Organic Chemistry

Synthesis of alkynylbenzo-15-crown-5 ethers*

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Reactions of 4´-iodobenzo-15-crown-5 ether with ethynylarenes or 4´-ethynylbenzo-15-crown-5 ether with haloarenes in the presence of catalytic amounts of Pd^{II} complex salts, CuI, and Et_3N gave 4´-(arylethynyl)benzo-15-crown-5 ethers in 55—80% yields.

Key words: benzocrown ethers, alkynes, cross-coupling, homogeneous catalysis.

Crown ethers have found wide use in organic, analytical, and coordination chemistry, as well as in biology.[2] In recent years, crown ethers containing alkynyl substituents have attracted the attention of researchers. In particular, a series of studies[3—5] has been devoted to the investigation of structure—property relationships (thermal and spectral properties and selectivity of cation binding) for liquid crystals based on ethynylbenzocrown ethers in solution and in the nematic phase. Compounds of this type were also found[6] to be convenient precursors for construction of assemblies containing two benzocrown ether fragments.

Currently, the sole method for the synthesis of ethynylbenzocrown ethers is the Heck—Sonogashira cross-coupling of aryl(hetaryl) halides with terminal alkynes,[7,8] which is widely applied even to low-reactivity aryl halides (with reduced nucleofugicity of a halogen atom) and ethynylarenes (with reduced CH acidity).[9] However, the small number of the synthesized alkynylbenzocrown ethers does not cover the whole pattern of cross-coupling applicability, especially for both halogen and ethynyl derivatives of crown ethers of low reactivity due to the presence of deactivating alkoxy groups (+M-effect) in the aromatic part of their molecules.

In connection with this, a comparative study of "direct" and "inverse" cross-coupling reactions was performed. In the former reaction (method *A*), an iodobenzocrown ether was used as a halogen-containing component and an ethynylarene as an alkyne component; in the latter reaction (method *B*), an iodo- or bromoarene was used in cross-coupling with an ethynylbenzocrown ether (Scheme 1).

Results and Discussion

The yields of alkynes **3a—e** obtained by methods *A* and *B* are close (55—80%). The reaction time varies from one to four hours; as expected, electron-withdrawing substituents both in halo- (method *B*) and ethynylarenes (method *A*) only slightly accelerate the reaction:

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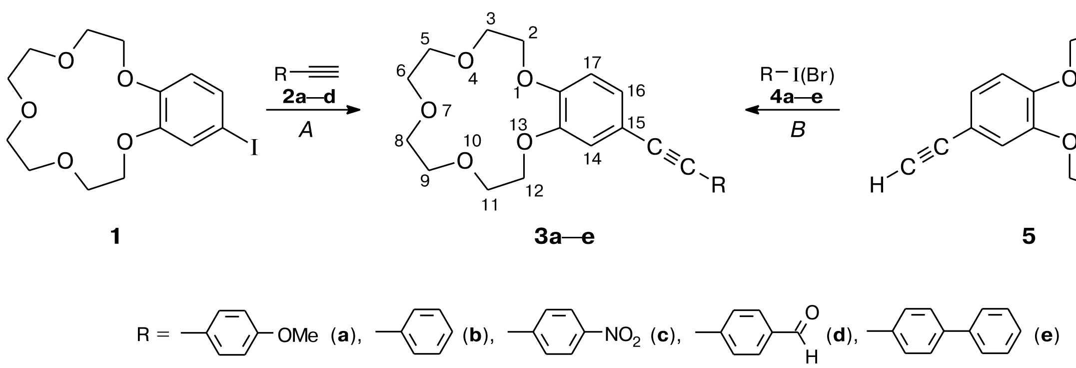
Scheme 1



Reagents and conditions: $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$, PPh_3; CuI, Et_3N, C_6H_6, 70—75 °C, an Ar atmosphere.

OMe (4 h, *A* and *B*) > H (2 h, *A* and *B*) > Ph (2.5 h, *B*) > > CHO (1.5 h, *A* and *B*) > NO_2 (1 h, *A* and *B*).

