

Study and Compraison catalysts that use in producing 1,4-dihydropyridine derivatives compounds

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Abstract: A simple, inexpensive and efficient one-pot synthesis of 1,4-dihydropyridine derivatives at room temperature by using catalyst to promote reaction and achieve to high yield of products. In recent years, an increasing interest has been focused on the synthesis of 1,4-dihydropyridyl compounds owing to their significant biological activity. In particular, dihydropyridine drugs such as nifedipine, cardipine, amlodipine and others are effective cardiovascular agents for the treatment of hypertension. 4-Aryl-1,4-dihydropyridines have been explored for their calcium channel activity and the heterocyclic rings are found in a variety of bioactive compounds such as vasodilator, bronchodilator, antiatherosclerotic, antitumour, antidiabetic, geroprotective and heptaprotective agents. Moreover studies have discovered that these compounds exhibit diverse medical functions such as neuroprotectants, compounds with platelet antiaggregators, cerebral antiischaemic agents and chemosensitizers. The remarkable drug activity of these compounds not only attracted many chemists to synthesize this heterocyclic nucleus but also became an active research area of ontinuing interest. It has been mostly reported that there are many methods to synthesize 1,4-dihydropyridine derivatives, in view of the biological importance associated with these compounds. in this review we have studied about some catalyst and its effect on the reaction process that used to synthesize DHP derivatives.

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Introduction

4-Substituted 1,4-dihydropyridines (DHPs) comprise a large family of medicinally important compounds. They can cure the disordered heart ratio as a chain-cutting agent of factor IV channel, possess the calcium channel agonist-antagonist modulation activities [1]. and also behave as neuroprotectants, cerebral antiischaemic agents and chemosensitizers [2] A recent computational analysis of the comprehensive medicinal chemistry database found that the DHP framework to be the most prolific chemotypes. Quinolines having 1,4-dihydropyridine nucleus are very important compounds because of their pharmacological properties. Members of this family are being used as antimalarial, antiinflammatory, antiasthmatic, antibacterial, and tyrosine kinase inhibiting agents [3]. For these reasons, polyhydroquinoline compounds not only attract the attention of chemists to synthesize but also

Represent an interesting research challenge. The classical methods involve the three-component condensation of an aldehyde with alkyl acetoacetate, and ammonia in acetic acid or in refluxing alcohol [4–6]. However, these methods suffer from drawbacks such as long reaction time, use of large quantities of organic solvents, lower product yields or harsh refluxing conditions. Researchers recently have developed several alternate and more efficient methods

for the synthesis of polyhydroquinoline derivatives, which include the use of microwaves [7], autoclave [8], ionic liquids [9], iodine [10], metal triflates [11], ceric ammonium nitrate (CAN) [12], L-proline [13], PTSA-SDS [14] and BINOL-phosphoric acid derivatives [15]. But some of those methods still have their own limitation in terms of yields, longer reaction time, difficult work-up. In some cases, catalysts used are harmful to environment and cannot be reused. Therefore, a novel method for the preparation of polyhydroquinoline derivatives is still desired.

The search continues for a better catalyst for the synthesis of polyhydroquinolines on terms of perational simplicity, reusability, economic viability, and greater selectivity.

Result and discution

A straightforward and general method has been developed for the synthesis of polyhydroquinoline derivatives by simply combining aldehyde, ethyl acetoacetate, dimedone, and ammonium acetate in the presence of some catalysts. developing rare earth metal triflates especially Yb(OTf)₃ and Sc(OTf)₃ catalyzed organic synthesis. As a new type of Lewis acid, they have been applied in a variety of reactions [16] The most characteristic feature of these rare earth metal triflates is that they act as water-compatible strong Lewis acids in aqueous solvents. Only catalytic amount

of the catalysts is enough to complete reactions in most cases. Moreover, they can be easily recovered after reactions and reused without any loss of activity.

