Synthesis of Polyazamacrocyclic Compounds via Modified Richman−Atkins Cyclization of β-Trimethylsilylethanesulfonamides

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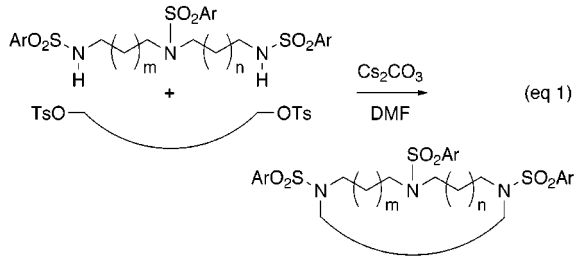
The Richman−Atkins cyclization remains one of the most widely used methods for the preparation of macrocyclic polyamines. The use of β-trimethylsilylethanesulfonamides (SES-sulfonamides) for the preparation of polyazamacrocyclic compounds is described. This expands existing Richman−Atkins sulfonamide macrocyclization methodology, and it successfully enables preparation of labile polyaza[*n*](1,4)naphthalenophanes and polyaza[*n*](9,10)anthracenophanes, not previously available in appreciable quantities.

The Richman−Atkins cyclization (eq 1)[1] remains one of the most widely used methods for the preparation of macrocyclic polyamines (polyazamacrocycles). This general procedure is best effected by the reaction of a bis-*p*-toluenesulfonamide salt with a bis-tosylate or mesylate in anhydrous DMF.[2] The bis-*p*-toluenesulfonamide salt can conveniently be formed in situ when the reagents are combined in DMF in the presence of potassium or cesium carbonate.[3] High dilution conditions often are not required for this macrocyclization reaction, as the bulky nature of the tosyl group contributes to preorganization of the intermediates and favors the transition state leading to intramolecular cyclization as opposed to intermolecular oligomerization.



Although the macrocyclization step is generally efficient, harsh conditions are required to remove the tosyl groups. Detosylation with liberation of the secondary amines can be accomplished, but most of the methods are relatively harsh. Thus, hot concentrated sulfuric acid,[1,4] HBr−AcOH in the presence or absence of phenol,[5] sodium or lithium in ammonia,[6] sodium naphthalenide,[7] or lithium aluminum hydride[8] have all been used to cleave the sulfonamides. Reduced yields of the deprotected polyamines result when labile benzylic C−N bonds are present in the polyazamacrocycle, and reactive functional groups are precluded. It has also been shown that trifluoroacetamide derivatives,[9a] mesylates,[9b] and the diethylphosphoryl derivatives[9c] can similarly be used in a Richman−Atkins-like cyclization. These groups have not been widely adopted for polyazamacrocyle synthesis since they either also require deprotection under drastic conditions, suffer from decreased yields in the macrocyclization, or require arduous reagent preparation.

Fukuyama and co-workers have recently reported the utilization of the nosyl group (2-and/or 4-nitrobenzenesulfonyl) as an amine protecting group that can be removed under mild conditions.[10] The utility of the nosyl group in the Richman−Atkins macrocyclization was demonstrated by Cook et al. during the preparation of orthogonally protected polyazapyridinophane scaffolds for solution-phase combinatorial chemistry.[11]

We report here our results on the use of the β-trimethylsilylethanesulfonamides (SES-sulfonamides) **3a**

