Synthesis of 1,3-Bis(trimethylcyclam) and 1,3-Bis(trimethylcyclozen)
Substituted Benzenes

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 Introduction

Tetraazamacrocyclic compounds, mainly cyclams and cyclens, are of major importance due to their unique properties for selective binding of metal ions.[1,2] Numerous derivatives of these molecules find application as highly efficient sequestrating agents,[3,4] sensors,[5,6] catalysts,[7] and are used in biochemistry[8,9] or medicine.[10,11] Moreover, bis(polyazamacrocycles) exhibit significant interest due to their abilities to form binuclear complexes.[12,13] Over the last decades, the use of saturated bismacrocyclic ligands instead of bisporphyrin compounds has been studied because of their easier synthesis.[14,15] They contain two polyazamacrocycles which are linked, either through aliphatic (or aromatic) spacers bonded to nitrogen atoms or through two covalently bonded carbon atoms.[16-21] The synthesis of a variety of bismacrocycles bound through aryl spacers was described by the authors.[22] However, in all cited syntheses only aliphatic or benzyl-type linkers have been used to prepare these models; direct bonding of two polyazamacrocycles to an aryl spacer could hardly be achieved with known synthetic procedures, and this fact strictly limited any progress in this area. We proposed the application of the Pd-catalyzed amination of aryl halides for this purpose and demonstrated. Scope and limitations for the synthesis of N-phenyl and N-(3-bromophenyl) derivatives of trimethylcyclam and trimethylcyclozen were provided. Pd-catalyzed amination of 1,3-dibromobenzene with N,N,N''-trimethylcyclam and N,N,N''-trimethylcyclozen provided corresponding 1,3-bis(tetraazamacrocyclic) derivatives of benzene in 25-32% yields. The dependence of the products yields on the phosphate ligand applied (BINAP, DavePHOS) as well as on the stoichiometry of starting compounds was established. and limitations for the synthesis of N-phenyl and N-(3-bromophenyl) derivatives of trimethylcyclam and trimethylcyclozen were demonstrated.

Keywords: Tetraazamacrocycles, amination, Pd catalysis, aryl halides.

Experimental

NMR spectra were registered using Bruker Avance 400 spectrometer, MALDI-TOF spectra were obtained with Bruker Ultraflex spectrometer using 1,8,9-trihydroxyanthracene as matrix. 1,3-Dibromobenzene, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 2-dimethylamino-2'-dicyclohexylphosphinobiphenyl (DavePHOS) and other phosphate ligands, benzyl bromide, formic acid, formalin, acetic acid, sodium tert-butylation were purchased from Aldrich and Acros and used without further purification; cyclam and N-benzylcyclen were provided by Chemathec Co, Pd dibenzylidenate acetonate (Pd(dba)) was synthesized according to the method described.[23] Dioxane was distilled over NaOH followed by the distillation over sodium in argon, dichloromethane and methanol were distilled. Synthesis of N,N,N''-trimethylcyclam was carried out using a three-step procedure from cyclam by its benzylation with benzyl bromide, followed by methylation with formalin and formic acid, and reduction of N-benzyl-N,N,N''-trimethylcyclam with hydrogen catalyzed by Pd on carbon.[20] N,N,N''-trimethylcyclozen was obtained according to a similar procedure which was found to be easier than an alternative one described in literature.[21] 1-Benzyl-1,4,7,10-tetraazacyclododecane, 3. N-benzylcyclen 2 (5 g, 0.019 mol) was mixed with 99% formic acid (3.5 ml, 0.091 mol), 37% formalin (4.7 g, 0.058 mol) and 0.45 ml water. The mixture was refluxed for 24 h, cooled to ambient temperature, the excess of formic acid and formaldehyde was evaporated in vacuo, and the residue was dissolved in water (40 ml). The solution of KOH (4.5 g) in 40 ml water was added to make pH 10, the resulted solution was extracted with dichloromethane (2 x 75 ml), organic phases were combined and dried over MgSO4. Dichloromethane was evaporated in vacuo, and the product 3 was obtained as viscous oil. Yield 4.92 g (85%), m/z (MALDI-TOF) 305.4 [M+H]+. 1H NMR (CDCl3, 297 K) δ ppm: 2.19 (6H, s, 2 x Me), 2.28 (3H, s, Me), 2.49-2.60 (12H, m, CH2N), 2.66 (4H, t, J = 5.3 Hz, CH2), 3.55 (2H, s, NCH2Ph), 7.21 (1H, t, J = 7.3 Hz, p-Ph), 7.29 (2H, t, J = 7.4 Hz, m-Ph), 7.33 (2H, d, J = 7.4 Hz, o-Ph). 13C NMR (CDCl3, 297 K) δ ppm: 44.5 (IC), 45.4 (2C), 53.0 (2C), 56.0 (IC), 56.2 (2C), 56.6 (2C), 61.1 (2C), 127.1 (IC), 128.5 (2C), 129.4 (2C), 140.2 (IC).
carbon (0.5 g) in acetic acid (200 ml). The mixture was saturated with hydrogen at atmospheric pressure and under stirring for 2 h. Then the catalyst was filtered off, acetic acid was evaporated in vacuo, and KOH solution in water was added to make pH 9. The product was extracted with dichloromethane (3 x 100 ml). Combined organic phases were dried over MgSO₄. Dichloromethane was evaporated in vacuo, and the product 4 was obtained as viscous oil. Yield 3.25 g (95%). m/z (MALDI-TOF) 214.7 [M+H]+, δ<sup>1</sup>H NMR (CDCl₃, 297 K) δ ppm: 2.15 (3H, s, Me), 2.34 (6H, s, 2 x Me), 2.47 (8H, br s, CH₃N), 2.62 (4H, br s, CH₃N), 2.73 (4H, br s, CH₃N), 3.48 (8H, br s, CH₃N). 13C NMR (CDCl₃, 297 K) δ ppm: 23.4, 24.5, 42.3, 42.7, 48.0, 49.7, 53.6, 53.9, 54.3, 54.5, 54.9, 55.5, 110.9, 115.0, 118.9, 123.5, 130.5, 149.6.

