P_2O_5/Al_2O_3 as an effieientcatalystfor one-potsynthesis of polyhydroquinoline derivativesundersolvent-free conditions

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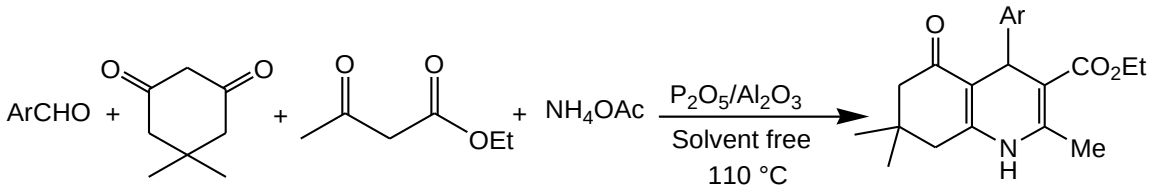
Abstarct- The condensation of aromatic aldehydes, dimedone, ethylacetoacetate and ammonium acetate promoted by was Phosphorus pentoxide supported on alumina carried out under solvent-free conditions to afford corresponding polyhydroquinolinederivatives. This method provides several advantages including highyields, low reaction times, easy work up and little catalyst loading.

Keywords**:** Polyhydroquinoline, Solvent-free, Multicomponent reactions, Phosphorus pentoxide supported on alumina

Introduction

In recent years, great attention has been paid tothe synthesis of polyhydroquinolines because of itshighly absolute biological and physiologicalactivitiessuch as calcium channel blockers,asodilator,hepatoprotective,antiatherosclerotic,bronchodilator, antitmor, geroprotective,antidiabetic activity, etc [1].In addition, these compoundshave found wide usage in drugs includingnifedipine,nicardipine and amlodipine [2].Recently, the synthesis of polyhydroquinolines has been achieved by the condensation of aromatic aldehydes, dimedone, ethylacetoacetate and ammonium acetate in the presence of various catalysts, such asL-proline [3], PEG-400 [4],microwave [5], PTSA [6], tin dioxide nanoparticles[7], copper perchlorate hexahydrate [8], 1,3-dibromo-5,5-dimethylhydantoin (DBH) [9], alumina sulfuric acid (ASA)[10], molybdenum(VI) complex [11], t-BuOK[12],cobalt nanoparticles [13],aqueous media [14], ionic liquid[15],$(NH_4)_6[Mn^{IV}Mo_9O_{32}]$[16], liquid phase [17], Amberlite IR-120 [18], Nafin-H[19]and $ZrCl_4$[20].

In view of the above observation, we decided to develop an environmentally and green approach for the synthesis of some polyhydroquinolines catalyzed by Phosphorus pentoxide supported on alumina solvent-free neat conditions (Scheme 1).



1 **2** **3** **4** **5**

Scheme 1

Experimental

All chemicals were purchased from Merck and used without further purification. IR spectra were recorded on a Shimadzu IR-460 spectrometer. ^{1}Hspectra were recorded on a Bruker DRX-300 AVANCEinstrument with $CDCl_3$ as solvent**.**

General procedure for the synthesis of polyhydroquinolines.

A mixture of dimedone (1 mmol), benzaldehyde (1 mmol), ethylacetoacetate (1 mmol), ammonium acetate (1 mmol) and Phosphorus pentoxide supported on alumina (8 % mol) was stirred at 110 ˚C for the appropriate time (monitored by TLC). On completion of reaction, the reaction mixture was cooled and was triturated with 10 mL of dichloromethane to get the solid product. The product obtained was filtered, washed with cold water, dried, and recrystallized from ethanol and water.

