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# Synthesis of anionic chemodosimeters based on silylated pyridinium *N*-phenolate betaine dyes

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ABSTRACT

Three novel silylated pyridinium *N*-phenolate betaine dyes were synthesized and characterized. These compounds were used in acetonitrile as anionic chemodosimeters for the colorimetric detection of $F^-$ and $CN^-$. In addition, the system was made highly selective to $CN^-$ in relation to other anions in acetonitrile/water mixtures. The nucleophilic attack of the anion on the silicon center of the chemodosimeters, through a nucleophilic substitution at silicon ($S_N2@Si$), immediately breaks the Si–O bond, with the formation of their corresponding colored pyridinium *N*-phenolate betaine dyes as the leaving groups. Thus, this process is effective for the detection of $F^-$ and $CN^-$, which are strongly nucleophilic analytes in anhydrous acetonitrile. Fluoride is strongly hydrated when water is present in the medium, this being the reason for the pronounced reduction in the selectivity of this anion in comparison with $CN^-$.

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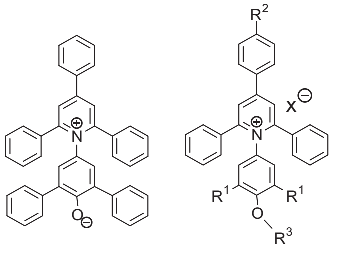
Pyridinium *N*-phenolate betaine dyes comprise a family of zwitterionic compounds recognized for their solvatochromic properties, the most important and interesting example of which is compound **1**, 2,6-diphenyl-4-(2,4,6-triphenylpyridinium-1-yl)phenolate.[1–4] The solvatochromic visible charge-transfer (CT) band of dye **1** is hypsochromically shifted from $\lambda_{max}$ = 810 nm in diphenyl ether to $\lambda_{max}$ = 453 nm in water, corresponding to a solvent-induced band shift of $\Delta\lambda_{max} = -357$ nm ($\Delta E_T$ = 117 kJ mol$^{-1}$).[3,4] This enables dye **1** and related compounds to be applied in the study of the polarity of pure solvents, ionic liquids, electrolyte solutions, and solvent mixtures.[4] The very popular Reichardt $E_T(30)$ solvent polarity scale is based on the position of the visible CT absorption band of **1**.[1,4] These dyes exhibit also thermosolvatochromic, chiro-solvatochromic, and piezo-solvatochromic properties.[1,4] Pyridinium *N*-phenolate dyes are also commonly applied in systems other than liquid solvents as probes to measure the polarity of solid surfaces, micelles, vesicles, polymers, glasses, and gels, and their more general use means that they are considered as perichromic dyes.[4] These dyes have been used as signalizing units in the construction of various optical devices, especially for the detection of neutral,[4–12] cationic,[4,13–15] and anionic[4,16–18] species. The recognition and detection of anions represent a field of great interest.[19–28] Many strategies for the optical detection of $CN^-$ have been reported[17,18,28–35] due to the fact that this anion is present in several industrial processes, such as metallurgy, mining, and the fabrication of polymers.[36] $CN^-$ is also delivered through hydrolysis from warfare neurotoxic agents[37] and from some fruit seeds and roots.[38–40] The lethality of this anion in very low concentrations is due to its strong binding to the active site of cytochrome-oxidase, which causes a decrease in the oxidative metabolism.[41] Fluoride, another anion of interest in terms of detection, plays an important role in environmental pollution, in industry, and in many diseases.[42–44]



| | R1 | R2 | R3 | X- |
|---|---|---|---|---|
| **2** | H | H | TIPS | $ClO_4^-$ |
| **3** | $CH_3$ | H | TIPS | $ClO_4^-$ |
| **4** | H | CN | TIPS | $BF_4^-$ |
| **5a** | H | H | H | $ClO_4^-$ |
| **6a** | $CH_3$ | H | H | $ClO_4^-$ |
| **7a** | H | CN | H | $BF_4^-$ |

The chemodosimeter approach is a very attractive optical technique among the various strategies which have been developed in recent years for the detection of anionic species.[19,21,26] This is based

