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Synthesis of macrocycles containing two pyridine and two polyamine moieties via Pd-catalyzed amination

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Abstract—The synthesis of macrocycles containing two pyridine and two polyamine fragments was carried out by the Pd-catalyzed amination of 2,6-dihalopyridines using polyamines and dioxadiamine. Two alternative approaches were elaborated and compared: via intermediate formation of N^{α},N^{ω}-bis(6-halopyridin-2-yl)polyamines or via 2,6-bis(polyamino)substituted pyridines. The yields of linear and cyclic products were shown to be strongly dependent on the nature of the starting polyamines and that of the halogen atom.

Macrocycles of different structures which contain polyamine and pyridine fragments have attracted the interest of researchers during last decade.[1–4] The introduction of a pyridine moiety strongly influences the thermodynamic properties and the complexation kinetics by increasing the conformational rigidity of the ligand and by changing its basicity. While the stability of the metal complexes of such macrocycles are usually decreased compared to tetraazamacrocycles, their rates of formation are often higher. In previously obtained macrocycles, the nitrogen atoms of the polyamine chain and pyridine ring are separated by methylene, methyne or carbonyl groups, and a compound with C(sp^2)–N bond was obtained by reduction of the corresponding diamide formed in the reaction of 2,6-diaminopyridine with diacyl dichloride.[5] Recently the synthesis of a number of pyridine-containing macrocycles by the reaction of dimethyl 2,6-pyridinedicarboxylates with linear diamines has been reported.[6,7] The resulting macrocycles were found to be interesting for anion binding. Our interest lies in the application of Pd-catalyzed amination reactions to the synthesis of polyazamacrocycles in which nitrogen atoms are directly linked to the aromatic fragments. Using this approach, we have synthesized a series of macrocycles incorporating 2,6- and 3,5-disubstituted pyridines.[8–10] Here we report the application of this method to the synthesis of these compounds with a larger cavity size which may be interesting for binding larger cations, cations with high coordination numbers or for the preparation of binuclear complexes.

During previous studies on the reactions of 2,6-dibromo- and 2,6-dichloropyridines **1a**,**b** with polyamines **2a**–**d** in dilute conditions we established that the macrocyclic compounds which contain two pyridine and two polyamine moieties ('cyclodimers' **7**) were not formed even as by-products in the majority of cases, except for dioxa- and trioxadiamines like **2c**. Changing the reaction conditions did not lead to the one-pot formation of these compounds in notable quantities. This result was different from the previously studied amination of 1,8-dichloroanthracene and 1,8-dichloroanthraquinone where cyclodimers and even cyclotrimers were often obtained as by-products.[11] Therefore, we have elaborated two alternative methods for the synthesis of these macrocyclic molecules. According to the first approach (a) polyamines are arylated with two equivalents of 2,6-dihalopyridines to form N^{α},N^{ω}-bis(6-halopyridin-2-yl)polyamines **3** and **5** which further react with the second equivalent of polyamine giving the desired cyclodimers **7**. In the second method (b) the intermediate 2,6-bis(polyamino)pyridine **8** is formed by the reaction of 2,6-dibromopyridine **1a** with an excess of

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polyamine **2** and compound **8** gives the corresponding cyclodimer **7** upon reaction with a second molecule of 2,6-dibromopyridine.