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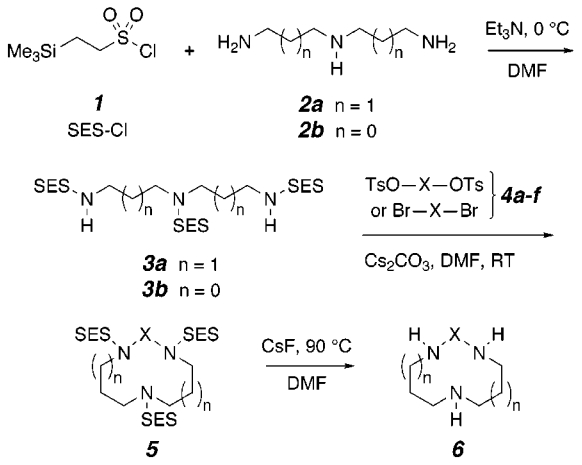
Scheme 1



and **3b** for the preparation of macrocyclic polyamines via the Richman–Atkins cyclization. We anticipated that the SES group would perform the same role as the tosyl/nosyl group: increasing the acidity of the remaining N–H group for deprotonation by relatively weak bases, preorganization of a favorable intramolecular transition state, and protection of other secondary nitrogen atoms that are present in the polyamine substrate. A potential advantage of using the SES protecting group is that the SES-sulfonamide can be easily cleaved under mild conditions to generate the parent amine with cesium fluoride in DMF,[12] thereby offering potential compatibility with a wider array of functionality.

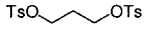
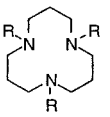
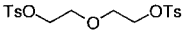
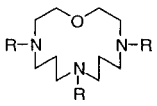
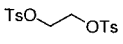
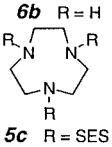
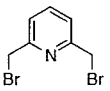
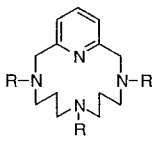
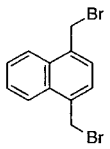
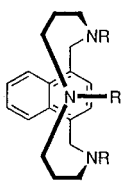
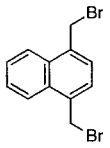
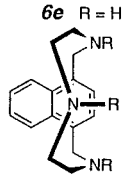
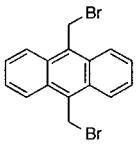
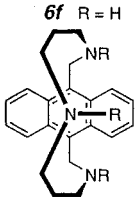
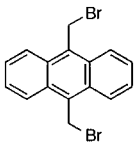
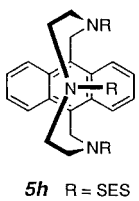
β-Trimethylsilylethanesulfonyl chloride (SES-Cl), **1**, was prepared according to the procedure of Weinreb et al.[13] Reaction with *N*-(3-aminopropyl)-1,3-propanediamine (**2a**) or diethylenetriamine (**2b**) (Scheme 1) gave the tris-SES sulfonamide derivatives **3a** or **3b**. Macrocyclization by treatment with alkyl α,*ω*-ditosylates or -dibromides **4** in the presence of Cs_2CO_3 in DMF afforded the *N*,*N*′,*N*″ -tris(*β*-trimethylsilylethanesulfonyl)triazamacrocycles **5**, as shown in Table 1.

The cyclization reactions are remarkably clean. Examination of an aliquot taken after the 48 h reaction time by ^{1}H NMR spectroscopy routinely reveals virtually quantitative formation of the product. High dilution conditions are not needed for the macrocyclization; little or no evidence of oligomerization is seen.

Removal of the SES group occurs smoothly upon treatment of the macrocyclic tris-sulfonamides **5** with CsF in DMF at 95 °C for 24 h. Examination of an aliquot of the crude reaction mixture by ^{1}H NMR spectroscopy shows complete, clean conversion to the parent triamine **6**. Since all byproducts from fluoride-induced decomposition of the SES-sulfonamide moiety are volatile, the crude products **6a**–**h** are generally very pure. The parent macrocyclic polyamines can be further purified, if desired, by chromatography on neutral alumina.

