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$LaCl_3.7H_20$: An efficient catalyst for one-pot multi-component Synthesis of 1,4-polyhydroquinoline derivatives through unsymmetrical Hantzsch Reaction

Abhijeet S. Somwanshi[a], Vishal U. Pandit[b], Akash D. Gholap[a], Rushikesh D. Ghogare[a], Shivaji S. Pandit[a,*]

[a]*Post Graduate and Research Centre, Department of Chemistry, Padmashri Vikhe Patil College of Arts, Science and Commerce Pravaranagar (Loni kd) Tal. Rahata. Dist. Ahmednagar-413713 (Affiliated to Savitribai Phule Pune University, Pune) (MS), India*

[b]*Sun Pharmaceutical Industries Limited Ahmednagar-414001 (MS, India*

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Abstract

An efficient one-pot multi component synthesis of 1, 4-Polyhydroquinoline derivatives through unsymmetrical Hantzsch reaction using lanthanum chloride heptahydrate ($LaCl_3.7H_2O$) from an aromatic aldehyde, ethyl acetoacetate, dimedone and ammonium acetate as a nitrogen precursor in ethanol at room temperature is described. In the present work, we report lanthanum chloride heptahydrate remarkably non-toxic in nature and ease of handling, we explored the utility of lanthanum chloride heptahydrate as a catalyst for the synthesis of 1, 4-polyhydroquinoline derivatives. We newly report *p*-N, N-dimethylamino-cinnamaldehyde and *m*-chlorobenzaldehyde for the synthesis of 1, 4-Polyhydroquinoline derivatives through unsymmetrical Hantzsch reaction and the products were characterized by IR and ^{1}HNMR spectroscopic methods.

Keywords: Hantzsch reaction; lanthanum chloride heptahydrate; polyhydroquinoline derivatives; aromatic aldehydes.

Introduction

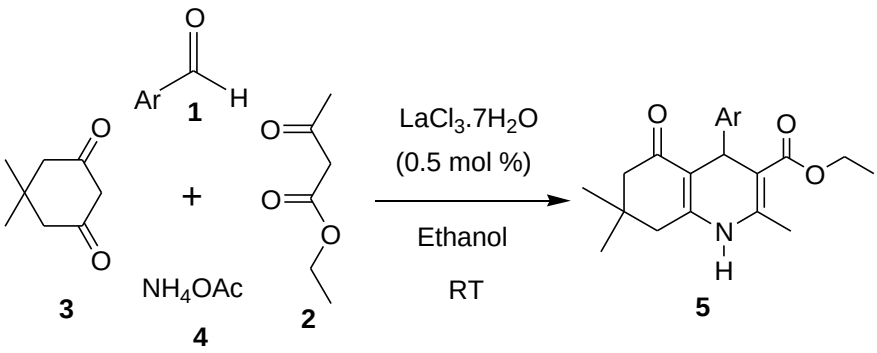
In synthetic organic chemistry, there have been tremendous developments in multi component reactions in modern drug discovery to extent the formation of carbon-carbon bond [1]. Polyhydroquinoline derivatives could be obtained through Hantzsch reaction involving enamine or imine formation-Knoevenagel-Michael cyclocondensation reaction of aromatic aldehydes, dimedone, β-keto esters and ammonium acetate. Polyhydroquinoline derivatives are important due to their biological properties [2]. Furthermore, 1, 4-polyhydroquinoline derivatives have diverse applications in medicinal chemistry such as antiasthmatic, antihypertensive, anti-inflamatory, antimalarial, tyrosine kinase inhibiting materials, neuroprotectant, platelet anti-aggregators activity and chemo sensitizer in tumour therapy [3].

Due to the diverse importance of polyhydroquinoline derivatives several methods have been developed using several catalysts like molecular I_2 [4], TMSCl-NaI [5], ionic liquids [6], HY-

*Corresponding author: Shivaji S. Pandit
Tel: +91 (2422) 273425, Fax: +91 (2422) 273426
E-mail: akankshapandit2002@yahoo.com

Zeolites [7], CAN [8], *p*-TSA [9], polyacids [10], *L*-proline [11], $ZrCl_4$ [12], $Yb(OTf)_3$ [13], TiO_2 and Fe_3O_4 nanoparticles [14], Mont. K-10 [15], $Bi(NO_3)_3.5H_2O$ [16], MW irradiation [17], and ultrasound [18]; solvent free conditions [19] and catalyst free [20] methods are also reported. However, many of these methods have some drawbacks such as low yields, high temperature, long reaction time, occurrence of side products and relatively expensive catalysts.

