A NEW FLUORESCENT INDOLIZINE. SYNTHESIS AND SPECTRAL CHARACTERIZATION

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O nouă indolizină substituită a fost sintetizată pentru a investiga proprietăţile optice şi posibilele întrebuiţări în optoelectronică ca marker fluorescent. Structura moleculară a fost verificată prin spectroscopie RMN şi IR şi confirmată de analiza elementală.

A new substituted indolizine was synthesized in order to investigate its optical properties and evaluate possible uses in optoelectronic devices or as fluorescent marker. Structural assignment was provided by NMR and IR spectroscopy and confirmed by elemental analysis.

Keywords: fluorescence, N-ylide, 1,3-dipolar cycloaddition, indolizine

1. Introduction

Pyrroloazines are an important class of *N*-bridgehead heterocycles as demonstrated by the large volume of literature available on the subject [1-6]. This is due to their interesting biological [7, 8] and optical properties [9, 10]. One of the most recent developments is the use of such compounds in optoelectronic devices, mostly as pure-color luminophores in OLEDs (organic light emitting diodes) [11, 12]. Also, similar molecules are being used as fluorescent markers for biological and medical applications. Indolizines are the simplest pyrroloazines, formally obtained by the condensation of a pyridine and a pyrrole ring, being isomeric to indole. This relatively simple indolizine skeleton offers the possibility of fine tuning certain properties by varying the number and type of substituents [9, 10, 13, 14]. Such an example is the synthesis of highly specific chemosensors obtained by linking 7-substituted indolizines to a cyclodextrine moiety [18].

Several synthetic methods for obtaining indolzines are known, one of the most versatile being *N*-ylide 1,3-dipolar cycloadditions [9,10,13-17]. These have

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been successfully applied for the synthesis of a number of substituted indolizines and offer the advantages of few reaction steps and simple work-up. Furthermore, the method has recently been reconsidered as a one-pot multicomponent process [19, 20].

Our interest in pyrroloazines and 1,3-dipolar cycloadditions lead us to investigate the synthesis and spectral characterization of a new 7-[1-(2-pyridyl)vinyl]indolizine presented herein.

2. Experimental

2.1. Materials

Melting points were determined on a Boëtius hot plate. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for 1H and 75 MHz for 13C. Supplementary evidence was given by HETCOR and COSY experiments. The IR spectra (ATR) were recorded on a Vertex 70 Brucker instrument. Elemental analyses were determined on COSTECH Instruments EAS32 (Centre for Organic Chemistry, Spl. Independentei 202B, Bucharest 060023, Romania). Satisfactory microanalyses for all new compounds were obtained. All precursors were purchased from Sigma-Aldrich and were used without further purification.

The absorption spectra have been acquired using a JASCO V550 UV-VIS spectrometer. The emission and three-dimensional fluorescence spectra have been acquired using a JASCO FP-6500 fluorescence spectrophotometer, using the following settings: Data pitch of 1 nm for emission spectra and 5 nm for three-dimensional spectra, response time of 0.02 seconds, PMT Voltage of 550 V, and scanning speed of 1000 nm/minute. Spectrophotometric grade solvents, purchased from Sigma-Aldrich, have been used without further purification in all the cases. All spectra were recorded at 25 ^{o}C. The relative fluorescence quantum yield values have been determined by comparison with a deoxygenated dilute solution of anthracene in 95% ethanol, with an absolute quantum yield of 0.27, as described in [21].

2.2. General procedure for compound 2

5 Mmol of trans-1-(2-pyridyl)-2-(4-pyridyl)ethylene was dissolved in 50 ml of acetone. To this solution 6 moles of 2-bromoacetophenone was added. The mixture was left over night in a sealed Erlenmeyer flask. The precipitate was filtered off and washed with acetone. Salt **2** was subsequently used without any further purification.