β-Trimethylsilylethanesulfonamides are excellent substrates for the construction of polyazamacrocycle skeletons under Richman–Atkins-like conditions. Yields are generally comparable to tosyl- or nosylsulfonamide derivatives. A distinct advantage of the mild conditions for SES-sulfonamide cleavage is illustrated by the preparation of naphthalenophane (**6e**, **6f**) and anthracenophane (**6g**, **6h**) derivatives. The SES-sulfonamide derivatives described here alleviate the problem of deprotection with

Table 1. Structures of 4–6 and Yields for Formation of Tris-SES-triazamacrocycles 5 from the Alkylation of 3 with 4 and for SES Removal in 5 To Give 6

3	4	5/6	% yield 5 % yield 6
3a	 4a	 **5a** R = SES **6a** R = H	73 81
3a	 4b	 **5b** R = SES **6b** R = H	71 71
3b	 4c	 **5c** R = SES **6c** R = H	68 68
3a	 4d	 **5d** R = SES **6d** R = H	61 83
3a	 4e	 **5e** R = SES **6e** R = H	74 93
3b	 4e	 **5f** R = SES **6f** R = H	84 86
3a	 4f	 **5g** R = SES **6g** R = H	83 87
3b	 4f	 **5h** R = SES **6h** R = H	72 90

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concomitant naphthylic and anthrylic C−N bond cleavage as observed with the corresponding nosyl and tosyl derivatives.[14] ^{1}H NMR examination of the crude reaction product shows clean conversion to the desired naphthalenophane (**6e** or **6f**) or anthracenophane (**6g** or **6h**). No products resulting from cleavage of the naphthylic or anthrylic C−N bonds are observed. Rapid chromatography on neutral alumina affords the pure products in good yields. Polyazacyclophanes, -naphthalenophanes, and -anthracenophanes are currently of interest as synthetic receptors and as potential molecular signals for the detection and/or removal of metal ions and cations.[15]

Handling of the polyazaanthracenophanes **6g** and **6h** as the free bases is complicated by their facile decomposition. Triazaanthracenophanes **6g** and **6h** are stable when protected from oxygen and light.

In summary, we have demonstrated that β-trimethylsilylethanesulfonamides efficiently undergo macrocyclization with dibromides and ditosylates. Removal of the SES-sulfonamide occurs under mild conditions to liberate the free polyazamacrocycle in good yield. This methodology complements and expands the existing Richman−Atkins sulfonamide macrocyclization methodology. It enables preparation of labile polyazamacrocyclic compounds **6e**−**6h** not previously characterized or available in useful quantities. In addition, isolation and purification of the parent polyazamacrocycles is greatly facilitated by the fact that all of the organic byproducts from the deprotection are volatile.

Experimental Section

General Experimental Details. Flash chromatography was performed using the indicated solvent system on EM reagent silica gel 60 (230−400 mesh).[17] DMF was distilled from CaH_2 and stored over 4 Å molecular sieves. Triethylamine was distilled from KOH and stored over 4 Å molecular sieves. CsF was dried at 100 °C for 2 h in vacuo.[18] β-Trimethylsilylethanesulfonyl chloride (SES-Cl) was prepared according to the procedure of Weinreb et al.[13] Air- and/or moisture-sensitive reactions were carried out under N_2 or Ar using oven-dried glassware and standard syringe/septa techniques.

***N,N′,N″*-Tris(β-trimethylsilylethanesulfonyl)-1,5,9-triazanonane (3a).** *N*-(3-Aminopropyl)-1,3-propanediamine (**2a**, 0.50 g, 3.8 mmol, 1.0 equiv) and triethylamine (2.6 mL, 19.0 mmol, 5 equiv) were combined in 5 mL of DMF and cooled to 0 °C. A solution of SES chloride (**1**, 3.43 g, 17.2 mmol, 4.5 equiv) in 5 mL of DMF was added dropwise. The reaction mixture was stirred at 0 °C for 1.5 h and then poured into 30 mL of water. The resulting aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 9:1 CH_2Cl_2:ethyl acetate) to afford **3a** (1.52 g, 2.4 mmol, 63%) as a colorless solid: mp 106.5−107.5 °C; IR (neat) 3288, 3059, 2955, 1324 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (br s, 2H), 3.33 (t, 4H, J = 6 Hz), 3.18 (t, 4H, J = 6 Hz), 2.90 (m, 6H), 1.82 (tt, 4H, J = 6, 6 Hz), 0.99 (m, 6H), 0.05 (s, 9H), 0.03 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.6, 46.9, 46.5, 39.9, 30.4, 10.2, 9.9, −2.3. Anal. Calcd for $C_{21}H_{53}N_3O_6S_3Si_3$: C, 40.41; H, 8.56; N, 6.73. Found: C, 40.49; H, 8.96; N, 6.49.

