Pergamon

Tetrahedron Letters, Vol. 37, No. 13, pp. 2213-2216, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00255-9

Synthesis of New Dibenzo-diaza-crown Ethers

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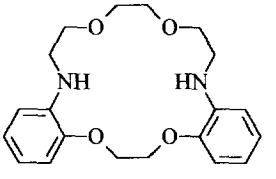
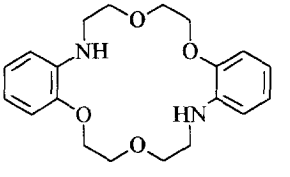
Abstract: A new method for the synthesis of dibenzo-diaza-crown ethers involving the 1:1-cyclocondensation of α,ω-contrafunctional amines is reported.

Diaza-crown ethers are very useful building blocks for the synthesis of cryptands. The chemistry of these compounds has been widely reviewed.[1] Because of the ability of these macrocyclic ligands to bind cations with high selectivity, they are of potential interest in analytical chemistry. A disadvantage of diaza-crown ethers, as compared with crown ethers, is the fact that their nitrogen atoms act as proton acceptors, since protonation competes with cation coordination. Consequently, the scope of applications in aqueous solution of these compounds is normally restricted to high pH values, because at neutral pH their cation affinities are markedly reduced due to protonation.[2] Benzoannellation yielding aniline type nitrogens should result in a substantial decrease of basicity. This concept has been realized in the macrocycle **1**.[3] We decided to synthesize the benzoannellated crown ether **2**, because this macrocycle is expected to be more flexible than **1** and therefore it should be able to take up an optimal conformation for cation complexation.

Cyclocondensation reactions are standard methods in benzo-aza-crown ether synthesis.[1] While condensation reactions involving compounds with intermolecular contrafunctionality are well established, there are only a few examples for the application of condensation reactions employing compounds bearing intramolecular contrafunctionality[4,5] and in these cases C_3-fragments have been attached to the nitrogen atoms. We describe here a new synthetic method for the preparation of dibenzo-diaza crown ethers with aniline moieties by 1:1-cyclocondensation of ω-iodo-2-amino-phenols. As a typical example we report the synthesis of the macrocycle **2**.