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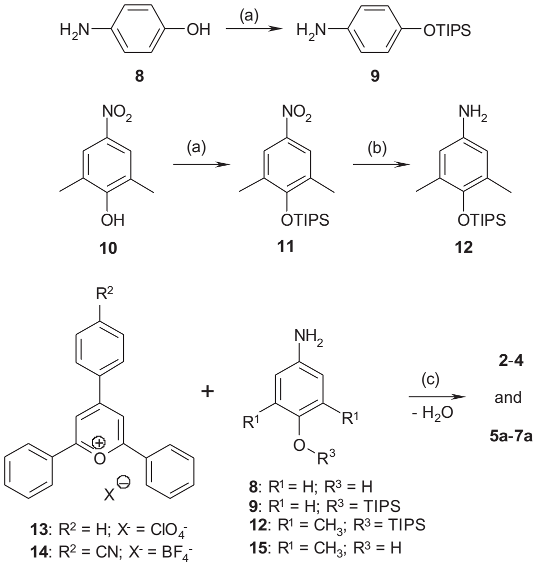
on the use of the target analyte, for instance a nucleophile, in an irreversible process, in order to generate a chromophore and/or fluorophore species. When these signalizing units are released into a solution, the quantitative naked-eye detection of the species can be performed. One possible design for a chemodosimeter is the reaction of the electron-donor group in a dye with a protective group, leading to the product being colorless in solution. The addition of a nucleophilic species to the medium leads to the dye release, which signals the presence of these species. Many chemodosimeters have been assessed using classical reactions involving protection of the hydroxylic group in phenols with, for instance, triisopropylsilyl chloride (TIPS-Cl) to form *O*-silyl ethers,[26,44–46] which are colorless in solution. The addition of $F^-$ to the solutions of these ethers in organic solvents displaces the dye as the leaving group, leading to the detection of the anion.[26,44] Recently, we demonstrated that adequately designed leaving group dyes can be used to synthesize *O*-silyl chemodosimeters highly selective toward $CN^-$,[47] the anion selectivity being determined by the presence of water in the medium, which acts by strongly solvating $F^-$ and hindering the nucleophilic attack of the anion on the silicon center.

Herein, we report the synthesis and characterization of three novel silylated pyridinium *N*-phenolate betaine dyes (**2**–**4**). These compounds were used in acetonitrile as anionic chemodosimeters for the colorimetric detection of nucleophilic anions, such as $F^-$ and $CN^-$. In addition, we also demonstrate that the system is made highly selective for $CN^-$ in relation to other anions in acetonitrile/water mixtures. In order to verify the products of the reaction of **2**–**4** with the anions, compounds **5a**–**7a** were also prepared, which could be deprotonated in solution to generate the corresponding pyridinium *N*-phenolate betaine dyes **5b**–**7b**.

Scheme 1 shows the route used for the synthesis of the compounds. Silylated compounds **2**–**4** and their corresponding phenols **5a**–**7a** were synthesized by means of the classical methodology available in the literature,[11,48,49] which involves the reaction of the pyrylium salts **13** and **14** with the corresponding 4-aminophenols (**8** and **15**) or their silylated derivatives **9** and **12**. The reactions were carried out by refluxing the reactants in ethanol in the presence of acetic acid (one drop) at 70 °C and in argon atmosphere. Silylated compounds **9** and **11** were prepared through the reaction of 4-aminophenol (**8**) or 2,6-dimethyl-4-nitrophenol (**10**) with TIPS-Cl in DMF using imidazole as a base. Amine **12** was synthesized through the catalytic reduction of compound **11** in the presence of Pd and $H_2$, using THF as the solvent. Novel compounds **2**–**4**, as well as compounds **5a**–**7a**, were characterized by means of IR, $^1$H NMR, $^{13}$C NMR, and HRMS spectrometric techniques. All compounds were sufficiently pure to be used in the further assays.



**Scheme 1.** Synthetic route for the synthesis of compounds **2**–**4** and **5a**–**7a**. Reagents and conditions: (a) TIPS-Cl, imidazole, DMF; (b) Pd, $H_2$, THF; (c) acetic acid (one drop), EtOH, argon, 70 °C.

Figure 1 shows the behavior of solutions of compounds **2**–**4** in acetonitrile in the absence and presence of various anions. The solutions of these compounds are colorless, but when several anions ($HSO_4^-$, $H_2PO_4^-$, $NO_3^-$, $CN^-$, $CH_3COO^-$, $F^-$, $Cl^-$, $Br^-$, and $I^-$) are added individually, only $F^-$ and $CN^-$ are responsible for the appearance of vivid colors in the solutions, dark red for compound **2** and dark blue for compounds **3** and **4**. The colors of the solutions correspond to the color of the corresponding pyridinium *N*-phenolate betaine dyes **5b**–**7b**, which were generated from the deprotonation of **5a**–**7a**. This suggests that the reaction of compounds **2**–**4** with $F^-$ and $CN^-$ leads to the formation of **5b**–**7b**. Figure 1 also shows that $CH_3COO^-$ and, to a lesser extent, $H_2PO_4^-$ change the color of the solutions of the compounds to pale yellow, suggesting a weak interaction between these anions and the compounds.

