SYNTHESIS OF NEW FLUORESCENT β-CYCLODEXTRIN SENSOR

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Abstract : The synthesis of a new fluorescent sensor incorporating a fluoro pyridine indolizinic unit and a β-cyclodextrin fragment by two different synthetic ways is described.

Keywords: β-cyclodextrin, indolizine, fluorescent sensor

Introduction

Designing functionalisable fluorescent organic compounds which can be used as building blocks for the synthesis of new chromogenic derivatives with distinctly different physical and/or chemical properties is a great interest to biologists [1] and organic chemists [2].

The attachment of fluorophores to synthetic or natural receptors has received considerable attention over the last few years, in endeavors to furnish new fluorescent sensor [3]. In particular, fluorescent cyclodextrins have generated considerable interest from the synthetic community as witnessed by recent articles dealing with their synthesis and emphasizing their sensory [4] and also their biochemical properties [5]. On the other hand, indolizinic derivatives are of interest as biologically active products and are well known to exhibit a variety of pharmacological effects including cardiovascular [6] and anti-inflammatory activities [7]. In addition to exhibiting a spectrum of pharmacological effects, synthetic indolizinic derivatives are also well known for their fluorescent properties and some of them have already described as dyes and biological markers [8].

In previous papers [9], we reported the synthesis of a new class of fluorescent β-cyclodextrins by two different chemical ways: (i) an amidation between 4-nitrophenyl 3-[carbetoxy or 4-substitued benzoyl]-7-[pyridin-4-yl]indolizin-1-carboxylate and 6-deoxy-6-amino-β-cyclodextrin and (ii) a 3+2 cycloaddition between 4-[pyridin-4-yl]pyridinium methylides and 6-deoxy-6-propynamido-β-cyclodextrin.

As a part of our ongoing research program in the reactivity of cycloimmonium ylides [10] and with the aim of synthesizing a new range of fluorescent β-cyclodextrins, we herein report the synthesis of a pyridinoindolizine β-cyclodextrin having a fluor in its structure. The presence of fluor attached to fluorescent indolizine fragment of cyclodextrin sensor could open new applications in pharmacological area and chemical detection of Volatile Organic Compounds [9].

Results and discussion

The N-(6-deoxy-β-cyclodextrin-6-yl)-1-aminocarbonyl)-3-(4-fluorobenzoyl)-7-pyridin-4-yl indolizine 9 was synthesized by two different ways a and b (Scheme *1*).

The salt method [11] has been applied in order to obtain the bipyridinium ylide **4**. Thus, the commercially available 4,4'-bipyridine was reacted with 2-bromo-4-fluoroacetophenone **2**, in boiling dry acetone, to furnish, after recrystallization (ethanol), the corresponding salt **3**. This salt, in the presence of the mild base triethylamine (TEA) gave *in situ*, at 0-5°C in DMF, the red-violet monosubstitued carbanion ylide **4**. That ylide was involved in both synthetic ways **a** and **b** as 1,3-dipole. It should be noted that these reactions must be carried out without light in order to prevent cleavage of the N^+-C^- ylide bond [12].

The 6-deoxy-6-amino-β-cyclodextrin **6** was prepared according to the Hamasaki method [13], *e.g.* β-cyclodextrin → 6-tosyl-β-cyclodextrin → 6-azido-β-cyclodextrin → 6-deoxy-6-amino-β-cyclodextrin. The 6-propynamido-β-cyclodextrin was prepared by condensation of 6-deoxy-6-amino-β-cyclodextrin with 4-nitrophenyl propynoate [9a, 14]. The ester **5** could be easier obtained by direct esterification of propynoic acid with 4-nitrophenol in presence of dicyclohexylcarbodiimide (DCC) [15].

Next, the ylide **4**, generated "in situ" in N-methylpyrrolidone (NMP), was reacted with propynoate **5** to generate the primary cycloadduct 6, which subsequently eliminate hydrogen to give the indolizine **7**.

Both synthesis **a** and **b** of sensor 9 have been performed in the dark, in homogeneous phase, using DMF as solvent. The crude product **9** was isolated by precipitation from acetone and successively purified by chromatography using Sephadex CM25, then G15 resins. Analysis of new products **3**, **7** and **9** reported in this paper for the first time using FTIR, NMR and ESIM procedures are in agreement with the proposed structures and with the literature data. [9a,b]. The presence of two overlapping absorption bands at 1652 cm^{-1} proves the existence of two different CO groups.

