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A ONE POT MULTI-COMPONENT SYNTHESIS OF POLYHYDROQUINOLINE DERIVATIVES USING MONTMORILLONITE K10 AS SOLID ACID CATALYST

Santosh V. Padghan[a*], B.K. Magar[b], M.U. Chopade[c]

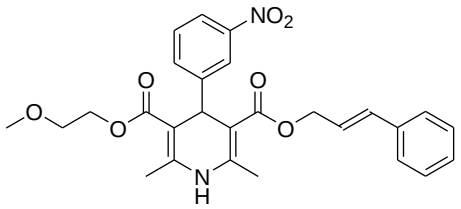
[a,c]Department of Chemistry, Sant Dnyaneshwar Mahavidyalaya, Soegaon, Dist-Aurangabad, Pincode-431120, Maharashtra, India
[b]Departmentof Chemistry, Shivaji Arts, Commerce and Science College, Kannad, Dist-Aurangabad, Pncode-431103, Maharashtra, India
Email- svpadghan@gmail.com, chopademanojkumar@gmail.com

ABSTRACT:
A simple, facile and efficient procedure for the synthesis of polyhydroquinolines via one pot four component condensation of different aromatic aldehyde with dimedone, ethylacetoacetate and ammonium acetate using montmorillonite K10 as solid acid catalyst has been developed. The new synthesis technique offers numerous advantages of safety, mild conditions, simplicity, short reaction time, high yields and easy work up compared to traditional synthesis method.

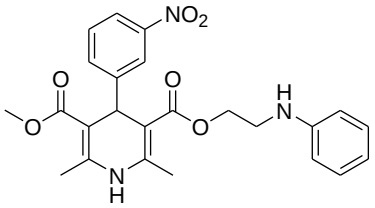
KEYWORDS: Polyhydroquinoline, One Pot Reaction, MontmorilloniteK10

INTRODUCTION

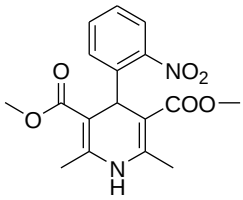
Among various biologically active heterocyclic scaffolds, polyhydroquinolines are an important class of biologically active heterocycles. In recent years, much attention has been focused on the synthesis of 1, 4-dihydropyridine [1, 4-DHPs] compounds due to their significant biological and pharmacological activities [1]. In particular, dihydropyridine drugs such as clinidipine, nicardipine, nifedipine (figure 1) and others are effective cardiovascular agent for the treatment of hypertension [2].



Clinidipine



Nicardipine



Nifedipine

Figure 1: Dihydropyridine drug

Some of them have anti tubercular properties [3], anticancer [4], neurotropic [5], neuropeptide YY1 receptor antagonists [6], neuroprotective [7], platelet ant aggregation [8], bronchodilating [9], and antidibetic activities [0].1, 4-dihydropyridine is analogues of NADH coenzymes which have been explored for their calcium channel activity. Numerous methods have been reported for the synthesis of polyhydroquinoline derivatives because of the biological importance associated with these compounds. The classical method for the synthesis of 1, 4-dihydropyridine is one pot condensation of aldehydes with ethylacetoacetate and ammonia either in acetic acid or by refluxing in alcohol [11]. Several other methods are also reported for the synthesis of , 4-DHPs like , the promotion of microwave[12], ionic liquid[13],TMSCL[13], polymer[14], $Yb(OTf)_3$[15], silicasulphuricacid[16], $Sc(OTf)_3$[17], MCM41[18], Lproline[19],sulfamicacid[20],hafnium(IV)bis(perflourooctanesulfonyl)imide[21],
Guanidine hydrochloride [GuHcl] [22], gridding till [23], fluoroalcohols [24], ceric(IV) ammonium nitrate[25] and $Cs_{2.5}H_{0.5}W_{12}O_{40}$ [26]. These methods however involve high temperature, expensive metal precursors, catalyst harmful to environment, longer reaction times, harsh reaction conditions, and low yields. Therefore, the development of simple and efficient methods for the preparation of polyhydroquinoline derivative is an active area of research and there is scope for further improvement involving milder reaction conditions and higher product yields.
Montmorillonite is a member of phyllosilicate mineral group which has two tetrahedral sheets sandwiching one octahedral sheet. Silicon is substituted by aluminium in octahedral structure caused an excess of negative charge in the structure which is balanced by other cations (Na^+, K^+, Mg^+, Ca^{++}) in the interlayer space. These ions can be exchanged by other cations; it makes montmorllonite become a useful catalyst [27-29]. In addition, this catalytic property is also improved with acid modification [30]. Acid activated montmorillonite are widely used in various fields for example, solid acid catalyst and solid support in chemical industry [31-33].
The use of solid acid catalyst such as clays has recently received considerable attention because they are inexpensive, non-toxic, non-corrosive and easy to handle. To overcome the limitations involved in the synthesis of 1,4-DHPs we introduce an efficient, rapid and clean procedure for the synthesis of 1,4-DHPs using Montmorillonite K10 as solid acid catalyst.

