

EFFECTIVE SYNTHESIS OF SUBSTITUTED QUINOXALINONES AND THEIR COMPLEXATION

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Received: 08 January 2019 / Accepted: 12 June 2019 / Published online: 01 September 2019

ABSTRACT

The objective of this work is the synthesis and complexation of heterocycles under simple reaction conditions. We performed an effective synthesis of substituted quinoxalinones followed by a complexation with transition metals in 1/1 ratio in ethanol. The products obtained were characterized by ¹H NMR, ¹³C NMR, mass spectrometry and IR

Keywords: Dipyrromethanes, Bodipy, Quinoxalinones, Transition metals, Complexes.

1. INTRODUCTION

Transition metal complexes have been known for a long time. One of the interests of heterocyclic systems having the NCCN motif which makes it possible to form stable complexes with transition metals such as the Bodipy which represent an example of supramolecular coordination architectures and which currently constitute a highly promotive axis of research for the development of new materials for their fluorescence properties [1], their uses among others as fluorescence switch [2], electroluminescent film [3], molecular dye lasers [4], molecular probes in biomedical imaging [5] and as chemosensors especially for the detection of cations (Cd²⁺ and Na⁺) [6,7], anions (F⁻) [8] and gas [9].

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doi: <http://dx.doi.org/10.4314/jfas.v11i3.14>



First we prepared the meso-substituted borandipyrromethane (Bodipy) having remarkable fluorescence properties. Following a clean method followed by oxidation using trifluoroborate etherate $\text{BF}_3\text{-OEt}_2$.

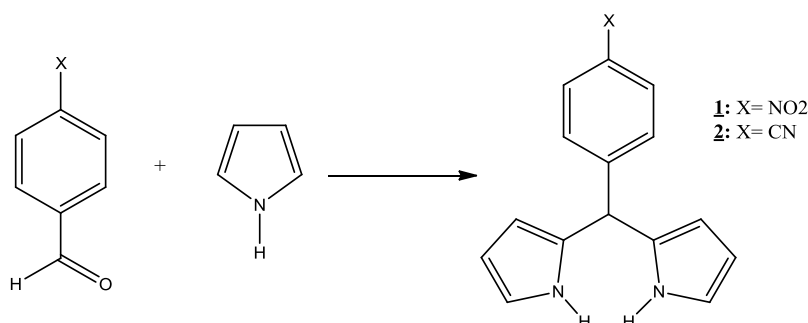
Then we became interested in quinoxalinones. Indeed, these heterocyclic products are of considerable importance in various fields, such as H.I.V.1 inhibitors to medicines [10], anti-cancer agents [11,12]. These heterocyclic compounds have the ability to form complexes with transition metals to produce products that are characterized by biological activity, particularly oxidative stress.

The complexation of these compounds by metals can modify the therapeutic properties by involving a new stereochemistry and an electronic redistribution. For this purpose, our work focuses on the study of the reactivity of amide and amine functions with respect to transition metal salts.

2. RESULTS AND DISCUSSION

2.1. Synthesis and complexation of dipyrromethenes

When three equivalents of pyrrole and one equivalent of aldehyde are dissolved in aqueous solution and catalyzed by HCl (0.18M) under magnetic agitation and at room temperature, the dipyrromethanes **1** and **2** are obtained in good yield and excellent purity (Scheme 1).



The ^1H NMR spectrum confirms the structure of the dipi-CN particularly by a removal of the protons carried by the two pyrrolic nitrogen atoms (10.7 ppm), which denotes their acidic character, as well as by the presence of a singular peak bearing a proton bonded to the carbon of the meso position (5.5 ppm).

Table 1 summarizes the physico-chemical properties of derivatives **1** and **2** at room temperature.

