PYRROLOPYRIDAZINE DERIVATIVES SUBSTITUED WITH FLUOR: SYNTHESIS AND FLUORESCENT PROPRIETIES

DERIVAŢI PIROLOPIRIDAZINICI SUBSTITUIŢI CU FLUOR: SINTEZĂ ŞI STUDIUL PROPRIETĂŢILOR FLUORESCENTE

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Abstract. *1,2-diazines derivatives are invaluable materials in the fields of medicine (such as anti-HIV, antiviral and anticancer, antibacterial and antifungus medicines), opto-electronics (compounds with liquid crystal properties and highly fluorescent derivatives: sensors and biosensors, electroluminescent materials, lasers) and agriculture (herbicidal activity and the grow up factor for plants). 1,3-Dipolar cycloaddition is one the most important methods of constructing the pyrrolopyridazine, in classical conditions and using microwave irradiation. For pyrrolopyridazine derivatives was studied the absorption and emission spectra, in ethanol, chloroform and cyclohexane solutions at room temperature.*
Key words: *pyrolopiridazine derivatives, fluorescence, 3+2 dipolar cycloadditions.*

Rezumat. *Derivaţii 1,2-diazinici sunt compuşi cu proprietăţi deosebite în medicină (anti-HIV, medicamente antivirale şi împotriva cancerului, proprietăţi antibacteriene şi antifungice), cu proprietăţi opto-electronice (compuşi cu proprietăţi de cristale lichide şi produse derivate foarte fluorescente: senzori şi biosenzori materiale electroluminiscente, lasere) şi în agricultură (compuşi cu activitate erbicidă şi stimulatori în creşterea şi dezvoltarea plantelor). Reacţiile de cicloadiţie 1,3-dipolare sunt cea mai accesibilă metodă în sinteza derivaţilor pirolopiridazinici, în condiţii clasice şi sub acţiunea microundelor. Pentru derivaţii sintetizaţi au fost înregistrate spectrele de absobţie şi emisie, în etanol, cloroform şi ciclohexan la temperatura camerei.*
Cuvinte cheie*: derivaţi pirolopiridazinici, fluorescenţă, cicloadiţii 3+2 dipolare.*

INTRODUCTION

1,2-diazines are reviewed in literature for their applications: compounds with different biological activities (anticancer, antituberculosis, antimicrobial, antihypertensive etc.), opto-electronics properties (fluorescent derivatives used as sensors and biosensors, electroluminescent materials, lasers and other semiconductor devices) and compounds with liquid crystal properties (Mangalagiu, 2011). Herbicidal activity and grow up factor for plants are also reviewed (Mitsumori et al., 2005; Valeur, 2002).

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In a preliminary communication (Zbancioc et al., 2006; Butnariu et al., 2009; Tucaliuc et al., 2013) is presented the synthesis and spectral analysis of pyrrolopyridazine derivatives. The reaction pathway involves, in the most frequent cases, a Huisgen [3+2] dipolar cycloaddition of ylides to dipolarophiles (activated alkenes and alkynes).

However, this strategy has some disadvantages: lack of control over stereo- and regioselectivity, long reaction times, high energy consumption, and sometimes, low yields.

During the last few decades microwave irradiation (MW) has become an increasingly valuable tool in organic chemistry, since it offers a versatile and facile pathway in a variety of syntheses.

Furthermore, interphase transfer catalysis reactions under MW conditions have the great advantage of using small amounts of, or even no organic solvents ('solvent free'), such reactions are more environmentally friendly and generate less side products (Van der Eycken et al., 2006; Loupy, 2002).

The aim of this work was to study the relationship between optical properties and structure (the effect of substituents and conjugation).

MATERIAL AND METHOD

The strategies adopted for construction of fluorescent derivatives, are depicted in figure 1 and 2. The preparation of all derivatives (**9a, 9b', 9b'', 9c, 10a, 10b, 10c)** involves two steps: initially N-alkylation of the pyridazine (**1**), fig. 1, followed by a 3 +2 dipolar cycloaddition of diazinium ylides (**8a-8b**) (generated *in situ* from the corresponding salts) to the corresponding dipolarophiles (activated alkenes and alkynes nonsymmetrical substitued: ethyl 4,4,4-trifluorocrotonate and ethyl 4,4,4-trifluorobutinoate), fig. 2.

