A Convenient Synthesis of Trifluoroacetamide Derivatives of Diaza[3_2]cyclophanes and Triaza[3_3]cyclophanes

Hideki Okamoto,*[a] Hiroyuki Takemura,[b] Kyosuke Satake[a]

[a] Division of Chemistry and Biochemistry, The Graduate School of Natural Science and Technology, Okayama University, Tsushima-Naka 3-1-1, Okayama 700-7530, Japan
E-mail: hokamoto@cc.okayama-u.ac.jp

[b] Department of Chemistry and Biological Science, Japan Women's University, Tokyo 112-8681, Japan

Received 22 August 2007; revised 10 October 2007

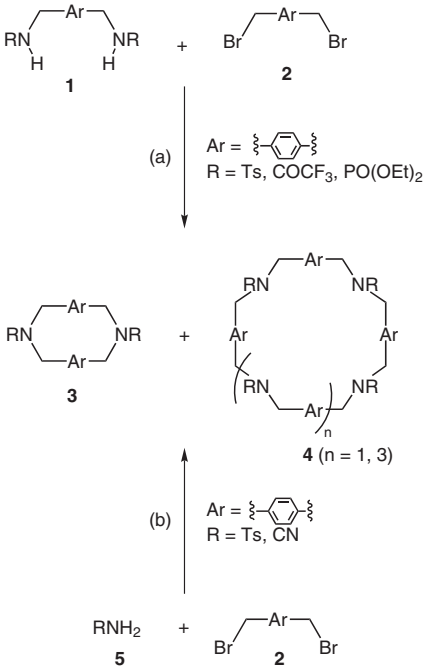
Abstract: The diaza[3_2]cyclophane skeleton has been constructed by the bis-N-alkylation of 1,4-bis[(4-nitrophenylsulfonylamino)methyl]benzene with 1,4-bis(halomethyl)benzene in the presence of sodium hydride. The 4-nitrophenylsulfonyl (Ns) amides in the bridge chains of the cyclophane were effectively deprotected by sodium ethanethiolate and the resulting free amine moieties were reprotected as the trifluoroacetamide under mild conditions to afford 3,7-bis(trifluoroacetyl)-3,7-diaza-1,5(1,4)-dibenzenacyclooctaphane in 26% overall yield. This Ns-amide method has also been applied for the preparation of a higher homologue, the trifluoroacetamide derivative of triaza[3_3]cyclophane, 3,5,7-tris(trifluoroacetyl)-3,7,10-triaza-1,5(1,3,5)-dibenzenabicyclo[3.3.3]undecaphane, in 18% overall yield. Thus, the present procedure provides a convenient synthetic route to azacyclophane derivatives possessing trifluoroacetamide groups in the bridge chains.

Key words: cyclophanes, sulfonamides, amides, chromophores, amines

Cyclophanes possessing nitrogen atoms in their bridge chains have been of photochemical interest because they sometimes display different reactions than those of the corresponding carbon-bridged analogues or nonbridged chromophores.[1–4] We have recently disclosed that diaza[3_2]cyclophane **11** afforded an interesting octahedrane cage upon photoirradiation, while the corresponding carbon-bridged analogue, [3_2]cyclophane, was almost inert under the same conditions.[2] Thus, it would be interesting to reveal the details of the unique photoproperties of the diazacyclophane system. Although the diaza[3_2]cyclophane **11** has been prepared by Shinmyozu et al.,[5] the yield was quite low.[6] Thus, it is highly desirable to establish an efficient synthetic route to the azacyclophane system.

Conventionally, there are two methodologies for the construction of diaza[3_2]cyclophane as shown in Scheme 1; (i) cyclization of amide-activated diamine **1** and xylylene dihalide **2** (path a)[5,7,8] and (ii) coupling of 4-toluenesulfonamide (Ts-amide) or cyanamide **5** with xylylene dihalide **2** (path b).[9–11] Among these procedures, the Ts-amide methods (Scheme 1, path a, R = Ts; path b, R = Ts) have been used as practical routes to the diaza[3_2]cyclophane skeleton **3**,[7,10] while the others (Scheme 1, path a, R = $COCF_3$, $PO(OEt)_2$; path b, R = CN) resulted in the formation of higher oligomers **4** rather than the desired diaza[3_2]cyclophane **3**.[5,7–11] The Ts-amide methods are thus effective for preparing the Ts-amide derivative of diaza[3_2]cyclophane. However, absorption of the aromatic Ts-amide chromophores overlaps with that of the diaza[3_2]cyclophane chromophore thus preventing evaluation of the photoproperties of the aza[3_2]cyclophane system. Additionally, deprotection of the Ts-amide moieties required severe conditions, such as Birch reduction conditions or a highly acidic medium.[7,10] Thus, a simple synthetic route is needed for the construction of an azacyclophane possessing bridge nitrogen substituents that display no absorption band in the absorption region of the azacyclophane chromophore (>250 nm).

