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Copper–Catalyzed Amination in the Synthesis of Polyoxadiamine Derivatives of Aza– and Diazacrown Ethers

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Cu(I)-Catalyzed amination of N-(iodobenzyl) substituted azacrown ethers with propane-1,3-diamine and several polyoxadiamines was investigated. In the case of diamine excess and the use of CuI/l-proline catalytic system in EtCN the formation of the compounds with one azacrown and one diamine moieties was observed. When taking the excess of N-(iodobenzyl) derivative of azacrown ether and CuI/2-(isobutyryl)cyclohexanone catalytic system in DMF, bis(azacrown) substituted oxadiamine could be obtained. Amination of N,N'-di(iodobenzyl) substituted diazacrown ether was studied under the same conditions. The comparison of Pd(0)- with Cu(I)-mediated amination reactions was done using N-(bromobenzyl) substituted azacrown ethers.

Keywords: Catalysis by Cu(I) complexes, amination, azacrown ethers, diamines.

Медь–катализируемое аминирование в синтезе полиоксадиаминовых производных аза– и диазакраун–эфиров

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Изучено Cu(I)-катализируемое аминирование N-(иодбензил) замещенных азакраун-эфиров пропан-1,3-диамином и некоторыми полиоксадиаминами. При использовании избытка диаминов и каталитической системы CuI/l-пролин в EtCN наблюдалось образование соединений, содержащих один азакраун-эфирный и диаминовый фрагменты. При использовании избытка N-(иодбензил) производных азакраун-эфиров и каталитической системы CuI/2-(изобутирил)циклогексанон в ДМФА могут быть получены бис(азакраун) замещенные оксадиамины. Аминирование N,N'-ди(иодбензил) замещенного дизакраун-эфира исследовано в тех же условиях. Проведено сравнение Pd(0)- и Cu(I)-катализируемого аминирования с использованием N-(бромбензил) замещенных азакраун-эфиров.

Ключевые слова: Cu(I)-Катализ, аминирование, азакраун-эфиры, диамины.

Introduction

Oxygen- and nitrogen-containing macrocyclic compounds attract researchers' attention due to their unique properties of efficient and selective binding of metal cations, inorganic anions and small polar organic molecules. Introduction of additional donor atoms in the exocyclic substituents of such macrocycles may increase selectivity, binding constants and thus is widely used in coordination and supramolecular chemistry. One of the most important and renowned compounds of such type is *N,N',N'',N'''*-tetrasubstituted 1,4,7,10-tetraazacyclododecane (DOTA) bearing four carboxylic groups. It has been widely used in the coordination studies with various metal cations including rare earth metals and lanthanides.[1-4] Well-studied are other tetrasubstituted tetraazamacrocycles like cyclen and cyclam (1,4,8,11-tetraazacyclotetradecane) with phosphonate,[5-10] amide,[11] nitrile,[12] primary and tertiary amino groups.[13,14] In many cases additional donor atoms are present in C-substituted macrocycles like cyclam[15,16] or crown ethers.[17] Special interest is paid to substituents bearing several donor atoms (podands), among them oligoethylene oxides are very attractive due to an easy introduction of such podands into macrocycles, possibility to vary the number of donor atoms and their non-ionogenic character. Aza-crown ethers are usually modified with these podands at the nitrogen atom,[18-20] while crown ethers may contain these substituents only at carbon atoms.[21-23] We have developed a simple and efficient approach to macrobicycles and trismacrocycles compounds using Pd(0)-catalyzed macrocyclization of *N,N'*-di(bromobenzyl) substituted diazacrown ethers with polyamines and polyoxadiamines,[24,25] also we carried out the synthesis of various bismacrocycles based on *N*-benzyl substituted azacrown ethers.[26] Recently we have started thourough investigation of Cu(I)-catalyzed arylation and heteroarylation of polyamines and polyoxadiamines[27-29] as well as Cu(I)-mediated amination of steroids.[30] In this connection, the aim of the present research is to apply Cu(I)-catalyzed amination to the synthesis of polyoxadiamine derivatives of aza- and diazacrown ethers and to compare it with the approach which exploits Pd(0) catalysis.

Experimental

NMR spectra were registered using Bruker Avance 400 spectrometer, MALDI-TOF spectra were obtained with Bruker Autoflex II spectrometer using 1,8,9-trihydroxyanthracene as matrix and PEGs as internal standards. Propane-1,3-diamine, dioxa- and trioxadiamines, aza- and diazacrown ethers, 1-(bromomethyl)-3-bromobenzene, *l*-proline, 2-isobutyrylcyclohexanone, BINAP, cesium carbonate, potassium carbonate, sodium *tert*-butoxide, CuI were purchased from Aldrich and used without further purification, $Pd(dba)_2$ was synthesized according to the method described,[31] 1-(bromomethyl)-3-iodobenzene was obtained from commercially available *m*-iodotoluene by a standard bromination with NBS in CCl_4. Dioxane was distilled over NaOH followed by the distillation over sodium under argon, acetonitrile was distilled over CaH_2, DMF, EtCN, dichloromethane and methanol were used freshly distilled.

*Typical procedure for the synthesis of aza- and diazacrown derivatives **1-4, 9***. A flask equipped with a condenser and magnetic stirrer was charged with corresponding azacrown ether (1 mmol), MeCN (3 ml), 1-(bromomethyl)-3-bromobenzene or 1-(bromomethyl)-3-iodobenzene (1 mmol), potassium carbonate (2.5 mmol) and stirred under reflux for 15 h. In the case of compound **9** diaza-18-crown-6 ether (1 mmol) was reacted with 1-(bromomethyl)-3-iodobenzene (2 mmol) in the presence of potassium carbonate (4 mmol). After cooling the reaction mixture down to room temperature the reaction mixture was diluted with CH_2Cl_2 (10 ml), the solution was filtered, evaporated *in vacuo*, dissolved in CH_2Cl_2 (10 ml), washed with an equal volume of water and dried over molecular sieves. After evaporating the solvent, target *N*-halogenobenzyl derivatives of aza- and diazacrown ethers were obtained as viscous yellowish oils.