Li-Min et al. reported about the $\text{Yb}(\text{OTf})_3$ catalyzed four-component Hantzsch reaction using ethanol

As a solvent at ambient temperature. In this study, $\text{Yb}(\text{OTf})_3$ has been employed as a mild and efficient catalyst for Hantzsch condensation.[17] the mixture of benzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate was chosen as the model reaction (Scheme 1) to detect whether the use of ytterbium triflate was efficient and investigate the optimized conditions. The results were summarized in Table 1. It was found that the conventional Lewis acids such as AlCl_3 and FeCl_3 , as well as the condition of no catalyst showed poor effect to the yield of the product, which was probably due to their poor water tolerance. Even large amount of catalysts was used, the results were still unsatisfactory and many side reactions could be observed (entry 1–4). When using the rare earth metal compounds (entry 5–6), the results seemed to be better. While adding 0.5 mol% of $\text{Yb}(\text{OTf})_3$ into the system under similar reaction conditions, the speed of reaction was obviously accelerated, but the yield was not yet satisfactory (entry 7). Further studies showed that increasing the amount of $\text{Yb}(\text{OTf})_3$ could improve the reaction significantly. Inspired by the results, changing the amount from 0.5 to 10 mol%, finding that 5 mol% of $\text{Yb}(\text{OTf})_3$ was good enough (entry 7–12). After the reaction was completed, the product was filtered directly and the catalyst can be extracted by water from the residue. Lanthanide triflates are more soluble in water than that in organic solvents. The catalyst could be recovered almost quantitatively from the aqueous layer, which could be subsequently reused several times. As indicated in Table 1, it showed almost no loss of activity after four successive runs. The yields obtained were from 91 to 89% (with yields of product 4a being 90, 91, 90, 89% in the first, second, third and fourth run, respectively). In view of environmental friendly methodologies, recovery and reuse of the catalyst is highly preferable.

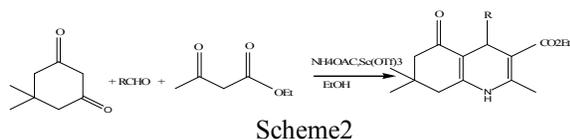
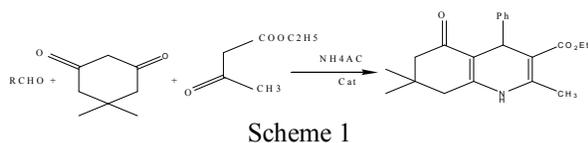


Table 1. the reaction of benzaldehyde, ethyl acetoacetate, dimedone, and ammonium acetate. Effect of catalyst

Entry	Catalyst	Amount of catalyst(mol%)	Time (h)	Yield
1	None		24	36
2	ZnCl_2	150	12	42
3	AlCl_3	200	12	43
4	FeCl_3	200	12	48
5	NdCl_3	25	12	76
6	$\text{La}(\text{OTf})_3$	15	12	84
7	$\text{Yb}(\text{OTf})_3$	0.5	5	75
8	$\text{Yb}(\text{OTf})_3$	1	5	80
9	$\text{Yb}(\text{OTf})_3$	2	5	82
10	$\text{Yb}(\text{OTf})_3$	5	5	90
11	$\text{Yb}(\text{OTf})_3$	7.5	5	90
12	$\text{Yb}(\text{OTf})_3$	10	5	89
13	$\text{Yb}(\text{OTf})_3$	5	5	90,91,90,89

James L. et al. reported that the scandium triflate as earth metal catalyst to producing polyhydroquinoline. They have examined other Lewis acids for this reaction (Table 2), $\text{Sc}(\text{OTf})_3$ was found to be the most effective catalyst at room temperature. (Scheme 2)[18]. The Hantzsch condensation of dimedone, benzaldehyde, ethyl acetoacetate, and ammonium acetate in the presence of catalyst amount of scandium triflate at room temperature (Scheme 2). result in the formation of 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenyl-3-quinolinecarboxyl acid ethyl ester in 92% yield. The result shown in Table 2. They examined other Lewis acids for this reaction. The $\text{Sc}(\text{OTf})_3$ was found to be most effective catalyst in terms of conversion and reaction rates.