We now describe the convenient synthesis of the title nitrogen-bridged cyclophanes **11** and **15**. In the present procedure, 4-nitrobenzenesulfonamide (Ns-amide) was used as the activating group (cf., Scheme 1, path a). The Ns-amide method was developed by Fukuyama and was used for the synthesis of a variety of functionalized amines,[12]

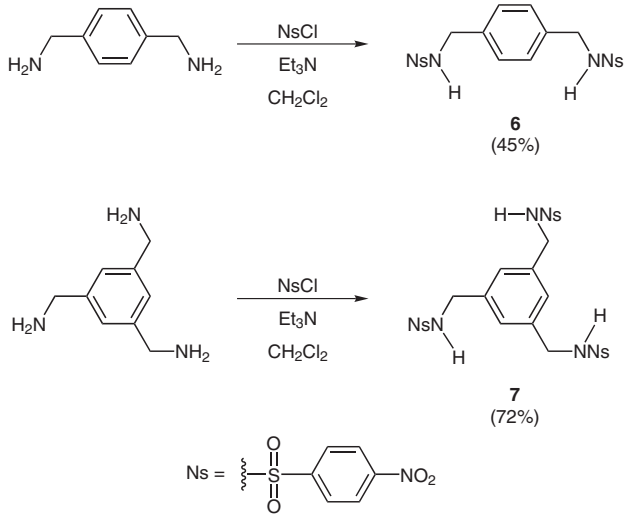


Scheme 1

SYNTHESIS 2008, No. 1, pp 0039–0044
Advanced online publication: 07.12.2007
DOI: 10.1055/s-2007-1000825; Art ID: F15307SS

however, it has rarely been used for the construction of azacyclophanes. The Ns-amide method would be promising for the synthesis of the azacyclophane skeletons because (i) the electronic structure of the Ns-amide is similar to that of the Ts-amide, thus, effective formation of the diaza[3_2]cyclophane skeleton is expected,[7] and (ii) functional group conversion is easy since the Ns group can be removed by a thiolate reagent.[12]

