

One-Pot Synthesis of Squaraine Fluoroionophores

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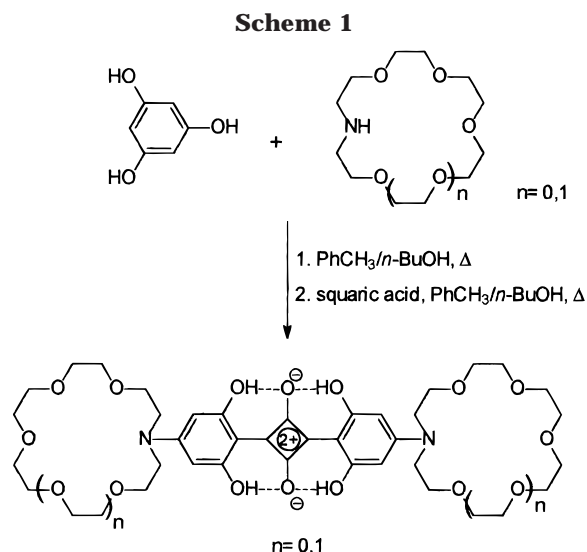
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Squaraines are 1,3-disubstituted squaric acid derivatives with sharp visible absorption peaks in solution and panchromatic absorption in the solid state. This class of fluorescent dyes and pigments is well-known for their applications in electrophotography,¹ organic solar cells,² nonlinear optics,³ and optical data storage.⁴ Their photochemistry has been extensively studied,⁵ and many derivatives of the parent squaraine skeleton have been synthesized mostly for improvements in technical applications. In recent years, squaraines also received attention as fluorescent labels.⁶ Their very promising spectral properties such as long wavelength absorption and emission, high extinction coefficients, and quantum yields make them particularly attractive in this area. In addition, the rational design of fluorescent chemosensors⁷ is a vibrant field of organic chemistry, and appropriately derivatized squaraines could lead to novel sensing technologies as they can be excited with solid-state lasers.

There are already successful examples of squaraine-based chemosensors in the literature,⁸ and such modified squaraines were shown to signal pH, alkaline, and earth-alkaline metals in various solvent systems. When the range of selectivities that could be achieved by the judicious choice of the crown ethers is considered, azacrown-appended squaraines (squaraine fluoroionophores) are targets of prime importance.

The general synthetic methodology used in the preparation of squaraines is rather simple.⁹ It involves a reaction of 2 equiv of dialkylanilines with 1 equiv of squaric acid, preferably in *n*-BuOH/toluene (50:50) at reflux temperatures. Water formed could be either



removed azeotropically or taken up by molecular sieves. The synthetic challenge in the preparation of azacrown-squaraines is essentially the preparation of phenyl- or ((di)hydroxyphenyl)azacrowns, as the rest of the synthesis is straightforward. Phenylazacrowns were synthesized in 1985 by Gokel,¹⁰ and the synthesis involves a multistep synthesis with at least one high-dilution step. No literature reports of 3-hydroxy- or (3,5-dihydroxyphenyl)azacrowns were encountered, and that is unfortunate because such hydroxy substitutions would not only increase the yield⁵ in squaraine synthesis but also result in higher-quantum yield squaraines with improved solubility characteristics.⁵ We report here the use of a novel one-pot reaction that provides an entry to such derivatized squaraines using simple commercially available synthons.

Synthesis

Our synthesis makes use of the general reactivity of phloroglucinol (1,3,5-trihydroxybenzene) with secondary amines through its keto tautomer. The fact that this reaction could be made to proceed in the same azeotropic solvent mixture as that of squaraine synthesis proved to be very convenient, and our azacrown-appended squaraine synthesis became a one-pot reaction. Thus, the azacrown was reacted with equimolar phloroglucinol in *n*-BuOH/toluene (50:50) in a Dean–Stark apparatus, where water that formed was removed continuously. (3,5-Dihydroxyphenyl)azacrown formation was complete in 6–8 h depending on the type of azacrown used. The *N*-phenylazacrown derivative was not isolated; instead, 0.5 equiv of squaric acid was added, and heating was continued. Typically in 15 min, the characteristic intense green color of the squaraines was observed. The reflux was continued for 4 h. On cooling, the squaraine–azacrown conjugates crystallized out of the solution. The precipitate was washed with MeOH and dried. Recrystallization was not necessary as evidenced from the analytical data. The new compounds were fully characterized by ¹H and