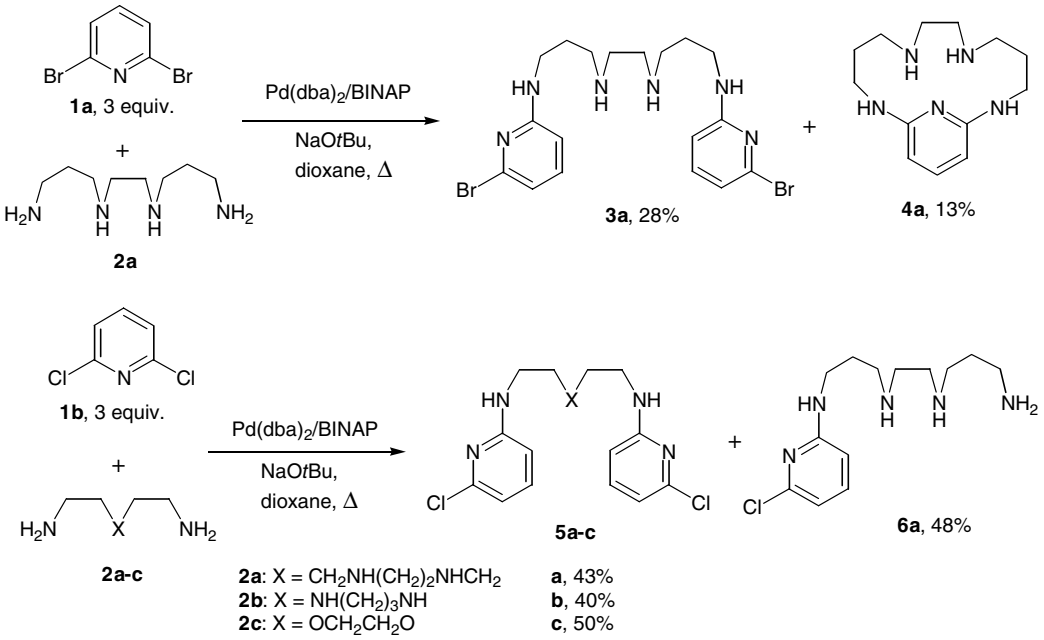
Method A: The reaction of tetraamine **2a** with 3 equiv of 2,6-dibromopyridine **1a** in boiling dioxane ($c = 0.1$ M) for ca. 5 h, in the presence of 8 mol % $Pd(dba)_2$, 9 mol % BINAP and NaO*t*Bu as a base provided a mixture of the target bis(pyridinyl)substituted tetraamine **3a** and the macrocycle **4a**, which was formed in a substantial amount due to the concentration of reactants (0.1 M) (Scheme 1). This undesirable formation of the macrocycle is consistent with the fact already described by us previously[8] that macrocycles generated from 2,6-dibromopyridine were readily formed at high concentrations due to the possible chelation of the Pd atom by the pyridine nitrogen.

The use of 2,6-dichloropyridine **1b** (3 equiv) in this reaction led to a higher yield (43%) of the desired product **5a** and none of the macrocycle **4a**. Monoarylated compound **6a** was isolated in 48% yield as a by-product (Scheme 1). Another tetraamine **2b** and dioxadiamine **2c** were also employed in this reaction to produce the corresponding bis(pyridinyl)substituted polyamines **5b**,**c** in 40–50% yields.

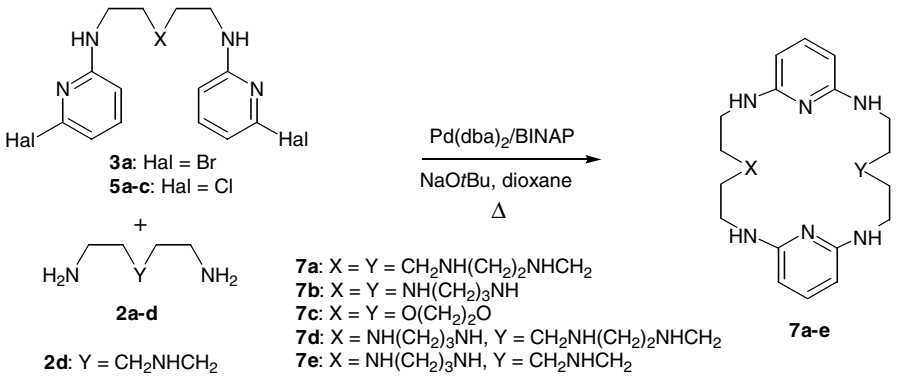
Macrocycles **7a**–**e** were synthesized by the reaction of bis(pyridinyl)substituted polyamines **3a** and **5a**–**c** with polyamines **2a**–**d** (Scheme 2). The reaction conditions and product yields are presented in Table 1. The syntheses were conducted in boiling dioxane (reaction time ca. 10 h), under dilute conditions ($c = 0.01$–0.05 M), which favoured cyclization. We have found that the use of the dibromo derivative **3a** provided the corresponding cyclodimer **7a** in a poorer yield than the dichloro derivative **5a** (entries 1 and 2). Usually bromoarenes are more active in amination reactions, in this case the lower yield could be due to excessive formation of linear oligomers. For the synthesis of two other symmetric cyclodimers **7b**,**c**, the corresponding bis(chloropyridinyl)polyamines **5b**,**c** were used (entries 3 and 4). The same procedure was successful for the synthesis of the macrocycles **7d**,**e** containing two different polyamine chains (entries 5 and 6).

