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Pd-catalyzed amination in the synthesis of a new family of polyazamacrocycles containing 1,3-disubstituted adamantane moieties

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Pd-catalyzed amination of a number of dihaloarenes with equimolar amounts of 1,3-bis(2-aminoethyl)adamantane in dilute dioxane solution provided one-step route to a new family of polyazamacrocycles with various cavity sizes containing one or several adamantane and aromatic fragments.

A reliable synthesis of 1,3-bis(2-aminoethyl)adamantane **1** was patented three decades ago[1] and since that time it found many useful applications. Free diamine **1** together with its analogue, 1,3-bis(aminomethyl)adamantane, as well as their dihydrochlorides were tested as antiviral agents.[2] While the former was found to be active against the poultry plague,[3] the latter was patented as an antiviral agent for home animals.[4,5] Diamine **1** was used as a component of epoxide polymers,[6] especially for the improvement of their optical properties and durability,[7] and for modifying aromatic polyimides.[8–10] Polyamides with higher thermal and hydrolytic stabilty were synthesized on the basis of this diamine,[11] and its chemical derivatives were also found to be of use: diisocyanates were introduced into polymeric chains of polyuretanes to increase their chemical and light stability, whereas 1,3-bis(2-*m*-fluorobenzylideneaminoethyl)adamantane or 1,3-bis(2-*m*-methoxybenzylideneaminoethyl)adamantane were found to improve mechanical properties of rubber.[12] Free diamine was also used for rubber stabilization.[13,14] Cyclic Schiff bases were synthesized using diamine **1** for biological activity studies.[15] Our own interest in this diamine, as well as in other adamantane-containing amines, lies in the field of their catalytic N-arylation for the synthesis of potential pharmacologically active compounds. Its *N*,*N*′-dipyridyl derivative has been already found to have nootropic effect on mice.[16] We supposed that the introduction of adamantane fragments into polyazamacrocycles would increase their lipophilicity and favor membrane transport; for this reason, we decided to carry out the synthesis of such cyclic molecules whose cavities could serve as hosts for small organic molecules. Having acquired a good experience in the synthesis of polyazamacrocycles *via* Pd-catalyzed amination reactions,[17–20] we decided to investigate the applicability of this approach to previously unknown adamantane-containing macrocycles.

We carried out the reactions of equimolar amounts of 1,3-bis-(2-aminoethyl)adamantane **1** with a variety of dihaloarenes **2**–**6** (Scheme 1).† They were catalyzed with $Pd(dba)_2$/BINAP (8/9 mol%), Bu^{t}ONa was used as base, dilute solutions of reagents in dioxane (c = 0.02 mol dm^{-3}) were employed. To run the reactions to completion, they were refluxed for 24–30 h in the case of 1,3-dibromobenzene **2**, 3,3′-dibromobiphenyl **4**, and 1,8-dichloroanthracene **6**; for 15 h in the case of 2,6-dibromopyridine **3**, and for 7 h in the case of the most reactive 2,7-dibromonaphthalene **5**. The results of the experiments are presented in Scheme 1. 1,3-Dibromobenzene **2** and 2,7-dibromonaph-

