Palladium-catalyzed Reaction of 4′-Iodobenzocrown Ethers with Acetylenes. Convenient Synthesis of Alkyl-substituted Benzocrown Ethers and Bis(benzocrown ether)s *via* Alkynyl-substituted Benzocrown Ethers

Kiyoshi KIKUKAWA,* AkitoABE, Fumio WADA, and Tsutomu MATSUDA

Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812

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Synopsis. 4′-Iodobenzo-15-crown-5 and -18-crown-6 were alkynylated by heptyne, propargyl alcohol, 1,7-octadiyne and acetylene in good yields with use of $Pd(PPh_3)_2Cl_2$ and CuI as catalysts. The latter two acetylenes gave bis(crown ether)s in one step. Hydrogenation of the alkynylated benzocrown ethers gave 4′-heptyl, 4′-(3-hydroxypropyl)-benzocrown ethers and bis(benzocrown ether)s connected with ethylene or octamethylene linkage.

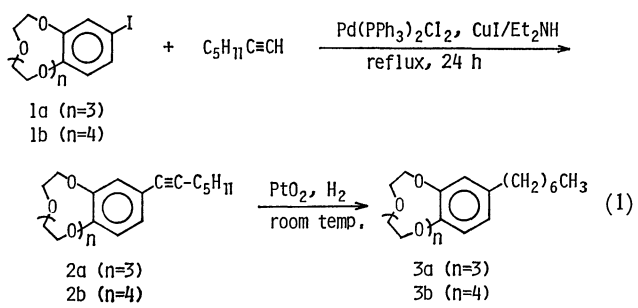
Functionalized benzocrown ethers have received much attention through not only their modified nature of complexation with cations, but also their specialized utility for analytical[1] and pharmaceutical applications,[2] and as potential intermediates for other functionalized crown ethers, such as polymer-bound crown ethers[3] or bis(crown ether)s.[4] Since halogenation and nitration of benzocrown ethers at 4′-position can be carried out with excellent yields, the transformation of halo[5] or nitro group[6] on benzocrown ethers is one of the promising methods to obtain the functionalized benzocrown ethers. Alkenylated benzocrown ethers have been synthesized by palladium-catalyzed reaction of 4′-halobenzocrown ethers with olefins, such as styrene or acrylic acid and its derivatives.[5] The alkenylation of haloarenes with simple olefins such as 1-octene, however, gives a mixture of regioisomers, *i.e.*, 1-aryloctenes and 2-aryloctenes.[7] Whereas there is no ambiguity of the substituted position in the palladium-copper-catalyzed alkynylation of iodoarenes by terminal acetylenes.[8]

Now we wish to report a convenient transformation of 4′-iodobenzocrown ethers to the alkylbenzocrown ethers and bis(benzocrown ether)s *via* the alkynylated benzocrown ethers.

Results and Discussion

*Alkynylation of 4′-Iodobenzocrown Ethers (**1**).* A solution of a 4′-iodobenzocrown ether(**1**), 1-heptyne, $Pd(PPh_3)_2Cl_2$, and CuI in diethylamine was refluxed for 24 h under nitrogen (Eq. 1).

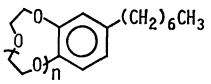
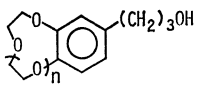
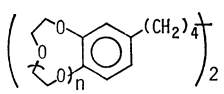
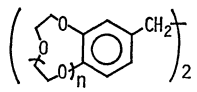
After evaporation of diethylamine from the reaction mixture, the residue was purified by passing it through a short alumina column with chloroform as eluent.



(1)

On being conducted at room temperature as the alkynylation of iodobenzene in the original report,[8] the reaction did not proceed to lead recovery of **1**. Longer reaction time (for 2 d), however, reduced the yield. The use of triethylamine or morpholine instead of diethylamine did not give **2**. Purification of

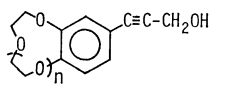
Table 1. Hydrogenation of alkynylated benzocrown ethers

Products	*n*	Yield[a] %	Mp θ_m/°C	Found (Calcd) (%) C	H
	3	76	Oil	68.58, (68.82,	9.30 9.35)
	4	84	Oil	66.65, (67.30,	9.33 9.32)
	3	70	45.3—48.3	62.30, (62.56,	8.14 8.03)
	4	68	Oil	61.25, (61.61,	8.18 8.16)
	3	76	97.1—99.9	66.72, (66.85,	8.55 8.41)
	4	69	88.4—89.4	65.93, (65.38,	8.76 8.50)
	3	75	106.5—108.7	63.97, (64.04,	7.67 7.52)
	4	69	87.6—89.4	62.71, (62.76,	7.80 7.74)

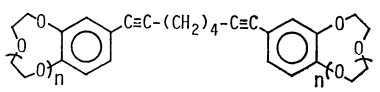
a) Isolated and purified yields based on alkynylated benzocrown ethers.

1 by recrystallization from heptane was found to be essential to obtain good yields, and the present reaction did not proceed when **1** was purified only by column chromatography (alumina–chloroform).