1



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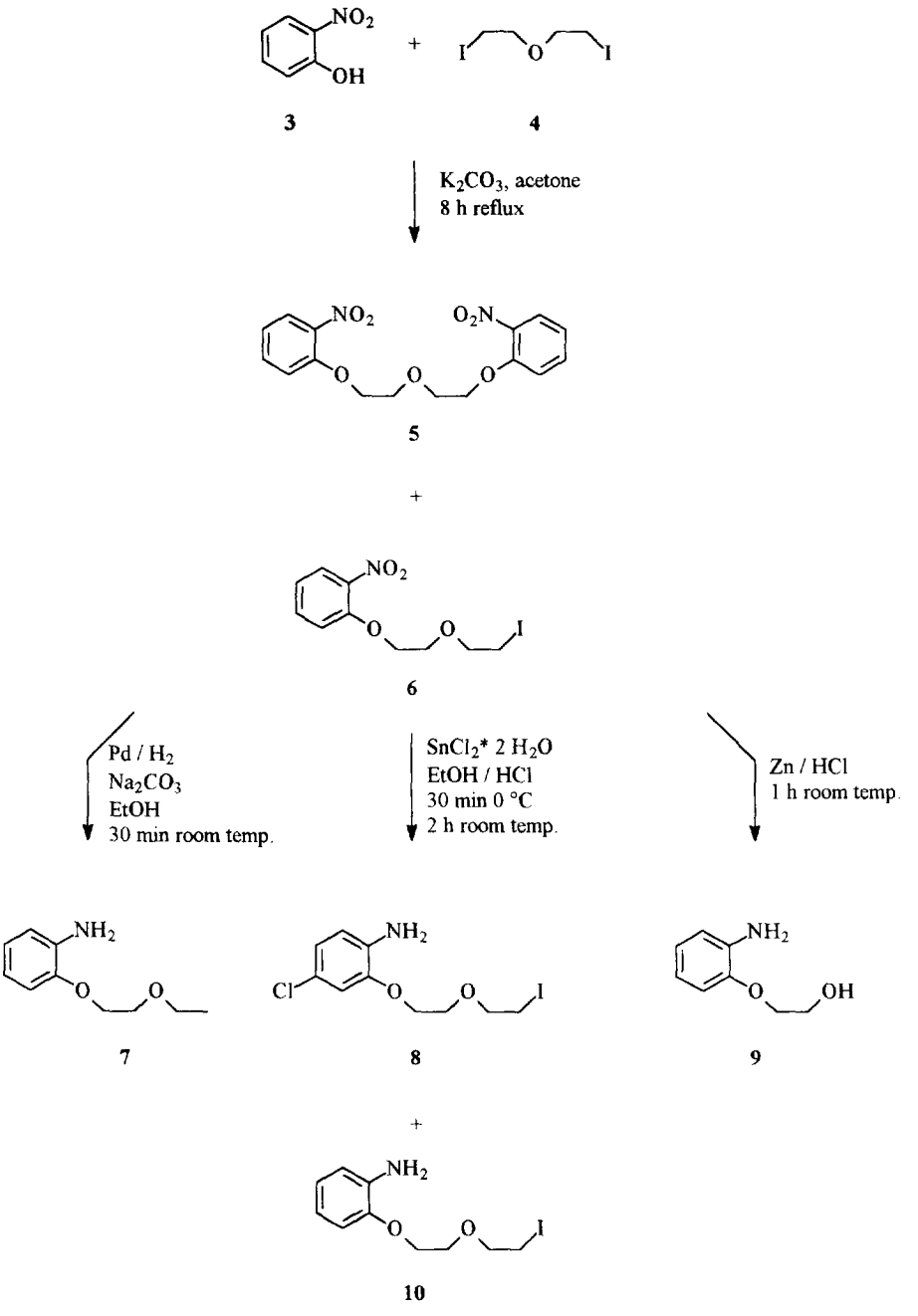
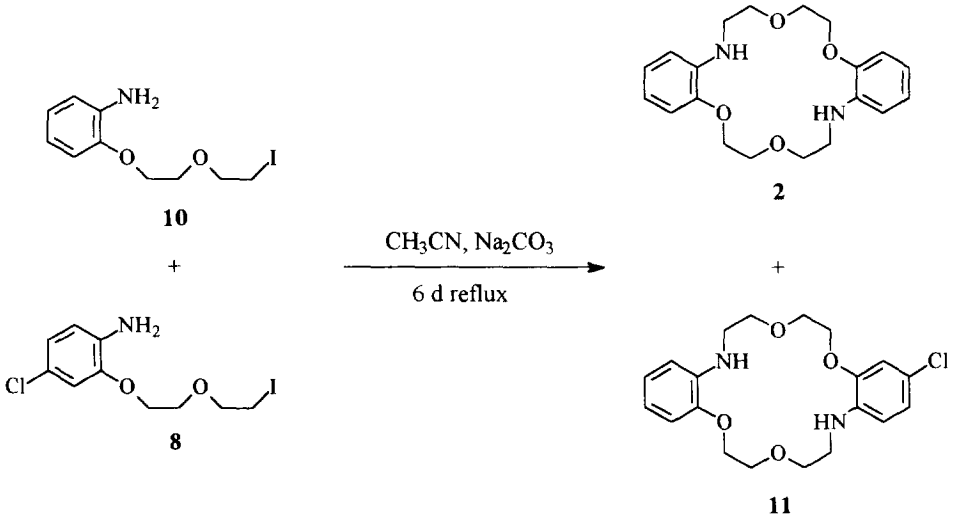


