Journal of Fluorescence (2023) 33:1995–2001
https://doi.org/10.1007/s10895-023-03212-4

RESEARCH

Synthesis of Highly Heterocyclic Fluorescent Molecules: 2-imino-2H-pyrano[3,2-*c*] Pyridin-5(6*H*)-ones Derivatives

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Received: 9 February 2023 / Accepted: 13 March 2023 / Published online: 22 March 2023

Abstract
New highly fluorescent 2-imino-2*H*-pyrano[3,2-*c*]pyridin-5(6*H*)-onesderivatives were synthesized using a simple route. The present molecules were prepared by two methods with good yield. The structures were characterized by NMR^{1}H, ^{13} C, and elemental analysis. Also, the effect of solvent and concentration on the fluorescence properties were demonstrated. However, the high fluorescence intensity in the range of 70,000–75,000 a. u. was obtained with a concentration equal to 10^{-6} M of prepared molecules. The intensity was influenced also by the molecule structure and solvent.

Keywords Pyrane · N-alkylated 2-pyridone · 2*H*-pyrans · 2-imino-2*H*-pyrano[3,2-*c*]pyridin-5(6*H*)-ones · Fluorescence

Introduction

Pyrano[3,2-*c*]pyridines are functionalized oxygen and nitrogen containing heterocyclic consisting of pyrane and pyridone units (Fig. 1). Generally, pyranes compounds have been considered as biologically active molecules, and valuable scaffolds founded in many natural products including carbohydrates, antibiotics, and pheromones [1]. Also, it can be used as ligands for metal complexes, electroluminescent devices,and medicinal chemistry [2, 3] because of their potential fluorescent properties [4]. However, pyrane [5] and 2-pyridone rings were used as fluorophores and presented a high fluorescent properties [6].Also, it formed a new fluorescent dyes [7].

Recently, the N-Alkylated 2-pyridone is one of the most important heterocyclic compounds which have lately attracted considerable interest owing to their wide range of applications in various fields [8, 9] as fluorescence, and pharmacology [10]. Multi-compound reaction is one of the most methods to produce heterocyclic derivatives [11–13]. However, the synthesis of pyrano[3,2-c]pyridones have been reported. In 2010,Xuesen Fan et al. [14] reported the synthesis of novel pyrano[3,2-*c*]pyridines via a multicomponent reaction of 5-formyl-2'-deoxyuridine and 4-hydroxylpyridones and malononitrile using [bmim]BF_4 as an ionic liquid at 80 °C. Then, Anatoliy et al. [15] reported two stepwise versions of this process involving the synthesis of the intermediate Knoevenagel products and their subsequent reactions with 4-hydroxy-6- methyl-2(1*H*)-pyridone derivative in refluxing methanol in the presence of NEt_3.In 2016,Michail studied another domino reaction for synthesized Spiro[indoline-3,4'-pyrano[3,2-*c*] pyridine]-2,5'(6'*H*)-diones, by condensing of one pot isatin, 4-hydroxy-6-methylpyridin-2(1*H*)-one, and malononitrile in the presence sodium acetate as a catalyst under refluxing ethanol for 15 min [16]. Fluorescencebased on heterocyclicmolecules gives solution of several chemistry problems, such as metal ion detection, cancer imaging, cyanure elimination [17].Therefore, the development of fluorescent properties of molecules adds a considerable value for environmental and life science. Several researchers reported the synthesis of fluorescent molecules such as coumarins [18], imidazole [19], pyrazole [20, 21], chromene [22], pyrimidin-one [23] and bis-3-cyano-2-pyridones [24], this later presented a high fluorescent intensity and can be used as ion indicator.