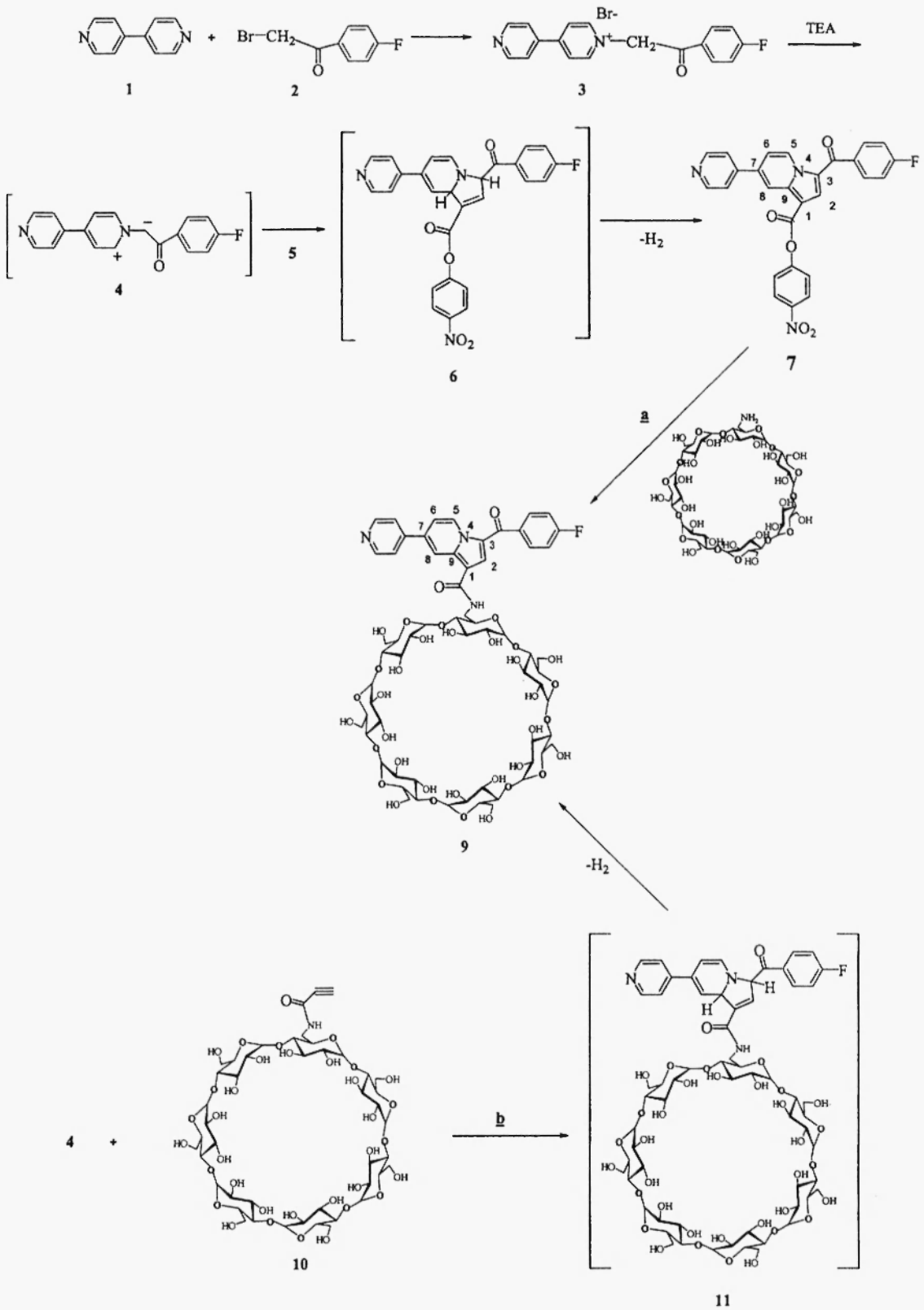
Moreover, in MS-spectra, the peak at 1498 corresponds to m/z + 23 molecular weight of sensor **9**. The structure of sensor **9** has been established by comparison of its ^{1}H-NMR data with previously published results on the sensors comparable series [9,16]. The examination of ^{1}H-NMR spectra of the sensor **9** revealed the presence of the glycon moiety and indolizine fragment in a correct structural ratio.

Conclusions

The present work provides the first synthesis of a cyclodextrin-indolizine sensor incorporating in its structure a fluor atom. It is likely that this new type of fluorescent β-cyclodextrin will find applications as biological markers.

Experimental

^{1}H-NMR spectra were recorded on a Bruker AMX 250 spectrometer with tetramethylsilane as internal standard. Chemical shift values δ are reported in ppm and coupling constants J are expressed in Hz. The used abbreviations are: s (singlet), d (doublet), t (triplet) and m (multiplet). Mass spectra were measured using a Platform II Micromass Apparatus. FTIR spectra were recorded using a Perkin-Elmer 2000 instrument. Melting points were obtained with a digital IA 9000 Apparatus.



Scheme-1

Synthesis of N-(6-deoxy-β-cyclodextrin-6-yl)-1-(aminocarbonyl)-3-(4-fluorobenzoyl)-7-pyridyn-4-yl indolizine **9**.

1-(4-fluorophenacyl)-4-pyridin-4-yl pyridinium bromide 3

In a 100 ml round-bottomed flask of 4,4'-bipyridyne (10 mmol) is dissolved in dry acetone (25 mL). Next, 4-fluoro-2-bromoacetophenone (10 mmol) dissolved in acetone (35 mL) is added. The reaction mixture is refluxed for 6h under magnetic stirring. The formed solid is filtered then washed with anhydrous ether. The salt is finally purified by recrystallization from ethanol.

Yield 88%, m.p.> 250°C.

