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Hantzsch 1,4-dihydropyridine synthesis in aqueous ethanol by visible light

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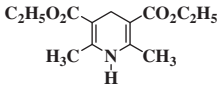
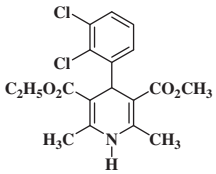
ABSTRACT

A highly efficient environment-friendly Hantzsch 1,4-dihydropyridine synthesis under visible light in aqueous ethanol has been achieved in excellent yield via a one-pot three component reaction of various types of aliphatic and aromatic aldehydes with ethyl acetoacetate and ammonium hydroxide solution.

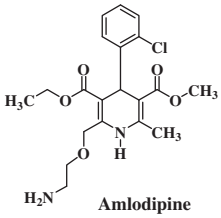
1,4-Dihydropyridines, first synthesized by Arthur Hantzsch in 1882,[1] are an important class of heterocyclic compounds and exhibit a wide range of biological and pharmacological actions such as calcium channel blockers,[2] antitumor,[3] anti-inflammatory,[4] and analgesic[5] activities and more than 12 medicinally important drugs viz. Diludine, Felodipine, Amlodipine, Nimodipin, and so forth are manufactured and used worldwide.[6]



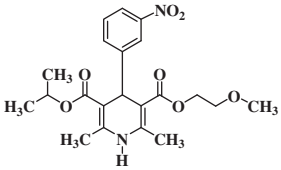
Diludine



Felodipine



Amlodipine



Nimodipin

A large number of methods for the synthesis of the title compounds have been reported using various processes based on microwave assisted reaction,[7] solar thermal energy,[8] ultrasound irradiation,[9] green solvents like ionic liquids or water or ethanol,[10] solid support,[11] and Grignard reagent.[12] It is noteworthy to observe that all these protocols have been accomplished under thermal reaction conditions and disposal of toxic solvents and catalysts often pose a problem.

An attractive area in organic synthesis involves photochemical reactions particularly using visible light in environment-friendly solvents like water or aqueous-ethanol and is generally considered as a clean and green procedure. This type of *photo*-activation of substrates very often minimizes the formation of byproducts and requires much lesser time compared to thermal methods and for this reason, photochemical reactions occupy an interesting position and excellent reviews[13,14] have been published.

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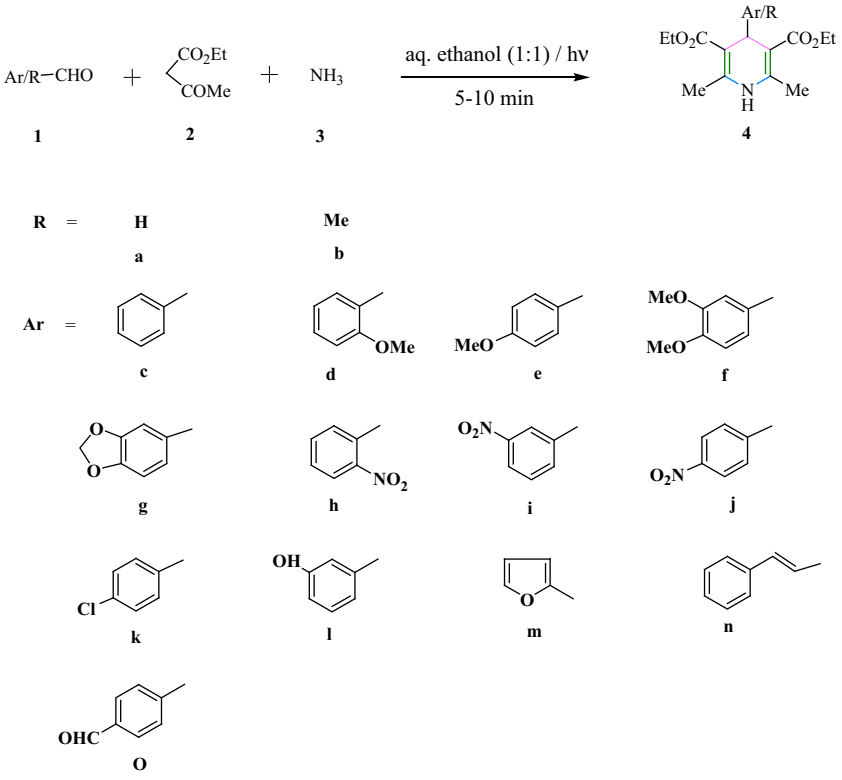
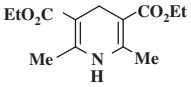
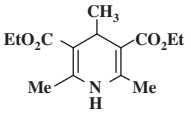
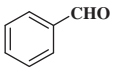
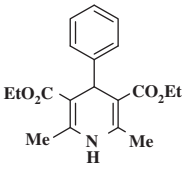
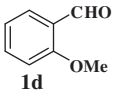
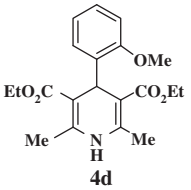


Scheme 1. Photochemical synthesis of Hantzsch 1,4-dihydropyridines.

