Application of Palladium-catalyzed Amination to the Synthesis of Polyazamacrocycles Containing 3,5-Disubstituted Pyridine

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(Received May 12, 2005; CL-050632)

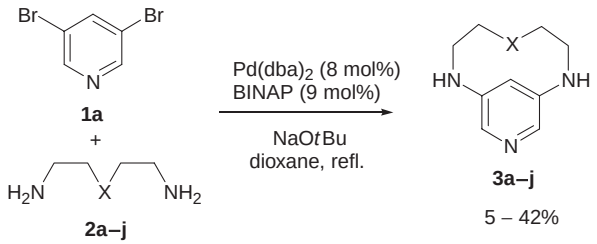
The synthesis of a new family of nitrogen- and oxygen-containing macrocycles, which employs palladium-catalyzed amination of 3,5-dihalopyridines, is described. Synthetic approaches to cyclodimers have been elaborated via bis(pyridyl)substituted polyamines and bis(polyamino) substituted pyridines.

Catalytic amination of 3-halopyridines attracts researchers' attention since 1996 when Buchwald was the first to obtain 3-aminopyridines via catalytic process using his famous $Pd(dba)_2$/BINAP system.[1] This work was followed by the investigations of 3-bromopyridine amination in which ligands other than BINAP were tried: PPFOMe,[2] *t*-Bu_3P,[3] or dppf.[4] 3-Chloropyridine proved to be substantially less reactive than 2-chloropyridine,[5,6] while 2-chloro-3-iodopyridine was efficiently aminated giving 2-chloro-3-aminopyridines as has been shown in the recent reports.[7–9] Nickel-catalyzed reactions turned to be efficient for 3-chloropyridine amination,[10] and the possibility of the synthesis of 3,5-diaminosubstituted pyridine was reported by Fort. Recently we have proposed a simple one-pot approach to polyazamacrocycles derived from 2,6-dibromopyridine using palladium-mediated amination with linear polyamines.[11] Such macrocycles possess highly nucleophilic pyridine nitrogen atom in an *endo*-position as regards macrocycle's cavity.

Here we report the synthesis of isomeric polyazamacrocycles based on 3,5-diaminosubstituted pyridine, with an *exo*-oriented pyridine nitrogen atom. These isomeric macrocycles might possess different complexing properties due to spatially isolated donor sites: sp^2-N of the pyridine ring and secondary amino groups of the polyamine chain. First we explored the possibilities of 3,5-dibromopyridine **1a** to form polyazamacrocycles upon reacting with linear triamines **2a** and **2b**, tetraamines **2c**–**2f**, pentaamine **2g**, hexaamine **2h**, dioxadiamine **2i**, and trioxadiamine **2j** (Scheme 1).

The reactions were run in diluted solutions of boiling dioxane ($c = 0.02$ M) to favour intramolecular cyclization, $Pd(dba)_2$ (8 mol %) and BINAP (9 mol %) were used in all cases, *t*-BuONa (3 equiv.) was used as a base.[12] The reaction time was 4–6 h to ensure full consumption of starting dibromopyridine. When using less amount of the catalyst (6 mol %), longer heating (10 h) was necessary to obtain a standard yield. The data are collected in the Table 1.

The yields of corresponding macrocycles **3a**–**3j** ranged from 5 to 42%, and were essentially dependent on the nature of starting polyamines **2**. It is clearly seen that the yield generally is not only a function of polyamine's length but also depends on C to N atoms ratio. Indeed, whereas amines **2b**, **2d**–**2f**, **2i**, and **2j** provided 18–42% yields (Table 1, Entries 2, 4–8, 11, and 12), amines **2a**, **2c**, **2g**, and **2h**, which can be genaralized as polyethylene-polyamines, gave tiny 5–6% yields (Entries 1, 3, 9, and 10).



2 a: $H_2N(CH_2)_2NH(CH_2)_2NH_2$
b: $H_2N(CH_2)_3NH(CH_2)_3NH_2$
c: $H_2N(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2$
d: $H_2N(CH_2)_2NH(CH_2)_3NH(CH_2)_2NH_2$
e: $H_2N(CH_2)_3NH(CH_2)_2NH(CH_2)_3NH_2$
f: $H_2N(CH_2)_3NH(CH_2)_3NH(CH_2)_3NH_2$
g: $H_2N(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2$
h: $H_2N(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2$
i: $H_2N(CH_2)_2O(CH_2)_2O(CH_2)_2NH_2$
j: $H_2N(CH_2)_3O(CH_2)_2O(CH_2)_2O(CH_2)_3NH_2$

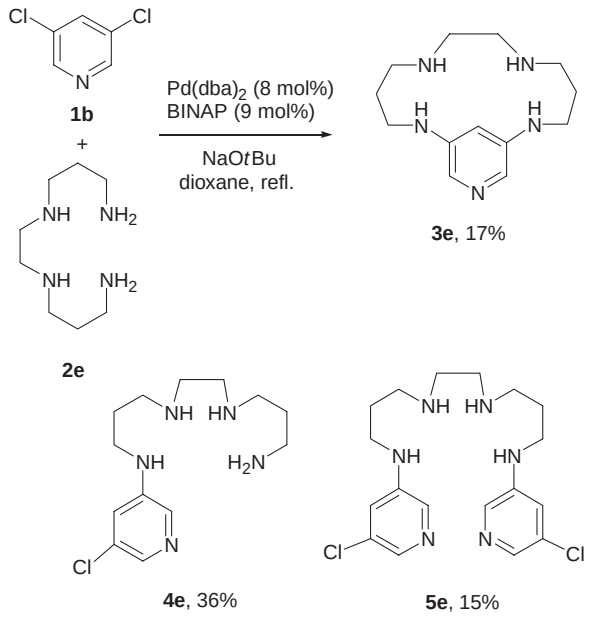
Scheme 1.

