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Facile $Yb(OTf)_3$ promoted one-pot synthesis of polyhydroquinoline derivatives through Hantzsch reaction

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Abstract—$Yb(OTf)_3$ catalyzed efficient Hantzsch reaction via four-component coupling reactions of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate at ambient temperature was described as the preparation of polyhydroquinoline derivatives. The process presented here is operationally simple, environmentally benign and has excellent yield. Furthermore, the catalyst can be recovered conveniently and reused efficiently.

1. Introduction

4-Substituted 1,4-dihydropyridines (1,4-DHPs) are analogues of NADH coenzymes and an important class of drugs.[1] Current literature reveals that these compounds possess a variety of biological activities. For example, they can cure the disordered heart ratio as the chain-cutting agent of factor IV channel and also have the calcium channel agonist–antagonist modulation activities.[2–6] Furthermore, the hydrogenation methods of these compounds to pyridines are intensively investigated.[7] Classical method for the synthesis of 1,4-dihydropyridines is one-pot condensation of aldehydes with ethyl acetoacetate, and ammonia either in acetic acid or by refluxing in alcohol.[8] This method, however, involves long reaction time, harsh reaction conditions, the use of a large quantity of volatile organic solvents and generally gives low yields. Therefore, it is necessary to develop an efficient and versatile method for the preparation of 1,4-DHPs and the progress in this field is remarkable including recently the promotion of microwave,[9] TMSCl,[10] ionic liquid[11] and polymer.[12,13] But few of them finished the reaction at ambient temperature.

Over the past few years, much effort has gone into 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.[14] 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. As a part of our program aiming at developing selective and environmental friendly methodologies for the preparation of fine chemicals and in continuation of our interest in lanthanide triflates catalyzed organic reactions,[15] in this paper, we wish to highlight our finding about the $Yb(OTf)_3$ catalyzed four-component Hantzsch reaction using ethanol as a solvent at ambient temperature. In this study, $Yb(OTf)_3$ has been employed as a mild and efficient catalyst for Hantzsch condensation.

2. Results and discussion

Firstly, 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 $AlCl_3$

Keywords: $Yb(OTf)_3$; Four-component coupling reactions; Dimedone; Polyhydroquinoline.

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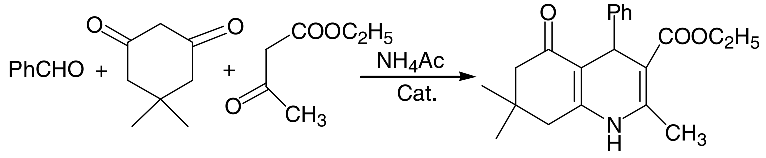


1a **2** **3** **4a**

Scheme 1.

Table 1. The reaction of benzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate:[a] effect of catalysts

Entry	Catalyst	Amount of catalyst (mol%)	Time (h)	Yield[b]
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	$La(OTf)_3$	15	12	84
7	$Yb(OTf)_3$	0.5	5	75
8	$Yb(OTf)_3$	1	5	80
9	$Yb(OTf)_3$	2	5	82
10	$Yb(OTf)_3$	5	5	90
11	$Yb(OTf)_3$	7.5	5	90
12	$Yb(OTf)_3$	10	5	89
13	$Yb(OTf)_3$[c]	5	5	90,91,90,89

[a] All reactions were carried out in ethanol at room temperature.
[b] Isolated yields.
[c] Catalyst was reused four times.

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 $Yb(OTf)_3$ 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 $Yb(OTf)_3$ could improve the reaction significantly. Inspired by the results, we have changed the amount from 0.5 to 10 mol%, finding that 5 mol% of $Yb(OTf)_3$ 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.

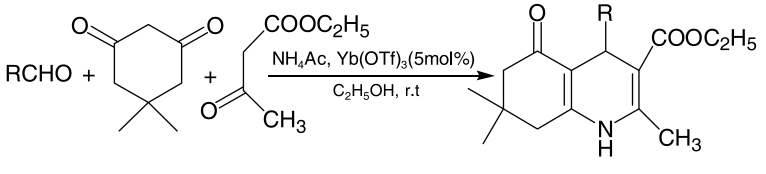
Table 2. The reaction of benzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate:[a] effect of solvents

Entry	Solvent	Time (h)	Yield (%)[b]
1	C_2H_5OH	5	90
2	CH_3CN	5	83
3	Acetone	5	54
4	Toluene	24	26
5	CH_2Cl_2	24	35
6	Cyclohexane	24	17

[a] All reactions were carried out using $Yb(OTf)_3$ at room temperature.
[b] Isolated yields.

