Synthesis and interpretation of NMR & IR for 1, 4-dihydropyridine Derivatives

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Abstract: *Hantzsch reported the synthesis of functionalized .1,4−dihydropyridines via three component condensation of an aromatic aldehyde, b−ketoester and ammonium hydroxide. This multi-component reaction is of much importance due to excellent pharmacological properties of dihydropyridines. A series of 1, 4 dihydropyridine derivatives were synthesized by Hatnzsch method. All the synthesized compounds were Confirmed by IR, NMR, Mass spectral analysis and elemental analysis. All the compounds were useful for development of large dataset for QSAR study.*

Keywords: *Hantzsch method, dihydropyridine derivatives, one pot synthesis, IR, NMR, Mass Analysis.*

1. INTRODUCTION:

1.4 dihydropyridine are well known as calcium channel blockers and have emerged as one of the important classes of drugs for the treatment of hypertension.1, 4 dihydropyridine plays a significant role in the world of medicine because of the effectiveness as calcium channel blockers[1].
1,4-Dihydropyridine derivatives are of interest because of their biological activity, such as vasodilators, antihypertensive[2], anti-inflammatory, antihypoxic and anti-ischemic agents and calcium channel modulators of the Nifedipine type[3].DHPs are not only important as cardiovascular drugs but also have been extensively used to study the structure and function of voltage-activated calcium channels[4].

The discovery that the 4-aryl-1,4-dihydropyridine (DHP) (Nifedipine, Nimodipine) class of calcium channel blockers (CCBs) inhibits Ca2+ influx represented a major therapeutic advance in treatment of cardiovascular diseases such as hypertension, vasospastic angina, and other spastic smooth muscle disorders[5].
Looking to these multifold properties[6] exhibited by them we are reporting here the synthesis and their Spectral analysis I.e. C_1-C_4 derivatives.

2. EXPERIMENTAL SECTION:

The melting points were determined in open capillary tube and are uncorrected. IR spectra were recorded on a PerkinElmer spectrophotometer using KBr disc.^{1}H NMR ($CDCl_3$) spectra of synthesized compounds were recorded on a Bruker DRX-300 NMR spectrometer (300 MHz) using TMS as internal standard. Mass spectra were recorded on a TOF-MS mass spectrometer .all the compounds gave satisfactory elemental analysis through CARLO-ERBA. All the analytical data showed in Table.

Comp	R	M.P.	Molecular Weight	Molecular Formula	Cal (Found)		
					C	H	N
C_1	NMe_2	227°C	372	$C_{21}H_{28}N_2O_4$	67.72 69.72	7.58 8.02	7.52 8.80
C_2	2'OH	235°C	345	$C_{19}H_{23}NO_5$	69.07 69.31	6.71 5.38	4.02 3.44
C_3	4'Cl	240°C	363	$C_{19}H_{22}ClNO_4$	62.72 67.45	6.09 6.97	3.85 4.2
C_4	4'OCH_3	197°C	359	$C_{20}H_{25}NO_5$	66.83 67.45	7.01 7.64	3.90 3.95

Table-1: Analytical and Physical data of Synthesized Compounds

General procedure for synthesis of substituted 1, 4-dihydropyridines.
The mixture of aryl aldehyde (1mole), β–ketoester (2mole) and ammonium hydroxide (8ml) was refluxed together in ethanol for about 5-18 hours. Then the reaction-mixture was cooled and recrystallized with ethyl alcohol.

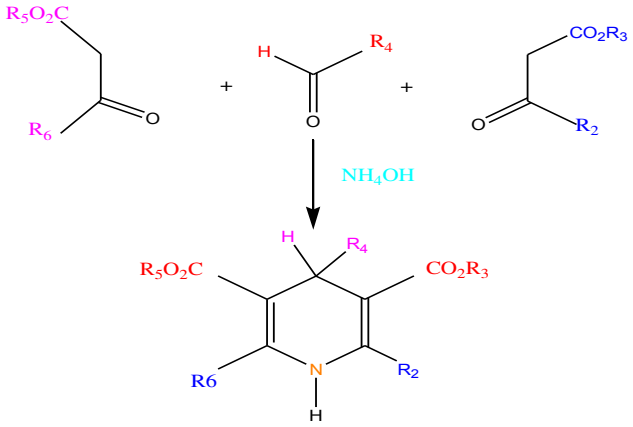

Figure-1

1) Synthesis of 3,5-diethyl-2,6-dimethyl4-(4-dimethylamino)-1,4-dihyropyridine-3,5- dicarboxylate.C_1

For the preparation of 3,5 diethyl 2,6 dimethyl 4(4-dimethylamino) phenyl) 1,4 dihyropyridine 3,5 dicarboxylate we take 7.45 gm of di-amino-Benz aldehyde(1 mole) , 63.22 ml of ethyl aceto-acetate (2 mole) and conc. ammonium hydroxide 9.6 ml with 60 ml ethanol was heated at reflux for 10hrs .The obtained solid was filtered off, washed with warm water and recrystallized using ethyl alcohol.

