Synthesis of Sulfonylmethylated and Cyanomethylated Nitrobenzocrown Ethers. Potential Reagents for Colourimetric Analysis of Alkali Cations

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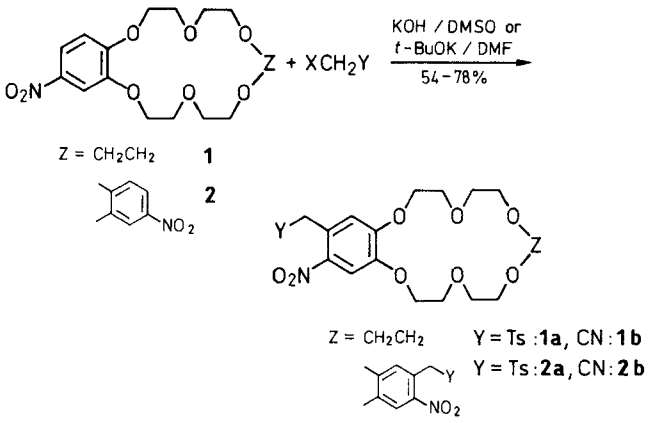
Sulfonylmethyl and cyanomethyl derivatives of nitrobenzocrown ethers were prepared via vicarious nucleophilic substitution of hydrogen. These compounds form highly coloured internal potassium salts soluble in nonpolar solvents.

Macrocyclic polyethers known as crown ethers form relatively stable complexes with alkali metal cations[2] and are widely used in organic synthesis as phase transfer catalysts[3] and also for analytical and separation purposes.[4] Particularly interesting practical applications have been found for crown ethers and cryptands containing pH sensitive chromophoric groups which are used for colourimetric determination of cations with high sensitivity and selectivity.[5] Thus synthesis of such crown ethers is of substantial interest. The most intensely coloured species are carbanions of *o*- and *p*-nitrobenzyl sulfones and nitroarylacetonitriles. For example, the molar extinction coefficient of the sodium salt of *p*-nitrobenzyl phenyl sulfone carbanion in dimethylformamide solution amounts to 43000.

It was therefore reasonable to expect that benzocrown ethers containing nitro groups in the aromatic rings and sulfonylmethyl or cyanomethyl substituents in the *ortho*- or *para*-position can be of interest for analysis of cations. Although there are a few methods of synthesis of nitrobenzyl sulfones or nitroarylacetonitriles such as nitration or S_N2-type substitution of the corresponding benzyl halides none of them can be readily applied to the synthesis of the desired crown ether derivatives because the necessary intermediates are not readily available. The most general method for the preparation of such compounds is the vicarious nucleophilic substitution of hydrogen (VNS). This allows direct replacement of hydrogen on nitroaromatic rings with a functionalized methyl group by the reaction of nitroarenes with carbanions containing leaving groups at the carbanion centers.[6,7] Application of this process for synthesis of such substituted crown ethers is presented in this paper.

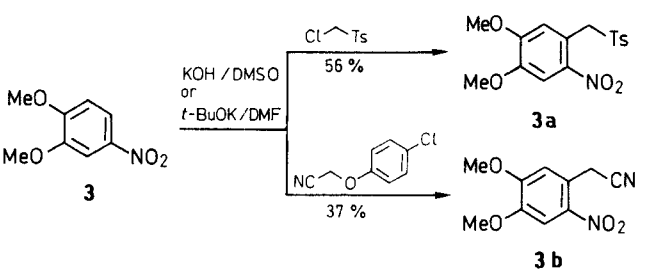
Nitro derivatives of benzocrown ethers are readily available via direct nitration processes.[8] For example, nitration of the commercial benzo[18]crown-6 and dibenzo-[18]crown-6 gave the desired 4-nitro-(1,2-benzo)-[18]crown-6 (**1**) and 4,4'-dinitro-(1,1',2,2'-dibenzo)-[18]crown-6 (**2**).[9,10] The latter compound can exist in the form of two geometric isomers "*cis*" and "*trans*" which can be simply separated in the course of recrystallization.[10] For further studies, the more soluble "*cis*" isomer of **2** was used.

