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Sodium Perchlorate Catalysed Synthesis Of Hantzsch 1,4-Dihydropyridine Derivatives Under Mild Conditions

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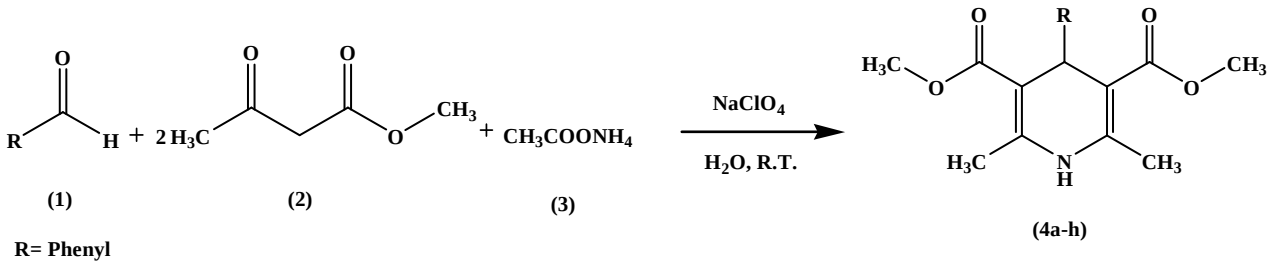
Abstract: Sodium perchlorate catalysed synthesis of Hantzsch 1,4-dihydropyridine derivatives using aldehydes, methyl acetoacetate and ammonium acetate in an aqueous media at room temperature is described. This method offers several advantages including high yields, an environmentally friendly procedure, mild reaction conditions and economic viability.



Keywords : 1,4-dihydropyridines, sodium perchlorate, methyl acetoacetate, ammonium acetate.

Introduction

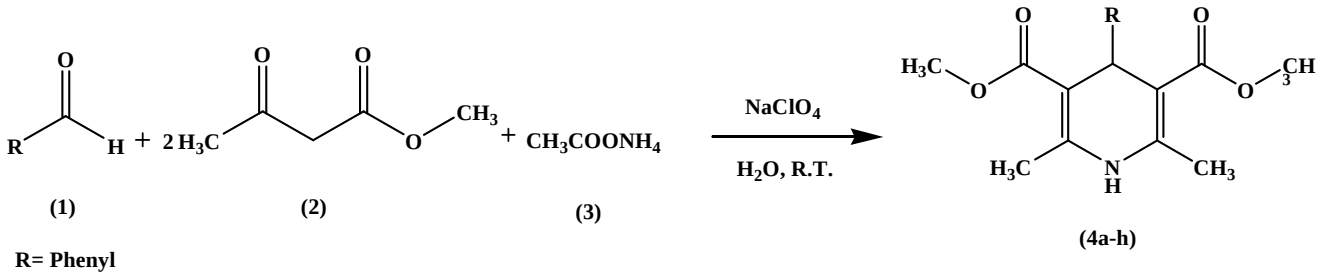
The pyridine moiety has been found in a wide variety of both naturally occurring and synthetic bioactive compounds. 1,4-Dihydropyridines (1,4-DHPs) are important class of compounds in the field of drugs and pharmaceuticals.Hantzsch 1,4-dihydropyridines (dialkyl1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates) are widely used clinically as calcium channel blockers for the treatment of cardiovascular diseases, including hypertension[1,2]. 1,4-Dihydropyridines possess a wide range of biological activities, being vasodilators, bronchodilators, geroprotectives, hepatoprotectives, antitumor, antiatherosclerotic and antidiabetic agents[3a-e]. The simple and direct method for the synthesis of 1,4-Dihydropyridines was first reported by Hantzsch and involved the one pot condensation of an aldehyde with ethyl acetoacetate and ammonium acetate[4]. In recent years, there are several modifications of the Hantzsch synthesis of 1,4-Dihydropyridines derivatives, including the use of microwaves[5], ionic liquids[6], TMSCl-NaI[7], metal triflates[8], molecular iodine[9], SiO_2-$NaHSO_4$[10], SiO_2-$HClO_4$[11], CAN[12], Phenyl boronic acid[13], TsOH-sodium dodecyl sulfate[14], and organocatalysts[15].

The number of synthetic protocols for synthesis of 1,4-dihydropyridines are available in the literature using ammonia[16], urea-silica gel[17], refluxing ammonium hydroxide in a closed vessel microwave synthesizer[18],

ammonium hydroxide in ethanol[19], 2,4,6-trichloro-1,3,5-triazine[20], magnesium nitride[21] in water at an elevated temperature in a sealed vessel using stoichiometric excess of organic reactants, and many others. Recently, solvent free synthesis[22] and catalyst free synthesis of 1,4-dihydropyridines have been reported by using liquid ammonia[23] and ammonium acetate[24].

