Synthesis of Macropolycycles Comprising Diazacrown and Adamantane Moieties via Pd–Catalyzed Amination Reaction

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N,N’-bis(bromobenzyl) substituted diazacrown ethers were obtained in the reactions of corresponding free diazacrown with two equivalents of bromobenzyl bromides in high yields. These compounds were introduced in the Pd-catalyzed amination reaction with 1,3-bis(aminomethyl) and 1,3-bis(2-aminomethyl) adamantanes to give macrobicyclic products. The yields were shown to be dependent on the nature of starting diazacrown derivatives and diamines. N,N’-bis(3-bromobenzyl) substituted diazacrown ethers provided better yields of the target macrobicycles than N,N’-bis(4-bromobenzyl) derivatives. In the latter case substantial amounts of cyclic oligomers were formed and isolated.

Keywords: Diazacrown ethers, macropolycycles, palladium-catalyzed amination, adamantane.

Синтез макрополициклов с фрагментами диазакрауна и адамантана с помощью реакции Pd–катализируемого аминирования

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N,N’-бис(бромбензил)замещенные диазакраун-эфиры были получены с высокими выходами по реакции соответствующих диазакраун-эфиров с двумя эквивалентами бромбензилбромидов. Данные соединения были введены в реакции палладий-катализируемого аминирования с 1,3-бис(аминометил) и 1,3-бис(2-аминометил) адамантанами в образовании макробициклических продуктов. Показано, что выходы зависят от природы производных диазакраун-эфиров и диаминов. N,N’-бис(3-бромбензил)замещенные диазакраун-эфиры обеспечивают более высокие выходы целевых макробициклических, чем N,N’-бис(4-бромбензил) замещенные изомеры. При использовании последних образовались значительные количества циклических олигомеров.

Ключевые слова: Диазакраун-эфиры, макрополициклы, палладий-катализируемое аминирование, адамантан.
Introduction

During last three decades various synthetic approaches were elaborated for the synthesis of polymacrocyclic compounds comprising two or more crown and azacrown ether moieties. In particular, bis(azacrown) ethers with isolated macrocycles linked via aliphatic bridges were described,[10] as well as the molecules with spiro-conjugated macrocycles,[11] and with condensed macro rings possessing saturated and unsaturated cyclic spacers.[12] The majority of known bis(azacrown) ethers possess two macrocyclic units which are symmetrically arranged around the aromatic,[4,13]

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mg, 8-16 mol%), diphenylsphogene ligand BINAP or DavePhos (9-18 mol%), and absolute dioxane (12 ml). The mixture was stirred for several min, then appropriate diamine 7a,b (0.25 mmol) and BuONa (72 mg, 0.75 mmol) were added, and the reaction mixture was refluxed for 24-30 h. After the reaction was complete, the mixture was cooled, filtered, the residue was washed with CH2Cl2, the combined organic solvents were evaporated in vacuo, the residue was dissolved in CH2Cl2 (5 ml), washed with water (3-10 ml), aqueous phase was washed with CH2Cl2 (3-15 ml). Combined organic phases were dried over molecular sieves 4 Å, the solvent evaporated in vacuo, and the residue chromatographed on silica gel using a sequence of eluents: CH2Cl2, CH2Cl2-MeOH-CH3OH-Me2CO 25:1-3:1, MeOH-CH3OH-NH3(aq) 100:20:1 (4:1).

28, 31, 34-Trioxo-1,8,18,25-tetraazaheptacyclo[23.8.5.4.1.1.0.1.4.0.10.1.6.0.12.1.8.0.27.1.5.0.1.10.1]tritreatraconta-3(4),6(4),19(39),20,22-hexaene (8a). Obtained from compound 3 (139 mg, 0.25 mmol), diamine 7a (49 mg, 0.25 mmol) in the presence of Pd(db)2 (23 mg, 16 mol%) and DavePhos (18 mg, 18 mol%). Eluent CH2Cl2-MeOH 10:1 – 5:1. Yield 50 mg (34 %), yellow glassy compound. (MALDI-TOF) found: 589.4072. C72H105N8O6 requires 589.4117 [M+H]+. 1H NMR (CDCl3, 298 K) δ ppm: 1.38-1.57 (8H, m, H-A), 1.62-1.68 (4H, m, H-A), 2.08 (2H, brs, H-Ad), 2.78 (4H, s, CHNH2), 2.84 (8H, brs, CHN), 5.35-5.65 (12H, m, CH2Ar, CH2NAr), 3.65 (4H, t, J = 5.5 Hz, OCH2), 6.41 (2H, d, J = 7.6 Hz, H4-Ar or H6-Ar), 6.43 (2H, d, J = 7.1 Hz, H6-Ar or H4-Ar), 6.97 (2H, brs, H-Ar), 7.01 (2H, t, J = 7.5 Hz, H5-Ar), NH protons were not assigned. 13C NMR (CDCl3, 298 K) δ ppm: 28.5 (2C, C-Ad), 35.4 (2C, C-Ad), 36.8 (1C, CH2Ad), 40.4 (4C, CH2Ad), 42.3 (1C, CHAd), 52.3 (2C, CH2NAr), 50.2 (2C, CHN), 51.5 (2C, CH2N), 57.0 (3C, CH2N), 68.8 (2C, CH2), 69.2 (2C, CH), 69.9 (2C, CH2), 110.9 (2C, CH-Ar), 112.7 (2C, CH-Ar), 116.6 (2C, CH-Ar), 128.7 (2C, C5-Ar), 140.5 (2C, C1-Ar), 149.5 (2C, C3-Ar).