Figure 1 also shows that the addition of water volumes to the solutions of **2**–**4** changes the ability of the anions to color the solutions: with the addition of 10% of water only $CN^-$ causes a change in the color of the solutions of the compounds, to orange for compounds **2** and **4** and dark red for compound **3**. The selectivity of chromogenic chemosensors in solution toward $CN^-$ in the presence of other anions, obtained applying different acid–base strategies, in which the anion acts as a base generating the dye in solution, has been reported in other papers with the addition of small amounts of water to organic solvents.[17,18,30,33,50–52] This is commonly explained as being due to the high hydration energies of $F^-$ ($-465$ kJ mol$^{-1}$), $CH_3COO^-$ ($-365$ kJ mol$^{-1}$), and $H_2PO_4^-$ ($-465$ kJ mol$^{-1}$) in comparison with that obtained for $CN^-$ ($-295$ kJ mol$^{-1}$).[53] In our study, the strong hydration of the anions makes them less able to act as nucleophilic species. Since $CN^-$ is less hydrated after the addition of water, this more nucleophilic species (in comparison with the others) is consequently more able to nucleophilically attack the silicon center in each compound, generating **5b**–**7b**.

Additional evidence concerning the products of the reaction of the chemodosimeters with the anions was obtained through mass spectrometry. The mass spectrum for compound **2** exhibits a peak corresponding to $[M]^+$ at 556.3029 while the mass spectrum for compound **5a** shows $[M]^+$ at 400.1696 (see Supporting Information). The addition of $F^-$ and $CN^-$ to solutions of compound **2** causes a change in the spectrum, with the appearance of a peak at 400.13, which coincides with the peak corresponding to compound **5a**. Therefore, the ensemble of data, as summarized in Scheme 2, indicates that the anions $F^-$ and $CN^-$ nucleophilically attack the silicon center at chemodosimeters **2**–**4**, through a $S_N2@Si$ mechanism,[54] releasing pyridinium *N*-phenolate betaines **5b**–**7b** as leaving groups.

Figure 2A shows the UV–vis spectra for **2** in acetonitrile in the absence and in the presence of added anions. Only $F^-$ and $CN^-$ cause significant spectral changes, with the appearance of a band with a maximum at 542 nm. This band occurs at the same position as that observed for **5b** under the same experimental conditions, providing further evidence for the fact that these anions react with compound **2** at the silicon atom, releasing **5b** as a product. Figure 2B shows the UV–vis spectra for **2** with anions added in acetonitrile in the presence of 10% (v/v) of water. Under this condition, only $CN^-$ causes the appearance of a band in the visible region, with a maximum at 455 nm. Again, this band occurs at the same position as that observed for **5b** under the same experimental conditions and the fact that it shows a hypsochromic shift is because **5b** is a solvatochromic dye.[1–4]

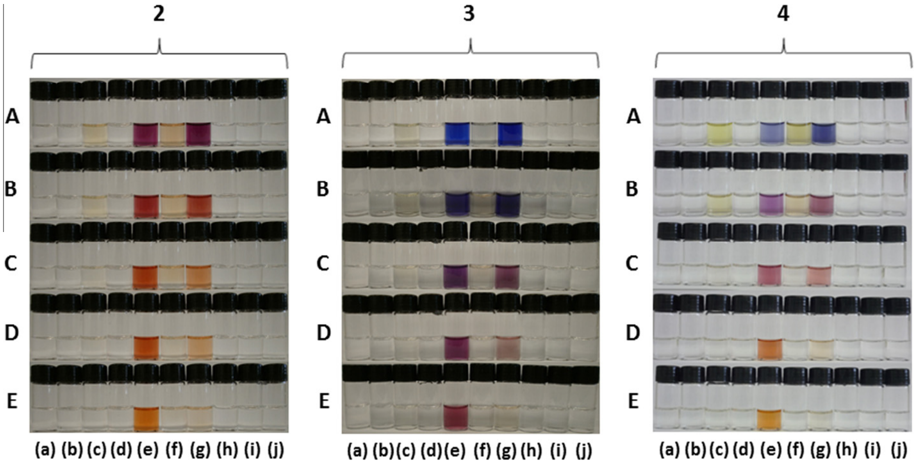
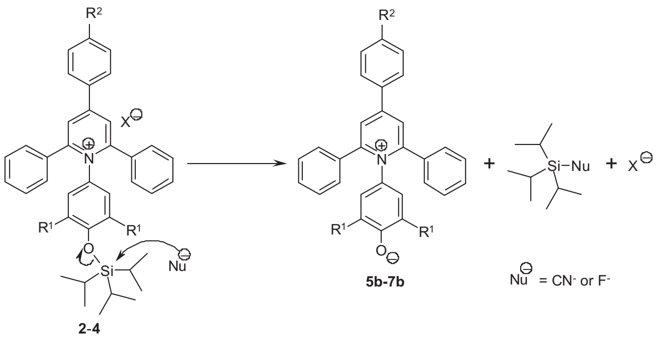