In connection with our enduring interest for the synthesis of heterocyclic compounds by photochemical reactions both by employing ultraviolet radiation[15] and visible light,[16] we wish to report here, for the first time, a highly efficient, rapid, and useful Hantzsch reaction for the synthesis of 4-alkyl/aryl-1,4-dihydropyridines stimulated by visible light (Scheme 1).

Table 1
Results of the photochemical Hantzsch reaction of aromatic aldehydes, ethyl acetoacetate, and ammonia

Entry	Substrate	Product[a]	Yield[b] (%)	Mp[c] [lit. mp °C]	Time (min)
1	HCHO **1a**	 **4a**	92	182 [183][21]	10
2	H_3C–CHO **1b**	 **4b**	86	130 [130–31][22]	10
3	 **1c**	 **4c**	89	159 [158–160][23]	10
4	 **1d**	 **4d**	96	157 [138–143][12]	5

(*continued on next page*)

Table 1 (*continued*)

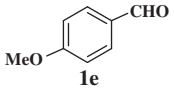
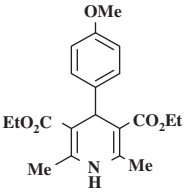
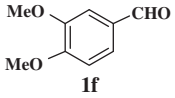
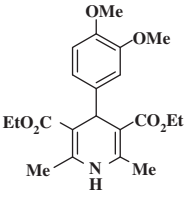
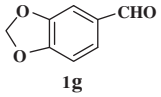
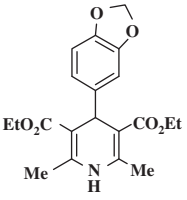
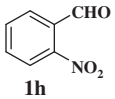
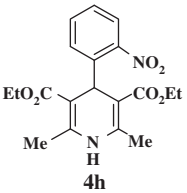
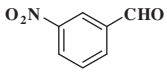
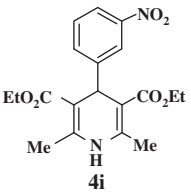
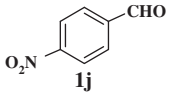
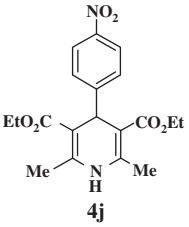
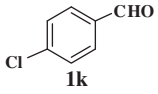
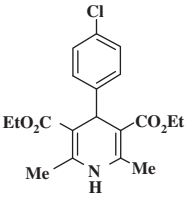
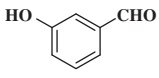
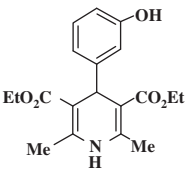
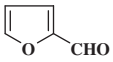
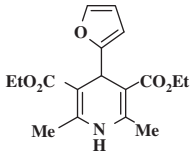
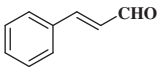
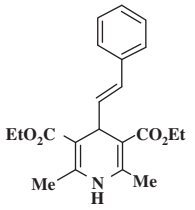
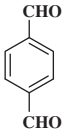
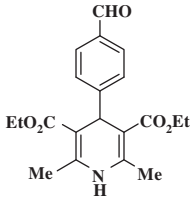
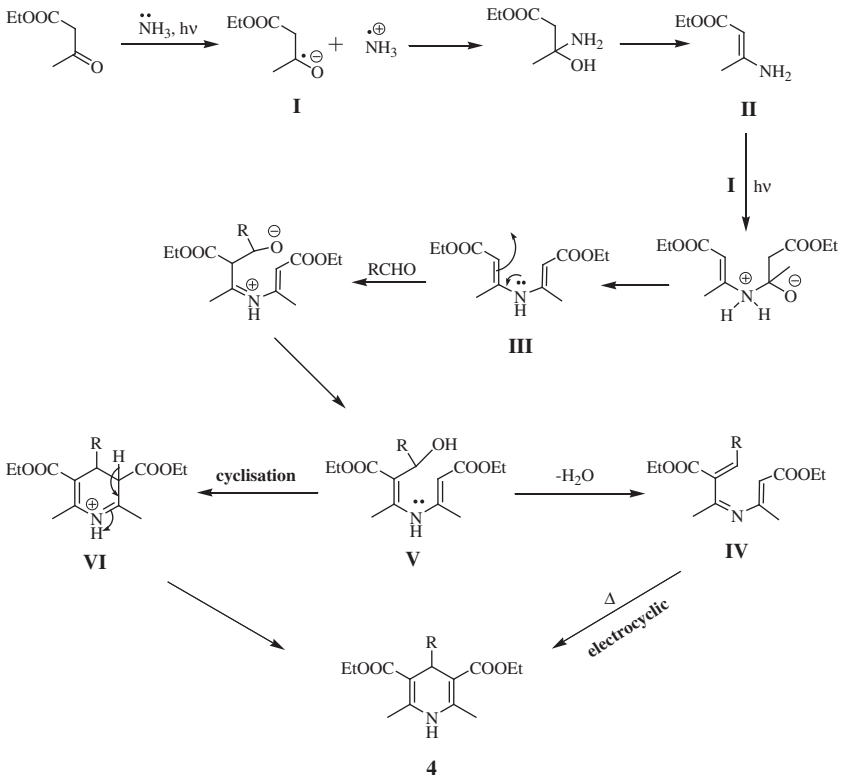
Entry	Substrate	Product[a]	Yield[b] (%)	Mp[c] [lit. mp °C]	Time (min)
5	 **1e**	 **4e**	96	160 [158–160][23]	10
6	 **1f**	 **4f**	91	147	5
7	 **1g**	 **4g**	93	135	5
8	 **1h**	 **4h**	60	118	10
9	 **1i**	 **4i**	63	163 [163][23]	10
10	 **1j**	 **4j**	61	132 [136][23]	10
11	 **1k**	 **4k**	93	150 [144–146][23]	5
12	 **1l**	 **4l**	65	180 [180–182][10e]	10