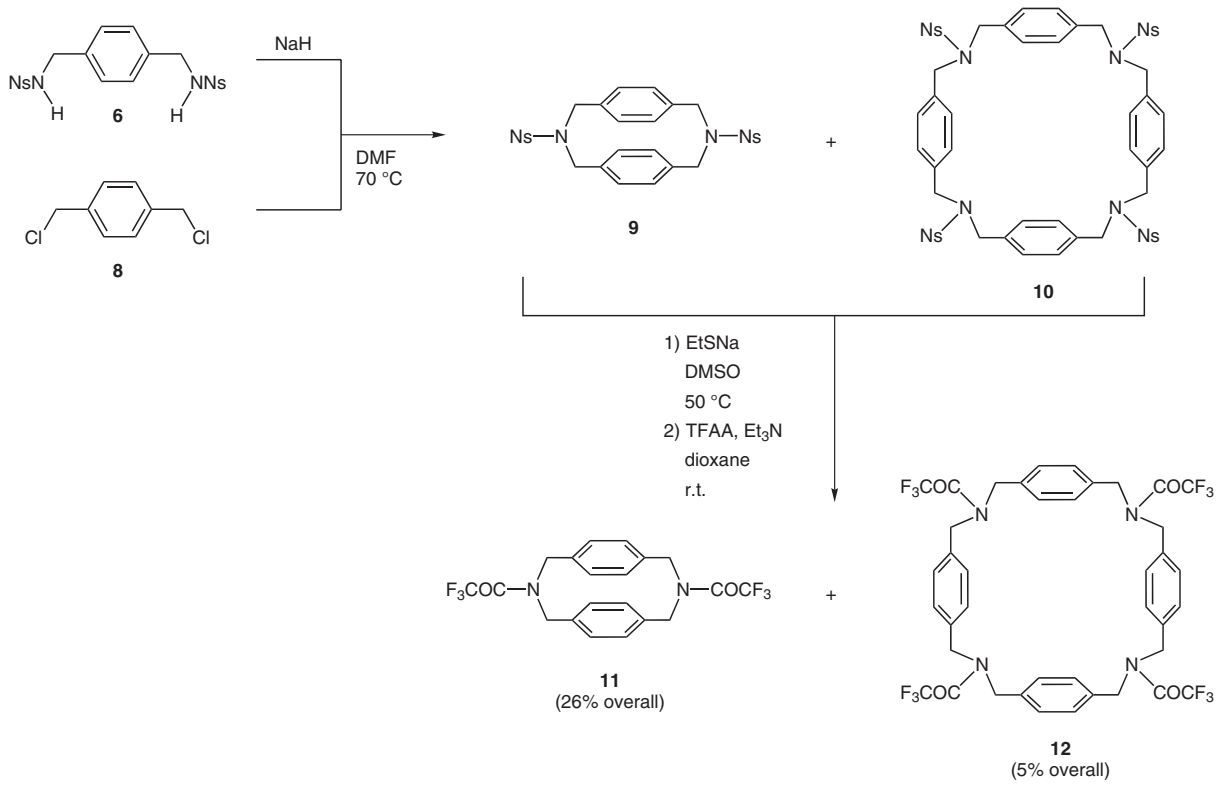
The doubly and triply armed Ns-amides **6** and **7**, as precursors for the azacyclophanes **11** and **15**, were readily prepared by the reaction of 1,4-bis- and 1,3,5-tris(aminomethyl)benzenes, respectively, with 4-nitrobenzenesulfonyl chloride (NsCl) under the usual conditions[12] (Scheme 2). These new Ns-amides were characterized by their ^{1}H NMR and IR spectra as well as elemental analyses.



Scheme 2

The synthetic route to the diaza[3_2]cyclophane skeleton using the bis-Ns-amide **6** is shown in Scheme 3. Ns-amide **6** was treated with sodium hydride in *N*,*N*-dimethylformamide to generate the corresponding bis-amidate anion. The bis-amidate anion and 1,4-bis(chloromethyl)benzene (**8**) were coupled under high-dilution conditions at 70 °C to afford the desired dimeric adduct **9** as well as tetramer **10**. As the solubility of these Ns-amides **9** and **10** in common organic solvents was quite poor, they were characterized by ^{1}H NMR spectroscopy and used in the following reaction without separation: Ns-amides **9** and **10** displayed ^{1}H NMR spectral patterns that were similar to those of the corresponding Ts-amide derivatives.[7b,10]

Removal of the Ns groups and reprotection by trifluoroacetylation were accomplished through the following successive reaction sequence. The mixture of Ns-amides **9** and **10** was treated with sodium ethanethiolate at 50 °C,[13] then the resulting bridge amine moieties were acetylated with trifluoroacetic anhydride to afford the corresponding trifluoroacetamides, **11** and **12**. These azacyclophanes were successfully isolated by silica gel chromatography and the overall yields were 26% for **11** and 5% for **12**. Their physical data were identical to those already reported.[5] In the present reaction, no higher oligomer, such as a hexamer (cf., Scheme 1, **4**, n = 3)[5,7–10] was obtained. As previously discussed, direct coupling of 1,4-bis[(trifluoroacetylamino)methyl]benzene with 1,4-bis(bromometh-



Scheme 3

yl)benzene afforded the tetramer **12** as the main product and the dimeric cyclophane **11** was only a minor product (Scheme 1, path a).[5,6] Thus, the present procedure provides a practical route to the diaza[3_2]cyclophane **11**.

