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Synthesis and reactions of ethynylbenzocrown ethers

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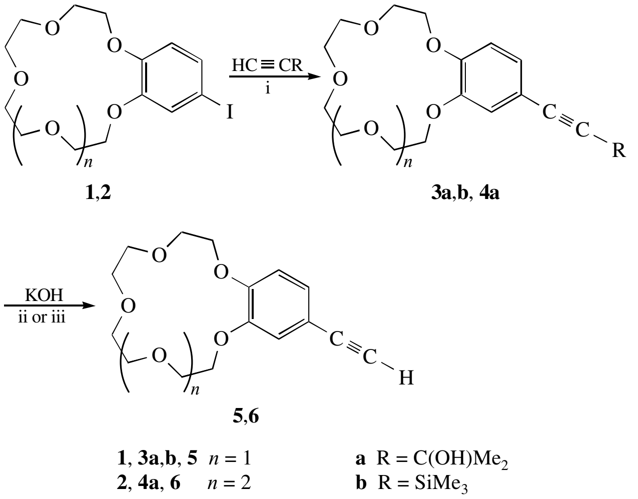
The interaction of 4′-iodobenzo-15-crown-5 and -18-crown-6 ethers with 2-methyl-3-butyn-2-ol and trimethylsilylacetylene followed by treatment of the reaction products with alkali yields ethynylbenzocrown ethers; chemical transformations such as cross- and homo-coupling and Cadiot–Chodkiewicz and Mannich reaction of the ethynyl derivatives have been carried out.

The crown ethers have aroused considerable interest in several areas of chemistry because they selectively bind specific cations. The introduction of functional substituents into the aromatic ring increases the synthetic and applied potential of these compounds. Acetylenic derivatives, especially the terminal ones, are thought to be interesting starting materials for the latter purpose due to the high reactivity of the –C≡C–H group. Thus, alkynylbenzocrown ethers can be utilised as potential intermediates in the preparation of various bis(benzocrown ether)s and polymer-bonding crown ethers.[1,2]

Nevertheless, as far as we know, general methods for the synthesis of alkynylbenzocrown ethers have not so far been developed. The preparation of only three individual acetylenylbenzocrown ethers by cross-coupling halobenzocrown ethers with terminal acetylenes has been described.[3] The limited number of acetylenylbenzocrown ethers synthesised and the absence among them of any monosubstituted acetylene derivatives do not give sufficient information about the application of the cross-coupling reaction for their preparation, especially taking into consideration the low reactivity of halobenzocrown ethers. In addition, the behaviour of the ethynylbenzocrown ethers is not clear in the typical reactions that are carried out in the presence of either copper(I) salts (Mannich, Cadiot–Chodkiewicz and Hey reactions) or inorganic base (KOH-catalysed retro-Favorsky reaction of acetylenic alcohols), because it is known that the crown ethers are able to form complexes not only with appropriately-sized cations (K^+–crown-6), but also with the larger ones (‘sandwich’ type). This paper describes the synthesis of ethynylbenzo-15-crown-5 **5** and -18-crown-6 **6** and some of their transformations.

The successful preparation of ethynyl derivatives **5** and **6** was achieved by the following route (Scheme 1). 4′-(3-Methyl-3-hydroxy-1-butynyl)benzocrown ethers **3a** and **4a** were prepared by cross-coupling of the corresponding 4′-iodobenzocrown ethers **1** and **2** with 2-methyl-3-butyn-2-ol.[†]

Retro-Favorsky cleavage of tertiary acetylenic alcohols **3a** and **4a** affords ethynylcrown ethers **5** and **6**. It should be stressed that the use of standard conditions for the reverse Favorsky reaction (catalytic amounts of KOH) was impractical because the formation of alkynes **5** and **6** does not take place, probably due to the complexing of KOH by the crown ether.[4] The cleavage of **3a** and **4a** to ethynylcrown ethers **5** and **6** was carried out with 1.5 mol of KOH at 80 °C for 2–2.5 h.[‡] An elegant alternative for preparing monosubstituted acetylenylcrown ethers involves the coupling between iodobenzocrown ether **1** and trimethylsilylacetylene at room temperature to give trimethylsilylethynylated benzocrown ether **3b**.[§] Subsequent treatment of **3b** with KOH in methanol at 25 °C gave **5** in 97% yield.



Scheme 1 *Reagents and conditions*: i, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, C_6H_6, argon; ii, benzene, 80 °C, 2–2.5 h; iii, methanol, 25 °C, 2–2.5 h.