*13-(3-Bromobenzyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (**1**)*. Obtained from 1-aza-15-crown-5 (2 mmol, 438 mg) and 3-bromobenzyl bromide (2 mmol, 500 mg) in the presence of K_2CO_3 (5 mmol, 695 mg) in 7 ml MeCN. Yield 728 mg (94 %). (MALDI-TOF) found: 388.1167. $C_{17}H_{27}BrNO_4$ requires 388.1123 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.76 (4H, t, ^3J = 5.8 Hz), 3.60-3.64 (10H, m), 3.65-3.69 (8H, m), 7.13 (1H, t, ^3J = 7.8 Hz), 7.24 (1H, d, ^3J = 7.8 Hz), 7.33 (1H, d, ^3J = 7.8 Hz), 7.51 (1H, s). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 54.2 (2C), 60.1 (1C), 69.9 (2C), 70.2 (2C), 70.5 (2C), 70.9 (2C), 122.4 (1C), 127.3 (1C), 129.7 (1C), 129.9 (1C), 131.6 (1C), 142.3 (1C).

*16-(3-Bromobenzyl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**2**)*. Obtained from 1-aza-18-crown-6 (1 mmol, 263 mg) and 3-bromobenzyl bromide (1 mmol, 250 mg) in the presence of K_2CO_3 (2.5 mmol, 348 mg) in 4 ml MeCN. Yield 415 mg (96 %). (MALDI-TOF) found: 432.1425. $C_{19}H_{31}BrNO_5$ requires 432.1386 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.76 (4H, t, ^3J = 5.3 Hz), 3.57-3.62 (8H, m), 3.63-3.69 (14H, m), 7.13 (1H, t, ^3J = 7.7 Hz), 7.24 (1H, d, ^3J = 8.0 Hz), 7.32 (1H, d, ^3J = 7.6 Hz), 7.50 (1H, s). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 53.9 (2C), 59.5 (1C), 69.9 (2C), 70.4 (2C), 70.8 (4C), 70.9 (2C), 122.4 (1C), 127.3 (1C), 129.7 (1C), 129.9 (1C), 131.6 (1C), 142.5 (1C).

*13-(3-Iodobenzyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (**3**)*. Obtained from 1-aza-15-crown-5 (4 mmol, 876 mg) and 3-iodobenzyl bromide (4 mmol, 1188 mg) in the presence of K_2CO_3 (8 mmol, 1104 mg) in 12 ml MeCN. Yield 1.600 g (92 %). (MALDI-TOF) found: 436.0932. $C_{17}H_{27}INO_4$ requires 436.0985 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.70 (4H, t, ^3J = 5.9 Hz), 3.54-3.59 (10H, m), 3.60-3.64 (8H, m), 6.96 (1H, t, ^3J = 7.7 Hz), 7.23 (1H, d, ^3J = 7.6 Hz), 7.49 (1H, d, ^3J = 7.8 Hz), 7.65 (1H, s).

*16-(3-Iodobenzyl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**4**)*. Obtained from 1-aza-18-crown-6 (1 mmol, 263 mg) and 3-iodobenzyl bromide (1 mmol, 297 mg) in the presence of K_2CO_3 (2.5 mmol, 348 mg) in 4 ml MeCN. Yield 445 mg (93 %). (MALDI-TOF) found: 480.1289. $C_{19}H_{31}INO_5$ requires 480.1247 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.76 (4H, t, ^3J = 5.7 Hz), 3.59-3.64 (10H, m), 3.64-3.70 (12H, m), 7.01 (1H, t, ^3J = 7.7 Hz), 7.29 (1H, d, ^3J = 7.7 Hz), 7.54 (1H, d, ^3J = 7.8 Hz), 7.70 (1H, s). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 53.9 (2C), 59.4 (1C), 69.9 (2C), 70.4 (2C), 70.8 (4C), 70.9 (2C), 104.5 (1C), 128.0 (1C), 129.9 (1C), 135.9 (1C), 137.6 (1C), 142.6 (1C).

*7,16-Bis(3-iodobenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**9**)*. Obtained from diaza-18-crown-6 (4 mmol, 1.060 g) and 3-iodobenzyl bromide (8 mmol, 2.376 g) in the presence of Na_2CO_3 (16 mmol, 1.696 g) in 15 ml MeCN. Yield 2.498 g (90 %). (MALDI-TOF) found: 695.0802. $C_{26}H_{37}I_2N_2O_4$ requires 695.0843 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.76 (8H, t, ^3J = 5.3 Hz), 3.52-3.65 (20H, m), 6.98 (2H, t, ^3J = 7.7 Hz), 7.26 (2H, d, ^3J = 7.7 Hz), 7.51 (2H, d, ^3J = 7.7 Hz), 7.67 (2H, s).

*Typical procedure for the Cu(I)-catalyzed amination of compounds **3, 4, 9***. A two-necked flask equipped with a condenser and magnetic stirrer was flushed with argon, charged with corresponding azacrown ether derivative **3**, **4**, **9** (0.5 mmol for the monoamination or diamination or 1 mmol for the diarylation), CuI (10 mol% for the monoamiantion or 20 mol% for the diamination and diarylation), *l*-proline or 2-isobutyrylcyclohexanone (20 mol% for the monoamination or 40 mol% for the diamination and diarylation), EtCN or DMF (1 ml), corresponding diamine/

oxadiamine (1 mmol for the monoamination, 2 mmol for the diamination, or 0.5 mmol for the diarylation), cesium carbonate (1.5 equiv. for each NH_2 group participating in the arylation). The reaction mixture was stirred under reflux (EtCN) or at 140 °C (DMF) for 24 h. After cooling the reaction mixture down to room temperature the reaction mixture was diluted with CH_2Cl_2 (10 ml), the solution was filtered, evaporated *in vacuo*, dissolved in CH_2Cl_2 (10 ml), and additional precipitate was separated. After evaporating the solvent, the residue was chromatographed on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2/MeOH (50:1–3:1), CH_2Cl_2/MeOH/NH_3aq (100:20:1–10:4:1).