However, many of these methods have some drawbacks such as low yields, high temperature, long reaction time, occurrence of side products and relatively expensive catalysts and solvents. Therefore, the search continues for better catalyst and solvent for the synthesis of 1,4-DHPs derivatives in terms of operation simplicity and economic viability. In continuation of our work on use of water as environmental benign solvent in multi-component synthesis, here we wish to report synthesis of 1,4-dihydropyridine derivatives via sodium perchlorate catalyzed reaction of aldehydes, methyl acetoacetate and ammonium acetate in water (Scheme 1).

General scheme



(1) (2) (3) (4a-h)

R= Phenyl

Scheme 1

Experimental

The melting points were recorded on Programmable Melting Apparatus (VEEGO) and are reported uncorrected. The IR spectra were recorded in KBr on a Shimadzu 8201pc FTIR spectrometer (4000–400 cm^{-1}). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DRX-300 MHz instrument. The mass spectra (EI) were obtained on a Jeol JMS D-300 spectrometer operating at 70eV. Solvents used are double distilled.

General procedure for the synthesis of 1,4-DHP's

To a mixture of aldehyde (1.0 mmol), methylacetoacetate (2.0 mmol) and ammonium acetate (1.5 mmol) in water (2 ml), sodium perchlorate (10 % mmol) was added in a 50 ml flask. The reaction mixture was magnetically stirred at room temperature for required time (Table 1) till the completion of the reaction (monitored by TLC). After completion of the reaction, the product was filtered to separate crude product form the mixture. Further the product was purified by using column chromatography over silica gel (9:1, Hexane : Ethyl acetate as eluent) wherever needed. The authenticity of the known products was established by comparing their melting points and spectral data with the literature.

Spectral data of some compounds

2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dimethylcarboxylate (Table 1, Entry a):

IR (cm^{-1}) : 3358 , 3101, 2958-2872, 1699, 1653, 1491-1381, 1325-1100 ;
^{1}HNMR (δ) : 7.25-7.18 (m,5H), 5.64 (s, N-H), 5.00 (s, 1H), 3.64 (s,6H), 2.34 (s, 6H) ;
^{13}CNMR(δ) : 168.00, 147.35, 144.16, 128.01, 127.60, 126.19, 103.90, 50.97, 39.23, 19.60 ;
Mass (m/z) $[M+Na]^{+}$: 301 + 23 = 324.

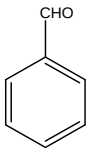
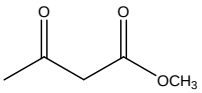
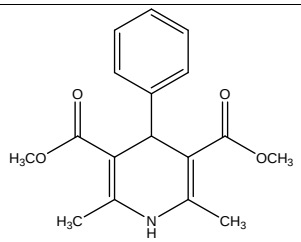
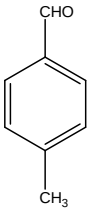
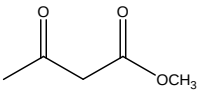
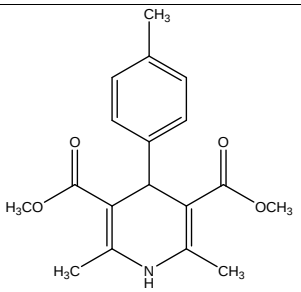
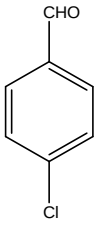
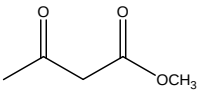
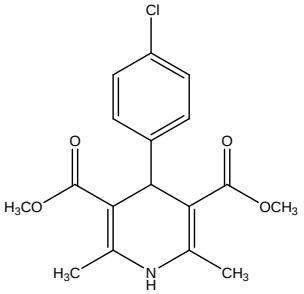
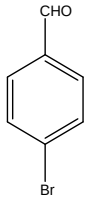
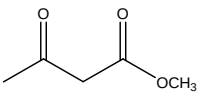
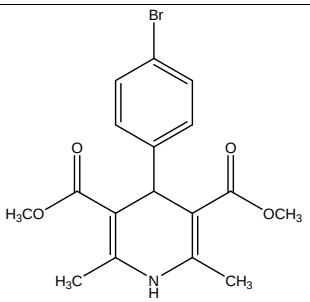
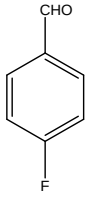
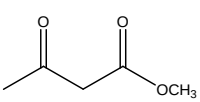
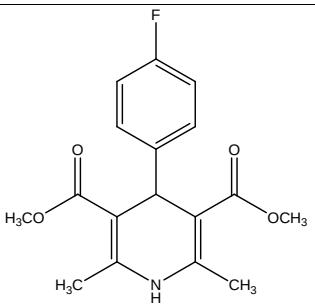
2,6-Dimethyl-4-p-chlorophenyl-1,4-dihydropyridine-3,5-dimethylcarboxylate(Table 1,Entry c):