Table 1. Physico-chemical properties of derivatives **1** and **2** at room temperature

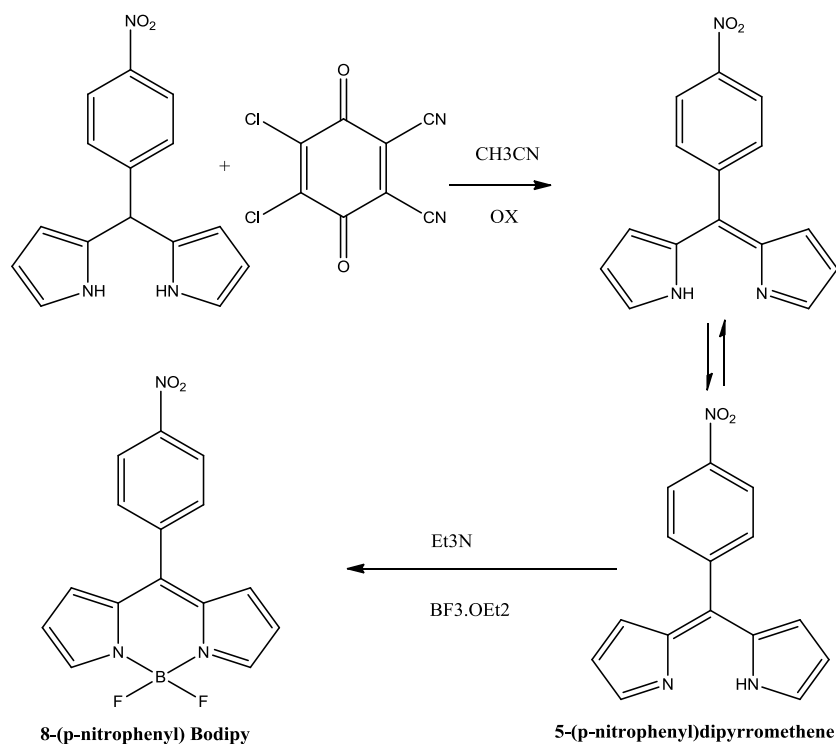
Aldehyde	Dipyrrométhane	Time (h)	Rapport (pyrrole/aldehyde)	Yield (%)
4-nitrobenzaldehyde	1	3,5	3/1	85%
4-formylbenzonitrile	2	3,5	3/1	80%

The control of the reaction time is crucial to obtain the desired dipyrromethanes (DPM) with high purity, a long lasting of reaction leads to a high content of tripyrromethane impurity (TPM). Apparently the success of this synthesis is based on the fact that the reaction between the pyrrole and the carbonyl compound is carried out at the interface between the pyrrole and the acidulated aqueous solution. We succeeded in synthesizing 5-aryldipyrromethane products in a medium aqueous with excellent yields, requiring only a simple manipulation, without going through the evaporation of excess pyrrole and not requiring purification by chromatography, since the product is obtained in the solid state.

Water has the advantage of being an inexpensive, non-toxic and environmentally friendly solvent, we think that this way of synthesis of (green chemistry) is essential at present and is part of the innovative efforts of the synthesis of oligopyrrole macromolecules. The obtained aryldipyrromethanes are used as a precursor in the synthesis of the desired Bodipy compounds, for this we have used a synthesis in three steps:

The first step is the oxidation of the dipyrromethane compound **1** to form the uninsulated dipyrromethene intermediate. This is carried out using 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in acetonitrile CH₃CN. The second step of deprotonation using a triethylamine base Et₃N followed by complexation with boron trifluoroetherate BF₃.OEt₂, allows to obtain the product, which is collected and evaporated under vacuum and subsequently purified by silica gel column chromatography using CH₂Cl₂. A red brick precipitate is obtained with a yield R = 20%

The low yield can be explained by the high instability of parent dipyrromethenes which are very sensitive to nucleophiles attacks, making it a very unstable compound that decomposes above -40 ° C. On the other hand, there may be degradation of dipyrromethane during its oxidation by the DDQ. (Scheme 2).