When the dipolarophile was ethyl 4,4,4-trifluorocrotonate (*trans*-isomer, nonsymmetrically diactivated olefine) the reactions involved additional stereo and regiochemical problems, in one therm chorochemistry (Epiotis, 1978). While for ylides **8a** and **8c** the reaction occur chorospecifically, for ylide **8b** (R = Cl) they occur choroselectively**,** after flash chromatography and crystallization from an appropriate solvent, we recovered an inseparable mixture of two regisomers (**9b'**and **9b''**, 1:1)**.**

The reaction with ethyl 4,4,4-trifluorobutinoate leads to the aromatised pyrrolopyridazine **10a-c**. Aromatisation of the initially hyrogenated diazine **iii** occurs spontaneously and could be explained by oxidative dehydrogenation.

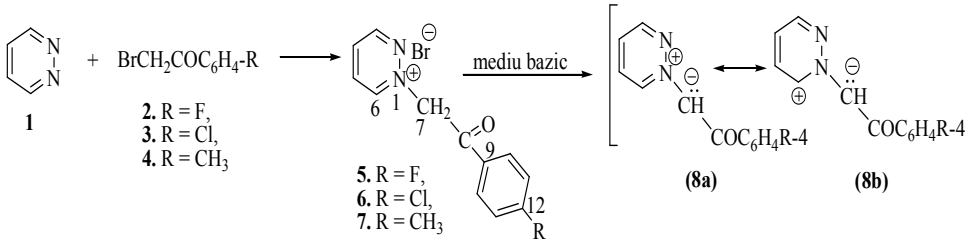

Fig. 1 - N-alkylation of the pyridazine.

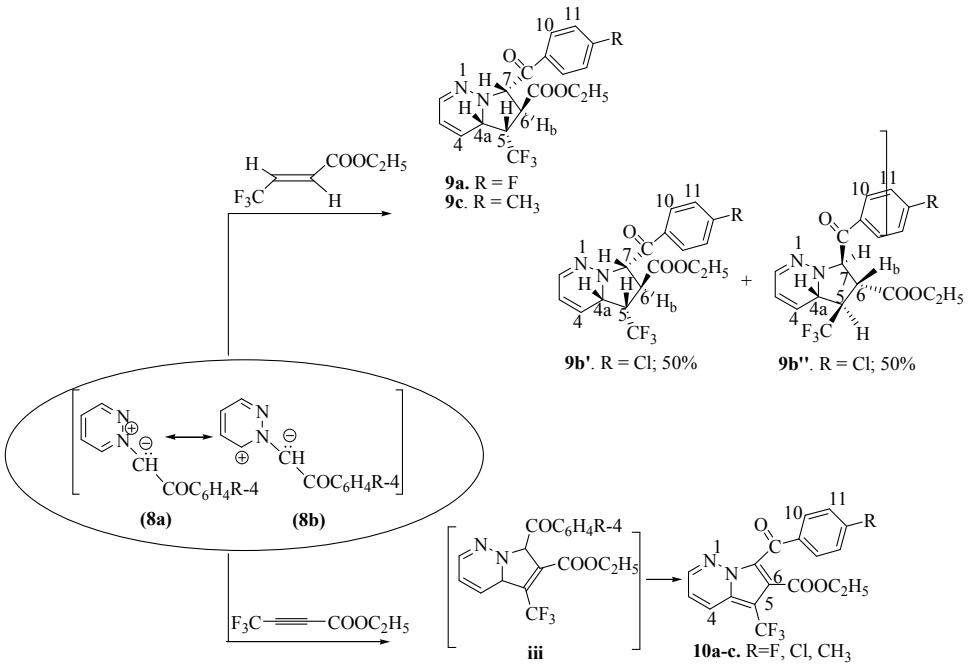

Fig. 2 - 3 +2 dipolar cycloaddition of diazinium ylides.