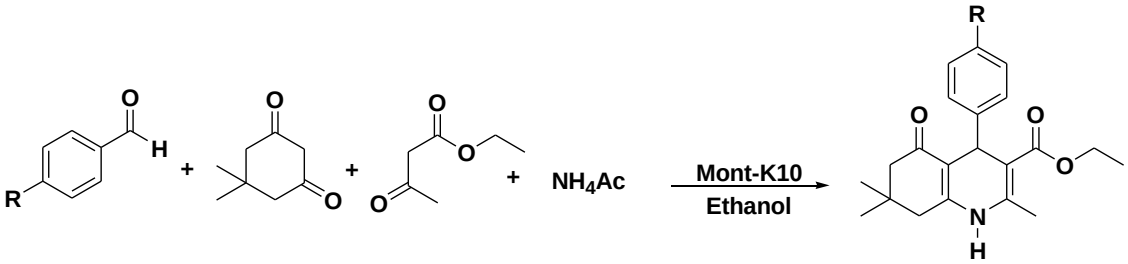
MATERIAL AND METHODS:

GENERAL

All solvents and chemicals were obtained commercially and used as received. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (Kieselgel 60 F_{254}, Merck). Visualization of the spots on TLC plates was achieved either by UV light or by staining the plates in 2, 4-dinitrophenylhydrazine/ anisaldehyde and charring on hot plate. Melting points were determined in open capillary and are uncorrected.IR spectra were obtained on a Shimadzu FTIR-8400 with samples loaded as thin films on KBr plate, neat or with CH_2Cl_2 as indicated.^{1}H NMR and ^{13}C NMR spectra were taken with Bruker Avance III HD at 500 MHz using $CDCl_3$and DMSO solvent.All chemical shifts are reported in δ downfield from TMS

GENERAL PROCEDURE FOR THE SYNTHESIS OF 1, 4-DIHYDROPYRIDNES AND POLYHYDROQUINOLINE:

To a mixture of benzaldehyde (1mmol), dimedone (1mmol),ethylacetoacetate (1mmol) and ammonium acetate (1mmol)in ethanol (10mL), montmorillonite K10 (5 mol %) was added in round bottom flask equipped with magnetic stirrer. The reaction mixture was stirred at room temperature for about 5-6 hours and a solid product was gradually formed. The progress of the reaction was monitored by TLC. After the completion of reaction, the solid was evaporated under reduced pressure. The pure product was purified by recrystallization from ethanol and water.



Scheme: 1

RESULT AND DISCUSSION

In search for an efficient solid acid catalyst, the reaction of aldehyde, dimedone, ethylacetoacetate and ammonium acetate at room temperature has been considered as standard model reaction. First of all, a number of catalysts have been screened using the model reaction in ethanol (table I). Montmorillonite was found to be the best catalyst under these conditions.

OPTIMIZATION OF REACTION CONDITIONS:

Table 1: Effect of various catalysts on synthesis of polyhydroquinoline

Entry.	Catalyst	Time (h)	Yield (%)[b]
1	No Catalyst	24	20
2	$ZnCl_2$	24	32
3	$AlCl_3$	24	42
4	$FeCl_3$	24	45
5	$Ba(OH)_2$	24	48

6	SiO_2	24	55
7	CAN	18	58
8	L-Proline	18	60
9	I2	12	67
10	Montmorillonite(K10)	6	89

[a]**Reaction conditions:** Benzaldehyde(1mmol), dimedone(1mmol),ethylacetoacetate(1mmol),ammonium acetate(1mmol),various catalysts were stirred at room temp, [b]Isolated Yield

To examine the efficiency of various solvents, initially the model reaction was performed under solvent free condition; low yield of desired product was obtained. In each case the substrate were mixed together with 5 mol% of montmorillonite agitated with 8-10 ml solvent. It is indicated in table 2, among all these solvents in EtOH maximum yield was obtained hence EtOH was selected as optimal solvent

Table 2: Solvent effect for the synthesis

Entry	Solvent	Time (h)	Yield (%)
1	Ethanol	6	89
2	Methanol	6	79
3	Acetonitrile	6	81
4	t-BuOH	9	60
5	1,4-Dioxane	9	58
6	Toluene	24	45
7	DCM	24	40
8	cyclohexane	24	30

[a]**Reaction conditions: :** Benzaldehyde(1mmol), dimedone(1mmol),ethylacetoacetate(1mmol),ammonium acetate(1mmol), various catalysts were stirred at room temp, [b]Isolated Yield