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^{13}C NMR, mass spectrometry, and elemental analysis. NMR spectra reveal the highly symmetrical nature of the squaraines and the presence of strong internal hydrogen bonding between the ArOH and the squaryl oxygens.

Experimental Section

General. All reagents were purchased from commercial suppliers and used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 solution with TMS as an internal reference at 400 MHz (^1H) and 100 MHz (^{13}C). Mass spectra were recorded by electron impact (70 eV). Melting points reported are uncorrected. Elemental analyses were performed by TUBITAK Instrumental Analysis Laboratory (Ankara, Turkey).

Bis[4-*N*-(1-aza-4,7,10,13-tetraoxacyclopentadecyl)-3,5-dihydroxyphenyl]squaraine ($n = 0$). 1-Aza-15-crown-5 (0.438 g, 2 mmol) and phloroglucinol (0.252 g, 2 mmol) were heated to reflux in a solvent mixture containing toluene (10 mL) and *n*-butanol (10 mL), accompanied by azeotropic distillation of water, overnight. Without any isolation attempt, the resulting (3,5-dihydroxyphenyl)azacrown was reacted in the same solvent system with 3,4-dihydroxy-3-cyclobutene-1,2-dione (squaric acid, 0.114 g, 1 mmol) by refluxing for 6 h in the same Dean–Stark apparatus. The reaction mixture was cooled to room temperature. The precipitated product was collected by filtration and

washed with cold methanol (100 mL). The resulting dark green solid was dried in vacuo. The yield was 1.0248 g (70%): mp $>250\text{ }^\circ\text{C}$; ^1H NMR (CDCl_3 , 400 MHz) δ 3.82–3.65 (m, 40 H), 5.84 (s, 4 H), 10.99 (s, 4 H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 53.62, 68.59, 70.08, 70.49, 71.26, 94.11, 103.0, 158.00, 162.00, 163.03, 181.00; MS (EI) m/e 730 [$(M - 2\text{H})^+$], 367 [(azacrown-Ar-CH=C=O) $^+$]. Anal. Calcd for $\text{C}_{36}\text{H}_{48}\text{N}_2\text{O}_{14}$: C, 9.01; H, 5.56; N, 3.83. Found: C, 59.17; H, 5.66; N, 3.85.

Bis[4-*N*-(1-aza-4,7,10,13,16-pentaoxacyclooctadecyl)-3,5-dihydroxyphenyl]squaraine ($n = 1$). The same procedure applied 1-aza-18-crown-6 yielded dark green crystals with a metallic luster. The product was collected by filtration washed with cold methanol (100 mL) and 2-propanol (50 mL), and dried in vacuo. The yield was 1.23 g (75%): mp $>250\text{ }^\circ\text{C}$; ^1H NMR (CDCl_3 , 400 MHz) δ 3.48–3.73 (m, 48 H), 5.86 (s, 4 H), 10.84 (s, 4 H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 57.12, 73.88, 75.69, 75.85, 75.96, 99.13, 107.82, 163.87, 166.05, 167.70, 186.63 (one of the peaks obscured by CDCl_3); MS (EI) m/e 818 [$(M - 2\text{H})^+$], 411 [(azacrown-ArCH=C=O) $^+$]. Anal. Calcd for $\text{C}_{40}\text{H}_{56}\text{N}_2\text{O}_{16}\cdot 0.25\text{H}_2\text{O}$: C, 58.21; H, 6.89; N, 3.39. Found: C, 57.86; H, 6.50; N, 3.47.

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