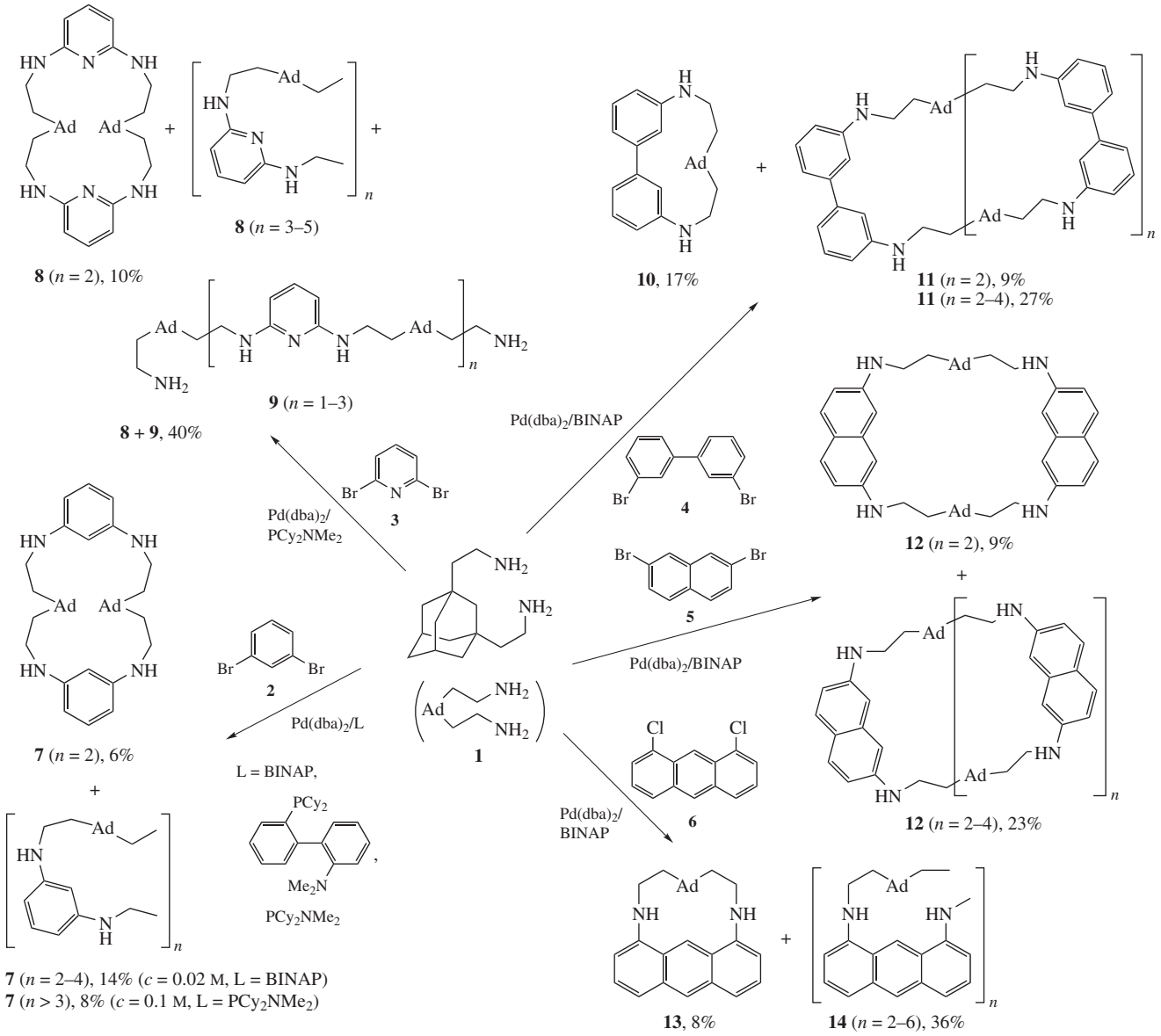
† *Typical procedure for the synthesis of macrocycles* **7**, **8**, **10**–**14**. A two-neck flask (50 ml) flushed with dry argon and equipped with a magnetic stirrer was charged with appropriate dihaloarene (0.5 mmol), $Pd(dba)_2$ (8 mol%, 23 mg), BINAP or 2-dicyclohexylphosphino-2′-dimethylaminobiphenyl (9 mol%, 28 or 18 mg), absolute dioxane (25 ml), 1,3-bis-(2-aminoethyl)adamantane **1** (0.5 mmol, 111 mg), Bu^{t}ONa (~1.5 mmol, 150 mg), and the reaction mixture was refluxed for 7–30 h. It was cooled to ambient temperature, filtered and evaporated *in vacuo* to give brown crude mass which was chromatographed on silica using a sequence of eluents: CH_2Cl_2, CH_2Cl_2/MeOH (500:1–3:1).

Cyclodimer **7** (n = 2): eluent, CH_2Cl_2/MeOH (500:1), yield 9 mg (6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30–1.64 (m, 24H), 1.45 (t, 8H, J 7.8 Hz), 2.06 (s, 4H), 3.11 (t, 8H, J 7.8 Hz), 3.41 (br. s, 4H), 5.86 (s, 2H), 5.93 (d, 4H, J 7.8 Hz), 6.87 (t, 2H, J 7.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 28.9 (4C), 32.7 (4C), 36.5 (2C), 38.5 (4C), 42.3 (8C), 43.9 (4C), 46.7 (2C), 94.1 (2C), 103.8 (4C), 129.5 (2C), 149.9 (4C). MS (MALDI-TOF), *m*/*z*: 592.58 [M$^+$].

