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An efficient and simple un-catalysed synthesis of 1,4-dihydropyridines in an aqueous media

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ABSTRACT

An efficient, un-catalysed and green method for the synthesis of 1,4-dihydropyridine derivatives in an aqueous media under reflux condition through a three component one pot condensation process of aldehyde, β-dicarbonylcompounds and liquid ammonia has been developed. This procedure offers several advantages including high yields, environmentally benign solvent and simple work up process.

Keywords: Un-catalysed synthesis, 1,4-dihydropyridine, aqueous media, β-dicarbonyl compounds.

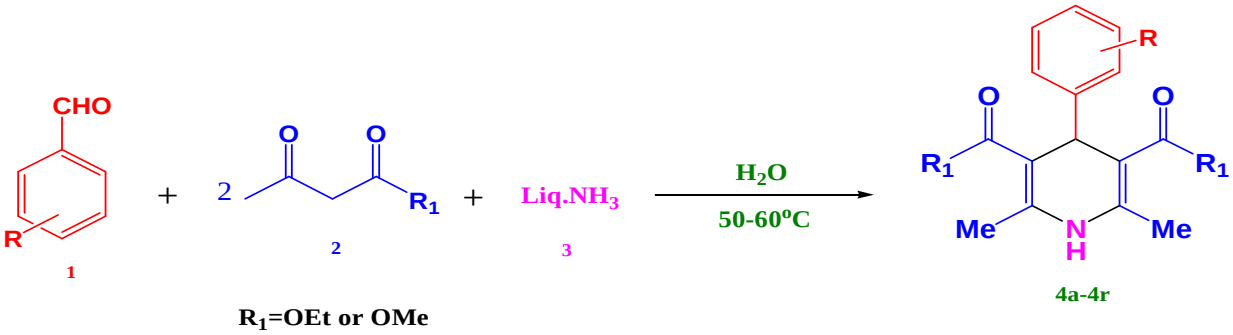
INTRODUCTION

Arthur Hantzsch first reported an efficient way to prepare the 1,4-dihydropyridine in 1882[1]. The 1,4-dihydropyridine exhibits special biological activities in the treatment of cardiovascular diseases as a calcium channel blockers. More than twelve commercial, clinically important drugs such as Amlodipine, Nifedipin, Nimodipin, Felodipine, Isradipine and Nicardipine containing the 1,4-dihydropyridine parent nucleus have been manufactured and used worldwide[2]. This 1,4-dihydropyridine nucleus is a common feature of various bioactive compounds such as vasodialator, branchiodialator, antiatherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agents[3,4]. On the molecular level 1,4-dihydropyridine compounds causes vasorelaxation by blocking voltage-operated calcium channel in smooth muscle cell and also by increasing NO release from intact endothelium[5]. The metabolism of 1,4-dihydropyridine is catalysed by the cytochrome P450(CYP) 3A4 isoform[6,7]. 1,4-dihydropyridine are class of N containing heterocycles having a six membered ring, generated by a complex molecular system via Hantzsch (Multicomponent reaction). Almost all of the new methodologies of organic synthesis, for instance microwave assisted synthesis[8], the promotion of solar thermal energy[9] and ultrasound radiation[10], the replacement of organic solvent by ionic liquids or water[11], the use of various metal halides or triflates as Lewis catalysts[12] have been employed for synthesis of 1,4-dihydropyridines. However most of the research has been focused on the modification and optimization of the Hantzsch reaction to maximise reaction conversion, minimise reaction time and offer high purity of 1,4-dihydropyridine compounds. Most of the existing methods for the synthesis of 1,4-dihydropyridine suffer from drawbacks such as low yield, long reaction time, occurrence of several side products, use of stoichiometric amount of reagents, strong oxidants and the expensive and toxic transition metallic reagents and catalysts.

The avoidance of catalyst and solvent in chemical process or the replacement of the hazardous solvents with more benign solvents have become major concerns in academia and industry, so the need of green reactions are now globally accepted. Therefore, exploring the new un-catalysed system preferably in an environmentally benign method to overcome these drawbacks is a challenging task to the organic chemists. Literature survey reveals that number of 1,4-dihydropyridine derivatives have been synthesized by three component condensation using aldehyde, ethyl aceto acetate and ammonium acetate[13] also catalyst free and solvent free synthesis have been found using

aldehydes, amines, diethyl acetylene dicarboxylate and malononitrile/ethyl cyanoacetate[14]. Recently synthesis of 1,4-dihydropyridine derivatives has been described using as a catalyst clay K-10 [15], Bismuth nitrate[16], Barium nitrate[17].

In view of the above observation and in continution of our work on catalyst free and use of environmental benign solvent as water in multi-component synthesis, here we wish to report an efficient and simple un-catalysed synthesis of 1,4-dihydropyridine derivatives in an aqueous media via one pot three component reaction of aldehydes, β-dicarbonyl compound and liq. ammonia as a source of nitrogen at 50-60^{o}C using green solvent.