Table 1 (*continued*)

Entry	Substrate	Product[a]	Yield[b] (%)	Mp[c] [lit. mp °C]	Time (min)
13	 **1m**	 **4m**	86	161 [160–161][23]	5
14	 **1n**	 **4l**	83	147 [147][22]	5
15	 **1o**	 **4o**	59	136–38	15

[a] All products were characterized by their satisfactory spectral data and also by comparison with the literature data (vide Supplementary data).
[b] Yield refers to combined amounts of first and second crops of crystallized products obtained either directly or after chromatography.
[c] Literature reference of melting point.



Scheme 2. Plausible mechanistic pathway for the photochemical Hantzsch synthesis of 1,4-dihydropyridines.

The photochemical reactions were found to be very clean and the products were obtained in extremely pure crystalline states with an average yield of 59–96%. The reaction time varied on an average from 5–10 min (monitored by TLC) and the products are isolated from the reaction mixture in crystalline form by cooling in an ice-bath and need no further crystallization. However, for

entries 1 and 2 (Table 1), the dihydropyridines are obtained by chromatographic separation over silica gel and the results of these experiments are given in Table 1.

When the same reactions were performed under refluxing conditions for 10 min, only ca. 5–10% of the corresponding dihydropyridines were obtained; and the yield of the products increased to 55–65% after 5 h. Thus, the present method, in comparison with thermal ones, is encouragingly effectual and works smoothly both for aromatic or aliphatic aldehydes free from any adhering byproducts or side reactions.

It is well-known that the formation of dihydropyridines by Hantzsch reaction under thermal conditions mechanistically involves reactions of:

a 1,5-dicarbonyl compound formed in situ from ethyl acetoacetate and aldehydes followed by reaction with ammonia,[17]

an α,β-unsaturated carbonyl compound and an enamino ester derived from active methylene component, aldehydes, and ammonia,[18]

a 1,5-dienamino-ammonium salt obtained from an imino ester and enamine,[19]

Aza-Diels–Alder reaction of an aza-diene and a dienophile.[20]

In the present instance, we speculate that the reaction may plausibly be initiated by an electron transfer from ammonia in the presence of light to the carbonyl group of ethyl acetoacetate to produce a radical anion (**I**) that subsequently transforms into an enamino-ester (**II**). Further combination of the anion-radical (**I**) and enamino-ester (**II**) gives rise to bis-enamino-diester (**III**) which on reaction with aldehydes produces the intermediate (**IV**). The product (**4**) is then obtained from **IV** through the intermediacy of either **V** or **VI** as depicted in Scheme 2.