Cyclodimer **8** (n = 2): eluent, CH_2Cl_2/MeOH (25:1), yield 16 mg (10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36–1.60 (m, 24H), 1.39 (t, 8H, J 7.7 Hz), 2.01 (br. s, 4H), 3.28 (t, 8H, J 7.7 Hz), 4.14 (br. s, 4H), 5.62 (d, 4H, J 7.8 Hz), 7.12 (t, 2H, J 7.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 29.1 (4C), 32.8 (4C), 36.6 (2C), 36.7 (4C), 42.2 (8C), 44.0 (4C), 47.2 (2C), 94.9 (4C), 138.4 (2C), 158.8 (4C). MS (MALDI-TOF), *m*/*z*: 594.25 [M$^+$].

Macrocycle **10**: eluent, CH_2Cl_2/MeOH (500:1), yield 32 mg (17%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35–1.70 (m, 16H), 2.03 (s, 2H), 3.15 (br. s, 2H), 3.41 (br. s, 2H), 3.93 (br. s, 2H), 6.54 (d, 2H, J 7.9 Hz), 6.99 (br. s, 2H), 7.18 (t, 2H, J 7.8 Hz), 7.22 (br. s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 29.0 (2C), 33.2 (2C), 36.8 (1C), 37.3 (2C), 38.7 (2C), 43.4 (2C), 44.4 (2C), 48.4 (1C), 109.2 (2C), 114.3 (2C), 115.1 (2C), 129.4 (2C), 147.8 (2C) (two aromatic quaternary carbon atoms were not assigned). MS (MALDI-TOF), *m*/*z*: 372.38 [M$^+$].

Cyclodimer **11** (n = 2): eluent CH_2Cl_2/MeOH (200:1), yield 16 mg (9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25 (s, 4H), 1.40 (s, 4H), 1.48 (t, 8H, J 7.8 Hz), 1.51 (br. s, 12H), 1.63 (s, 4H), 2.05 (s, 4H), 3.15 (t, 8H, J 7.8 Hz), 3.56 (br. s, 4H), 6.55 (d, 4H, J 8.2 Hz), 6.78 (s, 4H), 6.89 (d, 4H, J 7.7 Hz), 7.18 (t, 4H, J 7.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 29.0 (4C), 32.8 (4C), 36.6 (2C), 38.7 (4C), 42.2 (8C), 43.7 (4C), 47.0 (2C), 111.5 (4C), 111.9 (4C), 116.5 (4C), 129.4 (4C), 143.2 (4C), 148.6 (4C). MS (MALDI-TOF), *m*/*z*: 744.44 [M$^+$].



Scheme 1

thalene **5** provided macrocycles with two adamantane and two aromatic moieties (cyclodimers) **7** ($n = 2$) and **12** ($n = 2$), respectively, in 6–9% yields. Surprisingly, cyclodimer **12** ($n = 2$) turned to be quite insoluble in chloroform, and this property was used for its easy separation from higher mass oligomers. The reaction of 2,6-dibromopyridine **3** in the presence of BINAP was not successful, but the application of another phosphine ligand, 2-dicyclohexylphosphino-2′-dimethylaminobiphenyl, provided desired macrocycle **8** ($n = 2$) in 10% yield. Cyclic oligomers with higher masses [**7**, **8** and **12** ($n > 2$)] were isolated apart from cyclodimers by column chromatography in 14–40% yields (in the case of **8**, as a mixture with linear 2,6-diamino derivatives of pyridine **9**). In these reactions, the geometry of starting compounds could not provide the formation of 1:1 products. On contrary, such compounds were formed in the case of 3,3′-dibromobiphenyl and 1,8-dichloroanthracene, namely, **10** (17%) and **13** (8%). Cyclodimer **11** ($n = 2$) was obtained in 9% yield, whereas the mixtures of cyclooligomers with higher masses **11** ($n = 2$–4) and **14** ($n = 2$–6) were isolated in 27 and 36% yields, respectively. Note that NMR spectra of the macrocycles with one set of adamantane and aromatic fragments substantially differed from those of cyclodimers due to a close position of aromatic and aliphatic parts of the molecule in the first case.

