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Abstract: The diaza[3₂]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)-dibenzenacyclopentaphane in 26% overall yield. This Ns-amide method has also been applied for the preparation of a higher homologue, the trifluoroacetamide derivative of triaza[3₃]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[3₂]cyclophane 11 afforded an interesting octahedrane cage upon photoradiation, while the corresponding carbon-bridged analogue, [3₂]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[3₂]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[3₂]cyclophane as shown in Scheme 1; (i) cyclization of amide-activated diamine 1 and xylylene dihalide 2 (path a)⁷,⁸ and (ii) coupling of 4-toluene-sulfonamide (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 = CN) resulted in the formation of higher oligomers 4 rather than the desired diaza[3₂]cyclophane 3.⁵,⁷–¹¹ The Ts-amide methods are thus effective for preparing the Ts-amide derivative of diaza[3₂]cyclophane. However, absorption of the aromatic Ts-amide chromophores overlaps with that of the diaza[3₂]cyclophane chromophore thus preventing evaluation of the photoproperties of the aza[3₂]cyclophane system. Additionally, deprotection of the Ts-amide moieties required severe conditions, such as Birch reduction conditions or a highly acidic medium.¹²–¹⁰ 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

\[ \text{R} = \text{COCF}_3, \text{PO(OEt)}_2; \text{path b, } \text{R} = \text{CN} \]
however, it has rarely been used for the construction of azacyclopahnes. 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, and (ii) functional group conversion is easy since the Ns group can be removed by a thiolate reagent.

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.

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 1H NMR spectroscopy and used in the following reaction without separation. Ns-amides 9 and 10 displayed 1H NMR spectral patterns that were similar to those of the corresponding Ts-amide derivatives.

Removal of the Ns groups and reprotction 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, then the resulting bridge amine moieties were acetylated with trifluoroacetic anhydride to afford the corresponding trifluoroacetamides, 11 and 12. These azacyclopahnes 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.

In the present reaction, no higher oligomer, such as a hexamer (cf., Scheme 1, n = 3) was obtained. As previously discussed, direct coupling of 1,4-bis(trifluoroacetylamino)methyl]benzene with 1,4-bis(bromometh-
yl)benzene afforded the tetramer 12 as the main product and the dimeric cyclophane 11 was only a minor product (Scheme 1, path a). Thus, the present procedure provides a practical route to the diaza[32]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,5,13 (ii) the absorption band of the trifluoroacetamide does not overlap with that of the azacyclophane system, thus the unique photochemical properties of the azacyclophane chromophore2 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 1H 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. 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 1H and 19F 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-d6). 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, C2v isomer of 11 displayed the two singlet signals while the
In summary, the present Ns-amide coupling method provides a convenient route to nitrogen-bridged [3,3]- and [3,2]-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.5,6

All melting points were uncorrected. 1H NMR spectra were collected with Varian Mercury 300 (300 MHz), XVR-500 (500 MHz) or Inova AS600 (600 MHz) spectrometers. 19F NMR spectra (564 MHz) were measured using C6F6 (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-nitrophenylsulfonyl]amino)methyl]benzene (6)

To a mixture of 1,4-bis(aminomethyl)benzene (0.75 g, 5.5 mmol) and Et3N (0.56 g, 5.5 mmol) in CH2Cl2 (20 mL) was dropwise added a soln of NsCl (2.22 g, 10 mmol) in CH2Cl2 (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. The precipitate formed was collected, washed with CHCl3, 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.

Anal. Calcd for C20H18N4O8S2: C, 47.43; H, 3.58; N, 11.06. Found: C, 47.52; H, 3.53; N, 10.71.

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

To a soln of 1,3,5-tris(aminomethyl)benzene11 (6.68 g, 40.4 mmol) and Et3N (11.65 g, 115.2 mmol) in CH2Cl2 (200 mL) was dropwise added a soln of NsCl (25.5 g, 115.2 mmol) in CH2Cl2 (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 H2O 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.

1H NMR (300 MHz, DMSO-d6): δ = 3.88 (d, J = 6.3 Hz, 6 H, CH2Ar), 7.97 (m, 6 H, Ns), 8.35 (m, 6 H, Ns), 8.50 (s, J = 6.3 Hz, 6 H, Ns).

Anal. Calcd for C35H28N12O18S3: 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)-dibenzenacycloctahene (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.

IR (KBr): 1150, 1303, 1336, 1371, 1420, 1502, 1619, 1649, 3152, 3267 cm–1.
tracts were washed with H_2O, dried (anhyd Na_2SO_4), and concen-... 1H NMR (300 MHz, DMSO-d_6): δ = 4.05 (br, 12 H, CH_2Ar), 6.82 (s, 16 H), 8.07 (m, 8 H, Ns), 8.37 (m, 8 H, 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 (anhdy Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in dioxane (15 mL) and Et_3N (982 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. 238–239 °C).

The 1H NMR data were identical to those already reported.5

3.5,7-Tris(4-nitrophenylsulfanyl)-3,7,10-triaza-1,5(1,3,5)-dibenzenacyclo[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 recrystallized (DMSO–EtOH) as off-white fine crystals; mp 237–238 °C (Lit.5 238–239 °C).

Anal. Calcd for C_{36}H_{30}N_{6}O_{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)-dibenzenacyclo[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 (anhydy 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.

1H 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).

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References

6. Shinmyozu et al. has reported that, according to the method shown in Scheme 1, path a (R = COCF_3), the diazacyclophane 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. Our own examination according to their method (Scheme 1, path a (R = COCF_3)) resulted in a 3% yield of diazacyclophane 11.
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. 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.