*Typical procedure for the Pd(0)-catalyzed synthesis of compounds **7a,b.*** A two-necked flask equipped with a condenser and magnetic stirrer was flushed with argon, charged with corresponding azacrown ether derivative **1** or **2** (0.5 mmol), $Pd(dba)_2$ (4 mol%, 12 mg), BINAP (4.5 mol%, 14 mg), absolute dioxane (10-20 ml), propane-1,3-diamine (1.5 or 2 mmol, 111 or 148 mg) was added followed by sodium *tert*-butoxide (0.75 mmol, 72 mg). The reaction mixture was refluxed for 8 h, after cooling the reaction mixture down to room temperature the reaction mixture was diluted with CH_2Cl_2 (10 ml), the solution was filtered, evaporated *in vacuo*, dissolved in CH_2Cl_2 (10 ml), and additional precipitate was separated. After evaporating the solvent, the residue was chromatographed on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2/MeOH (50:1–3:1), CH_2Cl_2/MeOH/NH_3aq (100:20:1–10:4:1) to produce target compounds as viscous yellowish oils or glassy solids.

*N^1-(3-((1,4,7,10-Tetraoxa-13-azacyclopentadecan-13-yl)-methyl)phenyl)propane-1,3-diamine (**6a**)*. Obtained from compound **1** (1 mmol, 388 mg), propane-1,3-diamine (**5a**) (3 mmol, 222 mg), in the presence of $Pd(dba)_2$ (4 mol%, 24 mg), BINAP (4.5 mol%, 28 mg), *t*BuONa (1.5 mmol, 144 mg) in 20 ml dioxane. Eluent: CH_2Cl_2/MeOH/NH_3aq (100:25:5–100:35:6). Yield 221 mg (58 %). (MALDI-TOF) found: 382.2670. $C_{20}H_{36}N_3O_4$ requires 382.2706 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.75 (2H, quintet, ^3J = 6.6 Hz), 2.73 (4H, t, ^3J = 5.7 Hz), 2.79 (2H, br. t, $^3J_{obs}$ = 6.2 Hz), 3.14 (2H, t, ^3J = 6.6 Hz), 3.56 (2H, s), 3.57-3.65 (16H, m), 6.44 (1H, dd, ^3J = 7.8 Hz, ^4J = 1.0 Hz), 6.56 (1H, d, ^3J = 7.3 Hz), 6.67 (1H, s), 7.04 (1H, t, ^3J = 7.7 Hz). (Three NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 32.1 (1C), 39.8 (1C), 41.7 (1C), 54.2 (2C), 60.7 (1C), 69.5 (2C), 69.9 (2C), 70.0 (2C), 70.6 (2C), 110.7 (1C), 113.7 (1C), 117.7 (1C), 128.8 (1C), 140.0 (1C), 148.5 (1C).

*N^1-(3-((1,4,7,10,13-Pentaoxa-16-azacyclooctadecan-16-yl)-methyl)phenyl)propane-1,3-diamine (**7a**)*. Obtained from compound **2** (0.9 mmol, 389 mg), propane-1,3-diamine (**5a**) (3.6 mmol, 266 mg), in the presence of $Pd(dba)_2$ (4 mol%, 21 mg), BINAP (4.5 mol%, 25 mg), *t*BuONa (1.4 mmol, 134 mg) in 9 ml dioxane. Eluent: CH_2Cl_2/MeOH (3:1). Yield 178 mg (46%). (MALDI-TOF) found: 426.2995. $C_{22}H_{40}N_3O_5$ requires 426.2968 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.79 (2H, quintet, ^3J = 6.5 Hz), 2.72 (4H, t, ^3J = 5.6 Hz), 2.87 (2H, t, ^3J = 6.6 Hz), 3.14 (2H, t, ^3J = 6.4 Hz), 3.52 (2H, s), 3.55-3.65 (20H, m), 6.43 (1H, dd, ^3J = 7.8 Hz, ^4J = 1.1 Hz), 6.53 (1H, d, ^3J = 7.5 Hz), 6.59 (1H, s), 7.01 (1H, t, ^3J = 7.8 Hz). (Three NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 31.0 (1C), 39.3 (1C), 41.4 (1C), 54.0 (2C), 59.6 (1C), 69.6 (2C), 70.2 (2C), 70.5 (4C), 70.7 (2C), 110.9 (1C), 113.5 (1C), 117.5 (1C), 128.8 (1C), 140.0 (1C), 148.5 (1C).