Table 1. Synthesis of macrocycles **3a**–**3j**

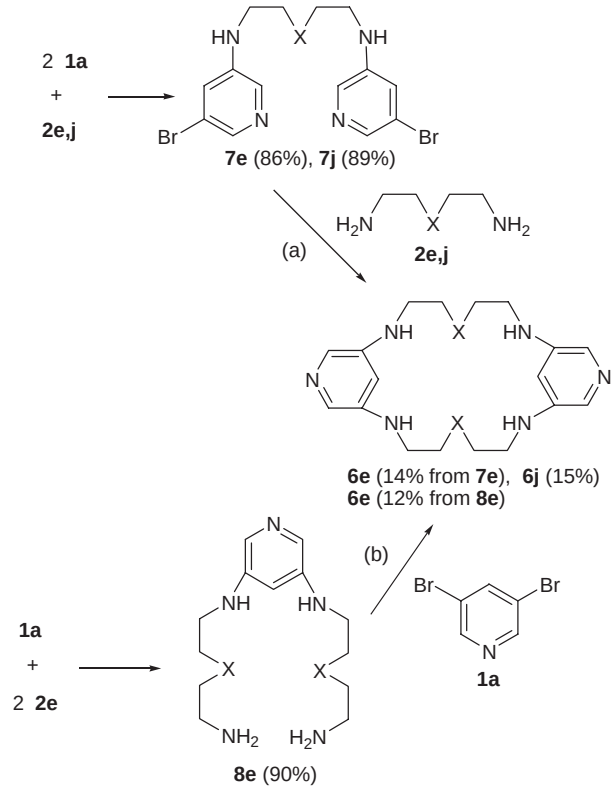
Entry	Polyamine	Reaction time/h	Yield of **3**[a]
1	**2a**	5	5(3)
2	**2b**	5.5	42(33)
3	**2c**	4	5(3)
4	**2d**	6	29(17)
5	**2e**	6	36(16)[b]
6	**2e**	4	19(17)
7	**2e**	10[c]	30(17)
8	**2f**	5	18(15)
9	**2g**	4.5	6(5)
10	**2h**	4.5	5(4)
11	**2i**	6	—[d](27)
12	**2j**	5.5	22(20)

[a]NMR yields, yields after chromatography are given in brackets. [b]Yield after treatment with CH_2Cl_2/H_2O before chromatography. [c]With 6 mol % $Pd(dba)_2$/6.5 mol % BINAP. [d]No data available for the reaction yield.

We have tried 3,5-dichloropyridine **1b** in the reaction with **2e** (Scheme 2). To provide a better yield of desired macrocycle **3e** prolonged heating (69 h) was necessary, and even in this case



Scheme 2.



Scheme 3.

the yield was substantially poorer (17% instead of 36%).

Cyclodimers of type **6** are of special interest due to their large cavities and greater number of donor nitrogen atoms, including two *exo*-pyridine nitrogens. For this reason we attempted to elaborate synthetic routes to this type of macrocycles trying two ways: (a) the synthesis of dipyridyl substituted tetraamines **7e** and **7j** and its cyclization into **6e** and **6j** using second equivalent of **2e** and **2j**; (b) the formation in situ of bis(polyamino) substituted tetraamine **8e** followed by its reaction with **1a** (Scheme 3).

Method (a) provided 14% yield of the target molecule **6e** (15% for **6j**), whereas method (b) afforded 12% yield. Both schemes gave rise also to linear oligomers.

In conclusion, we have proposed a simple one-pot catalytic method of the synthesis of a new type of pyridine-containing macrocycles with an *exo*-oriented pyridine nitrogen atom, we have also shown the possibility of the synthesis of cyclodimers which possess a greater cavity.

This work was supported by RFBR grants N 02-03-33331, 03-03-22001, and 03-03-32627 and PICS grant N 2105.

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12 *Typical experimental procedure*: An argon-flashed flask equipped with a condenser was charged with 3,5-dibromopyridine (0.5 mmol, 119 mg), $Pd(dba)_2$ (8 mol %, 23 mg), BINAP (9 mol %, 27 mg), absolute dioxane (25 mL), polyamine (0.5 mmol), sodium *tert*-butylate (1.5 mmol, 150 mg). The reaction mixture was refluxed for 4–6 h, cooled down to ambient temperature, a drop of water was added, organic solution was filtered off, evaporated in vacuo, and the crude mass was chromatographed on silica using a sequence of eluents: CH_2Cl_2, CH_2Cl_2/MeOH 50:1-3:1, CH_2Cl_2/MeOH/NH_3-aq 100:20:1–10:4:1. **3e**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.69 (q, $J = 5.7$ Hz, 4H), 2.66 (t, $J = 5.3$ Hz, 4H), 2.69 (s, 4H), 3.36 (t, $J = 6.3$ Hz, 4H), 6.59 (t, $J = 2.3$ Hz, 1H), 7.30 (d, $J = 2.3$ Hz, 2H) (NH protons are not indicated). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 31.8 (2C), 40.6 (2C), 45.7 (2C), 49.4 (2C), 99.0 (1C), 126.2 (2C), 146.0 (2C). IR (KBr): ν 3277, 2924, 2851, 1653, 1587, 1525, 1472, 1317, 1219, 1165, 821, 708 cm^{-1}. UV/MeOH (ε) 326 (4000) nm. MALDI-TOF (dithranol) m/z 250.1 ($[M + H]^+$).

Published on the web (Advance View) July 2, 2005; DOI 10.1246/cl.2005.1100