Ethynylbenzocrown ethers **5** and **6** are suitable for chemical transformation to various carriers. The preparation of bis(benzocrown ether) linked by butadiyne linkages **7** was readily performed by the oxidative coupling of ethynyl derivatives **5** in 69% yield.[¶] The Cadiot–Chodkiewicz reaction catalysed by CuCl occurred without complications and this method was applied in the preparation of an unsymmetrical butadiyne **8** in 62% yield.[††]

The Pd/Cu-catalysed cross-coupling of ethynylbenzocrown ethers **5** with iodoarenes gave, in general, high overall yields of the final ethynylated products. For example, when alkyne **5** was stirred with 4-bromobenzaldehyde in benzene at 80 °C in the presence of triethylamine and catalytic amounts of palladium acetate, copper iodide and triphenylphosphine, 4′-(4-formylphenylethynyl)benzocrown ether **9b** was obtained in 82% yield. The coupling of iodo derivatives **5** with 4-iodobiphenyl in benzene in the presence of triethylamine, bis(triphenylphosphine)palladium chloride and copper iodide at 80 °C gave alkynylbenzocrown ether **9a** in 75% yield.[‡‡]

The copper-catalysed aminomethylation of ethynylcrown ethers **5** and **6** was performed in dioxane. With diethylamine

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[†] **3a**: mp 64–66 °C (from hexane); yield 85.6%. ^{1}H NMR ($CDCl_3$) δ: 1.45 (s, 6H, CMe_2), 3.49–3.69 (m, 16H, OCH_2CH_2), 6.41 (d, 1H, arom. H), 6.98 (s, 1H, arom. H), 7.12 (d, 1H, arom. H); IR (KBr, ν/cm^{-1}): 2221 (C≡C), 3326 (br., OH).

4a: mp 58–60 °C (from hexane); yield 69.3%. ^{1}H NMR ($CDCl_3$) δ: 1.54 (s, 6H, CMe_2), 4.12–3.78 (m, 20H, OCH_2CH_2), 6.79 (d, 1H, arom. H), 6.93 (s, 1H, arom. H), 7.01 (d, 1H, arom. H); IR (KBr, ν/cm^{-1}): 2200 (C≡C), 3357 (br., OH).

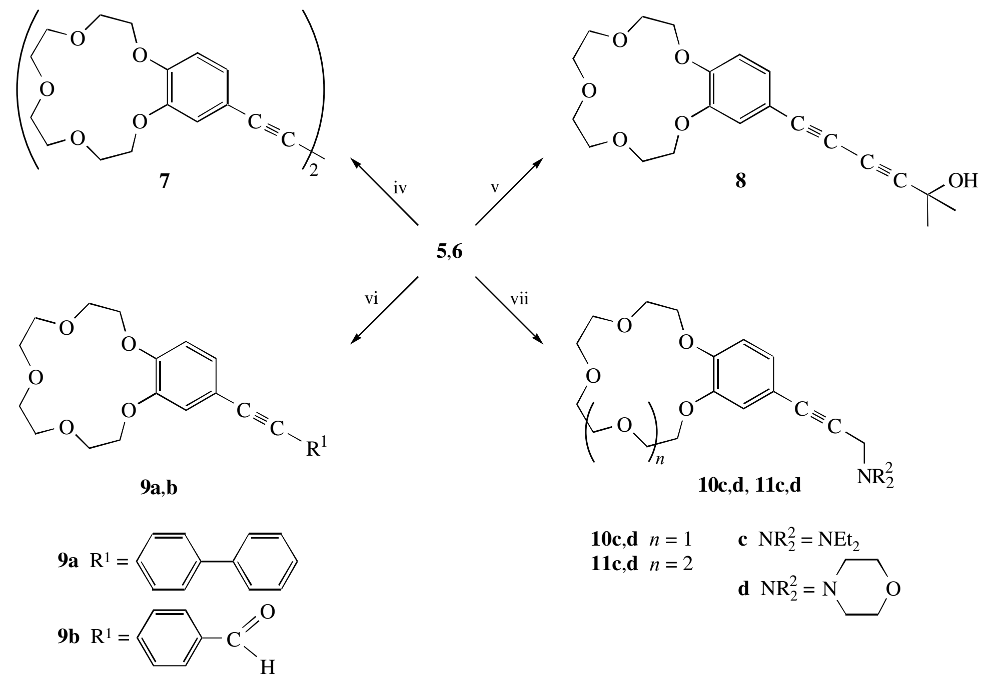
[‡] **5**: mp 60–61 °C (from benzene–hexane); yield 63.0% (method ii), 96.8% (method iii). ^{1}H NMR ($CDCl_3$) δ: 2.75 (s, 1H, C≡CH), 3.41–3.59 (m, 16H, OCH_2CH_2), 6.51 (d, 1H, arom. H), 6.91 (s, 1H, arom. H), 7.15 (d, 1H, arom. H); IR (KBr, ν/cm^{-1}): 2221 (C≡C), 2868 (C≡CH).

6: mp 95–96 °C (from benzene–hexane); yield 69.0% (method ii). ^{1}H NMR ($CDCl_3$) δ: 3.0 (s, 1H, C≡CH), 3.75–4.17 (m, 20H, OCH_2CH_2), 6.81 (d, 1H, arom. H), 7.01 (s, 1H, arom. H), 7.09 (d, 1H, arom. H); IR (KBr, ν/cm^{-1}): 2225 (C≡C), 2860 (C≡CH).

[§] **3b**: mp 48–49.5 °C (from benzene–hexane); yield 96.6%. ^{1}H NMR ($CDCl_3$) δ: 0.24 (s, 9H, $SiMe_3$), 3.72–4.17 (m, 16H, OCH_2CH_2), 6.77 (d, 1H, arom. H), 6.97 (s, 1H, arom. H), 7.06 (d, 1H, arom. H); IR (KBr, ν/cm^{-1}): 2146 (C≡C), 2869, 2955 (Me).

