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Improved synthesis of a C_3-symmetrical pyridinophane

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Abstract

The formation of the C_3-symmetrical 2,11,20-triaza[3.3.3](2,6)pyridinophane **1** was undertaken with the aim of improving the synthesis of this highly desirable macrocycle, with the future aim of functionalizing **1** with amide pendent arms for the recognition of lanthanide ions. The synthesis of **1** involves the stepwise transformation of pyridine-2,6-dicarboxylic acid into two key intermediates; *N*,*N*-bis[(6-hydroxymethyl)pyridin-2-yl]-*p*-tosylamide **7** and 6-bis[(amino-*p*-tosyl)methyl]pyridine **5**. The macrocyclization of these two intermediates gave **8**, from which **1** was formed upon deprotection of the three tosyl groups.

The design and synthesis of highly structurally organized molecules or macrocycles as molecular scaffolds or as ion receptors is of great current interest within the field of supramolecular chemsitry.[1–3] Many classical examples exist where scaffolds, such as calixarenes,[4] azamacrocycles,[5] and cyclophens[6] have been developed. The use of pyridine as a coordinating ligand in these structures has been extensively studied.[7,8] In particular, such ligands have been used as hosts for lanthanide ions, which possess valuable photophysical and paramagnetic properties, as well as being of great importance in organic synthesis as catalysts.[9]

We have been interested in the use of simple macrocyclic structures as platforms for the development of sensors[10] and catalysts[11] for biological detection and hydrolysis of biologically important molecules such as RNA. We have focused our efforts on the use of the well-known macrocycle, cyclen (1,4,7,10-tetraazacyclododecane)[12,13] and furnished this structure with amide pendent arms such as dipeptides and aromatic antennae for use as chelating ligands for lanthanide ions. With the aim of developing other ligands for lanthanide ions, we looked towards synthesizing highly symmetrical and reorganized macrocyclic structures that could facilitate the incorporation of such pendent arms that could fulfil the rather high coordination environments, usually of 9–10.[14] We focused on developing pyridine based ligands, such as 2,11,20-triaza[3.3.3](2,6)-pyridinophane, **1**, which contains three pyridine rings and three secondary amino moieties in a C_3-symmetrical macrocycle. This target has previously been synthesized in 2% yield in a one-pot synthesis by Kaptein[15] as well as by Miyahara and co-workers[16] who made the cyclophane via a number of elegant steps. However, as we were unable to repeat all these steps successfully in good yield, we embarked on attempting to improve the synthesis of this compound, which is the focus of this Letter.

The synthesis of **1** (Scheme 1) began with the synthesis of dimethyl pyridine-2,6-dicarboxylate from 2,6-pyridine dicarboxylic acid in 87% yield.[17] The diester was then reduced using $NaBH_4$ in ethanol, to give 2,6-bis(hydroxymethyl)pyridine (yield) in 65% after continuous extraction from aqueous solution. This compound is the starting material for the two key intermediates, **5** and **7**, shown in Scheme 1.

The synthesis of both **5** and **7** involved the bromination of the diol, by simply reacting it with 48% HBr solution under reflux. After cooling to room temperature, and subsequent neutralization using 40% NaOH solution, a pink precipitate was formed upon cooling to 0 °C. This solid was shown to contain a mixture of two products; the bis-bromo derivative **2** and the bromo-alcohol **3**. Both of these

