SYNTHESIS OF WATER-SOLUBLE DIAZA-1,2,5-THIADIAZOLO-CYCLOPHANES

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Abstract - The reaction of 3,4-bis(*p*-bromomethylphenyl)-1,2,5-thiadiazole (**1**) with bis(*N*-alkylaminomethyl)benzenes under high dilution conditions gave the diaza-1,2,5-thiadiazolo[3.3.2]cyclophanes, while **1** reacted with xylylenediamines to give cupped diazathiadiazolocyclophanes as major products. The reaction of **1** with the amino analog of **1** furnished the diaza-1,2,5-thiadiazolo[3.2.3.2]cyclophane in an excellent yield. These diazacyclophanes were soluble in acidic media.

Hetera-heterocyclophanes having the well-designed lipophilic cavity possess the ability to form an inclusion complex and thus attracted extensive attention as artificial hosts in host-guest chemistry.[1] Since heterocycles are known as latent functional group equivalents,[2] the conversion of a heterocyclic ring in a heterophane into the corresponding functional group(s) may provide a promising route to a cyclophane bearing *functional group(s) in its bridge.*

Previously, we have reported the synthesis of 1,2,5-thiadiazolo[2.2.2]cyclophanes and their conversion into 1,2-diketo-[3] and 1,2-diaminocyclophanes.[4] Our continuing interest in 1,2,5-thiadiazolophanes was directed to new heteracyclophanes bearing 1,2,5-thiadiazole ring(s). In this paper, we wish to report the synthesis of new acidic water-soluble diaza-1,2,5-thiadiazolocyclophanes by the reaction of 3,4-bis(*p*-bromomethylphenyl)-1,2,5-thiadiazole (**1**)[3a] with several bis(aminomethyl) compounds.

m- (**2**), *p*-Xylylenediamine (**3**) and their dialkylamino derivatives (**6**, **7**) were first chosen as bis(amino-methyl) compounds; *m*- (**6**) and *p*-bis(*N*-alkylaminomethyl)benzenes (**7**) were prepared *via* the acylation of **2** and **3**, followed by $LiAlH_4$ reduction, respectively.

After the reaction of dibromide (**1**) with *m*-bis(*N*-ethylaminomethyl)benzene (**6a**) was investigated under various conditions, it has been found that the reaction under high dilution conditions in the presence of Na_2CO_3 in CH_3CN gave the expected *N*,*N*'-diethyldiaza-1,2,5-thiadiazolo[3.3.2]metacyclophane (**8a**) in