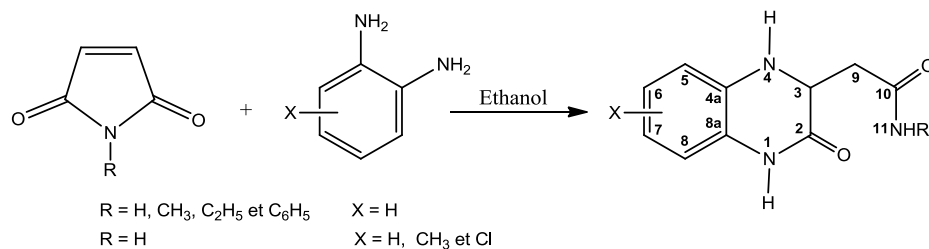


Scheme 2

The structure of the $\text{dipiNO}_2\text{-BF}_3$ is confirmed particularly by the disappearance of the proton peak of tertiary carbon, reflecting the loss of it and the formation of a double bond and the disappearance of the peak of the pyrrole nitrogens, which are very deblinded, as a result of the deprotonation of the pyrroles by the base and the coordination bond formation between the pyrrolic nitrogen and the metal.

2.2. Synthesis and complexation of quinoxalinones

The Condensation of maleimide with orthophenylenediamine at room temperature in the presence of ethanol has allowed the obtaining of different ligands (scheme 3).



Scheme 3

Table 2 groups the physical properties of quinoxalinones derivatives.

Table 2. physical properties of quinoxalinones

Compounds	R	X	Yield (%)	mp (°C)
4	H	H	80	278-280
5	CH ₃	H	70	194-196
6	C ₂ H ₅	H	60	203-205
7	H	CH ₃	70	258-260
8	H	Cl	60	180-183

From the table 2, we notice that the derivative having the lowest molecular weight, has the highest melting point. This observation is explained by the fact that, when R = H, the molecule has more freedom of intramolecular hydrogen bridge formation. The structures of the compounds were determined by the usual spectroscopic methods (¹H and ¹³C NMR, IR and mass spectrometry).

The complexes are prepared by using quinoxalinones ligands with Cu(NO₃)₂.3H₂O ; Co(NO₃)₂, 6H₂O and FeCl₂.4H₂O in proportion 1 / 1 in ethanol (Scheme 4).

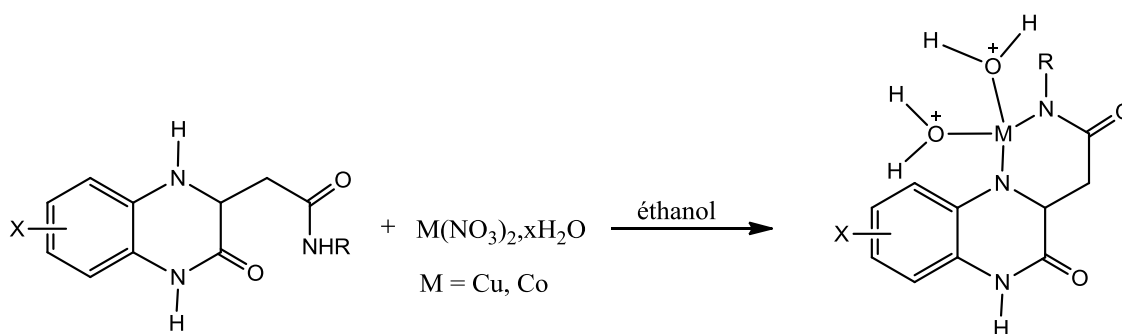
**Scheme 4**

Table 3 summarizes the physical properties of complexes

Table 3. conditions of formation and physical data of complexes

Complexes	Time (h)	Yield (%)	mp (°C)
A	24	40,53	258
B ₁	24	82,14	> 300
B ₂	24	46,70	> 300
B ₃	48	21,54	> 300
C ₁	48	56,89	> 300
C ₂	48	23,57	> 300
D ₁	24	52,52	210
D ₂	48	63,30	210
D ₃	72	69,20	210

The complexation of the transition metals by our ligands involves several types of equilibrium. In this equilibrium, coordination bonds are formed between the deprotonated nitrogen atoms of the secondary amides functions and the metallic cation.

