.2 (C_2&C_6), 120.2 (C_3&C_5), 49.8 (C_4), 129.9, 120.66, 124.77, 124.2, 137.9, 128.9, 125.3, 129.5, 18.544, 166.9. Elemental analysis $C_{28}H_{27}N_3O_2$: Molecular weight: 437. Calculated C: 76.89, H: 6.28, N: 9.61%. Found: C: 76.63, H: 6.18, N: 9.56%. Mass: m/z 437.19 (100%), 399.25(32%), 302.14(12%), MS-MS of m/z 437: 413.11(100%), 399.06(11%), 294.26 (7%), 159 (12%).

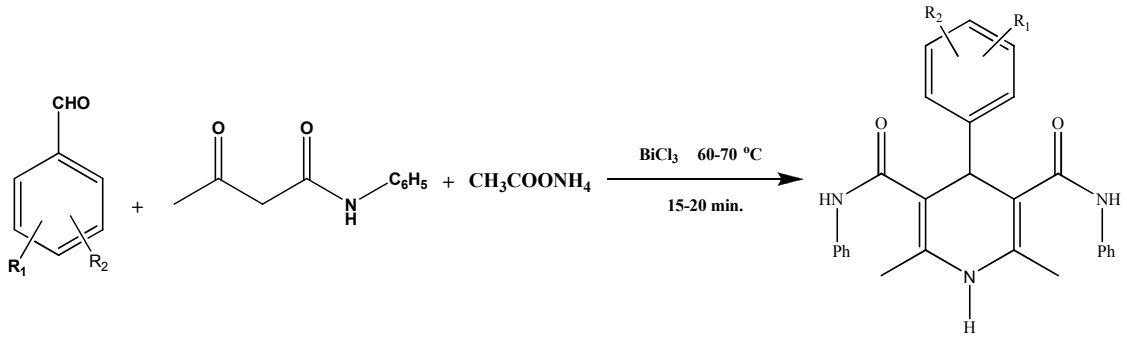
4-(3-hydroxy phenyl) - 2,6 dimethyl – N^3,N^5 – diphenyl - 1,4 dihydro pyridine 3,5 dicarboxamide (4i): pale yellow solid, m.p.:165-167^{0}C IR (KBr ν cm^{-})^1: 3257 (N-H endo), 3152 (N-H exo), 3069.2 (Ar-H), 1539 (C=C), 1660.8 (CO-NH), 3395 (CO-OH), ^{1}HNMR ($CDCl_3$ TMS): δ 2.342(s 3H) 3.578 (s 1H), 8.97 (s NH), 9.96 (s NH), 7.119-7.302 (m 5H). 7.324-7.549 (m 4H). ^{13}C NMR ($CDCl_3$,TMS): δ 14.3 (-CH_3), 140.9(C_2&C_6), 119.8 (C_3&C_5), 43.2 (C_4), 120.21, 120.66, 120.77, 123.2, 124.2, 139.2, 137.5, 129.2, 129.9, 137.9, 163.5. Elemental analysis: $C_{27}H_{25}N_3O_3$ Molecular weight: 439. Calculated C: 73.80, H: 5.72, N: 9.68%. Found: C: 73.95, H: 5.58, N: 9.61%. Mass: m/z: 439.29 (100%), 302.56(10%), 399.65(23%), MS-MS of m/z 439: 423.32 (100%), 399 (14%), 294(5%), 159 (11%).

4-(4-hydroxy 3-methoxy phenyl) - 2,6 dimethyl – N^3, N^5 – dipphenyl - 1,4 dihydro pyridine - 3,5 dicarboxyamide (4j): pale yellow solid, m.p.:169-170^{0}C IR (KBr ν cm^{-1})**:** 3257 (N-H endo), 3137 (N-H exo), 3070 (Ar-H), 1541 (C=C), 1660.8 (CO-NH), 1120(C-O-C). ^{1}HNMR ($CDCl_3$ TMS): δ 2.342 (s 3H), 3.578 (s 1H), 8.97 (s NH), 9.96 (s NH), 7.119-7.302 (m 5H), 7.324-7.549 (m 4H). ^{13}C NMR($CDCl_3$,TMS): δ 14.198 (-CH_3), 143.9 (C_2&C_6), 120.6 (C_3&C_5), 49.8 (C_4), 120.23, 1 20.66, 120.77, 124.2, 124.6, 137.4, 129.9, 128.9, 139.2, 171.2. Elemental analysis: $C_{28}H_{27}N_3O_4$ Molecular weight: 469. Calculated C: 71.64, H: 5.76, N: 8.96%. Found: C: 72.26, H: 5.21, N: 9.15%.

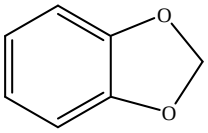
RESULTS AND DISCUSSION

It was assumed to prepare 1,4 Dihydropyridine derivatives with use of $BiCl_3$ as a Lewis acid catalyst, promoter and as non toxic agent for the production of 1,4-dihydropyridines [26,27]. When $BiCl_3$, aldehyde, 1,3 dicarbonyl compound and ammonium acetate were heated to 60-70^{0}C under solvent free condition, DHPs were obtained in excellent yield ranging from 85-95% within 15-20 minutes. 1:2:2 ratio of $BiCl_3$, acetoacetanilide, aldehyde were used and they condensed like Knovengel, Michel condensation reactions [28]. All these compounds were colourless, pale yellow and reddish brown in colour and melting in the range of 122-182 ^{0}C. The reaction scheme is shown in Scheme 1. All these compounds (**4a-j**) are characterised by IR, H^1, ^{13}C NMR, mass spectroscopy and elemental analysis. In IR spectra, the characteristic –NH peak for both endo and exo cyclic groups were observed in the range of 3250 – 3288 cm $^{-1}$ and 3132 – 3198 cm^{-1} respectively [29]. The ^{1}H NMR and ^{13}C NMR spectral data shows the values in the expected ranges as reported. In proton NMR all the peaks were singlets, except aromatic protons which were multiplets. The mass spectral data showed the molecular ions in all these compounds and in most of the compounds it was the base peak indicating the stability of these molecules. In addition MS-MS was recorded for all these compounds and showed the important daughter ions obtained from the molecular ion. Compounds **4a, 4b, 4c, 4d, 4f, 4g, 4i** cleaved at the ester amide group knocking out $PhNH_2$ group in successive manner as indicated by MS-MS.

Scheme 1



4 a-j

Comp. No.	R_1	R_2	Comp. No.	R_1	R_2
4a	4-Cl	H	4f	4-COOH	H
4b	4-F	H	4g		
4c	4-NO_2	H	4h	4-Me	H
4d	2-NO_2	H	4i	3-OH	H
4e	4-OH	H	4j	4-OH	3-OMe

CONCLUSION

In summary, we developed an efficient and simple route to the synthesis of 1, 4-dihydropyridines in presence of Lewis acid (BiCl3) in excellent yields. This reaction is also advantageous due to the small time and easy workup procedure.

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