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Enaminones in a multicomponent synthesis of 4-aryldihydropyridines for potential applications in photoinduced intramolecular electron-transfer systems

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Full Research Paper

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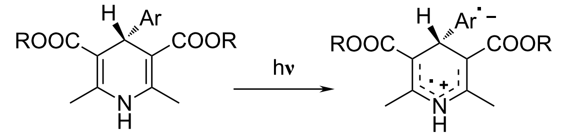
Abstract

An efficient three component reaction with enaminones, primary amines and aldehydes resulted in easy access to 1,4-dihydropyridines with different substituents at the 1-, 3-, 4- and 5-positions. Microwaves improved the reaction yield, reducing also considerably the reaction time and the amount of solvent used. Chiral primary amines gave chiral 1-substituted-1,4-dihydropyridines. The 4-(1-naphthyl) and 4-(phenanthren-9-yl)dihydropyridine derivatives exhibited an interesting photoluminescence behavior, which suggests their potential application as suitable photoinduced intramolecular electron-transfer systems.

Introduction

There is a lot of interest in supramolecular assemblies based on transition-metal ions, which have proved to be useful for a variety of light-induced applications, from molecular machines to systems that mimic chlorophyll photosynthesis [1-6]. Recently, 4-aryl-2,6-dihydropyridine-3,5-dicarboxylate have been investigated as useful organic dyads for the vectorial transport of energy or charge transfer [7,8] (Scheme 1). A few photochemical applications of dyads of this structure have been demonstrated including their use in photosensitive polymers [9,10], in biosensors or in the mapping of enzyme kinetics by means of the fluorescence similarity to NADH [11-13].



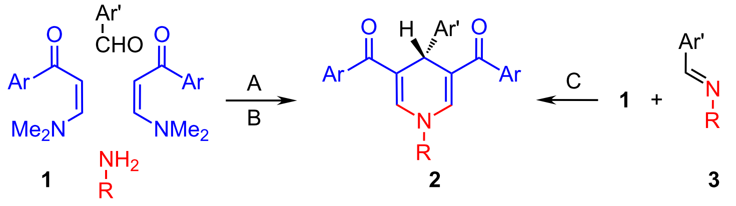
Scheme 1: 2,6-Dihydropyridine-3,5-dicarboxylates as useful organic dyads.

Moreover, there has been recent interest in the synthesis of dihydropyridine derivatives, due to their wide range of biological activity [14,15], by a one-pot three-component reaction with aliphatic/aromatic amines, ethyl propiolate and benzaldehyde [14], or by a cascade reaction of 1-phenylpropynone or ethyl propiolate with primary amines and aldehyde [15].

Enaminones are versatile starting materials for the synthesis of many classes of organic compounds and heterocyclic systems [16,17], and are prepared by various methods, for example, **1** is readily obtained in excellent yield by the condensation of different methylketones with dimethylformamide dimethylacetal (DMFDMA) [16,17]. In this work we investigated the potential utility of **1** in a three-component synthesis of dihydropyridines (DHP) (Scheme 2). This is expected to produce DHP with no substitution at the 2-position and different substituents at the 1-, 3-, 4- and 5-positions. This system contains the characteristic cyclic enaminone chromophore, which is expected to exhibit strong UV absorption with a maximum around 350 nm and extending to the border of the visible region. In the presence of an appropriate electron-acceptor substituent in position 4, the absorbed UV irradiation can cause intramolecular electron transfer, thus converting light into charge separation over a distance of ca. 6 Å. This expectation is based on the recent studies of DHPs containing the enaminocarboxylate chromophore with suitable substituents in the 4-position [7,8]. The DHP products reported in the present synthesis allow an easy method for a wide range of DHP derivatives having this expected characteristic of a photoinduced intramolecular electron-transfer system.