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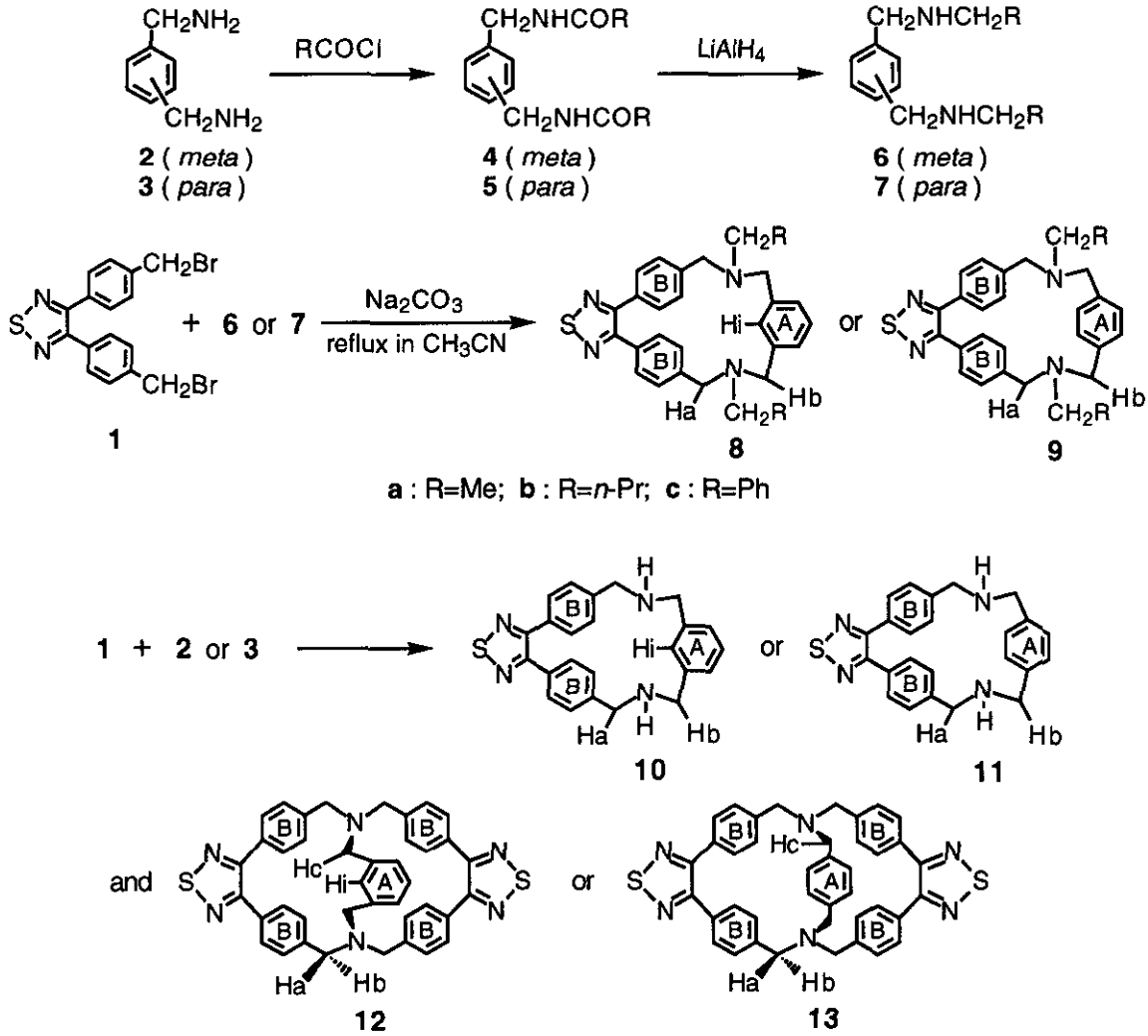
Dedicated to the memory of Professor Shunichi Yamada, Professor Emeritus, University of Tokyo.

49% yield. In the reaction of **1** with *m*-bis(*N*-*n*-butylaminomethyl)- (**6b**), *m*-bis(*N*-benzylaminomethyl)- (**6c**), and *p*-bis(*N*-ethylaminomethyl)benzene (**7a**) under similar conditions, the corresponding *N,N'*-dialkyldiazathiadiazolocyclophanes (**8b**), (**8c**) and (**9a**) were provided in 20, 19 and 19% yields, respectively.

In the reaction of **1** with primary diamines, *m*-xylylene- (**2**) and *p*-xylylenediamine (**3**), however, the corresponding 2:1 coupling cupped compounds (**12**) and (**13**) consisting of both the diaza[3.3.2]- and diaza[3.2.3.2]cyclophane skeletons were isolated in 45 and 22% yields, together with 5 and 9% yields of 1:1 condensed-ring compounds (**10**) and (**11**).



Scheme 1

Table 1 shows ^{1}H-NMR spectral data for **8a**, **9a**, **12**, and **13** as representative ones of diaza-1,2,5-thiadiazolocyclophanes.