Lanthanum chloride heptahydrate ($LaCl_3.7H_2O$) is known as an efficient catalyst in the literature for various organic transformations [21-26]. In continuation with our interest in lanthanum chloride heptahydrate [27] due to their remarkably non-toxic nature and ease of handling we explored the utility of lanthanum chloride heptahydrate as a catalyst for the synthesis of 1, 4-polyhydroquinoline derivatives by the condensation of aromatic aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in ethanol at room temperature where the yields obtained are good to excellent (Scheme 1).



Scheme 1. Synthesis of 1,4-polyhydroquinoline derivatives

Experimental

General

All chemicals were used as AR grade purchased from *sd* fine and Loba chemical companies. The solid aldehydes, dimedone, ethyl acetoacetate and ammonium acetate were also used and the liquid aldehydes were used after vacuum distillation. The solvents like methanol, acetonitrile, 1, 4-dioxane, THF, and dichloroethane were used for the optimization of solvents effect for the synthesis of 1, 4-polyhydroquinoline derivatives (5b). The reactions were monitored by TLC using silica gel 60–120 mesh (petroleum ether: ethyl acetate; 7:3). Melting points were recorded by open capillary method and are uncorrected. IR spectra were recorded on Bruker FTIR-240C spectrophotometer on KBr disc. ^{1}H NMR spectra were recorded on 200 MHz spectrometer in $CDCl_3$ using TMS as an internal standard.

Typical procedure

The mixture of 4-methoxy benzaldehyde (5 mmol), dimedone (5 mmol), ethylacetoacetate (5 mmol), ammonium acetate (7.5 mmol) and lanthanum chloride heptahydrate (0.5 mol %) in ethanol (5 mL) was stirred at room temperature. After complete conversion (monitored by TLC) a solid product obtained was filtered and washed with water. The crude product obtained was recrystallized from ethanol. The MP^s are taken by open capillary method and matched with

authentic samples characterized by FTIR and ^{1}HNMR spectroscopy.

Spectroscopic data for newly synthesized compounds

Ethyl 4-(3-chlorophenyl)-1, 4, 5, 6, 7, 8-hexahydro-2, 7, 7-trimethyl-5-oxoquinoline-3-carboxylate (5h)

IR (KBr) $\bar{\upsilon}$ = 3289, 2948, 1677, 1610, 1150, 755 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$) : δ = 1.1 (s, 3H, C-CH_3), 1.8 (s, 3H, C-CH_3), 1.3 (t, *J* = 7.2 Hz, 3H, CH_3 CH_2O), 1.8-2.8 (m, 4H, 2 x CH_2), 1.7 (s, 3H, =C-CH_3), 4.1 (q, *J* = 6.8 Hz, 2H, OCH_2CH_3), 4.4 (s, 1H, Ar-CH), 5.9 (s, 1H, NH), 6.9 (d, *J* = 8.4Hz, 1H, Ar-H), 7.08 - 7.15 (m, 2H, 2 x Ar-H), 7.28 (d, *J* = 8.4Hz, 1H, Ar-H).

Ethyl 4-(4-(dimethylamino)styryl)-1, 4, 5, 6, 7, 8-hexahydro-2, 7, 7-trimethyl-5-oxoquinoline-3-carboxylate (5l)

IR (KBr) $\bar{\upsilon}$ = 3284, 3210, 3056, 2950, 2800, 1676, 1610, 1210 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$): δ= 0.94 (s, 3H, C-CH_3), 1.04 (s, 3H, C-CH_3), 1.33 (t, J = 7.1 Hz, 3H, OCH_2-CH_3), 2.18–2.16 (m, 4H, 2 x CH_2), 2.33 (s, 3H, C-CH_3), 2.85 (s, 6H, $N(CH_3)_2$), 4.07 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.94 (s, 1H, Ar-CH), 5.7 (s, 1H, NH), 6.07 (d, J = 13.7Hz, 1H, C=CH), 6.3 (d, J = 13.7 Hz, 1H, C=CH), 6.57 (d, J = 8.8 Hz, 2H, Ar-H), 7.15 (d, J = 8.8 Hz, 2H, Ar-H).

Results and discussion

A blank experiment was carried out with *p*-methoxybenzaldehyde (5b) (Table 1), dimedone ethylacetoacetate and ammonium acetate in absence of the $LaCl_3.7H_2O$ and the required product was not found (monitored by TLC) even after grinding for 3 h at room temperature (Table 2). Our optimisation studies revealed that the yield increased smoothly with catalyst load up to 0.5 mol % and after that there was sharp drop in the yield. This drop may be attributed to the coagulation of lanthanum chloride heptahydrate which decreases the effective surface area of the catalyst.

