Efficient Synthesis of 2,11,20-Triaza[3.3.3](2,6)pyridinophane

Geunsu Lee, Masakazu Oka, Hiroyuki Takemura, Yuji Miyahara,* Nobujiro Shimizu, and Takahiko Inazu

Department of Chemistry, Faculty of Science, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812, Japan

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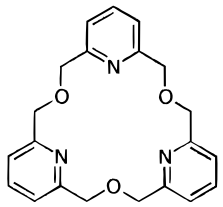
A number of 18-membered azacrowns have been synthesized in order to utilize them as pendant groups to capture alkali metal cations in place of 18-crown-6.[1] However, the nitrogen atoms in such saturated chains behave as rather poor donors compared to oxygen atoms. In contrast, the nitrogen atoms in unsaturated systems like pyridine have been recognized as excellent donors for alkali metal and ammonium ions.[2] Thus, the strong affinity of trioxa[3.3.3](2,6)pyridinophane **1** for ammonium ions has been shown by Cram et al.[3] However, very



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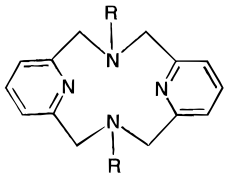
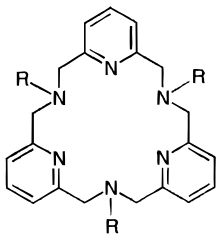


2a: R = H, **2b**: R =Ts,

low yields for its synthesis have apparently precluded further applications. While dinuclear pyridinophane **2a** and its derivatives have now been synthesized by several methods and extensively[4] studied,[4a−e] little is known about the trinuclear pyridinophane **3a**. This appears to

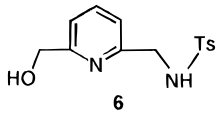


3a: R = H, **3b**: R =Ts,

be due mainly to low yields and difficult separation procedures for the reported methods.[5] Here we report a new stepwise method which, though somewhat lengthy, is efficient and suitable for large-scale preparations (Scheme 1).

The starting 2-(hydroxymethyl)-6-(bromomethyl)pyridine (**4**) was prepared by treating 2,6-bis(hydroxymethyl)pyridine with hydrobromic acid.[3]

The condensation of **4** with *p*-$TsNH_2$ in the presence of K_2CO_3 in acetone required long reaction times. Even after refluxing for 2 days the desired bisadduct, *N*,*N*-bis-[[6-(hydroxymethyl)pyridin-2-yl]methyl]-*p*-tosylamide (**5**) (71% yield), was accompanied by monoadduct *N*-[[6-(hydroxymethyl)pyridin-2-yl]methyl]-*p*-tosylamide (**6**) (15% yield). However, further improvement in the reaction



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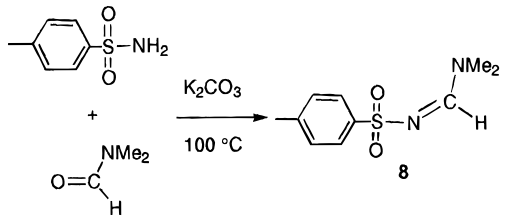
conditions was so far unsuccessful. To be noted is the fact that when we tried to accelerate the reaction by running it in *N*,*N*-dimethylformamide (DMF) at 100 °C, an unexpected reaction occurred. After heating for 1 day, a new compound was formed with consumption of *p*-$TsNH_2$ but without affecting the starting bromide. This product proved to be *N*-*p*-tosyl-*N*′,*N*′-dimethylformamidine (**8**), which has been obtained from the reaction of *p*-TsNCO and DMF.[6]



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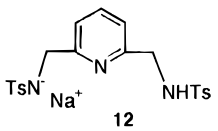
Bromination of **5** with PBr_3 in chloroform readily provided *N*,*N*-bis[[6-(bromomethyl)pyridin-2-yl]methyl]-*p*-tosylamide (**7**) (mp 103−104 °C, 68%).