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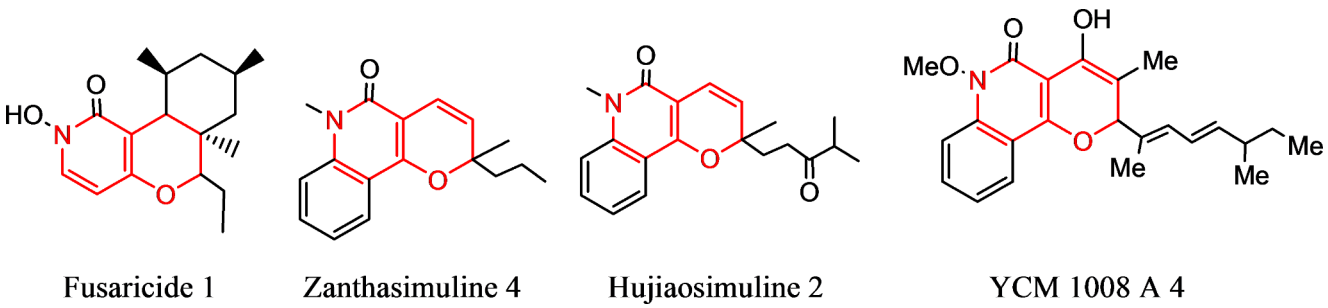
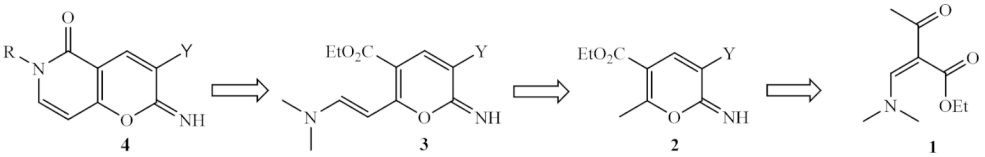


Fig. 1 Alkaloids based on pyrano[3,2-*c*]pyridone scaffolds

Scheme 1 General retro-synthetic rote of 2-imino-2*H*-pyrano[3,2-*c*] pyridin-5(6*H*)-ones



As a part of our aim at the development of new simple and efficient procedures for the synthesis of some important heterocyclic systems and their application [25], herein, we report a novel approach to synthesize various pyrano[3,2-*c*]pyridones derivatives. Also, to our knowledge, the fluorescence properties of substituted pyrano[3,2-*c*]pyridones derivatives was studied for the first time till now.

