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Synthesis of diazacrown ethers based on anthracene and anthraquinone by Pd-catalyzed amination reactions

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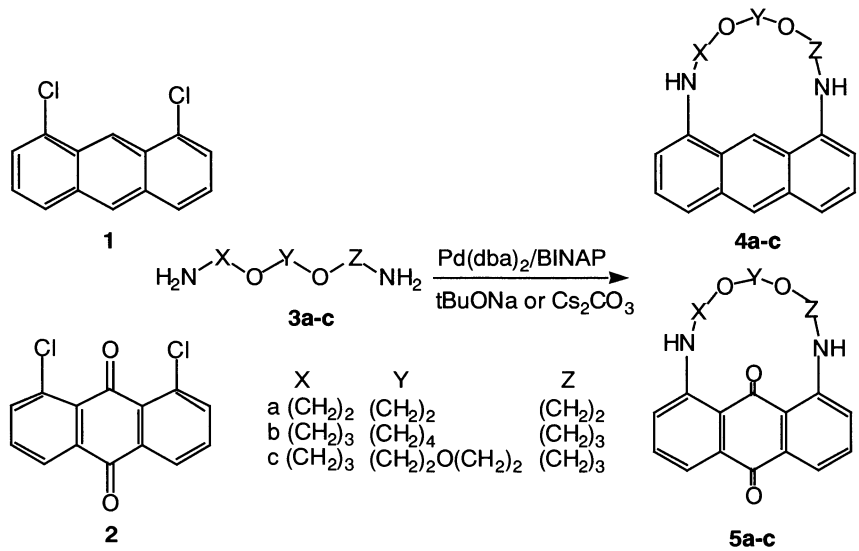
Abstract—Pd-catalyzed amination reactions of 1,8-dichloroanthracene and 1,8-dichloroanthra-9,10-quinone with di- and trioxadiamines can serve a convenient one-pot synthetic approach to diazacrown ethers.

Crown ethers have been exhaustively studied over the last decades and data about their synthesis is well-documented.[1] They proved to be remarkable ligands that coordinate metal cations, other cationic species and even neutral molecules. The well-studied chemistry of crown ethers now extends to supramolecular chemistry.[2] Indeed, macrocycles possessing fluorescent properties, especially the combination of anthracene with crown ethers, appear to be very promising.[3] Proton sensors were produced either by attaching one or two crown ether cycles to anthracene or by attaching a macrocycle to positions 9 and 10 of the anthracene moiety.[4] A macrocycle bonded to two anthracenes or two anthracenes attached to a crown ether generated a crown–cryptand photoswitch.[5,6] Anthracene was also used for detecting Cu^{2+} ions and D-glucoseamine.[7,8] Complexation abilities of substituted crown ethers, whose macrocycle is bound to two anthracene or naphtalene rings, have recently been studied.[9,10] Among all these macrocycles, oxygen or nitrogen atoms incorporated in the cycle are linked to arene moieties through at least one methylene group.



Scheme 1.

Keywords: macrocycles; Pd catalysis; amines; arylation.

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Here, we report the synthesis of a new family of diazacrown ethers that use anthracene or anthraquinone moiety as an assembling unit, by means of a Pd-catalyzed amination reaction of arylhalides.[11] For the first time, the formation of a direct bond C(sp^2)-N in the synthesis of macrocycles has been achieved with precursors which did not contain any activated chlorine atom. 1,8-Dichloroanthracene **1** and 1,8-dichloroanthraquinone **2** were selected as appropriate substrates; 3,6-trioxa-1,8-diaminooctane **3a**, 4,9-dioxa-1,12-diaminododecane **3b**, and 4,7,10-trioxa-1,13-diaminotridecane **3c** were used as aminating agents (Scheme 1).

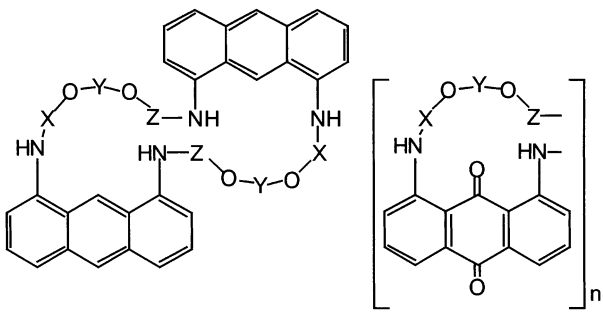
The $Pd(dba)_2$/BINAP (8 mol%) catalytic system introduced by Buchwald for arylhalides amination turned out to be an efficient catalyst.[12] Sodium *tert*-butoxide was used as a base for aminating dichloroanthracene while cesium carbonate was utilized in the case of dichloroanthraquinone. Diluted solutions of reagents in 1:1 mole ratio in dioxane (0.017–0.025 M) were used so as to eliminate any undesirable formation of oligomers with higher molecular masses, and prolonged reflux (72–103 h) was required to complete cyclization.