Table 2: the reaction of benzaldehyde, ethyl acetoacetate, dimedone, and ammonium acetate: effect of catalyst

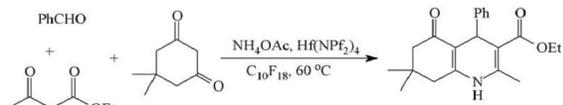
Entry	Catalyst	Amount of catalyst(mol%)	Time(h)	Yield(%)
1	None	-	24	30
2	None	-	24	52
3	AlCl_3	100	24	48
4	ZnCl_2	100	24	42
5	FeCl_3	100	24	38
6	$\text{Lu}(\text{OTf})_3$	20	24	64
7	$\text{Nd}(\text{OTf})_3$	20	24	60
8	$\text{Yb}(\text{OTf})_3$	10	5	85
9	$\text{Y}(\text{OTf})_3$	10	6	77
10	$\text{Sc}(\text{OTf})_3$	10	3	96
11	$\text{Sc}(\text{OTf})_3$	5	4	93
12	$\text{Sc}(\text{OTf})_3$	1	9	64

The reaction is fairly general, clean, and efficient. The present method does not require high temperatures to produce polyhydroquinoline. They demonstrated a simple and efficient procedure for synthesis of

polyhydroquinoline using scandium triflate as reusable catalyst. The main advantage of this methodology are: (a) operational simplicity, (b) short reaction times, (c) high yield of product, and (c) the use of relatively non-toxic reagent and solvent.

Metal (e.g. Hf, Yb, Sc) complexes with bis(perfluorooctanesulfonyl)imide ponytails are active and recyclable catalysts which could be immobilized in the fluorous phase for synthesis of substituted quinolines [19] and 14-substituted-14H-dibenzo[a,j]xanthenes [20] and allylation of 1,3-dicarbonyl compounds [21].

Furthermore, Mei Hong et al. studied about other earth metals as catalysts in the Hantzsch condensation. First a mixture of benzaldehyde, 5,5-dimethylcyclohexane-1,3-dione, ethyl acetoacetate, and ammonium acetate in perfluorodecalin (C10F18, cis- and trans-mixture) was chosen as the model reaction (Scheme 3) to detect whether the use of catalyst hafnium (IV) bis(perfluorooctanesulfonyl)imide complex is efficient and to investigate the optimal conditions.[22]



Scheme 3

The results are summarized in Table 3. As shown in Table 3, hafnium (IV), tin (IV), and lanthanide

(III) bis(perfluorooctanesulfonyl)imide complexes screened were effective in catalyzing the reaction with the product yield in the order of hafnium (IV) > tin (IV) > lanthanide (III) (Table 1, entries 2, 4, 5, 8 and 11–14). It was also found that metal (e.g. Sc, Yb) complexes with the –N(SO2C8F17)2 (NPF2) ligand gave better yields than those with the –OSO2C8F17 (–OPf) ligand or –OSO2CF3

(OTf) ligand in fluorous solvent (Table 3, entries 5–10). It is reasonable to speculate that the stronger electron-withdrawing ligand of M[N(SO2C8F17)2]_n (n = 3, 4) complex renders it super

Lewis acidity in fluorous solvent and hence shows better catalytic activity. Bis(perfluorooctanesulfonyl)imide (NHPf2) itself can promote the reaction, but it was found to be less effective than the corresponding metal complexes. We also carried out the reaction without any catalyst, poor yield (<5%) (Table 3, entry 16) of the desired product was isolated, and the major product isolated was dimedone/aldehyde adduct. The use of just 1 mol% of Hf(NPF2)4 in fluorous solvent is sufficient. After the reaction was completed, the fluorous phase containing catalyst could be reused for several times. As indicated

in Table 3, almost the similar catalyst activity remained after five successive runs. The yields obtained were between 93 and 95%.

Table 3. the reaction of benzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate. Effect of catalysts

Entry	Catalyst	Amount of catalyst(mol%)	Yield (%)
1	Hf(NPF ₂) ₄	0.5	73
2	Hf(NPF ₂) ₄	1	95,95,93,93,94
3	Hf(NPF ₂) ₄	1.5	96
4	Sn(NPF ₂) ₄	1	91
5	Yb(NPF ₂) ₃	2	82
6	Yb(OPf) ₃	2	73
7	Tb(OTf) ₃	5	65
8	Sc((NPF ₂) ₃)	2	85
9	Sc(OPf) ₃	2	77
10	Sc(OTf) ₃	5	68
11	La(NPF ₂) ₃	2	60
12	Nd(NPF ₂) ₃	2	65
13	Y(NPF ₂) ₃	2	71
14	sm (NPF ₂) ₃	2	73
15	NHPf ₂	2	42
16	-	-	<5

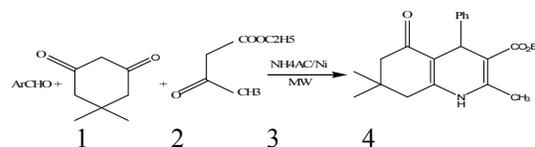
The efficiency of heterogeneous catalysis in organic synthesis can be improved by employing nanosized catalysts because of their extremely small size and large surface to volume ratio.