We then continued to optimize the model process mentioned above by detecting the efficiency of several classic solvents chosen as the medium for comparison (Table 2). In each case, the substrates were mixed together with 5 mol% $Yb(OTf)_3$ agitated with 3–5 ml solvent. Obviously, the polar solvents such as ethanol and acetonitrile (entry 1, 2) were much better than non-polar solvents (entry 4–6). The results could be interpreted with the much better solubility of the catalyst and the reagents in the polar solvents. When acetone was applied (entry 3), it was found that the reaction proceeded quickly but the obtained yellow solid contained many other by-products which were probably due to the fast self-assembling of reagents or some competitive reactions promoted by $Yb(OTf)_3$ in acetone.

Thus, we selected the optimized reaction condition to exam the universality of this catalyst's application. Various aromatic, aliphatic and heterocyclic aldehydes were selected to undergo the Hantzsch reaction in the presence of catalytic amount of $Yb(OTf)_3$ in ethanol at room temperature (Scheme 2). The results of this study are summarized in Table 3. It was indicated that both electron-rich and electron-deficient aldehydes as well as heterocyclic ones such as furfural, thiophene-2-carboxaldehyde and



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

Scheme 2.

Table 3. $Yb(OTf)_3$ Catalyzed Hantzsch synthesis of polyhydroquinoline derivatives[a]

Entry	R	Time (h)	Product	Yield (%)[b]
1	C_6H_5	5	**4a**	90
2	*p*-MeC_6H_4	2	**4b**	94
3	*p*-$MeOC_6H_4$	4	**4c**	94
4	*p*-HOC_6H_4	8	**4d**	90
5	*p*-$(Me)_2NC_6H_4$	7	**4e**	90
6	*p*-$(Ph)_2NC_6H_4$	2	**4f**	95
7	*p*-FC_6H_4	4	**4g**	91
8	*p*-BrC_6H_4	4	**4h**	95
9	2,4-$Cl_2C_6H_3$	6	**4i**	92
10	$C_6H_5CH{=}CH$	8	**4j**	90
11	2-furyl	2	**4k**	94
12	3-Me-2-thienyl	3	**4l**	94
13	5-Me-2-thienyl	2	**4m**	95
14	2-thienyl	2	**4n**	95
15	3-pyridyl	8	**4o**	90
16	C_2H_5	5	**4p**	86
17	*n*-C_3H_7	8	**4q**	85

[a] All reactions were carried out using $Yb(OTf)_3$ at room temperature in EtOH.
[b] Isolated yields.

pyridine-3-carboxaldehyde worked well, giving high yields of products with little difference. However, aliphatic aldehydes afforded relevant lower yields (entry 16–17).

3. Conclusions

In conclusion, we have demonstrated that four-component Hantzsch reaction can effectively be performed with the promotion of $Yb(OTf)_3$, which provides a simple and efficient method for the synthesis of polyhydroquinoline derivatives. The present method has many obvious advantages compared to those reported in the previous literatures, including the avoidance of discharging harmful organic solvents, the generality, the simplicity of the methodology and the recycling of the catalyst.

4. Experimental

4.1. Methods and apparatus

Melting points were determined on a Kofler hot plate. ^1H NMR spectra were recorded at Bruker WP-500SY (500 MHz) in $CDCl_3$ using TMS as internal standard. FT-IR spectra were obtained as KBr discs on Nicolet 5SXC spectrometer. Mass spectra were determined on a Micromass GCT spectrometer.

4.2. General experiment

To a stirred mixture of dimedone (2 mmol), ethyl acetoacetate (2 mmol) and $Yb(OTf)_3$ (0.06 g, 5 mol%) in ethanol (5 mL), aldehyde (2 mmol) and ammonium acetate (2 mmol) were added at room temperature. The reaction mixture was stirred at room temperature for 5 h. The resulting yellow solid was filtered and recrystallized to give the pure product. The filtrate was concentrated diluted with ethyl acetate, washed with water and the aqueous layer containing the catalyst could be evaporated under reduced pressure to give a white solid, which could be reused without losing catalytic activity.