R_1=OEt or OMe

Scheme 1

MATERIALS AND METHODS

General procedure for the synthesis of 1,4-dihydropyridine derivatives

A mixture of aldehyde (1 mmol), β-dicarbonylcompounds (2 mmol) was mixed in 10 ml distilled water in 50 ml round bottom flask and refluxed for 10-15 minutes. Then reaction mixture was cooled and liquid NH_3 (3 ml) was added in reaction mixture. Then the reaction mixture was refluxed at 50-60^{o}C until the reaction was completed (as monitored by TLC). After the completion of the reaction, reaction mixture was filtered and washed with distilled water. The obtained crude product was dried and purified by column chromatography over silica gel.
Characterization data of compounds.

dimethyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (4a)

IR (KBr in cm^{-1}) 3358, 3101, 2957, 2872, 1699, 1653, 1491, 1381, 1325, 1100. ^{1}HNMR (300 MHz, $CDCl_3$) δ7.25-7.28 (m, 5H), 5.64 (s, N-H), 5.00 (s, 1H), 3.64 (s, 6H), 2.34 (s, 6H). ^{13}CNMR (300 MHz, $CDCl_3$) δ168.00, 147.35, 144.16, 128.01, 127.60, 126.19, 103.90, 50.97, 39.23, 19.60. MS (EI): m/z 324.

dimethyl 1,4-dihydro-2,6-dimethyl-4-p-methylpyridine-3,5-dicarboxylate(4i)

IR (KBr in cm^{-1}) 3315, 3106, 2943, 1698, 1655, 1497, 1435, 1305, 1122. ^{1}HNMR (300 MHz, $CDCl_3$) δ7.17-7.00 (m, 4H), 5.71 (s, N-H), 4.96 (s, 1H), 3.64 (s, 6H), 2.33-2.27 (s, 9H). ^{13}CNMR (300 MHz, $CDCl_3$) δ168.05, 144.10, 135.64, 128.74, 127.45, 103.96, 50.97, 38.72, 21.03, 19.59.

dimethyl4-(4-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate(4j)

IR (KBr in cm^{-1}) 3317, 3100, 2947, 2842, 1698, 1651, 1487, 1434, 1342, 1122, 848, 839, 745. ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.27-7.19 (m, 4H), 5.72 (s, N-H), 4.97 (s, 1H), 3.65 (s, 6H), 2.34 (s, 6H). ^{13}CNMR (200 MHz, $CDCl_3$) δ 167.83, 145.95, 145.37, 144.34, 131.09, 129.04, 128.09, 103.55, 51.02, 38.87, 19.54. MS (EI): m/z 358.

diethyl4-(2,4-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate(4l)

IR (KBr in cm^{-1}) 3340 , 3095 , 2980 , 1694 , 1682 , 1492 , 1278 , 1302 , 1213 , 1101 , 756. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, 6H, *J* 7.12 Hz), 2.27 (s, 6H), 3.77 (s, 3H), 4.04 (q, 4H, *J* 7.12 Hz), 5.27 (s, 1H), 5.72 (s, NH), 6.77-6.82 (m, 2H), 7.09 (dt, 1H, $J_1$7.74 Hz, $J_2$1.46 Hz), ^{13}C NMR (300 MHz, $CDCl_3$) δ13.30, 18.61, 36.27, 58.84, 102.49, 125.98, 127.85, 131.06, 131.49, 132.14, 143.07, 143.24, 166.41. MS (EI): m/z 396.1.

dimethyl 4-ethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4q)

IR (KBr in cm^{-1}) 3358, 2956, 1699, 1653, 1325, 1140. ^{1}HNMR (300 MHz, $CDCl_3$) δ 5.54 (s, N-H), 3.94-3.88 (t, 1H), 3.73 (s, 6H), 2.34 (s, 6H), 1.44-1.30 (p, 2H), 0.79-0.72 (t, 3H). ^{13}CNMR (300 MHz, $CDCl_3$) δ145.08, 109.46, 50.91, 33.97, 29.20, 19.42, 9.00.MS (EI): m/z 276.

dimethyl4-(4-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate(4r)
IR (KBr in cm^{-1}) 3351, 3248, 3102, 3002, 2950, 2843, 1698, 1654, 1503, 1443, 1304, 1121, 1096, 850, 800 . ^{1}HNMR (200 MHz, $CDCl_3$) : δ 7.26-7.21 (m, 2H), 6.93-6.84 (m 2H), 5.68 (s, N-H), 4.97 (s, 1H), 3.65 (s, 6H), 2.34 (s, 6H). ^{13}CNMR (300 MHz, $CDCl_3$) : 167.92, 144.15, 144.89, 144.46, 129.16, 129.00, 126.19, 103.87, 51.68, 38.68, 19.56.MS (EI): m/z 341.

RESULTS AND DISCUSSION

As part of our efforts towards green synthesis a catalyst- free and use of water as a green solvent in multicomponent synthesis, we have developed an efficient, simple one pot synthesis of 1,4-dihydropyridines derivatives using aldehydes, β-dicarbonyl compound and liq. ammonia in an aqueous media under catalyst free condition at reflux condition.

