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Light induced synthesis of symmetrical and unsymmetrical dihydropyridines in ethyl lactate–water under tunable conditions

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ABSTRACT

A highly efficient environment-friendly one-pot green methodology has been developed for the synthesis of symmetrical and unsymmetrical 1,4-dihydropyridines and polyhydroquinolines following the multicomponent Hantzsch synthesis under visible light irradiation in ethyl-L-lactate–water solution at room temperature. The present methodology offers several advantages such as simple procedure, greener condition, excellent yields and short reaction time *sans* any catalyst, support or promoter. The developed protocol has been materialized with the involvement of a household compact tungsten lamp as the visible light source, and the manifested high selectivity of the reaction performed in ethyl lactate–water solvent mixture under tunable conditions. The Ca^{2+} channel blocker nitrendipine and nemadipine B were also successfully synthesized applying the developed methodology in high yields.

In recent years, multicomponent reactions (MCRs)[1] have attracted much attention and frequently used to synthesize highly functionalized molecules in a single flask operation. In addition, MCRs in water have been shown to be a powerful tool for developing libraries of medicinal scaffolds as well as for the requirements of green chemistry because of its cheapness, easy availability and benign character.[2]

In continuation of our ongoing research work employing water as a solvent in the multicomponent organic transformation,[3] we have found that the Hantzsch reaction can be designed very smoothly in the presence of water, tuning the polarity by ethyl lactate in the presence of visible light.

1,4-Dihydropyridines (DHPs) are an important class of N-heterocyclic scaffolds of low molecular weight in medicinal field, providing important ligands for biological receptors.[4] These compounds, although described for the first time by Arthur Hantzsch in 1882[5] by successive structural modifications involving additions, reductions and condensations mainly in the 1,2 and 6-positions of the dihydropyridine ring, its unique structural features have recently been recognized as vital drugs in the treatment of angina pectoris,[6] blood pressure and hypertension.[7] Many DHPs are already commercial products such as: amlodipine, felodipine, isradipine, lacidipine, nicardipine, nitrendipine, nifedipine and nemadipine B, of which nitrendipine and nemadipine B exhibit potent calcium channel blocking activities (Fig. 1).

These molecules have gained therapeutic success due to the efficient binding to the active site of the receptors of calcium channels.[8] Their pharmacological properties include neuro and radio protective effects,[9,10] anti-inflammatory[11], and HIV protease inhibition and in the treatment of Alzheimer's disease.[12] Due to the unique molecular structure, certain Hantzsch dihydropyridines are considered as imitates of the biological redox system NAD/$NADH^+$ and have emerged as hydrogen transfer agents in biomimetic reductions[13] and also as photoactive materials.[14]

A variety of methods have been emerged to achieve the synthesis of this dihydropyridine nucleus. Most of the methods[15–27] reported previously have focused on the modification and the optimization of the process parameters of the Hantzsch reaction to minimize reaction time and maximize reaction conversion to achieve the desired 1,4-DHP in high purity. These methodologies are generally based on the usage of ionic liquids, metal/metal-free catalysts, microwave and ultrasound irradiation.[28] Ananthakrishnan et al.[29] have recently reported visible light irradiated Hantzsch reaction in the presence of $[Ru(bpy)_3]^{2+}$ complex under a molecular oxygen atmosphere, where substituted 2-arylpyridine was formed (Scheme 1, case I). But all the literature reports revealed that there still remains the scope to work on the Hantzsch reaction in materializing the synthesis of 1,4-dihydropyridine structural core if visible light can trigger the reaction. Our thinking and untiring effort gave us the success and hence, we report for the first time, a clean, safe, high yielding green methodology for the visible light induced synthesis of symmetrical and unsymmetrical 1,4-dihydropyridines (Scheme 1, case II) in ethyl lactate–water medium.