Results and Discussion

In the present work we have investigated the synthesis of DHPs **2** from **1**, aromatic aldehydes, and ammonia or primary amines, in a three-component one-pot reaction. First, we investigated different conditions to achieve this goal (Scheme 2, Table 1). Thus, the reaction (2.1:1:1 molar ratios) of **1**, different primary amines or ammonium acetate, and aromatic aldehydes in acetic acid under reflux (condition A) for 2–4 h gave the corres-



(A) AcOH, reflux 1–3 h, 66–86%
(B) AcOH, MW, 150 °C, 2 min, 84–95%
(C) AcOH, reflux 1–3 h, 74–85%

Scheme 2: Synthesis of dihydropyridine derivatives from enaminones.

Table 1: Synthesis of dihydropyridine derivatives **2a**–**o**, reaction conditions and % yield.

Compound	R	Ar	Ar’	Conditions (% yield)
2a	H	C_6H_5	C_6H_5	A (68), B (94)
2b	H	C_6H_5	*p*-ClC_6H_4	A (70), B (92)
2c	H	C_6H_5	*p*-$CH_3C_6H_4$	A (72)
2d	H	2-thienyl	C_6H_5	A (74)
2e	H	2-furyl	C_6H_5	A (75)
2f	C_6H_5	C_6H_5	C_6H_5	A (66), B (95), C (76)
2g	*p*-HOC_6H_4	C_6H_5	C_6H_5	A (85), B(93), C (74)
2h	C_6H_5	2-furyl	C_6H_5	A (68), B (91)
2i	*p*-$CH_3OC_6H_4$	2-furyl	C_6H_5	A (66)
2j	*p*-$CH_3OC_6H_4$	*p*-ClC_6H_4	C_6H_5	A (85)
2k	*p*-$CH_3OC_6H_4$	2-thienyl	C_6H_5	A (86), B (92), C (85)
2l	C_6H_5	2-thienyl	C_6H_5	A (84), B (90), C (84)
2m	*o*-NCC_6H_4	C_6H_5	C_6H_5	C (77)
2n	*t*-butyl	C_6H_5	C_6H_5	A (78), B (84)
2o	CH_2CO_2H	C_6H_5	C_6H_5	A (73)

A: **1** (2.1 mmol), ArCHO (1 mmol), amine or ammonium acetate (1 mmol) in AcOH (10 mL) heated under reflux for 1–3 h; B: **1** (2.1 mmol), ArCHO (1 mmol), amine or ammonium acetate (1 mmol) in AcOH (1 mL) heated in MW at 150 °C for 2 min; C: **1** (2.2 mmol), **3** (1 mmol) and heating under reflux in AcOH for 1–3 h.

ponding dihydropyridine derivatives **2a**–**o** in 66–86% yields. Conducting this reaction in a microwave at 150 °C increased the yields to 84–95%, decreased the reaction time to 2 min and also reduced the amount of the solvent used by ca. 90% (condition B, Scheme 2). Alternatively, compounds **2** were obtained also in good yield by reacting one equiv of the appropriate Schiff's base **3** with two equiv of the enaminones **1** in acetic acid (condition C, Scheme 2). Table 1 summarizes the dihydropyridines prepared and the yields obtained under different reaction conditions shown in Scheme 2.