For our initial studies the effect of solvent on the reaction were examine under catalyst free condition at reflux condition with different reaction times. Selecting the reaction of 4-nitrobenzaldehyde, ethyl acetoacetate and liq. NH_3 in excess as representative reactants we compare the reaction rate in different solvents by measuring the isolated yields using identical amount of reactants. in various solvents **Table 1**. The desired product was obtained with low yield **(Entry 1,2,4)** by prolonging reaction time, when same reaction was studied under solvent free conditions the corresponding product was obtained 2.5 hr with 74% **(Entry 3)** yield of the product. Comparatively higher yields were obtained with short duration of reaction time **(Entry 5,6,7)**. Due to numerous advantages like cheapest, easily available and non-hazardous nature of solvent and as an excellent yield (98%) was obtained with short duration of reaction time **(Entry 7)** we selected water as a choice of solvent as excellent results were obtained with water.

Table 1 Synthesis of compound 4c in different solvents at 50-60^{o}C under reflux condition[a]

Entry	Solvent used	Time(hr)	Yield(%)[a]
1	Dimethylformamide	7	70
2	Chloroform	5	78
3	Solventless	2.5	74
4	Tetrahydrofuran	5	75
5	Acetonitrile	3	90
6	Ethanol	4	92
7	Water	1	98

Aldehyde(1mmol), Ethylacetoacetate (2mmol), Liq: Ammonia (3ml), Isolated Yield[a].

Table 2 : Un-catalysed synthesis of 1,4-dihydropyridine compounds in an aqueous media.

Entry	R	R_1	Product	Time in hr	Yield(%)[c]
1	C_6H_5	OCH_3	4a	4	98
2	4-OH-C_6H_4	OC_2H_5	4b	2	96
3	4-NO_2-C_6H_4	OC_2H_5	4c	2	98
4	3-NO_2-C_6H_4	OC_2H_5	4d	4	94
5	3,4-OCH_3-C_6H_3	OCH_3	4e	5	96
6	4-OH-C_6H_4	OCH_3	4f	3	97
7	C_6H_{13}	OCH_3	4g	7	96
8	3-OCH_3-4-OH-C_6H_3	OCH_3	4h	4	95
9	4-CH_3-C_6H_4	OCH_3	4i	4	96
10	4-Cl-C_6H_4	OCH_3	4j	2	98
11	2-OCH_3-C_6H_4	OC_2H_5	4k	4	95
12	2,4-Cl-C_6H_4	OC_2H_5	4l	3	96
13	3-Cl-C_6H_4	OC_2H_5	4m	4	94
14	3-OCH_3-4-OH-C_6H_3	OC_2H_5	4n	3	97
15	4-Br-C_6H_4	OC_2H_5	4o	2	98
16	4-C_2H_5-C_6H_4	OC_2H_5	4p	5	94
17	C_2H_5	OCH_3	4q	6	96
18	4-F-C_6H_4	OCH_3	4r	3	98

[c]All yields refer to isolated yields. All the products were characterized by IR spectra, mass spectra, 1H NMR spectroscopy.

However when reaction conditions were varied using microwave irradiation up to 3 minutes the reaction did not afford the desired product in high yield (67%) and frequent addition of source of nitrogen containing agent i.e. liq. ammonia was required. When the reaction was carried at grinding upto 3 hrs low yield were obtained (73%). Finally the excellent yield (98%) of the desired product was obtained with short reaction time at reflux condition(50-60^{o}C) for same representative reaction.

With the optimised condition established above, under reflux condition a wide range of aromatic aldehydes were tested for the synthesis of 1,4-dihydropyridine derivatives using water as a solvent under catalyst-free conditions. The results have been summarized in **Table 2**. The aldehydes with electron donating substituents **(4b,4c,4j,4o,4r)** produce excellent yield 95-98%. The aldehydes with electron realeasing sustituents **(4i, 4p)** produce good yields 94-96%. These suggest that method is suitable for synthesis of large varity of 1,4-dihydropyridine derivatives. Intrestingly when the representative reaction of an aliphatic aldehyde **(4g, 4q)** such as propanal, methylaceoacetate and liq: ammonia in an aqueous media at reflux condition was studied. The reaction was completed in 06 hr producing 96% yield. This general protocol gives satisfactory results when methyl acetoactetate is used as dicarbonyl compounds for various aldehydes. Thus we have developed a simple, efficient, general, un-catalysed protocol for the synthesis of 1,4-dihydropyridine derivatives using water as a green solvent under reflux condition.

CONCLUSION

In conclusion, we have developed a novel, efficient and environmentally benign one pot conversion of three components aldehyde, β-dicarbonylcompounds and liquid ammonia into corresponding 1,4-dihydropyridine derivatives in an aqueous media at reflux condition. Additionally the reaction was efficeint for aromatic as well as aliphatic aldehydes. Excellent yields were obtained for aromatic aldehydes substituted with electron donating and electron withdrawing groups. This general protocol for the synthesis of 1,4-dihydropyridine derivatives will receive considerable attention as it is catalyst free synthesis in an aqueous media producing excellent yields.

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