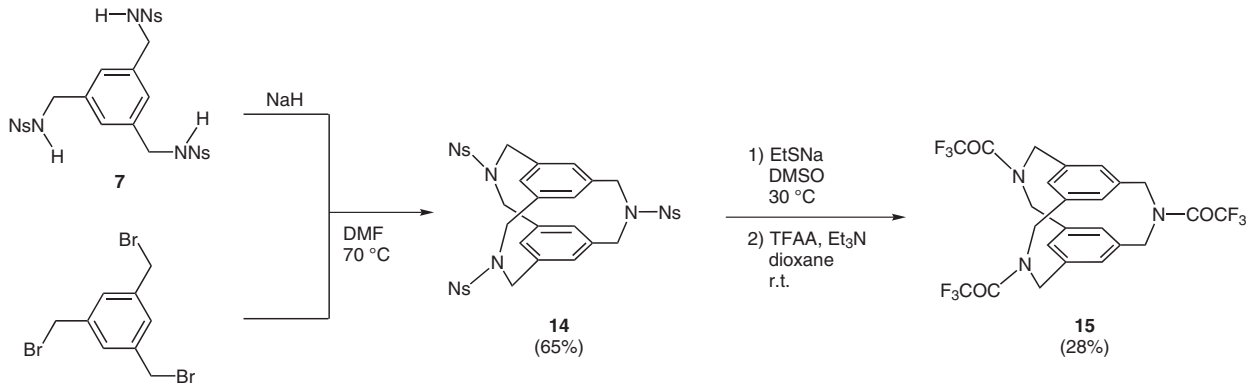
The trifluoroacetamide possesses advantages over the conventional Ts-amides; (i) facile functional group conversion on the bridge nitrogen atoms is possible as previously shown,[3,5] (ii) the absorption band of the trifluoroacetamide does not overlap with that of the azacyclophane system, thus the unique photochemical properties of the azacyclophane chromophore[2] can be investigated.

The present Ns-amide method was applied for preparation of a higher-bridged cyclophane system, triaza[3_3]cyclophane **15** (Scheme 4). Tris-Ns-amide **7** and tribromide **13** were coupled under similar conditions as in the case of diazacyclophane **9**. A triply bridged cyclophane skeleton **14** was obtained in an unexpectedly high yield (65%). The tris-Ns-amide **14** was isolated from the reaction mixture as a 3:2 complex of **14** and *N*,*N*-dimethylformamide (the ratio was determined by ^{1}H NMR spectroscopy). An *N*,*N*-dimethylformamide-free analytical sample of **14** was obtained by recrystallization from a mixed solvent of dimethyl sulfoxide–ethanol.

Concerning triaza[3_3]cyclophane synthesis, Vögtle reported that coupling of 1,3,5-tris[(tosylamino)methyl]benzene with tribromide **13** produced a Ts-amide derivative of triaza[3_3]cyclophane,[14] and one of the present authors has reported that reaction of cyanamide **5** (R = CN) and tribromide **13** afforded an *N*-cyano derivative of triaza[3_3]cyclophane.[11]

The bridge functional group transformation was investigated as in the case of diaza[3_2]cyclophane **9**. The bridge Ns-amide was converted into its trifluoroacetamide by successive treatment of the Ns-amide **14** with sodium ethanethiolate and trifluoroacetic anhydride to afford trifluoroacetamide **15**.[13] The resulting triaza[3_3]cyclophane **15** was characterized by spectroscopic and elemental analyses.

The structural features of the azacyclophanes, **11** and **15**, were investigated by ^{1}H and ^{19}F NMR spectroscopy. The aromatic protons of diazacyclophane **11** appeared as a pair of singlets at δ = 6.74 and 6.82, and a pair of doublet signals at δ = 6.73 and 6.84 (at 21.8 °C, DMSO-d_6). Since the activation energy for a ring flipping motion is much lower than that for the amide rotation,[1,15–17] two rotamers are considered at ambient temperature due to the restricted rotation of the amide moieties (Figure 1). Thus, the *syn*, C_{2v} isomer of **11** displayed the two singlet signals while the



Scheme 4

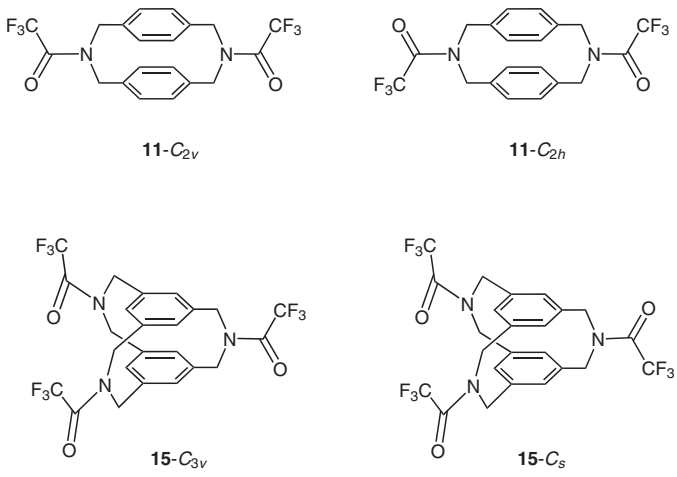


Figure 1

anti, C_{2h} symmetrical one showed two doublets in the aromatic region. These ^{1}H NMR spectral features are consistent with those already reported.[5] At 85 °C, the aromatic signals coalesced to show a single peak at δ = 6.80.