Results and Discussions

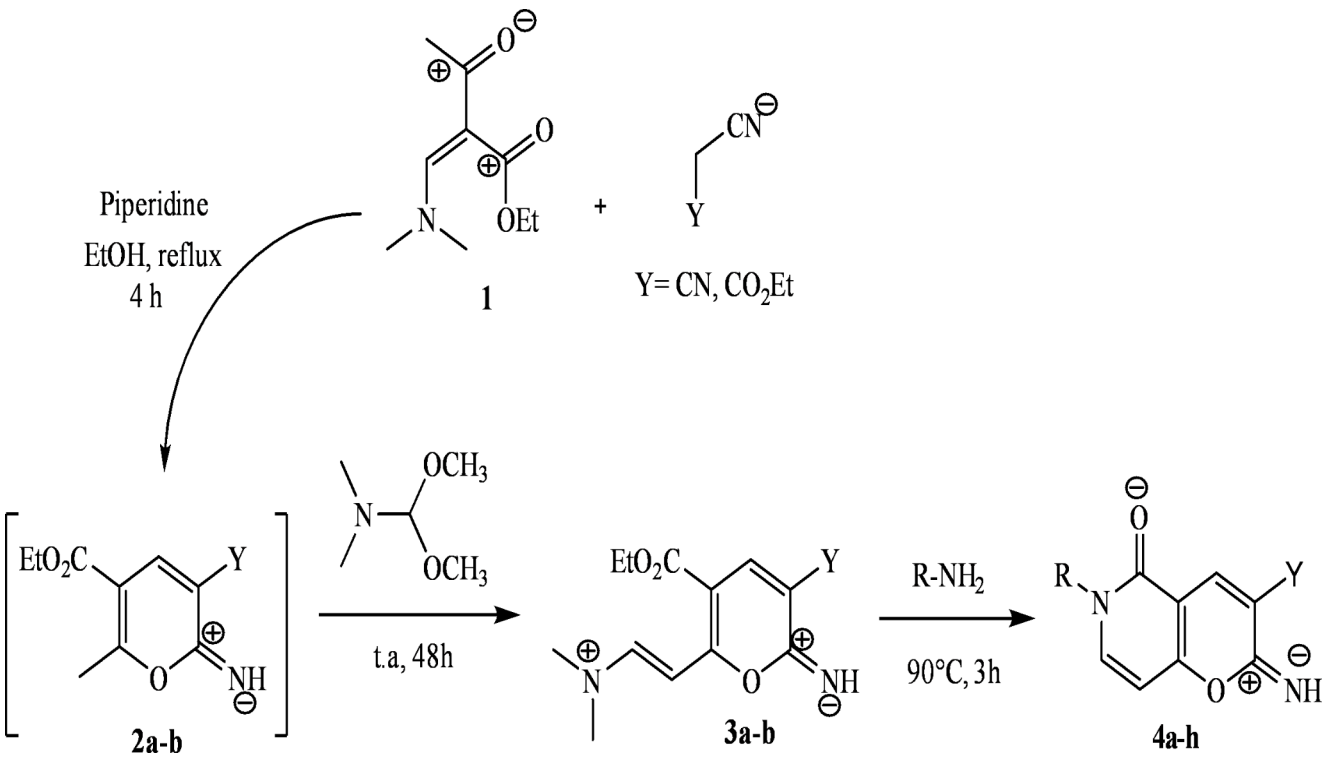
Synthesis of Heterocyclic Molecules

Initially, we were interested tosynthesize2-imino-2*H*-pyrano[3,2-*c*]pyridin-5(6*H*)-ones derivatives alkylated on nitrogen. Theretrosynthetic pathway for their synthesis is shown in Scheme 1. Two methods has been investigated for the 2-imino-2*H*-pyrano[3,2-*c*] pyridin-5(6*H*)-ones synthesis.

For the method (a): The first step is based on the formation of pyrane ring from the reaction of intermediate 1 with malononitrile or ethylcyanoacete in methanol in presence of piperidine as basic catalyst at reflux for 4hresulting in the formation of 2imino-2*H*-pyrane as starting material. The intermediate 2-((diméthylamino)methylene)-3-oxobutanoate d'éthyle was synthesized according to the previous literature procedure [26]. The second step involved the use of enaminopyranes (**3a-b**) as key intermediates. These latter were prepared by the reaction of 2-iminopyranes (**2a-b**) derivatives with amount of dimethylacetal dimethyl-formamide (DMFDMA). The mixture was stirred at room temperature for 48 h without solvent, this leads to a precipitate corresponding to **3a-b**. Thus, new enaminone esters (**3a-b**) are prepared in moderate yields (59–67%).The enaminones formed are then condensed with various primary amines (Phenethylamine, Benzylamine, Cyclohexylamine, Aniline, Sec-butylamine, propylamine, Buthylamine, Hexylamine) as nucleophilic agents at 90 °C during 3 h, under solvent freeconditions to give the iminopyranopyridone ring(**4a-h**). The synthetic method was shown in Scheme 2 respectively.