According to the Infrared spectroscopy of the complexes A, B, C and D:

- the low intensity absorption bands existing in the region of 3200 cm⁻¹, which are attributed to the NH vibrations of the ligands, appear in the complexes. This can be interpreted by a deprotonation of the NH amine.

- the low intensity absorption bands existing in the 3300 cm⁻¹ region attributable to the NH vibrations of the cyclic amides (lactams) of the ligands, undergo a slight decrease in the frequency ν_{NH} , which would indicate a disturbance of the electronic distribution of these systems.

- the low intensity absorption bands existing in the region of 3300-3400 cm⁻¹ attributable to the NH vibrations of the free amide -CONHR are replaced by a wide band in the complexes, this wide band corresponds to the OH function of water in the complex. What is consistent with the proposed structure.

The complexation of the amides by the transition metals involving C=O carbonyl or NH amine will have to show a disappearance or a decrease in the frequency of one of these functional groups. The IR spectra of our complexes show a disappearance of the NH bands and thus suggest deprotonation of NH group followed by N-M coordination.

3. EXPERIMENTAL

All chemicals were obtained from Aldrich. Melting points were taken on a Thomas Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained with a Bruker AC 300 at 300 MHz (^1H) or 75 MHz (^{13}C). The chemical shifts are reported in ppm (δ -scale) relative to internal TMS and coupling constants are reported in Hertz (Hz). The impact ionization mass spectra were recorded on a Nermag R10-10C at 70 eV.

General procedure for synthesis of **1** and **2**

100 ml of an aqueous solution of hydrochloric acid (0,18 M) containing 2.7 ml of pyrrole (36 mmol, 3 eq.) we add 2 g of 4-nitrobenzaldehyde (12 mmol). The mixture was stirred at room temperature for 3 hours under magnetic agitation. We obtained, after filtration and dry vacuum. The corresponding compounds **1** and **2**.

2,2'-((4-nitrophenyl)methylene)bis(1H-pyrrole) **1**

Yield = 85%

^1H NMR (300MHz, DMSO), δ (ppm) : 5,36 (s, 1H, CH), 5,92 (d, $J=1,5\text{Hz}$, 2H, H(α) Pyrr 1 and Pyrr 2), 6,15 (q, $J=1,5\text{Hz}$, 2H, H(β) Pyrr1 and Pyrr2), 6,6 (m, 4H, H benz), 6,98 (d, $J=1,5\text{Hz}$, 2H, H(γ) Pyrr₁ and Pyrr₂), 8,3(s, 2H, NH).

E.I. (70 eV), m/z (%) : M^{+} = 267(100), 221 (66), 145 (83), 66 (45), 39(15).

4-(di(1H-pyrrol-2-yl)methyl)benzotrile **2**

Yield = 80%

^1H NMR (300MHz, DMSO), δ (ppm) : 5,5 (s, 1H, CH), 5,7 (d, $J=1,5\text{Hz}$, 2H, H(γ) Pyrr₁ and Pyrr₂), 5,9 (q, $J=1,7\text{Hz}$, 2H, H(β) Pyrr₁ and Pyrr₂), 6,6 (d, $J=1,5\text{Hz}$, 2H, H(α) Pyrr₁ and Pyrr₂), 7,4(d, $J=9\text{Hz}$, 2H, H($_{ortho}$)benz), 7,7(d, $J=9,2\text{Hz}$, 2H, H($_{meta}$)benz), 10,7(s, 2H, NH).

E.I. (70 eV), m/z (%) : M^{+} = 247 (100), 181 (35), 145 (85), 39(12).

General procedure for synthesis of **3**

In a flask, containing 30 ml of CH_3CN , 1 g of product **1** and 0.84 g of 2,3-dichloro-5,6-diciano-1,4-benzoquinone (DDQ) were added. The mixture was stirred at room temperature for 20 minutes under magnetic agitation. Then, we added 1,7 ml of Et_3N under agitation at room temperature during 5 minutes. We end with an addition of 1,7ml of $\text{BF}_3 \cdot \text{OEt}_2$. We obtained after evaporation under vacuum a red-brick solid which will be purified on a column of silica gel with CH_2Cl_2 .