**Figure 1.** Solutions of compounds **2**–**4** in: acetonitrile (A) and acetonitrile with (B) 1%, (C) 3%, (D) 5%, and (E) 10% (v/v) of water, without anion added (a) and after the addition of $HSO_4^-$ (b), $H_2PO_4^-$ (c), $NO_3^-$ (d), $CN^-$ (e), $CH_3COO^-$ (f), $F^-$ (g), $Cl^-$ (h), $Br^-$ (i), and $I^-$ (j) as tetra-*n*-butylammonium salts. The concentration of compounds **2**–**4** was $4.0 \times 10^{-4}$ mol $L^{-1}$ and values for the anions were $1.0 \times 10^{-3}$ mol $L^{-1}$.



**Scheme 2.** Reaction of compounds **2**–**4** with $CN^-$ or $F^-$ to generate dyes **5b**–**7b**.

Compounds **3** and **4** exhibited a similar behavior in pure acetonitrile (Figs. S33A and S34b) and with water added (Figs. 33B and S34B). Compound **3** reacts with $F^-$ and $CN^-$ in acetonitrile, leading to the appearance of a band with a maximum at 624 nm, which corresponds to the same band observed for **6b**. Only $CN^-$ reacts with **3** in the acetonitrile/water mixture, with the formation of **6b**, as demonstrated by the appearance of a band with a maximum at 508 nm. For compound **4**, the reaction with $F^-$ and $CN^-$ in acetonitrile leads to the appearance of a band with a maximum at 587 nm, which coincides with the position of the band verified for dye **7b**. The spectrum for **7b** in acetonitrile with water (10%, v/v) shows that its solvatochromic band is hypsochromically shifted to $\lambda_{max} = 476$ nm, which corresponds to the same band obtained when **4** is mixed with $CN^-$, under the same experimental conditions.

Figure 3 shows the relative absorbances for the reaction of compounds **2**–**4** with the anions in acetonitrile. The data show that on using the same concentration of anions, 100% of the compounds react with $F^-$ while with $CN^-$ only 68% and 86% of product was obtained for **2** and **3**, respectively. In the case of compound **4**, only 50% of product was obtained. The data suggested that the electron-withdrawing cyano group in the molecular structure of **4** influences the reactivity of the compound. Thus, an experiment was carried out, adding $CN^-$ to the products of the reaction of **2**–**4** with $F^-$. The results for the compounds generated are summarized in Figure 4 and they show that while $CN^-$ has practically no effect

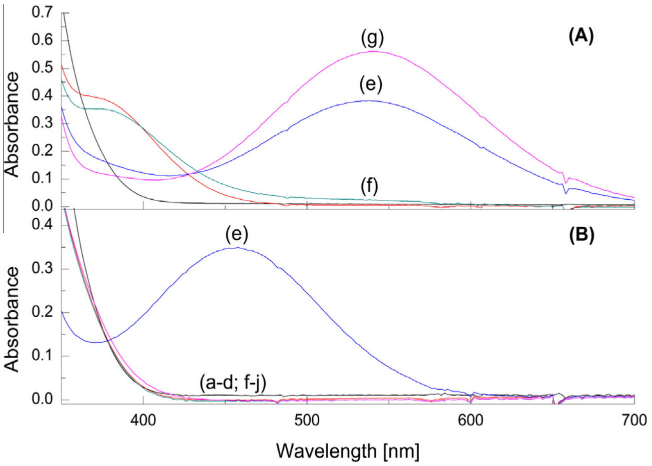


**Figure 2.** UV–vis spectra for solutions of **2** (a) and **2** in the presence of $HSO_4^-$ (b), $H_2PO_4^-$ (c), $NO_3^-$ (d), $CN^-$ (e), $CH_3COO^-$ (f), $F^-$ (g), $Cl^-$ (h), $Br^-$ (i), and $I^-$ (j), as tetra-*n*-butylammonium salts in (A) pure acetonitrile and (B) acetonitrile with 10% (v/v) of water. For concentrations of **2** and the anions see Figure 1.