Table 1. ^{1}H-NMR spectral data for diaza-1,2,5-thiadiazolocyclophanes (δ, $CDCl_3$)

Cyclophane	Bridged H	A-ring H	B-ring H
8a	3.27 (4H, s, Hb)	6.68 (br s, Hi)	7.10, 7.27 (each
	3.60 (4H, s, Ha)	6.97-7.27 (m, others)	d, J=8 Hz)
9a	3.56 (4H, s, Hb)	7.14 (s)	6.94 (s)
	3.68 (4H, s, Ha)		
	3.35 (4H, d, J=13 Hz, Ha)	7.25 (br s, Hi)	6.82 (s)
12	3.39 (4H, s, Hc)	7.05-7.20 (m, others)	
	3.61 (4H, d, J=13 Hz, Hb)		
	3.57 (4H, s, Hc)	5.94 (s)	7.26 (s)
13	3.86 (4H, d, J=13 Hz, Ha)		
	4.22 (4H, d, J=13 Hz, Hb)		

The ^{1}H NMR spectra of **8a** and **9a** display sharp singlets for the bridge methylene protons, respectively, which may indicate for these systems a rapid conformational change at room temperature. The A-ring protons in these systems are observed at slight upfields compared with the corresponding signals of the reference compounds (**6a**, δ 7.13, 7.40) and (**7a**, δ 7.27), respectively; these upfield shifts are presumably attributed to the shielding effect of the two B-rings. The protons in B-rings in these systems show again upfield shifts compared with the corresponding signals (δ 7.30, 7.50) of reference compound, 3,4-bis(*p*-aminomethylphenyl)-1,2,5-thiadiazole (**15**) prepared from **1** by the Gabriel synthesis (Scheme 2); it suggests that B-rings are not only subject to shielding effect of A-ring, but also to that of the vicinal B-ring itself each other.

On contrary, methylene protons connecting B-ring with nitrogen atom in both the cupped cyclophanes (**12**) and (**13**) are observed as AB patterns with coupling constant 13 Hz. These patterns showed no significant change in the range of about -60 °C to 100 °C; it is thus suggested that these systems are rigid structures, respectively. The structure of **13** was unambiguously established by the X-Ray crystallographic analysis (Figure 1).[5]

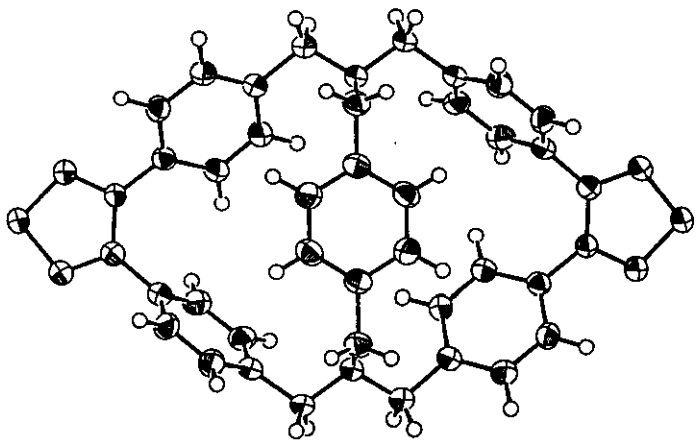
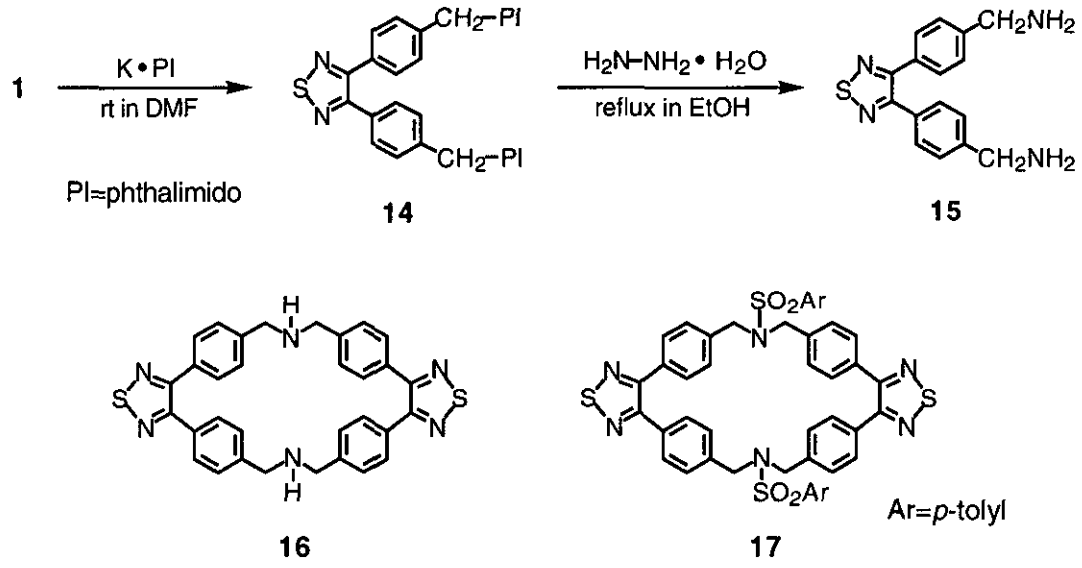