30, 31, 33, Hexa-1,8,17,20,27-tetraazaheptacyclo[23.8.5.4.1.1.0.1.4.0.10.1.6.0.12.1.8.0.27.1.5.0.1.10.1]hexatetraconta-3(8),4(4),6(21),4(4),24-hexaene (10b). Obtained from compound 4 (150 mg, 0.25 mmol), diamine 7b (56 mg, 0.25 mmol) in the presence of Pd(db)2 (12 mg, 8 mol%) and BINAP (14 mg, 9 mol%). Eluent CH2Cl2-MeOH 1:1 – 10:9. Yield 89 mg (54 %), yellow glassy compound. (MALDI-TOF) found: 661.4720. C72H105N8O6 requires 661.4693 [M+H]+. 1H NMR (CDCl3, 298 K) δ ppm: 1.39 (2H, brs, H-A), 1.40-1.44 (4H, m, AdCH2), 1.51 (8H, brs, H-A), 1.63 (2H, brs, H-A), 2.05 (2H, brs, H2-Ar), 2.81 (8H, brs, CHN), 3.12-3.16 (4H, m, CH2NAr), 3.58-3.63 (2OH, m, CH2, ArCH2N), 6.44 (2H, dd, J = 8.0 Hz, H6-Ar, H5-Ar), 6.54 (2H, brd, J = 6.7 Hz, H4-Ar), 6.75 (2H, brs, H2-Ar), 7.03 (2H, t, J = 7.7 Hz, H5-Ar), NH protons were not assigned. 13C NMR (CDCl3, 298 K) δ ppm: 29.0 (2C, CH2Ad), 32.8 (2C, CAd), 36.6 (1C, CH2Ad), 42.6 (4C, CH2Ad), 47.2 (1C, CHAd), 54.1 (2C, CHAd), 70.0 (4C, CH2), 70.4 (4C, CH2), 110.6 (4C, CH-Ar), 134.6 (4C, CH-Ar), 117.3 (4C, CH-Ar), 125.8 (5C, C5 Ar), 140.8 (5C, C1 Ar), 148.5 (4C, C3 Ar).

28, 29, 34-Tetraoxo-1,8,16,23-tetraazaheptacyclo[23.8.5.4.1.1.0.1.4.0.10.1.6.0.12.1.8.0.27.1.5.0.1.10.1]hexatetraconta-3(8),4(4),6(21),4(4),24-hexaene (11a). Obtained from compound 5 (139 mg, 0.25 mmol), diamine 7a (49 mg, 0.25 mmol) in the presence of Pd(db)2 (23 mg, 16 mol%), and DavePhos (18 mg, 18 mol%). Eluent CH2Cl2-MeOH-NH3(aq) 100:20:1. Yield 16 mg (12 %). Yellow glassy compound. (MALDI-TOF) found: 611.4143. C72H105N8O6 requires 611.4183 [M+H]+. 1H NMR (CDCl3, 298 K) δ ppm: 1.39-1.66 (12H, m, H-A), 2.10 (2H, brs, H2-Ar), 2.70-2.82 (2H, m, CHN), 2.84 (4H, s, CH2NAr), 3.50 (4H, s, CH2O or ArCH2N), 3.55-3.63 (8H, m, CH2O or CH2O, ArCH2N), 3.69 (4H, t, J = 5.1 Hz, CH2O), 6.48 (4H, d, J = 8.5 Hz, H3-Ar, H3'-Ar), 7.14 (4H, d, J = 8.5 Hz, H2-Ar, H2'-Ar), NH protons were not assigned. 13C NMR (CDCl3, 298 K) δ ppm: 28.5 (2C, CH2Ad), 34.8 (4C, CH2Ad), 35.4 (2C, C-Ad), 42.0 (4C, CH-Ad), 42.0 (4C, CH-Ad), 42.0 (4C, CH-Ad), 47.7 (1C, CH-Ad), 54.1 (2C, CHN), 55.4 (2C, CHN), 61.1 (2C, ArCH2), 70.4 (2C, CHO), 70.7 (4C, CHO), 111.3 (2C, C6-Ar), 113.3 (2C, C4-Ar), 117.5 (2C, C2-Ar), 128.6 (2C, C5-Ar), 141.2 (2C, C1-Ar), 148.5 (2C, C3-Ar).

