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Direct Heterocyclization of Benzocrown Ethers

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ABSTRACT: *The synthesis of novel 3,3-dialkyl-3,4-dihydroisoquinoline derivatives via direct heterocyclization of benzocrown ethers is described.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:192–195, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20092

INTRODUCTION

In 1967 Pedersen initially observed an affinity of crown compounds (macrocyclic polyethers) to alkali and alkaline earth cations [1]. Since then, several new types of crown's ligands have been synthesized to increase the stability of the cation-crown complex or to improve the cation selectivity of the ligands [2 and references cited there in]. Benzocrown ethers are widely used in the syntheses of biological active compounds [3] and/or derivatives of natural products [4].

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There exists a considerable number of publications concerning heterocyclization of benzocrown ethers, but nearly all of them describe the preparation of annulated heterocycles either with the use of functional group preincorporated into a crown-ether benzene ring [5] or through the creation of C—C bond via attack of an already prepared electron-deficient heterocycle onto the benzocrown ether molecule [6].

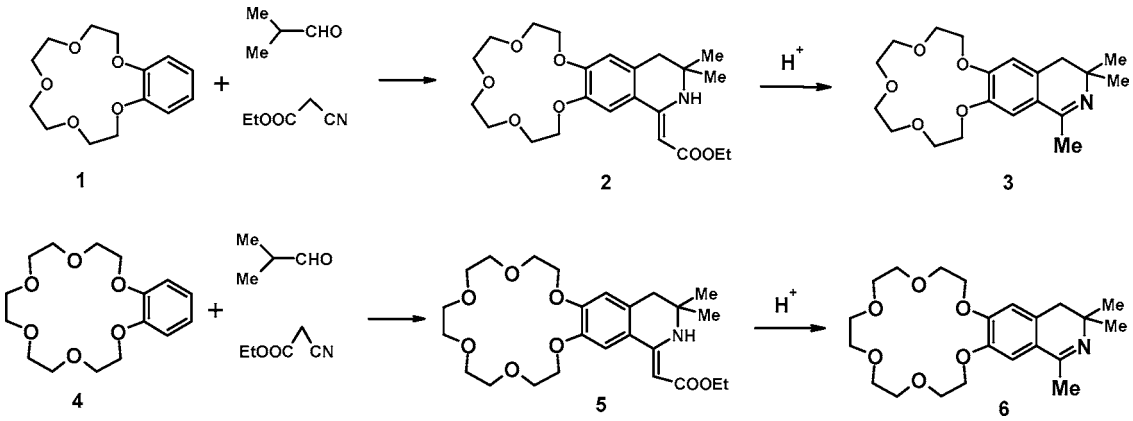
We continue our studies of 3,3-dialkyl-3,4-dihydroisoquinolines [7,8], and here we report the synthesis of some novel benzocrown ether derivatives.

RESULTS AND DISCUSSION

Recently, we have demonstrated that activated arenes readily participate in tandem with heterocyclization involving isobutyraldehyde and nitriles with different properties [9]. Naturally, it was of great interest to us to apply this synthetic motif toward benzocrown ethers.

Benzo-15-crown-5 (**1**) and benzo-18-crown-6 (**4**) were found to yield readily the corresponding 3,4-dihydroisoquinoline derivatives **2** and **5**. Their hydrolysis (10% sulfuric acid) proceeds thought decarboxylation to give 1-methyl derivatives **3** and **6** (Scheme 1).

Enamine form of compounds **2** and **5** was proved by their presence in ^{1}H NMR spectra with the signals of a vinyl proton ($\delta = 4.93$) and NH ($\delta = 8.85$). Besides, there were found the signals of gem-dimethyl groups ($\delta = 1.20$) superimposed on CH_3



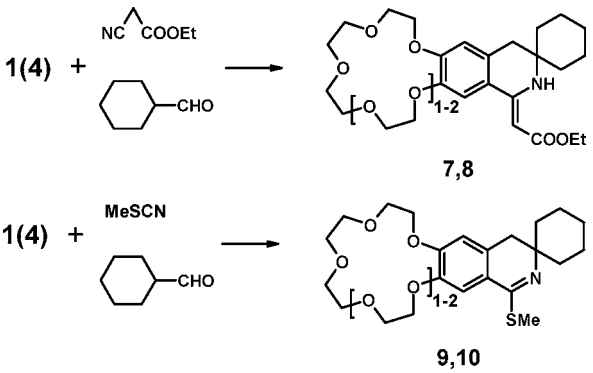
SCHEME 1

(ethoxy moiety), 4-CH_2 at $\delta = 1.89$ and 2.66, C5 and C8 aromatic protons of isoquinoline ring ($\delta =$ 6.53 and 7.06 correspondingly), and three groups of nonequivalent protons of ether moieties at $\delta = 3.69$, 4.06, and 4.10. Despite repeated recrystallization of **2**, all the lines in its spectra were widened; this can be a result of interesting interaction of isoquinoline amine group of one molecule with a crown-moiety of another molecule [10]. Hydrolysis of **2** affords **3** (Scheme 1) whose spectra have a "normal" appearance: gem-dimethyl groups ($\delta = 1.11$), 1-CH_3 ($\delta = 2.25$), 4-CH_2 ($\delta = 2.52$), alkoxy groups multiplets ($\delta = 3.69$, 3.86, and 4.10) and aromatic protons ($\delta = 6.56$ and 6.95) are present as narrow peaks.