Figure 1. X-Ray structure of **13**.

The preparation of diazathiadiazolo[3.2.3.2]cyclophane system was next carried out. The reaction of **1** with diamine (**15**), which was prepared *via* the Gabriel synthesis from **1**, under the similar conditions in the presence of potasium carbonate furnished diaza-1,2,5-thiadiazolo[3.2.3.2]-cyclophane (**16**) in an excellent yield. Also, **1** reacted with *p*-toluenesulfonamide to give *N,N'*-ditosylated compound (**17**), whose detosylation to **16** was very difficult.[6]



Scheme 2

All of diaza-1,2,5-thiadiazolocyclophanes (**8-13, 16**) were soluble in acidic water (below pH 2). Conversion of the above diazathiadiazolocyclophanes to the corresponding 1,2-diketo- and 1,2-diamino-diazacyclophanes is now being studied in our laboratory.

EXPERIMENTAL

All melting points were measured with a Yanagimoto Micro Melting Point apparatus and are uncorrected. IR spectra were recorded on a Nippon Bunko FT/IR-7000 spectrophotometer. ^{1}H-NMR spectra were recorded on a Nippon Densi JNM-EX90 and JNM-EX270 spectrometer using TMS as an internal standard and measured in $CDCl_3$ unless otherwise indicated. MS spectra were obtained on a Nippon Densi JMS-AX500 mass spectrometer at 70 eV using a direct inlet system unless otherwise noted. Column chromatography was carried out on silica gel (Wako gel, C-300).

Bis(acylaminomethyl)benzenes (4, 5). To a vigorously stirred suspension of xylylenediamine (**2** or **3**) *(10.0 g, 73.5 mmol) in 32% aqueous NaOH solution (40 mL) in an ice bath was added dropwise the* corresponding acyl chloride (161.5 mmol) over a 1 h period. After the reaction mixture was stirred at the same temperature for an additional 3 h, the insoluble solid was filtered and washed with water to give the corresponding acylated product (**4** or **5**).

4a: 8.42 g (52%); mp 140-141 °C (AcOEt); colorless prisms; IR (KBr) 3300, 3075; 1640 cm^{-1}; ^{1}H-NMR δ 1.95 (6H, s, CH_3), 4.23 (4H, d, J=6 Hz, CH_2), 6.63 (2H, br t, J=6 Hz, exchanged with D_2O, NH), 6.93-7.35 (4H, m, ArH); MS *m/z* 220 (M^+).

4b: 16.4 g (81%); mp 126-127 °C (AcOEt); colorless prisms; IR (KBr) 3276, 3082, 1638 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.88 (6H, t, J=6 Hz, CH_3) 1.22-1.92 (4H, m, CH_2), 2.10 (4H, t, J=6 Hz, $COCH_2$), 4.23 (4H, d, J=6 Hz, $ArCH_2$), 6.87-7.43 (4H, m, ArH), 8.25 (2H, br t, J=6 Hz, exchanged with D_2O, NH); MS *m/z* 276 (M^+).