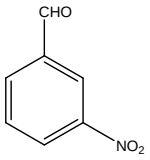
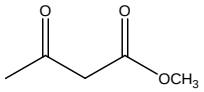
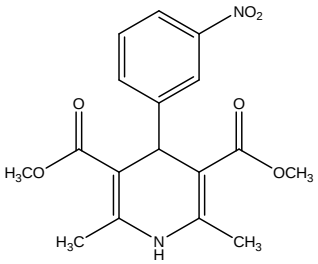
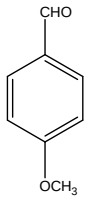
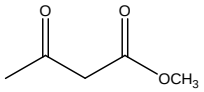
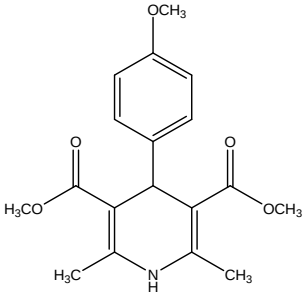
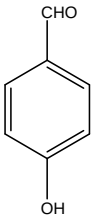
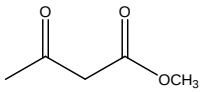
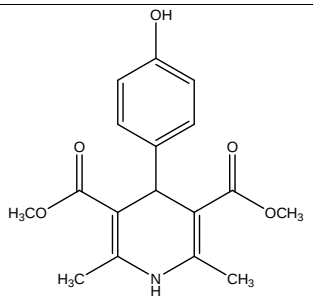
IR (cm^{-1}) : 3317, 3100, 2947-2842, 1698, 1651, 1487-1434, 1342-1122, 848-817, 745-507;
^{1}HNMR (δ): 7.27-7.19 (m,4H), 5.72, (s, N-H), 4.97 (s, 1H), 3.65 (s,6H), 2.34 (s, 6H)
^{13}CNMR (δ): 167.83, 145.95, 144.34, 131.76, 129.04, 128.09, 103.55, 50.02, 38.87, 19.54
Mass (m/z): $[M+Na]^{+}$: 335 + 23 = 358.

2,6-Dimethyl-4-p-fluorophenyl-1,4-dihydropyridine-3,5-dimethylcarboxylate(Table1,Entry e):

IR (cm^{-1}) : 3351-3248, 3102-3002, 2950-2843, 1698, 1654-1600, 1503-1443, 1304-1121, 1096-1019, 850-800 ;
^{1}HNMR (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 (δ): 167.92, 144.15, 129.16, 129.00, 144.89, 144.46, 103.87, 51.00, 38.68, 19.56 ;
Mass (m/z): $[M+Na]^{+}$: 318 + 23 = 341.

Table 1: Synthesis of 1,4-dihydropyridine derivatives using $NaClO_4$.

Entry	Aldehydes	β-dicarbonyl compounds	Product	Rea. Time (h)	Yields (%)[a]	M.P. (^{o}C)
a				3	89	155-157
b				3.5	92	121-122
c				3	91	155-160
d				3.5	90	141-142
e				2.5	83	135-138

f				2	93	169-171
g				5	87	124-125
h				5.5	85	185-186

a – Yields are isolated.

Result and discussion

In this article, we have described a new approach for the synthesis of 1,4-DHPs (4a-h) from aldehydes, methylacetoacetate and ammonium acetate using sodium perchlorate catalyst in aqueous media at room temperature (Scheme 1). Various aromatic aldehydes were investigated to explore the wide applicability of this method using water as a solvent at room temperature to produce corresponding 1,4-dihydropyridine derivatives in good to excellent yields. The reaction of various aldehydes with methyl acetoacetate and ammonium acetate in presence of $NaClO_4$ in water at room temperature were investigated and results are shown in Table 1. To explain the scope and limitations of this reaction, it has been extended to various aryl aldehydes with electron releasing or electron withdrawing substituent's and found to be proceeded very efficiently in all cases. Aromatic aldehydes with electron-withdrawing groups -Cl, -Br, $-NO_2$ (Table 1, entries c, d & f) offered high yields where as in case of aromatic aldehydes containing electron-donating groups $-CH_3$, $-OCH_3$ (Table 1, entries b & g) gives satisfactory results with good yields.

Conclusion

In conclusion, we have developed new alternative for synthesis of 1,4-dihydropyridine derivatives in an aqueous media using sodium perchlorate as a catalyst. This method offers several advantages such as mild conditions, high yields, simple work-up procedure and economic viability.

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