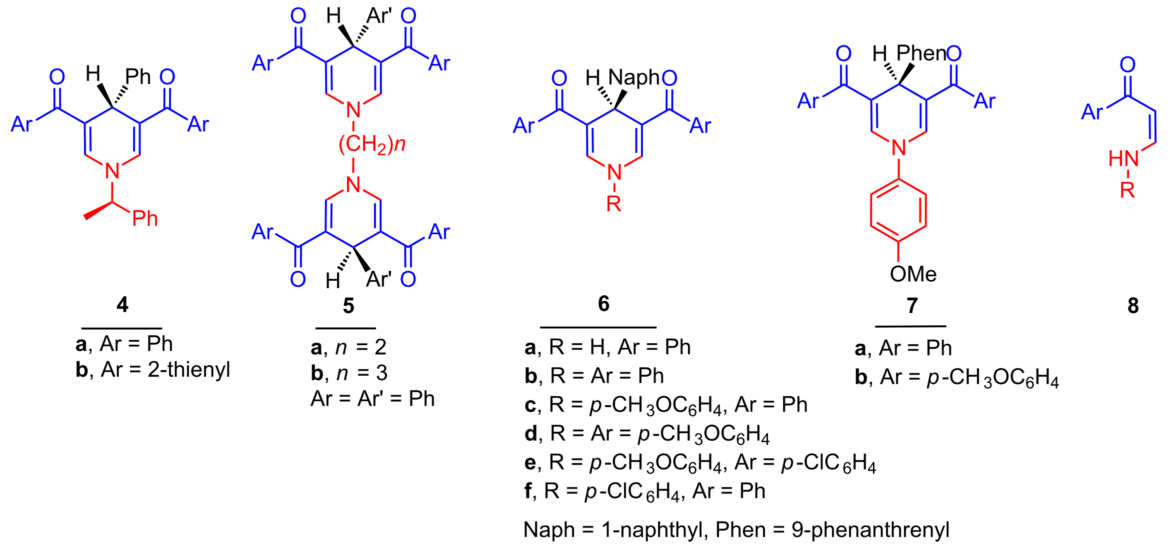
This study was extended to include the synthesis of the chiral (*R*)-1-(1-phenylethyl)dihydropyridines **4a**,**b** obtained in 78% yield by heating in acetic acid and in 93–94% yield by microwave irradiation with *R*-1-phenylethylamine in this three-component reaction. The bis(dihydropyridines) **5a**,**b** were obtained in 75–92% yield with ethylenediamine and 1,3-diaminopropane as the primary amines, respectively. The 4-(1-naphthyl)dihydropyridines **6a**–**f** and 4-(phenanthren-9-yl)dihydropyridine derivatives **7a**,**b** were obtained from 1-naphthaldehyde and phenanthrene-9-carboxaldehyde in moderate yields after heating in acetic acid for 24 h (Scheme 3). The intermediate *N*-substituted enaminones **8** were isolated as the main product when the reaction was conducted for shorter time [15]. The longer reaction time and the low yields are attributed to the steric hindrance of the bulky naphthyl and phenanthryl groups. The flanking dione groups in positions 3 and 5 keep the aryl groups in position 4 perpendicular to the dienaminoketone moiety of the dihydropyridine ring, and this is shown in the X-ray crystal structure of **4b**, **6d**,**f** and **7a** (Figure 1) [18].

Compounds **6** and **7** are similar to the recently reported dihydropyridine dicarboxylate derivatives and are expected to act as photoinduced intramolecular electron-transfer systems [7,8]. Table 2 shows the UV–vis absorption–emission maxima of compounds **6a**–**f** and **7a**,**b**. The investigated compounds exhibit absorption spectra (Figure 2) with λ_{max} = 277–308 nm and

Table 2: The absorption and fluorescence of **6a**–**f**, **7a**,**b**, **2j** and **4a**.

Compound[a]	λ_{max}[b]	log ε_{max}	λ_{em}[c]	Φ_f[d]	Φ_f[e]
6a	383 277	4.125 4.019	454 456	0.0176	0.007
6b	393 303	4.024 4.149	457 457	0.045	0.024
6c	398 301	3.509 3.608	476 476	0.050	0.030
6d	400 294	4.243 4.502	467 469	0.013	0.009
6e	406 305	3.911 3.941	486 488	0.035	0.025
6f	389 306	4.102 4.327	456 456	0.034	0.017
7a	400 301	4.152 4.354	475 475	0.024	0.014
7b	397 301	4.284 4.590	466 475	0.096	0.057
2j	391 308	4.140 3.766	492	0.034	0.015
4a	396 240	3.716 3.745	468	0.035	0.021

[a]All spectra were measured for a 1 × 10^{-4} M solution in acetonitrile; [b]absorption and excitation; [c]emission; [d]taking quinine bisulfate Φ_f = 0.58 as standard at λ_{ex} 350 nm; [e]taking quinine bisulfate Φ_f = 0.55 at λ_{ex} 365 nm.



