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

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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-dicarboxylates 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].

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, I 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 I 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 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 molar ratios) of I, different primary amines or ammonium acetate, and aromatic aldehydes in acetic acid under reflux (condition A) for 2–4 h gave the corres-

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

| Compound | R    | Ar      | Ar′     | Conditions (% yield) |
|----------|------|---------|---------|----------------------|
| 2a       | H    | C6H5    | C6H5    | A (68), B (94)        |
| 2b       | H    | C6H5    | p-ClC6H4| A (70), B (92)        |
| 2c       | H    | C6H5    | p-CH2C6H4| A (72)              |
| 2d       | H    | 2-thienyl | C6H5 | A (74)            |
| 2e       | H    | 2-furyl  | C6H5    | A (75)              |
| 2f       | C6H5 | C6H5    | C6H5    | A (66), B (95), C (76) |
| 2g       | p-HOC6H4 | C6H5 | C6H5    | A (85), B (93), C (74) |
| 2h       | C6H5 | 2-furyl  | C6H5    | A (68), B (91)        |
| 2i       | p-CH2OC6H4 | 2-furyl | C6H5    | A (66)              |
| 2j       | p-CH2OC6H4 | p-ClC6H4 | C6H5 | A (85)            |
| 2k       | p-CH2OC6H4 | 2-thienyl | C6H5 | A (86), B (92), C (85) |
| 2l       | C6H5 | 2-thienyl | C6H5 | A (84), B (90), C (84) |
| 2m       | α-NCC6H4 | C6H5    | C6H5    | C (77)              |
| 2n       | t-butyl | C6H5    | C6H5    | A (78), B (84)        |
| 2o       | CH2CO2H | C6H5    | C6H5    | 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.
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

| Compound | λ_max (nm) | log ε_max | λ_em (nm) | Φ_f | Φ_e |
|----------|-----------|-----------|-----------|-----|-----|
| 6a       | 383       | 4.125     | 454       | 0.0176 | 0.007 |
| 6b       | 393       | 4.024     | 457       | 0.045 | 0.024 |
| 6c       | 398       | 3.509     | 476       | 0.050 | 0.030 |
| 6d       | 400       | 4.243     | 467       | 0.013 | 0.009 |
| 6e       | 406       | 3.911     | 486       | 0.035 | 0.025 |
| 6f       | 389       | 4.102     | 456       | 0.034 | 0.017 |
| 6g       | 400       | 4.152     | 475       | 0.024 | 0.014 |
| 6h       | 397       | 4.284     | 466       | 0.096 | 0.057 |
| 6i       | 308       | 3.766     | 492       | 0.034 | 0.015 |
| 4a       | 396       | 3.716     | 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_e = 0.55 at λ_{max} 365 nm.

![Scheme 3: Dihydropyridine derivatives 4–7 and enaminone 8.](image-url)
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 \( \lambda_{\text{max}} \) these compounds gave fluorescence spectra (Figure 3 and Figure 4) with \( \lambda_{\text{max}} = 454–492 \) 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 \( \text{H}_2\text{SO}_4 \), 22 °C) as standard (\( \Phi_f = 0.58 \) at \( \lambda_{\text{ex}} = 350 \) nm, \( \Phi_f = 0.55 \) at \( \lambda_{\text{ex}} = 365 \) nm).

This synthesis of dihydropyridines was extended to enamine aldehyde 9, enaminoo 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).

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.

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:

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 enaminooaldehydes 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 $\lambda_{\text{max}}$ were used to calculate the extinction coefficient. The emission
spectra were measured at the same concentration after excitation at the specified \( \lambda \) shown in Figure 2, by using a Horiba-Jobin Vyon Fluoromax-4 instrument. Relative fluorescence quantum yields were measured at 25 °C taking quinine bisulfate (in 0.1 M H\(_2\)SO\(_4\), 22 °C) as standard (\( \Phi_F = 0.58 \) at \( \lambda_{ex} = 350 \text{ nm} \), \( \Phi_F = 0.55 \) at \( \lambda_{ex} = 365 \text{ nm} \)) [19]. X-rays structures were determined by single-crystal X-ray crystallography RIGAKU RAPID II. Enaminoles 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/supporting/1860-5397-8-50-S1.pdf]

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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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