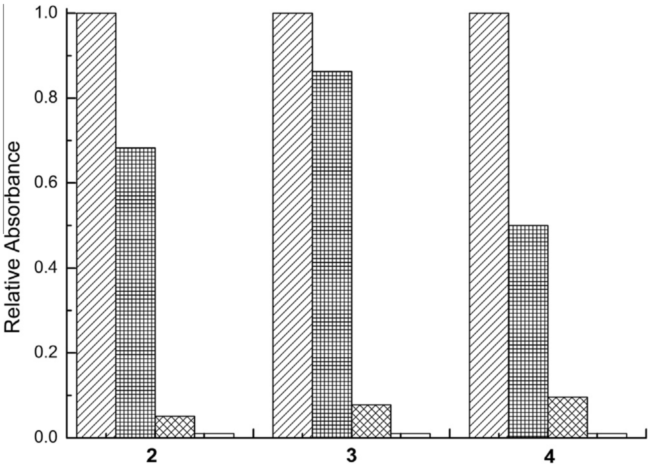


**Figure 3.** Relative absorbance values for the reaction of compounds **2**–**4** with $F^-$ (▨), $CN^-$ (▦), $CH_3COO^-$ (▩) and other anions (☐) in acetonitrile. The concentrations of **2**–**4** and of the anions are described in Figure 1 and the absorbance values were obtained at 542 nm for **2**, and at 624 and 587 nm for **3** and **4**, respectively.

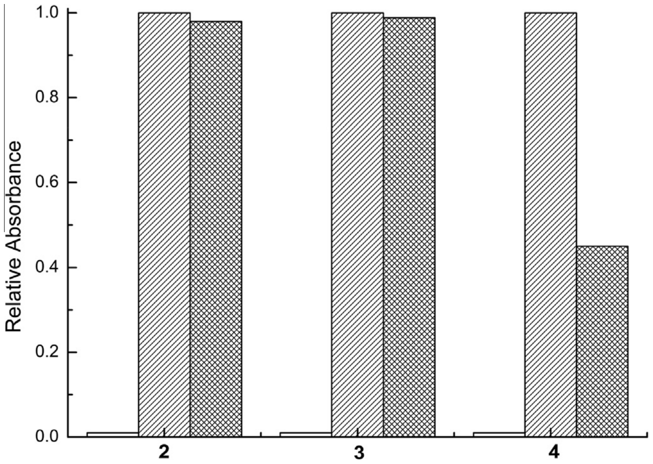


**Figure 4.** Relative absorbance values for compounds **2**–**4** in the absence (□), after the addition of F$^-$ (▨), and after the addition of F$^-$, followed by the addition of CN$^-$ (▩) in acetonitrile. The concentrations of **2**–**4** and of the anions are described in Figure 1.

on the spectra for compounds **5b** and **6b**, for the solution of **7b** a fast reaction with CN$^-$ was observed. Since the pyridinium moiety is potentially electrophilic, appended electron-withdrawing groups activate electrophilically this center to react with CN$^-$. Thus, the data show that in the design of this class of chemodosimeters a compromise is required considering the use of substituents since, although electron-withdrawing groups are of interest in relation to increasing the rate of the process, they can cause the color of the solution to fade due to the reaction of the anion with the pyridinium center.

In conclusion, the results reported herein demonstrate the potential of the use of classical pyridinium *N*-phenolate betaine dyes in the design of novel chromogenic chemodosimeters for the development of simple assays for the naked-eye detection of the strongly nucleophilic species F$^-$ and CN$^-$ in acetonitrile, and for the highly selective detection of CN$^-$ in acetonitrile/water mixtures. This new application of an old class of solvatochromic dyes paves the way for the use of these compounds in the development of other strategies for the detection of anionic species, for instance, anchoring these compounds in polymeric matrices or solubilizing them in aqueous micellar system.

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## Supplementary data

Supplementary data (materials and methods, UV–vis spectra, synthetic procedures, and characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.06.037.

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