***N,N′,N″*-Tris(β-trimethylsilylethanesulfonyl)-1,4,7-triazaheptane (3b).** By a similar procedure, diethylenetriamine (**2b**, 1.03 g, 10 mmol, 1.0 equiv), triethylamine (7.0 mL, 5.05 g, 50 mmol, 5 equiv), and SES chloride (**1**, 8.00 g, 40 mmol, 4 equiv) in 20 mL of DMF afforded after purification **3b** (4.03 g, 6.8 mmol, 68%) as a colorless solid.

***N,N′,N″*-Tris(β-trimethylsilylethanesulfonyl)-1,5,9-triazacyclododecane (5a).** Compound **3a** (500 mg, 0.80 mmol, 1 equiv) and Cs_2CO_3 (785 mg, 2.4 mmol, 3 equiv) were combined in 20 mL of DMF. A solution of 1, 3-propanediol di-*p*-tosylate (307 mg, 0.80 mmol, 1 equiv) in 5 mL of DMF was added dropwise. The reaction mixture was stirred at room temperature for 48 h. The solvent was removed in vacuo, and the residue was transferred to a separatory funnel with CH_2Cl_2 and water. The aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Chromatography (SiO_2, 20:1 CH_2Cl_2:EtOAc) afforded the product (396 mg, 0.59 mmol, 73%) as a white solid: mp 177.6−178.7 °C; IR (KBr) 2954, 2901, 1330, 1240 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38 (t, 12H, J = 6 Hz), 2.86 (m, 6H), 2.03 (tt, 6H, J = 6, 6 Hz), 0.98 (m, 6H), 0.06 (s, 27H); ^{13}C NMR (75 MHz) δ 46.1, 45.4, 27.9, 9.8, −2.3. Anal. Calcd for $C_{24}H_{57}N_3O_6S_3Si_3$: C, 43.40; H, 8.65; N, 6.33. Found: C, 43.32; H, 8.96; N, 6.07.

***N,N′,N″*-Tris(β-trimethylsilylethanesulfonyl)-1-oxa-4,8,12-triazacyclotetradecane (5b).** By a similar procedure, **3a** (624 mg, 1 mmol, 1 equiv) and Cs_2CO_3 (978 mmol, 3 equiv) in 20 mL of DMF were treated with di(ethylene glycol) di-*p*-tosylate (414 mg, 1.0 mmol, 1 equiv) in 5 mL of DMF. Chromatography (SiO_2, 7:3 hexanes/EtOAc) afforded the product (492 mg, 0.71 mmol, 71%) as a white solid.

***N,N′,N″*-Tris(β-trimethylsilylethanesulfonyl)-1,4,7-triazacyclononane (5c).** By a similar procedure, **3b** (300 mg, 0.50 mmol, 1 equiv), Cs_2CO_3 (488 mg, 1.50 mmol, 3 equiv) and ethylene glycol di-*p*-tosylate (185 mg, 0.50 mmol, 1 equiv) were combined in 10 mL of DMF. Chromatography (SiO_2, 40:1 CH_2Cl_2/EtOAc) afforded the product (247 mg, 0.34 mmol, 68%) as a white solid.