The other coupling partner **11** was obtained from 2,6-bis(chloromethyl)pyridine (**9**) via the Gabriel reaction, followed by tosylation of the resulting 2,6-bis(aminomethyl)pyridine (**11**: mp 126−127 °C, 70% from **9**).

The coupling of **7** and **11** was best achieved under phase transfer conditions (aqueous KOH/*n*-Bu_4NI/CH_2Cl_2) under reflux for 24 h. The use of KOH as the base is essential in this reaction. When NaOH was utilized, the monosodium salt **12** immediately precipitated out, and because of its remarkably low solubility in both aqueous and organic phases, no coupling occurred.



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Even though high-dilution conditions were not employed, the reaction readily gave *N*,*N*′,*N*″-tritosyl pyridinophane **3b**, mp 250−251 °C (lit.[4a] mp >230 °C) in 83%

(1) For reviews, see, for example: Gokel, G. W.; Dishong, D. M.; Schultz, R. A.; Gatto, V. J. *Synthesis* **1982**, 997. Krakowlak, K. E.; Bradshaw, J. S. *Isr. J. Chem*. **1992**, *32*, 3.

(2) Bell, T. W.; Guzzo, F. *J. Am. Chem. Soc.* **1984**, *106*, 6111.

(3) Newcomb, M.; Timko, J. M.; Walba, D. M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6392.

(4) (a) Bottino, F.; Grazia, M. D.; Finocchiaro, P.; Fronczek, F. R.; Mamo, A.; Pappalardo, S. *J. Org. Chem.* **1988**, *53*, 3521. (b) Che, C.-M.; Li, Z.-Y.; Wong, K.-Y.; Poon, C.-K.; Mak, T. C. W.; Peng, S.-M. *Polyhedron* **1994**, *13*, 771. (c) Krüger, H.-J. *Chem. Ber.* **1995**, *128*, 531. (d) Kim, W. D.; Hrncir, D. C.; Kiefer, G. E.; Sherry, A. D. *Inorg. Chem.* **1995**, *34*, 2225. (e) Kim, W. D.; Kiefer, G. E.; Maton, F.; McMillan, K.; Muller, R. N.; Sherry, A. D. *Inorg. Chem.* **1995**, *34*, 2233.

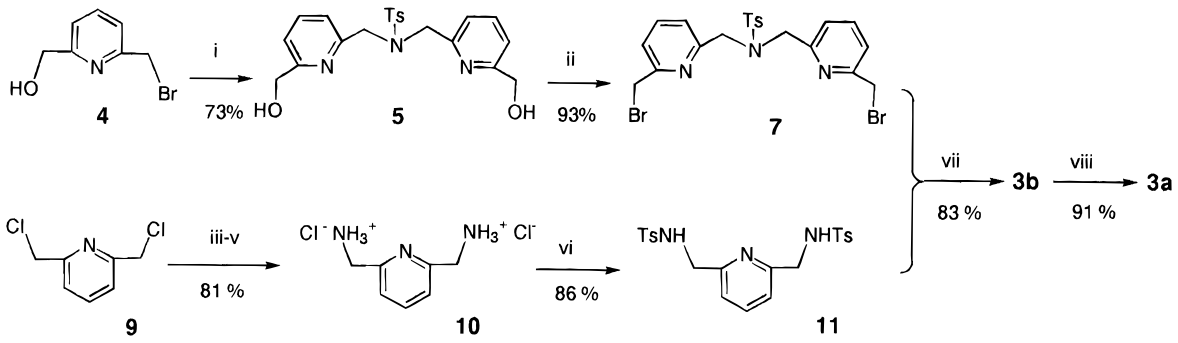
(5) We have mentioned the synthesis of **2b** and **3b** by the coupling of *p*-$TsNH_2$ and 2,6-bis(bromomethyl)pyridine using NaH in refluxing dioxane: Takemura, H.; Suenaga, M.; Sakai, K.; Kawachi, H.; Shinmyozu, T.; Miyahara, Y.; Inazu, T. *J. Inclusion Phenom.* **1984**, *2*, 207. Both of these methods and closely related reactions in DMF by Pappalardo et al.[4a] have provided very low yields of **3b** after tedious chromatographic separation and recrystallization.