Cross-coupling was carried out under standard conditions (boiling benzene, Et_2NH, $Pd(PPh_3)_2Cl_2$ (2 mol %), and CuI (4 mol %)).[6] However, the use of Et_3N instead of Et_2NH reduced the reaction time from 24 to 1—4 h. For carbonyl-containing substrates, the reaction was catalyzed by $Pd(OAc)_2$ (4 mol %) (in the presence of other catalysts, the reaction mixture undergoes strong resinification[10]), PPh_3 (11 mol %), and CuI (3 mol %).

Thus, we developed two alternative methods for the synthesis of various arylalkynylbenzo-15-crown-5 ethers by the Heck—Sonogashira cross-coupling of the corresponding halides with alkynyl components.

Experimental

^1H NMR spectra were recorded on a Bruker Avance 300 spectrometer (300 MHz) in $CDCl_3$ with Me_4Si as a standard. IR spectra were recorded on a Bruker IFS-66 spectrometer (KBr). Mass spectra were recorded on a Finnigan SSQ-710 instrument (EI, direct inlet, ionization chamber temperature 220—270 °C, ionizing voltage 70 eV). Column chromatography was carried out on KSK silica gel (60/200 μm). The course of the reaction was monitored and the purity of the products obtained was checked by TLC on Silufol UV-254 plates. 4´-Iodobenzo-15-crown-5 ether (**1**),[11] *p*-ethynylbenzaldehyde (**2d**),[10] 4-iodobiphenyl (**4e**), iodobenzene (**4b**), *p*-iodonitrobenzene (**4c**),[12] and *p*-nitrophenylacetylene (**2c**)[13] were prepared according to the known procedures. 4´-Ethynylbenzo-15-crown-5 ether (**5**)[1,14] was synthesized by the reverse Favorsky reaction from a corresponding tertiary alkynol. *p*-Methoxyphenylacetylene (**2a**) was prepared as described earlier,[9] b.p. 82—87 °C (10 Torr), m.p. 27—28 °C (*cf.* Ref. 15: b.p. 86 °C (9 Torr), m.p. 29 °C).

Copper(I) iodide, PPh_3, $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, phenylacetylene (**2b**), *p*-iodoanisole (**4a**), and *p*-bromobenzaldehyde (**4d**) (Lancaster Co.) were used without additional purification; the other reagents and organic solvents were purified according to standard procedures.[16]

15-[2-(4-Methoxyphenyl)ethyn-1-yl]-2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-pentaoxabenzocyclopentadecine (3a). Method *A*. A solution of iodide **1** (0.8 g, 2 mmol), alkyne **2a** (0.3 g, 2.4 mmol), $Pd(PPh_3)_2Cl_2$ (30 mg, 0.04 mmol), and CuI (15 mg, 0.08 mmol) in a mixture of Et_3N (2 mL) and benzene (8 mL) was stirred in an atmosphere of Ar at 70—75 °C for 4 h. Then the reaction mixture was cooled and filtered through an SiO_2 layer (2.5×2 cm). The solvents were removed *in vacuo*, and the residue was recrystallized from benzene—hexane. The yield of crown ether **3a** was 0.43 g (54%).

Method *B*. A solution of iodide **4a** (0.51 g, 2.2 mmol), alkyne **5** (0.58 g, 2 mmol), $Pd(PPh_3)_2Cl_2$ (30 mg, 0.04 mmol), and CuI (15 mg, 0.08 mmol) in a mixture of Et_3N (2 mL) and benzene (8 mL) was stirred in an atmosphere of Ar at 70—75 °C for 3.5 h. Then the reaction mixture was cooled and filtered through an SiO_2 layer (2.5×2 cm). The solvents were removed *in vacuo*, and the residue was recrystallized from benzene—hexane. The yield of crown ether **3a** was 0.45 g (57%).