Cyclodimers **7a**–**e** were isolated by column chromatography on silica gel. The experimental data indicates that the best results are achieved at lower concentrations and at higher catalyst loadings as the reactivity of tri- and tetraamines **2a**,**b**,**d** are similar in the amination reactions. The reaction with dioxadiamine **2c** proved to be the most successful, possibly due to the presence of two oxygen atoms in the chain instead of two nitrogens which can cause chelation of the palladium thus removing it from the catalytic cycle and decreasing the macrocycle yields. In the ^{1}H NMR spectra of compounds **7a**,**b** the signals are notably broadened; in both the proton and ^{13}C NMR spectra the two pyridine fragments are identical and the two polyamine chains being symmetrical are also identical. In contrast, for the macrocycle **7c** the signals are sharp, but the two pyridine and two dioxadiamine chains are different and unsymmetrical. This fact might be explained by the difference in the conformational rigidity of these macrocycles. It is interesting that the method provided two macrocycles (**7a** and **7c**) in very good yields which are higher than the yields of the corresponding macrocycles containing one pyridine and one polyamine fragment (**4a** and **4c** 24%) obtained by us previously.[9]

Method B: According to this approach we attempted an alternative synthesis of the macrocycles **7**. Initially 2,6-dibromopyridine **1a** was reacted with 4 equiv of poly-



Scheme 1. Synthesis of bis(pyridinyl)substituted polyamines.



Scheme 2. Synthesis of cyclodimers **7a–e** according to Method A.

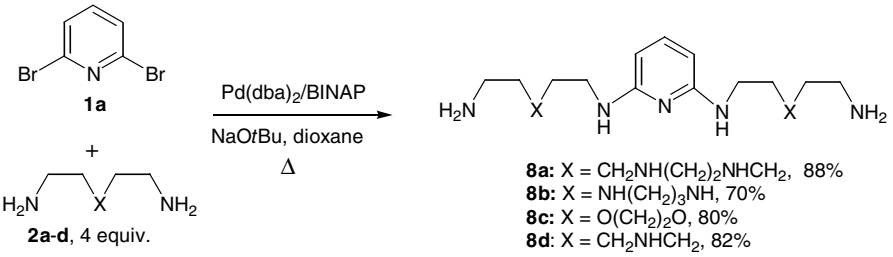
Table 1. Synthesis of cyclodimers **7a–e** via bis(pyridinyl)substituted polyamines **3** and **5a–c**

Entry	Starting compounds	$Pd(dba)_2$/BINAP (mol %)	Concentration (M)	Yield[a] (%)
1	**3a**+**2a**	10/14.5	0.01	**7a**, 16
2	**5a**+**2a**	18/18	0.017	**7a**, 38
3	**5b**+**2b**	6/7	0.05	**7b**, 14
4	**5c**+**2c**	8/9	0.025	**7c**, 43
5	**5b**+**2a**	6/7	0.05	**7d**, 19
6	**5b**+**2d**	6/7	0.05	**7e**, 11

