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New Applications of Crown Ethers. II.
Synthesis of 4′-Formylbenzocrown Ethers[1]

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Synopsis. 4′-Formylbenzo-15-crown-5, -18-crown-6, and bis(4′-formylbenzo)-18-crown-6 were conveniently synthesized in excellent yields by Smith modification of Duff reaction: formylation with hexamethylenetetramine and trifluoroacetic acid or methanesulfonic acid.

4′-Formylbenzocrown ethers are considered to be useful intermediates for the preparation of various substituted benzocrown ethers with the use of the carbonyl function, and have been utilized for the preparation of 4′-(2-carboxyvinyl)-benzo-15-crown-5 (or 3-[3′,4′-(1″,4″,7″,10″,13″-pentaoxacyclopentadeca-2″-ene)phenyl]acrylic acid),[2] phosphine derivatives,[3] bis(crown ether)s[3,4] and oximes.[5] 4′-Formylbenzo-15-crown-5 (**1**) and -18-crown-6 (**2**) were first prepared from 4-formylcatechol by Smid *et al.*,[6] using the conventional crown ring-forming cyclization. Direct formylation of benzo-15-crown-5 by Vilsmeyer reaction were reported recently by Hyde *et al.*[3] to give **1** in 54% yield. Electrophilic substitution in general seems to be promising for the synthesis of substituted benzocrown ethers. However, the reactions, especially those carried out under the catalysis of metal salts, frequently encounter with deactivation of the catalyst[7] and complexity in the isolation of the product[3] owing to the formation of crown ether complexes.

In our study to get a variety of substituted benzocrown ethers, we needed to disclose a simple method for the preparation of **1** and **2**. Among many reactions being attempted, formylation by Smith modification[8] of Duff reaction was found to be most promising because no inorganic reagent is required in the reaction, and preliminary experiments gave **1** and **2** in 58% and 32% yields, respectively. Other organic acids weaker than trifluoroacetic acid, except for methanesulfonic acid, gave only low yields. In the course of the study to optimize the reaction conditions it was found that the method of isolation of the products was also important factor and marked improvement of the yields could be attained by omission of neutralization of the reaction mixture. The results obtained under optimized conditions are summarized in Table 1. Formylation of dibenzo-18-crown-6 with excess reagents gave bis(4′-formylbenzo)-18-crown-6 (**3**) under similar reaction conditions. Methanesulfonic acid (98%) can be used in place of trifluoroacetic acid, but in certain cases it caused some problems in the isolation of the product due to the formation of emulsion, and led to a depressed yield.

One reason for lowering the yields in the conventional work-up containing neutralization of the excess acid is attributable to the increased solubility of sodium-crown ether complexes in aqueous phase. Another factor may be condensation of formylbenzocrown ethers during the repeated extractions from basic solution. The reasoning is based on the following observation that a mixture consisted of **1** and 4′-acetylbenzo-15-crown-5 in ethanolic sodium hydroxide gave 18% of 1,3-bis-[3′,4′-(1″,4″,7″,10″,13″-pentaoxacyclopentadeca-2″-ene)phenyl]-propen-1-one after 3 h stirring at room temperature, but after 4 h oily condensation product was the principal product.

Experimental

Materials. Benzo-15-crown-5, -18-crown-6, and dibenzo-18-crown-6 were obtained according to the procedure of Pedersen.[7] Commercial trifluoroacetic acid (99%), methanesulfonic acid (98%) and hexamethylenetetramine were used as received.

*4′-Formylbenzo-15-crown-5 (**1**).* A mixture of benzo-15-crown-5 (2.0 g, 7.5 mmol), trifluoroacetic acid (5.6 ml) and hexamethylenetetramine (1.1 g, 7.5 mmol) was stirred at 85—90 °C under nitrogen for 12 h. The reaction mixture was added to the concentrate and stirred for 1 h. The mixture was extracted with benzene, and the extract was dried ($MgSO_4$). Concentration of the benzene extract under vacuum gave yellow oil, which on cooling solidified to faint yellow crystals, 1.8 g (82%), mp 78.2—81.0 °C. The product could be further purified by either extraction with hot heptane or chromatography on a short alumina column (chloroform–methanol) to give white crystals, mp 80.0—81.5 °C (lit,[6] mp 78—79 °C). When methanesulfonic acid

Table 1. Formylation of benzocrown ethers

Crown (mmol)		Acid (ml)		Hexamine (mmol)	Temp / °C	Time / h	Yield / %
B15C5	7.5	CF_3CO_2H	5.6	7.5	85—90	12	82
	7.5	CH_3SO_3H	4.5	7.5	85—90	11	77
B18C6	7.5	CF_3CO_2H	5.6	7.5	85—90	24	86
	7.5	CH_3SO_3H	4.5	15.0	79—83	24	81
DB18C6	5.6	CF_3CO_2H	8.3	22	94—102	24	90[a]
	3.8	CH_3SO_3H	4.7	15	90—95	24	58[a]

a) 4′,4″-Diformyl-DB18C6.

was used, the reaction mixture was poured into ice-water and extracted with benzene or benzene-chloroform.

The formylation of benzo-18-crown-6 under similar conditions gave **2**, mp 61.3—62.8 °C (after the purification) (lit,⁶⁾ mp 60—62 °C). The structure of **1** and **2** were identified by comparisons (mixed-melting point) with authentic samples prepared by the method of Smid *et al.*⁶⁾

Formylation of dibenzo-18-crown-6 with **1** to 1.2 molar equivalent of hexamethylenetetramine gave a mixture of mono- and diformylated product along with the starting material. Use of excess amount of the amine afforded **3**, mp 231—233 °C. Found: C, 62.84; H, 5.77%. MS: *m/e*, 416, 169, 164, 163, 149. Calcd for $C_{22}H_{24}O_8$: C, 63.43; H, 5.76%.

References

1) Part I, F. Wada, R. Ishihara, Y. Kamohara, and T. Matsuda, *Bull. Chem. Soc. Jpn.*, **52**, 2959 (1979).

2) G. R. Brown and A. J. Foubister, *J. Med. Chem.*, **22**, 997 (1979).

3) E. M. Hyde, B. L. Shaw, and I. Shephered, *J. Chem. Soc., Dalton Trans.*, **1978**, 1696.

4) K. Kimura, H. Tamura, T. Tsuchida, and T. Shono, *Chem. Lett.*, **1979**, 611.

5) B. L. Shaw and I. Shephered, *J. Chem. Soc., Dalton Trans.*, **1978**, 1634.

6) R. Ungaro, B. El Haj, and J. Smid, *J. Am. Chem. Soc.*, **98**, 5198 (1976).

7) (a) W. W. Parish, P. E. Scott, and C. W. McCausland, *J. Org. Chem.*, **43**, 4577 (1978); (b) F. Wada and T. Matsuda, *Bull. Chem. Soc. Jpn.*, **53**, 421 (1980).

8) W. E. Smith, *J. Org. Chem.*, **37**, 3972 (1972).