4c: 24.6 g (97%); mp 173-175 °C (EtOH); colorless prisms; IR (KBr) 3324; 3060, 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$- DMSO-d_6) δ 4.48 (4H, d, J=6 Hz, CH_2), 7.00-7.57 (10H, m, COPh), 7.63-8.00 (4H, m, ArH), 8.42 (2H, br t, J=6 Hz, exchanged with D_2O, NH); MS *m/z* 344 (M^+).

5a: 8.75 g (54%); mp 228-229 °C (CH_3CN); colorless prisms; IR (KBr) 3296, 3076, 1651 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.85 (6H, s, CH_3), 4.17 (4H, d, J=6 Hz, CH_2), 7.12 (4H, s, ArH), 8.17 (2H, br t, J=6 Hz, exchanged with D_2O, NH); MS *m/z* 220 (M^+).

Reduction of bis(acylaminomethyl)benzenes(4,5) to bis(*N*-alkylaminomethyl)benzenes (6, 7). As a typical procedure, the reduction of **4b** is described as follows. To a suspension of $LiAlH_4$ (15.2 g, 400 mmol) in dry THF (100 mL) under reflux was added dropwise a suspension of **4b** (8.0 g, 29.0 mmol) in dry THF (80 mL) for 2 h under nitrogen, and the mixture was refluxed for an additional 48 h. Into the reaction mixture cooled with ice was added water in small portions until evolution of gas ceased. Insoluble materials were filtered off, and the filtrate was dried ($MgSO_4$) and evaporated in vacuo. The residue was distilled under reduced pressure to give 3.59 g (50% yield) of *m*-bis(*N*-*n*-butylaminomethyl)-benzene (**6b**): Colorless oil; bp 124 °C/1.3 mmHg; IR (neat) 3320 cm^{-1}; ^{1}H-NMR δ 0.90 (6H, t, J=6 Hz, CH_3), 1.10-1.82 (8H, m, CH_2), 1.97 (2H, br s, exchanged with D_2O, NH), 2.60 (4H, t, J=7 Hz, $NHCH_2$), 3.75 (4H, s, $ArCH_2$), 6.93-7.43 (4H, m, ArH); MS *m/z* 248 (M^+).

6a: Yield 46%; colorless oil; bp 92-95 °C/0.9 mmHg; IR (neat) 3400 cm^{-1}; ^{1}H-NMR δ 1.12 (6H, t, J=7 Hz, CH_3), 1.34 (2H, s, exchanged with D_2O, NH), 2.68 (4H, q, J=7 Hz, CH_2), 3.77 (4H, s, $ArCH_2$), 7.00-7.60 (4H, m, ArH); MS *m/z* 192 (M^+).

6c: Yield 54%; pale yellow oil; IR (neat) 3310 cm^{-1}; ^{1}H-NMR δ 1.77 (2H, br s, exchanged with D_2O, NH), 3.75 (8H, s, CH_2), 7.00-7.43 (14H, m, ArH); MS *m/z* 316 (M^+).

7a: Yield 61%; colorless oil; bp 92-95 °C/1.2 mmHg; IR (neat) 3302 cm^{-1}; ^{1}H-NMR δ 1.11 (6H, t, J=7 Hz, CH_3), 1.31 (2H, s, exchanged with D_2O, NH), 2.66 (4H, q, J=7 Hz, CH_2), 3.76 (4H, s, $ArCH_2$), 7,26 (4H, s, ArH); MS *m/z* 192 (M^+).

***N,N'*-Dialkyldiazametacyclophanes (8a-8c).** To a suspension of Na_2CO_3 (11.1 g, 105 mmol) in CH_3CN (3 L) at reflux were added dropwise at the same rate each over a 48 h period from a separated Hershberg funnel a solution of **1** (1.3 g, 3.1 mmol) in benzene (120 mL) and a solution of **2a-2c** (3.1 mmol) in benzene (120 mL). After refluxing for an additional 16 h, two-thirds of the solvent was distilled away and the residue was filtered. The filtrate was concentrated in vacuo and the residue was chromatographed using $CHCl_3$ as an eluent to give cyclophanes (**8a-8c**) which were recrystallized from benzene.