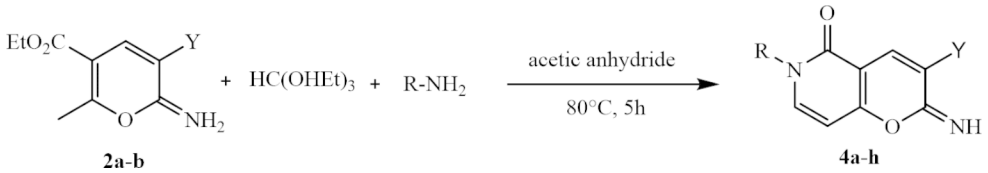
Secondly,the2-imino-2*H*-pyrano[3,2-*c*]pyridin-5(6*H*)-ones derivativeswere also synthesized by method (b) which consisting the multicomponent reaction between synthesized2H-iminopyranes (**2a-b**),triethylorthoformate, and primary amine in the presenceof acetic anhydride at 80 °C for 5 h (Scheme 3). Various primary aliphatic, aromatic, and cyclic amines were used to investigating the versatility of this methodology and synthesizing new structures. The resultsof afforded products prepared by method (a) and (b) were showed in Fig. 2.

Figure 2 shows that the 2-iminopyranes intermediates (**2a-3b**) were synthesized with moderate yields (40–59%). For the synthesis of 2-imino-2H-pyrano[3,2-*c*]pyridin-5(6*H*)-ones by the method (a) give high yield (59–85%) compared with the method (b).The mechanism proposed for the preparation of substituted 2-imino-2H-pyrano[3,2-*c*]pyridin-5(6*H*)-ones (**4a-h**) was described in Scheme 4. First, intermediate **I** was obtained by a nucleophile addition reaction between primary amines and double bond of enamino-2-imino-2*H*-pyran (**3a-b**). Then, an intermolecular cyclization reaction between thedouble bond of amino group and ester groupin intermediate **I** to obtain intermediate II. Finally, thesubstituted 2-imino-2*H*-pyrano[3,2-*c*]pyridin-5(6*H*)-ones (**4a-h**) were obtained by an aromatization step with the elimination of ethanol.



Scheme 2 Approach to 2-imino-2*H*-pyrano[3,2-*c*]pyridin-5(6*H*)-ones(4a-h)

Scheme 3 One pot cascade synthesis of 2-imino-2*H*-pyrano[3,2-c]pyridin-5(6*H*)-ones (4a-h)



Fluorescence Properties of 2-imino-2*H*-Pyrano[3,2-*c*]pyridin-5(6*H*)-ones Derivatives

The photophysicalproperties of fluorescent molecules were recorded to identify the highly, more intense and sensitive prepared molecules. However, the effect of concentration, and solvent on the intensity was studied for six derivatives:**4a**, **4b**, **4c**, **4e**, **4f**, and **4h** at room temperature. First, four solutions were prepared withdifferent concentrations of each heterocyclic molecule in methanol:10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7} M with specific excitation wavelengths λ_{ex} for each compound (Fig. 3).The fluorescence spectra of all products showed good fluorescence intensity at theirwavelength excitation in methanol except in higher concentration (10^{-4}, 10^{-5}), where the intensity decreases. With higher concentration, all spectra demonstrate a red shift of bands to higher wavelength with a curios decreasing of fluorescence intensity (Table 1). The results closed that molecular aggregation and the fluorescence quenching occur when the concentration increases [27].

Comparing the fluorescence intensity of compounds in methanol (10^{-6} M), they are classified in order of decrease as follows: **4c**, **4a**, **4f**, **4b**, **4e**, and **4h** (Table 1). It is known in the literature that the cyclic substituents and the presence of electron donor groups (-OH, = NH) increase the fluorescence intensity, which verifies the principle of fluorescence based on the delocalization of π electrons, the reason why that high intensity were recorded [28].The compound **4c**gave the highest intensity due to the presence of the benzyl ring (aromatic ring and H acid of -CH_2), and it decreases for the compound **4f** (2 H acid - CH_2-CH_2) to **4h** which contains a linear aliphatic chain (R = Hexyl).