4
a, Ar = Ph
b, Ar = 2-thienyl

5
a, *n* = 2
b, *n* = 3
Ar = Ar' = Ph

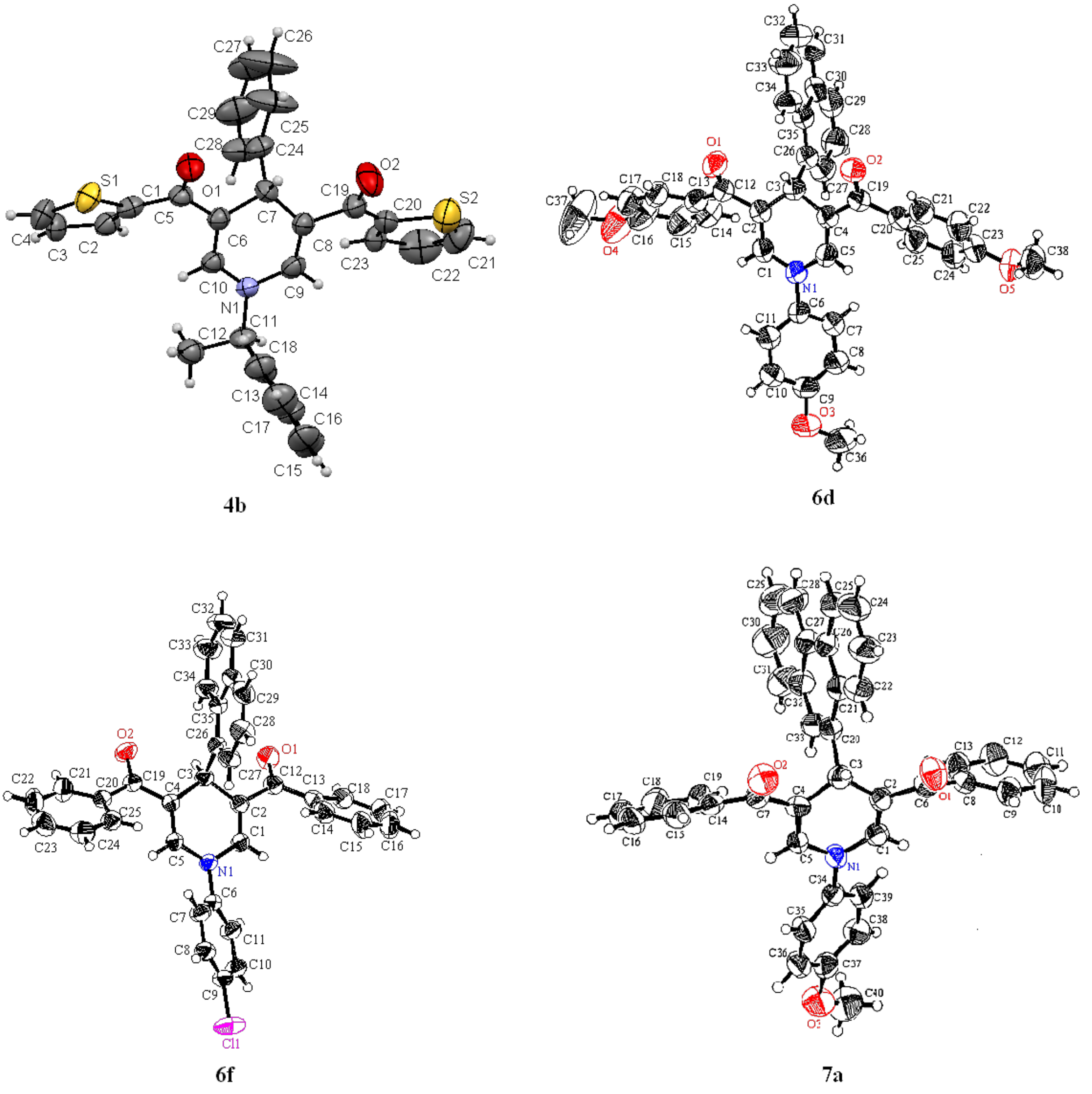
6
a, R = H, Ar = Ph
b, R = Ar = Ph
c, R = *p*-$CH_3OC_6H_4$, Ar = Ph
d, R = Ar = *p*-$CH_3OC_6H_4$
e, R = *p*-$CH_3OC_6H_4$, Ar = *p*-ClC_6H_4
f, R = *p*-ClC_6H_4, Ar = Ph

