



# Utilization of the hydroxyalkylation reaction to prepare bis(benzocrown ethers)

Matthew E. Zielinski, Adam F. Tracy, Douglas A. Klumpp\*

Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, IL 60115, United States

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## ABSTRACT

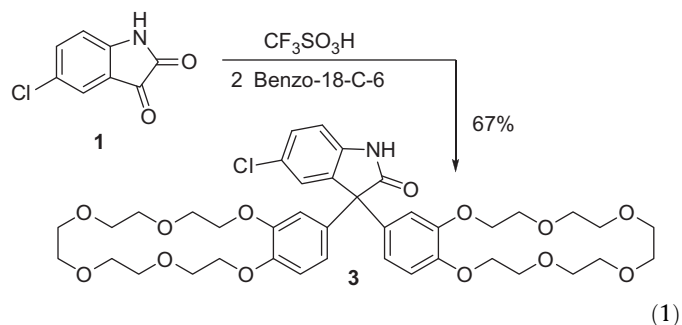
The hydroxyalkylation reaction has been used to condense benzocrown ethers with various aldehydes and ketones. The condensation reactions are catalyzed by triflic or sulfuric acid. The products from the reactions are bis(benzocrown ethers) and they are formed in good yields (42–98%, 13 examples).

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Since their discovery by Pederson in 1967, crown ethers and related substances have been useful in a variety of applications.<sup>1</sup> Their abilities to complex metal cations have made them useful as ionophores, phase transfer catalysts, and components in ion-selective electrodes.<sup>2</sup> Because of the many applications of crown ethers and functionalized derivatives, there continues to be a need for new synthetic methods leading to crown ether products. Benzocrown ethers may be considered activated, electron rich arenes. As such, functionalized benzocrown ethers may be readily prepared using Friedel–Crafts type chemistry.<sup>3</sup> We and others have recently demonstrated that the hydroxyalkylation condensation is an outstanding synthetic method leading triarylmethanes,<sup>4</sup> functionalized heterocycles,<sup>5</sup> and condensation polymers.<sup>6</sup> The hydroxyalkylation reaction typically involves the condensation of an aldehyde or ketone with activated aromatic compounds, such as aryl ethers or phenols.<sup>7</sup> Less reactive arenes may also form condensation products if the aldehyde or ketone generates highly electrophilic intermediates. In the following manuscript, we describe our studies involving the hydroxyalkylation reaction with benzocrown ethers leading to the preparation of bis(benzocrown ether) products.

Our initial studies involved reacting a series of aldehydes and ketones with benzo-18-crown-6 in the presence of the Brønsted superacid, CF<sub>3</sub>SO<sub>3</sub>H (Eq. 1 and Table 1). For example, 5-chloroisatin (1) is reacted with benzo-18-crown-6 (2) in CF<sub>3</sub>SO<sub>3</sub>H and the condensation product 3 is formed in a good yield (Eq. 1). The reaction is best done with an excess of CF<sub>3</sub>SO<sub>3</sub>H (8 equiv). Analysis

of the crude mixture by NMR reveals very high regioselectivity in the reaction with benzo-18-crown-6 (2).



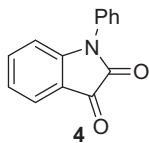
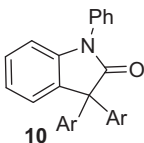
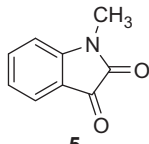
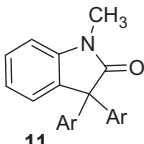
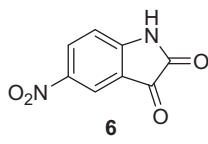
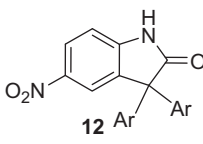
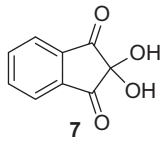
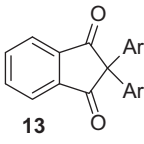
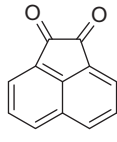
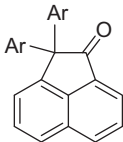
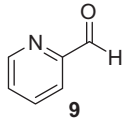
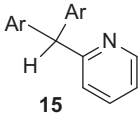
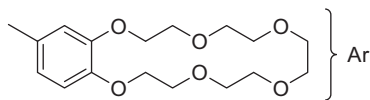
Other isatins (4–6) likewise give the condensation products (10–12) in reactions with benzo-18-crown-6 (2). Ninhydrin (7) reacts efficiently with arenes at the 2-position, so condensation with compound 2 gives product 13 in a good yield. In this case, H<sub>2</sub>SO<sub>4</sub> is superior to CF<sub>3</sub>SO<sub>3</sub>H in promoting the condensation. The quinone 8 also provides a bis(benzocrown ether) product (14), as does the heterocyclic aldehyde (9). Condensation reactions were also accomplished with benzo-15-crown-5 (22) and benzo-12-crown-4 (23, Table 2).