Secondly, the solvent effect on the fluorescence was studied using the concentration 10^{-6} M for **4a-c**, **4e-f**, and **4h** molecules. Figure 4 shows the solvent effect on the fluorescence of **4a**, **4b** and **4c** compounds. For the compound **4a**, the best fluorescence intensity was recorded with methanol, acetonitrile, and H_2O and slowly lowers with dichloromethane. While the **4b** compound presentsa high intensity in methanol and chloroformwith a shift of bands to lower wavelength in the lastone and it presentsmoderatefluorescence

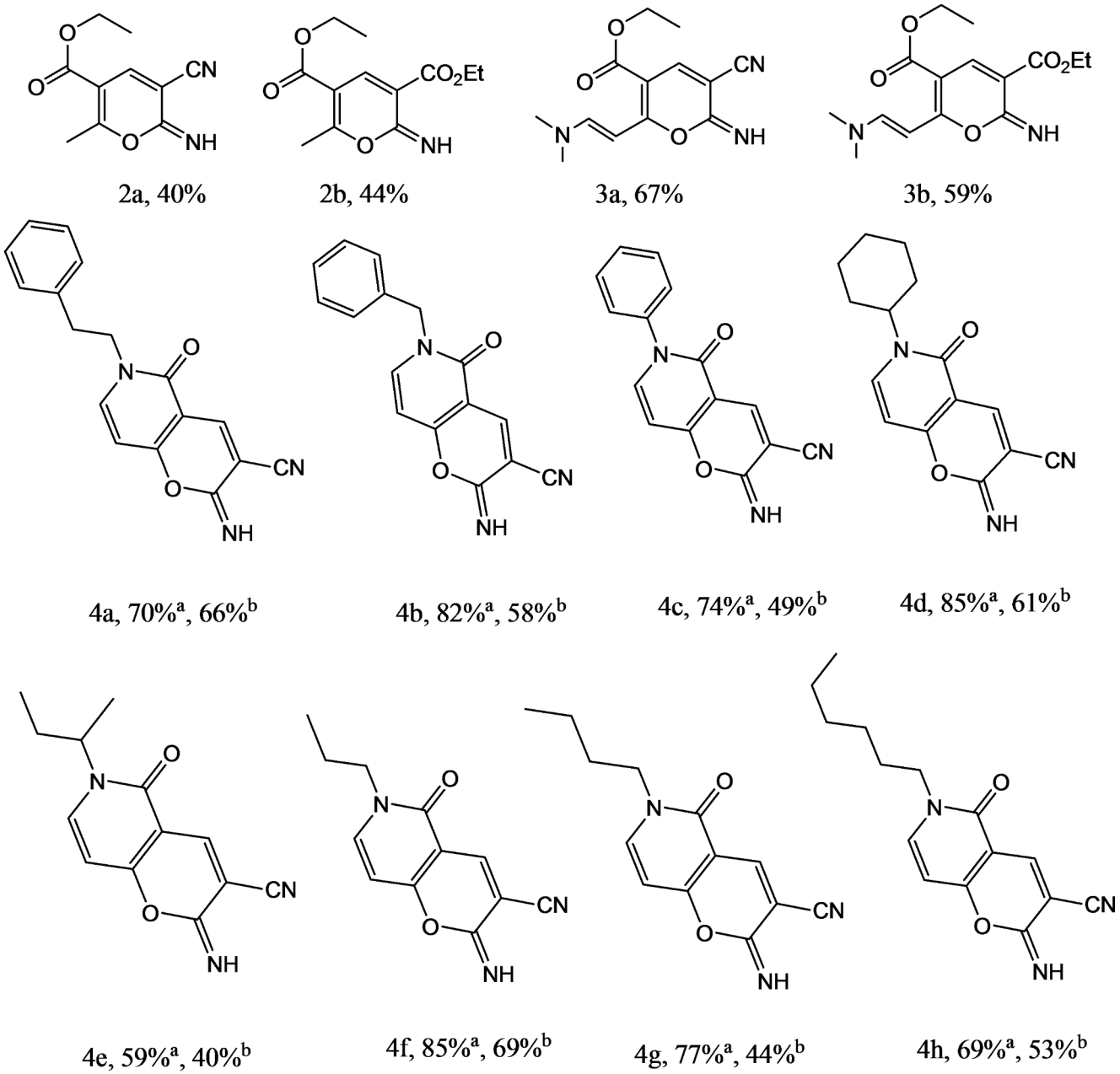
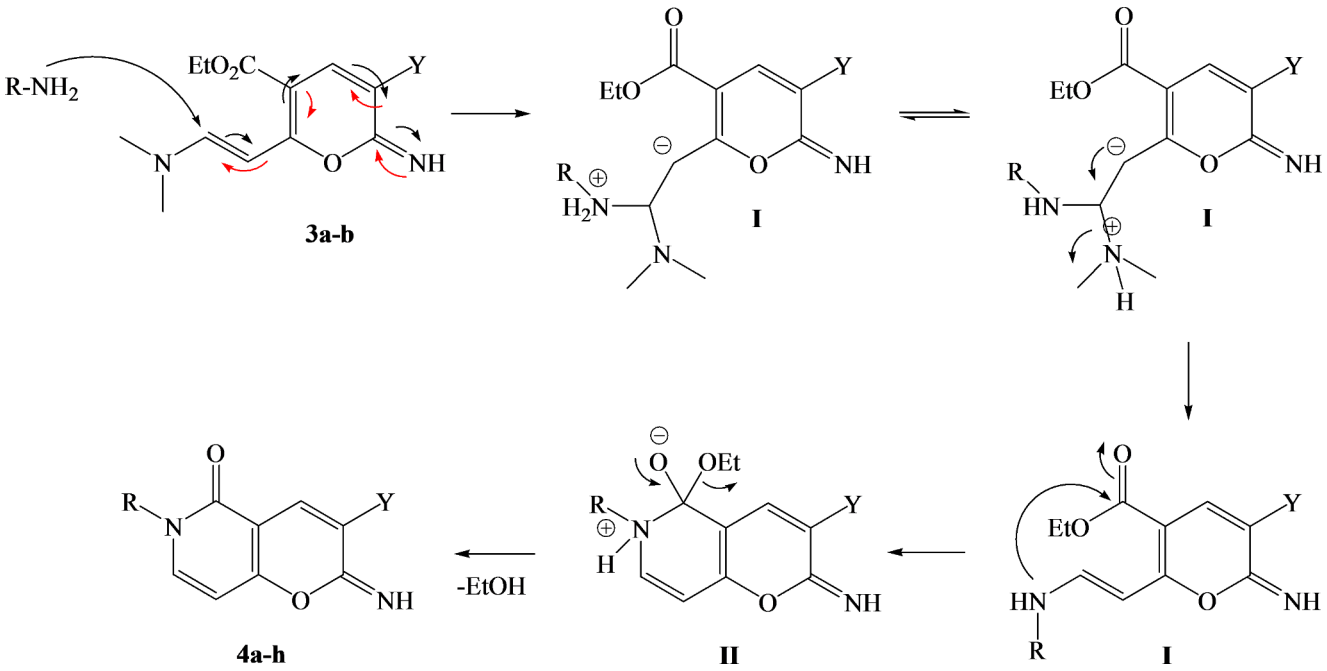