3,7,11-Tris(β-trimethylsilylethanesulfonyl)-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (5d). By a similar procedure, **3a** (323 mg, 0.52 mmol, 1 equiv), Cs_2CO_3 (508 mg, 1.56 mmol, 3 equiv), and 2,6-bis(bromomethyl)-pyridine were combined in 10 mL of DMF. Chromatography (SiO_2, 20:1 CH_2Cl_2/EtOAc) afforded the product (231 mg, 0.32 mmol, 61%) as a white solid.

***N,N′,N″*-Tris(β-trimethylsilylethanesulfonyl-2,6,10-triaza[11](1,4)naphthalenecyclophane (5e).** By a similar procedure, **3a** (162 mg, 0.26 mmol, 1 equiv), Cs_2CO_3 (942 mg, 1.28 mmol, 5 equiv), and 1,4-bis(bromomethyl)naphthalene[17] (100 mg, 0.26 mmol, 1 equiv) were combined in 3 mL of DMF. Chromatography (SiO_2, 100:1 CH_2Cl_2/CH_3OH) afforded the product (140 mg, 0.19 mmol, 74%) as a colorless solid.

***N,N′,N″*-Tris(β-trimethylsilylethanesulfonyl-2,5,8-triaza-[9](1,4)naphthalenecyclophane (5f).** By a similar procedure, **3b** (154 mg, 0.26 mmol, 1 equiv), Cs_2CO_3 (420 mg, 1.28 mmol, 5 equiv), and 1,4-bis(bromomethyl)naphthalene[19] (100

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mg, 0.26 mmol, 1 equiv) were combined in 3 mL of DMF. Chromatography (100:1 CH_2Cl_2/CH_3OH) gave the product (163 mg, 0.22 mmol, 84%) as a colorless solid.

***N,N′,N″*-Tris(*β*-trimethylsilylethanesulfonyl)-2,6,10-triaza[11](9,10)anthracenecyclophane (5g).** By a similar procedure, **3a** (750 mg, 1.19 mmol, 1 equiv), Cs_2CO_3 (1.94 g, 5.95 mmol, 5 equiv), and 9,10-di(bromomethyl)anthracene (436 mg, 1.19 mmol, 1 equiv) were combined in 30 mL of DMF. Chromatography (SiO_2, 40:1 CH_2Cl_2/EtOAc) gave the product (817 mg, 0.98 mmol, 83%) as a yellow solid.

***N,N′,N″*-Tris(*β*-trimethylsilylethanesulfonyl)-2,5,8-triaza[9](9,10)anthracenecyclophane (5h).** By a similar procedure, **3b** (600 mg, 1.01 mmol, 1 equiv), Cs_2CO_3 (1.63 g, 5.00 mmol, 5 equiv), and 9,10-bis(bromomethyl)anthracene (364 mg, 1.00 mmol, 1 equiv) were combined in 30 mL of DMF. Chromatography (SiO_2, 200:1 CH_2Cl_2/CH_3OH) yielded the product (581 mg, 0.72 mmol, 72%) as a pale yellow solid.

General Procedure for Sulfonamide Cleavage. The tris-sulfonamide **5** (1 equiv) and CsF (10−20 equiv) were combined in DMF (3 mL/100 mg of substrate) and heated at 95 °C for 24 h, at which time an aliquot was removed and stripped to ascertain by ^{1}H NMR analysis that the reaction was complete. Methanol (1 mL) was added to the reaction mixture and it was concentrated in vacuo. Purification by chromatography on neutral alumina (2:1 CH_2Cl_2/MeOH) afforded the desired product.

1,5,9-Triazacyclododecane (6a). Compound **5a** (30 mg, 0.05 mmol, 1 equiv) and CsF (75 mg, 0.50 mmol, 10 equiv) in 0.5 mL of DMF afforded **6a**[20] after purification (6.2 mg, 0.04 mmol, 81%).