(6) Logeman, W.; Artini, D. *Chem. Ber.* **1957**, *90*, 2527.

(7) The elemental analysis of the precipitate agrees more with the monosodium salt than a disodium salt. Anal. calcd for $C_{21}H_{22}N_3O_4S_2Na$: C, 53.95; H, 4.74; N, 8.99 (calcd for $C_{21}H_{21}N_3O_4S_2Na_2$: C, 51.52; H, 4.32; N, 8.58). Found: C, 53.39; H, 4.63; N, 8.50. This Na salt was transformed back to **10** by treatment with an excess of a KOH solution, which dissolved the salt, but gradually, and then with HCl.

S0022-3263(96)01081-X CCC: $12.00

Scheme 1[a]



[a] (i) $TsNH_2/K_2CO_3$/acetone, reflux, 2 days; (ii) PBr_3/chloroform; (iii) potassium phthalimide/DMF, 140 °C, 6 h; (iv) $NH_2NH_2 \cdot H_2O$/EtOH, reflux, 5 h; (v) concd HCl, reflux, 2 h; (vi) TsCl/aq KOH, dioxane, rt, 8 h; (vii) KOH/*n*-Bu_4NI, H_2O/CH_2Cl_2, reflux, 24 h; (viii) H_2SO_4, 115−120 °C, 2 h.

yield. Although **3b** has been reported to be isolated in 9% yield from the one-step coupling of 2,6-bis(chloromethyl)pyridine and *p*-TsNHNa in DMF, obtention of pure **3b** was very difficult in our hands, because **3b** produced as a trimer was very similar in solubility and chromatographic behavior to the corresponding dimer **2b**, the major product of the reaction.

Finally, the detosylation of **3b** was readily achieved by heating in H_2SO_4 at 115−120 °C for 2 h. After alkaline workup, the parent pyridinophane **3a** was obtained in 91% yield as hygroscopic, but not deliquescent, crystals from benzene with mp 136−137 °C (thoroughly dried sample in a sealed tube; reported as an oil[4a]).

With pure **3a** in gram quantities, complexation studies of this pyridinophane and its derivatives are now in progress and will be reported elsewhere.

Experimental Section

General Comments. Melting points were determined in capillaries and are not corrected. Elemental analyses were performed by Center of the Elementary Analysis of Organic Compounds affiliated with Faculty of Science in Kyushu University. Fuji Davison BW-200 silica gel was utilized for column chromatography.

***N,N*-Bis[[6-(hydroxymethyl)pyridin-2-yl]methyl]-*p*-tosylamide (5).** To a mixture of *p*-$TsNH_2$ (6.44 g, 37.62 mmol) and K_2CO_3 (10.35 g, 75.24 mmol) in acetone (300 mL) was added dropwise a solution of **4** (15.20 g, 75.24 mmol) in acetone (150 mL) over a period of 1 h. Stirring under reflux was continued for 2 days. After cooling, the reaction mixture was filtered and the filtrate was evaporated. The residual oil was separated by column chromatography (SiO_2, $CHCl_3$/AcOEt = 5:1) to give the desired bisadduct **5** as colorless granules (7.22 g, 71%), along with the monoadduct 2-(hydroxymethyl)-6-[(*p*-tosylamino)methyl]pyridine (**6**) (2.38 g, 15%). A small portion of each was crystallized from EtOH to give analytically pure samples.

5: colorless granules; mp 59−61 °C; FAB MS *m*/*z* 414.0 (M + 1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.92 (br, 2H), 4.54 (s, 4H), 4.57 (s, 4H), 7.01 (d, *J* = 7.59, 2H), 7.21 (d, *J* = 7.92, 2H), 7.30 (d, *J* = 8.25, 2H), 7.49−7.55 (dd, *J* = 7.58, 7.92, 2H), 7.73 (d, *J* = 8.25, 2H). Anal. Calcd for $C_{21}H_{23}N_3O_4S \cdot H_2O$: C, 58.45; H, 5.84; N, 9.74. Found: C, 58.68; H, 5.84; N, 9.65.