Scheme 1: Synthesis of the α,ω-contrafunctional amine **10**

Starting from 2-nitrophenol **3** the macrocyclic diamine **2** is synthesized in a three step procedure. First **3** is converted to the acyclic ether **6** by reaction with a five-fold excess of bis-(2-iodoethyl)-ether **4** in the presence of K_2CO_3 (acetone, 8 h reflux). Purification of the crude product by silicagel chromatographpy with CH_2Cl_2 leads to the isolation of the desired iodo-alkane **6** (83%, yellow oil) as well as bis-(2-(2-nitrophenoxy)-ethyl)ether (**5**) (5%, m.p. 56-58 °C). The reduction of **6** to the contrafunctional amine **10** represents the key step of this synthesis. After reduction of **6** with Pd/H_2 in ethanol at room temperature only complex product mixtures are isolated. If the reduction with Pd/H_2 is carried out in the presence of Na_2CO_3 (30 h room temp.), the amine 7 is obtained in 72% yield (colourless oil), whereas the use of zinc in concentrated hydrochloric acid as reducing agent leads to the formation of the alcohol **9** (56%, m.p. 85-86 °C). The reduction of the ether **6** to the contrafunctional amine **10** can be achieved with $SnCl_2$ * 2 H_2O under acidic conditions (37% HCl/EtOH 1:1; 30 min 0 °C, 2 h room temp.), but chlorination of the benzene moiety is observed as a side reaction (10% acc. to ^1H NMR, as estimated from the integration of the corresponding ^1H NMR signals of the aromatic protons using the separated doublet at δ = 6.63 ppm, assigned to **8**, as reference signal). Because of the low stability of the amines **8** and **10** the crude product is used without any further purification. The 1:1-cyclocondensation of **10** (contaminated with **8**) is carried out in acetonitrile with Na_2CO_3 as template base (6 d reflux). After silicagel column chromatography with CH_2Cl_2/MeOH (50:1) the dibenzo-diaza macrocycles **2** and **11** are isolated in 15% and 6% yield referring to **6**.



Scheme 2: Synthesis of dibenzo-diaza-crown ethers

All new compounds have been characterized by combustion analyses (except **8** and **10**), ^{1}H and ^{13}C NMR spectroscopy. The structures of macrocycles **2** and **11** are consistent with the results of FAB-MS spectroscopy. The substitution pattern of the macrocycle **11** has been confirmed by ROESY spectroscopy.[6]

We have been able to demonstrate that the 1:1-cyclocondensation of α,ω-contrafunctional amines is a suitable method for the synthesis of dibenzo-diaza-crown ethers with aniline type nitrogen atoms. These macrocycles are expected to act as useful building blocks for the synthesis of new cryptands with special features such as photocleavable cryptates for cation concentration jump experiments.[7] Because of the expected decrease of the basicity of their bridgehead nitrogens, such cryptands are assumed to exhibit high affinities to cations in aqueous solution at neutral pH.

Acknowledgement

We are grateful to A.M. Albrecht-Gary and G. Quinkert for helpful discussions. B. Gersch thanks the Fonds der Chemischen Industrie for a Kekulé grant.

References and Notes

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6. ^{1}H NMR of **11** ($CDCl_3$, 250 MHz): δ = 3.27 - 3.34 (m; 4H, CH_2-N), 3.79 -3.88 (m; 8H, CH_2O), 4.08 - 4.05 (m; 4H, C*H2*-OPh), 4.73 (s; 2H, N*H*), 6.47 (d, ^{3}J = 8.4 Hz; 1H, H_{ar}), 6.59 - 6.72 (m; 4H, H_{ar}), 6.75 - 6.92 (m; 2H, H_{ar}). In the ROESY spectrum of **11** the doublet at 6.47 ppm shows a significant contact with the multiplet at 3.27 - 3.34 ppm.
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(*Received in Germany* 11 *January* 1995; *accepted* 5 *February* 1996)