2.3. General procedure for compound 3

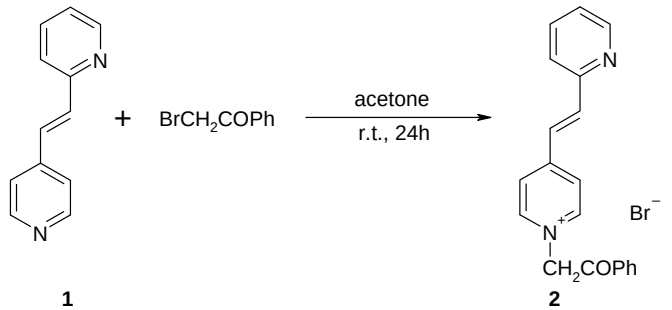
2 Mmol of the corresponding salt were suspended in dichloromethane (20 mL) and methyl propiolate (2 mmol) was then added. Under vigorous stirring, triethylamine (0.3 mL, 2 mmol, dissolved in 5 mL of methylene chloride) was added dropwise. After 20 min the reaction mixture was washed with water. 30 ML of ethanol 96% were added and the resulting precipitate was filtered off and washed with absolute ethanol. The crude product was purified by chromatography with a short column (Aluminium oxide 90 standardized, methylene chloride).

3-Benzoyl-7-(*trans*-2-pyridin-2-yl-vinyl)-indolizine-1-carboxylic acid methyl ester (3). Bright yellow powder with mp 193-195 °C, yield 31 %. Anal. Calc. for $C_{24}H_{18}N_2O_3$: C, 75.38; H, 4.74; N, 7.33. Found: C, 75.02; H, 4.55; N, 7.68. FT-IR (cm^{-1}): 3023; 2952; 1697; 1602; 1337; 1215. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 9.90 (d, 1H, *J*=7.4 Hz, H-5); 8.79 (d, 1H, *J*=5.5 Hz, H-15); 8.66 (s, 1H, H-8); 8.52 (t, 1H, *J*=7.4 Hz, H-12); 8.25 (d, 1H, *J*=7.4 Hz, H-6); 7.90-7.65 (m, 8H, Ph, H-2, H-9, H-13); 7.59 (d, 1H, *J*=16.5 Hz, H-10); 7.48 (dd, 1H, *J*=7.4, 1.6 Hz, H-14); 4.00 (s, 3H, Me). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 186.6 (CO); 165.9 (CO_2Me); 150.0 (Cq); 146.5 (CH); 141.7 (CH); 140.5 (Cq); 139.3 (CH); 136.8 (Cq); 134.8 (Cq); 132.4 (CH); 132.0 (CH); 130.8 (CH); 130.2 (Cq); 128.2 (Cq); 125.5 (CH); 124.6 (CH); 123.6 (CH); 121.4 (CH); 121.0 (CH); 113.4 (CH); 108.7 (C-1); 52.8 (CH_3).

3. Results and discussion

3.1. Synthesis and structural characterization

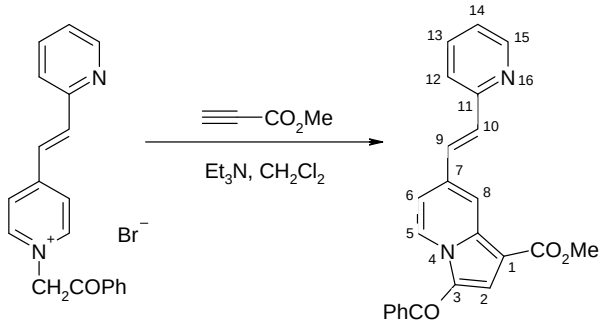
The key intermediate, pyridinium salt **2** was obtained quantitatively from 1-(4-pyridyl)-2-(2-pyridyl) ethene **1** and equimolar amounts of 2-bromoacetophenone by reacting them in acetone at room temperature overnight (Scheme 1).



1 **2**

Scheme 1. Synthesis of pyridinium salt **2**

Compound **3** was obtained in moderate yield (31%) by reacting the pyridinium salt **2** with methyl propiolate in the presence of triethylamine as base and methylene chloride as reaction medium. Although this method is known to yield dihydro derivatives of the corresponding pyrroloazine as byproducts, NMR spectroscopy indicated only trace amounts of such compounds. (Scheme 2).