General procedure for the Pd-catalyzed arylation of N,N′,N″-trimethylcyclam 1 and N,N″-N‴-trimethylcyclen 4.

A two-necked flask equipped with a condenser and magnetic stirrer, flushed with dry argon, was charged with tetradecane, tert-butyllate (1.5 equiv. per bromine atom), and the reaction mixture was refluxed for 24-30 h. After cooling to ambient temperature, the solution was filtered off, evaporated in vacuo, and the residue was chromatographed on silica gel using a sequence of eluents: CH₂Cl₂, CH₂Cl₂-MeOH 3:1, CH₂Cl₂-MeOH-NH₃aq 100:20:3. Yield 70 mg (25%).

1-(3-Bromophenyl)-4,7,10-trimethyl-1,4,7,10-tetraazacyclododecane, 3. According to the method described, compound 8 was obtained from 1,3-dibromobenzene (118 mg, 0.5 mmol), trimethylcyclen 4 (107 mg, 0.5 mmol), in the presence of Pd(dba)₂ (23 mg, 0.08 mmol), BINAP (28 mg, 0.09 mol), sodium tert-butyllate (72 mg, 0.75 mmol) in dioxane (5 ml, 0.1 M). Eluent: CHCl₃-MeOH 3:1. Yield 23 mg (13%). m/z (MALDI-TOF) 369.0 [M+H]+. δ<sup>1</sup>H NMR (CDCl₃, 297 K) δ ppm: 2.22 (3H, s, Me), 2.37 (6H, s, 2 x Me), 2.49 (8H, br s, CH₃N), 2.80 (4H, br s, CH₃N), 3.45 (4H, br s, CH₃N), 6.35 (1H, d, J = 7.3 Hz, H₆-Ph), 6.70 (1H, s, H₂-Ph), 6.88 (1H, J = 7.7 Hz, H₄-Ph) ppm: 1.76 (4H, t, J = 6.5 Hz, CH₂NPh), 4.05 (2H, t, J = 8.4 Hz, CCH₂C), 7.08 (1H, t, J = 7.7 Hz, H₄-Ph). 13C NMR (CDCl₃, 297 K) δ ppm: 23.4, 24.5, 42.1, 42.3, 43.7, 48.0, 49.7, 53.6, 53.9, 54.3, 54.5, 54.9, 55.5, 110.9, 115.0, 118.9, 123.5, 130.5, 149.6.