Ethyl 1,4,5,6,7,8–hexahydro-4-(phenyl)-7,7-dimethyl-5-oxoquinoline–3-carboxylate **(5a)**: M.P. 205-207ºC,^{1}H NMR (300 MHz, $CDCl_3$):δppm = 0.91 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.17 (t, J=7.1 Hz, 2H , CH_2), 2.14-2.20 (m, 4H, $2CH_2$), 2.28 (s, 3H, CH_3), 4.03 (q, J=7.1 Hz, 3H, CH_3), 5.02 (s, 1H, CH), 5.96 (s, 1H, CH),7.04-7.09 (m, 1H, CH), 7.14-7.19 (m, 2H, CH), 7.23-7.26 (m, 2H.CH_2).^{13}C NMR ($CDCl_3$, 75 MHz): δppm= 14.18, 19.45, 27.16, 29.41, 32.72, 36.53, 41.16, 50.70, 59.81, 100.33, 106.29, 112.61, 126, 127.86, 143.83, 146.99, 147, 167.68, 195.75; IR (KBr,cm^{-1}): 3289, 3080, 2959, 1698, 1610.

Ethyl1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-methoxyphenyl)-5(6H)-oxoquinolin-3-carboxylate (5f): M.P. 258-260 ºC:^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 0.95 (s, 3H, CH_3), 1.09 (s, 3H, CH3),1.21 (t, J=7.2 Hz, 3H, CH_3), 2.01-2.10 (m, 4H, $2CH_2$), 2.30 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.00 (q, J=7.2 Hz, 2H, CH_2), 4.80 (s,1H, CH), 6.65 (d, J=7.3 Hz, 2H, ArH), 7.10 (d, J=7.3 Hz, 2H, ArH), 8.65 (s, 1H,NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ =195.7,

167.5, 157.7, 149.1, 142.9, 139.8, 128.9, 113.7, 113.3, 106.4, 59.8, 55.1, 37.0, 35.4, 27.5, 21.1, 19.4, 14.2; IR (KBr, cm-1): 3276, 2956, 1703, 1648,1606, 1496, 1381, 1215, 1031, 765.

Result and Discussion

In the initial experiments, the effect of reaction temperature was examined using the reaction of aromatic aldehydes, dimedone, ethylacetoacetate and ammonium acetate in the presence of8 % mol of Phosphorus pentoxide supported on alumina under solvent-free conditions. As can be seen from Table 1, the optimum temperature was at 110 ˚C. The effect of the amount of catalyst was also examined. It was found that the use of 8 mol % of Phosphorus pentoxide supported on alumina was sufficient to progress the reaction. Although an increase of the amount of catalyst lead to shorterreaction time, reductive yields also were observed.

Table1. Effect of different reaction conditions for the condensation of aromatic aldehydes, dimedone, ethylacetoacetate and ammonium acetate under solvent free

ENTRY	TEMPERATURE (˚C)	AMOUNT OF CATALYST (MOL%)	TIME (MIN)	YIELD (%)
1	**70**	**8**	**15**	**70**
2	**80**	**8**	**10**	**75**
3	**100**	**8**	**6**	**90**
4	**110**	**8**	**2**	**95**
5	**110**	**4**	**2**	**90**
6	**110**	**15**	**2**	**80**

