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SYNTHESIS OF POLYHYDROQUINOLINES USING PHENYL PHOSPHONIC ACID AS CATALYST

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ABSTRACT

A facile and efficient method has been developed for the one pot synthesis of polyhydroquinolines *via* four component reaction of ethyl acetoacetate, aldehyde, dimedone and ammonium acetate in the presence of catalytic amount of phenyl phosphonic acid in ethanol through Hantzsch reaction. The method described herein is simple, environmentally benign and provides good yields of the products.

KEYWORDS: Polyhydroquinolines, phenyl phosphonic acid, ethyl acetoacetate, aldehyde, dimedone.

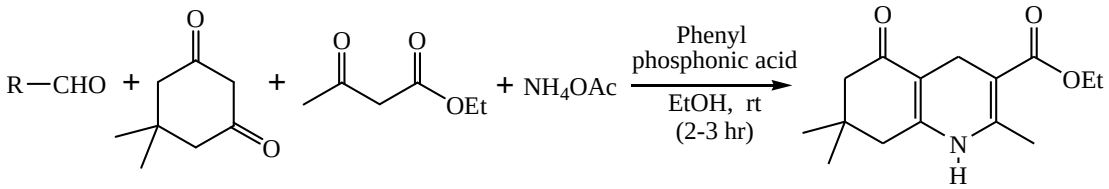
INTRODUCTION

1,4–Dihydropyridines (DHPs) are important class of nitrogen containing compounds which received much attention due to their wide range of pharmaceutical and biological properties.[1] They are found in biologically active products such as vasodilator, bronchodilator, antitumor, hepatoprotective, geroprotective, anti-atherosclerotic and antidiabetic agents.[2] 1,4-DHP compounds have their important role in medicinal chemistry as calcium channel blockers as exemplified by therapeutic agents such as nifedine, nitrchdipine, amlodipine, felodipine and nicardipine which are the important drugs used in cardiovascular disease.[3] Recent studies have revealed that 1,4-DHPs exhibit several medicinal applications which include neuroprotectant[4] and plate anti aggregatery activity.[5] Also they have been reported for their applications in treatment of Alzheimet disease due to their cerebral antischematic activity and chemo-sensitizer in tumor-therapy.[6] These properties and applications clearly show the potential of 1,4-DHPs as valuable drug candidates.

In 1882, Arthur Hantzsch reported first synthesis of substituted 1,4-dihydropyridine by one pot condensation of ethyl acetoacetate, aromatic aldehyde, dimedone and ammonia. The reaction was conducted in acetic acid or at reflux in ethanol for long periods resulting in low to moderate yield of products.

Owing to the wide range of biological and medicinal applications, the synthesis of such compounds has created much attention in recent years. Many synthetic methods have been reported for the preparation of polyhydroquinoline derivatives. Some of the techniques, catalysts and reagents such as Microwave[7], Solid phase organic synthesis technique[8], Molecular iodine[9], TMSCl[10], $HClO_4$-SiO_2[11], Ceric (IV) ammonium nitrate[12], L- Proline[13], Without catalyst[14], Ionic liquids[15], Polymers[16], Alumina sulphuric acid[17], $ZrCl_4$[18], Iron (III) trifluoroacetate[19], Heteropoly acids[20], *p*-Toluene sulphonic acid[21], Organo catalyst[22], 3-Nitrophenyl boronic acid[23], Copper perchlorate hexahydrate[24], Metal triflates[25], Nafion-H[26], Aluminum phosphate $[AlPO_4(H)]$[27], Palladium (0) nanoparticles[28], ZnO-beta zeolite[29], Hg- II Complex[30], Cu –II Comples[31], MNPs –TBSA[32], Nicotinic acid[33], have been used for the synthesis of polyhydroquinolines Each of these above methods have their own merits while some of the methods suffer from long reaction times, low yields, harsh reaction conditions, tedious work ups, etc. For these reasons, efforts have been made to replace such conventional catalysts by other catalysts. The research activities and industrial sections now a days require development of catalysts[34] and the eco-friendly catalytic synthesis which offer strong potential for fast application in industries.[35]

We herein report phenyl phosphonic acid as an efficient Bronsted acid catalyst for the synthesis of polyhydroquinolines V in the condensation reaction of *β*-keto ester III, ammonium acetate IV, dimedone II and various aromatic aldehydes I in ethanol at room temperature (Scheme 1).



I **II** **III** **IV** **V**

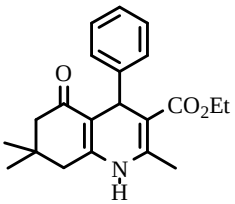
Scheme 1.

Experimental procedure

A mixture of dimedone (1 mmol), aromatic aldehyde (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1 mmol) and phenyl phosphonic acid (30 mg) was stirred in ethanol (3 mL) for 2-3 hours at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was poured into ice cold water and stirred for about 10 -15 minutes. The product was then filtered, dried and recrystallized from ethanol to get pure polyhydroquinoline derivatives.

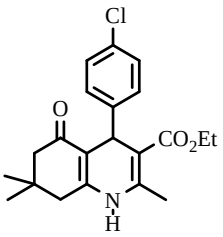
Spectral analysis

The products obtained were characterized by their IR, ^{1}H NMR and Mass spectra. The analysis of some of the representative compounds is given below.