In the ^{19}F NMR spectrum of the diazacyclophane **11**, two signals assigned to the trifluoroacetyl groups were observed at δ = –67.59 and –67.47 (Figure 2a). These observations are consistent with the coexistence of the two rotamers.

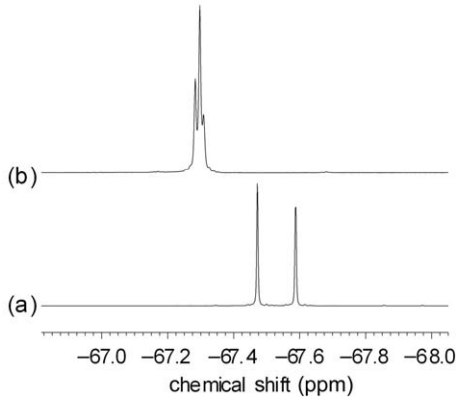


Figure 2 ^{19}F NMR spectra of (a) diazacyclophane **11** and (b) triazacyclophane **15** (564 MHz, $CDCl_3$).

For the structure of triazacyclophane **15**, two C_{3v}- and C_s-symmetrical rotamers are also possible as depicted in Figure 1. Actually, in the ^{1}H NMR spectrum, triazacyclophane **15** displayed complex signals of aromatic protons at ambient temperature, δ = 6.67–6.88 (DMSO-d_6), due to the restricted rotation of the three amide moieties. At elevated temperature (95 °C), these signals coalesced into a single peak at δ = 6.81 as expected for [3$_3$]cyclophane skeleton.[14,17] For the two rotamers, three non-equivalent trifluoroacetyl groups are expected (Figure 1). In the ^{19}F NMR spectrum, triazacyclophane **15** displayed three signals at δ = –67.31, –67.30, and –67.28 as shown in Figure 2b that supported the coexistence of these rotamers.

In summary, the present Ns-amide coupling method provides a convenient route to nitrogen-bridged [3$_2$]- and [3$_3$]cyclophane skeletons (Schemes 3 and 4). The Ns-protecting groups on the bridge nitrogen atoms can be removed by the reaction of the Ns-amides, **9** and **14**, with sodium ethanethiolate under the mild conditions, and the resulting free-amine bridges are reprotected by a common procedure, e.g., trifluoroacetylation by trifluoroacetic anhydride, thus the azacyclophanes **11** and **15** are obtained in reasonable overall yields (**11**: 26%, **15**: 18%).

The trifluoroacetamide bridge chains satisfy the demands for our investigations; (i) no absorption of the trifluoroacetamide function in the wavelength region >250 nm and (ii) facile functional group conversion on the bridge nitrogen atoms. Currently, investigations on the photoproperties of the azacyclophanes **11** and **15** are underway. Furthermore, the present azacyclophanes **11** and **15** would be promising platforms for construction of a highly functionalized azacyclophane system since the bridge substituents can be easily modified using various kinds of functional groups.[3,5]

All melting points were uncorrected. ^{1}H NMR spectra were collected with Varian Mercury 300 (300 MHz), XVR-500 (500 MHz) or Inova AS600 (600 MHz) spectrometers. ^{19}F NMR spectra (564 MHz) were measured using C_6F_6 (δ = –162.9) as an internal standard. IR spectra were measured with Jasco FT-IR 5000 spectrophotometer. Silica gel chromatography was performed using silica gel 60 (63–230 μm). The preparative liquid chromatography was carried out using silica gel 60 (40–60 μm, Wakogel LP-60).

1,4-Bis[(4-nitrophenylsulfonylamino)methyl]benzene (6)

To a mixture of 1,4-bis(aminomethyl)benzene (0.75 g, 5.5 mmol) and Et_3N (0.56 g, 5.5 mmol) in CH_2Cl_2 (20 mL) was dropwise added a soln of NsCl (2.22 g, 10 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. The precipitate formed was collected, washed with $CHCl_3$, then recrystallized (MeCN) to afford **6** (1.28 g, 45%) as off-white plates; mp 235–236 °C.