7	**110**	**20**	**3**	**85**

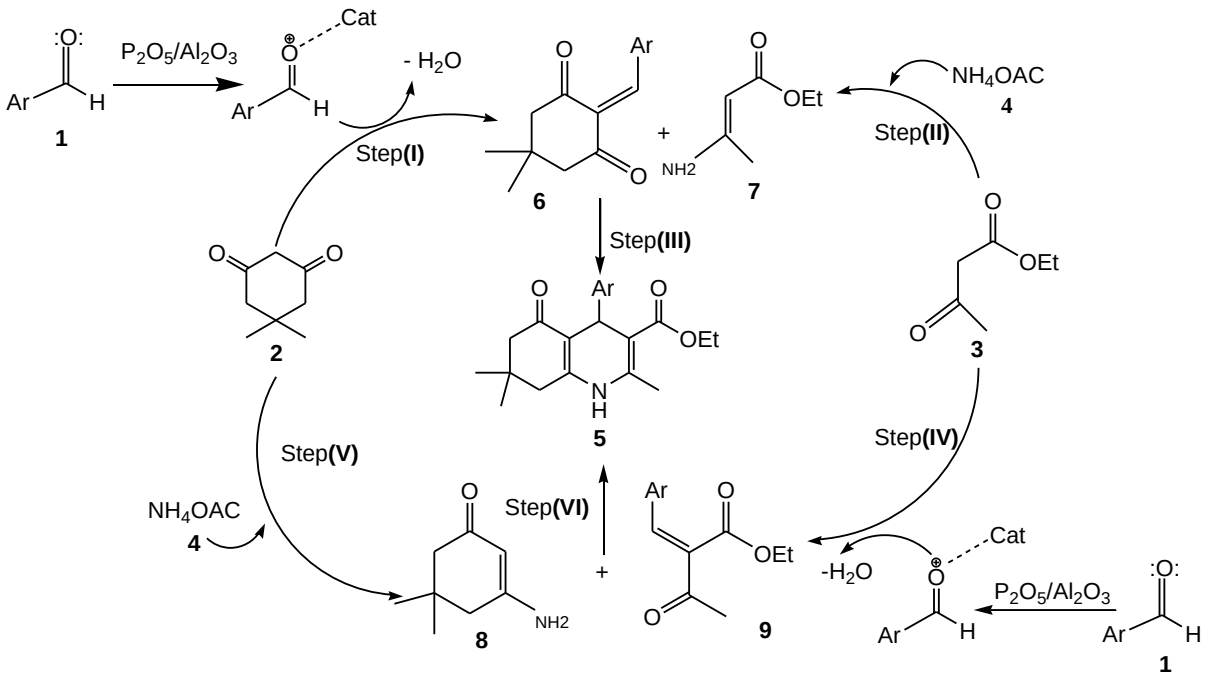
As can be seen from Table 2, dimedone, ethylacetoacetate and ammonium acetate with various aromatic aldehydes at 110 ^{o}C using 8 mol% of Phosphorus pentoxide supported on alumina as catalyst, carrying either electorn-donating or electron-withdrawing substituents, gave the corresponding polyhydroquinolines under solvent-free condition in excellent yields.

Table2. Synthesis of substituted polyhydroquinolines

ENTRY	AR	PRODUCT	TIME(MIN)	YIELD (%)	M.P (˚C)	REF.M.P(˚C)
1	**C_6H_5**	**5A**	**120**	**84**	**208-210**	**202-204**[6]
2	**3-$NO_2C_6H_4$**	**5B**	**90**	**86**	**170-172**	**178-180**[9]
3	**4-$NO_2C_6H_4$**	**5C**	**90**	**88**	**242-244**	**242-244**[8]
4	**4-CLC_6H_4**	**5D**	**90**	**76**	**238-241**	**244-246**[10]
5	**4-$CH_3C_6H_4$**	**5E**	**90**	**70**	**254-258**	**265-268**[11]
6	**4-$OMEC_6H_4$**	**5F**	**90**	**72**	**250-254**	**257-259**[20]
7	**4-CNC_6H_4**	**5G**	**90**	**90**	**149-151**	**143-145**[7]

A tentative mechanism to rationalize the product formation is shown in scheme2. Polyhydroquinoline**5** may be formed either through steps **(I—III)** or through steps (**IV—V)**. The role of Phosphorus pentoxide supported on alumina (Lewis Acid) comes in steps (**I**) and (**IV)**, where it catalyzes the Knoevenagel type coupling of aldehydes with active methylene

compounds and in steps **(III)** and (**VI**), where it catalyzes the Michael type addition of intermediates **6**, **7** and **8**, **9** to give product**5**.



Scheme 2

Conclusions

This report describes an efficient procedure for the synthesis ofpolyhydroquinolines derivatives by solid phase catalyst with improved yields. This procedure offers several advantages including high yields, low reaction times, easy work up and little catalyst loading, cleaner reaction, high yields of products as well as a simple experimental and work-up procedure which makes it a useful, economical and waste-free process for the synthesis of thesecompounds.So we can say this method is faster and easier than other published method.

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