Yields of anthracene-based macrocycles **4a–c** ranged from 20 to 29%, while anthraquinone-based crowns **5a–c** ranged from 29 to 37% (Table 1). A complete consumption of starting arylhalides has been observed in all cases. Target macrocycles were isolated from reaction mixtures by column chromatography on silica and appeared to be either brown (**4a–c**) or red (**5a–c**) solids.

The nature of by-products formed in these reactions was also partially determined. They can be divided into two types: cyclic and linear oligomers. The reaction of **1** with diamines provided rather small amounts (<10%) of cyclic oligomers, which were mainly dimers **6a–c** ($n=2$, n is the number of monomer units in a macrocycle). On the contrary, in the case of **3c**, the formation of trimer and tetramer was obvious. However, amounts of linear species with 2:1 and 3:2 anthracene/amine ratios were quite negligible, and 1-amino-8-chloroanthracene was isolated from the reaction mixture in 18% yield only once.

The reaction of 1,8-dichloroanthraquinone **2** with diamines led to a high ratio of cyclic oligomers. Dioxadiamine **3a** generated only a tiny quantity (about 1%) of a mixture of cyclic tetra- and pentamers while arylation of diamines **3b,c** yielded a substantial amount of cyclic and linear oligomers of type **7**, **8**, and **9** (Schemes 2 and 3). With regards to dioxadiamine **3b**, dimer and trimer were isolated separately, their yields being, respectively, equal to 12 and 8%, and a mixture of oligomers with higher masses **7b**, **8b**, **9b** (with n up to 8) was obtained in 20% yield (Scheme 3).

We have therefore, shown that the dilution of a reaction mixture has a strong effect on the yield of the desired macrocycle. Such a dependence of the monomeric molecule on the concentration of reagents has been demonstrated in the case of trioxadiamine **3c**. When carrying out the reaction with 0.025 M concentration of starting compounds, diazacrown ether **5c** was formed in 29% yield whereas the total yield of higher mass oligomers exceeded 50%. When a more diluted solution of reagents was used (0.017 M), the target molecule's yield increased to 37%, that of the dimer to 18%, whereas higher oligomers **7c**, **8c**, **9c** corresponded to 25% of the mixture.

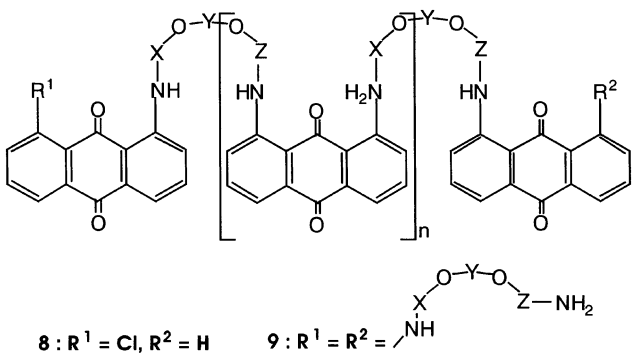


Scheme 2.

Table 1. Reaction conditions and yields of isolated compounds **4–7**

Starting arylhalide	Starting diamine	Product	Reaction time (h) (reflux)	Concentration of reagents (M)	Yield (%)[a]
1	**3a** $(NH_2(CH_2)_2OCH_2)_2$	**4a**	103	0.02	28
		6a ($n=2$)			8
1	**3b** $(NH_2(CH_2)_2OCH_2CH_2)_2$	**4b**	77	0.017	20
1	**3c** $(NH_2(CH_2)_2OCH_2CH_2)_2O$	**4c**	78	0.025	29
		6c ($n=2$)			10
2	**3a** $(NH_2(CH_2)_2OCH_2)_2$	**5a**	96	0.017	36
2	**3b** $(NH_2(CH_2)_2OCH_2CH_2)_2$	**5b**	77	0.017	33
		7b ($n=2$)			12
		7b ($n=3$)			8
2	**3c**	**5c**	72	0.025	29
2	**3c** $(NH_2(CH_2)_2OCH_2CH_2)_2O$	**5c**	80	0.017	37
		7c ($n=2$)			18

[a] Yields after column chromatography.



Scheme 3.