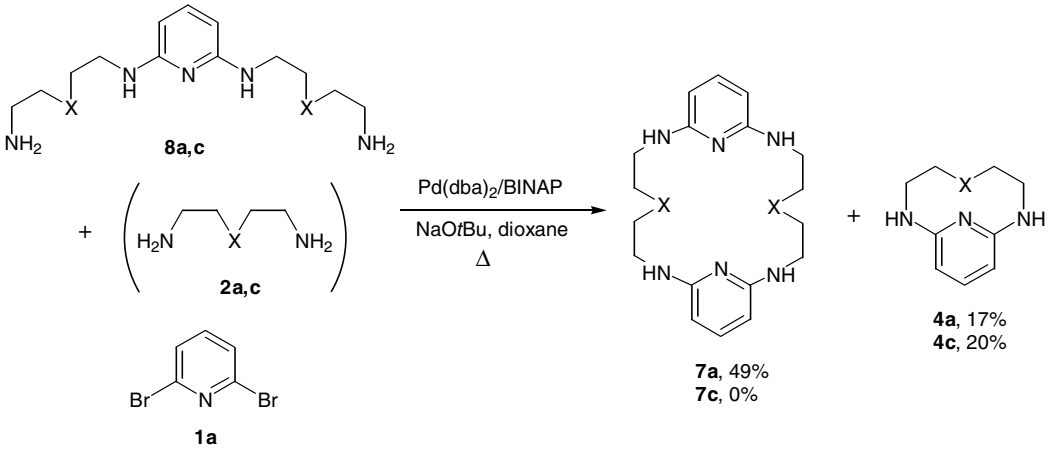
[a] The yields after column chromatography.

amines **2a–d** to give the corresponding bis(polyamino)-substituted pyridines **8a–d** in high yields (Scheme 3). The reactions were conducted in the presence of the $Pd(dba)_2$/BINAP system (8/9 mol %); sufficiently concentrated dioxane solutions ($c = 0.1$–0.2 M) were refluxed for 2–5 h. Column chromatography of these compounds led to significant losses, moreover, the products contained mixtures of starting polyamines. Thus they were used in situ for further transformation.

Macrocycles **7a**,**c** were chosen as target compounds for this synthetic route as they had been obtained in higher yields according to Method A. Compounds **8a**,**c** and 2,6-dibromopyridine **1a** were reacted in equimolar amounts (Scheme 4) using the $Pd(dba)_2$/BINAP catalytic system (13/14 mol %), in boiling dioxane ($c = 0.025$ M). Reflux was continued for several hours.



Scheme 3. Synthesis of bis(polyamino)substituted pyridines **8a–d**.



Scheme 4. Synthesis of cyclodimers **7a** and **7c** via Method B.

The results of Method B were different from those of Method A: while **7a** was isolated in 49% yield, cyclodimer **7c** was registered only in the reaction mixture and could not be isolated by column chromatography. It should be noted that the corresponding macrocycles **4a**,**c** were isolated in 17% and 20% yields, respectively, from the reaction of 2,6-dibromopyridine with excess of polyamines **2a**,**c** which had been used for the synthesis of intermediates **8a**,**c**.

In conclusion, we have reported two alternative methods for the synthesis of macrocycles **7** containing two 2,6-disubstituted pyridine moieties and two polyamine chains. The yields of these compounds are dependent on the nature of the starting polyamines and on the method used. The cyclodimers were obtained in useful yields (38–49%). Further studies on the scope and versatility of these methods is underway. A typical procedure[12] and selected spectroscopic data[13] are given below.