Superacid-promoted hydroxyalkylations have been utilized in several types of condensations leading to macromolecules.<sup>6</sup> Recently, Zolotukhin and co-workers described the hydroxyalkylation reaction of isatin with a series of dibenzocrown ethers using methanesulfonic acid and P<sub>2</sub>O<sub>5</sub> as an acid catalyst.<sup>8</sup> By the utilization of dibenzo-18-crown-6 and triflic acid, we have accomplished similar condensations to prepare crown-containing

\* Corresponding author. Tel.: +1 815 753 1959; fax: +1 815 753 4802.

E-mail address: [dklumpp@niu.edu](mailto:dklumpp@niu.edu) (D.A. Klumpp).

**Table 1**  
Acid-catalyzed reactions of carbonyl compounds (**4–9**) with benzo-18-crown-6 (**2**)

Starting material	Product	Yield (%)
 <p><b>4</b></p>	 <p><b>10</b></p>	55 <sup>a</sup>
 <p><b>5</b></p>	 <p><b>11</b></p>	68 <sup>a</sup>
 <p><b>6</b></p>	 <p><b>12</b></p>	97 <sup>a</sup>
 <p><b>7</b></p>	 <p><b>13</b></p>	72 <sup>b</sup>
 <p><b>8</b></p>	 <p><b>14</b></p>	98 <sup>a</sup>
 <p><b>9</b></p>	 <p><b>15</b></p>	65 <sup>a</sup>
		

<sup>a</sup> Reaction with 2.0 equiv (**2**), 8 equiv TfOH, CHCl<sub>3</sub>, 25 °C.

<sup>b</sup> Reaction with 2.0 equiv (**2**), 8 equiv H<sub>2</sub>SO<sub>4</sub>, CHCl<sub>3</sub>, 25 °C.

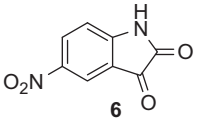
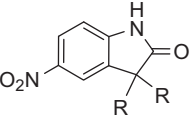
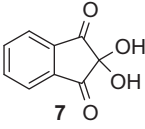
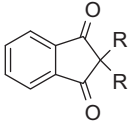
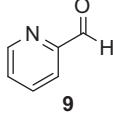
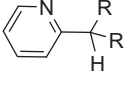
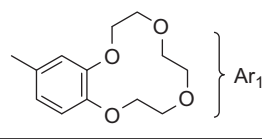
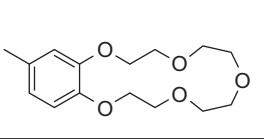
macromolecules (Scheme 1). Reaction of isatin **5** leads to the A<sub>2</sub>B<sub>2</sub>-type condensation polymer **24**, a hard off-white solid which softens at about 170 °C.

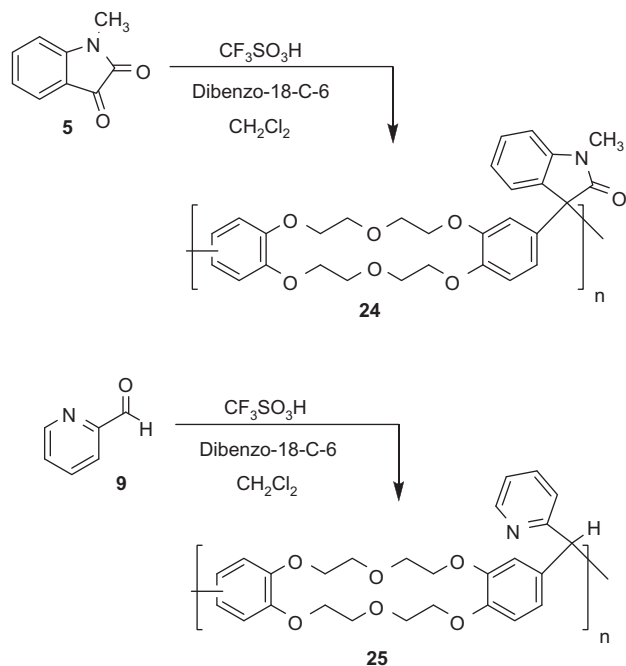
A similar condensation was accomplished with 2-pyridinecarboxaldehyde (**9**) to give the macromolecule **25**. Poor solubility in organic solvents prevented GPC analysis of polymers **24** and **25**, however NMR analysis could be accomplished by dissolving the polymers in CF<sub>3</sub>CO<sub>2</sub>D.<sup>9</sup> For structure **24**, the <sup>1</sup>H NMR spectrum is consistent with the presence of both oxyindole and crown ether structures. Further analysis was done by infrared spectroscopy,<sup>11</sup> comparing the carbonyl absorption bands of compound **5** and the polymeric product. *N*-Methylisatin exhibits strong absorption bands at 1727 and 1604 cm<sup>-1</sup>, respectively, for the ketone and