Typical experimental procedure

A two-necked round flask filled with dry argon is charged with a mixture of 247 mg (1 mmol) of 1,8-dichloroanthracene (or 277 mg of 1,8-dichloroanthraquinone),[13] 1 mmol of diamine, 46 mg (0.098 mmol) of $Pd(dba)_2$,[14] 55 mg (0.084 mmol) of BINAP, 400 mg (4 mmol) of tBuONa (1.4 g (4 mmol) of Cs_2CO_3 for **2**), and 40–60 ml of absolute dioxane. The reaction mixture is refluxed for 72–103 h. Then, after filtration, dioxane is evaporated in vacuum and produces a dark brown residue (deep-red in case of **2**). The solid is dissolved in 30 ml of dichloromethane and extracted with 15 ml of water. The water layer is extracted by 3×25 ml of dichloromethane, organic fractions are combined, dried over Na_2SO_4 and the solvent evaporated. The residue is chromatographed on silica using subsequently dichloromethane, CH_2Cl_2/MeOH = 500:1, 200:1, 100:1, 50:1 eluents. All obtained compounds were characterized by ^1H and ^{13}C NMR spectroscopy, MALDI-TOF spectroscopy and elemental analysis.

Selected NMR data (in $CDCl_3$, ^1H: 200 MHz, δ_H, ppm, J_{HH}, Hz; ^{13}C: 50 MHz, δ_C, ppm)

Compound **4a**. ^1H: 3.50t (4H, 4.8), 3.84t (4H, 4.8), 3.85s (4H), 6.72d (2H, 7.1), 7.32dd (2H, 8.3, 7.1), 7.49d (2H, 8.3), 8.31s (1H), 9.04s (1H); ^{13}C NMR: 47.4 (2C), 70.3 (2C), 71.1 (2C), 108.1 (2C), 114.7 (1C), 119.5 (2C), 124.4 (1C), 126.1 (2C), 126.5 (2C), 132.7 (2C), 144.9 (2C). MALDI-TOF [M^+] 321.75 (calcd 322.17).

Compound **5b**. ^1H: 1.75bs (4H), 1.90q (4H, 5.0), 3.34q (4H, 4.8), 3.48bs (4H), 3.53t (4H, 5.4), 6.87d (2H, 8.2), 7.34dd (8.2, 7.5), 7.44d (2H, 7.5), 9.77t (4.6); ^{13}C NMR: 26.3 (2C), 28.1 (2C), 40.9 (2C), 68.8 (2C), 71.3 (2C), 114.3 (4C), 117.2 (2C), 133.7 (2C), 134.3 (2C), 150.9 (2C), 184.6 (1C), 188.3 (1C). MALDI-TOF [M^+] 408.13 (calcd 408.20).

Compound **6c**. ($n=2$) ^1H: 1.98q (8H, 6.0), 3.37t (8H, 6.2), 3.51t (8H, 5.5), 3.54dd (8H, 5.0, 3.0), 3.69dd (8H, 5.0, 3.0), 6.40m (4H), 7.25–7.32m (8H), 8.23s (2H), 8.45s (2H); ^{13}C NMR: 29.0 (4C), 42.9 (4C), 70.5 (4C), 70.6 (4C), 70.6 (4C), 101.7 (4C), 112.3 (2C), 116.9 (4C), 123.1 (2C), 126.8 (4C), 127.1 (4C), 132.9 (4C), 144.5 (4C). MALDI-TOF [M^+] 788.06 (calcd 788.45).

Compound **7b**. ($n=3$) ^1H: 1.77q (12H, 2.6), 1.95q (12H, 6.0), 3.32q (12H, 6.0), 3.46t (12H, 2.6), 3.53t (12H, 5.9), 6.94dd (6H, 8.2, 1.4), 7.38dd (6H, 8.2, 7.2), 7.45dd (6H, 7.2, 1.4), 9.58d (6H, 5.0); ^{13}C NMR: 26.5 (6C), 29.3 (6C), 40.1 (6C), 68.2 (6C), 70.8 (6C), 114.3 (6C), 114.7 (6C), 117.5 (6C), 133.9 (6C), 134.2 (6C), 151.0 (6C), 184.4 (3C), 188.7 (3C). MALDI-TOF [M^+] 1224.83 (calcd 1224.61).

Compound **7c**. ($n=2$) ^1H: 1.98q (8H, 6.2), 3.30q (8H, 6.0), 3.62t (8H, 6.2), 3.63m (8H), 3.70m (8H), 6.88dd (4H, 7.9, 2.0), 7.29–7.41m (8H), 9.54t (4H, 4.8). ^{13}C NMR: 29.6 (4C), 40.4 (4C), 69.2 (4C), 70.8 (4C), 71.1 (4C), 114.7 (4C), 115.2 (4C), 117.8 (4C), 134.3 (4C), 134.6 (4C), 151.4 (4C) 184.8 (2C), 188.9 (2C). MALDI-TOF [M^+] 848.11 (calcd 848.40).

Acknowledgements

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