Ethyl-1, 4, 7, 8-tetrahydro-2, 7,7-trimethyl-4(phenyl)-5-(6H)-oxoquinolin-3-carboxylate

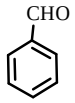
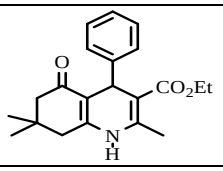
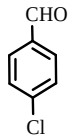
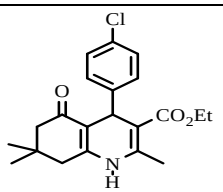
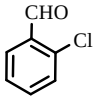
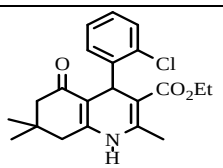
IR (cm^{-1}) : 3286(-NH-), 1697(C=O), 1608 (C=O)
^{1}H NMR (δ) :0.98(s,3H,CH_3), 1.05(s,3H,CH_3), 1.15(t,3H,CH_3), 2.13-2.36(m,4H,2x CH_2), 2.4(s,3H,CH_3), 7.1-7.4(m, 5H,Ar-H)
Mass : 328 (M+)

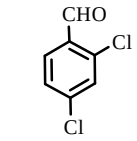
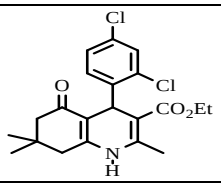
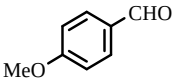
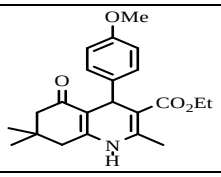
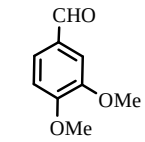
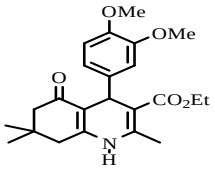
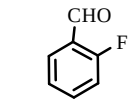
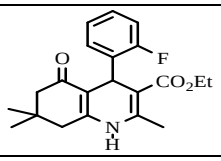


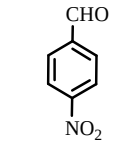
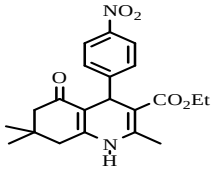
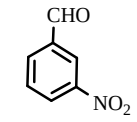
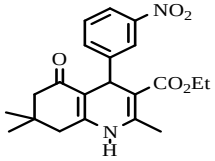
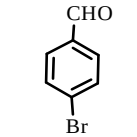
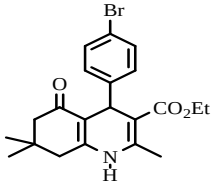
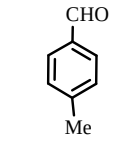
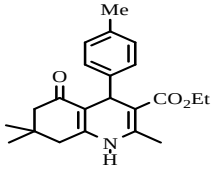
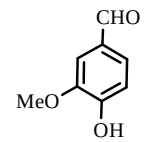
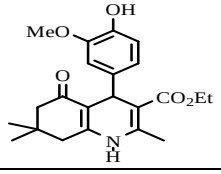
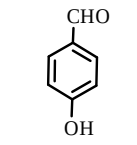
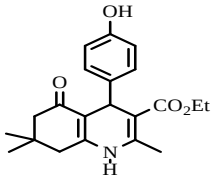
Ethyl-1, 4, 7, 8-tetrahydro-2, 7,7-trimethyl-4(4-chlorophenyl)-5-(6H)-oxoquinolin-3-carboxylate

IR (cm^{-1}): 3276(-NH-), 1705(C = O), 1605 (C = O)
^{1}H NMR (δ): 0.92(s,3H,CH_3), 1.07(s,3H,CH_3), 1.15(t,3H,CH_3),2.13-2.35(m,4H,2xCH_2),2.38(s,3H,CH_3), 4.05(q,2H,CH_2),5.02(s,1H,CH), 5.5(s,1H,NH), 7.12-7.28(m,4H,Ar-H)
Mass **:** 363 (M+)

Table 1: Synthesis of polyhydroquinoline derivatives using phenyl phosphonic acid.

Entry	Aldehyde	Product	Time (hrs)	Yield (%)	M.P.(°C) [Observed]	M.P.(°C) [Reported]
1			3	92	203-205	202-204 [13]
2			2.5	92	230-232	232-234 [13]
3			2	89	207-208	208-210 [15a]

4			3	90	242-243	241-243 [25b]
5			3	91	260-262	-
6			3	90	288-290	-
7			3	93	108-110	-

Entry	Aldehyde	Product	Time (hrs)	Yield (%)	M.P. (°C) [Observed]	M.P. (°C) [Reported]
8			2.5	92	240-242	241-243 [13]
9			3	90	182-184	-
10			2.5	92	252-253	253-255 [25b]
11			2.5	91	265-266	-
12			2	89	200-202	-
13			2	90	232-234	233-234 [13]

RESULTS AND DISCUSSION

The studies of facile four-component Hantzsch condensation reactions in presence of phenyl phosphonic acid catalyst at room temperature were explored. The results are summarized in Table 1. The condensation of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate was found to be effective within 2-3 hours in ethanol to produce the corresponding pharmacologically useful polyhydroquinoline derivatives in good yields. Various aromatic aldehydes having electron-donating and electro-withdrawing substituent underwent the smooth reaction. It is noteworthy that the structural variation of the aldehydes and substituent on the aromatic ring did not show any effect on the conversion, as the products were obtained in good yields in short reaction times at mild reaction conditions. Thus phenyl phosphonic acid, Bronsted acid catalyst was found to be an efficient catalyst for the Hantzsch polyhydroquinoline derivatives.

CONCLUSION

Polyhydroquinoline derivatives *via* Hantzsch condensation were obtained in good yields using phenyl phosphonic acid as a Bronsted acid promoter. The method was found to be suitable with various functional groups under mild conditions in one-pot condensation.

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