amide-type carbonyl groups. Analysis of the polymer **24** shows single carbonyl absorption at 1684 cm<sup>-1</sup>. This is consistent with the formation of a condensation polymer, because entrapped or unreacted isatin **5** would exhibit two carbonyl absorptions. Likewise, polymer **25** shows no absorptions in the carbonyl region of the infrared spectrum.<sup>9</sup> As noted previously by Zolotukhin, the condensation reactions with dibenzo-18-crown-6 likely produces the pair of regioisomeric repeat units (electrophilic attack at the 4,4' positions and at the 4,5' positions of the dibenzo-18-crown-6).

In summary, we have found that hydroxyalkylation reactions can lead to products having two benzocrown units.<sup>10</sup> These conversions are effectively promoted by triflic acid and in some cases sulfuric acid. With a variety of electrophilic systems, good regiose-

**Table 2**  
Condensations with benzo-15-crown-5 and benzo-12-crown-4

Starting material	Product	Yield
 6	 16, R = Ar <sub>1</sub> 95% 19, R = Ar <sub>2</sub> 92%	
 7	 17, R = Ar <sub>1</sub> 77% 20, R = Ar <sub>2</sub> 65%	
 9	 18, R = Ar <sub>1</sub> 49% 21, R = Ar <sub>2</sub> 94%	
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">   Ar<sub>1</sub> </div> <div style="text-align: center;">   Ar<sub>2</sub> </div> </div>		



**Scheme 1.**

lectivities are observed in these conversions. Bis(benzocrown ethers) are useful in a variety of applications and this chemistry provides ready access to these systems. In addition to the bis(benzocrown ether) products, we have found that macromolecules can be produced by hydroxyalkylation with dibenzo-18-crown-6 as a substrate.

## Acknowledgment

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## Supplementary data

Supplementary data (NMR spectra of products) associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2012.01.049](https://doi.org/10.1016/j.tetlet.2012.01.049).

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9. *Data for polymeric products*. **24**:  $^1\text{H}$  NMR ( $\text{CF}_3\text{CO}_2\text{D}$ , 300 MHz):  $\delta$  = 3.15–3.22, 3.60–3.90, 3.95–4.05, 6.50–6.64, 6.67–6.75, 6.75–6.88, 7.00–7.14, 7.24–7.38. IR: 2914, 2871, 1719, 1520, 1255, 1123, 750, 639  $\text{cm}^{-1}$ . **25**:  $^1\text{H}$  NMR ( $\text{CF}_3\text{CO}_2\text{D}$ , 300 MHz):  $\delta$ , 3.4–3.8, 5.44 and 5.46, 6.10–6.12, 6.36–6.43, 7.15–7.20, 7.34–7.37, 7.93–7.95, 8.05–8.09. IR: 2855, 1506, 1249, 1118, 1052, 944, 751  $\text{cm}^{-1}$ .
10. *General procedure*: The carbonyl substrate (0.1 g) is dissolved in 1–2 mL of anhydrous  $\text{CHCl}_3$  and 2.0 equiv of a benzocrown ether is added to the solution. To this mixture,  $\text{CF}_3\text{SO}_3\text{H}$  (8.0 equiv;  $\text{H}_2\text{SO}_4$  may be used in some cases) is added dropwise with stirring. The reaction is stirred at room temperature for at least 2 h, after which, the mixture is poured over several grams of ice. The resulting solution is extracted three times with  $\text{CHCl}_3$ . The organic phase is subsequently washed three times with water and dried over  $\text{MgSO}_4$  solution. Removal of the solvent provides the product.