7
a, Ar = Ph
b, Ar = *p*-$CH_3OC_6H_4$

8

Naph = 1-naphthyl, Phen = 9-phenanthrenyl

Scheme 3: Dihydropyridine derivatives **4**–**7** and enaminone **8**.



4b 6d 6f 7a

Figure 1: ORTEP of compounds **4b**, **6d**, **6f** and **7a**.

389–406 nm. The shorter absorption wavelength is attributable to the aryl groups and the longer absorption is due to the DHP moiety [8]. Upon excitation at each of these two λ_{max} these compounds gave fluorescence spectra (Figure 3 and Figure 4) with λ_{max} = 454–492 nm (Table 2). This photoluminescence behavior of **6** and **7** resembles that of dihydropyridinedicarboxylate derivatives [7,8], which suggests their potential application as suitable photoinduced intramolecular electron-transfer systems. For comparison the absorption and emission spectra of **2j** and **4a** have also been measured, and the results indicate weak emissions relative to **7b**. This compound, with the *p*-methoxyphenyl groups in the 1, 3 and 5 positions, showed the most intense absorption (Figure 2) and emission spectra (Figure 4) upon excitation in the 400 nm ranges. Relative fluorescence quantum yields (Table 2) were measured at 25 °C, taking quinine bisulfate (in 0.1 M H_2SO_4, 22 °C) as standard (Φ_f = 0.58 at λ_{ex} = 350 nm, Φ_f = 0.55 at λ_{ex} = 365 nm).

This synthesis of dihydropyridines was extended to enamino aldehyde **9**, enamino ester **11** and enaminonitrile **13**. Thus, 1,4-dihydropyridine-3,5-dicarboxaldehyde **10a**,**b**, 1,4-dihydropyridine-3,5-dicarboxylate **12** and 1,4-dihydropyridine-3,5-dicar-