Optimization of catalyst loading

In order to determine the role of catalyst in the synthesis of polyhydroquinoline, we investigated the model reaction using various concentrations of montmorillonite. In the absence of catalyst, the yield of product was very low but after the addition of catalyst, there is significant increase in the yield of product which indicates the crucial role of catalyst in polyhydroquinoline synthesis. Table 3 indicates that, the yield of product increases with increase in the amount of catalyst up to 15 mol%

Table 3: Optimization study for the amount of montmorilloniteas catalyst[a]

Entry	Catalyst (mol %)	Time(h)	Yield %[b]
1	0	6	10
2	2	6	30
3	5	6	45
4	10	6	65
5	15	6	89

[a]**Reactionconditions:** Benzaldehyde(1mmol), dimedone(1mmol),ethylacetoacetate(1mmol),ammonium acetate(1mmol), various catalysts were stirred at room temp, [b]Isolated Yield

SPECTRAL ANALYSIS:

Ethyl-4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydrquinoline-3-carboxylate (4b): MP: 243-245^{0}C; **IR(KBr):** 3276, 3199, 3077, 2964, 1716, 1738 cm^{-1} ; **^{1}H-NMR:** (500MHz, DMSO, δppm) δ=0.94 (s, 3H) 1.08 (s,3H), 1.18 (t,3H), 2.12-2.34 (m,4H), 2.37(s, 3H),4.04(q, 2H),5.04(s, 1H),7.15-7.19(d, 2H), 7.24-7.26(d, 2H);**^{13}CNMR**: (DMSO,125MHz, ppm) δ =12.09, 18.0, 25.8, 28.1, 31.3, 34.9, 39.6, 49.4, 58.6, 104.4, 110.4, 126.4, 128.1, 130.3, 142.4, 144.3, 147.2, 165.9, 194.3

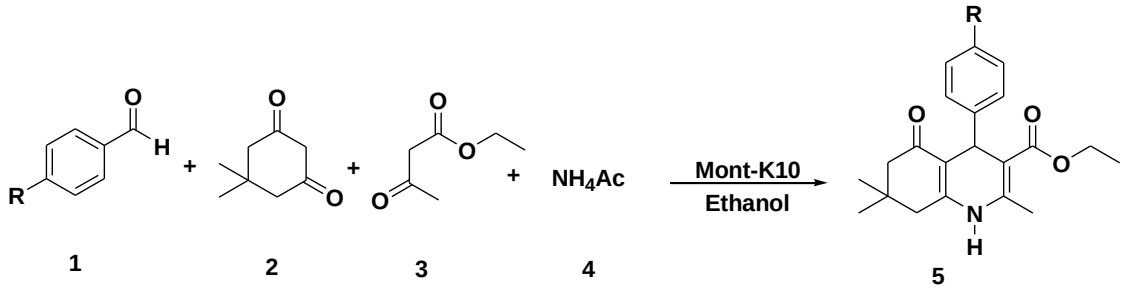
Ethyl-4-(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydrquinoline-3-carboxylate (4c): MP: 232-233^{0}C; **IR(KBr):** 3331, 3132, 1718, 1737, 1495, 1234, 730 cm^{-1} ; **^{1}H-NMR:** (500MHz, DMSO, δppm) δ=0.94 (s, 3H) 1.08 (s, 3H), 1.20 (t, 3H), 2.08-2.18 (m, 4H), 2.20-2.35(s, 3H), 4.07(q, 2H), 4.98(s, 1H), 6.65(d, 2H),7.16(d, 2H);**^{13}CNMR**: (DMSO,125MHz, ppm) δ =15.1, 19.1, 19.1, 27.4, 33.4, 36.7, 41.1, 51.7, 54.9, 60.2, 106.2, 112.6, 115.5, 130.1, 131.3, 140.4, 145.3, 149.7, 156.6, 168.4, 195.3

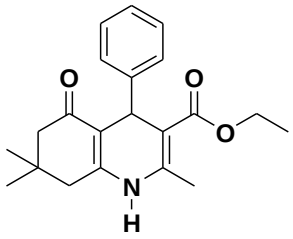
Ethyl-4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydrquinoline-3-carboxylate (d): MP: 260-261^{0}C; **IR(KBr):** 3292, 3224, 3087, 2958, 1716, 1735, 1491 cm^{-1} ; **^{1}H-NMR:** (500MHz, DMSO, δppm) δ=0.94 (s, 3H) 1.07 (s, 3H), 1.21 (t, 3H), 2.13-2.36 (m, 4H), 3.74(s, 3H), 4.06(q, 2H), 5.00(s, 1H), 6.74(d, 2H),7.22(d, 2H);**^{13}CNMR**: (DMSO,125MHz, ppm) δ =14.2, 19.4, 27.1, 29.4, 32.6, 35.6, 41.1, 50.7, 55.1, 59.7, 106.3, 112.4, 113.2, 128.9, 139.5, 139.5, 143.1, 147.7, 157.7, 167.4, 195.5