28, 31, 33, Hexa-1,8,17,20,27-tetraazaheptacyclo[23.8.5.4.1.1.0.1.4.0.10.1.6.0.12.1.8.0.27.1.5.0.1.10.1]hexatetraconta-3(8),4(4),6(21),4(4),24-hexaene (12a). Obtained as the second product in the synthesis of compound 11a. Eluent CH2Cl2-MeOH-NH3(aq) 100:20:1. Yield 16 mg (12 %). Yellow glassy compound. (MALDI-TOF) found: 611.4143. C72H105N8O6 requires 611.4183 [M+H]+.
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NMR (CDCl3, 298 K) δ ppm: 1.39-1.66 (24H, m, H-Ad), 2.10 (4H, brs, H-Ad), 2.70-2.83 (24H, m, CH3-CH2NAr), 3.54 (8H, s, CH2O or ArCH2N), 3.55-3.63 (24H, m, CH2O, ArCH2N), 6.54 (8H, d, J = 8.3 Hz, H3-Ar, H3'-Ar), 7.09 (8H, d, J = 8.3 Hz, H2-Ad, H2'-Ad), NH protons were not assigned. 13C NMR (CDCl3, 298 K) δ ppm: 28.5 (4C, CH-Ad), 34.5 (4C, C-Ad), 36.6 (2C, CH2-Ad), 40.2 (8C, CH2-Ad), 43.0 (2C, CH2-Ad), 53.8 (4C, CH2N), 54.1 (4C, CHN), 60.1 (4C, ArCH2N), 69.4 (9C, CH2O), 70.5 (4C, CH2N), 70.6 (4C, CH2O), 112.3 (8C, C3-Ar, C3'-Ar), 128.1 (4C, C1-Ar), 130.1 (8C, C2-Ar, C2'-Ar)*, 148.1 (4C, C-Ad)*. Cycloditeria 13b: Obtained as the third product in the synthesis of compound 11b. Obtained from compound 15a (130 mg, 0.25 mmol), diamine 7a (49 mg, 0.25 mmol) in the presence of Pd(dba)2 (23 mg, 16 mol%), and DavePhos (18 mg, 18 mol%). Eluent CH3Cl-MeOH-NaH(aq) 100:20:3. Yield 22 mg (14 %), yellow glassy compound. (MALDI-TOF) found: 633.4380 [M+H]+. 1H NMR (CDCl3, 298 K) δ ppm: 1.34 (4H, d, J = 10.9 Hz, CH2NAr), 1.42 (2H, s, H-Ad), 1.57 (4H, d, J = 11.7 Hz, H-Ad), 1.66 (2H, brs, H-Ad), 2.09 (2H, brs, H-Ad), 2.75 (8H, t, J = 5.4 Hz, CH2NAr), 2.82 (4H, s, CH2O), 3.60 (12H, s, CH2O, ArCH2N), 3.62 (8H, t, J = 5.6 Hz, CH2N), 6.48 (4H, d, J = 8.5 Hz, H3-Ar, H3'-Ar), 7.10 (4H, d, J = 8.5 Hz, H2-Ad, H2'-Ad), NH protons were not assigned. 13C NMR (CDCl3, 298 K) δ ppm: 28.5 (2C, CH-Ad), 35.7 (2C, C-Ad), 37.1 (1C, CH2-Ad), 40.1 (4C, CH2-Ad), 44.0 (1C, CH2-Ad), 54.3 (4C, CH2N), 56.3 (2C, CH2O), 59.3 (2C, ArCH2N), 70.1 (4C, CH2O), 70.9 (4C, CH2O), 112.6 (8C, C3-Ar, C3'-Ar)*, 128.1 (4C, C1-Ar), 130.0 (8C, C2-Ar, C2'-Ar)*, 148.5 (4C, C-Ad)*.