*N^1,N^3-bis(3-((1,4,7,10,13-Pentaoxa-16-azacyclooctadecan-16-yl)methyl)phenyl)propane-1,3-diamine (**8a**)* was obtained as the second product in the synthesis of compound **7a** from compound **2** (0.92 mmol, 396 mg), propane-1,3-diamine (**5a**) (2.7 mmol, 200 mg), in the presence of $Pd(dba)_2$ (4 mol%, 21 mg), BINAP (4.5 mol%, 26 mg), *t*BuONa (1.4 mmol, 134 mg) in 10 ml dioxane. CH_2Cl_2/MeOH/NH_3aq (100:35:6). Yield 30 mg (8 %). (MALDI-TOF) found: 777.48. $C_{41}H_{69}N_4O_{10}$ requires 777.50 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.90 (2H, quintet, ^3J = 6.7 Hz), 2.75 (8H, t, ^3J = 5.6 Hz), 3.22 (4H, t, ^3J = 6.6 Hz), 3.55-3.67 (44H, m), 3.90 (2H, br. s), 6.46 (2H, d, ^3J = 7.7 Hz), 6.60 (2H, d, ^3J = 7.5 Hz), 6.65 (2H, s), 7.06 (2H, t, ^3J = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 29.2 (1C), 41.9 (2C), 54.0 (4C), 60.0 (2C), 69.8 (4C), 70.2 (4C), 70.6 (8C), 70.7 (4C), 110.9 (2C), 113.5 (2C), 117.8 (2C), 128.9 (2C), 140.6 (2C), 148.3 (2C).

*3-((1,4,7,10-Tetraoxa-13-azacyclopentadecan-13-yl)methyl)-N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-aniline (**6b**)*. Obtained from compound **3** (0.15 mmol, 66 mg), dioxadiamine (**5b**) (0.3 mmol, 44 mg), in the presence of CuI (10 mol%, 3 mg), *l*-proline (20 mol%, 3.5 mg), Cs_2CO_3 (0.225 mmol, 73 mg) in 1 ml EtCN. Eluent: CH_2Cl_2/MeOH (3:1), CH_2Cl_2/MeOH/NH_3aq (100:20:1–100:20:3). Yield 51 mg (75 %). (MALDI-TOF) found: 456.3132. $C_{23}H_{42}N_3O_6$ requires 456.3074 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 3.03 (2H, br. s), 3.19 (4H, bs), 3.35 (2H, t, ^3J = 4.8 Hz), 3.59-3.70 (20H, m), 3.74 (2H, t, ^3J = 4.8 Hz), 3.82 (4H, t, ^3J = 4.7 Hz), 4.02 (1H, bs), 6.56-6.63 (2H, m), 7.14 (1H, t, ^3J = 7.7 Hz), 7.22 (1H, bs). (NH_2 protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 39.5 (1C), 43.3 (1C), 53.7 (2C), 56.7 (1C), 66.5 (2C), 68.4-70.1 (10C, m), 112.0 (1C), 116.2 (1C), 119.3 (1C), 129.5 (1C), 136.9 (1C), 149.0 (1C).

*3-((1,4,7,10-Tetraoxa-13-azacyclopentadecan-13-yl)methyl)-N-(2-(2-(2-(2-aminoethoxy)ethoxy)-ethoxy)ethyl)aniline (**6c**)*. Obtained from compound **3** (0.15 mmol, 66 mg), trioxadiamine (**5c**) (0.3 mmol, 58 mg), in the presence of CuI (10 mol%, 3 mg), *l*-proline (20 mol%, 3.5 mg), Cs_2CO_3 (0.225 mmol, 73 mg) in 1 ml EtCN. Eluent: CH_2Cl_2/MeOH (3:1). Yield 25 mg (33 %). (MALDI-TOF) found: 500.3301. $C_{25}H_{46}N_3O_7$ requires 500.3336 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.81 (2H, bs), 2.87 (4H, br. s), 3.25 (2H, t, ^3J = 4.7 Hz), 3.55-3.69 (26H, m), 3.71 (2H, t, ^3J = 5.1 Hz), 3.78 (2H, t, ^3J = 5.1 Hz), 4.12 (1H, bs), 6.53 (2H, d, ^3J = 8.0 Hz), 7.09 (1H, t, ^3J = 7.7 Hz), 7.09 (1H, s). (NH_2 protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 39.6 (1C), 43.6 (1C), 53.9 (2C), 58.7 (1C), 66.3 (2C), 68.2 (1C), 68.9-70.4 (11C, m), 111.6 (1C), 116.3 (1C), 119.5 (1C), 129.3 (1C), 136.6 (1C), 149.0 (1C).

*3-((1,4,7,10-Tetraoxa-13-azacyclopentadecan-13-yl)methyl)-N-(3-(2-(2-(3-aminopropoxy)ethoxy)-ethoxy)propyl)aniline (**6d**)*. Obtained from compound **3** (0.29 mmol, 128 mg), trioxadiamine (**5d**) (0.58 mmol, 128 mg), in the presence of CuI (10 mol%, 5.5 mg), *l*-proline (20 mol%, 6.7 mg), Cs_2CO_3 (0.435 mmol, 142 mg) in 2 ml EtCN. Eluent: CH_2Cl_2/MeOH (5:1-3:1). Yield 57 mg (37 %). (MALDI-TOF) found: 528.3577. $C_{27}H_{50}N_3O_7$ requires 528.3649 $[M+H]^+$. ^{1}H NMR (CD_3OD, 298 K) δ_H ppm: 1.88 (4H, quintet, ^3J = 6.1 Hz), 2.72 (4H, t, ^3J = 4.5 Hz), 3.03 (2H, bs), 3.19 (2H, t, ^3J = 6.6 Hz), 3.56-3.72 (30H, m), 6.55 (1H, d, ^3J = 7.1 Hz), 6.59 (1H, s), 6.60 (1H, d, ^3J = 8.0 Hz), 7.11 (1H, t, ^3J = 7.5 Hz). (NH protons were not observed). ^{13}C NMR (CD_3OD, 298 K) δ_c ppm: 28.9 (1C), 29.4 (1C), 38.6 (1C), 40.8 (1C), 53.0 (2C), 57.7 (1C), 66.9 (2C), 68.0 (1C), 68.5-70.1 (9C, m), 111.8 (1C), 114.8 (1C), 118.6 (1C), 129.0 (1C), 136. 2 (1C), 149.1 (1C).