In the preliminary stage of investigation, we focused on the effect of the heat and visible light on the isolated yield of the model

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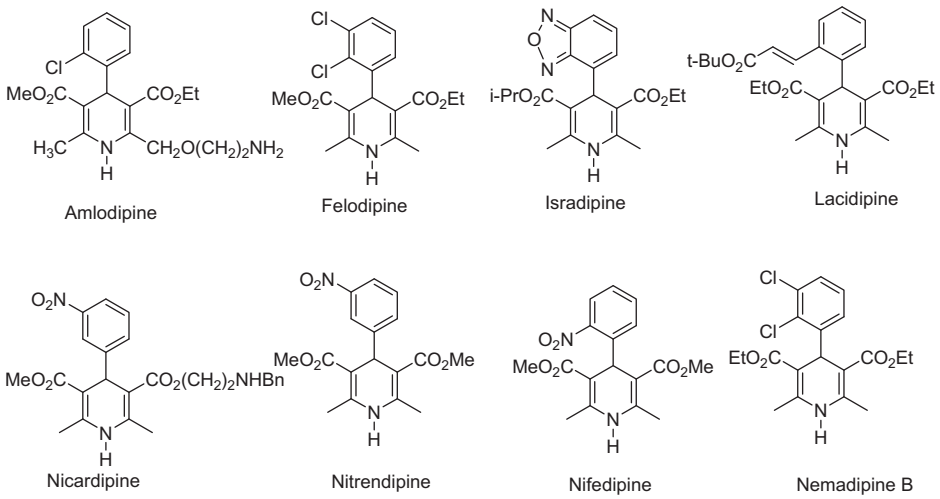
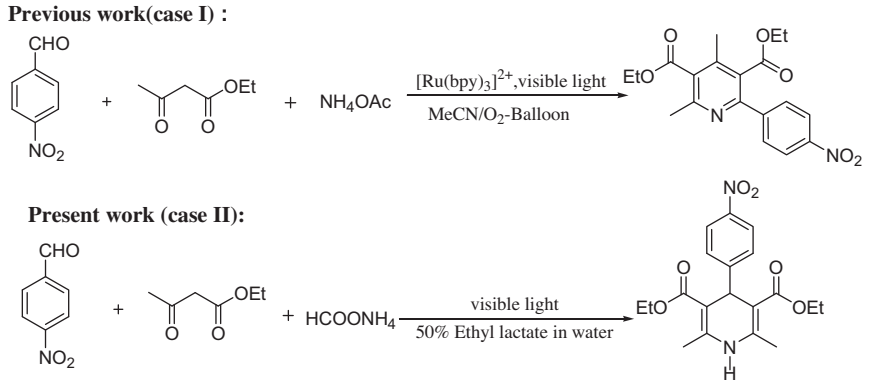
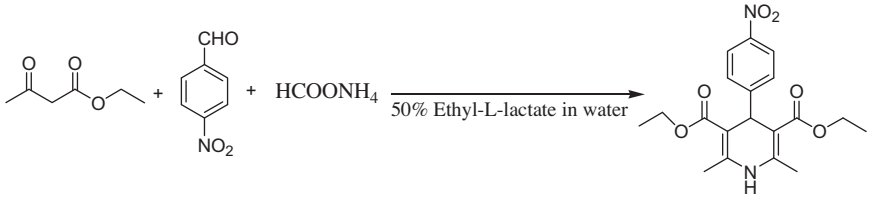


Figure 1. Some bioactive dihydropyridines.



Scheme 1. Comparative study for the formation of 1,4-dihydropyridine.

Table 1
Synthesis of 1,4-dihydropyridines under thermal and light mediated conditions



Reaction condition	Temperature (°C)	Time	Yield[a] (%)
Thermal [b]	27	72 h	–
Visible light (150 W tungsten lamp)[c]	27	150 min	92
Visible light (150 W tungsten lamp)[d]	27	90 min	95
Visible light (150 W tungsten lamp)[e]	27	120 min	88
Visible light (150 W tungsten lamp)[f]	27	135 min	85