Acknowledgements

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12. Typical procedure. Method A: An argon-flushed flask equipped with a condenser was charged with 2,6-dihalopyridine **1** (1.5 mmol), $Pd(dba)_2$ (0.04 mmol), BINAP (0.045 mmol), abs. dioxane (5 ml), the appropriate polyamine **2** (0.5 mmol) and sodium *tert*-butoxide (1.5 mmol) and the reaction mixture was refluxed for 5 h. After evaporation of the solvent the residue was taken in dichloromethane (1–2 ml) and chromatographed on silica gel using a sequence of eluents CH_2Cl_2, CH_2Cl_2/MeOH 200:1–3:1 and CH_2Cl_2/MeOH/NH_3(aq) 100:20:1–10:4:1 depending on the nature of polyamine. The resulting bis-(6-halopyridinyl)polyamine **3** or **5** was reacted with an equimolar amount of the appropriate polyamine **2** under similar conditions (the concentration of starting compounds was 0.01–0.05 M). For catalyst loadings see Table 1. Column chromatography was carried out using the same sequence of eluents as above. Method B: An argon-flushed flask equipped with a condenser was charged with 2,6-dibromopyridine **1a** (0.5 mmol), $Pd(dba)_2$ (0.04 mmol), BINAP (0.045 mmol), abs. dioxane (2.5–5 ml), the appropriate polyamine **2** (2 mmol) and sodium *tert*-butoxide (1.5 mmol) and the reaction mixture was refluxed for 2–5 h. After cooling the reaction mixture under argon, a sample was taken for ^{1}H NMR assessment of the yield of bis(polyamino) substituted pyridine **8**. An equimolar amount of 2,6-dibromopyridine **1a**, $Pd(dba)_2$ (8–13 mol %), BINAP (9–14 mol %) in abs. dioxane (20 ml) and sodium *tert*-butoxide (1.5 mmol) were added and the reaction mixture was refluxed for 10 h. Column chromatography was carried out using the sequence of eluents described for Method A.
13. *Selected spectroscopic data*. Compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.77$ (q, $J = 6.3$ Hz, 4H), 2.02 (br s, 2 H), 2.73 (s, 4H), 2.74 (t, $J = 6.3$ Hz, 4H), 3.32 (br s, 4H), 5.37 (br s, 2H), 6.25 (d, $J = 8.1$ Hz, 2H), 6.67 (d, $J = 7.4$ Hz, 2H), 7.19 (t, $J = 7.8$, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 29.2$ (2C), 40.8 (2C), 47.7 (2C), 49.1 (2C), 104.5 (2C), 115.2 (2C), 139.2 (2C), 140.2 (2C), 158.8 (2C); MALDI-TOF $m/z = 485.5$ MH^+. Compound **7a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.73$ (q, $J = 6.3$ Hz, 8H), 2.70 (t, $J = 6.2$ Hz, 8H), 2.71 (s, 8H), 3.25 (t, $J = 6.4$ Hz, 8 H), 4.29 (br s, 4H), 5.64 (d, $J = 7.9$ Hz, 4H), 7.16 (t, $J = 7.9$ Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 29.3$ (4C), 40.7 (4C), 47.6 (4C), 48.8 (4C), 94.1 (4C), 138.9 (2C), 158.4 (4C); MALDI-TOF $m/z =$ 499.5 MH^+. Compound **7c**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.40$–3.80 (m, 24H), 3.88 (t, $J = 6.4$ Hz, 2H), 4.37 (t, $J = 6.6$ Hz, 2H), 5.92 (d, $J = 7.9$ Hz, 1H), 5.93 (d, $J =$ 7.9 Hz, 1H), 6.39 (d, $J = 7.9$ Hz, 1H), 6.47 (d, $J = 7.9$ Hz, 1H), 7.17 (t, $J = 7.9$ Hz, 1H), 7.21 (t, $J = 7.9$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 41.6$ (2C), 42.1 (1C), 47.8 (1C), 69.9 (2C), 70.1 (2C), 70.3 (2C), 70.9 (2C), 99.0 (1C), 100.7 (1C), 102.1 (1C), 102.7 (1C), 138.1 (1C), 138.3 (1C), 155.8 (1C), 156.1 (1C), 157.8 (2C); MALDI-TOF $m/z = 446.5$ M^+. Compound **8a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.57$ (q, $J = 7.0$ Hz, 4H), 1.70 (q, $J =$ 6.7 Hz, 4H), 2.61 (t, $J = 7.0$ Hz, 4H), 2.65 (s, 8H), 2.68 (t, $J = 7.0$ Hz, 4H), 2.69 (t, $J = 6.9$ Hz, 4H), 3.20 (t, $J = 6.7$ Hz, 4H), 5.62 (d, $J = 7.9$ Hz, 2H), 7.14 (t, $J =$ 7.9 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 29.6$ (2C), 33.5 (2C), 40.2 (2C), 40.3 (2C), 47.5 (4C), 49.2 (4C), 94.0 (2C), 138.7 (1C), 158.1 (2C); MALDI-TOF $m/z =$ 424.4 MH^+.