Cycloditeria 15a: Obtained as the second product in the synthesis of compound 14a. Eluent CH3Cl-MeOH-NaH(aq) 100:20:3. Yield 30 mg (19 %). Additionally a mixture of 15a with a cyclic trimer 16a was obtained. Eluent CH3Cl-MeOH-NaH(aq) 100:20:3. Yield 40 mg (25 %). Cycloditeria 15a: (MALDI-TOF) found: 1265.89. C114H169N12O12 requires 1265.87 [M+H]+. 1H NMR (CDCl3, 298 K) δ ppm: 1.37-1.64 (24H, m, H-Ad), 2.09 (4H, brs, H-Ad), 2.77 (16H, t, J = 5.8 Hz, CH2NAr), 2.81 (8H, s, CH2O), 3.54 (8H, s, ArCH2N), 3.57-3.62 (32H, m, CH2O, ArCH2N), 6.52 (8H, d, J = 8.5 Hz, H3-Ar, H3'-Ar), 7.07 (8H, d, J = 8.5 Hz, H2-Ad, H2'-Ad), NH protons were not assigned. 13C NMR (CDCl3, 298 K) δ ppm: 28.5 (4C, CH-Ad), 34.5 (4C, C-Ad), 36.6 (2C, CH2-Ad), 40.4 (8C, CH2-Ad), 43.8 (2C, CH2-Ad), 53.4 (8C, CH2N), 56.2 (4C, CH2O), 59.4 (4C, ArCH2N), 70.0 (8C, CH2O), 70.6 (8C, CH2O), 112.3 (8C, C3-Ar, C3'-Ar), 127.5 (8C, C2-Ar, C2'-Ar), 147.5 (4C, C-Ad)*.

NMR (CDCl3, 298 K) δ ppm: 1.39-1.66 (24H, m, H-Ad), 2.10 (4H, brs, H-Ad), 2.70-2.83 (24H, m, CH3-CH2NAr), 3.54 (8H, s, CH2O or ArCH2N), 3.55-3.63 (24H, m, CH2O, ArCH2N), 6.54 (8H, d, J = 8.3 Hz, H3-Ar, H3'-Ar), 7.09 (8H, d, J = 8.3 Hz, H2-Ad, H2'-Ad), NH protons were not assigned. 13C NMR (CDCl3, 298 K) δ ppm: 36.8 (1C, CH2-Ad), 44.0 (1C, CH2-Ad), 47.9 (2C, CH2-Ad), 53.8 (4C, CHN), 53.9 (4C, CH2N), 60.1 (4C, ArCH2N), 69.5 (4C, CH2O), 70.6 (8C, CH2O), 112.5 (8C, C3-Ar, C3'-Ar), 127.8 (4C, C1-Ar), 130.0 (8C, C2-Ar, C2'-Ar)*, 147.5 (4C, C-Ad)*.

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Macropolycycles Comprising Diazacrown and Adamantane Moieties

H2-Ar, H2'-Ar), NH protons were not assigned. 13C NMR (CDCl3, 298 K) δ ppm: 29.0 (2C, CH-Ad), 32.8 (2C, C-Ad), 36.7 (1C, CH2-Ad), 39.0 (2C, AdCH2), 42.6 (4C, CH2-Ad), 43.1 (2C, CH2NAr), 45.2 (1C, CH2-Ad), 54.5 (4C, CH2N), 59.6 (2C, ArCH2N), 69.9 (4C, CH2O), 70.8 (4C, CH2O), 112.6 (4C, C3-Ar, C3'-Ar), 128.0 (2C, C1-Ar), 129.8 (4C, C2-Ar, C2'-Ar), 147.4 (2C, C4-Ar).