8a: 0.68 g (49% yield) as colorless needles; mp 201-202 °C; MS *m/z* 454 (M^+). Anal. Calcd for $C_{28}H_{30}N_4S \cdot 1/3C_6H_6$: C, 74.96; H, 6.71; N, 11.66. Found: C, 74.59; H, 6.65; N, 11.65.

8b: 0.31 g (20%) as colorless prisms; mp 180-181 °C; ^{1}H-NMR δ 0.79 (6H, t, J=6.5 Hz, CH_3), 1.00-1.90 (8H, m, $NCH_2\underline{CH_2}\underline{CH_2}CH_3$), 2.64 (4H, t, J=7 Hz, $NC\underline{H_2}C_3H_7$), 3.29 (4H, s, Hb), 3.62 (4H, s, Ha), 6.77 (1H, br s, Hi), 7.00-7.28 (3H, m, A-ring H), 7.17, 7.33 (each 4H, d, J=8.5 Hz, B-ring H); MS *m/z* 510 (M^+). Anal. Calcd for $C_{32}H_{38}N_4S$: C, 75.26; H, 7.50; N, 10.97. Found: C, 75.45; H, 7.25; N. 11.16.

8c•C_6H_6: 0.38 g (19%) as colorless prisms; mp 100 °C (decomp); ^{1}H-NMR δ 3.40 (4H, s, Hb), 3.53 (4H, s, Ha), 3.73 (4H, s, $PhCH_2$), 6.92 (1H, br s, Hi), 7.00-7.40 (13H, m, A- and Ph-rings), 7.10, 7.25 (each 4H, d, J=8 Hz, B-ring), 7.27 (6H, s, C_6H_6). When the above benzene complex was heated at 140-150 °C in vacuo (2 mmHg) for 14 h, pure **4c** was obtained. **4c**: Colorless prisms; mp 170-172 °C; MS *m/z* 578 (M^+). Anal. Calcd for $C_{38}H_{34}N_4S$: C, 78.86; H, 5.92; N, 9.68. Found: C, 79.20; H, 6.02; N, 9.63.

***N,N'*-Diethyldiazaparacyclophane (9a)**. To a suspension of Na_2CO_3 (22.3 g, 210 mmol) in CH_3CN (2 L) at reflux were added dropwise at the same rate each over a 10 h period from a separated Hershberg funnel a solution of **1** (3.0 g, 7.0 mmol) in benzene (60 mL) and a solution of **7** (1.35 g, 7.0 mmol) in benzene (60 mL). After the resultant mixture was refluxed for an additional 2 h, two-thirds of the solvent was distilled away and the residue was filtered. The filtrate was concentrated in vacuo and the residue was extracted with hot benzene (150 mL). The extract was chromatographed using benzene-ethyl acetate (12:1) as an eluent to give crude **9a**, which on recrystallization from cyclohexane gave 0.60 g (19%) of pure **9a**: Colorless needles; mp 152-153 °C; MS *m/z* 454 (M^+). Anal. Calcd for $C_{28}H_{30}N_4S$: C, 73.97; H, 6.65; N, 12.32. Found: C, 73.84; H, 6.68; N, 12.09.

Reaction of 1 with 2. To a suspension of Na_2CO_3 (15.0 g, 142 mmol) in refluxing CH_3CN (3 L) were added dropwise at the same rate each over a 51 h period from a separated Hershberg funnel a solution of **1** (2.0 g, 4.7 mmol) in benzene (120 mL) and a solution of **2** (0.64 g, 4.7 mmol) in benzene (120 mL). After refluxing for an additional 14 h, two-thirds of the solvent was distilled away and the residue was divided into soluble and insoluble materials by filtration. The insoluble materials were extracted with $CHCl_3$ (100 mL) and the extract was concentrated in *vacuo*, and the residue was recrystallized from benzene to give 0.60 g (39%) of the cupped cyclophane (**12**). The soluble materials were concentrated in *vacuo*, and the residue was chromatographed to give 90 mg (6%) of **12** and 85 mg (5%) of the 1:1 condensed-ring compound (**10**) from benzene- and ethyl acetate-eluent, respectively.