IR (KBr): 1154, 1309, 1352, 1539, 3270 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.99 (d, J = 6.2 Hz, 4 H, CH_2Ar), 7.11 (s, 4 H, ArH), 7.99 (m, 4 H, Ns), 8.37 (m, 4 H, Ns), 8.51 (t, J = 6.2 Hz, 2 H, NH).

Anal. Calcd for $C_{20}H_{18}N_4O_8S_2$: C, 47.43; H, 3.58; N, 11.06. Found: C, 47.52; H, 3.53; N, 10.71.

1,3,5-Tris[(4-nitrophenylsulfonylamino)methyl]benzene (7)

To a soln of 1,3,5-tris(aminomethyl)benzene[18] (6.68 g, 40.4 mmol) and Et_3N (11.65g, 115.2 mmol) in CH_2Cl_2 (200 mL) was dropwise added a soln of NsCl (25.5 g, 115.2 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. The precipitated salt was filtered off and the filtrate was concentrated under reduced pressure. The residue was washed with H_2O and dried. The crude product was recrystallized (THF–EtOH) to afford **7** (20.18 g, 72%) as pale yellow crystals; mp 225–226 °C.

IR (KBr): 1164, 1311, 1350, 1528, 3308 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.88 (d, J = 6.3 Hz, 6 H, CH_2Ar), 6.91 (s, 3 H, ArH), 7.97 (m, 6 H, Ns), 8.35 (m, 6 H, Ns), 8.50 (t, J = 6.3 Hz, 3 H, NH).

Anal. Calcd for $C_{27}H_{24}N_6O_{12}S_3$: C, 45.00; H, 3.36; N, 11.44. Found: C, 45.19; H, 3.40; N: 11.44.

3,7-Bis(trifluoroacetyl)-3,7-diaza-1,5(1,4)-dibenzenacyclooctaphane (11)

To a soln of bis-Ns-amide **6** (2.53 g, 5.0 mmol) in DMF (100 mL) was added NaH (60% in mineral oil, 440 mg, 11 mmol), and the mixture was stirred at r.t. for 2 h. The resulting dark red soln and a soln of 1,4-bis(chloromethyl)benzene (**8**, 876 mg, 5 mmol) in DMF (100 mL) were added dropwise to DMF (240 mL) at 70 °C over a period of 4 h. The soln was then stirred overnight at 70 °C. The mixture was cooled to r.t. and the precipitate formed was collected by suction filtration (fraction A, 1.39 g). The filtrate was concentrated to ca. 100 mL under reduced pressure and the precipitated products were collected (fraction B, 1.03 g). Fraction A mainly contained **9** and fraction B was a mixture of **9**, **10**, and unidentified materials.

9

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.39 (br, 8 H, CH_2Ar), 6.89 (s, 8 H, Ar), 8.23 (m, 4 H, Ns), 8.46 (m, 4 H, Ns).

10

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.05 (br, 16 H, CH_2), 6.82 (s, 16 H), 8.07 (m, 8 H, Ns), 8.37 (m, 8H, Ns).

Fraction A was suspended in DMSO (20 mL) and a soln of EtSNa (1.16 g, 13.8 mmol) in DMSO (15 mL) was slowly added at 50 °C. The resulting dark-red soln was stirred for a further 30 min at 50 °C. The mixture was poured into brine (200 mL) and extracted with $CHCl_3$ (4 × 40 mL). The combined extracts were washed with H_2O, dried (anhyd Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in dioxane (15 mL) and Et_3N (892 mg, 9.16 mmol) was added. To the soln was added a soln of TFAA (1.91 g, 9.16 mmol) in dioxane (5 mL). The mixture was stirred at r.t. for 30 min. The solvent was evaporated under reduced pressure and the residue was chromatographed (silica gel, $CHCl_3$). The crude product was separated by preparative liquid chromatography (silica gel, hexane–EtOAc, 1:1) to afford the trifluoroacetamide derivative **11** (523 mg).

Fraction B was successively treated with EtSNa (850 mg, 10.1 mmol) in DMSO and TFAA (1.41 g, 6.74 mmol) in dioxane as described for fraction A. By the repeated chromatographic separation as stated above, diazacyclophane **11** (20 mg) and tetramer **12** (108 mg) were isolated. The total yields of the azacyclophanes, **11** and **12**, were thus 543 mg (26%) and 108 mg (5%), respectively.

