Facile Synthesis of Hydroxymethylcrown Ethers

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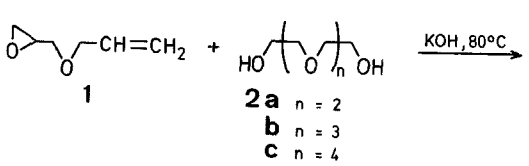
Since functional crown ethers are required to prepare bis-crown ethers, polymer-bound crown ethers, lipophilic phase transfer catalysts *etc.*[1-6], many derivatives of parent crown ethers and their synthetic methods have been reported. Among them, hydroxymethylcrown ethers are useful for these applications by modification via esterification or etherification, and several synthetic approaches have been proposed[7-16].

We previously presented two synthetic methods, which included the preparation of benzyloxymethylcrown ethers as the intermediates[13,15]. This communication deals with a more practical method for the preparation of hydroxymethylcrown ethers starting from commercially available allyl glycidyl ether and oligoethylene glycols.

Allyloxymethyl derivatives have fairly low boiling points compared to the corresponding benzyloxymethyl derivatives, and the allyl moiety can be easily deblocked from the protected products[17].

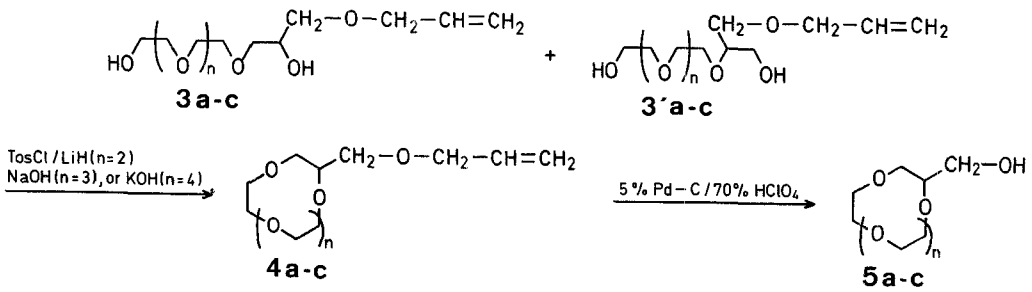


Allyloxymethyl oligoethylene glycols **3**, starting materials for the cyclization, were prepared by an improved method[13] in one step from allyl glycidyl ether **1** and oligoethylene glycols **2**. Although these are possibly composed of two isomers **3** and **3'**[13], they were used for the successive reaction without separation, since both isomers should afford the same substituted crown ether by intramolecular cyclization. Moreover, primary-secondary glycols show the same reactivity as those of primary-primary glycols in the cyclization[18].

Cyclization of the glycols **3** to allyloxymethylcrown ethers **4** was accomplished by the reported method[13,19] using potassium hydroxide, sodium hydroxide, and lithium hydride for the preparation of 18-crown-6, 15-crown-5, and 12-crown-4 derivatives, respectively.

Deblocking of allyloxymethylcrown ethers **4** was achieved by a one-pot process including the isomerization of allyl ether to 2-methylvinyl ether by palladium-on-carbon followed by acidic hydrolysis of the vinyl ether[17]. Although the reactivity in deblocking of benzyloxy derivatives having oligo(oxyethylene) moiety is different from those of usual benzyloxy derivatives[13,15], the deblocking of allyloxy compounds by this method proceeds smoothly irrespective of the kind of allyloxy substrate used, as briefly reported[16].

Thus, the emphasis of this study is the demonstration of a new synthetic methodology for the preparation of functionalized crown ethers **5** in fewer steps utilizing easy-to-handle, allyloxymethyl compounds **4** as intermediates.



The compounds prepared showed a single peak in G.L.C. (Shimadzu GC-8APF; 5% Silicon OV-1 on 60–80 mesh Uniport KS glass column, 2.6 mm × 2 m; 200 to 300 °C), thus attesting their purity.