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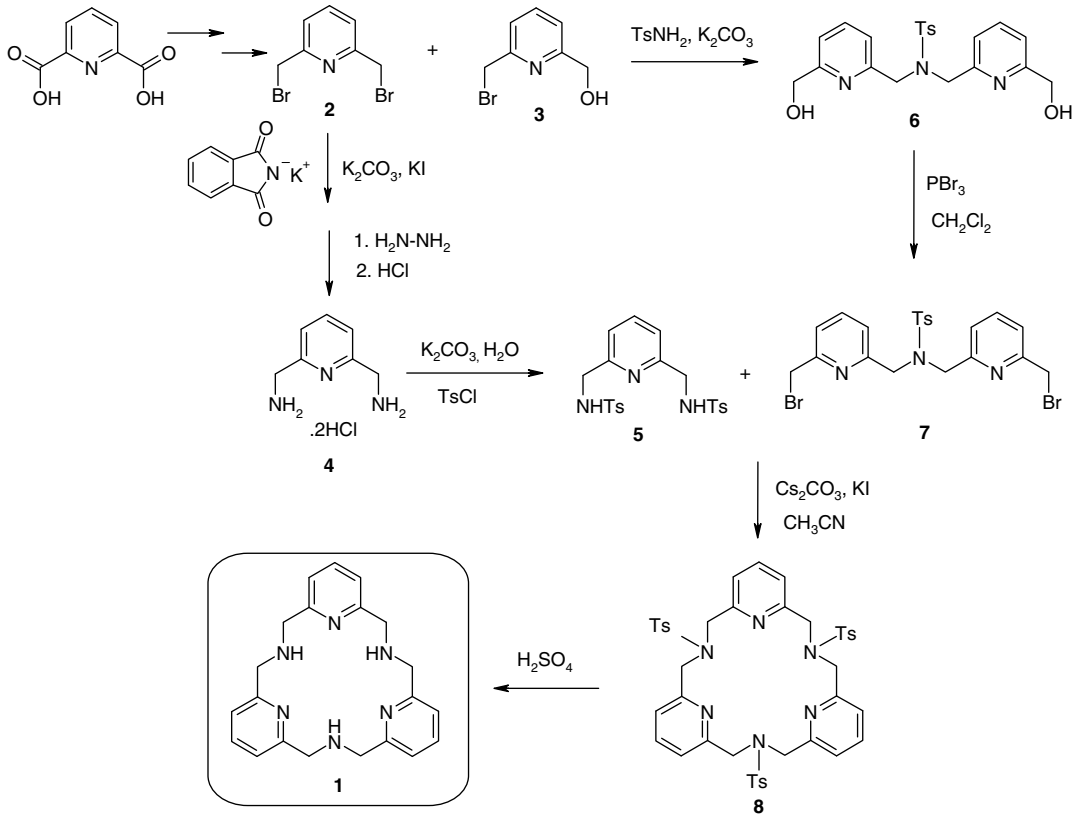

Scheme 1. The synthesis of **1** from pyridine-2,6-dicarboxylic acid.

compounds are central to the synthesis of **1**. From this mixture, compound **2** was isolated by flash silica chromatography, using CH_2Cl_2 as eluent, in 27% yield. By simply changing the eluent (gradually) to 98:2 CH_2Cl_2/CH_3OH, compound **3** could be isolated in 41% yield. Attempts to make **2** in high yield, as described in the work of Rabjohn[18] by using 2,6-lutidine and *N*-bromosuccinimide, failed to give the desired product in more than 5% yield. However, it was possible to improve the yield of **2** to 87% by reacting the pyridine diol with PBr_3 instead of HBr. Compound **2** was transformed into the corresponding di-amine **4** using the classical Gabriel synthesis, by first refluxing **2** overnight with potassium phthalimide in the presence of K_2CO_3 and KI, in dry DMF under an inert atmosphere. This gave 2,6-bis(phthalimomethyl)pyridine in 78% yield, which could be carried forward, without the need of further purification, to give compound **4**. This was achieved by refluxing the bisphthalimide for 5 h in a mixture of hydrazine monohydrate and ethanol in 92% yield, followed by aqueous HCl workup after cooling to room temperature. The transformation of this product into the di-tosyl amide **5** was unsuccessful using several literature procedures.[19] However, the desired product **5** was eventually formed in 55% yield as a grey solid, by refluxing **4** in water with K_2CO_3 and *p*-tosyl chloride, for 12 h, after which a black precipitate was formed that was collected, washed with water, methanol and diethyl ether, and finally dried in the presence of P_2O_5 under vacuum. Despite its low yield, this reaction could easily be scaled-up to give **5** in multigram quantities.

The synthesis of the second intermediate, **7**, in the synthesis of **1**, was achieved in two steps from **3**, by firstly making **6** (*N*,*N*-bis[(6-hydroxymethyl)pyridin-2-yl]-*p*-tosylamide) from the condensation of 2 equiv of **3** with *p*-tosylamide in acetone in the presence of K_2CO_3. After refluxing the mixture for four days, the reaction was cooled to room temperature and the resulting precipitate removed by filtration. The filtrate was then evaporated (collected), giving a brown oil. This brown residue was then dissolved in $CHCl_3$ and washed with 10% aqueous K_2CO_3 solution and evaporated to dryness to give **6** as brown crystals in 62% yield, which did not require any further purification. This product was characterized by conventional methods, as well as by using X-ray crystallography. Interestingly, using several other solvents such as CH_3CN instead of acetone in the above synthesis did not give rise to the formation of **6**. Converting the two methyl alcohols of **6** into the corresponding dibromide, **7**, was achieved using PBr_3 in CH_2Cl_2 over 12 h. The reaction was neutralized with 40% NaOH and the organic layer collected, giving **7** as pink crystals in 97% yield.