11

Mp 212–213 °C (Lit.[5] 211–213 °C).

12

Mp 237–238 °C (Lit.[5] 238–239 °C).

The ^{1}H NMR data were identical to those already reported.[5]

3,5,7-Tris(4-nitrophenylsulfonyl)-3,7,10-triaza-1,5(1,3,5)-dibenzenabicyclo[3.3.3]undecaphane (14)

A mixture of tris-Ns-amide **7** (3.60 g, 5 mmol) and NaH (60% in mineral oil, 660 mg, 16.5 mmol) in DMF (200 mL) was stirred at r.t. for 2 h. The resulting dark-red soln and a soln of 1,3,5-tris(bromomethyl)benzene (**13**, 3.57 g, 10 mmol) in DMF (200 mL) were added dropwise to DMF (200 mL) at 70 °C over a period of 4 h. The resulting soln was stirred overnight at 70 °C. The soln was concentrated to ca. 40 mL, and the precipitate formed was collected and successively washed with DMF, H_2O, and EtOH, then dried under reduced pressure to afford Ns-amide **14** (2.90 g, 65% as 3:2 complex of **14**–DMF). A DMF-free analytical sample was obtained by recrystallization (DMSO–EtOH) as off-white fine crystals; mp >300 °C.

IR (KBr): 1170, 1350, 1524, 3308 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.44 (br, 12 H, CH_2Ar), 6.90 (s, 6 H, ArH), 8.22 (m, 6 H, Ns), 8.46 (m, 6 H, Ns).

Anal. Calcd for $C_{36}H_{30}N_6O_{12}S_3$: C, 51.79; H, 3.62; N, 10.07. Found: C, 51.49; H, 3.57; N, 9.84.

3,5,7-Tris(trifluoroacetyl)-3,7,10-triaza-1,5(1,3,5)-dibenzenabicyclo[3.3.3]undecaphane (15)

To a suspension of the Ns-amide **14** (3:2 complex of **14**-DMF, 1.77 g, 2.0 mmol) in DMSO (20 mL) was dropwise added a soln of EtSNa (1.52 g, 18 mmol) in DMSO (20 mL). The mixture was stirred at 30 °C for 14 h. The resulting dark-red soln was poured into brine (200 mL) and extracted with $CHCl_3$ (4 × 50 mL). The combined extracts were washed with H_2O, dried (anhyd Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in dioxane (20 mL), and Et_3N (0.95 g, 12 mmol) was added. To the soln was dropwise added a soln of TFAA (2.52 g, 12 mmol) in dioxane (5 mL) at 0 °C. The mixture was then stirred at r.t. for 30 min. The solvent was removed under reduced pressure, and the residue was separated by chromatography (silica gel, $CHCl_3$) followed by preparative liquid chromatography (silica gel, hexane–EtOAc, 1:1) to afford **15** (352 mg, 28%); mp 247–247.5 °C.

IR (KBr): 1135, 1680 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.74 (br, 6 H, CH_2Ar), 4.85 (br, 6 H, CH_2Ar), 6.64–6.78 (6 H, ArH).

^{19}F NMR (564 MHz, $CDCl_3$): δ = –67.31, –67.30, –67.28.

MS (FAB): m/z = 568 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{18}F_9N_3O_3$: C, 50.80; H, 3.20; N, 7.41. Found: C, 50.52; H, 3.13; N: 7.29.

Acknowledgment

The authors are grateful to the SC-NMR Laboratory of Okayama University for the NMR spectral measurements. H. Okamoto thanks Professor Teruo Shinmyozu (IMCE, Kyushu University) for his active discussions and the gift of 1,3,5-tris(bromomethyl)benzene.