[a] Isolated yield of the pure compound.
[b] A mixture of 4-nitrobenzaldehyde (1.0 mmol), ethyl acetoacetate (2.0 mmol) and ammonium formate (1.5 mmol) in 3 mL solvent (1:1 mixture of ethyl-L-lactate and water) was stirred at room temperature (27 °C).
[c] A mixture of 4-nitrobenzaldehyde (1.0 mmol), ethyl acetoacetate (2.0 mmol) and ammonium formate (1.5 mmol) in 3 mL solvent (1:1 mixture of ethyl-L-lactate and water) was irradiated with a 150 W tungsten lamp at room temperature (27 °C).
[d] A mixture of 4-nitrobenzaldehyde (1.0 mmol), ethyl acetoacetate (2.0 mmol), ammonium formate (1.5 mmol) and 10 mol % benzoyl peroxide in 3 mL solvent (1:1 mixture of ethyl-L-lactate and water) was irradiated with a 150 W tungsten lamp at room temperature (27 °C).
[e] A mixture of 4-nitrobenzaldehyde (1.0 mmol), ethyl acetoacetate (2.0 mmol), ammonium formate (1.5 mmol) and 5 mol % benzoyl peroxide in 3 mL solvent (1:1 mixture of ethyl-L-lactate and water) was irradiated with a 150 W tungsten lamp at room temperature (27 °C).
[f] A mixture of 4-nitrobenzaldehyde (1.0 mmol), ethyl acetoacetate (2.0 mmol), ammonium formate (1.5 mmol) and 1 mol % benzoyl peroxide in 3 mL solvent (1:1 mixture of ethyl-L-lactate and water) was irradiated with a 150 W tungsten lamp at room temperature (27 °C).

Table 2
Screening of solvents for the synthesis of 1,4-dihydropyridines under light mediated conditions

Entry	Solvent	Yield[a] (%)
1	Toluene	49
2	Acetonitrile	52
3	DMSO	67
4	Ethanol	70
5	Water	60
6	Ethyl-L-lactate	75

[a] Isolated yield of the pure compound.

Table 3
Effect of solvent polarity on the yield for the one pot synthesis of 1,4-dihydropyridines

Entry	Solvent	Yield[a] (%)
1	100% Ethyl-L-lactate	75
2	85% Ethyl-L-lactate in water	80
3	75% Ethyl-L-lactate in water	86
4	50% Ethyl-L-lactate in water	92
5	25% Ethyl-L-lactate in water	82
6	10% Ethyl-L-lactate in water	73
7	5% Ethyl-L-lactate in water	66

[a] Isolated yield of the pure compound.

reaction of 4-nitrobenzaldehyde (1.0 mmol), ethyl acetoacetate (2.0 mmol) and ammonium formate (1.5 mmol) using ethyl-L-lactate as a solvent. Table 1 clearly exposed the greater efficiency of the visible light mediated protocol than the thermal one.

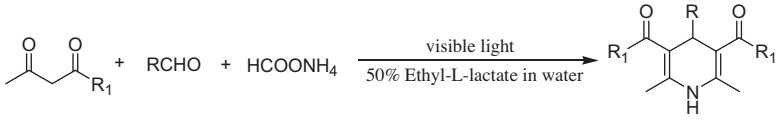
In order to optimize the reaction condition we applied some polar and nonpolar solvents in the three-component reaction for preparing dihydropyridine derivatives (Scheme 1, case II) and also to understand the effect of the solvents. In each case, the substrates were mixed together with 3 mL solvent and were irradiated with a 150 W tungsten lamp for 150 min. at room temperature. The results are shown in Table 2. It is noteworthy to mention that the polar solvents afforded a better yield than the nonpolar ones.

In addition, to obtain a high yielding neat protocol, the polarity of the solvent was tuned[30] by employing water as a cosolvent with ethyl-L-lactate in different proportions. The reaction (Scheme 1, case II) was performed in pure ethyl-L-lactate and then the polarity was tuned with water for better results. Table 3 clearly indicates that 50% ethyl-L-lactate in water produced the optimum polarity of the solvent in which the speedy reaction took place with maximum isolated yield.

To examine the versatility of this methodology, the preparation of symmetrical 1,4-DHPs (Table 4) including the synthesis of the calcium channel blockers nitrendipine and nemadipine B (Table 4, entries 19 and 20), some new unsymmetrical 1,4-DHPs (Table 5) and polyhydroquinolines (Table 6) were carried out using a modified Hantzsch procedure (Scheme 1, case II), developed by us (electronic supplementary information). Investigations of the reaction scope revealed that various aromatic (bearing electron-withdrawing and electron-donating groups), heteroaromatic, aliphatic aldehydes as well can be utilized in this protocol (Tables 4 and 5). The choice of ammonium formate in water as an in situ ammonia and formic acid donor in the presence of visible light drives the reaction very efficiently and eventually satisfied our demand in obtaining optimum yield than other conventional ammonia donor for the specific synthesis of symmetrical and unsymmetrical 1,4 DHPs.[19,25]