*3-((1,4,7,10,13-Pentaoxa-16-azacyclooctadecan-16-yl) methyl)-N-(3-(2-(2-(3-aminopropoxy)ethoxy)-ethoxy)propyl) aniline (**7d**)*. Obtained from compound **4** (0.5 mmol, 222 mg), trioxadiamine (**5d**) (1 mmol, 220 mg), in the presence of CuI (10 mol%, 9.5 mg), *l*-proline (20 mol%, 10.5 mg), Cs_2CO_3 (1.5 mmol, 489 mg) in 2 ml EtCN. Eluent: CH_2Cl_2/MeOH/NH_3aq (100:20:1–100:20:3). Yield 185 mg (65 %). (MALDI-TOF) found: 572.3950. $C_{29}H_{54}N_3O_8$ requires 572.3911 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 328 K) δ_H ppm: 1.76 (2H, quintet, ^3J = 6.8 Hz), 1.83 (2H, quintet, ^3J = 6.0 Hz), 2.85-2.94 (6H, m), 3.18 (2H, t, ^3J = 6.4 Hz), 3.50 (2H, t, ^3J = 5.7 Hz), 3.50-3.64 (28H, m), 3.69 (4H, bs), 6.47 (1H, d, ^3J = 7.5 Hz), 6.50 (1H, d, ^3J = 8.0 Hz), 6.65 (1H, s), 7.02 (1H, t, ^3J = 7.7 Hz). (NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 27.9 (1C), 29,2 (1C), 37.7 (1C), 41.6 (1C), 54.2 (2C), 57.0 (1C), 66.9 (2C), 68.1 (1C), 69.5-70.5 (13C, m), 112.0 (1C), 114.8 (1C), 118.1 (1C), 129.2 (1C), 149.2 (1C). (One aromatic quaternary carbon was not assigned).

*N^1,$N^{1'}$-(3,3'-(1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene)bis(3,1-phenylene))dipropane-1,3-diamine (**10a**)*. Obtained from compound **9** (0.15 mmol, 104 mg),

propane-1,3-diamine (**5a**) (0.6 mmol, 44 mg), in the presence of CuI (20 mol%, 6 mg), *l*-proline (40 mol%, 7 mg), Cs_2CO_3 (0.45 mmol, 147 mg) in 1 ml EtCN. Eluent: CH_2Cl_2/MeOH/NH_3aq (100:35:6–10:4:1). Yield 52 mg (36 %). (MALDI-TOF) found: 587.4349. $C_{32}H_{55}N_6O_4$ requires 587.4285 $[M+H]^+$. ^{1}H NMR (CD_3OD, 298 K) δ_H ppm: 1.79 (4H, quintet, ^3J = 7.0 Hz), 2.71 (8H, t, ^3J = 4.9 Hz), 2.81 (4H, t, ^3J = 6.5 Hz), 3.17 (4H, t, ^3J = 6.5 Hz), 3.51 (4H, s), 3.54 (8H, s), 3.61 (8H, t, ^3J = 4.9 Hz), 6.47 (2H, d, ^3J = 7.2 Hz), 6.53 (2H, s), 6.54 (2H, d, ^3J = 7.6 Hz), 7.06 (2H, t, ^3J = 7.7 Hz). (NH protons were not assigned). ^{13}C NMR (CD_3OD, 298 K) δ_c ppm: 31.8 (2C), 39.9 (2C), 42.0 (2C), 55.2 (4C), 58.6 (2C), 69.8 (4C), 71.3 (4C), 112.5 (2C), 115.7 (2C), 119.4 (2C), 130.0 (2C), 139.3 (2C), 150.0 (2C).

*3,3'-(1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene)bis(N-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy) ethyl)aniline) (**10d**)*. Obtained from compound **9** (0.5 mmol, 347 mg), trioxadiamine (**5d**) (2 mmol, 440 mg), in the presence of CuI (20 mol%, 20 mg), *l*-proline (40 mol%, 24 mg), Cs_2CO_3 (2 mmol, 652 mg) in 1 ml EtCN. Yield in the reaction mixture 76%. (MALDI-TOF) found: 823.58. $C_{42}H_{75}N_6O_{10}$ requires 823.55 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.63 (4H, bs), 1.79 (4H, quintet, ^3J = 6.1 Hz), 2.66 (8H, bs), 2.70 (4H, bs), 3.10 (4H, t, ^3J = 6.1 Hz), 3.40-3.56 (32H, m), 6.38 (2H, d, ^3J = 7.7 Hz), 6.46 (2H, d, ^3J = 6.8 Hz), 6.52 (2H, s), 6.98 (2H, t, ^3J = 7.7 Hz). (NH protons were not assigned).