IR (KBr, $\bar{\nu}$ cm^{-1}): 3021, 2830, 1689, 1594, 1545, 1456, 1409, 1230, 1155, 993, 816, 724.

^{1}H-NMR (DMSO-d_6, δ ppm): 9,17 (d, 2H, ortho/N^+, *J*= 6,7 Hz); 8,91 (d, 2H, ortho/N, *J*= 6,0 Hz); 8,78 (d, 2H, meta/N^+, *J*= 6,7 Hz); 8,20 (t, 2H, ortho/F, *J*= 8,7 Hz); 8,10 (d, 2H, meta/N, *J*= 6,0 Hz); 7,55 (t, 2H, meta/F, *J*= 8,7 Hz); 6,55 (s, 2H, CH_2/N^+).

SM ES^+ m/z (%): 293 [M+] (70%), 141 (42%), 114 (100%).

3-(4-fluorobenzoyl)-7-(pyridin-4-yl)-1-(4-nitrophenylcarbonyl) indolizine 7

In a 100 ml round-bottomed flask, the salt **3** (0.4 mmol) is dissolved in anhydrous N-methylpyrrolidone (NMP, 35 mL). 4-nitrophenyl propynoate **5** (0.4 mL), also dissolved in NMP (20 mL) is then added. To the stirred and cooled (0-5°C) reaction mixture, a solution of TEA (0.55 mmol) in NMP (5 mL) is added over a period of 15 minutes using a dropping funnel. Stirring is continued in the dark, at room temperature, for 2 hours. The mixture is then added drop wise into acetone (70 mL). The resultant precipitate was collected and washed with acetone, then diethyl ether.

Yield 40%, m.p.> 250°C.

IR (KBr, $\bar{\nu}$ cm^{-1}): 3382, 1722, 1596, 1518, 1417, 1344, 1211, 1158, 1067, 987, 847, 751.

^{1}H-NMR (DMSO-d_6 + 30 µl CF_3COOD, δ ppm): 9,93 (d, 1H, *H-5*, *J*= 7,2 Hz); 8,79 (d, 2H, meta/N, *J*= 6,0 Hz); 8,71 (s, 1H, *H-8*); 8,37 (d, 2H, ortho/N, *J*= 6,0 Hz); 8,15-7,85 (m, 6H, *H-2*, *H-6*, ortho/F and ortho/NO_2); 7,65 (d, 2H, meta/NO_2, *J*= 8,9 Hz); 7,46 (t, 2H, *J*= 8,5 Hz).

SM ES^+ m/z (%): 482 $[M+H]^+$ (100%), 375 (90%), 361 (82%).

N-(6-deoxy-β-cyclodextrin-6-yl)-1-(amino carbonyl)-3-(4-fluorobenzoyl)-7-pyridyn-4-yl indolizine 9

(**a**) A homogeneous mixture of amino-β-cyclodextrin **6** (0,35 mmol) and fluorescent indolizine **7** (0,35 mmol) in dry DMF (40 mL) is stirred in the dark and under argon at 60°C over a 12 hours period. The reaction mixture is poured in acetone (100 mL) and the resultant precipitate was dissolved in distilled water. After filtration and concentration, the water solution of the fluorescent product 9 was firstly filtered on a Sephadex CM-25 column and next purified on a Sephadex G-15, to give the pure compound **9** as an orange powder (Yield 22%).

(**b**) A solution of freshly distilled TEA (0.65 mmol) in DMF (1 mL) was gradually added, under Argon, to a stirred solution of salt **3** (0,45 mmol) and propynamido-β-cyclodextrin **10** (0,45 mmol) at 0-5°C. The reaction mixture was allowed to warm to room temperature in the absence of light, over a 12 hours period. The solution was then poured into acetone (50 mL), and the resultant precipitate of crude compound 9 was purified as in the previous synthetic way **a** (Yield 14%).

IR (KBr, $\bar{\nu}$ cm^{-1}): 3378, 1652, 1457, 1407, 1343, 1259, 1154, 1078, 1024, 799.

^{1}H-NMR (DMSO-d_6, δ ppm): 9,84 (d, 1H, *H*-4', *J*= 7,5 Hz); 8,95 (s, 1H, *H*-5'); 8,67 (d, 2H, *H*-1', *J*= 6,1 Hz); 8,31 (m, 1H, *NH*); 8,16 (s, 1H, *H*-6'); 7,93 (d, 2H, *H*-2', *J*= 5 Hz); 7,84 (d, 2H, *H*-7', *J*= 8,5 Hz); 7,70 (dd, 1H, *H*-3', *J*= 4,4 Hz); 7,40 (d, 2H, *H*-8', *J*= 6.2 Hz); 7,26 (m, 14H, *-OH*-2, *-OH*-3); 5,96-5,36 (m, 7H, *H*-1); 4,94-4,10 (m, 6H,-*OH*-6) ; 4,05-2,88 (m, 42H , *H-2, H*-4, *H*-3, *H*-5, *H*-6^{a,b})

SM ES$^+$ m/z (%): 1498 $[M+Na]^+$ (100%), 1496 $[M+Na-2]^+$ (85%), 1280 (41%), 1256 (12%).

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Received on October 11, 2004.