2) Preparation of 3,5-diethyl-2,6-dimethyl-4-(2-hyroxyphenyl)-1,4-dihyropyridine-3,5-dicarboxylate.C_2

For the synthesis of 3,5-diethyl-2,6-dimethyl-4-(2-hyroxyphenyl)-1,4dihyropyridine-3,5-dicarboxylate10.5ml solution of 2-hydroxy-benzaldehyde, 25.29ml of ethyl aceto-acetate and 3.8 ml of conc. ammonium hydroxide with 24ml ethanol was heated at reflux for 8hours when the solid product crystallized out; it was dried and recrystallized with ethyl alcohol to remove for all impurities.

3) Preparation of 3,5-diethyl-2,6-dimethyl-4-(4-chlorophenyl)-1,4-dihyropyridine-3,5-dicarboxylate. C_3

The synthesis of 3,5-diethyl-2,6-dimethyl-4-(4-chlorophenyl)–1,4dihyropyridine-3,5-dicarboxylate 12.2gm of p-chloro-Benz aldehyde, 25.29ml of ethyl aceto-acetate and 3.8 ml of conc. ammonium hydroxide with 24ml ethanol was heated at reflux for 10hours.solid product recrystallized through ethyl alcohol.

4) Preparation of 3, 5-diethyl-2, 6-dimethyl-4-(4-methoxyphenyl)-1,4-dihyropyridine-3,5-dicarboxylate.C_4

A mixture of p-methyl-Benz aldehyde 12.1ml, ethyl aceto-acetate 25ml and conc. ammonium hydroxide 3.8ml was taken in round bottom flask containing 25ml ethanol. Round bottom flask was fitted with a condenser the mixture was heated for at reflux 5hours. The reaction was cooled the solid product was filtered and washed with 60% aqueous ethanol. When the solid product was completely dried out; recrystallized with ethyl alcohol.

Spectral Data of Compound (C1-C4)

1) 3,5-diethyl-2,6-dimethyl4-(4-dimethylamino)-1,4-dihyropyridine-3,5- dicarboxylate.C_1

IR (KBr, cm–1): 3418.4 (N–H str), 2909.4 (C–H str of CH3), 1667.11 (C=O, ester), 723.7(Ar–H). 1370.5(CH3 group),1H-NMR (300 MHz,CDCl3, δ/ ppm): 7.26 (1H, *s*, NH of pyridinering),6.6-6.7(4H,*m*,Ph-ring), 1.32(6H,t,C3,5-CH2-CH3),2.3(6H,s,C2,6-CH3) ,3.0-3.3 (4H,m,C3,5-CH2-CH3).MS (*m/z* (relative abundance, %):415 (M+, 5.5).

2) 3,5-diethyl-2,6-dimethyl-4-(2-hyroxyphenyl)-1,4-dihyropyridine-3,5-dicarboxylate.C_2

IR (KBr, cm-1):3347.54(N-H str.), 3034.19 (C-H str of CH3), 735.8 (C=O, ester), 756.07 (Ar-H), 1361.7(CH3 group) ^{1}H-NMR (300 MHz, CDCl3, δ/ppm):8.51(1H,*s*,NH of pyridine ring),7.3-7.7(4H, *m*, Ph-ring), 1.01-1.05(6H,t,C3,5-CH2-CH3),2.3(6H,s,C2,6-CH3), 4.0-4.3(4H,m ,C3,5-CH2-CH3).5.0(1H,s,C4-CH) , MS (*m/z* (relative abundance,):556(M+ 2.3).

3) 3,5-diethyl-2,6-dimethyl-4-(4-chlorophenyl)-1,4-dihyropyridine-3,5-dicarboxylate.C3

IR(KBr,cm-1):3354.7(N-H str.),2987.3(C-H str of CH3), 1696.1(C=O,ester),831.57(Ar-H),1387.7(CH3 group),660.0(Cl) : 1H-NMR(300 MHz,CDCl3, δ / ppm): 7.26(1H, *s*, NH of pyridine ring), 7.1-7.2 (4H, *m*, Ph-ring), 1.19-1.31(6H,t,C3,5-CH2-CH3),2.4(6H,s,C2,6-CH3) ,4.01-4.16 (4H,m,C3,5-CH2-CH3).4.9 (1H,s,C4-CH) , MS (*m/z* (relative abundance, %):389.13 (M+, 1.8).

4) 3, 5-diethyl-2, 6-dimethyl-4-(4-methoxyphenyl)-1,4-dihyropyridine-3,5-dicarboxylate.C_4

IR(KBr,cm-1):3341.5(N-H str.),2980.2(C-H str of CH3), 1690.4(C=O, ester),836.5(Ar-H),1377.9(CH3 group), : 1H-NMR(300 MHz,CDCl3, δ / ppm): 7.26(1H, *s*, NH of pyridine ring), 7.18-7.23 (4H, *m*, Ph-ring), 1.20-

1.24(6H,t,C3,5-CH2-CH3),2.3-2.4(6H,s,C2,6-CH3) ,4.03-4.14 (4H,m,C3,5-CH2-CH3).4.92 (1H,s,C4-CH) , MS (*m/z* (relative abundance, %):387.15 (M+, 5.4).

3. CONCLUSION:

Four compounds were screened with spectral analysis. As a result all the new Synthesized having spectral analysis useful for the further study of quantitative structure activity relationship (QSAR) as well as for the development of large datasets published in previous literature[7,8]

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