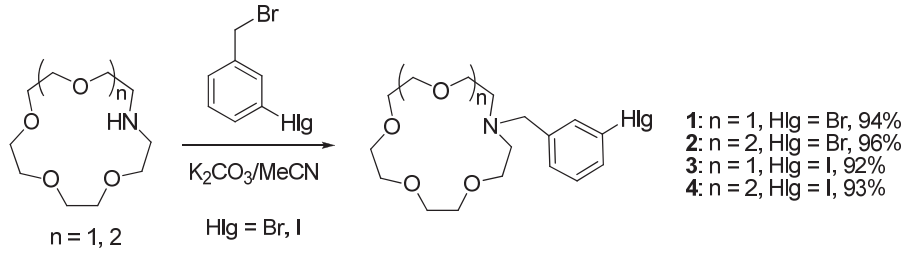
*3-((1,4,7,10-Tetraoxa-13-azacyclopentadecan-13-yl)methyl)-N-(3-(2-(2-(3-(4-((1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)methyl)phenylamino)propoxy)ethoxy)ethoxy)propyl)aniline (**11d**)*. Obtained from compound **3** (0.78 mmol, 340 mg), trioxadiamine (**5d**) (0.39 mmol, 85 mg), in the presence of CuI (20 mol%, 15 mg), 2-(isobutyryl)cyclohexanone (40 mol%, 26 mg), Cs_2CO_3 (1.5 mmol, 489 mg) in 1 ml DMF. Eluent: CH_2Cl_2/MeOH/NH_3aq (100:20:2). Yield 92 mg (28 %). (MALDI-TOF) found: 835.5380. $C_{44}H_{75}N_4O_{11}$ requires 835.5432 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.86 (4H, quintet, ^3J = 6.3 Hz), 2.77 (8H, t, ^3J = 5.8 Hz), 3.19 (4H, t, ^3J = 6.6 Hz), 6.44 (2H, dd, ^3J = 7.8 Hz, ^4J = 1.3 Hz), 6.59 (2H, d, ^3J = 7.6 Hz), 6.62 (2H, s), 7.05 (2H, t, ^3J = 7.8 Hz). (NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 29.2 (2C), 41.6 (2C), 54.3 (4C), 60.8 (2C), 69.6 (2C), 69.8 (4C), 70.1 (4C), 70.2 (2C), 70.4 (4C), 70.6 (2C), 70.8 (4C), 111.0 (2C), 113.4 (2C), 117.6 (2C), 128.9 (2C), 140.4 (2C), 148.6 (2C).

*N,N'-(3,3'-(2,2'-Oxybis(ethane-2,1-diyl)bis(oxy)) bis(propane-3,1-diyl))bis(3-((16-(3-iodobenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)aniline) (**12d**)*. Obtained from compound **9** (1 mmol, 694 mg), trioxadiamine (**5d**) (0.5 mmol, 110 mg), in the presence of CuI (20 mol%, 19 mg), 2-(isobutyryl)cyclohexanone (40 mol%, 34 mg), Cs_2CO_3 (1.5 mmol, 489 mg) in 1 ml DMF. Eluent: CH_2Cl_2/MeOH/NH_3aq (100:25:1-100:25:2). Yield 120 mg (18 %). (MALDI-TOF) found: 1353.54. $C_{62}H_{95}I_2N_6O_{11}$ requires 1353.51 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.86 (4H, quintet, ^3J = 5.9 Hz), 2.74-2.86 (16H, m), 3.19 (4H, t, ^3J = 6.4 Hz), 3.51-3.70 (40H, m), 6.45 (2H, d, ^3J = 7.2 Hz), 6.58 (2H, s), 6.62 (2H, d, ^3J = 7.3 Hz), 7.00 (2H, t, ^3J = 7.6 Hz), 7.06 (2H, t, ^3J = 7.5 Hz), 7.29 (2H, d, ^3J = 7.3 Hz), 7.53 (2H, d, ^3J = 7.3 Hz), 7.69 (2H, s). (NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 29.2 (2C), 41.6 (2C), 53.6 (4C), 53.7 (4C), 59.2 (2C), 60.0 (2C), 69.7 (2C), 69.9 (8C), 70.2 (2C), 70.6 (8C), 94.3 (1C), 111.2 (2C), 113.3 (2C), 117.7 (2C), 127.9 (2C), 128.9 (2C), 129.9 (2C), 135.8 (2C), 137.5 (2C), 141.8 (2C), 142.4 (2C), 148.5 (2C).

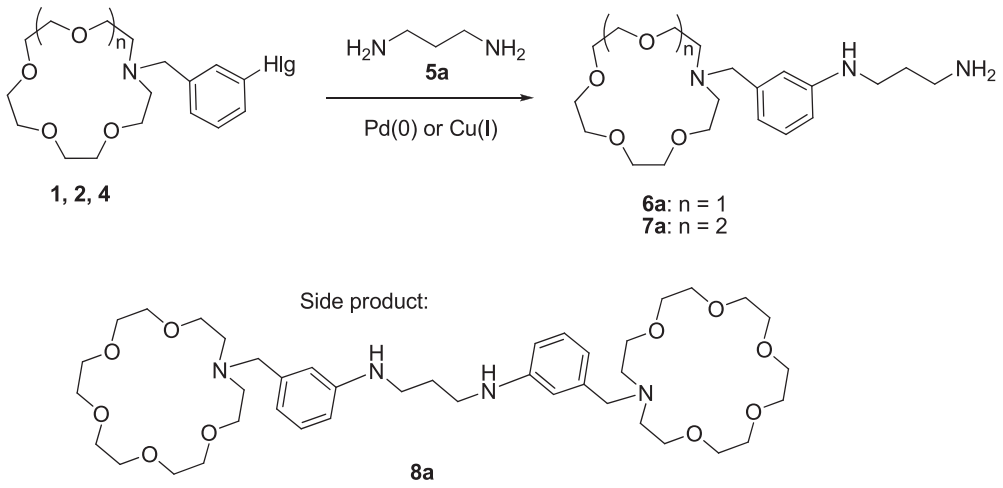
Results and Discussion

Initially 1-aza-15-crown-5 and 1-aza-18-crown-6 were modified with 3-bromobenzyl or 3-iodobenzyl substituents using simple nucleophilic substitution reactions with corresponding benzyl bromides (Scheme 1). Target products **1-4** were obtained in high yields (92-96 %) after simple work-up of the reaction mixtures.

