



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

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ABSTRACT

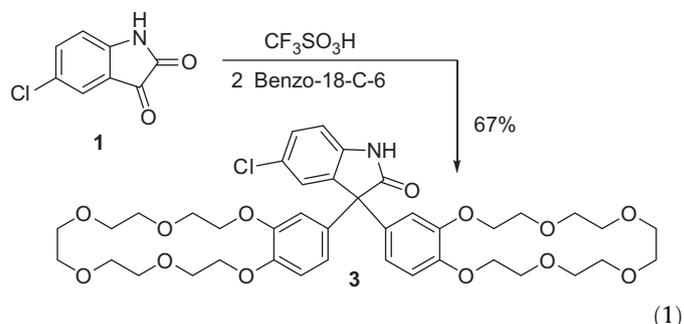
The hydroxyalkylation reaction has been used to condense benzocrown ethers with various aldehydes and ketones. The condensation reactions are catalyzed by triflic or sulfuric acid. The products from the reactions are bis(benzocrown ethers) and they are formed in good yields (42–98%, 13 examples).

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Since their discovery by Pederson in 1967, crown ethers and related substances have been useful in a variety of applications.¹ Their abilities to complex metal cations have made them useful as ionophores, phase transfer catalysts, and components in ionselective electrodes.² 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.³ We and others have recently demonstrated that the hydroxyalkylation condensation is an outstanding synthetic method leading triarylmethanes,⁴ functionalized heterocycles,⁵ and condensation polymers.⁶ The hydroxyalkylation reaction typically involves the condensation of an aldehyde or ketone with activated aromatic compounds, such as aryl ethers or phenols.⁷ 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, CF₃SO₃H (Eq. 1 and Table 1). For example, 5-chloroisatin (1) is reacted with benzo-18-crown-6 (2) in CF₃SO₃H and the condensation product 3 is formed in a good yield (Eq. 1). The reaction is best done with an excess of CF₃SO₃H (8 equiv). Analysis

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



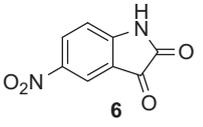
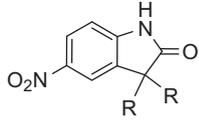
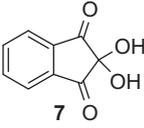
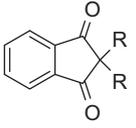
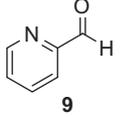
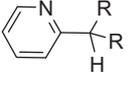
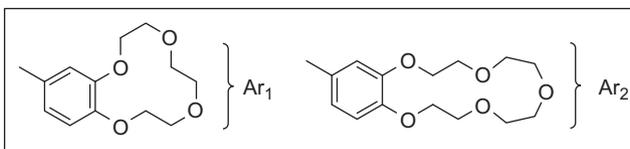
Other isatins (4–6) likewise give the condensation products (10–12) in reactions with benzo-18-crown-6 (2). Ninhydrin (7) reacts efficiently with arenes at the 2-position, so condensation with compound 2 gives product 13 in a good yield. In this case, H₂SO₄ is superior to CF₃SO₃H in promoting the condensation. 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).

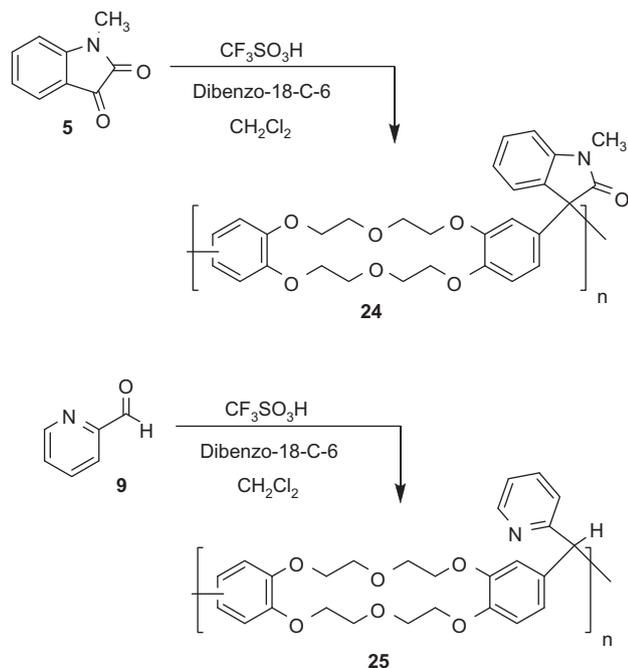
Superacid-promoted hydroxyalkylations have been utilized in several types of condensations leading to macromolecules.⁶ Recently, Zolotukhin and co-workers described the hydroxyalkylation reaction of isatin with a series of dibenzocrown ethers using methanesulfonic acid and P₂O₅ as an acid catalyst.⁸ By the utilization of dibenzo-18-crown-6 and triflic acid, we have accomplished similar condensations to prepare crown-containing

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

| Starting material | Product | Yield |
|---|---|--|
|  |  | 16 , R = Ar ₁ 95% 19 , R = Ar ₂ 92% |
|  |  | 17 , R = Ar ₁ 77% 20 , R = Ar ₂ 65% |
|  |  | 18 , R = Ar ₁ 49% 21 , R = Ar ₂ 94% |
|  | | |



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.

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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): δ = 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 cm^{-1} . **25**: $^1\text{H NMR}$ ($\text{CF}_3\text{CO}_2\text{D}$, 300 MHz): δ , 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 cm^{-1} .
10. *General procedure*: The carbonyl substrate (0.1 g) is dissolved in 1–2 mL of anhydrous 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; H_2SO_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 CHCl_3 . The organic phase is subsequently washed three times with water and dried over MgSO_4 solution. Removal of the solvent provides the product.