1,4,8-Trimethyl-11-phenyl-1,4,8,11-tetraazacyclotetradecane, 6. Obtained as the second product in the same synthesis. Eluent: CHCl₃-MeOH 3:1. Yield 19 mg (13%). m/z (MALDI-TOF) 291.0 [M+H]+. δ<sup>1</sup>H NMR (CDCl₃, 297 K) δ ppm: 2.16 (3H, s, Me), 2.28 (6H, s, 2 x Me), 2.49 (8H, br s, CH₃N), 2.66 (4H, br s, CH₃N), 3.45 (4H, br s, CH₃N), 6.36 (2H, d, J = 8.4 Hz, o-Ph), 6.78 (1H, t, J = 7.0 Hz, p-Ph), 7.23 (2H, t, J = 7.9 Hz, m-Ph).

1,3-Bis(4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecan-1-yl)benzene, 7. According to the method described, bismacrocyclic compound 7 was obtained from 1,3-dibromobenzene (472 mg, 2 mmol), trimethylcyclam 1 (242 mg, 1 mmol), in the presence of Pd(dba)₂ (46 mg, 8 mol%), DavePHOS (31 mg, 8 mol%), sodium tert-butyllate (288 mg, 3 mmol) in dioxane (5 ml, 0.2 M). Eluent: CHCl₃-MeOH-NH₃aq 100:20:2, 100:20:3. Yield 700 mg (25%). m/z (MALDI-TOF) 559.5 [M+H]+. δ<sup>1</sup>H NMR (CDCl₃, 297 K) δ ppm: 1.60 (4H, quintet, J = 5.8 Hz, CCH₂C), 1.76 (4H, quintet, J = 5.6 Hz, CCH₂C), 2.19 (6H, s, 2 x Me), 2.23 (6H, s, 2 x Me), 2.27 (6H, s, 2 x Me), 2.37 (4H, t, J = 5.6 Hz, CH₃N), 2.43-2.57 (20H, m, CH₃N), 3.43 (4H, t, J = 6.5 Hz, CH₂NPh), 3.46 (4H, t, J = 6.8 Hz, CH₂NPh), 5.90 (1H, s, H₂-Ph), 5.98 (2H, dd, J = 8.3 Hz, J = 1.8 Hz, H₄₃⁻H₄⁻Ph), 6.99 (1H, t, J = 8.2 Hz, H₃⁻Ph). 13C NMR (CDCl₃, 297 K) δ ppm: 24.7 (2C), 25.1 (2C), 42.3 (2C), 43.2 (2C), 44.4 (2C), 47.5 (2C), 49.5 (2C), 53.7 (2C), 53.9 (2C), 54.7 (2C), 55.1 (4C), 55.4 (2C), 94.6 (1C), 99.8 (2C), 129.8 (1C), 149.5 (2C).

1-(Bromophenyl)-4,7,10-trimethyl-1,4,7,10-tetraazacyclotetradecane.
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Attempts to carry out such reactions were not encouraging and thus we decided to diminish the number of secondary amino groups active in the reduction process by using \(N,N',N''\)-trimethylsubstituted analogs of cyclen and cyclam. [24] Trimethylcyclam 1 was synthesized from free cyclam by a three-step procedure documented in literature, [26] and the same procedure was used to obtain trimethylcyclen 4 (Figure 1).

We started from \(N\)-benzylcyclen 2, carried out its exhaustive \(N\)-methylation with formic acid and formalin to obtain tetrasubstituted cyclen 3, and eliminated the benzyl group by the catalytic hydrogenation. As a result, trimethylcyclen 4 was synthesized in overall 80% yield.

First we tried the catalytic arylation of trimethylcyclam 1. To synthesize desired bis(cyclam) substituted benzene we applied 2 equivalents of trimethylcyclam in the presence of \(\text{Pd(dba)}_2/BINAP\) (8/9 mol%) which was well documented to be an universal and the most appropriate catalytic system for amines arylation [28] in general and for the diamination of 1,3-dibromobenzene, in particular. [29] Sodium tert-butylate was used as a base, and the reaction was refluxed for 24 h in dioxane (0.1 M) (Figure 2).

Under these conditions we obtained the target bismacrocycle 7 in 13% yield (Table 1, entry 1). We supposed that the change of BINAP for some donor phosphine ligands could improve the diamination process, and tried a series of biphenyl-based monophosphines (Figure 3).