First bromobenzyl derivatives of azacrown ethers **1** and **2** were employed in the Pd(0)-catalyzed reactions with 3 equiv. of propane-1,3-diamine **5a** to check the selectivity of the *N*-monoarylation *vs N,N'*-diarylation and to elaborate the conditions for the chromatographic isolation of the target products. Standard conditions for these processes were applied: $Pd(dba)_2$/BINAP catalytic system (4/4.5 mol%), 1.5 equiv. *t*BuONa as a base. The amination of compound **1** using 0.02 M solution of **1** led to 85 % yield of the monoarylation product **6a**, and after column chromatography it was isolated in 43 % yield, whereas the same reaction in a more concentrated solution (*C* = 0.05 M) led to 87 % yield of the target compound **6a** in the reaction mixture and 58 % yield after chromatography. In the case of compound **2** the similar reaction led to 77 % yield of the product of monoarylation **7a** and 23 % yield of the diarylated diamine **8a**. After column chromatography their yields were 30 and 8 % respectively (Scheme 2). The application of 4 equiv. of propane-1,3-diamine in the reaction with compound **2** resulted in 88 % yield of the target compound **7a** in the reaction mixture, thus it can be used *in situ* for some further transformations. The yield after chromatography in this case also increased to 46 %. Amination reactions were also conducted with iodobenzyl derivative **4** using either CuI/L1 (10/20 mol%) catalytic system (L1 = *l*-proline), 1.5 equiv. Cs_2CO_3 in boiling EtCN (*C* = 0.5 M), or CuI/L2 (10/20 mol%) catalytic system (L2 = 2-isobutyrylcyclohexanone), 1.5 equiv. Cs_2CO_3 in DMF (140 °C). The first reaction afforded 80 % yield of the compound **7a** in the reaction mixture and 22 % after chromatographic isolation, the second reaction produced 17 % of the same compound after chromatography. No product of diarylation **8a** was noted in both cases. For this reason we chose CuI/L1/EtCN for further syntheses of monoaryl derivatives of polyoxadiamines. It should be noted that as the excess of propane-1,3-diamine can easily be removed in high vacuum and only 2 equiv. of this diamine



Scheme 1.



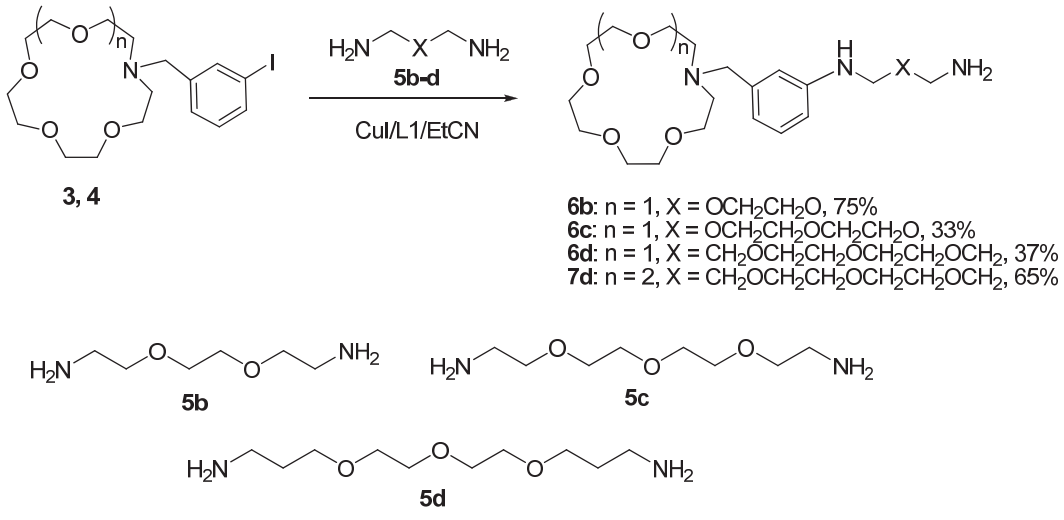
Scheme 2.

are needed to form the monoarylated derivative **7a**, in the case of further transformations of this compound one does not need its chromatographic purification and may use it *in situ*.

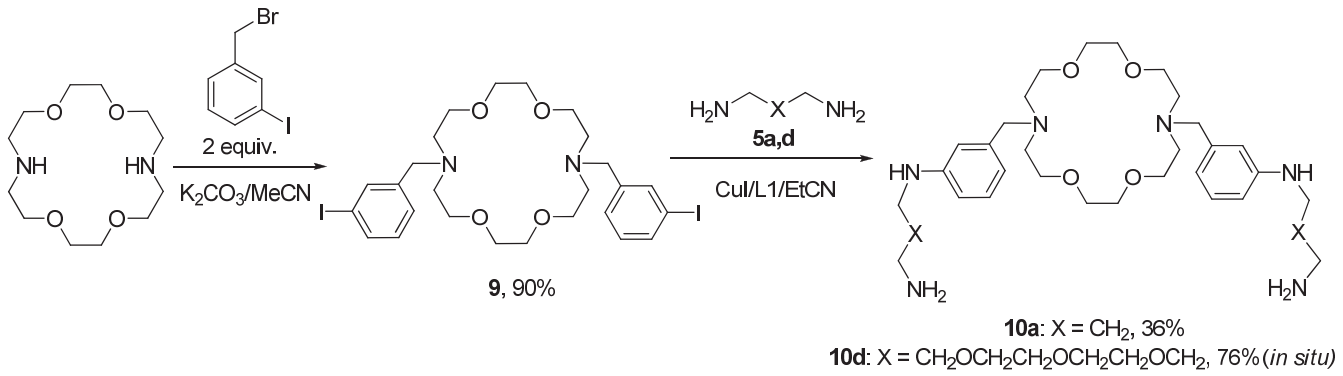
Further Cu(I)-catalyzed reactions were conducted using iodobenzyl derivatives **3** and **4** and a number of di- and trioxadiamines **5b-c** taken in two-fold excess (Scheme 3). These reactions were catalyzed by CuI/L1 (10/20 mol%) in the presence of Cs_2CO_3 in EtCN and the products were isolated by column chromatography. Dioxadiamine **5b** afforded 75 % yield of the target compound **6b**, while the reactions with trioxadiamines **5c,d** gave lower yields of corresponding derivatives **6c,d** (33 and 37 %). The amination of compound **4** with trioxadiamine **5d** was much more successful and the product **7d** was obtained in 65 % yield. No products of *N,N'*-diarylation of polyoxadiamiens were isolated in all cases. This fact is in a good correspondence with our previous results of the Cu-catalyzed arylation of polyoxadiamines.[27] In this research we did not use polyamines as substrates though they were found to participate better than oxadiamines in the copper-catalyzed arylation and heteroarylation reactions.[27,28] This was done in view of a practical impossibility of the isolation of their pure monoaryl derivatives bearing azacrown moiety from the reaction mixture with the excess of polyamine.

