

Synthesis and characterisation of new phosphonate labelled cyanines

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Abstract

We present the synthesis of new *N*-1,5 phosphosubstituted pentamethine cyanine dyes in high yields. The compounds are obtained from original *N*-phosphonates quaternary heterocyclic ammonium salts, with an activated methyl group in the 2-position. Moreover, the aqueous solubility of these new dyes is emphasized. The spectroscopic parameters of the new compounds are described together with a preliminary study of divalent cations complexation in fluorescence.

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1. Introduction

The synthesis [1,2] and the reactivity [3,4] of cyanine dyes were widely studied since years. They present numerous applications in large areas (chemistry, physics, materials ...). For our part, we are particularly interested in their biological applications. They are often used as fluorescent probes in the investigations of biological materials, to study the structure of DNA and its detection in cells [5]. They have also many biomedical applications like disease diagnosis and prevention or treatment [6].

The synthesis of phosphorus podands labelled by a cyanine probe and the fluorescence enhancement with calcium or magnesium complexation were described in a previous paper [7]. This initial work showed that cyanines are interesting fluorescent transmitters to give a macroscopic quantified response to the presence of biological cations. Our actual goal is to develop new phosphorus functionalized cyanine dyes in this series which can be used as biological probes. The searched enhancements concern mainly the introduction of new

phosphorus moieties, synthetic improvement, aqueous solubility and selectivity of the complexation.

Methods for the synthesis of new 1,5-substituted pentamethine cyanine dyes have been developed [8]. In the literature, there are many cyanines with *N*-alkyl substituent [9] but to the best of our knowledge, there is only one example with phosphonate moiety [10].

We present here the synthesis of new functionalized ammonium salt precursors and the derived cyanines dyes together with their preliminary photophysical results.

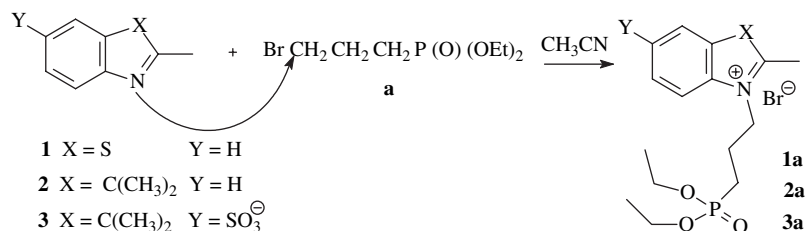
2. Results and discussion

We describe first the synthesis of the *N*-phosphonate quaternary ammonium salt precursors of new cyanines dyes. The ammonium salts **1a**, **2a** and **3a** bearing a phosphonate moiety as *N*-substituent were obtained by a classical nucleophilic substitution reaction. Following the procedure adapted from Almeida and others [11], by heating under reflux a solution of the corresponding 2-methylheterocyclic base **1**, **2** and **3** with an excess of diethyl 3-bromopropyl phosphonate **a** in acetonitrile (Scheme 1), **1a**, **2a** and **3a** are obtained in high yield.

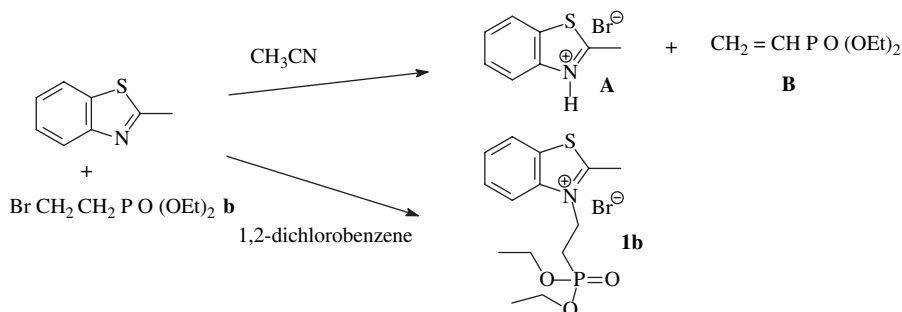
In the course of this work, we also studied the reactivity of diethyl 2-bromoethylphosphonate **b** in acetonitrile. With the

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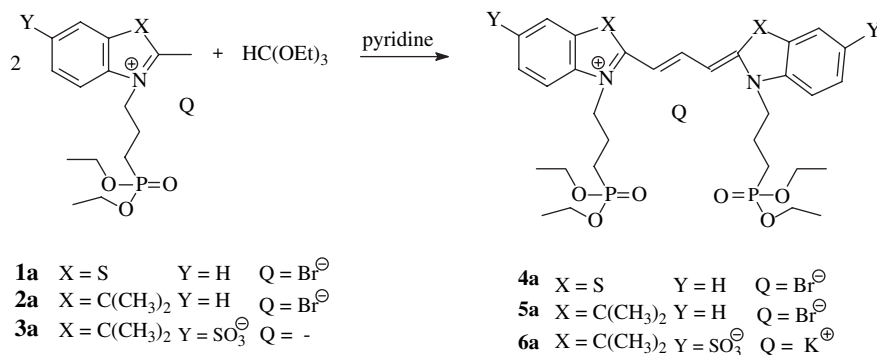
E-mail address: mrm@chimie.ups-tlse.fr (M.R. Mazières).



Scheme 1. Synthesis of ammonium phosphonate salts.



Scheme 2. Reactions with bromoethylphosphonate. Alternative pathways.

Scheme 3. Synthesis of cyanines **4**, **5** and **6**.

same operation conditions, the reaction proceeds differently following an elimination way of HBr and the formation of ammonium **A** and phosphonate **B**, compounds identified by NMR and mass spectra (Scheme 2, see Section 4). This is certainly due to a slight difference between acidity of the hydrogen atoms of the α methylene of the phosphonates **a** and **b**. With phosphonate **b**, these H atoms are quite more acidic due to the electro attractive effects of both the Br atom and phosphonate group, thus the benzothiazole acts as a base to abstract an α hydrogen with an elimination reaction of the bromine (probably E₂). With phosphonate, **a** there is an attenuation of the electro attractive effect of the Br atom due to the supplementary methylene group. In this case, the nitrogen atom of the ring attacks the terminal carbon of the diethyl 3-bromophosphonate (Scheme 1).

To favour the substitution mechanism with phosphonate **b**, we tried the reaction in dichlorobenzene at 80 °C during 24 h

and these conditions were convenient for the obtention of ammonium **1b** (Scheme 2, see Section 4), this showed that the polarity of the solvent greatly influences the reactivity of **b**.

The electro attractive effect of phosphonate group is also evidenced when we compare the reactivity of diethyl 2-bromoethylphosphonate **b** with 3-bromopropionic acid one: the reaction of **1** with 3-bromopropionic acid leads to the expected *N*-quaternary ammonium salt, without formation of acrylic acid [11].

2.1. Cyanine dyes synthesis

The process involves two steps:

- Synthesis of phosphorylated quaternary ammonium salt.
- The condensation of two equivalents of the ammonium salt with ethylorthoformate CH(OEt)₃ in dry pyridine

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