1,3-Bis(2-aminoethyl)adamantane possesses the diamine fragment with a chain length of nine atoms. In our previous research, we applied N^1-(3-aminopropyl)propane-1,3-diamine with the same chain length in the Pd-catalyzed amination of 1,3-dibromobenzene,[20] 2,6-dibromopyridine,[19] 1,8-dichloroanthracene,[17] 3,3′-dibromobiphenyl and 2,7-dibromonaphthalene.[21] We found that except for the last dihaloarene all other compounds provided corresponding triazacycles in 14–25% yields. The reaction with

Cyclodimer **12** ($n = 2$): eluent CH_2Cl_2/MeOH (200:1), yield 17 mg (9%). ^{1}H NMR (400 MHz, [$^2H_6$]DMSO) δ: 1.42–1.68 (m, 24H), 1.49 (t, 8H, J 8.0 Hz), 2.04 (s, 4H), 3.01 (t, 8H, J 8.0 Hz), 6.48 (d, 4H, J 1.8 Hz), 6.53 (dd, 4H, J 8.6 and 1.8 Hz), 7.23 (d, 4H, J 8.6 Hz) (NH protons were not assigned). ^{13}C NMR (100.6 MHz, [$^2H_6$]DMSO) δ: 28.7 (4C), 32.3 (4C), 36.5 (2C), 37.7 (4C), 42.4 (8C), 43.2 (4C), 44.7 (2C), 100.9 (4C), 113.9 (4C), 119.9 (2C), 127.8 (4C), 137.4 (2C), 147.2 (4C). MS (MALDI-TOF), m/z: 692.49 [M$^+$].

Macrocycle **13**: eluent CH_2Cl_2/MeOH (500:1), yield 16 mg (8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (s, 2H), 1.34 (d, 4H, J 11.8 Hz), 1.49 (d, 4H, J 12.3 Hz), 1.61 (s, 2H), 1.64 (t, 4H, J 5.4 Hz), 2.01 (br. s, 2H), 3.30 (t, 4H, J 5.4 Hz), 4.20 (br. s, 2H), 6.77 (d, 2H, J 7.1 Hz), 7.32 (dd, 2H, J 8.4 and 7.1 Hz), 7.53 (d, 2H, J 8.4 Hz), 8.32 (s, 1H), 8.97 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 29.0 (2C), 33.7 (2C), 36.8 (1C), 42.1 (4C), 43.4 (2C), 43.6 (2C), 46.7 (1C), 110.1 (2C), 116.8 (1C), 120.2 (2C), 125.0 (2C), 126.1 (2C), 126.3 (1C), 132.9 (2C), 145.5 (2C). MS (MALDI-TOF), m/z: 396.33 [M$^+$].

2,7-dibromonaphthalene, on contrary, gave only cyclodimer and cyclic oligomers. Indeed, the aliphatic chain of the corresponding hypothetical triazacycle should be almost planar lying in the same plane with the naphthalene ring what is impossible due to steric reasons. Moreover, the adamantane part of the diamine fragment in **1** is rigid and this makes the geometrical factor more exacting in the formation of macrocycles with benzene and pyridine moieties.

We tried some other dihaloarenes in this reaction (1,5-dichloroanthracene, 1,8- and 1,5-dichloroanthraquinones) but they provided corresponding cyclodimers and cyclotrimers only in trace amounts as admixtures to linear oligomers. Note that this difference in the results observed with various dihaloarenes stems mainly from the position of halogen substituents and from the geometry of intermediate amino derivatives but not from the concentration of the reaction mixtures. Indeed, we carried out the reaction of diamine **1** with dibromobenzene **2** in 0.1 M dioxane solution and obtained cyclodimer **7** in 6% yield.

To sum up, we have found a simple one-step catalytic approach to novel adamantane-containing di- and polyazamacrocycles using 1,3-bis(2-aminoethyl)adamantane, revealed its scope and limitations. The results of the amination reactions, first of all, the size of macrocycles, turned to be strongly dependent on the nature of dihaloarenes used.

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