Cyclodimer 15b. Obtained as the second product in the synthesis of compound 14b. Eluent CH2Cl2-MeOH-NH3(aq) 100:25:5. Yield 26 mg (16 %). Additionally a mixture of 15b with a cyclic trimer 16b was obtained. Eluent CH2Cl2-MeOH-NH3(aq) 100:25:5. Yield 37 mg (22 %). Cyclodimer 15b: (MALDI-TOF) found: 1321.91. C 80H121N8O8 requires 1321.93 [M+H]+. 1H NMR (CDCl3, 298 K) δ ppm: 1.32 (4H, br.s, H-Ar), 1.39-1.43 (8H, m, AdCH2), 1.43-1.63 (20H, m, H-Ad), 2.03 (4H, br.s, H2-Ad), 2.78 (16H, t, J = 5.6 Hz, CH2N), 3.07-3.10 (8H, m, CH2NAr), 3.55 (8H, s, ArCH2N), 3.57-3.63 (32H, m, CH2O), 6.52 (8H, d, J = 8.1 Hz, H3-Ar, H3'-Ar), 7.09 (8H, d, J = 8.1 Hz, H2-Ar, H2'-Ar), NH protons were not assigned. 13C NMR (CDCl3, 298 K) δ ppm: 28.9 (4C, CH-Ad), 32.7 (4C, C-Ad), 36.4 (2C, CH2-Ad), 38.8 (4C, AdCH2), 42.0 (8C, CH-Ad), 43.8 (4C, CH2NAr), 47.9 (2C, C1-Ar), 53.4 (8C, CH2N), 59.4 (4C, ArCH2N), 70.0 (8C, CH2O), 70.7 (8C, CH2O), 112.5 (8C, C3-Ar, C3'-Ar), 128.0 (4C, C1-Ar), 130.0 (8C, C2-Ar, C2'-Ar), 147.5 (4C, C4-Ar). Cyclotrimer 16b: (MALDI-TOF) found: 1982.34. C120H181N12O12 requires 1982.39 [M+H]+. 1H NMR (CDCl3, 298 K) δ ppm: 1.31 (6H, br.s, H-Ar), 1.39-1.42 (12H, m, AdCH2), 1.43-1.61 (30H, m, H-Ad), 2.04 (6H, br.s, H2-Ad), 2.78 (24H, t, J = 5.4 Hz, CH2N), 3.06-3.10 (12H, m, CH2NAr), 3.55 (12H, s, ArCH2N), 3.57-3.63 (48H, m, CH2O), 6.52 (12H, d, J = 8.3 Hz, H3-Ar, H3'-Ar), 7.09 (12H, d, J = 8.3 Hz, H2-Ar, H2'-Ar), NH protons were not assigned. 13C NMR (CDCl3, 298 K) δ ppm: 28.9 (6C, CH-Ad), 32.7 (6C, C-Ad), 36.4 (3C, CH2-Ad), 38.7 (6C, AdCH2), 41.9 (12C, CH2-Ad), 43.7 (6C, CH2NAr), 47.9 (3C, CH2-Ad), 53.4 (12C, CH2N), 59.4 (6C, ArCH2N), 69.9 (12C, CH2O), 70.6 (12C, CH2O), 112.4 (12C, C3-Ar, C3'-Ar), 127.6 (6C, C1-Ar), 130.0 (12C, C2-Ar, C2'-Ar), 147.5 (6C, C4-Ar).

Results and Discussion

To synthesize macrobicyclic compounds comprising diazacrown units, first we synthesized N,N'-bis(bromobenzyl) derivatives of diazacrown ethers 3-6 (Scheme 1). The reactions were carried out using exactly two equivalents of bromobenzyl bromides, in boiling acetonitrile, K2CO3 was used as base in the case of a smaller macrocycle 1 whereas Na2CO3 was employed in the reaction with a larger diazacrown ether 2 in order to minimize the coordination of the cation. However, the work-up of the reaction mixtures included a meticulous washing of the resulting compounds 3-6 with water to avoid coordinated salts. As a result, the target compounds were obtained in high yields 89-95 %.