MW assisted reactions were carried out using a monomod reactor (STAR-2, CHEM corporation, USA). Table 1 lists the optimized conditions, under MW and classical heating. Using MW irradiation, in liquid phase, the best results were obtained applying a constant irradiation power (25% of the full power of the magnetron, 50 W) and varying the temperature ("power control").

Attention was then focused on interphase transfer catalysis reactions. In this study, the solid phase was a mixture of potassium fluoride and N-(p-R-phenacyl)-pyridazinium bromides; the liquid phase consisted of dipolarophiles dissolved in trioctyl-methyl-ammonium chloride–Aliquat 336 (a tensioactive compound that acts as transfer catalyst). The resultant biphasic system is subjected to the action of microwaves using the monomode reactor at 50 W. The best results have been obtained by applying a constant temperature and varying the irradiation power („temperature control").

We presume that the MW heating approach is more effective in [3+2] dipolar cycloaddition reactions due to two factors: the mode of action under MW irradiation and the structure of the ylide intermediate.

It is well known that the magnetic field component of MW radiation is responsible for the dielectric heating effect. The greater the dipole moment of the molecule, the larger the effect of the MW energy will be. The ylides having a 1,2-dipolar structure are excellent dipoles and, therefore, the efficiency of MW heating increases considerably when compared with classical heating.

The results listed in table 1, show the efficiency of the MW irradiation in comparison with the classical heating: the yields were increased in some cases, and the amount of solvent required was reduced.

Table 1

Cycloaddition reactions of pyridazinium ylides with activated alkenes and alkynes under microwave heating and classical conditions

Compd.	Classical		Microwaves			
	Reaction time/min	Yield %	Liquid phase		Interphasic transfer catalysis (KF-Aliquat)	
			Reaction time/min	Yield %	Reaction time/min	Yield %
9a	180	14	5	10	15	-
9b'+9b''	180	16	5	11	15	-
9c	180	9	5	7	15	-
10a	180	38	5	59	15	56
10b	180	41	5	59	15	52
10c	180	46	5	68	15	58

All reagents and solvents employed were of the best grade available and were used without further purification.

The structure of the compounds was proved by spectral analysis: the 1H NMR and 13C NMR spectra and two-dimensional experiments 2D-COSY, 2D-HETCOR(HMQC), long range 2D-HETCOR (HMBC) were recorded on a Bruker Avance 400 DRX spectrometer at 400/100 MHz. Chemical shifts are given in parts per million (δ-scale), coupling constants (J) in hertz and downfield shift from internal tetramethylsilane (δ 0.00 ppm). The IR spectra were recorded on an FT-IR Shimadzu Prestige 8400s spectrophotometerin KBr. Melting points were determined using an electrothermal apparatus and are uncorrected. Flash chromatography was performed with Aldrich 230e400 mesh silica gel. TLC was carried out on Merck silica gel 60-F-254 plates.