Crown ether **3a**, m.p. 109—110 °C. ^1H NMR, δ: 3.74—3.81 (m, 8 H, OCH_2CH_2O); 3.84 (s, 3 H, OMe); 3.93—4.17 (m, 8 H, Ar—OCH_2CH_2O); 6.84 (d, 1 H, H(17), *J* = 9 Hz); 6.92 (d, 2 H, H(3), H(5), *J* = 8.5 Hz); 7.03 (s, 1 H, H(14)); 7.11 (d, 1 H, H(16), *J* = 9 Hz); 7.46 (d, 2 H, H(2), H(6), *J* = 8.5 Hz). IR, ν/cm^{-1}: 2225 (C≡C). MS, m/z (I_{rel} (%)): 398.1 $[M]^+$ (25.68), 350.1 (21.28), 262.1 (11.07), 204.0 (14.89), 203.0 (100.00), 159.1 (3.81), 175.0 (13.04), 161.1 (11.80), 148.6 (48.18), 114.1 (15.07). Found: M = 398.1734 $[M]^+$. $C_{23}H_{26}O_6$. Calculated: M = 398.17292.

15-(2-Phenylethyn-1-yl)-2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-pentaoxabenzocyclopentadecine (3b). Method *A*. A solution of iodide **1** (0.98 g, 2.5 mol), alkyne **2b** (0.3 g, 2.7 mol), $Pd(PPh_3)_2Cl_2$ (40 mg, 0.05 mmol), and CuI (20 mg, 0.1 mmol) in a mixture of Et_3N (2 mL) and benzene (8 mL) was stirred in an atmosphere of Ar at 70—75 °C for 2 h. Then the reaction mixture was cooled and filtered through an SiO_2 layer (2.5×2 cm). The solvents were removed *in vacuo*, and the residue was recrystallized from benzene—hexane. The yield of compound **3b** was 0.66 g (72%).

Method *B*. Compound **3b** was obtained from alkyne **5** (0.58 g, 2 mmol) and iodide **4b** (0.45 g, 2.2 mmol) as described above for crown ether **3a**. The yield of compound **3b** was 0.55 g (75%); the reaction time was 2 h.

Crown ether **3b**, m.p. 112—113 °C (benzene—hexane). ^{1}H NMR, δ: 3.75—4.26 (m, 16 H, OCH_2CH_2O); 6.76 (d, 1 H, H(17), *J* = 8 Hz); 6.95 (s, 1 H, H(14)); 7.03 (d, 1 H, H(16), *J* = 8 Hz); 7.21—7.26 (m, 3 H, H(3), H(4), H(5)); 7.46—7.49 (m, 2 H, H(2), H(6)). IR, ν/cm^{-1}: 2200 (C≡C). MS, *m/z* (I_{rel} (%)): 368.1 $[M]^+$ (51.08), 280.2 (10.86), 237.1 (18.73), 236.1 (100.00), 221.1 (26.29), 210.1 (10.63), 180.1 (47.39), 163.1 (13.79), 152.1 (30.26), 110.6 (17.05). Found: M = 368.1625 $[M]^+$. $C_{22}H_{24}O_5$. Calculated: M = 368.16236.

15-[2-(4-Nitrophenyl)ethyn-1-yl]-2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-pentaoxabenzocyclopentadecine (3c). Method *A*. Compound **3c** was obtained from iodide **1** (0.98 g, 2.5 mmol) and alkyne **2c** (0.4 g, 2.7 mmol) by analogy with **3b**. The yield of crown ether **3c** was 0.78 g (76%); the reaction time was 1 h.

Method *B*. Compound **3c** was obtained from alkyne **5** (0.58 g, 2 mmol) and iodide **4c** (0.55 g, 2.2 mmol) by analogy with **3a**. The yield of crown ether **3c** was 0.61 g (74%); the reaction time was 1 h.

Crown ether **3c**, m.p. 108—110 °C (benzene—hexane). ^{1}H NMR, δ: 3.75—4.17 (m, 16 H, OCH_2CH_2O); 6.83 (d, 1 H, H(17), *J* = 8 Hz); 7.05 (s, 1 H, H(14)); 7.12 (d, 1 H, H(16), *J* = 8 Hz); 7.06 (d, 2 H, H(2), H(6), *J* = 9 Hz); 8.16 (d, 2 H, H(3), H(5), *J* = 9 Hz). IR, ν/cm^{-1}: 2210 (C≡C). MS, *m/z* (I_{rel} (%)): 412.9 $[M]^+$ (44.22), 325.0 (8.68), 292.0 (10.96), 282.0 (18.41), 280.9 (100.00), 265.9 (15.97), 235.0 (11.14), 224.9 (22.31), 163.0 (12.53), 151.1 (9.74). Found: M = 413.1476 $[M]^+$. $C_{22}H_{23}O_7N$. Calculated: M = 413.14744.