We also checked the ferrocene-based ligand \(\text{PPFNMe}_2\) because it proved to be useful in the arylation of free cyclam. [24] However, the most of these ligands did not work at all in the catalytic process, except for 2-dicyclohexylphosphino-2’-dimethylaminobiphenyl (DavePHOS) which was demonstrated to improve the amination of aryl chlorides. [30] The use of 16 mol% catalyst promoted the diamination process and provided 22% yield of target bismacroyclic compound 7 (Table 1, entry 2). We were also interested in the synthesis of monocyclam derivative of bromobenzene 5 in order to study further the possibilities of its catalytic amination with various amines. To synthesize it, we applied 2 equivalents of 1,3-dibromobenzene with \(\text{Pd(dba)}_2/BINAP\) (8/9 mol%) catalytic system. The target monomacrocyclic compound 5 was isolated in 26% yield, together with the product of bromine reduction 6 (18%, entry 3).

In order to increase the product yield, we ran the same reaction in a more concentrated solution (0.2 M), however, in this case the yield of 5 was merely the same (24%, entry 4). The use of \(\text{Pd(dba)}_2/\text{DavePHOS}\) (8 mol%) system led to an unexpected result: instead of desired monocyclic derivative 5, bismacroyclic...
Synthesis of Cyclam and Cyclen Substituted Benzenes

Table 1. Pd-catalyzed amination of 1,3-dibromobenzene with trimethylcyclam and trimethylcyclen.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tetraaza-macrocycle</th>
<th>Ratio 1,3-dibromobenzene/ tetraaza-macrocycle</th>
<th>Concentration, M</th>
<th>Ligand</th>
<th>Pd/L, mol%</th>
<th>Products yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1:2</td>
<td>0.1</td>
<td>BINAP</td>
<td>8/9</td>
<td>7, 13%</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1:2</td>
<td>0.1</td>
<td>DavePHOS</td>
<td>16/16</td>
<td>7, 22%</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2:1</td>
<td>0.1</td>
<td>BINAP</td>
<td>8/9</td>
<td>5, 26%; 6, 18%</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2:1</td>
<td>0.2</td>
<td>BINAP</td>
<td>8/9</td>
<td>5, 24%</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>2:1</td>
<td>0.2</td>
<td>DavePHOS</td>
<td>8/8</td>
<td>7, 25%</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>1:1</td>
<td>0.1</td>
<td>BINAP</td>
<td>8/9</td>
<td>8, 13%; 9, 13%</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>1:1</td>
<td>0.1</td>
<td>DavePHOS</td>
<td>8/16</td>
<td>10, 32%</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>2:1</td>
<td>0.2</td>
<td>BINAP</td>
<td>8/9</td>
<td>10, 20%</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>4:1</td>
<td>0.1</td>
<td>BINAP</td>
<td>4/9</td>
<td>8, 12%; 9, 3%; 10, 30%</td>
</tr>
</tbody>
</table>

compound 7 was isolated in 25% yield (entry 5). This meant that the application of less catalyst (8 mol% instead of 16 mol%) and, what is much more surprising, the excess of 1,3-dibromobenzene afforded the diamination product in even a better yield (ref. entries 2 and 5).

This unusual effect was more pronounced in the case of trimethylcyclen 4 arylation. The reaction of equimolar amounts of trimethylcyclen and 1,3-dibromobenzene catalyzed by Pd(dba)2/BINAP (8/9 mol%) provided N,N'-bischlorophenyltrimethylcyclen 8 and reduced N-pheynyltrimethylcyclen 9 in equal yields (13%, entry 6). The use of DavePHOS ligand under similar conditions gave rise to bismacroyclic compound 10 in 32% yield (entry 7). When we changed the ratio of starting compounds taking 2 equivalents of dibromobenzene and Pd(dba)/BINAP (8/9 mol%) catalytic system, we also obtained bicyclic derivative 10 in 20% yield instead of expected monocyclen compound 8 (entry 8). The most dramatic result was observed when using 4 equivalents of dibromobenzene and only 4 mol% Pd (entry 9): monocyclen compounds 8 and 9 were isolated in 12% and 3% yields while bismacrocycle 10 was obtained in 30% yield.

It is difficult to explain reliably why the results of the reactions were obviously opposite to the stoichiometric ratios of starting compounds. We may suppose that the excess of reactions were obviously opposite to the stoichiometric ratios 30% yield.

Conclusions

To sum up, we synthesized biscyclam and biscyclen derivatives of 1,3-disubstituted benzene, showed an unusual dependence of the yields of these products on the stoichiometric ratio of starting compounds. We demonstrated better efficacy of DavePHOS in the diamination process compared to BINAP and found out conditions for the monoamination of 1,3-dibromobenzene with trimethylcyclam and trimethylcyclen.

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References

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