4.2.1. Compound 4a. Mp: 202–204 °C. ^1H NMR (500 MHz, $CDCl_3$): $\delta=0.94$ (s, 3H), 1.08 (s, 3H), 1.19 (t, $J=7.1$ Hz, 3H), 2.14–2.33 (m, 4H), 2.38 (s, 3H), 4.05 (q, $J=7.1$ Hz, 2H), 5.05 (s, 1H), 5.78 (s, 1H), 7.08–7.31 (m, 5H). IR (KBr): 3290, 1698, 1612 cm^{-1}. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.57; H, 7.51; N, 4.06.

4.2.2. Compound 4b. Mp: 260–261 °C. ^1H NMR (500 MHz, $CDCl_3$): $\delta=0.95$ (s, 3H), 1.07 (s, 3H), 1.21 (t, $J=7.1$ Hz, 3H), 2.12–2.22 (m, 4H), 2.25 (s, 3H), 2.36 (s, 3H), 4.03–4.09 (m, 2H), 5.01 (s, 1H), 5.73 (s, 1H), 7.00 (d, $J=7.9$ Hz, 2H), 7.18 (d, $J=7.9$ Hz, 2H). IR (KBr): 3275, 1702, 1647 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.92; H, 7.79; N, 3.90.

4.2.3. Compound 4c. Mp: 257–259 °C. ^1H NMR

(500 MHz, $CDCl_3$): $\delta = 0.95$ (s, 3H), 1.08 (s, 3H), 1.20 (t, $J = 7.2$ Hz, 3H), 2.16–2.26 (m, 3H), 2.33–2.38 (m, 4H), 3.74 (s, 3H), 4.06 (q, $J = 7.1$ Hz, 2H), 5.00 (s, 1H), 5.81 (s, 1H), 6.72–6.75 (m, 2H), 7.20–7.22 (m, 2H).

4.2.4. Compound 4d. Mp: 232–234 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.94$ (s, 3H), 1.08 (s, 3H), 1.20 (t, $J = 7.2$ Hz, 3H), 2.08–2.18 (m, 3H), 2.20–2.35 (m, 4H), 4.07 (q, $J = 7.6$ Hz, 2H), 4.98 (s, 1H), 5.62 (s, 1H), 6.65 (d, $J = 8.9$ Hz, 2H), 7.16 (d, $J = 8.4$ Hz, 2H).

4.2.5. Compound 4e. Mp: 229–231 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.96$ (s, 3H), 1.07 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H), 2.12–2.23 (m, 3H), 2.28–2.35 (m, 4H), 2.86 (s, 6H), 4.07 (q, $J = 7.4$ Hz, 2H), 4.95 (s,1H), 5.87 (s, 1H), 6.60 (d, $J = 8.4$ Hz, 2H), 7.16 (d, $J = 8.6$ Hz, 2H).

4.2.6. Compound 4f. Mp: 260–262 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.98$ (s, 3H), 1.09 (s, 3H), 1.21 (t, $J = 7.1$ Hz, 3H), 2.19–2.36 (m, 4H), 2.38 (s, 3H), 4.08 (q, $J = 7.1$ Hz, 2H), 5.00 (s, 1H), 5.66 (s, 1H), 6.89–7.21 (m, 4H).

4.2.7. Compound 4g. Mp: 184–186 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.93$ (s, 3H), 1.08 (s, 3H), 1.18 (t, $J = 7.2$ Hz, 3H), 2.19–2.37 (m, 4H), 2.39 (s, 3H), 4.05 (q, $J = 7.2$ Hz, 2H), 5.03 (s, 1H), 5.67 (s, 1H), 6.88 (t, $J = 8.8$ Hz, 2H), 7.26 (t, $J = 7.2$ Hz, 2H).

4.2.8. Compound 4h. Mp: 253–255 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.93$ (s, 3H), 1.08 (s, 3H), 1.19 (t, $J = 7.1$ Hz, 3H), 2.19–2.25 (m, 3H), 2.33–2.40 (m, 4H), 4.05 (q, $J = 7.1$ Hz, 2H), 5.01 (s, 1H), 5.71 (s, 1H), 7.19 (d, $J = 8.2$ Hz, 2H), 7.32 (d, $J = 8.1$ Hz, 2H).