Interaction of crown-ether **1** and **4** with cyclohexylcarbaldehyde runs in a similar way (Scheme 2) that proves a common character of reaction between α-branched aliphatic aldehydes, nitriles, and 1, 2-dialkoxyarenes.

EXPERIMENTAL

IR spectra were taken in Nujol, using UR-20 spectrometer; ^{1}H NMR spectra were recorded at 320 MHz on a Mercury-plus-300 spectrometer ($CDCl_3$, HMDS as internal standard). Reaction progress was monitored by TLC (Silufol U-254, $CHCl_3$/acetone = 9:1, spots were visualized by 5% toluene solution of chloroanile).



SCHEME 2

General Procedure for Synthesis of **2, 5, 7**, *and* **8**

A mixture of **1** (1 g, 3.7 mmol), cyanoacetic ester (0.45 g, 3.7 mmol), and ~3.7 mmol of isobutyraldehyde (compounds **2** and **5**) or cyclohexylcarbaldehyde (compounds **7** and **8**) in chloroform (15 mL) was added dropwise to conc. sulfuric acid (10 mL) at stirring and cooling. After stirring for 15 min, the reaction mixture was poured into ice (50 g), then basified by $(NH_4)_2CO_3$ to pH 8, and extracted by methyl-*tert*-butyl ether (3 × 50 mL). The combined ether layers were dried over Na_2SO_4. Evaporation of the solvent and recrystallization of a residue from ethanol afforded 1 g of **2**.

*Ethyl Ester of 6,7-(1′,4′,7′,10′,13′-Pentaoxatridecylene)-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidene-1-acetic Acid (***2***).* 62% yield, mp 162.5–164°C (ethanol). IR ν, (sm^{-1}): 1630; 1595; 1510. ^{1}H NMR, δ (ppm): 1.24 (t, 3 H, $\underline{CH_3}CH_2O$); 1.28–1.80 (m,10 H, pentamet.); 2.67 (s, 2 H, 4-CH_2); 3.60–3.74, 3.80–3.93, 4.00–4.15 (m, $O(CH_2)_2O_{crown}$); 4.00–4.15 (m, $CH_3\underline{CH_2}O$); 4.95 (s, 1 H, CH=C); 6.53 (s, 1 H, $H(5)_{aryl}$); 7.06 (s, 1 H, $H(8)_{aryl}$); 9.22 (s, 1 H, NH). The product is distinctly soluble in water.

*Ethyl Ester of 6,7-(1′,4′,7′,10′,13′,16′-Hexaoxahexadecylene)-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidene-1-acetic Acid (***5***).* 65% yield, mp 78–80°C (hexane). IR, ν (sm^{-1}): 1630; 1595; 1510. ^{1}H NMR, δ (ppm): 1.13-1.26 (m, 3,3-Me_2 + $\underline{CH_3}CH_2O$); 2.66 (s, 2 H, 4-CH_2); 3.62–3.72, 3.83–3.89, 4.05–4.13

(m, $O(CH_2)_2O_{crown}$); 4.05–4.13 (m, $CH_3\underline{CH_2}O$); 4.94 (s, 1 H, CH=C); 6.54 (s, 1 H, $H(5)_{aryl}$); 7.08 (s, 1 H, $H(8)_{aryl}$); 8.86 (s, 1 H, NH).

*Ethyl Ester of 6,7-(1′,4′,7′,10′,13′-Pentaoxatridecylene)-3,3-pentamethylene-1,2,3,4-tetrahydroisoquinolylidene-1-acetic Acid (***7***).* 48% yield, mp 189–191°C (isopropanol-ethanol). IR ν (sm^{-1}): 1630; 1595; 1510. ^{1}H NMR δ (ppm): 1.24 (t, 3 H, CH_3CH_2O); 1.28–1.80 (m,10 H, pentamethylene.); 2.67 (s, 2 H, 4-CH_2); 3.60–3.74, 3.80–3.93, 4.00–4.15 [m, $O(CH_2)_2O_{crown}$]; 4.00–4.15 (m, $CH_3\underline{CH_2}O$); 4.95 (s, 1 H, CH=C); 6.53 (s, 1 H, $H(5)_{aryl}$); 7.06 (s, 1 H, $H(8)_{aryl}$); 9.22 (s, 1 H, NH).