2-(1-(difluoroboryl)-2,3-dihydro-1H-pyrrol-2-yl)(4-nitrophenyl)methyl-1-methyl-1H-pyrrole **3**

Yield = 20 % ^1H NMR (300MHz, DMSO), δ (ppm) : 6,56 (d, $J=4,2\text{Hz}$, 2H, $\text{H}(\alpha)$ Pyrr₁ and Pyrr₂), 6,84 (d, $J=4,2\text{Hz}$, 2H, $\text{H}(\gamma)$ Pyrr₁ and Pyrr₂), 7,99 (s, 2H, $\text{H}(\beta)$ Pyrr₁ and Pyrr₂), 7,75 (d, $J=9\text{Hz}$, 2H, $\text{H}(\text{ortho})\text{benz}$), 8,40 (d, $J=8,7\text{Hz}$, 2H, $\text{H}(\text{meta})\text{benz}$).

E.I. (70 eV), m/z (%) : $\text{M}^{\dagger+}=3,13(100), 283(5), 267(45), 247(50), 218(9)$.

General procedure for synthesis of **4**

In 20 ml of ethanol, 0.97 g (0.01 mol) of maleimide and 1.08 g (0.01 mol) of orthophenylenediamine was mixed. The mixture was stirred at room temperature for 24 hours. After filtration under vacuum, a brown solid is recovered.

Compound **4**

Yield = 80 %

IR (KBr), ν (Cm^{-1}) : $\nu_{\text{NH}(1)}=3346, \nu_{\text{NH}(4)}=3188, \nu_{\text{CO}}=1686, \nu_{\text{NHR}}=3395$.

^1H NMR (300MHz, DMSO), δ (ppm) : 2,37 (dd, $J=15,48\text{Hz}$, 1H, CH), 2,44 (dd, $J=15,48\text{Hz}$, 1H, CH), 4,05 (m, 1H, CH), 5,75 (s, 1H, NH), 6,56-6,77 (m, 4H, H_{arom}), 6,88 (s, 1H, NH), 7,39 (s, 1H, NH), 10,19 (s, 1H, $\text{HNC}=\text{O}$).

^{13}C NMR (300MHz, DMSO), δ (ppm) : 37(CH_2), 52 (CH), 114, 115, 118, 122, 126, 134 (6C_{arom}), 167 ($\text{C}=\text{O}$), 172 ($\text{C}=\text{O}$).

E.I. (70 eV), m/z (%) : $\text{M}^{\dagger+}=204(100), 160(46,67), 147(16,12), 59(15,19), 52(8,80)$.

Compound **5**

This compound is obtained, according to the same protocol as **4**

Yield = 70 %

IR (KBr), ν (Cm^{-1}) : $\nu_{\text{NH}1}=3375, \nu_{\text{NH}(4)}=3200, \nu_{\text{CO}}=1686, \nu_{\text{NHR}}=3313$.

^1H NMR (300MHz, DMSO), δ (ppm) : 2,35 (dd, J , 2H, CH_2), 2,6 (d, 3H, CH_3), 4,08 (m, 1H, CH), 5,87 (s, 1H, NH), 6,74 (m, 4H, H_{arom}), 7,90 (s, 1H, NHCO), 10,27 (s, 1H, $\text{HNC}=\text{O}$).

Compound **6**

This compound is obtained, according to the same protocol as **4**

Yield = 60 %

IR (KBr), ν (Cm^{-1}) : $\nu_{\text{NH}1}=3380, \nu_{\text{NH}(4)}=3200, \nu_{\text{CO}}=1682, \nu_{\text{NHR}}=3294$.

^1H NMR (300MHz, DMSO), δ (ppm) : 1(t, 3H, CH_3), 2,65 (dd, 2H, CH_2), 3,09 (q, 2H, CH_2), 4 (m, 1H, CH), 5,8 (s, 1H, NH), 6,7 (m, 4H, H_{arom}), 7,9 (t, 1H, NH), 10,20 (s, 1H, $\text{HNC}=\text{O}$).