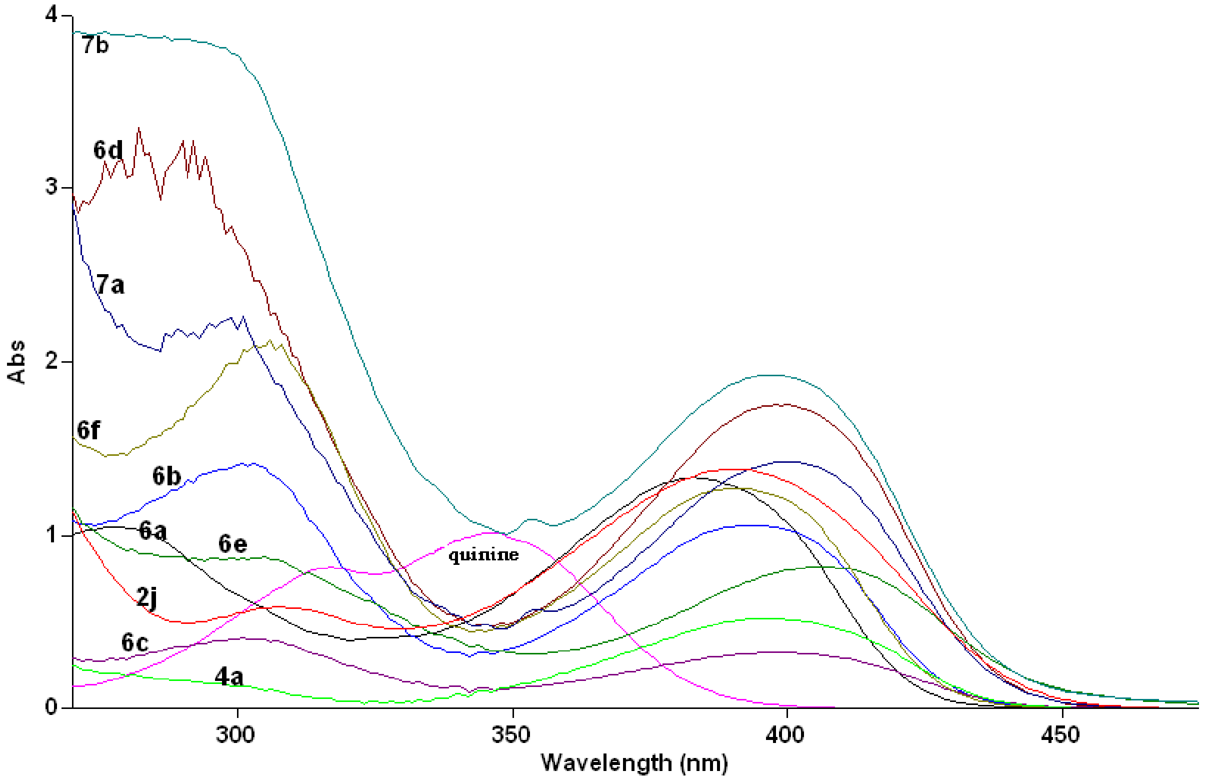


Figure 2: Absorption spectra of compounds **2j**, **6a**–**f** and **7a**,**b** in acetonitrile (1 × 10^{-4} M).

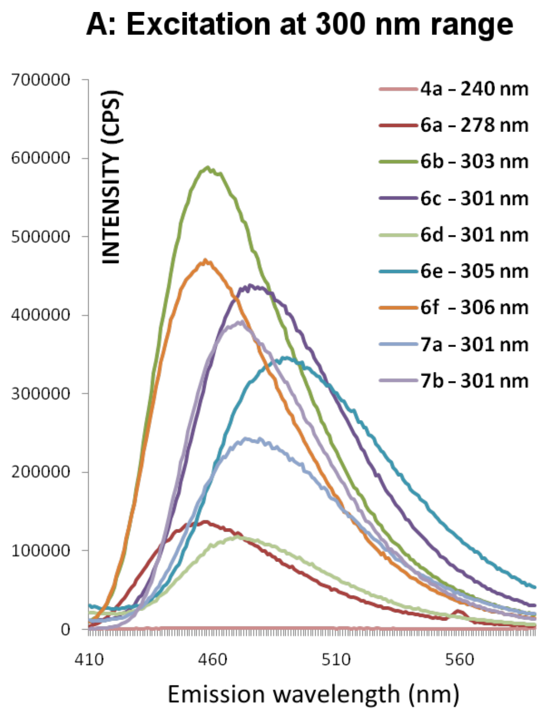


Figure 3: Emission spectra of compounds **4a**, **6a**–**f** and **7a**,**b** after excitation at their absorption λ_{max} in the range of 240–306 nm in acetonitrile (1 × 10^{-4} M).