Diazacrown derivatives 3-6 were introduced in the palladium-catalyzed reactions with adamantane-containing diamines 7a,b (Scheme 2). We employed Pd(dba)2/BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthalene) (8 mol%) catalytic system for the reactions with 1,3-bis(2-aminoethyl)-adamantane 7b, while the cyclization with 1,3-bis(aminomethyl)adamantane 7a was catalyzed in the presence of Pd(dba)/DavePhos (2-dicyclohexylphosphino-2' -dimethyl-aminobiphenyl) (16 mol%). The choice of the catalytic
Table 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazacrown ether derivative</th>
<th>Diamine</th>
<th>Ligand</th>
<th>Pd(dba)/L, mol%</th>
<th>Product, yield, %</th>
<th>By-product, yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 7a</td>
<td>BINAP</td>
<td></td>
<td>16/18</td>
<td>8a, 34</td>
<td>9a, 16</td>
</tr>
<tr>
<td>2</td>
<td>3 7b</td>
<td>BINAP</td>
<td></td>
<td>8/9</td>
<td>8b, 48</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 7a</td>
<td>DavePhos</td>
<td></td>
<td>16/18</td>
<td>10a, 29</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 7b</td>
<td>BINAP</td>
<td></td>
<td>8/9</td>
<td>10b, 54</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5 7a</td>
<td>DavePhos</td>
<td></td>
<td>16/18</td>
<td>11a, 12</td>
<td>12a, 12(^a)</td>
</tr>
<tr>
<td>6</td>
<td>5 7b</td>
<td>BINAP</td>
<td></td>
<td>8/9</td>
<td>11b, 35</td>
<td>12b, 10(^b)</td>
</tr>
<tr>
<td>7</td>
<td>6 7a</td>
<td>DavePhos</td>
<td></td>
<td>16/18</td>
<td>14a, 14</td>
<td>15a, 19(^c)</td>
</tr>
<tr>
<td>8</td>
<td>6 7b</td>
<td>BINAP</td>
<td></td>
<td>8/9</td>
<td>14b, 16</td>
<td>15b, 16(^d)</td>
</tr>
<tr>
<td>9</td>
<td>6 7b</td>
<td>BINAP</td>
<td></td>
<td>16/18</td>
<td>14b, 15</td>
<td>15b, 14</td>
</tr>
</tbody>
</table>

\(^a\) Additionally a mixture of 12a and 13a was isolated (10%).
\(^b\) Cyclotrimer 13b was isolated (10%).
\(^c\) Additionally a mixture of 15a and 16a was isolated (25%).
\(^d\) Additionally a mixture of 15b and 16b was isolated (22%).

system was based on our previous research of the Pd-catalyzed arylation of these diamines with dihalobenzenes.\(^{[32]}\) The results of the cyclization reactions are presented in Table 1.

The yields of the target macrobicycles were dramatically dependent on the nature of starting diazacrown derivatives and diamines. For the majority of cases, the reactions with the diamine 7b gave better results than with the diamine 7a, the best yields being 48 and 54 % (entries 2, 4). Probably it was due to the fact that amino groups in the diamine 7a are more sterically hindered by a closer adamantane core. Also the diamine 7a is more rigid compared to the diamine 7b, thus the geometric demands for a successful cyclization with this diamine are stricter. Derivatives of the 3-bromobenzyl substituted diazacrown ethers 3 and 4 provided higher yields of the macrobicycles 8 and 10 (entries 1-4) if compared with 4-bromobenzyl substituted diazacrowns 5 and 6 (entries 5-8). This fact might be also explained by a better adjustment of two bromine atoms to the nitrogen atoms of diamines in the diazacrown ethers with meta-bromobenzyl substituents. On the other hand, we did not observe a pronounced dependence of the reaction result on the size of the diazacrown moiety, thus the different ability of the starting compounds to coordinate sodium cation was not important. As the yield of the macrobicycle 14b was low (16 %, entry 8), we tried the application of the twofold amount of the catalyst (entry 9) but obtained almost the same result. It means that 8 mol% of the Pd(dba)/BINAP system is quite sufficient for the reaction with the diamine 7b while 7a demands greater catalyst loading.

In many cases we obtained not only the target macro-bicyclic compounds but also macrotricyclic cyclodimers and even macrotetracyclic cyclotrimeres. These compounds were formed primarily with para-bromobenzyl derivatives 5 and 6 and their yields were comparable with those of macrobicycles (entries 5, 7, 8). This fact can be also explained by the higher sterical demands of bis(4-bromobenzyl) substituted diazacrown ethers which hindered the intramolecular di-amination and decreased the yields of macrobicycles 11, 14 simultaneously boosting the formation of cyclic oligomers.

Conclusions

To sum up, we elaborated a convenient synthesis of the macrobicycles containing diazacrown ether and adamantane moieties using the Pd-catalyzed amination reaction, demonstrated the dependence of the macrobicycles yields on the nature of starting compounds. The reactions with 1,3-bis(2-aminomethyl)adamantane were catalyzed with Pd(dba)/BINAP whereas 1,3-bis(aminomethyl) adamantane needed the application of Pd(dba)/DavePhos catalytic system. N,N'-bis(3-bromobenzyl) substituted diazacrown ethers were shown to provide better yields of the target macrobicycles (up to 54 %), whereas the reactions with their 4-bromo-benzyl-containing isomers gave reasonable amounts of cyclic oligomers, i.e. macrotricycles and macrotetracycles.

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References

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