References

(1) (a) Okamoto, H.; Yamaji, M.; Satake, K.; Tobita, S.; Kimura, M. *J. Org. Chem.* **2004**, *69*, 7860. (b) Okamoto, H.; Kimura, M. In *New Trends in Structural Organic Chemistry*; Takemura, H., Ed.; Research Signpost: Kerala India, **2005**, 105.
(2) Okamoto, H.; Satake, K.; Ishida, H.; Kimura, M. *J. Am. Chem. Soc.* **2006**, *128*, 16508.
(3) (a) Usui, M.; Nishiwaki, T.; Anda, K.; Hida, M. *Nippon Kagaku Kaishi* **1988**, 1052. (b) Usui, M.; Nishiwaki, T.; Anda, K.; Hida, M. *Nippon Kagaku Kaishi* **1989**, 237.
(4) Okamoto, H.; Satake, K.; Kimura, M. *Chem. Lett.* **1997**, 873.
(5) Shinmyozu, T.; Shibakawa, N.; Sugimoto, K.; Sakane, H.; Takemura, H.; Sako, K.; Inazu, T. *Synthesis* **1993**, 1257.
(6) Shinmyozu et al. has reported that, according to the method shown in Scheme 1, path a, (R = $COCF_3$), the diaza[3_2]cyclophane **11** was prepared and isolated as its *N*-methyl derivative in 0.5% overall yield after removal of the trifluoroacetyl groups followed by methylation on the bridge nitrogen atoms.[5] Our own examination according to their method [Scheme 1, path a (R = $COCF_3$)] resulted in a 3% yield of diazacyclophane **11**.
(7) (a) Usui, M.; Nishiwaki, T.; Anda, K.; Hida, M. *Chem. Lett.* **1984**, 1561. (b) Bottino, F.; Grazia, M. D.; Finocchiaro, P.; Fronczek, F. R.; Mamo, A.; Pappalardo, S. *J. Org. Chem.* **1988**, *53*, 3521.
(8) Takemura, H.; Wen, G.; Shinmyozu, T. *Synthesis* **2005**, 2845.
(9) (a) Takemura, H.; Shinmyozu, T.; Inazu, T. *Coord. Chem. Rev.* **1996**, *156*, 183. (b) Takemura, H.; Wen, G.; Shinmyozu, T. In *New Trends in Structural Organic Chemistry*; Takemura, H., Ed.; Research Signpost: Kerala India, **2005**, 125.
(10) Takemura, H.; Suenaga, M.; Sakai, K.; Kawachi, H.; Shinmyozu, T.; Miyahara, Y.; Inazu, T. *J. Inclusion Phenom.* **1984**, *2*, 207.
(11) Wen, G.; Matsunaga, M.; Matsunaga, T.; Takemura, H.; Shinmyozu, T. *Synlett* **1995**, 947.
(12) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Kan, T.; Fukuyama, T. *Yuki Gosei Kagaku Kyokaishi* **2001**, *59*, 779. (c) Kurosawa, W.; Kan, T.; Fukuyama, T. *Org. Synth., Coll. Vol. X*; John Wiley & Sons: London, **2004**, 482. (d) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.
(13) In the originally reported Ns-amide strategy, PhSH–K_2CO_3 or $HSCH_2CO_2H$–LiOH mixtures were used as the typical deprotection reagents of Ns group, and aprotic solvents, e.g.

MeCN or DMF, were used.[12] In the present study, EtSNa was used for the deprotection of the cyclophanes **9** and **14** because this reagent is commercially available as a convenient thiolate source. Additionally, the bridge Ns amide parts are sterically hindered, we considered that primary alkyl thiolate would serve as an effective deprotection agent in the present case. As for the solvent employed in this work, the solubility of the Ns-protected cyclophanes **9** and **14** in the originally reported solvents was poor, thus, we selected DMSO in which Ns amides **9** and **14** were slightly soluble and the deprotection proceeded successfully.

(14) (a) Vögtle, F.; Neumann, P. *J. Chem. Soc. D* **1970**, 1464. (b) Schwierz, H.; Vögtle, F. *Synthesis* **1999**, 295.
(15) Stewart, W. E.; Siddall, T. H. III. *Chem. Rev.* **1970**, *70*, 517.
(16) (a) Sako, K.; Meno, T.; Takemura, H.; Shinmyozu, T.; Inazu, T. *Chem. Ber.* **1990**, *123*, 639. (b) Wen, G. *Thesis*; Kyushu University: Japan, **1998**.
(17) Meno, T.; Sako, K.; Suenaga, M.; Mouri, M.; Shinmyozu, T.; Inazu, T.; Takemura, H. *Can. J. Chem.* **1990**, *68*, 440.
(18) Garrett, T. M.; McMurry, T. J.; Hosseini, M. W.; Reyes, Z. E.; Hahn, F. E.; Raymond, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 2965.