4.2.9. Compound 4i. Mp: 241–244 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.95$ (s, 3H), 1.07 (s, 3H), 1.18 (t, $J = 7.0$ Hz, 3H), 2.10–2.22 (m, 4H), 2.32 (s, 3H), 4.05 (q, $J = 7.0$ Hz, 2H), 5.34 (s, 1H), 6.04 (s, 1H), 7.09–7.34 (m, 3H).

4.2.10. Compound 4j. Mp: 204–206 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.08$ (s, 3H), 1.10 (s, 3H), 1.25–1.31 (m, 3H), 2.29 (t, $J = 7.3$ Hz, 3H), 2.33–2.38 (m, 4H), 4.12–4.21 (m, 2H), 4.71 (d, $J = 7.0$ Hz, 1H), 5.76 (s, 1H), 6.22 (d, $J = 7.1$ Hz, 2H), 7.22–7.30 (m, 5H).

4.2.11. Compound 4k. Mp: 246–248 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.02$ (s, 3H), 1.11 (s, 3H), 1.26 (t, $J = 6.9$ Hz, 3H), 2.20–2.26 (m, 3H), 2.35–2.37 (m, 4H), 4.10–4.18 (m, 2H), 5.25 (s, 1H), 5.80 (s, 1H), 6.02 (s, 1H), 6.20 (s, 1H), 7.18 (s, 1H).

4.2.12. Compound 4l. Mp: 220–222 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.05$ (s, 3H), 1.09 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 2.22–2.36 (m, 4H), 4.15 (q, $J = 7.2$ Hz, 2H), 5.31 (s, 1H), 5.93 (s, 1H), 6.46 (q, $J = 3.2$ Hz, 1H), 6.60 (d, $J = 1.1$ Hz, 1H).

4.2.13. Compound 4m. Mp: 226–229 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.99$ (s, 3H), 1.09 (d, $J = 7.8$ Hz, 3H), 1.23 (t, $J = 7.1$ Hz, 3H), 2.21 (q, $J = 7.0$ Hz, 3H), 2.37 (d, $J = 3.0$ Hz, 4H), 2.40 (s, 3H), 4.06–4.15 (m, 2H), 5.35 (d, $J = 4.1$ Hz, 1H), 5.84 (s, 1H), 6.62 (q, $J = 9.5$ Hz, 1H), 6.90 (d, $J = 5.1$ Hz, 1H).

4.2.14. Compound 4n. Mp: 238–240 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.03$ (s, 3H), 1.10 (s, 3H), 1.26 (t, $J = 7.1$ Hz 3H), 2.26 (t, $J = 3.1$ Hz, 3H), 2.34–2.38 (m, 4H), 4.10–4.14 (m, 2H), 5.42 (s, 1H), 5.89 (s, 1H), 6.82–6.84 (m, 2H), 7.03 (q, 1H).

4.2.15. Compound 4o. Mp: 66–67 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.93$ (s, 3H), 1.08 (s, 3H), 1.18 (t, $J = 7.0$ Hz, 3H), 2.14–2.36 (m, 4H), 2.39 (s, 1H), 4.05 (q, $J = 7.0$ Hz, 2H), 5.03 (s, 1H), 5.71 (s, 1H), 6.87 (t, $J = 8.7$ Hz, 2H), 7.24–7.27 (m, 2H).

4.2.16. Compound 4p. Mp: 145–146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.75$ (t, $J = 7.5$ Hz, 3H), 1.10 (s, 6H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.40–1.46 (m, 2H), 2.16 (d, $J = 7.2$ Hz, 1H), 2.27 (d, $J = 3.1$ Hz, 2H), 2.31 (t, $J = 7.5$ Hz, 4H), 4.02 (t, $J = 5.1$ Hz, 1H), 4.17–4.20 (m, 2H), 5.55 (s, 1H).

4.2.17. Compound 4q. Mp: 147–148 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.78$ (t, $J = 7.2$ Hz, 3H), 1.08 (s, 6H), 1.10–1.37 (m, 6H), 2.13–2.32 (m, 7H), 4.01 (t, $J = 6.1$ Hz, 1H), 4.10–4.23 (m, 2H), 5.59 (s, 1H).

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