Synthesis of 7,8-Dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one Derivatives of Crown Ethers

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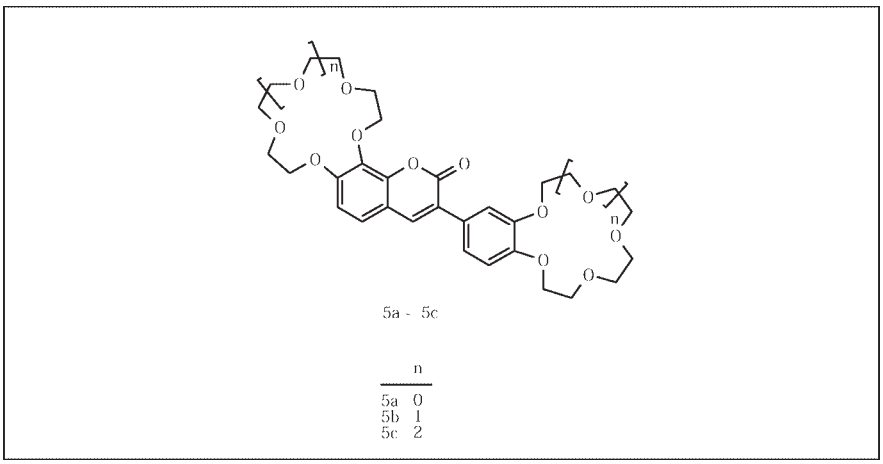

The novel 1-(3,4-dimethoxyphenyl)-2-(2,3,4-trimethoxyphenyl)acrylonitrile was prepared from the condensation of the mixture of 2,3,4-trimethoxybenzaldehyde and 3,4-dimethoxyphenylacetonitrile in ethanol at 70°C with 20% aqueous sodium hydroxide solution. Cyclization and demethylation of the acrylacetonitrile was performed using pyridine hydrochloride. The obtained 7,8-dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one was reacted with the poly(ethylene glycol) ditosylates in CH_3CN/alkali carbonate to afford bis-[12]crown-4, -[15]crown-5, and -[18]crown-6 chromenones. The chromatographically purified novel chromenone crown ethers were identified by IR, ^1H NMR, ^{13}C NMR, and MALDI-TOF mass spectrometry and elemental analysis.

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INTRODUCTION

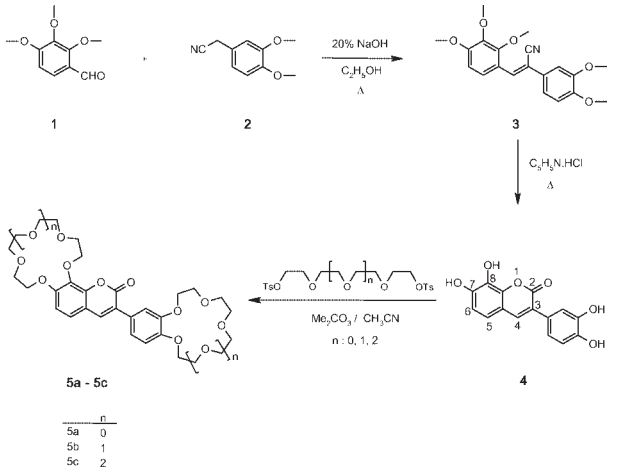
Macrocyclic molecules have attracted much attention because of their potential use in a variety of chemical processes, selective complexing agents for earth and alkaline metal ions, and photoinduced electron transfer [1]. Several macrocyclic ethers possessing oxygen dipoles have been synthesized to investigate their alkali and alkaline-earth cation membrane transport and binding properties by means of potentiometry, optical spectroscopy, as well as NMR spectroscopic methods [2,3]. The ionophores bearing suitable light sensitive moieties may undergo intermolecular changes at the electronic level upon cationic interactions of donor oxygen atoms [2]. Essentially, the fluorescence spectra of fluorogenic macrocycles is a reliable method to study cationic recognitions [2,4,5]. Crown ethers have also been used for chromatographic separations [6,7]. We have recently synthesized fluorogenic coumarin-[12]crown-4, -[15]crown-5, and -[18]crown-6 derivatives and examined cation binding effects using steady state fluorescence spectroscopy and reported their cationic interaction in acetonitrile [5,8–11]. However, the oxygen atom, which is contained in the phenyl moiety in coumarin arms potentially can participate along with the other oxygen atoms in the analog crown ether moiety formed 1:1 complex with a host ion [12–16].