Allyloxymethylpentaethylene Glycol (3b); Typical Procedure:
Potassium hydroxide (1.12 g, 0.02 mol) is dissolved in tetraethylene glycol (**2b**; 58.2 g, 0.3 mol) under stirring at 80 °C. To the resulting wine-red solution, allyl glycidyl ether (**1b**; 14.0 g, 0.1 mol) is added dropwise over a period of 1 h at the same temperature, and stirred for 1 h. After cooling to room temperature, the solution is neutralized with dilute sulfuric acid (0.6 ml of 95% sulfuric acid, diluted with 10 ml of water). The slightly basic solution obtained is fractionally distilled using a Vigreux column without the separation of the salt formed to give G.L.C.-pure **3b** as a colorless oil; yield: 23.0 g (75%); b.p. 160–174 °C/0.005 torr; (Ref.[13], b.p. 160 °C/0.03 torr, molecular distillation).

Allyloxymethyltetraethylene Glycol **(3a):** yield, 72%; b.p. 138–151 °C/0.01 torr (Ref.[13], b.p. 160 °C/0.03 torr, Kugelrohr distillation).

Allyloxymethylhexaethylene Glycol **(3c):** yield, 60%; b.p. 175–201 °C/0.005 torr (Ref.[16], b.p. 140 °C/0.003 torr, molecular distillation).

[(Allyloxy)-methyl]-12-Crown-4 (4a):
To a refluxing suspension of pulverized lithium hydride (3.2 g, 0.4 mol) in dioxan (300 ml) containing a small portion of **3a** (1.3 g, 0.005 mol), a mixture of **3a** (25.1 g, 0.095 mol) and *p*-toluenesulfonyl chloride (18.1 g, 0.095 mol) dissolved in dioxan (200 ml) is added dropwise

over a period of 10 h, and then *p*-toluenesulfonyl chloride (2.0 g, 0.01 mol) dissolved in dioxan (20 ml) is added over a period of 2 h. After refluxing for 4 h, methanol (20 ml) is added to quench the unreacted lithium hydride. The reaction system is cooled and neutralized with dilute sulfuric acid (15 ml of 95% sulfuric acid diluted with 5.3 ml of water). The solvent is evaporated as completely as possible at reduced pressure, and the residual viscous slurry is extracted with dichloromethane (80 ml). After removal of the solvent, the resulting yellow oil (25.5 g) is mixed with pulverized boron trioxide (0.7 g), and fractionally distilled using a Vigreux column to give G.L.C.-pure **4a**: 11.0 g (45%); b.p. 98–99°C/0.08 torr.

$C_{12}H_{22}O_5$	calc.	C 58.52	H 9.00
(246.31)	found	58.13	9.02

[(Allyloxy)-methyl]-15-crown-5 **(4b)** and *[(Allyloxy)-methyl]-18-crown-6* **(4c)** are prepared from **3b** and **3c** using sodium hydroxide and potassium hydroxide, respectively, using a reported method[13].

4b: yield, 58%; b.p. 135–143°C/0.01 torr (Ref.[13], b.p. 100°C/0.001 torr, Kugelrohr distillation).

4c: yield, 66%, b.p. 150°C/0.002 torr (Kugelrohr distillation); (Ref.[16], b.p. 130°C/0.002 torr, molecular distillation).

(Hydroxymethyl)-15-Crown-5 (5b); Typical Procedure for Deblocking of Allyloxymethylcrown Ethers 4 to 5:

To a suspension of perchloric acid (70%, 1 ml) and 5% palladium-on-carbon (2.5 g) in water/ethanol (1:1, 100 ml), **4b** (20.3 g, 0.07 mol) is added, dissolved, and heated for 24 h at 80°C. The completion of conversion of **4b** to **5b** is confirmed by G.L.C. After neutralization with aqueous sodium hydroxide, the catalyst is removed by filtration on a short column of silica gel and the solvent evaporated. The amber oil obtained is mixed with sodium carbonate (50 mg) and is fractionally distilled to give **5b** as a colorless oil; yield: 14.4 g (80%); b.p. 107°C/0.04 torr (Ref.[13], b.p. 113°C/0.01 torr, Kugelrohr distillation).

(Hydroxymethyl)-12-crown-4 **(5a)**: yield, 90%; b.p. 98°C/0.04 torr (Ref.[13], b.p. 115°C/0.04 torr, Kugelrohr distillation).

(Hydroxymethyl)-18-crown-6 **(5c)**: yield, 79%; b.p. 110°C/0.03 torr (Ref.[16], b.p. 120°C/0.03 torr).

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