4-[2-(2,3,5,6,8,9,11,12-Octahydro-1,4,7,10,13-pentaoxabenzocyclopentadecin-15-yl)ethyn-1-yl]benzaldehyde (3d). Method *A*. A solution of iodide **1** (1.2 g, 3 mmol), alkyne **2d** (0.43 g, 3.3 mmol), $Pd(OAc)_2$ (30 mg, 0.13 mmol), PPh_3 (90 mg, 0.34 mmol), and CuI (15 mg, 0.08 mmol) in a mixture of Et_3N (2 mL) and benzene (8 mL) was stirred in an atmosphere of Ar at 70—75 °C for 1.5 h. Then the reaction mixture was cooled and filtered through an SiO_2 layer (2.5×2 cm). The solvents were removed *in vacuo*, and the residue was recrystallized from benzene—hexane. The yield of compound **3d** was 0.97 g (82%).

Method *B*. A solution of bromide **4d** (0.57 g, 3.1 mmol), alkyne **5** (0.87 g, 3 mmol), $Pd(OAc)_2$ (30 mg, 0.13 mmol), PPh_3 (90 mg, 0.34 mmol), and CuI (15 mg, 0.08 mmol) in a mixture of Et_3N (2 mL) and benzene (8 mL) was stirred in an atmosphere of Ar at 70—75 °C for 1.5 h. Then the reaction mixture was cooled and filtered through an SiO_2 layer (2.5×2 cm). The solvents were removed *in vacuo*, and the residue was recrystallized from benzene—hexane. The yield of compound **3d** was 0.93 g (78%).

Crown ether **3d**, m.p. 140—141 °C (benzene—hexane). Found (%): C, 69.72; H, 6.19. $C_{23}H_{24}O_6$. Calculated (%): C, 69.68; H, 6.10. ^{1}H NMR, δ: 3.38—4.01 (m, 16 H, OCH_2CH_2O); 6.41 (d, 1 H, H(17), *J* = 9 Hz); 7.02 (s, 1 H, H(14)); 7.19 (d, 1 H, H(16), *J* = 9 Hz); 7.39 (d, 2 H, H(2), H(6), *J* = 8 Hz); 7.44 (d, 2 H, H(3), H(5), *J* = 8 Hz); 9.56 (s, 1 H, CHO). IR, ν/cm^{-1}: 2207 (C≡C), 1701 (C=O).

15-[2-(Biphenyl-4-yl)ethyn-1-yl]-2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-pentaoxabenzocyclopentadecine (3e) was obtained as described for crown ether **3a** (method ***B***). Condensation of alkyne **5** (0.75 g, 2.4 mmol) with iodide **4e** (0.84 g, 2.6 mmol) was carried out for 2.5 h. The yield of compound **3e** was 0.78 g (73%), m.p. 167—168 °C (benzene). ^{1}H NMR, δ: 3.51—4.09 (m, 16 H, OCH_2CH_2); 6.92 (d, 1 H, H(17), *J* = 9 Hz); 7.06—7.1 (m, 2 H, H(14), H(16)); 7.29 (t, 1 H, H(4´), *J* = 9 Hz); 7.41 (t, 2 H, H(3´), H(5´), *J* = 9 Hz); 7.55 (d, 2 H, H(3), H(5), *J* = 9 Hz); 7.62—7.71 (m, 4 H, H(2), H(6), H(2´), H(6´)). IR, ν/cm^{-1}: 2211 (C≡C). MS, *m/z* (I_{rel} (%)): 444.2 $[M]^+$ (69.18), 356.1 (15.23), 313.1 (24.64), 312.1 (100.00), 256.1 (29.55), 156.1 (33.09), 148.6 (48.18), 114.1 (15.07), 101.1 (9.60), 78.1 (24.23). Found: M = 444.1923 $[M]^+$. $C_{28}H_{28}O_5$. Calculated: M = 444.19366.

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