Having achieved the synthesis of the two key intermediates, the next step involved the macrocyclization of **5** and **7** to give **8**. This was achieved using a method discussed by Parker et al. for the synthesis of azacrown ethers.[20] We hoped that using a mild base and KI would both increase

the rate of the S_N2 reaction between **5** and **7**, and that K^+ would function as a template in the formation of the desired 18-membered macrocycle **8**. The synthesis involved adding **7** in CH_3CN to a stirring CH_3CN solution of **5**, which also contained Cs_2CO_3 and KI over 20 min. This solution was then stirred for further two days under an inert atmosphere and finally refluxed for a further 12 h. This led to the formation of a precipitate that was removed by filtration; the filtrate was reduced to dryness and the resulting residue taken up into $CHCl_3$ and washed with 10% K_2CO_3. This gave the desired macrocycle **8** as a solid in 59% yield after recrystallization from a mixture of $CHCl_3$ and diethyl ether.[21] The ^1H NMR spectrum of **8** (400 MHz, $CDCl_3$) showed that the product had high symmetry, with a singlet resonating at 2.44 ppm for the methyl group of the tosyl moiety, a singlet appearing at 4.30 ppm for the CH_2 group and a doublet and a multiplet resonating at 7.68 ppm and 7.29 ppm, respectively, for the tosyl group and a doublet and triplet at 7.14 and 7.44 ppm, respectively, for the pyridine protons. The final step was the deprotection of the tosylamide units of **8** to give the desired free amines. This was achieved using concd H_2SO_4, and refluxing the mixture for 2 h. The reaction was then cooled to room temperature before adding the reaction mixture to an ice/water mixture and adjusting the pH to 14 using 40% NaOH and extracting **1** into diethyl ether, giving the C_3-symmetrical pyridinophane in 89% yield.[22,23] The ^1H NMR of **1** recorded in $CDCl_3$ is shown in Figure 1, which clearly demonstrated the expected C_3-symmetry of **1**. The spectrum showed the presence of two resonances for the aryl protons and a characteristic singlet for the methylene spacers.

In summary, we have synthesized the C_3-symmetrical pyridinophane **1** by improving the synthesis of Miyahara and co-workers[16] The key transformations were the formation of **5**, which was achieved in water, the high yield of **6** and the use of Parker's macrocyclization, which gave precursor **8** in both high yield and high purity. The transformation of this product to **1** was then achieved using hot acid, which allows for the further functionalization of the three amino moieties to give additional donor moieties for the complexation of lanthanide ions such as Eu(III) and Tb(III). This work will be reported in due course.

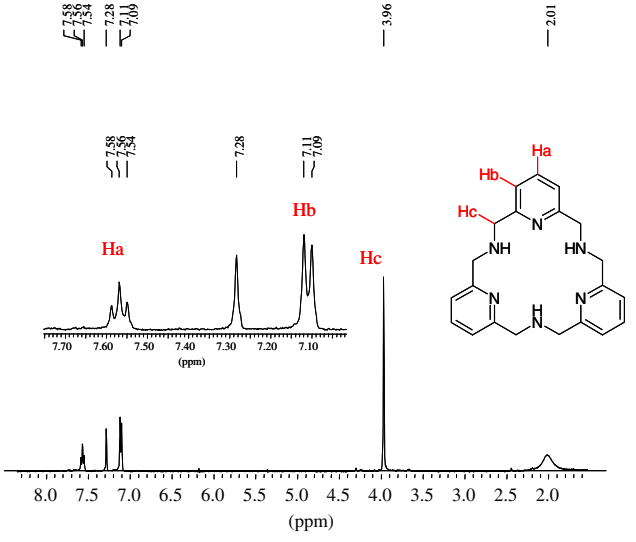

Fig. 1. The ^1H NMR (400 MHz) of **1** recorded in $CDCl_3$.

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21. Analyses were in agreement with those reported by Miyahara and co-workers[16] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (6H, d, $J = 8.04$ Hz, Ar–CH(tosyl)), 7.44 (3H, t, $J = 7.52$ Hz, Ar–CH(pyridine)), 7.29 (6H, m), 7.14 (6 H, d, $J = 7.52$, Ar–CH(pyridine)), 4.30 (12H, s, CH_2), 2.44 (9H, s, CH_3); ES-MS: m/z 822.7 (M^+).
22. Analyses were in agreement with those reported by Miyahara and co-workers:[16] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (3H, t, $J = 7.56$ Hz, Ar–CH), 7.12 (6H, d, $J = 7.52$ Hz, Ar–CH), 3.97 (12H, s, CH_2), 2.01 (3H, s, b, NH); ES-MS: m/z 361.4 (M^+).
23. This product was very pure when the reaction was carried out using a low concentration of **8**.