Ethyl-4-(4-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydrquinoline-3-carboxylate (4f): MP: 240-242^{0}C; **IR(KBr):** 3506, 3285, 3193, 2447, 1720, 1740, 1518, 1484, 1306, 1284, 1166, 870, 755 cm^{-1} ; **^{1}H-NMR:** (500MHz, DMSO, δppm) δ=0.89 (s, 3H) 1.09 (s, 3H), 1.08 (t, 3H), 2.05-2.25 (m, 4H), 2.37(s, 3H), 4.00(q, 2H), 5.05(s, 1H), 7.42(d, 2H),8.05(d, 2H);**^{13}CNMR**: (DMSO,125MHz, ppm) δ = 12.9, 18.1, 25.7, 28.1, 31.4, 35.7, 39.5, 49.3, 58.7, 103.7, 109.7, 119.9, 121.5, 127.3, 133.5, 143.4, 146.9, 148.1, 165.7, 194.3

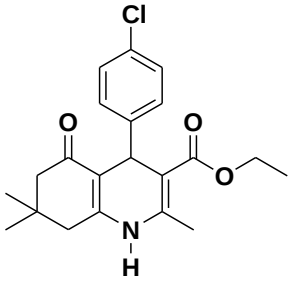
Synthesis of various polyhydroquinoline derivatives

A variety of aromatic aldehydes were selected to undergo the Hantzsch reaction in presence of catalytic amount of montmorillonite in ethanol at room temperature. The results of this study are summarised in table 4.

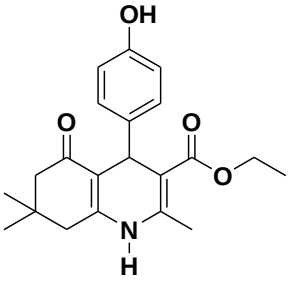




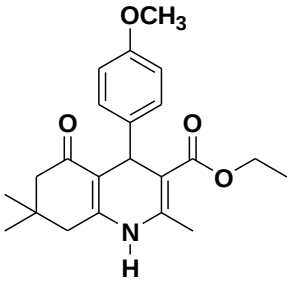
6 h, 89% yield (4a)



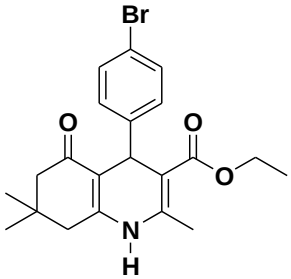
6 h, 82% yield(4b)



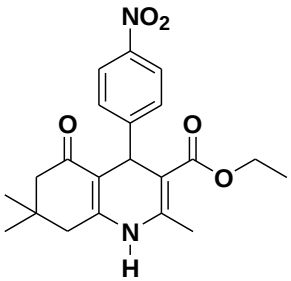
6 h,85% yield(4c)



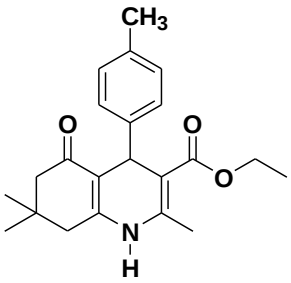
6 h,87% yield(4d)



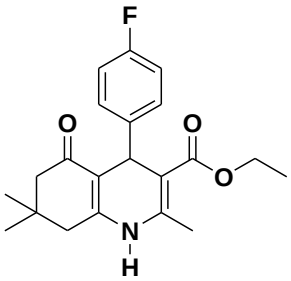
6 h, 83% yield(4e)



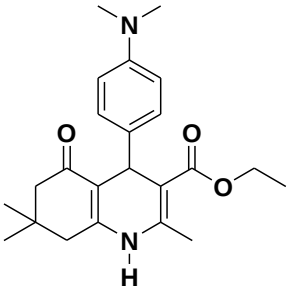
6 h, 80% yield(4f)



6 h, 88% yield(4g)



6 h, 86% yield(4h)



6 h, 82% yield(4i)

Table 4: synthesis of polyhydroquinoline 4a-4i from the four component aldehyde, dimedone, ethylacetoacetate and ammonium acetate at room temperature in ethanol.

CONCLUSION:

In conclusion, we successfully developed a facile and efficient method for the synthesis of a variety of polyhydroquinoline derivatives. The catalytic activity of montmorillonite K10 is remarkable and the use of efficient, environmentally benign, commercially available montmorillonite K10 as a catalyst in the synthesis of polyhydroquinoline derivatives in good yield is also significant. The present method has many advantages compared to those reported in literature including short reaction time, mild conditions, high yields and easy workup.

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