Fig. 2 Various 2-iminopyranes 2**a-b** and substituted 2-imino-2*H*-pyrano[3,2-*c*]pyridin-5(6*H*)-onesprepared by method a and b

intensity with other solvent. For the compound **4c**, the fluorescence intensity in chloroform and dichloromethane was slowly lower then methanol. And it demonstrates a very lower intensity with H_2O and acetonitrile.The difference between the three compounds **4a**, **4b**, and **4c** is the number of methylene fragment between azote and the phenyl ring. So, decreasing the methylene group between the phenylic and other cyclic fragment leads to the decrease of fluorescence intensity in polar and apolar solvents.

In the case of **4e**, **4f**, and **4h** (Fig. 5), high intensity was afforded with different solvents. The **4h** compound presents a high intensity with polar solvent such as methanol, dichloromethane, acetonitrile, ethyl acetate, and chloroform.This result confirms also that the number of methylene fragment influenced the fluorescence intensity.In addition, the presence of the acid protons on R substituent of the pyrano[3,2-*c*]pyridine ring has a positive effect.

The result shows that the solvation power increases the fluorescence intensity; moreover, the use of polar solvents such as methanol confirms the solvation parameter as well as the possibility of intermolecular hydrogen bonds formation with the free doubles of oxygen and nitrogen atoms of pyridine-2-one group (Fig. 6).



Scheme 4 Proposed mechanism for the synthesis of 2-imino-2*H*-pyrano[3,2-*c*]pyridin-5(6*H*) -ones **(4a-h)**

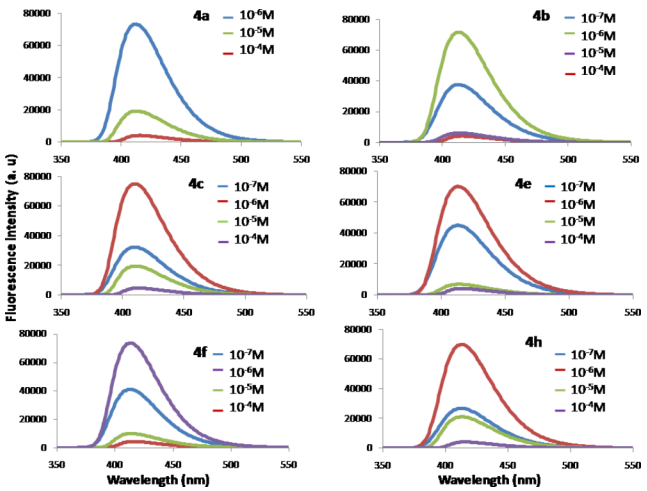


Fig. 3 Fluorescence spectra of **4a-c**, **4e-f**, and **4h** products in methanol

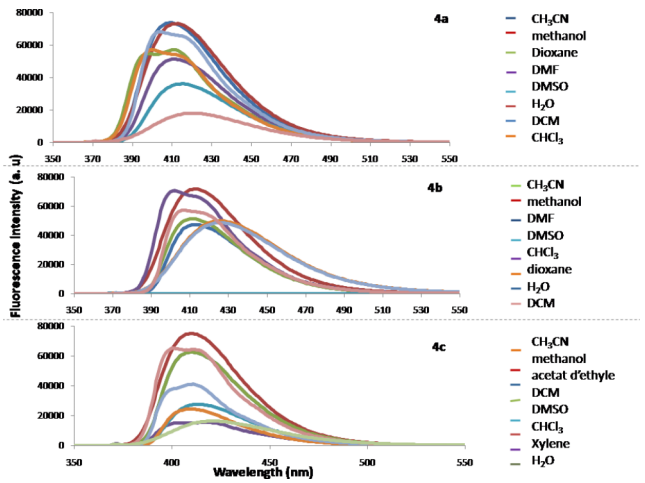


Fig. 4 Fluorescence spectra of **4a**, **4b**, and **4c** compound in different solvents (10^{-6}M)

Conclusion

In the present study, the heterocyclic 2-imino-2*H*-pyrano[3,2-*c*]pyridin-5(6*H*)-ones derivatives were prepared successfully with two methods affording high yield (40–85%) [25]. The method (a) gives products using two steps, and the method (b) involves the one pot synthesis of the derivatives. This one gives moderate yields (58–69%). Thesynthetic derivatives presented a high fluorescent intensity in methanol with a concentration of 10^{-6} M. The

Table 1 Concentration effect on the fluorescence intensity of compounds

Concentration (mol/L)	λ max (nm), Fluorescence intensity (a. u)					
	4a	4b	4c	4e	4f	4h
10^{-4}	417,4182	415, 6096	415, 4843	417, 4304	417, 4314	417, 4203
10^{-5}	413,19372	417,6012	412, 19,640	414,7068	414, 9881	414, 21,108
10^{-6}	412, 73,354	414, 71,596	411, 75,102	414, 70,203	415,73351	414, 69,779
10^{-7}	/	414, 37,531	411, 32,291	414, 45,089	414,40497	414, 26,778