We report here the synthesis of novel bis-[12]crown-4, -[15]crown-5, and -[18]crown-6 derivatives of 7,8-dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one.

RESULTS AND DISCUSSION

The synthesis of the precursor compound, 1-(3,4-dimethoxyphenyl)-2-(2,3,4-trimethoxyphenyl)acrylonitrile (**3**) was accomplished using Knoevenagel condensation reaction [17]. Equal molar amounts of 2,3,4-trimethoxybenzaldehyde **(1)** and 3,4-dimethoxyphenylacetonitrile **(2)** in ethanol at 70°C (see Scheme 1) was reacted with 20% aqueous sodium hydroxide solution. The Knoevenagel reaction is stereoselective and resulted in the *E*-product. The precipitated acrylonitrile **(3)** was collected by filtration, washed with distilled water, and dried. The crude product was purified by crystallization from ethanol. Then, the ring closure of **(3)** was

Scheme 1



performed with freshly prepared pyridine hydrochloride at 180 °C. The compound, 7,8-dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one, **(4)** was washed with water until neutral, dried, and recrystallized from acetic acid.

Compound **4** was reacted with poly(ethylene glycol) ditosylates in the presence of alkali carbonate in CH_3CN (Scheme 1) to give the 7,8-dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one crown ethers (coumarino crown ether) **5a**, **5b**, **5c**, respectively.

The purification of crown ethers were done by column chromatography (silica gel-chloroform) to give pure coumarino crown ethers **(5a–5c)** in 12–23% yields. They were soluble in $CHCl_3$ or CH_2Cl_2. The novel compounds have been characterized by elemental analysis IR, ^{1}H NMR, ^{13}C NMR, and MALDI-TOF-MS.

The IR spectra of **3** showed absorption bands at 2840 and 2973 cm^{-1} for the C—H stretching. The characteristic band of the nitrile group (CN), benzene ring (C=C), and methoxy group (OCH_3) appeared at 2206, 1583–1403, 1350–1023 cm^{-1}, respectively. The IR spectrum of **4** showed a characteristic band for the hydroxyl group (OH), carbonyl group (C=O), benzene ring (C=C), and (C—O) 3560–3328, 1681, 1618–1535, 1311–1109 cm^{-1}, respectively.

The ^{1}H NMR spectra of **5a–5c** showed characteristic signals for etheral (—O—CH_2—CH_2—O—) protons at δ 3.85–4.48 ppm, each a triplet. In addition, the chemical shifts of the aromatic protons are observed at δ 6.86–7.81 ppm.

The ^{13}C NMR spectrum of **5a–5c** showed expected signals for aromatic, carbonyl, and etheral carbons at δ 109.83–140.63, 160.46–173.90, 69.06–75.17 ppm, respectively. Also the MALDI-TOF-MS and elemental analysis confirmed the formation of coumarino crown ether derivatives.

The obtained new coumarino crown ether compounds will next be examined for their cation binding properties using fluorescence spectroscopy.

EXPERIMENTAL

The starting chemicals were purchased from Aldrich or Merck unless otherwise cited. Melting points have been obtained on a Gallenkamp apparatus and are uncorrected. IR spectra were obtained from KBr pellets with a Schimadzu FTIR spectrometer, model 8300. Mass spectra have been obtained with a MALDI-TOF instrument, model Bruker Autoflex III. The ^{1}H NMR spectra have been obtained with a BRUKER spectrometer, model AVANCE-400 Cpx and TMS was used as the internal reference. Combustion analyses have been acquired with a LECO-932 CHN.

Synthesis of 1-(3,4-dimethoxyphenyl)-2-(2,3,4-trimethoxyphenyl)acrylonitrile (3). The typical procedure for synthesis of acrylonitrile **(3)** is performed according to the literature [18]. A mixture of 2,3,4-trimethoxybenzaldehyde **(1)** (4.82 g, 24.59 mmol) and 3,4-dimethoxyphenylacetonitrile **(2)** (4.34 g, 24.59 mmol) in ethanol (100 mL) was heated to 70°C; 20% aqueous sodium hydroxide solution was then added dropwise to the stirred solution until the onset of turbidity. The acrylonitrile **(3)** precipitated when the solution was cooled to room temperature. The precipitate was collected by filtration, washed with water, and dried. The crude product was purified by recrystallization from ethanol. 6.85 g (78%), mp 114–115 °C. ir (KBr): 2973–2840 (C—H), 2206 (CN), 1583–1403 (C=C), 1350–1023 (C—O) cm^{-1}; ^{1}H NMR (400 MHz/$CDCl_3$): δ 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.78 (d, J = 9.0 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 7.15 (d, J = 2.3 Hz, 1H,), 7.24 (dd, J = 8.2 Hz and 2.3 Hz, 1H), 7.72 (s, 1H), 7.96 (d, J = 9.0 Hz, 1H); ms: m/z 355.14 (M^+), 356.15 $(M+1)^+$, 357.15 $(M+2)^+$.