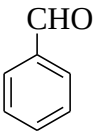
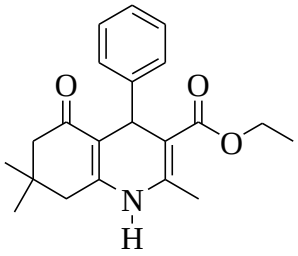
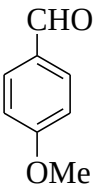
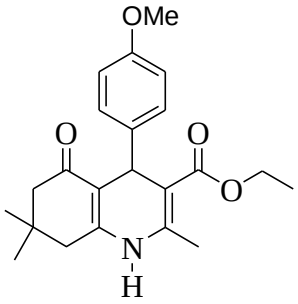
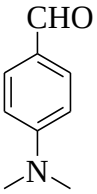
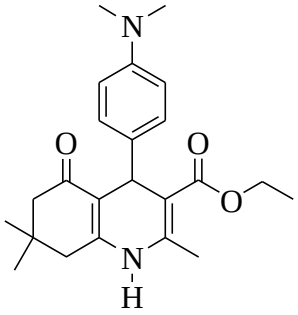
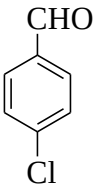
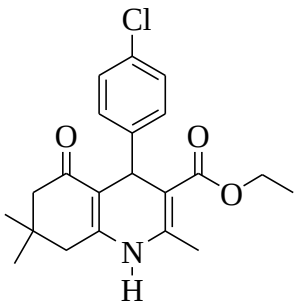
Later on, it was decided that the suitable conditions can be applied for condensation in a solvent. We follow several solvents like methanol, acetonitrile, tetrahydrofuran, ethanol and dichloroethane out of which we observed that ethanol was suitable solvent in presence of $LaCl_3.7H_2O$. The reaction took place within short period of time with good to excellent yield rather than all examined solvents (Table 3). As shown in Table 1, aromatic, hetero-aromatic (5g), and α-β unsaturated aldehydes (5k and 5l), were reacted very well to afford the corresponding products of 1, 4-polyhydroquinoline derivatives in very good to excellent yields. In general, it is to be observed that the aromatic aldehydes having electron-donating groups (5b, 5c, 5i, 5l) and hetero-aromatic compounds (5g) are reacting a little faster when compared with other aldehydes. In a similar manner, aromatic aldehydes containing electron withdrawing groups (5d, 5e, 5f, 5h, 5j, 5m) are reacting comparatively a little slower in term of conversion as well as yields in the presence of the catalyst $LaCl_3.7H_2O$. In general, all the reactions were completed within 1 to 3.5 h, and the obtained yields were 75% to 94% (Table 1).

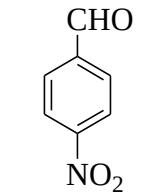
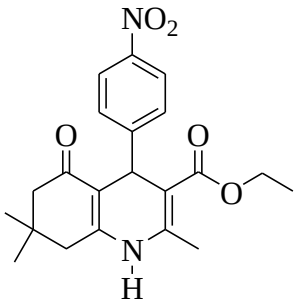
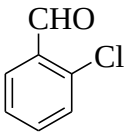
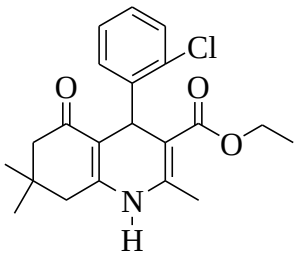
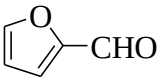
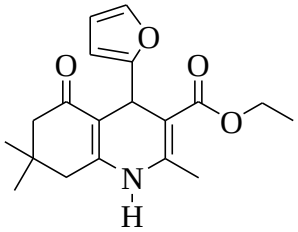
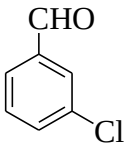
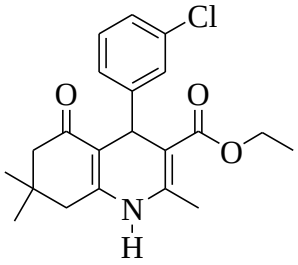
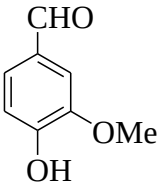
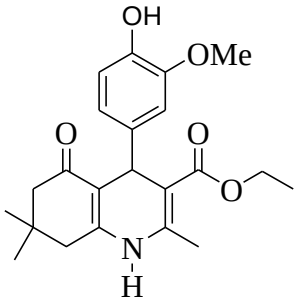
Conclusion