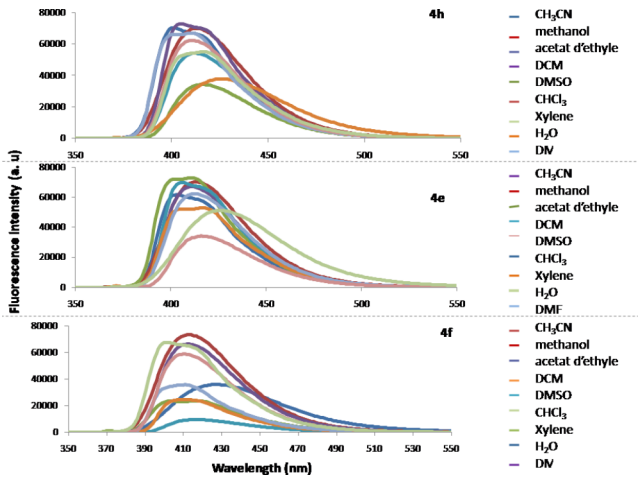


Fig. 5 Fluorescence spectra of **4e**, **4f**, and **4h** compound in different solvents (10^{-6}M)

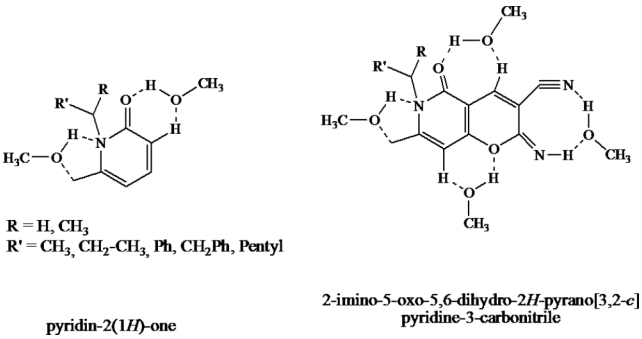


Fig. 6 Intermolecular hydrogen bonds

fluorescence intensity increases according to the structure of each prepared derivative. The study of solvent effect on the fluorescence intensity of **4a**, **4b**, **4c**, **4e**, **4f**, and **4h** demonstrates that the intensity is related to the structure and cyclic aromatic rings where the cyclic aromatic derivatives presented a high fluorescent intensity than the aliphatic one. In addition, with polar solvent, the cyclic aromatic compounds presented excellent fluorescence intensity in the range of 60,000 and 70,000 (a.u.).Our results demonstrates that 2-imino-2*H*-pyrano[3,2-*c*]pyridin-5(6*H*)-ones derivatives can be used as indictor for a next study.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10895-023-03212-4.

Acknowledgements The authors would like to thank the General Directorate for Scientific Research and Technological Development (DGRST) for the financial support.

Authors' Contributions Nawel Mehiaoui: redaction, synthesis of molecules and experimentale study.
Ridha Hassaine: fluorescence ananlysis end interpretation.
Amina Berrichi: redaction and interpretation.
Zahira Kibou: synthesis of substrate molecules.
Noureddine Choukchou-Braham analysis and interpretation.

Funding There is no funding for this researche.

Data Availability All of the material is owned by the authors and/or no permissions are required and it is aviable.

Declarations

Competing Interests The author declared that there is noconflict of interest.

Ethics Approval This study was performed in our laboratory and approved by our group.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent for Publication I give my consent for the publication of identifiable details, which can includeMaterial, Figures which to be published in this Journal. I confirm that I have seen and been given the opportunity to read both the Material and the Article as attached to be published by this journal. I havediscussed this consent form authors.

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