It has been observed that better yields are obtained with substrates having electron-withdrawing groups. In case of *ortho* substituted aldehydes, the yields are slightly lower (probably due to steric hindrance) than *para*-substituted ones. Moreover, the enhancement of the reaction rate was observed on addition of catalytic amount (10 mol %) of benzoyl peroxide to the reaction mixture at room temperature and the yield of the product was decreased when the amount of benzoyl peroxide reduced to 1 mol %, whereas the reaction failed to give any product in the absence of visible light source even after 72 h at room temperature. This observation may help us to propose that presumably the reaction takes the course of one-pot photochemical pathway[31] and probably the first step is the hitherto unknown visible light induced Knoevenagel condensation in the presence of ammonium formate to generate the intermediate (**I**). After that, intermediate

Table 4
Synthesis of symmetrically substituted 1,4-dihydropyridines under modified Hantzsch conditions



4a-r

Entry	R	R_1	Time (mins)	Product	Yield[a] (%)
1	C_6H_5	OEt	150	**4a**[15]	90
2	4-O_2N C_6H_4	OEt	150	**4b**[17]	92
3	4-MeO C_6H_4	OEt	160	**4c**[19]	81
4	4-HO C_6H_4	OEt	155	**4d**[19]	86
5	4-Cl C_6H_4	OEt	150	**4e**[19]	91
6	4-F C_6H_4	OEt	160	**4f**[20]	92
7	3-$O_2NC_6H_4$	OEt	150	**4g**[19]	90
8	2-Furyl	OEt	150	**4h**[19]	92
9	*n*-Propyl	OEt	150	**4i**[18]	82
10	2-Pyridyl	OEt	155	**4j**[16]	81
11	4-$Me_2NC_6H_4$	OEt	150	**4k**[17]	80
12	C_6H_5	Me	160	**4l**[17]	90
13	4-$O_2NC_6H_4$	Me	155	**4m**[22]	92
14	4-$MeOC_6H_4$	Me	150	**4n**[23]	85
15	4-HOC_6H_4	Me	160	**4o**[23]	87
16	4-ClC_6H_4	Me	165	**4p**[23]	87
17	2-Furyl	Me	160	**4q**[22]	89
18	*n*-Propyl	Me	160	**4r**[21]	85
19	3-NO_2	OMe	145	**4s**[25]	92
20	2,3-diCl	OEt	155	**4t**[25]	90

[a] Isolated yield of the pure compound.

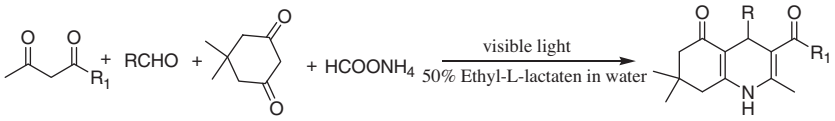
Table 5
Synthesis of unsymmetrically substituted 1,4-dihydropyridines under modified Hantzsch conditions

5a-c

Entry	R	R_1	R_2	Time (mins)	Product	Yield[a] (%)
1	4-$O_2NC_6H_4$	OEt	Me	155	**5a**	81
2	4-F C_6H_4	OEt	Me	150	**5b**	77
3	4-OMe C_6H_4	OEt	Me	160	**5c**	74

[a] Isolated yield of the pure compound.