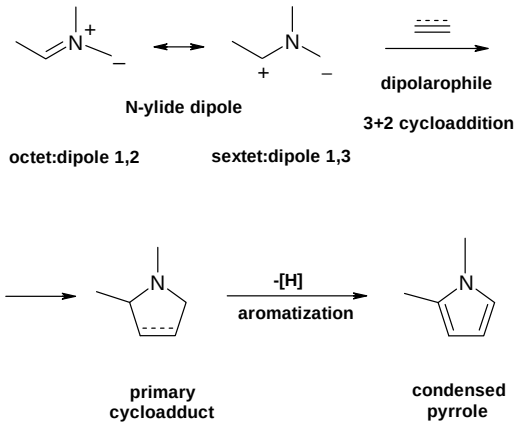


2 **3**

Scheme 2. Synthesis of compound **3**

In the H-NMR spectrum of compound **3** the most deshielded proton H-5, appears as a doublet at 9.90 ppm (*J*=7.4 Hz), due the proximity to the nitrogen atom and the COPh moiety. The protonation of the pyridine nitrogen atom by TFA results in a high deshielding of proton H-14, which appears at 8.79 ppm. Protons H-6 appears at 8.25 ppm as a singlet and proton H-8 appears at 8.66 ppm as a doublet (*J*=7.4 Hz). The vinylic proton H-10 appears as a doublet at 7.59 ppm (*J*=16.5 Hz). The C-NMR spectrum shows all expected signals and is in good agreement with the proposed structure. The most representative signals correspond to CO group (186.6 ppm), the ester moiety (165.9 ppm) and C-1 (108.2 ppm).

Pyridinium *N*-ylides are heteroaromatic *N*-ylides which are allyl type 1,3-dipoles characterized by four electrons in three parallel p_z orbitals with a sextet structure. Carbanion monosubstituted pyridinium *N*-ylides are generally unstable compounds, and thus are generated *in situ* by the action of a base. The triethylamine deprotonates the pyridinium salt **1**, resulting in the corresponding *N*-ylide, which in turn reacts in its sextet form with the acetylenic dipolarophile yielding the primary cycloadduct. The fully aromatic indolizine **3** is formed by the isomerisation and subsequent *in situ* oxidation of the primary cycloadduct.



Scheme3. reaction mechanism for *N*-ylide 1,3-dipolar cycloaddition

3.2. Spectral characterization

For the UV-VIS absorption spectra ethanol, 1-pentanol, acetonitrile, DMSO, dioxane, CCl_4 and *i*-octane have been investigated. It is worth mentioning that the compound has a reduced solubility in *i*-octane which removed the possibility of obtaining meaningful data. In the case of *i*-octane low absorption maxima have been obtained, due to the compound's low solubility and are not presented.

Compound **3** general absorption spectrum consists in three absorption peaks in the 264-278 nm, 389 – 397 nm and 410 – 417 nm. Except for DMSO and ethanol, the peak with maximum intensity was the second one; in the case of DMSO the 415 nm peak has a higher intensity, while in the case of ethanol the maximum absorption peak is obtained at 264 nm. From the low values of ε_{max} in the case of acetonitrile, 1-pentanol and ethanol it can be concluded that the compound was not completely soluble at the investigated concentration ($1 \cdot 10^{-4}$ M). The solvent's influence on the absorption peaks is further detailed in Table 1. From this data it can be seen that in the case of polar protic solvents there is a hypsochromic shift for the 390 nm and 410 nm maxima.