The VNS reaction is quite sensitive to the electrophilicity of the nitroarenes – the presence of two alkoxy type groups in the nitroaromatic rings of **1** and **2** could deactivate these nitroarenes in their reaction with carbanions.[6] No such effect was observed and both nitrobenzocrown ethers **1** and **2** readily entered the VNS reaction with chloromethyl *p*-tolyl sulfone and *p*-chlorophenoxy acetonitrile, carried out in the presence of potassium hydroxide in dimethyl sulfoxide or potassium *tert*-butoxide in dimethylformamide, correspondingly producing the desired sulfonylmethylated **1a, 2a** and cyanomethylated **1b, 2b** products in good yields (Scheme 1).



Scheme 1

It is well known that electron-donating substituents such as alkoxy or dialkylamino deactivate nitroarenes towards the VNS reaction. One could suppose therefore that the good yields of the products of VNS in the nitrocrown ethers is because the efficiency of the VNS reaction with **1** and **2** is enhanced due to complexation of potassium cation with the crown ether moiety which results in a substantial decrease of the electron-donating effect of the alkoxy substituents. This effect is, however, negligible because the acyclic analogue of **1**, namely 4-nitroveratrole (1,2-dimethoxy-4-nitrobenzene, **3**), under similar conditions also entered the VNS reaction with chloromethyl *p*-tolyl sulfone and *p*-chlorophenoxyacetonitrile giving the expected sulfonylmethylated and cyanomethylated products **3a** and **3b** (Scheme 2).



Scheme 2

As expected, **1a,b** and **2a,b** treated with potassium *tert*-butoxide or potassium hydroxide in toluene form intensely coloured solutions (blue–violet) of the internal salts whereas the corresponding salt of **3a** is soluble in dimethylformamide but not in toluene.

^{1}H NMR spectra were measured on a Varian Gemini spectrometer at 200 MHz, IR spectra ona Acculab (Beckman), and mass spectra on an AMD-604 spectrometer.

Nitrocrown ethers **1** and **2** were obtained as described,[9,10] 4-nitroveratrole via nitration of veratrole.[11] Preparation of chloromethyl phenyl sulfone[12] and *p*-chlorophenoxyacetonitrile[13] was described earlier. For all new compounds satisfactory microanalyses were obtained: C ± 0.25, H ± 0.22, N ± 0.27.

4-Nitro-5-tosylmethyl-(1,2-benzo)[18]crown-6 (1a):
A solution of **1** (300 mg, 0.84 mmol) and chloromethyl *p*-tolyl sulfone (172 mg, 0.84 mmol) in DMSO (2 mL) was added dropwise to a stirred suspension of powdered KOH (200 mg, 3.5 mmol) in DMSO (3 mL) at r.t. The mixture was stirred for 1 h, poured into 2% aq HCl (20 mL) and extracted with $CHCl_3$ (2 × 30 mL). The extract was washed, dried ($MgSO_4$), the solvent evaporated and the product purified by column chromatography on silica gel using benzene/MeOH, (10:1) and then MeCN as eluent; yield: 313 mg (71%); mp 149°C (EtOH).

HRMS: *m/z* calc. for $C_{24}H_{31}NO_{10}S$ 525.16687, found 525.16674.

IR (KBr): ν = 1528, 1318 (NO_2), 1140 cm^{-1} (SO).

^{1}H NMR (CCl_3): δ = 7.53 (d, J = 8.3 Hz, 2H), 7.50 (s, 1H), 7.24 (d, J = 8.3 Hz, 2H), 6.88 (s, 1H), 4.91 (s, 2H), 4.26–3.66 (m, 2H), 2.42 (s, 3H).

4,4′-Dinitro-5,5′-di(*p*-tosylmethyl)-1,2,1′,2′-dibenzo[18]crown-6 (2a):
To a solution of **2** (440 mg, 0.975 mmol) and chloromethyl *p*-tolyl sulfone (400 mg, 1.95 mmol) in DMSO (6 mL) was added powdered KOH (500 mg, 9 mmol) in portions. Further procedure as for **1a**; yield: 490 mg (61%); mp 245°C (EtOH).