6: colorless granules; mp 123−124 °C; FAB MS *m*/*z* 293.1 (M + 1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.92 (br, 2H), 4.54 (s, 4H), 4.57 (s, 4H), 7.01 (d, *J* = 7.59, 2H), 7.21 (d, *J* = 7.92, 2H), 7.30 (d, *J* = 8.25, 2H), 7.49−7.55 (dd, *J* = 7.58, 7.92, 2H), 7.73 (d, *J* = 8.25, 2H). Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.51; H, 5.52; N, 9.58. Found: C, 57.47; H, 5.54; N, 9.47.

When the reaction was conducted in DMF at 100 °C for 1 day, instead of the desired coupling product, *N*-*p*-tosyl-*N*′,*N*′-dimethylformamidine **8** was isolated as colorless crystals: mp 133−134 °C (lit.[6] mp 133−134 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 3H, Ts), 3.01 (s, 3H), 3.12 (s, 3H), 7.26 (d, *J* = 7.92, 2H), 7.78 (d, *J* = 8.25, 2H), 8.13 (s, 1H).

***N,N*-Bis[[6-(bromomethyl)pyridin-2-yl]methyl]-*p*-tosylamide (7).** To a solution of PBr_3 (5.2 mL, 15 g, 55.4 mmol) in $CHCl_3$ (300 mL) was added dropwise a solution of **5** (10.0 g, 241.9 mmol) over a period of 1 h at −5 to 0 °C with magnetic stirring. The reaction mixture was stirred for an additional 12 h at room temperature. The reaction mixture was neutralized by addition of 40% NaOH with cooling in an ice bath. The organic layer was separated, dried over $MgSO_4$, filtered, and evaporated to give a colorless oil (1.27 g, 98%). This oil was crystallized from a mixed solvent (benzene/diethyl ether = 5:2) to give **7** as colorless crystals (12.01 g, 93%): mp 103−103.5 °C; IR (KBr) ν_{SO} 1341, 1151 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.34 (s, 4H), 4.56 (s, 4H), 7.23 (d, *J* = 7.91, 4H), 7.26 (d, *J* = 8.25, 2H), 7.28 (d, *J* = 7.92, 2H), 7.52−7.57 (dd, *J* = 7.59, 7.91, 2H), 7.72 (d, *J* = 8.58, 2). Anal. Calcd for $C_{21}H_{21}N_3Br_2O_2S$: C, 46.77; H, 3.93; N, 7.79. Found: C, 46.97; H, 3.93; N, 7.63.

2,6-Bis(aminomethyl)pyridine Dihydrochloride (10). A mixture of 2,6-bis(chloromethyl)pyridine (**9**) (17.6 g, 100 mmol), phthalimide K salt (37.5 g, 202 mmol), DMF (400 mL), and K_2CO_3 (5.0 g, 27 mmol) was stirred and heated at 140 °C for 6 h. When cooled, the crystalline bis(phthalide) was collected by suction filtration. Concentration of the filtrate in vacuo provided an additional amount of the product, making a total yield of 36.2 g (91%).

A mixture of the bis(phthalide) (33.2 g, 83.5 mmol) and 100% $NH_2NH_2 \cdot H_2O$ (8.4 g, 168 mmol) in EtOH (500 mL) was stirred and heated under reflux for 5 h. Concd HCl (50 mL) was then added to the reaction mixture, and the mixture was heated gently at reflux with stirring for 2 h. When cooled, the reaction mixture was filtered and the filtrate was evaporated. The yellow powder obtained was dissolved in hot H_2O. After the insoluble materials were filtered off, the filtrate was evaporated to give a yellow powder (15.9 g, 90%; 81% from **9**), which was used in the following step without further purification.