*Ethyl Ester of 6,7-(1′,4′,7′,10′,13′,16′-Hexaoxahexadecylene)-3,3-pentamethylene-1,2,3,4-tetrahydroisoquinolylidene-1-acetic Acid (***8***).* 46% yield, mp 67–70°C (hexane). IR ν (sm^{-1}): 1650; 1595; 1510. ^{1}H NMR δ (ppm): 1.10–1.62 (m,10 H, pentamethylene); 1.24 (t, 3 H, $\underline{CH_3}CH_2O$); 2.67 (s, 2 H, 4-CH_2); 3.60–3.73, 3.80–3.90, 4.07–4.15 [m, $O(CH_2)_2O_{crown}$]; 4.04–4.16 (q, $CH_3\underline{CH_2}O$) [total intensity of 22H]; 4.95 (s, 1 H, CH=C); 6.54 (s, 1 H, $H(5)_{aryl}$); 7.06 (s, 1 H, $H(8)_{aryl}$); 9.22 (s, 1 H, NH).

General Procedure for Synthesis of **3** *and* **6**

An ester **2** (1 g) was dissolved in 10% H_2SO_4 (15 mL); the reaction mixture was heated for 2 h, cooled down to r.t., basified by $(NH_4)_2CO_3$ to pH 8 and extracted by methyl-*tert*-butyl ether (3×50 mL). Combined ether layers were dried over Na_2SO_4, whereupon the solvent was evaporated, and an obtained residue was purified by recrystallization from ethanol to give 0.6 g of **3**.

*1,3,3-Trimethyl-6,7-(1′,4′,7′,10′,13′-pentaoxadecylene)-3,4-dihydroisoquinoline (***3***).* 70% yield, mp 114–116°C. ^{13}C NMR δ (ppm): 21.55; 26.09; 36.70; 51.66; 66.74; 67.52; 67.78; 68.16; 68.49; 68.75; 69.07; 69.20; 110.89; 111.02; 119.95; 128.95; 145.26; 149.53; 158.66. ^{1}H NMR δ (ppm): 1.11 (s, 6 H, 3-Me); 2.25 (s, 3 H, 1-Me); 2.52 (s, 2 H, 4-CH_2); 3.69, 3.85, 4.08 (m, $O(CH_2)_2O_{crown}$); 6.56 (s, 1 H, $H(5)_{aryl}$);6.96 (s, 1 H, $H(8)_{aryl}$).

*1,3,3-Trimethyl-6,7-(1′,4′,7′,10′,13′,17′-hexaoxadecylene)-3,4-dihydroisoquinoline (***6***).* ~65% yield, mp 88.5–90.5°C (hexane). ^{1}H NMR δ (ppm): 1.12 (s, 3 H, 3-Me); 1.97 (s, 3 H, 3-Me); 2.26 (s, 3 H, 1-Me); 2.53 (s, 2 H, 4-CH_2); 3.62–3.73, 3.86–3.89, 4.10–4.14 (m, $O(CH_2)_2O_{crown}$); 6.56 (c, 1 H, $H(5)_{aryl.}$); 6.96 (c, 1 H, $H(8)_{aryl}$).

General Procedure for Synthesis of **9** *and* **10**

A mixture of **1** (1 g, 3.7 mmoL), methylthiocyanate (0.3 g, 4.1 mmoL), and cyclohexylcarbaldehyde (0.42 g, 3.75 mmoL) in chloroform (15 mL) was added dropwise to conc. sulfuric acid (10 mL) at stirring and cooling. After stirring for 15 min, the reaction mixture was poured into ice (50 g), then basified by $(NH_4)_2CO_3$ to pH 8, and extracted by methyl-*tert*-butyl ether (3×50 mL). The combined ether layers were dried over Na_2SO_4. Evaporation of the solvent and recrystallization of a residue from hexane afforded 1.12 g (70%) of **9**.

*1-Methylthio-6,7-(1′,4′,7′,10′,13′-pentaoxatridecylene)-3,3-pentamethylene-3,4-dihydroisoquinoline (***9***).* mp 115.5–117.5°C (hexane). IR ν (sm^{-1}): 1600; 1520; 1470. ^{1}H NMR δ (ppm): 1.24–1.76 (m,10 H, pentamethylene); 2.37 (s, 3 H, SCH_3); 2.58 (s, 2 H, 4-CH_2); 3.58–3.73, 3.80–3.90, 4.07–4.09 [m, 20H, $O(CH_2)_2O_{crown}$]; 6.54 (s, 1 H, $H(5)_{aryl}$; 7.09 (s, 1 H, $H(8)_{aryl}$).

*1-Methylthio-6,7-(1′,4′,7′,10′,13′,16′-Hexaoxahexadecylene)-3,3-pentamethylene-3,4-dihydroisoquinoline (***10***).* 67% yield, mp118–120°C (hexane). IR ν (sm^{-1}): 1600; 1520; 1470. ^{1}H NMR δ (ppm): 1.24–1.72 (m, 10 H, pentamethylene); 2.37 (s, 3 H, SCH_3); 2.51 (s, 2 H, 4-CH_2); 3.60–3.80, 3.82–3.90, 4.09–4.13 [m, $O(CH_2)_2O_{crown}$]; 6.56 (c, 1 H , $H(5)_{aryl}$); 7.11 (c, 1 H, $H(8)_{aryl}$).

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