IR (KBr): ν = 1525, 1336 (NO_2), 1152 cm^{-1} (SO).

^{1}H NMR (DMSO-d_6): δ = 7.51 (d, J = 8.3 Hz, 4H), 7.24 (d, J = 8.3 Hz, 4H), 7.47 (s, 2H), 6.90 (s, 2H), 4.91 (s, 4H), 4.27–3.95 (m, 16H), 2.41 (s, 6H).

4-Nitro-5-(*p*-tosylmethyl)veratrole (3a):
The reaction was carried out starting from **3** and chloromethyl *p*-tolyl sulfone according to the procedure for **2a**; yield: 56%, mp 142°C (MeOH).

IR (KBr): ν = 1527, 1340 (NO_2), 1148 cm^{-1} (S=O).

^{1}H NMR ($CDCl_3$): δ = 7.57 (d, J = 8.5 Hz, 2H), 7.54 (s, 1H), 7.27 (d, J = 8.5 Hz, 2H), 6.88 (s, 1H), 4.93 (s, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 2.43 (s, 3H).

4-Nitro-5-cyanomethyl-(1,2-benzo)[18]crown-6 (1b):
A solution of **1** (300 mg, 0.84 mmol) and *p*-chlorophenoxyacetonitrile (140 mg, 0.84 mol) in DMF (4 mL) was added dropwise to a solution of *t*-BuOK (190 mg, 1.7 mmol) in DMF (6 mL) at −15°C. The mixture was stirred at r.t. for 30 min and poured into 2% aq HCl (30 mL). The product was extracted with CH_2Cl_2, the extract washed and dried, the solvent evaporated and the residue chromatographed on silica gel ($CHCl_3$/MeOH/HCO_2H, 15:2:2 as eluent); yield: 260 mg (78%); mp 82°C (MeOH). Although TLC and HPLC indicated that the product **1b** was free of impurities, in spite of numerous recrystallizations we could not obtain a sample with correct elemental analysis. NMR and IR spectra as well as high resolution MS fully confirm the structure.

HRMS: *m/z* calc. for $C_{18}H_{24}N_2O_8$ 396.1533, found 396.1533.

IR (KBr): ν = 2254 (CN), 1525, 1340 cm^{-1} (NO_2).

^{1}H NMR ($CDCl_3$): δ = 7.76 (s, 1H), 7.07 (s, 1H), 4.33–4.20 (m, 4H), 4.21 (s, 2H). 3.99–3.91 (m, 4H), 3.80–3.66 (m, 12H).

4,4′-Dinitro-5,5′-dicyanomethyl-(1,2,1′,2′-dibenzo)[18]crown-6 (2b):
To a stirred solution of **2** (400 mg, 0.9 mmol) and *p*-chlorophenoxyacetonitrile (330 mg, 2 mmol) in DMF (3 mL) was added a solution of *t*-BuOK (440 mg, 3.9 mmol) in DMF (3 mL) at −20°C. The mixture was stirred at r.t. for 30 min and worked up as for **1b**. The product was purified by chromatography on silica gel (benzene/MeOH, 10:1 as eluent); yield: 253 mg (54%); mp 200°C (2-methoxyethanol).

IR (KBr): ν = 2287 (CN), 1524, 1338 cm^{-1} (NO_2).

^{1}H NMR (acetone-d_6): δ = 7.73 (s, 2H), 7.05 (s, 2H), 4.21 (s, 4H), 4.33–4.20 (m, 8H), 4.05–3.98 (m, 8H).

4-Nitro-5-cyanomethylveratrole (3b):
Procedure as for **1b**, starting from **3** and *p*-chlorophenoxyacetonitrile. The product was isolated and purified via recrystallization from MeOH; yield: 37%; mp 113°C.

IR (KBr): ν = 152, 1336 (NO_2), 1216, 1061 cm^{-1} (C–O).

^{1}H NMR (acetone-d_6): δ = 7.77 (s, 1H), 7.09 (s, 1H), 4.23 (s, 2H), 4.03 (s, 3H), 3.97 (s, 3H).

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