10: Colorless prisms; mp 228-229 °C; IR (KBr) 3336, 3276 cm^{-1}; ^{1}H-NMR δ 1.80 (2H, s, exchanged with D_2O, NH), 3.47 (4H, s, Hb), 3.80 (4H, s, Ha), 6.56 (1H, br s, Hi), 7.00-7.16 (3H, m, A-ring), 7.17, 7.27 (each 4H, d, J=8 Hz, ArH); MS *m/z* 398 (M^+). Anal. Calcd for $C_{24}H_{22}N_4S$: C, 72.33; H, 5.56; N, 14.06. Found: C, 72.66; H, 5.64; N, 13.80.

12: Colorless prisms; mp 248 °C (decomp); MS *m/z* 660 (M^+). Anal. Calcd for $C_{40}H_{32}N_6S_2$•1/2C_6H_6: C, 73.79; H, 5.04; N, 12.01. Found: C, 73.78; H, 5.13; N, 12.02.

Reaction of 1 with 3. To a suspension of Na_2CO_3 (11.1 g, 105 mmol) in refluxing CH_3CN (3 L) were added dropwise at the same rate each over a 48 h period from a separated Hershberg funnel a solution of **1** (1.5 g, 3.5 mmol) in benzene (120 mL) and a solution of **3** (0.48 g, 3.5 mmol) in benzene (120 mL). After refluxing for an additional 17 h, the reaction mixture was worked up in the same manner as described above to give 0.13 g (9%) of the 1:1 condensed-ring compound (**11**) and 0.256 g (22%) of the cupped

cyclophane (**13**).

11: Colorless prisms; mp 165-167 °C; IR (KBr) 3372 cm^{-1}; ^{1}H-NMR δ 1.97 (2H, s, exchanged with D_2O, NH); 3.77 (4H, s, Hb), 3.94 (4H, s, Ha), 6.90 (8H, s, B-ring), 7.03 (4H, s, A-ring), MS *m/z* 398 (M^+). Anal. Calcd for $C_{24}H_{22}N_4S$: C, 72.33; H, 5.56; N, 14.06. Found: C, 72.17; H, 5.54; N, 13.84.

13: Colorless prisms; mp 281-283 °C (decomp); MS *m/z* 660 (M^+), Anal. Calcd for $C_{40}H_{32}N_6S_2$: C, 72.70; H, 4.88; N, 12.72. Found: C, 72.80; H, 5.00; N, 12.51.

Preparation of 3,4-bis(*p*-aminomethylphenyl)-1,2,5-thiadiazole (15). i) A mixture of **1** (4.0 g, 9.43 mmol) and potasium phthalimide (3.85 g, 20.8 mmol) in dry DMF (25 mL) was stirred at rt for 7 h. The reaction mixture was filtered and insoluble materials were washed with water and dried to give 4.66 g (89%) of phthalimido derivative (**14**), which on recrystallization from dioxane gave colorless prisms, mp 292-293 °C; IR (KBr) 1773, 1717 cm^{-1}; ^{1}H-NMR δ 4.87 (4H, s, CH_2), 7.38, 7.49 (each 4H, d, J=9 Hz, ArH), 7.65-7.95 (8H, m, ArH); MS *m/z* 556 (M^+). Anal. Calcd for $C_{32}H_{20}N_4O_4S$• 1/4dioxane: C, 68.50; H, 3.83; N, 9.68. Found: C, 68.35; H, 3.92; N, 9.70.