Next we investigated the possibility to introduce diazacrown ethers in the reactions with propane-1,3-diamine and oxadiamines. *N,N'*-di(3-iodobenzyl) derivative of diaza-18-crown-6 **9** was synthesized in 90 % yield, and it was introduced in the reaction with 4 equiv. of propane-1,3-diamine catalyzed by CuI/L1 (20/40 mol%) (Scheme 4). The yield of the target compound **10a** exceeded 80 % in the reaction mixture, and after column chromatography it was 36 %. The same reaction with trioxadiamine **5d** afforded 76 % yield of the bis(trioxadiamine) derivative **10d** in the reaction mixture.

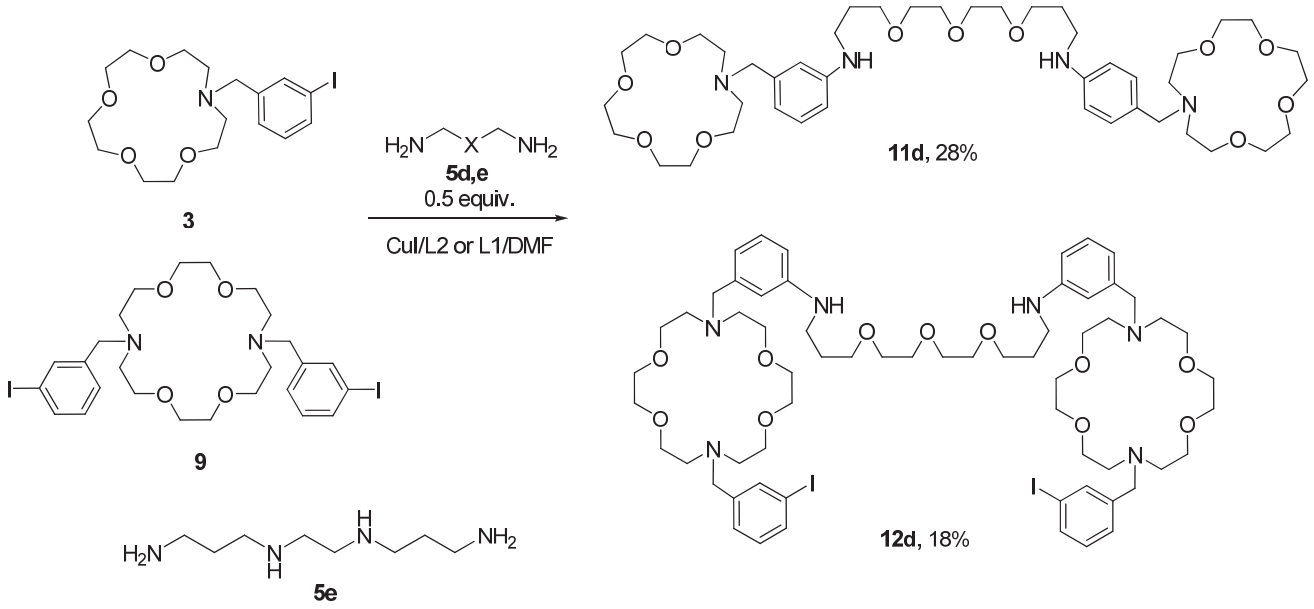
According to our previous investigations, the copper-catalyzed *N,N'*-diarylation of diamines and oxadiamines turned to be a challenging task. We carried out the diarylation of trioxadiamine **5d** using 2 equiv. of iodobenzyl substituted azacrown **3** (Scheme 5). In this case the catalytic system CuI/L2 in DMF (140 °C) was employed because we had shown it to promote *N,N'*-diarylation of oxadiamines with simple aryl



Scheme 3.



Scheme 4.



Scheme 5.

iodides.[27] The target product **11d** was isolated in 28 % yield. The same reaction with tetraamine **5e** catalyzed by CuI/L1 in DMF gave a complex mixture of the products of arylation among which the target compound was detected by NMR and MALDI-TOF spectroscopy, however, the pure product could not be isolated by column chromatography, probably due to the formation of isomers with close R_f. Similarly, the reaction of *N,N'*-di(3-iodobenzyl) substituted diazacrown **9** produced corresponding bisazacrown derivative of trioxadiamine **12d**, but the reaction with tetraamine **5e** gave only an inseparable mixture of unidentified compounds.

Conclusions

To sum up, we investigated the possibility to modify azacrown ethers with propane-1,3-diamine and polyoxadiamine podands using Cu(I)-catalyzed amination and found out that this approach is quite applicable. The reactions mediated by Cu(I) and Pd(0) were shown to produce the target arylation products in comparable yields. Moderate yields of the target compounds were due to their difficult isolation using column chromatography, and in the case of propane-1,3-diamine its excess can be removed *in vacuo*, and the product was shown to be enough pure for further transformations. Cu(I)-catalyzed diamination of the diazacrown derivative was also demonstrated as well as *N,N'*-diarylation of trioxadiamine with iodobenzyl derivatives of aza- and diazacrown ethers. Only diamines and polyoxadiamines but not polyamines can be employed in these reactions.

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