[¶] **7**: mp 144–145 °C (from benzene–hexane); yield 68.9%. ^{1}H NMR ($CDCl_3$) δ: 3.44–4.04 (m, 32H, OCH_2CH_2), 6.21 (d, 2H, arom. H), 6.83 (s, 2H, arom. H), 7.02 (s, 2H, arom. H); IR (KBr, ν/cm^{-1}): 2141 (C≡C).

[††] **8**: mp 107–108 °C (from benzene–hexane); yield 62.0%. ^{1}H NMR ($CDCl_3$) δ: 1.51 (s, 6H, Me), 3.76–4.18 (m, 16H, OCH_2CH_2), 6.79 (d, 1H, arom. H), 6.98 (s, 1H, arom. H), 7.11 (d, 1H, arom. H); IR (KBr, ν/cm^{-1}): 2150, 2250 (C≡C–C≡C), 3363 (br., OH).



Scheme 2 *Reagents and conditions*: iv, Py, CuCl, O_2; v, ethanol, 4-bromo-2-methyl-3-butyn-2-ol, $HNEt_2$, $NH_2OH{\cdot}HCl$, CuCl, argon, 30 °C, 1–1.5 h; vi, $Pd(PPh_3)_2Cl_2$ [or $Pd(OAc)_2$, PPh_3], CuI, NEt_3, C_6H_6, $Br(I)R^1$, argon, 80 °C, 2–2.5 h; vii, dioxane, secondary amine, $(CH_2O)_n$, CuCl, 80–100 °C, argon, 2–2.5 h.

the reaction ended in 2–2.5 h at 80 °C; the yields of aminoacetylenes **10c** and **11c** reached 70–80%. The interaction of both **5** and **6** with morpholine under the same conditions failed. This complication can be avoided by adding a small amount of sulfuric acid to the reaction mixture;[5] under such conditions aminoacetylenes **10d** and **11d** were prepared in 70–75% yield.[§§]

Thus, the development of convenient methods for the synthesis of ethynylbenzocrown ethers opens up a route to obtaining various functionally-substituted alkynylbenzocrown ethers.

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[‡] **9a**: mp 167–168 °C (from benzene); yield 75.0%. ^{1}H NMR ($CDCl_3$) δ: 3.51–4.09 (m, 16H, OCH_2CH_2), 6.21 (d, 2H, arom. H), 6.83 (s, 2H, arom. H), 7.02 (s, 2H, arom. H); IR (KBr, ν/cm^{-1}): 2211 (C≡C).

9b: mp 112–113 °C (from benzene–hexane); yield 82.0%. ^{1}H NMR ($CDCl_3$) δ: 3.38–4.01 (m, 16H, OCH_2CH_2), 5.93 (s, 1H, arom. H), 6.81 (m, 5H, arom. H), 6.57 (s, 1H, arom. H), 9.08 (s, 1H, CHO); IR (KBr, ν/cm^{-1}): 2207 (C≡C), 1701 (C=O).

[§§] Typical spectral data are given below.

10c: mp 51–52 °C (from benzene–hexane); yield 72.0%. ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, 6H, CH_2Me), 2.65 [m, 4H, $N(CH_2Me)_2$], 3.62 (s, 2H, CCH_2N), 3.81–4.11 (m, 16H, OCH_2CH_2), 6.79 (d, 1H, arom. H), 6.94 (s, 1H, arom. H), 7.02 (d, 1H, arom. H); IR (KBr, ν/cm^{-1}): 2220 (C≡C).

10d: oil; yield 70.9%. ^{1}H NMR ($CDCl_3$) δ: 2.45–2.58 (m, 4H, NCH_2), 2.94 (s, 2H, CCH_2N), 3.59–4.25 (m, 16H, OCH_2CH_2 and 4H, OCH_2CH_2N), 6.77 (d, 1H, arom. H), 6.94 (s, 1H, arom. H), 7.02 (d, 1H, arom. H); IR (KBr, ν/cm^{-1}): 2141 (C≡C).

11c: oil; yield 76.4%. ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, 6H, CH_2Me), 2.65 [m, 4H, $N(CH_2Me)_2$], 3.62 (s, 2H, CCH_2N), 3.81–4.11 (m, 16H, OCH_2CH_2), 6.79 (d, 1H, arom. H), 6.94 (s, 1H, arom. H), 7.02 (d, 1H, arom. H); IR (KBr, ν/cm^{-1}): 2220 (C≡C).

11d: oil; yield 74.5%. ^{1}H NMR ($CDCl_3$) δ: 2.68–2.59 (m, 4H, NCH_2), 3.48 (s, 2H, CCH_2N), 3.64–4.19 (m, 20H, OCH_2CH_2 and 4H, OCH_2CH_2N), 6.79 (d, 1H, arom. H), 6.94 (s, 1H, arom. H), 6.78 (d, 1H, arom. H); IR (KBr, ν/cm^{-1}): 2140 (C≡C).