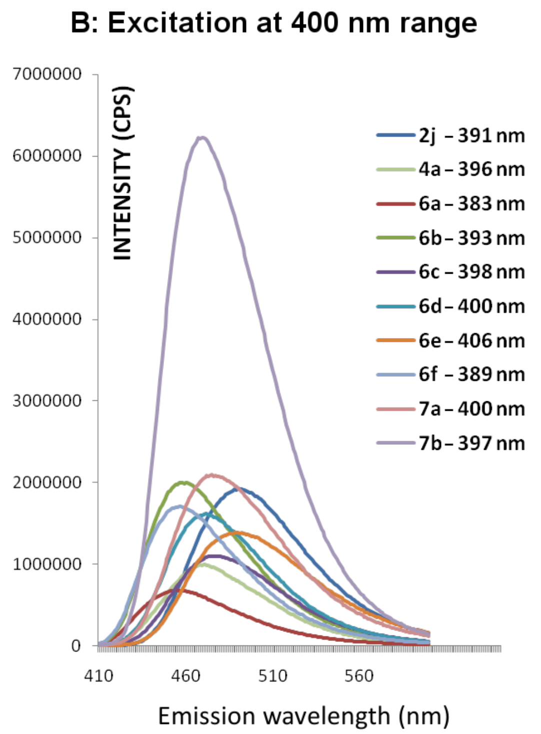
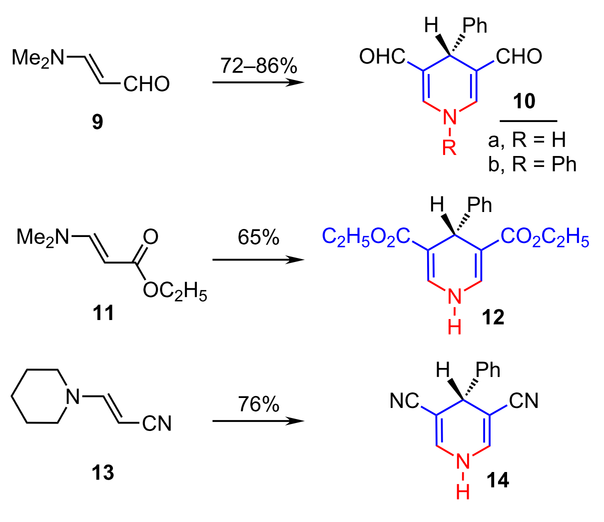


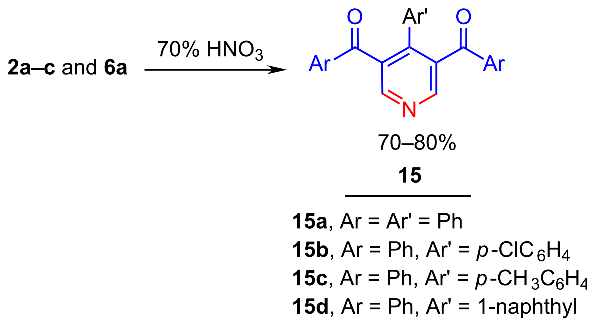
Figure 4: Emission spectra of compounds **2j**, **4a**, **6a**–**f** and **7a**,**b** after excitation at their absorption λ_{max} in the range of 383–406 nm in acetonitrile (1 × 10^{-4} M).

bonitrile **14** were successfully obtained by reacting β-*N,N*-dimethylaminoacrolein (**9**), ethyl β-*N,N*-dimethylaminoacrylate (**11**) or β-piperidinoacrylonitrile (**13**) with the appropriate aldehyde and primary amine under the same reaction conditions (A, B) (Scheme 4).



Scheme 4: Synthesis of dihydropyridines from an enamino aldehyde, an enamino ester and an enaminonitrile.

Compounds **2a–c** and **6a** were readily oxidized to the corresponding pyridine derivatives **15a–d** by stirring in aqueous nitric acid (70%) at 5 °C to room temperature (Scheme 5). The X-ray structure data of **15d** (Figure 5) [18] indicates the nonplanarity of the different aryl groups with respect to any of the conjugated systems involved in the pyridine ring.