In other report Suryakant B et al. demonstrated Nickel nanoparticle-catalyzed as Hantzsch reaction.

They reported that The nickel (Ni) nanoparticle has attracted much attention because of its applications as a catalyst and as conducting or magnetic material. [23]

Use of Ni-nanoparticles for the synthesis of polyhydroquinoline derivatives through a four component

Reaction including aromatic aldehydes 1, dimedone 2, and ethyl acetoacetate 3 to give compound 4 in one-pot under microwave irradiation[24] as shown in Scheme 4. It is evident that electron-rich and electron-deficient aldehydes as well as heterocyclic systems such as Thiophene-2-carboxaldehyde and Furan-2-carboxaldehyde reacted smoothly to produce high yields of products.



Scheme 4

They found that aromatic aldehydes containing different functional groups at different positions worked well and did not show differences in the yield

of products. They also examined the recovery and reuse of the catalyst. The catalysts were recovered by a simple work-up using the centrifugation method and reused during four consecutive runs without any apparent loss of activity for the same reaction.

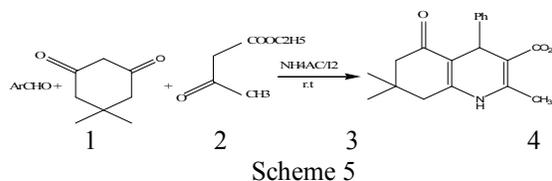
It is noteworthy that the yield of the product in the second, third, and fourth uses was almost the same as that in the first run as has been shown in Table 4. To determine the appropriate concentration of the catalyst Ni nanoparticles, they investigated the model reaction of benzaldehyde, dimedone, ethyl acetoacetate, and ammonium acetate at different concentrations of Ni nanoparticles such as 2, 4, 6, 8, 10, and 12 mol %. They found the products in 30%, 45%, 60%, 75%, 95%, and 95% yields, respectively. This indicates that 10 mol % of Ni nanoparticles produces the best results with respect to product yield.

Table 4. reutilization of Ni nanoparticles in the synthesis of polyhydroquinoline benzaldehyde

Run	Fresh	1	2	3	4
Yield (%)	95	95	93	93	94

In recent times, the use of molecular iodine[25] has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations to afford the corresponding products in excellent yields with high selectivity. The mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to realize several organic transformations using stoichiometric levels to catalytic amounts. Owing to numerous advantages associated with this eco-friendly element, iodine has been explored as a powerful catalyst for various organic transformations.[26]

Shengkai Ko et al. studied about Molecular iodine-catalyzed in one pot Hantzsch reaction [27]. They reported the synthesis of 1,4-DHPs promoted by the catalytic amount of iodine under ambient conditions with excellent yields. In an initial endeavour, benzaldehyde **1**, 1,3-cyclohexanedione **2**, ethyl acetoacetate **3** and ammonium acetate were stirred at room temperature in a few drops of ethanol. After 4 hours, only 56% of product **4** was realized after recrystallization of the crude product from ethanol (entry 1 of Table 5). To improve the product yields and to optimize the reaction condition, iodine was used in catalytic amount (15 mol %) and a reaction was carried out under similar conditions. A significant improvement in the yield of the product **5** (99% Y) was observed (entry 2).



The increase in the quantity of iodine from 15 to 30 mol % not only lessens the reaction time from 4 to 2.5 h, but also enhanced the product yield from 56% to 99% (entry 3). Similarly, using 50 mol % of iodine as catalyst the reaction time further reduced to 1.5 h along with a decrease in the yield of the product **5a** (70% Y). At little elevated temperature (40 °C) using 15 mol % of iodine also gave better results in terms of both yield and reaction time (Table 5).