^{13}C NMR (300MHz, DMSO), δ (ppm) : 15($\text{C}_{(\text{R}=\text{CH}_3)}$), 33($\text{C}_{(\text{R}=\text{CH}_2)}$), 37(CH_2), 53 (CH), 114, 115, 118, 123, 126, 134 (6C_{arom}), 167 ($\text{C}=\text{O}$), 171 ($\text{C}=\text{O}$).

Compound **7**

This compound is obtained, according to the same protocol as **4**.

Yield = 70 %

IR (KBr), ν (Cm^{-1}): $\nu_{\text{NH1}} = 3383$, $\nu_{\text{NH(4)}} = 3200$, $\nu_{\text{CO}} = 1666$, $\nu_{\text{NH2}} = 3433$.

^1H NMR (300MHz, DMSO), δ (ppm): 2,08(s,3H,CH₃), 2,22 (dd, J=15,5Hz, 1H, CH), 2,49 (dd, J=15,48Hz, 1H, CH), 3,90 (m, 1H, CH), 5,65 (s, 1H, NH), 6,44-6,55 (m, 3H, H_{arom}), 6,85 (s, 1H, NH), 7,32 (s, 1H, NH), 10,01 (s, 1H, HNC=O).

^{13}C NMR (300MHz, DMSO), δ (ppm): 20,37 (CH₃), 37 (CH₂), 52 (CH), 114, 116, 118, 123, 126, 133 (6C_{arom}), 167 (C=O), 172 (C=O).

E.I. (70 eV), m/z (%): $\text{M}^{1+} = 218(100)$, 161(27,71), 174 (56,76), 59(18,49), 52(7,38).

Compound **8**

This compound is obtained, according to the same protocol as **4**.

Yield = 60 %

IR (KBr), ν (Cm^{-1}): $\nu_{\text{NH1}} = 3344$, $\nu_{\text{NH(4)}} = 3195$, $\nu_{\text{CO}} = 1674$, $\nu_{\text{NH2}} = 3415$.

^1H NMR (300MHz, DMSO), δ (ppm): 2,36 (dd, J=15,51Hz, 1H, CH), 2,58 (dd, J=15,48Hz, 1H, CH), 4,15 (m, 1H, CH), 6,11 (s, 1H, NH), 6,66-6,84 (m, 3H, H_{arom}), 7,01 (s, 1H, NH₂CO), 7,47 (s, 1H, NH₂CO), 10,43 (s, 1H, HNC=O).

^{13}C NMR (300MHz, DMSO), δ (ppm): 37(CH₂), 52 (CH), 114, 115, 118, 122, 127, 133 (6C_{arom}), 167 (C=O), 172 (C=O).

E.I. (70 eV), m/z (%): $\text{M}^{1+} = 238,5(100)$, 221(1,622), 179(6,18), 152(12,47), 142(31,5)

General procedure for synthesis of complex **A**

In 20 ml of ethanol, we mixed 0.205 g of compound **4** with 0.41 g of Cu (NO₃)₂, 3H₂ O. We leave this mixture under magnetic stirring for 24 hours. After filtration, a green solid is recovered.

Complex **A**

IR (KBr), ν (Cm^{-1}): $\nu_{\text{NH}} = 3280$, $\nu_{\text{OH}} = 3300-3400$, $\nu_{\text{CO}} = 1664$, $\nu_{\text{CN}} = 1155$

General procedure for synthesis of complex **B₁**

In 20 ml of ethanol, we mixed 0.219 g of compound **5** with 0.241 g of Cu (NO₃)₂, 3H₂ O and 0.112 g of KOH. After 24 hours of magnetic stirring, a green solid is obtained

Complex **B₁**

IR (KBr), ν (Cm^{-1}): $\nu_{\text{NH}} = 3285$, $\nu_{\text{OH}} = 3300-3400$, $\nu_{\text{CO}} = 1664$, $\nu_{\text{CN}} = 1155$.