Synthesis of 7,8-dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one (4). A mixture of the acrylonitrile (**3**) (6.85 g, 19.24 mmol) and freshly prepared pyridine hydrochloride (11.11 g, 96.20 mmol) was heated for 2 h at 180°C; the cooled solution was treated with water. The precipitated coumarin was washed with water until neutral, dried, and recrystallized from acetic acid. 4.6 g (83%), mp 295°C (lit: 297 °C [19]); ir (KBr): 3560–3328 (Ar—OH), 1681 (C=O), 1618–1535 (C=C), 1311–1109 (C—O) cm^{-1}; ^{1}H NMR (400 MHz/DMSO-d_6): δ 6.71 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.95 (dd, J = 8.5 Hz and 2.0 Hz 1H), 7.15 (d, J = 8.5 Hz, 1H), 7.22 (d, J = 2 Hz, 1H), 7.95 (s, 1H), 9.05 (br-s, 1H), 9.12 (br-s, 1H), 9.40 (br-s, 1H), 9.95 (br-s, 1H).

General procedure for the synthesis of 7,8-dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one crown ethers (5a–5c). The typical procedure for the cyclization reaction leading to macrocyclic ethers **(5a–5c)** is as follows. A mixture of **4** (5 mmol), poly(ethylene glycol) ditosylate (10 mmol), and metal carbonate (20 mmol) was dissolved in 60 mL CH_3CN in a 100-mL reaction flask. The reaction mixture was heated for 35–40 h at 80–85°C. The solvent was distilled. Diluted HCl was added to the residue and the mixture was extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were washed with water, dried over $CaCl_2$, and the

$CHCl_3$ solution evaporated *in vacuo*. Chromatography of the crude products (silica gel 60, Merck) with chloroform gave pure coumarino crown ethers (**5a–5c**).

14-(2,3,5,6,8,9-Hexahydrobenzo[b][1,4,7,10]tetraoxacyclododecin-12-yl)-5,6,8,9-tetrahydro-2H-[1,4,7,10]tetra-oxacyclododeca[2,3-h]chromen-15(3H)-one (5a; $C_{27}H_{30}O_{10}$). Compound **4** (1.5 g, 5.2 mmol), Na_2CO_3 (2.2 g, 21 mmol), tri(ethylene glycol) ditosylate (4.8 g, 10 mmol) in CH_3CN (60 mL) was reacted as described earlier to afford light yellow solid **5a**, 0.6 g (22%), mp 126–128°C; ^{1}H NMR (400 MHz/$CDCl_3$): δ 3.85 (t, J = 4Hz, 4H), 3.95 (t, J = 4Hz, 4H), 3.97 (t, J = 4Hz, 4H), 4.21 (t, J = 4Hz, 4H), 4.23 (t, J = 4Hz, 4H), 4.40 (t, 4Hz, 4H), 6.86 (d, J = 8.7 Hz, 1H, H-5′), 7.01 (d, J = 8.5 Hz, 1H, H-6), 7.19 (d, J = 8.7 Hz, 1H, H-5), 7.31 (dd, J = 8.5 Hz and 1.5 Hz, 1H, H-6′), 7.37 (d, J = 1.5 Hz, 1H, H-2′), 7.69 (s, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ 69.75, 69.87, 70.31, 70.34, 70.51, 70.87, 71.18, 71.32, 71.66, 72.16, 72.23, 75.17, 111.06, 115.02, 117.74, 118.97, 123.17, 124.53, 126.25, 129.14, 136.26, 139.75, 147.72, 150.37, 151.25, 155.12, 160.46; ms: *m/z* 513.94 (M^+), 536.95 $(M+Na)^+$. Anal. Calc. for $C_{27}H_{30}O_{10}$: C, 63.03; H, 5.88. Found: C, 62.97; H, 5.68.

