

An efficient synthesis of polyhydroquinoline derivatives catalyzed by heteropolyacid

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Abstract: Green, mild and efficient condensation reactions of 1,3-cyclohexanediones with various aldehydes and ethylacetoacetate and ammonium acetate were carried out in the presence of catalytic amounts of $H_3PMO_{12}O_{40}$ as an inexpensive, eco-friendly and recyclable catalyst to afford the desired polyhydroquinoline derivatives in good to excellent yields.

Keywords: Polyhydroquinoline derivatives; 1,4-Dihydropyridines; *Keggin* type heteropolyacid; Dimedone; 1,3-Cyclohexanediones.

Introduction

1,4-Dihydropyridyl compounds are nitrogen heterocycles which have received considerable attention over the past years due to their wide range of biological activity [1]. 4-Aryl-1,4-dihydropyridines (*DHPs*) have been explored for their calcium channel activity and the heterocyclic rings are found in a large family of medicinally important compounds such as vasodilator, bronchodilator, antiatherosclerotic, antitumour, antidiabetic and heptaprotective agents [2]. In view of the importance of polyhydroquinoline derivatives, many classical methods for the synthesis of polyhydroquinoline derivatives were reported [3-7] by conventional heating and refluxing approaches in organic solvents. The preparation of polyhydroquinoline derivatives under microwave irradiation has also been reported [8, 9]. More recently, a variety of catalysts involving molecular iodine [10a], $HClO_4-SiO_2$ [10b], $Yb(OTf)_3$ [10c], CAN [10d], $Sc(OTf)_3$ [10e] and ionic liquid [11] have been employed for the synthesis of these compounds. These methods, however, suffer from some disadvantages involve long reaction time, harsh reaction conditions, the use of a large quantity of organic solvent and unsatisfactory yields. Therefore, the development of an efficient method for the synthesis of these compounds

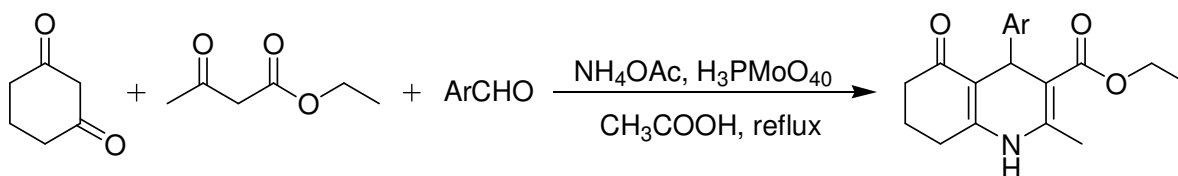
is an active ongoing research area and there is scope for further improvement toward milder reaction conditions and higher yields.

Over the last few years, there has been a considerable growth in interest in the use of heteropolyacids, *HPAs*, in organic synthesis because of their ease of handling, enhance reaction rates, low cost, simple work-up and recyclability of the catalyst [12-16].

Results and Discussion

In our continued interest in the development of highly expedient methods for the synthesis of nitrogen heterocycles [17] and in continuation of our investigation on the use of heteropolyacids as catalyst for chemical preparation [18], we wish to report a simple, convenient and efficient method for the preparation of polyhydroquinoline derivatives from 1,3-cyclohexanediones, aldehydes, ethylacetoacetate and NH_4OAc in the presence of catalytic amounts of *Keggin* type heteropolyacid, $H_3PMO_{12}O_{40}$, as an inexpensive, eco-friendly and recyclable catalyst (Scheme 1). The corresponding products were obtained after short reaction times under reflux conditions in the presence of 1 mol% of heteropolyacid.

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Scheme 1

The model reaction was carried out simply by refluxing a mixture of benzaldehyde, 1,3-cyclohexanedione, ethylacetoacetate, ammonium acetate and $H_3PMo_{12}O_{40}$ in acetic acid. The corresponding polyhydroquinoline derivative was obtained in high yield (85%).

We studied the effect of various solvents. The result of the reaction of benzaldehyde, 1,3-cyclohexanedione, ethylacetoacetate and ammonium acetate in the presence of 1 mol% of heteropolyacid in various solvents are shown that acetic acid is the best solvent with respect to times and yields of reactions.

When the reaction was carried out in CH_3CN , the desired product was obtained in low yield. Whereas an excellent yield of the product was obtained when the reaction was carried out in acetic acid. These results led to the suggestion that acetic acid is the best solvent for this reaction.

The optimized methodology was applied to the synthesis of a variety of polyhydroquinoline derivatives. The results are summarized in Table 1. In all cases good yields of products were obtained.