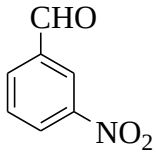
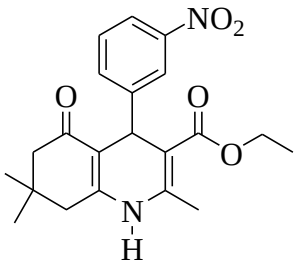
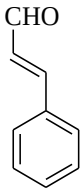
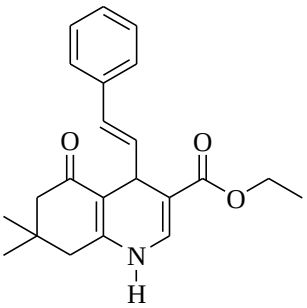
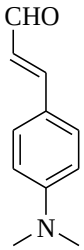
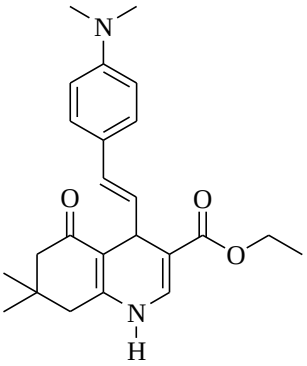
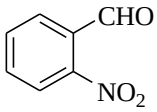
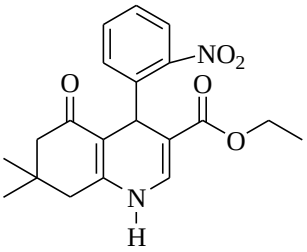
Herein, we report one-pot multi component synthesis of 1, 4-polyhydroquinoline derivatives by polycondensation of aromatic aldehydes, ethyl acetoacetate, dimedone and ammonium acetate using lanthanum chloride heptahydrate ($LaCl_3.7H_2O$) in ethanol at room

temperature. This method is valid alternative to other methods due to a simple workup procedure, mild reaction condition, selectivity, low toxicity, and good to excellent yields.

Table 1. $LaCl_3.7H_2O$ catalyzed synthesis of polyhydroquinoline derivatives.[a,b]

Entry	Aldehyde	Product	Time (h)	Yield[c] (%)	Ref
5a			1	84	[13]
5b			1	94	[13]
5c			2	90	[10]
5d			1.5	88	[6]

5e			3	86[10]
5f			2	82[6]
5g			0.5	90[13]
5h			5	75[d]
5i			2.5	92[6]

5j			3	79[10]
5k			3.5	86[13]
5l			1	89[d]
5m			3	79[10]

[a]Reaction Condition (5b) : aldehydes (5 mmol), dimedone (5 mmol), ammonium acetate (7.5 mmol) and ethylacetoacetae (5 mmol) in presence of $LaCl_3.7H_2O$ (0.5 mol %) in ethanol (5 mL).
[b]All reactions are carried at room temperature.
[c]Isolated Yields.
[d]Newly synthesized and characterized by IR and ^{1}HNMR.

Table 2. Optimization of catalyst for the synthesis of 1,4-polyhydroquinoline derivatives. [a,b]

Entry	Catalyst (mol %)	Time (h)	Yield[c] (%)
1	00	3	No reaction
2	0.1	3	52
3	0.2	3	68
4	0.3	3	75
5	0.4	2	87
6	0.5	1	94
7	0.6	0.5	85
8	0.7	0.5	78

[a]Reaction Condition (5b) : aldehydes (5 mmol), dimedone (5 mmol), ammonium acetate (7.5 mmol) and ethylacetoacetae (5 mmol) in presence of $LaCl_3.7H_2O$ (0.5 mol %) in ethanol (5 ml).
[b]All reactions are carried at room temperature.
[c]Isolated Yields.

Table 3. Optimization of solvent effect on the synthesis 1,4-polyhydroquinoline. [a,b]

Entry	Solvent	Amount of catalyst (mol %)	Time (h)	Yield [c] (%)
1	No solvent	0.5	3	00
2	Methanol	0.5	3	79
3	Acetonitrile	0.5	3.5	82
4	Tetrahydrofuran	0.5	6	60
5	Ethanol	0.5	1	94
6	Dichloroethane	05	4	74

[a]Reaction Condition (5b) : aldehydes (5 mmol), dimedone (5 mmol), ammonium acetate (7.5 mmol) and ethylacetoacetae (5 mmol) in presence of $LaCl_3.7H_2O$ (0.5 mol %) in ethanol (5 ml).
[b]All reactions are carried at room temperature.
[c]Isolated Yields

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