17-(2,3,5,6,8,9,11,12-Octahydrobenzo[b][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-5,6,8,9,11,12-hexahydro-2H-[1,4,7,10,13]pentaoxacyclopentadeca[2,3-h]chromen-18(3H)-one (5b; $C_{31}H_{38}O_{12}$). Compound 4 (1.0 g, 3.5 mmol), K_2CO_3 (1.93 g, 14 mmol), tetra(ethylene glycol) ditosylate (3.52 g, 7 mmol) in CH_3CN (60 mL) reacted as described earlier to afford light yellow solid 5b, 0.5 g (23%), mp: 136 °C; ^{1}H NMR (400 MHz/$CDCl_3$): δ 4.04 (t, J = 4Hz, 4H), 4.06 (t, J = 4Hz, 4H), 4.09 (t, J = 4Hz, 4H), 4.11 (t, J = 4Hz, 4H), 4.34 (t, J = 4Hz, 4H), 4.37 (t, 4Hz, 4H), 4.39 (t, 4Hz, 4H), 4.48 (t, 4Hz, 4H), 7.02 (d, J = 8 Hz, 1H, H-5′), 7.07 (d, J = 8 Hz, 1H, H-6), 7.25 (d, J = 8 Hz, 1H, H-5), 7.40 (dd, J = 8 Hz and 2 Hz, 1H, H-6′), 7.43 (d, J = 2 Hz, 1H, H-2′), 7.81 (s, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ 69.08, 69.26, 69.45, 69.47, 69.75, 69.78, 70.42, 70.53, 70.61, 70.72, 70.77, 71.08, 71.16, 71.28, 71.30, 73.79, 109.83, 113.93, 114.92, 121.86, 122.87, 124.81, 128.43, 135.47, 139.30, 139.35, 147.73, 148.96, 149.83, 154.92, 160.58; ms: *m/z* 602.07 (M^+), 625.04 $(M+Na)^+$, 641.02 $(M+K)^+$. Anal. Calc. for $C_{31}H_{38}O_{12}$: C, 61.78; H, 6.36. Found: C, 61.58; H, 6.05.

20-(2,3,5,6,8,9,11,12,14,15-Decahydrobenzo[b][1,4,7,10,13,16]hexaoxacyclooctadecin-18-yl)-5,6,8,9,11,12,14,15-octahydro-2H-[1,4,7,10,13,16]hexa-oxacyclooctadeca[2,3-h]chromen-21(3H)-one (5c; $C_{35}H_{46}O_{14}$). Compound **4** (1.0 g, 3.5 mmol), K_2CO_3 (1.93 g, 14 mmol), penta(ethylene glycol) ditosylate (3.52 g, 7 mmol) in CH_3CN (60 mL) reacted as described earlier to afford light yellow solid **5c**, 0.28 g (12%), mp: 95 °C; ^{1}H NMR (400 MHz/$CDCl_3$): δ 3.92 (t, J = 4Hz, 4H), 3.95 (t, J = 4Hz, 4H), 3.97 (t, J = 4Hz, 4H), 4.02 (t, J = 4Hz, 4H), 4.21 (t, J = 4Hz, 4H), 4.22 (t, J = 4Hz, 4H), 4.24 (t, J = 4Hz, 4H), 4.25 (t, J = 4Hz, 4H), 4.27 (t, 4Hz, 4H), 4.37 (t, 4Hz, 4H), 6.88 (brd, J = 8.6 Hz, 1H, H-5′), 6.93 (brd, J = 8.6 Hz, 1H, H-6), 6.99 (d, J = 8.6 Hz, 1H, H-5), 7.17 (dd, J = 8.7 Hz and 2 Hz, 1H, H-6′), 7.29 (d, J = 2 Hz, 1H, H-2′), 7.67 (s, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ: 69.06, 69.21, 69.36, 69.44, 69.68, 69.82, 70.55, 70.60, 70.67, 70.78, 70.84, 70.90, 70.94, 70.97, 71.01, 71.12, 71.18, 71.27, 71.39, 73.24, 110.62, 113.61, 114.57, 116.14, 121.78, 122.88, 124.97, 128.18, 136.19, 139.34, 148.63, 152.38, 152.45, 154.75, 173.90 ; ms: *m/z* 690.2 (M^+), 713.18 $(M+Na)^+$, 629.16 $(M+K)^+$. Anal. Calc. for $C_{35}H_{46}O_{14}$: C, 60.86; H, 6.71. Found: C, 60.36; H, 6.81.

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