A small portion of the sample was recrystallized from acetone/H_2O for characterization to give colorless plates: mp >246 °C dec; ^{1}H NMR (270 MHz, D_2O) δ 4.04 (s, 4H), 7.09 (d, *J* = 7.92, 2H), 7.57 (t, *J* = 7.92, 1H). Anal. Calcd for $C_7H_{13}N_3Cl_2$: C, 40.02; H, 6.24; N, 20.00. Found: C, 40.09; H, 6.25; N, 19.84.

2,6-Bis[(*p*-tosylamino)methyl]pyridine (11). A mixture of **10** (10.0 g, 47.8 mmol) and *p*-TsCl (27.2 g, 142.7 mmol) in dioxane (400 mL) was stirred at room temperature for 1 h. KOH (1.46 g) in water (30 mL) was added dropwise to the mixture over 1 h. The reaction mixture was stirred for an additional 6 h. Dioxane and H_2O were distilled off, and then $CHCl_3$ (200 mL) and H_2O (200 mL) were added to this mixture. The organic phase was separated and evaporated. To the residual oil was added EtOH to give white crystals (16.2 g, 86%; 70% from **9**): mp 126−127 °C; IR (KBr) ν_{NH} 3228, ν_{SO} 1321, 1149 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.38 (s, 6H), 4.16 (d, 4H, *J* = 5.61), 5.85 (t, *J* = 5.61, 2H), 7.03 (d, *J* = 7.59, 2H), 7.22 (d, *J* = 8.24, 4H), 7.50 (t, *J* = 7.59, 1H), 7.71 (d, *J* = 8.25, 4H). Anal. Calcd for $C_{21}H_{23}N_3O_4S_2$: C, 56.60; H, 5.26; N, 9.43. Found: C, 56.69; H, 5.20; N, 9.43.

***N,N′,N″*-Tri-*p*-tosyl-2,11,20-triaza[3.3.3](2,6)pyridinophane (3b).** To a vigorously stirred and refluxing mixture of *n*-Bu_4NI (1.56 g) and **11** (3.20 g, 7.08 mmol) in CH_2Cl_2 (400

mL) and KOH (20 g) in H_2O (80 mL) was added dropwise a solution of **7** (3.82 g, 7.08 mmol) in CH_2Cl_2 (300 mL) over 5 h. The mixture was stirred under reflux for 24 h. On cooling, the organic layer was separated and evaporated. Acetone was added to the residue to give colorless crystals. Recrystallization from $CHCl_3$ and benzene gave colorless granules (3.55 g, 83%): mp 250−251 °C; FAB MS *m*/*z* 823 (M + 1); IR (KBr) ν_{SO} 1334, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 9H), 4.26 (s, 8H), 7.11 (d, J = 7.81, 6H), 7.26 (d, J = 7.81, 6H), 7.40 (t, J = 7.81, 3H), 7.64 (d, J = 7.81, 6H). Anal. Calcd for $C_{42}H_{42}N_6O_6S_3$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.15; H, 5.14; N,10.06.

2,11,20-Triaza[3.3.3](2,6)pyridinophane (3a). A mixture of **3b** (300 mg, 0.36 mmol) and concd sulfuric acid (3 mL) was stirred at 115−120 °C for 2 h. After addition of ice, the reaction mixture was made alkaline with aqueous sodium hydroxide. The solution was extracted with chloroform (50 mL) in three portions. The chloroform phase was dried ($MgSO_4$) and evaporated to give a pale yellow oil, which was crystallized from benzene to give 120 mg of hygroscopic colorless crystals (91%); mp 136−137 °C (evacuated sealed tube); FAB MS *m*/*z* 361.3 (M + 1); IR (C_4Cl_6) ν_{NH} 3310 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (br, 3H), 3.94 (s, 8H), 7.09 (d, J = 7.81, 6H), 7.55 (t, J = 7.81, 3H). Anal. Calcd for $C_{21}H_{24}N_6$: C, 69.97; H, 6.71; N, 23.32. Found: C, 70.05; H, 6.69; N, 23.27.

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