ii) A suspension of **14** (2.0 g, 3.59 mmol) and 98% hydrazine hydrate (3.6 g, 71.9 mmol) in ethanol (100 mL) was refluxed for 12 h. The reaction mixture was filtered and the filtrate was concentrated in *vacuo* to leave a residue, which was extracted with 10% aqueous HCl solution (25 mL). The acid extract was made alkaline with 10% aqueous KOH solution (30 mL) and insoluble materials were extracted with $CHCl_3$ (250 mL). The extract was dried ($MgSO_4$) and concentrated in vacuo to give 0.89 g (84%) of **15** as pale yellow prisms, mp 90-92.5 °C; IR (KBr) 3358, 3300 cm^{-1}; ^{1}H-NMR δ 1.51 (4H, s, exchanged with D_2O, NH), 3.91 (4H, s, CH_2), 7.30, 7.50 (each 4H, d, J=8.5 Hz, ArH), MS *m/z* 296 (M^+).

Reaction of 1 with 15. To a suspension of K_2CO_3 (8.51 g, 61.6 mmol) in refluxing CH_3CN (3.5 L) were added dropwise at the same rate each over a 12 h period from a separated Hershberg funnel a solution of **1** (1.19 g, 2.80 mmol) in benzene (100 mL) and a solution of **15** (0.83 g, 2.80 mmol) in CH_3CN (100 mL). After refluxing for an additional 2 h, the solvent was evaporated in *vacuo*, and the residue was washed with water and dried to give 1.52 g (97%) of **16** (mp 275-278 °C (decomp)), which on recrystallization from DMSO gave colorless prisms, mp 280 °C (decomp); IR (KBr) 3330 cm^{-1}; ^{1}H-NMR (CF_3CO_2D) δ 4.56 (8H, br s, CH_2), 7.52 (16H, s, ArH); MS *m/z* 558 (M^+). Anal. Calcd for $C_{32}H_{26}N_6S_2$ •1/3DMSO: C, 67.10; H, 4.83; N, 14.37. Found: C, 67.17; H, 4.76; N, 14.01.

Reaction of 1 with *p*-toluenesulfonamide. To a suspension of K_2CO_3 (9.10 g, 66.0 mmol) in boiling CH_3CN (3.5 L) were added dropwise at the same rate each over a 10 h period from a separated Hershberg funnel a solution of **1** (1.27 g, 3.0 mmol) in benzene (100 mL) and a solution of *p*-toluenesulfonamide (0.51 g, 3.0 mmol) in CH_3CN (100 mL). After refluxing for an additional 3 h, the solvent was evaporated in vacuo and the residue was recrystallized from $CHCl_3$ to give 0.48 g (37%) of diazacyclophane (**17**): Colorless prisms; mp > 300 °C; IR (KBr) 1336, 1158 cm^{-1}; ^{1}H-NMR (CF_3CO_2D) δ 2.57 (6H, s, CH_3), 4.52 (8H, s, CH_2), 7.13, 7.46 (each 8H, d, J=8 Hz, ArH), 7.57, 7.97 (each 4H, d, J=8 Hz, ArH of Ts); FABMS *m/z* 867 (MH^+). Anal. Calcd for $C_{46}H_{38}N_6O_4S_4$•0.7$CHCl_3$: C, 59.00; H, 4.10; N, 8.84. Found: C, 59.20; H, 4.17; N, 8.57.

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5. Crystal data of **13**: $C_{40}H_{32}N_6S_2$, M=660.85, orthorhombic, space group Pbcn (#60), a=20.138 (2) Å, b=9.703 (2) Å, c=16.794 (4) Å, V=3281.6 (8) $Å^3$, Z=4, Dcalc=1.338 g/cm^3, μ(CuKα)=17.78 cm^{-1}, Rigaku AFC7R diffractometer, 2222 reflections with I>3.00σ(I), R=0.038, Rw=0.059.
6. Detosylation of **17** was very difficult, but ultimately achieved using 48% HBr in refluxing phenol for 19 h to give **16** in only 9% yield.

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