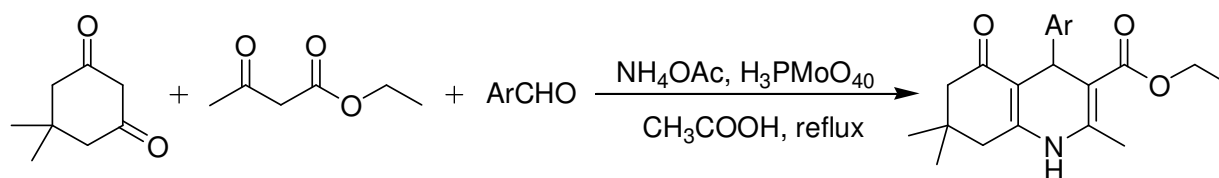
Table 1. Heteropolyacid catalyzed the synthesis of polyhydroquinoline derivatives.

Entry	Ar	Time (min)	Yield(%) ^a	mp (°C)	
				Found	Reported
1	C ₆ H ₅	30	85	239-240	240-241[10a]
2	<i>p</i> -MeC ₆ H ₅	35	83	239-240	241-242[10a]
3	<i>p</i> -MeOC ₆ H ₅	40	84	192-193	193-195[10a]
4	<i>o</i> -O ₂ NC ₆ H ₅	38	85	189-190	190-191[10a]
5	<i>m</i> -O ₂ NC ₆ H ₅	35	75	198-200	198-200[10a]
6	<i>p</i> -HOC ₆ H ₅	45	80	219-220	220-222[10a]
7	<i>p</i> -ClC ₆ H ₅	30	80	233-234	234-235[10a]

^aYields refer to isolated products.

Next, we investigated the effect of substitution in 1,3-cyclohexanedione system such as 5,5-dimethyl-1,3-cyclohexanedione (dimedone). Aromatic aldehydes such as benzaldehyde and different substituted benzaldehydes reacted with dimedone,

ethylacetoacetate and ammonium acetate in the presence of heteropolyacid as catalyst to afford the products in good yields (Scheme 2). The results are summarized in Table 2.



Scheme 2

Table 2. Heteropolyacid catalyzed the synthesis of polyhydroquinoline derivatives.

Entry	Ar	Time (min)	Yield(%) ^a	mp (°C)	
				Found	Reported
1	C ₆ H ₅	35	80	225-227	227-229[11]
2	<i>p</i> -HOC ₆ H ₅	40	85	231-232	232-234[10b]
3	<i>p</i> -O ₂ NC ₆ H ₅	30	80	242-243	242-244[11]
4	<i>p</i> -ClC ₆ H ₅	35	85	241-242	245-246[11]
5	<i>p</i> -MeOC ₆ H ₅	35	85	256-257	260-261[11]
6	C ₆ H ₅ CH=CH-	30	90	202-203	204-206[10b]

^aYields refer to isolated products.

It is noteworthy to mention that, the effect of the nature of the substituents on the aromatic ring showed no obvious effect on this conversion and they were obtained in high yields in relatively short reaction times.

All compounds were known and their physical data were compared with those of authentic compounds and found to be identical.

Conclusion

In conclusion, we have demonstrated an easy, clean, simple and efficient multicomponent reaction for the synthesis of a variety of polyhydroquinoline derivatives of potential biological importance in excellent yields. Relatively short reaction times, the simplicity of performance, easy work-up procedure as well as high yields make this procedure, valuable and environmentally friendly alternative to the currently available methods for the synthesis of title compounds. The catalyst is green and recyclable. It could be reused without significant loss of activity. The catalyst is also non-corrosive and environmentally benign and presents fewer disposal problems. The use of this solid

acid catalyst allows replacement of the usual soluble inorganic acids, contributing in this way to the reduction wastes.

Experimental

All products were identified by their spectra and physical data. Melting points were measured by using capillary tubes on an electro thermal 9100 apparatus. IR spectra were recorded as KBr disc on the FT-IR Bruker Tensor 27 spectrometer. ¹H NMR spectra were recorded on a Bruker AQS-AVANCE spectrometer at 500 MHz, using TMS as an internal standard. Mass spectra were recorded on MS 5973 Network Mass Selective detector. All the yields were calculated from isolated products and GC was used to establish their purities.

General Procedure for the synthesis of polyhydroquinoline derivatives catalyzed by H₃PMo₁₂O₄₀

The experimental procedure is simple: a mixture of equimolar amounts of aldehyde (1 mmol), ethylacetoacetate (1 mmol), 1,3-cyclohexanedione (1 mmol) and 2 mmol of ammonium acetate in the

presence of 0.03 g of heteropolyacid (1 mol%), in 5 cm³ acetic acid were refluxed for appropriate time. The progress of the reaction was monitored by TLC using petroleum ether-ethyl acetate (2:1) as eluent. After completion of the reaction, the catalyst was removed by simple filtration. The solvent was evaporated under reduced pressure. The crude product was purified by recrystallization from ethanol. In order to show generality of the procedure, the reaction was repeated with dimedone. The results are summarized in Tables 1 and 2.

Recycling of the catalyst

At the end of the reaction, the catalyst was filtered, washed with diethyl ether, dried at 80 °C for 1 h, and re-used in another reaction. Even after 5 runs for the reaction, the catalytic activity of H₃PMo₁₂O₄₀ was almost the same as that of the freshly used catalyst.

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