General procedure for synthesis of complex **B₂**

0.291 g of Co (NO₃)₂, 6H₂ O are mixed with 0.219 g of compound **5** and 0.112 g of KOH in 20 ml of ethanol with magnetic stirring and at room temperature. The end of the reaction is signified by a yellow-green precipitate.

Complex **B₂**

IR (KBr), ν (Cm^{-1}): $\nu_{\text{NH}} = 3280$, $\nu_{\text{OH}} = 3300-3400$, $\nu_{\text{CO}} = 1650$, $\nu_{\text{CN}} = 1150$.

General procedure for synthesis of complex C₁

In 20 ml of ethanol, 0.233 g of compound **6** are mixed with 0.241 g of Cu (NO₃)₂, 3H₂O and 0.112 g of KOH. The solution is green. After magnetic stirring the filtration gives us a dark brown precipitate.

Complex C₁

IR (KBr), ν (Cm⁻¹) : $\nu_{\text{NH}}= 3285$, $\nu_{\text{OH}}= 3300-3400$, $\nu_{\text{CO}}= 1664$, $\nu_{\text{CN}}=1155$.

General procedure for synthesis of complex C₂

0.291 g of Co (NO₃)₂, 6H₂O are mixed with 0.233 g of compound **6** and 0.112 g of KOH in 20 ml of ethanol with magnetic stirring and at room temperature. After 48 hours, the mixture is evaporated and a bright black precipitate is recovered.

Complex C₂

IR (KBr), ν (Cm⁻¹) : $\nu_{\text{NH}}= 3280$, $\nu_{\text{OH}}=3300-3400$, $\nu_{\text{CO}}= 1650$, $\nu_{\text{CN}}=1150$

General procedure for synthesis of complex D₁

In 20 ml of ethanol, 0.281 g of compound **7** is mixed with 0.241 g of Cu (NO₃)₂, 3H₂O and 0.112 g of KOH. The solution is green. After magnetic stirring at room temperature, a black precipitate is obtained.

Complex D₁

IR (KBr), ν (Cm⁻¹) : $\nu_{\text{NH}}= 3285$, $\nu_{\text{OH}}=3300-3400$, $\nu_{\text{CO}}= 1664$, $\nu_{\text{CN}}=1155$

General procedure for synthesis of complex D₂

0.291 g of Co (NO₃)₂, 6H₂O are mixed with 0.219 g of compound **7** and 0.112 g of KOH in 20 ml of ethanol with magnetic stirring and at room temperature for two days. The end of the reaction is signified by a yellow-green precipitate.

Complex D₂

IR (KBr), ν (Cm⁻¹) : $\nu_{\text{NH}}= 3280$, $\nu_{\text{OH}}= 3300$, $\nu_{\text{CO}}= 1650$, $\nu_{\text{CN}}=1150$.

4. CONCLUSION

We carried out a gentle oxidation reaction of the dipyrromethanes in the presence of the DDQ reagent to obtain the dipyrromethenes, which were complexed with BF₃-OEt₂, what allowed us to obtain the desired BODIPY molecules.

The synthesis of quinoxalinones and the demonstration of the potential of ligands to generate monometallic complexes with transition metals, these original molecules are likely to mimic the oxidoreductive activity of enzymes such as catalase and the superoxydismutase (SOD).

The spectroscopic IR identification of the complexes of copper and cobalt of the synthesized quinoxalinones was confirmed. On the other hand, the reaction of formations of the iron complexes did not give conclusive results.

5. ACKNOWLEDGEMENTS

The authors would like to thank the Department of Organic Chemistry. Laboratoire de Chimie Organique et des Substances Naturelles, Université Ziane Achour, Djelfa, Algeria and the Faculté de Chimie – USTHB – BP32, El-Alia, 16111 Bab Ezzouar, Alger, Algeria ;

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How to cite this article:

Bayou-Khier N, Benchikha N, Amari M, Hammadi M. Effective synthesis of substituted quinoxalinones and their complexation. *J. Fundam. Appl. Sci.*, 2019, 11(3), 1256-1266.