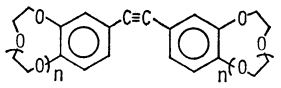
The reaction of **1** with propargyl alcohol and 1,7-octadiyne under the same reaction conditions gave the following compounds, **4** and **5**, respectively. Introduction of acetylene gas to a hot solution of **1**, Pd(PPh$_3$)$_2$Cl$_2$, CuI and diethylamine for 3 h gave the bis(benzocrown ether) (**6**). The alkynylated benzocrown ethers in general were obtained in excellent yields, irrespective of the nature of acetylenes.



4a (n=3)
4b (n=4)



5a (n=3)
5b (n=4)



6a (n=3)
6b (n=4)

Hydrogenation of Alkynylated Benzocrown Ethers. The alkynylated benzocrown ethers were effectively hydrogenated by atmospheric hydrogen under PtO_2 catalysis at room temperature (Eq. 1). Typical results are summarized in Table 1.

Since **1** is easily obtained from benzocrown ethers in a good yield, the present method provides a convenient route to prepare functionalized benzocrown ethers, especially a new type of bis(benzocrown ether)s connected with polymethylene linkage.

Experimental

Materials. 1-Heptyne, 1,7-octadiyne, propargyl alcohol, PPh_3, $PdCl_2$, CuI, and PtO_2 were used as received. Diethylamine and methanol were distilled before use. 4′-Iodobenzocrown ethers[9] and Pd(PPh$_3$)$_2$Cl$_2$[10] were prepared by the published methods, respectively. 4′-Iodobenzocrown ethers were purified by recrystallization from heptane.

General Procedure. A solution of a **1** (1.0 mmol), an acetylene derivatives (1.2 mmol as ethynyl unit), Pd(PPh$_3$)$_2$Cl$_2$ (0.01 mmol), and CuI (0.04 mmol) in diethylamine (10 ml) was refluxed for 24 h under nitrogen. When acetylene was used, acetylene gas was passed through a solution of **1**, Pd(PPh$_3$)$_2$Cl$_2$ and CuI in diethylamine under gentle reflux. After removal of diethylamine under reduced pressure, the residue was purified by chromatography (alumina–chloroform) or recrystallization from hexane. In the case of 4′-alkynylated benzo-18-crown-6s which were obtained in *ca.* 61—83% yields, however, small amounts of unknown impurities (2—5%) could not be removed even after purification was repeated several times, although hydrogenation of the crude crown ethers gave easily the corresponding pure hydrogenated products. Therefore the structure of 4′-alkynylated benzo-18-crown-6s was confirmed by both the IR & NMR spectra and elemental analysis of the corresponding hydrogenated crown ethers.

Analytical data of 4′-alkynylbenzo-15-crown-5s are as follows.

*4′-(1-Heptynyl)benzo-15-crown-5(**2a**)*: Yield 87%, oil, NMR ($CDCl_3$) δ=0.93 (–CH_3, t, 3H), 1.15—1.80 (–CH_2–, m, 6H), 2.05—2.55 (–C≡C–CH_2–, t, 2H), 3.50—4.25 (–OCH_2CH_2O–, m, 16H), 6.45—6.91 (aromatic protons, m, 3H), Found: C, 69.06; H, 8.29%. Calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34%.

*4′-(3-Hydroxy-1-propynyl)benzo-15-crown-5(**4a**)*: Yield 73%, mp 118.9—120.3 °C, NMR ($CDCl_3$) δ=2.05 (–OH, s, 1H), 4.4 (–C≡C–CH_2–O–, s, 2H), 3.5—4.3 (–OCH_2CH_2O–, m, 12H), 6.6—7.1 (aromatic protons, m, 3H). Found: C, 63.44; H, 6.93%. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88%. **5a**: Yield 88%, mp 108.5—110.7 °C, NMR ($CDCl_3$) δ=1.50—1.95 (–CH_2–, m, 4H), 2.10—2.60 (–C≡C–CH_2–, m, 4H), 3.45—4.15 (–OCH_2CH_2O–, m, 32H), 6.45—6.95 (aromatic protons, m, 6H), Found: C, 67.33; H, 7.37%. Calcd for $C_{36}H_{46}O_{10}$: C, 67.69; H, 7.26%. **6a**: Yield 98%, mp 125.4—127.0 °C, NMR ($CDCl_3$) δ=3.6—4.3 (–OCH_2CH_2O–, m, 32H), 6.6—7.2 (aromatic protons, m, 6H). Found: C, 64.33; H, 6.94%. Calcd for $C_{30}H_{38}O_{10}$: C, 64.50; H, 6.86%. The C≡C stretching of the alkynylated benzocrown ethers was generally not observed, except **4a**(2220 cm^{-1}) and 4′-(3-hydroxy-1-propynyl)benzo-18-crown-6 (2220 cm^{-1}).

Hydrogenation of the alkynylated benzocrown ethers was carried out by atmospheric hydrogen with PtO_2 in methanol at room temperature. After removal of solvent and catalyst, the products were easily purified by chromatography (alumina–chloroform) or recrystallization from hexane, The structure of 4′-alkylbenzocrown ethers was also confirmed by IR, NMR, and elemental analysis.

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