In conclusion, we have developed a potentially efficient, absolutely clean, and very high yielding eco-friendly methodology[24] for the Hantzsch synthesis of 4-alkyl/aryl-1,4-dihydropyridines in aqueous ethanol in one-pot three component condensation and cyclization of various types of aliphatic and aromatic aldehydes with ethyl acetoacetate and ammonium hydroxide solution devoid of any unwarranted side reactions such as Norrish Type I cleavage 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.2012.10.079.

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24. *Method:* Different aliphatic or aromatic aldehydes (**1a–o**) (10 mmol), ethyl acetoacetate (20 mmol), and ammonium hydroxide solution (25%) were taken in aqueous-ethanol mixture (20 mL, 1:1 proportion) and irradiated with a 150 W tungsten lamp (Philips India Ltd). The reaction time varied from 5–15 min (monitored by TLC after 5 min. interval). Upon completion of the reaction, the reaction mixture was cooled and the crystalline product (**4a–o**) so obtained was filtered, washed with water and dried in vacuo. The Hantzsch dihydropyridines were isolated in high yields in essentially pure form.
3,5-diethoxycarbonyl-4-(3,4-dimethoxy)phenyl-2,6-dimethyl-1,4-dihy-dropyridine (***4f***)*:* White needle shaped crystal, Yield: 3.55 g (91%), mp: 147 °C, IR (KBr): ν_{max} 3343, 2982, 1651, 1483, 1209, 770 cm^{-1} ^1H NMR (300 MHz, $CDCl_3$, 22 °C): 1.23 (t, 7.1 Hz), 2.32 (s, 6H), 3.81 (s, 3H), 3.83 (s, 3H), 4.09 (m, 4H), 4.94 (s, 1H) 5.69 (s, 1H), 6.71 (d, 8.2 Hz, 1H), 6.79 (dd, 8.2 Hz, 2.0 Hz, 1H), 6.87 (d,1.6 Hz, 1H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$, 22 °C): δ 167.7, 148.1, 147.2, 143.7, 140.7, 119.8, 111.8, 110.8, 104.1, 59.7, 55.9, 55.7, 38.98, 19.4, 14.3 ppm.
3,5-Diethoxycarbonyl-4-(3,4-methylenedioxy)phenyl-2,6-dimethyl-1,4-dihydropy-ridine (***4g***)*:* Off white flakes, Yield: 3.47 g (93%), mp: 135 °C. IR (KBr): ν_{max} 3307, 2902, 1652, 1486, 799 cm^{-1}.^1H NMR (300 MHz, CDCl3, 22 °C): δ 1.23 (t, 7.2 Hz, 6H), 2.30 (s, 6H), 4.10 (s, 4H), 4.91 (s, 1H), 5.77 (s, 1H), 5.87 (s, 2H), 6.64 (d, 7.9 Hz, 1H), 6.75 (m, 2H) ppm.^{13}C NMR (75 MHz, $CDCl_3$, 22 °C): δ 167.6, 147.1, 145.7, 143.6, 142.0, 120.9, 108.5, 107.5, 104.2, 100.6, 59.7, 39.3, 19.5, 14.2 ppm.
3,5-Diethoxycarbonyl-4-(2-nitro)phenyl-2,6-dimethyl-1,4-dihydropyridine (**4h**): Yellow needle shaped crystal, Yield: 2.25 g (60%), mp: 118 °C. IR (KBr): ν_{max} 3331, 1695, 1489, 1212, 716 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 22 °C): δ 1.15 (t, 7.1 Hz, 6H), 2.32 (s, 6H), 4.06 (m, 4H), 5.68 (s, 1H), 5.84 (s, 1H), 7.48 (m, 4H) ppm.
3,5-Diethoxycarbonyl-4-(4-formyl)phenyl-2,6-dimethyl-1,4-dihydropyri-dine (**4o**):
Faint yellow needle shaped crystal, Yield: 210 mg. (59%), mp: 136–138 °C. ^1H NMR (^1H NMR, $CDCl_3$, 22 °C): δ 9.93 (s, 1H), 7.74 (d, 8 Hz, 2H), 7.46, (d, 8 Hz, 2H), 5.95 (s, 1H), 5.06 (s, 1H), 4.08 (m, 4H), 2.34 (s, 6H), 1.20, (t, 7.1 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 22 °C): δ 192.2, 167.2, 154.8, 144.4, 134.6, 129.6, 128.8, 103.5, 59.9, 40.3, 19.6, 14.2 ppm. HRMS (ESI) *m*/*z* (%): 380.1473(M^++Na).