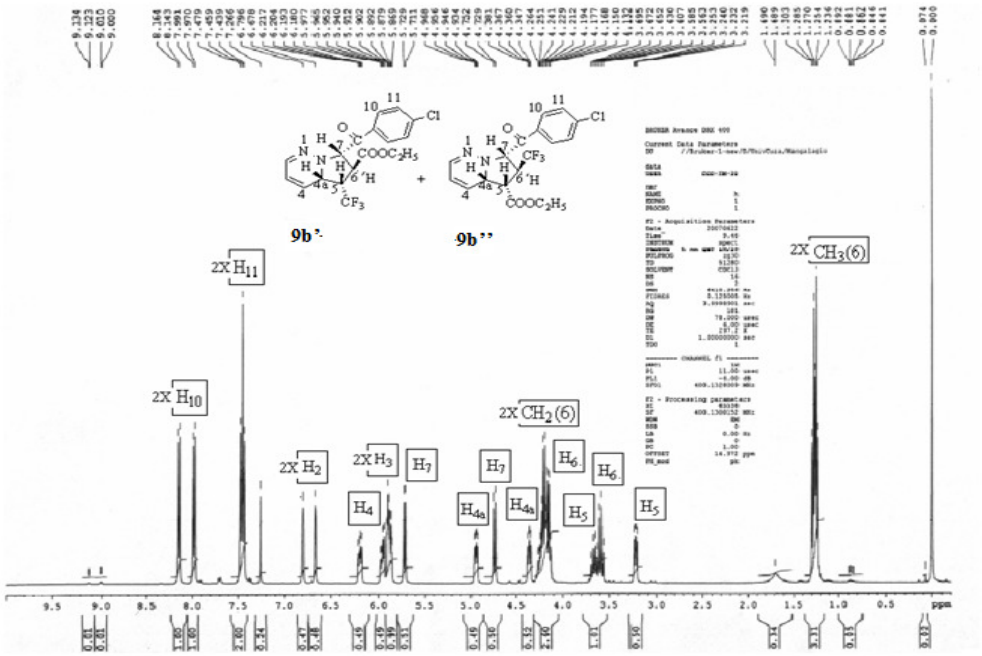

Fig. 3 - 1H-NMR spectrum for compounds **9b'+9b''**.

In the next stage of our work, we studied the absorption and emission spectra of the obtained compounds. The spectra of all the compounds were recorded in ethanol, chloroform and cyclohexane solutions at room temperature.

The fluorescence spectra were recorded with a Turner Bio Systems fluorimeter using FluoOpticalKitID PN: 9300-043 SN: F2000000BB5A4C2D SIG: UV with λ_{ex} = 365 nm and λ_{em} = 410–460 nm.

Relative quantum yields were determined by using anthracene in ethanol (= 0,27 at 25° C) (Parker, 1986). Although, compounds are relatively similar in molecular structure, exhibit clear differences in their experimental absorption and emission spectra, as summarised in table 2.

Table 2

λmax (nm) of absorption spectra and relative quantum yields (%) of piridazine derivatives

Comp.	Fluorescence (λ_{max}, nm) (quantum yield %)			Absorption (λ_{max}, nm)		
	Etanol	Cloroform	Ciclohexan	Etanol	Cloroform	Ciclohexan
9a	420	416	Insolubile	315	320	Insolubile
9b'+9b''	418	414	Insolubile	314	322	Insolubile
9c	430	424	Insolubile	318	320	Insolubile
10a	450	447	Insolubile	330	327	Insolubile
10b	452	449	Insolubile	332	325	Insolubile
10c	456	453	Insolubile	332	331	Insolubile

RESULTS AND DISCUSSIONS

The results listed in table 1 show the efficiency of the MW irradiation in comparison with the classical heating: the yields were increased in some cases, and the amount of solvent required was reduced.

As shown in table 2, the componds are blue emitters (λ_{max} of fluorescence around 420-456 nm, λ_{max} of absorption around 320-331 nm) and have low quantum yield.

The effect of conjugation and the presence of double bonds in azaheterocycles compounds determine fluorescence and quantum yields of the analyzed compounds.

If pyrroloderivatides were fully aromatised, then the quantum yield was extremely high (Zbancioc et al., 2010).

CONCLUSIONS

1. We report a fast, efficient and straightforward method for preparation of fluorescent derivatives containing the piridazine ring, , both in liquid phase and interphasic transfer catalysis.

2. The microwaves induceds a remarkable acceleration of the [3+2] dipolar cycloaddition reaction of pyridazinium ylides to activated alkene and alkyne and allowed a general and facile method for the preparation of pyrrolopyridazine derivatives.

3. Stereo-, regio- and chorochemistry of the cycloadditions were studied.

4. The compounds obtained and tested posses fluorescent proprieties (λ_{max} of fluorescence is around 420-456 nm, λ_{max} of absorption is around 320-331 nm).

5. A certain influence of the substituents concerning absorption and fluorescent properties were observed: the subtituent from the position 5 being important for fluorescence.

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