Scheme 5: Nitric acid oxidation of dihydropyridines **2a–c** and **6a**.

Conclusion

The present work offers an alternative and efficient method for the synthesis of dihydropyridines with potentially wide applicability, compared to the recently reported [14] synthesis of 3,5-dibenzoyl-1,4-disubstituted-dihydropyridine derivatives. The present method has the following advantages:

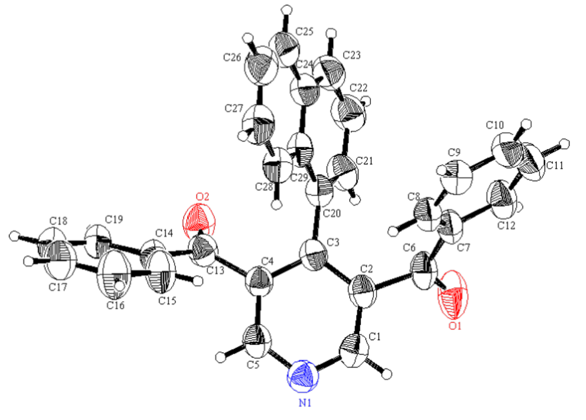


Figure 5: ORTEP of compound **15d**.

1. The starting enaminones **1** can be readily synthesized from any methylketone, whereas the reported method is limited to arylpropynones.
2. This is a one-pot three-component reaction; on the other hand, the reported method involves two steps starting with the reaction of phenylpropynone with a primary amine, followed by reaction with different aldehydes.
3. The synthesis of suitable substituted derivatives, such as **6** and **7**, possessing interesting fluorescence and structural characteristics for remarkable photoluminescence behavior, which suggests their potential application as suitable photoinduced intramolecular electron-transfer systems.
4. This method can be extended to the synthesis of enaminoaldehydes **10**, enaminoesters **12** and enaminonitriles **14**.

Experimental

General: All melting points are uncorrected. The microwave oven used was a single-mode cavity explorer microwave (CEM Corporation, NC, USA) and irradiation was conducted in heavy-walled pyrex tubes (capacity 10 mL). IR spectra were recorded in KBr disks on a Perkin Elmer System 2000 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX 400, 400 MHz, Avance II 600, 600 MHz superconducting NMR spectrometers. Mass spectra were measured on GCMSDFS-Thermo and with LCMS by using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Microanalyses were performed on LECO CH NS-932 Elemental Analyzer. The UV–vis absorption spectra were scanned by using a Varian Cary 5 instrument in the wavelength range 250–450 nm with dry, clean quartz cuvettes of 1.0 cm path length. From the spectra obtained, absorbance values at λ_{max} were used to calculate the extinction coefficient. The emission spectra were measured at the same concentration after excitation at the specified λ shown in Figure 2, by using a Horiba-Jobin Vyon Fluromax-4 instrument. Relative fluorescence quantum yields were measured at 25 °C taking quinine bisulfate (in 0.1 M H_2SO_4, 22 °C) as standard ($\Phi_f = 0.58$ at λ_{ex} = 350 nm, $\Phi_f = 0.55$ at λ_{ex} = 365 nm) [19]. X-rays structures were determined by single-crystal X-ray crystallography RIGAKU RAPID II. Enaminones **1** were prepared according to the previously reported procedure [16,17] and compound **8** was identical with an authentic sample that was prepared as reported [15].

Supporting Information

Supporting Information File 1

Experimental procedures and characterization of compounds, including copies of ^{1}H and ^{13}C NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-50-S1.pdf]

Acknowledgements

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18. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 867373 (**4b**), CCDC 827963 (**6d**), CCDC 827962 (**6f**), CCDC 827961 (**7a**), CCDC 827960 (**15d**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk).
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