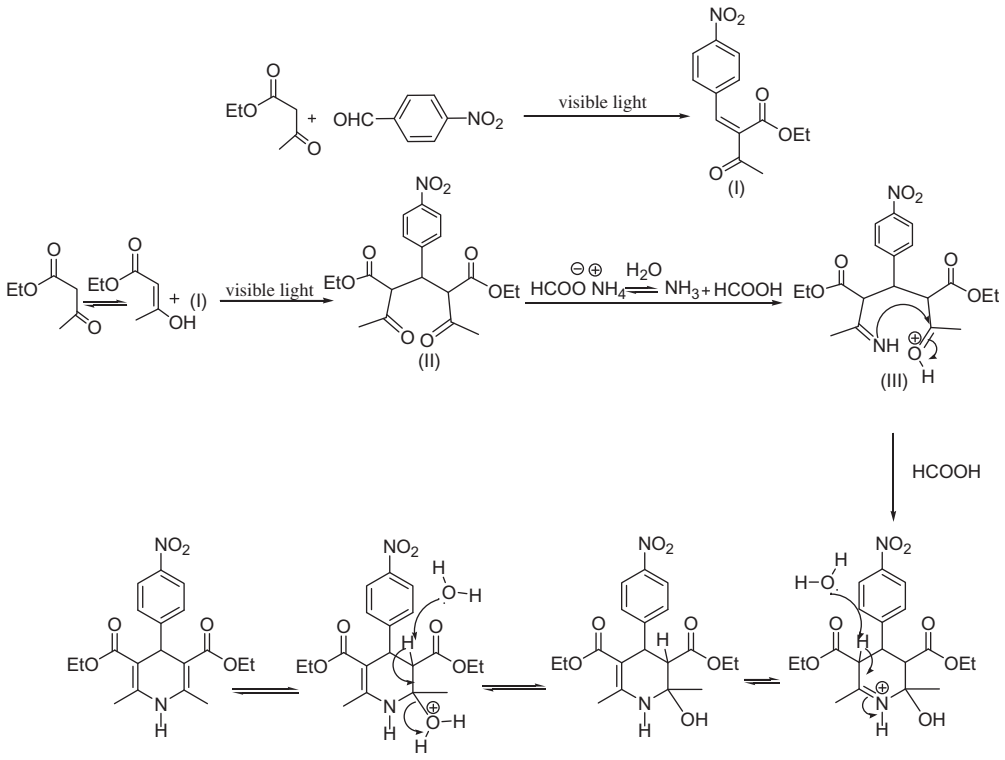
Table 6
Synthesis of polyhydroquinoline derivatives under modified Hantzsch conditions



6a-d

Entry	R	R_1	Time (mins)	Product	Yield[a] (%)
1	4-$O_2NC_6H_4$	OEt	155	**6a**[27]	91
2	4-$MeOC_6H_4$	OEt	160	**6b**[27]	88
3	4-$O_2NC_6H_4$	Me	160	**6c**[26]	83
4	4-$MeOC_6H_4$	Me	155	**6d**[24]	80

[a] Isolated yield of the pure compound.



Scheme 2. Plausible mechanism for the formation of 1,4-dihydropyridine.

(I) suffers nucleophilic attack by the enol form of dicarbonyl compound (already formed a complex with water and ethyl lactate possibly) and to follow the Michael addition sequence to generate 1,5-dioxo compound **(II)** photochemically. Ammonia and formic acid generated from ammonium formate in the presence of water at room temperature convert intermediate **(II)** into intermediate

(III), which then undergoes cyclocondensation and finally generates 1,4-dihydropyridine by following conventional acid catalysis (formic acid from ammonium formate) (Scheme 2) pathway. We have tried to isolate intermediate **(I)** by the two component reaction between ethyl acetoacetate and 4-nitrobenzaldehyde (1:1) in the presence of UV-visible light but the reaction offered no product. Again, the above reaction when carried out in the presence of catalytic amount of ammonium formate (10 mol %), 1,4-DHP (trace amount) was the only isolable product. Analysis of these results revealed that intermediate (**I**) is very much reactive towards the subsequent reaction under multicomponent reaction condition in the presence of visible light and hence could not be detected and evaluated.

In summary, we have developed a new, potentially efficient, absolutely clean, versatile and environment-friendly light induced green procedure devoid of any catalyst support or promoter for the synthesis of 1,4-dihydropyridine derivatives. Possibly, this is the first report for the successful synthesis of 1,4-DHP and polyhydroquinoline derivatives without using any photo-catalyst in the presence of visible light at room temperature. Additionally, the calcium channel blockers nitrendipine and nemadipine B were also successfully synthesized in this developed methodology with excellent yields. Moreover, milder conditions, shorter reaction times, low costs, easy work-up and high yields will make this process attractive over the other available methods and may be considered as an excellent improvement over the existing methods.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.106.

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