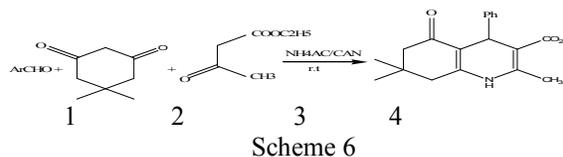
Table 5. the reaction of benzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate. Effect of catalysts

Entry	Iodone (mol%)	Time (h)	Yield (%)
1	0	4	56
2	15	4	99
3	30	2.5	99
4	50	1.5	70

The use of Ceric Ammonium Nitrate (CAN) has received considerable attention as an inexpensive, nontoxic, commercially available catalyst for various organic transformations to afford the corresponding products in excellent yields. Due to the numerous advantages associated with this eco-friendly compound, CAN has been explored as a powerful catalyst for different reactions, such as oxidation, nitration, 1,3-dipolar cycloaddition, thiocyanation, protection, esterification, 1,4-addition, and the Biginelli reaction.[28]

Shengkai Ko et al introduced Ceric Ammonium Nitrate (CAN) catalyzes the one-pot synthesis of polyhydroquinoline via the Hantzsch reaction.[29]

They reported a novel synthesis of 1,4-DHP promoted by a catalytic amount of CAN under ambient conditions to give excellent yields. In an initial endeavor, 1 equiv each of benzaldehyde **1**, 1,3-cyclohexanedione **2**, ethyl acetoacetate **3**, and ammonium acetate were stirred at ambient temperature in ethanol(Scheme 6).



After 4 h, only 56% of the expected. product **5**

was obtained when after workup and recrystallization of the crude product from ethanol (Eq. 1 and entry 1 of Table 6). To improve the yield and optimize the reaction conditions, the same reaction was carried out in the presence of a catalytic amount of 2 mol% of CAN under similar conditions. Surprisingly, a significant improvement was observed and the yield of **5** was dramatically increased to 93% after stirring; the mixture was stirred for only 2 h (entry 2). With this optimistic result in hand, they investigated the best reaction conditions by using different amounts of CAN. An increase in the quantity of CAN from 2 mol% to 5 mol% not only decreased the reaction time from 2 h to 1.5 h, but also increased the product yield slightly from 93% to 98% (entry 3). Although the use of 10 mol% of CAN permitted the reaction time to be decreased to 1 h, the yield unexpectedly decreased to 65% (entry 4). A possible explanation for the low product yield is that the starting material or the product may have been destroyed during the reaction when excess amount (10 mol %) of CAN was used in the exothermic reaction and that 5 mol% CAN was sufficient to catalyze the reaction effectively.

Table 6. the reaction of benzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate. Effect of catalysts

Entry	CAN (equiv)	Time (h)	Yield (%)
1	0	4	56
2	0.02	2	93
3	0.05	1.5	98
4	0.1	1	65

It is well known that bakers' yeast catalyzes the reduction of ketones to optically active alcohols.[29] Reduction of β -ketoesters to β -hydroxy esters provides a representative example[30]. Bakers' yeast has also been successfully used in acyloin type condensations, reduction of carbon-carbon double bonds and oxidative coupling of thiols to disulfides[31]

Lee et al. reported the synthesis of dihydropyridyl compounds via Hantzsch reaction using bakers' yeast as the catalyst[32].

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23. Synthesis of polyhydroquinoline derivatives: A mixture of aromatic aldehyde (1 mmol), dimedone (1 mmol), ammonium acetate (1.5 mmol), ethylacetoacetate (1 mmol), and Ni nanoparticle (10 mol %) which was taken in a Borosil beaker. The reaction mixture was homogenized with the help of a glassrod and irradiated in a microwave oven (540 W) by intervals of 5 s. The progress of the reaction was checked on TLC. After completion, the reaction mixture was cooled at room temperature. Then, it was extracted with ethyl acetate; the organic layer was dried over sodium sulphate and concentrated in a vacuum to afford the crude products. The pure products were obtained by recrystallization from ethanol. Nanoparticles were recovered by centrifuging the aqueous layer and reutilized four times for the same reaction.
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