Table 1

UV-VIS Absorption peaks and intensities (* = maximum absorption peaks)

Solvent	Peak	A	Peak	A	Peak	A	log ε_{max} [$L \cdot mol^{-1} \cdot cm^{-1}$]
CCl_4	397 *	1.622	417	1.600	266	1.307	4.210
Dioxane	396 *	2.709	415	2.675	267	2.180	4.433
DMSO	397	0.986	415 *	1.000	265	0.872	4.000
Acetonitrile	392 *	0.367	410	0.361	266	0.320	3.565
1-Pentanol	394 *	0.252	415	0.241	278	0.165	3.401
Ethanol	389	0.212	410	0.187	264 *	0.236	3.373

The fluorescence emission and excitation maxima have been determined from the corrected 3D fluorescence spectra, using the "Em. Search View" function of JASCO Corporation Spectra Manager software. The 3D fluorescence spectrum consists of the plot of fluorescence intensity versus emission wavelength and excitation wavelength and fully characterizes a compound by capturing all fluorescence transitions, as peaks. Such a fluorescence spectrum for the compound **3** is shown in figure 1, while the "Em. Search View" is shown in Figure 2.

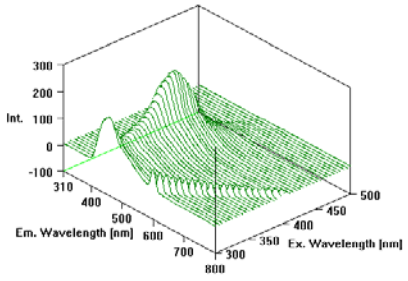


Fig. 1. Fluorescence 3D spectra of **3** in CCl_4

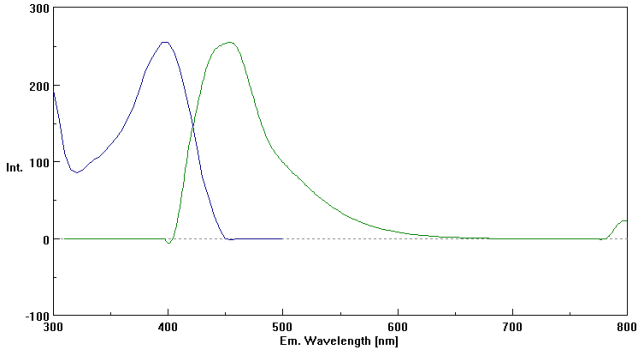


Fig. 2. "Em. Search View" of **3** in CCl_4

Anthracene has been chosen for quantum yield determinations due to suitable excitation range for both standard and sample. The fluorescence spectra

for compound **3** have been recorded in DMSO, CCl_4 and dioxane. The quantum yield has been computed using the formula (1), where Q.Y. is the quantum yield, A the absorbance at excitation wavelength, F the fluorescence emission area, n the refractive index of solvents and reference and compound subscripts refer to the reference and investigated compound, respectively [22].

$$Q.Y._{.} = (A_{ref} / A_{comp}) \cdot (F_{comp} / F_{ref}) \cdot (n_{comp} / n_{ref})^2 \cdot Q.Y._{.ref} \quad (1)$$

The fluorescence emission maxima (λm em), excitation maxima (λm ex), Stokes shifts (ΔS), absolute quantum yield (Q.Y.) as well as the absorption intensity at 350 nm (A) , integrated fluorescence area (F) and refractive index for the solvents used are presented in Table 2.

Table 2

Fluorescence data for compound 3 and anthracene

Compound	Solvent	λm em [nm]	λm ex [nm]	ΔS [nm]	Q.Y.	A (350 nm)	F	n_D
3	DMSO	461	409	52	0.0047	0.057	1545	1.479
	CCl4	453	400	53	0.0451	0.127	33794	1.4601
	Dioxane	458	400	58	0.0064	0.139	5603	1.4213
Anthracene	EtOH	-	-	-	0.2700	0.015	27506	1.3600

As it can be seen from Table 2, the compounds quantum yield is highest in the case of CCl_4 and lowest for DMSO. The direct variation of fluorescence with solvents polarity might be explained by fluorescence quenching through hydrogen bonds or other solvent effects (for example solvent reorganization free energy).

4. Conclusions

A new fluorescent indolizine was synthesized by the 1,3-dipolar cycloaddition of the corresponding N-ylide with methyl propiolate. The regioselectivity of the reaction and structural assignment were ascertained using H-NMR and C-NMR spectroscopy. Elemental analysis confirmed the proposed structure. UV-Vis and fluorescence measurements were conducted on the compound.

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