1-Oxa-4,8,12-triazacyclotetradecane (6b). Compound **5b** (100 mg, 0.14 mmol, 1 equiv) and CsF (425 mg, 2.8 mmol, 20 equiv) in 3 mL of DMF afforded **6b**[21] after purification (21 mg, 0.09 mmol, 71%).

1,4,7-Triazacyclononane (6c). Compound **5c** (100 mg, 0.16 mmol, 1 equiv) and CsF (486 mg, 3.2 mmol, 20 equiv) in 3 mL of DMF afforded **6c**[20] (14 mg, 0.11 mmol, 68%).

3,7,11,17-Tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (6d). Compound **5d** (70 mg, 0.10 mmol, 1 equiv) and CsF (305 mg, 2.0 mmol, 20 equiv) in 2 mL of DMF afforded **6d**[21] after purification (25 mg, 0.08 mmol, 83%).

2,6,10-Triaza[11](1,4)naphthalenecyclophane (6e). Compound **5e** (116.4 mg, 0.15 mmol, 1 equiv) and CsF (455 mg, 2.9 mmol, 20 equiv) in 3 mL of DMF afforded **6e** (39 mg, 0.14 mmol, 93%): IR (neat) 3305, 3045, 2925, 1265 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 8.19 (m, 2H), 7.37 (m, 2H), 7.00 (s, 2H), 4.54 (d, 2H, J = 13 Hz), 3.39 (d, 2H, J = 13 Hz), 2.56 (dt, 2H, J = 3, 12 Hz), 2.26 (dt, 2H, J = 2, 11 Hz), 1.77 (dt, 2H, J = 4, 11 Hz), 1.43 (dt, 2H, J = 3, 11 Hz), 1.40−0.91 (m, 4H), 0.61 (br s, 3H); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (m, 2H), 7.56 (m, 2H), 7.26 (s, 2H), 4.80 (d, 2H, J = 14 Hz), 3.61 (d, 2H, J = 14 Hz), 2.75 (ddd, 2H, J = 1, 5, 12 Hz), 2.34 (dt, 2H, J = 1, 11 Hz), 1.79 (dt, 2H, J = 4, 11 Hz), 1.71 (br s, 3H), 1.45−1.16 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.9, 132.3, 126.5, 125.9, 125.1, 51.3, 45.0, 42.3, 29.5; HRMS (FAB$^+$) calcd for $C_{18}H_{26}N_3$ $(M + H)^+$ 284.2126, found 284.2109.

2,5,8-Triaza[9](1,4)naphthalenecyclophane (6f). Compound **5f** (114 mg, 0.15 mmol, 1 equiv) and CsF (456 mg, 3.0 mmol, 20 equiv) in 3 mL of DMF afforded **6f** after purification (34.4 mg, 0.13 mmol, 86%).

2,6,10-Triaza[11](9,10)anthracenecyclophane (6g). Compound **5g** (200 mg, 0.24 mmol, 1 equiv) and CsF (763 mg, 4.8 mmol, 20 equiv) in 5 mL of DMF afforded **6g** (69.5 mg, 0.21 mmol, 87%) after purification.[22]

2,5,8-Triaza[9](9,10)anthracenecyclophane (6h). Compound **5h** (104 mg, 0.13 mmol, 1 equiv) and CsF (395 mg, 2.6 mmol, 20 equiv) in 3 mL of DMF afforded **6h** (38.5 mg, 0.14 mmol, 90%) after purification.

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Supporting Information Available: Product characterization data for **3b**, **5b**−**h**, and **6f**−**h**; ^{1}H NMR and ^{13}C NMR spectra for compounds **6e**−**h**. This information is available free of charge via the Internet at http://pubs.acs.org.

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(22) This compound was also prepared by a one-pot procedure. After **3a** (1 equiv), 9.10-di(bromomethyl)anthracene (1 equiv), and Cs_2CO_3 (5 equiv) were stirred in DMF at room temperature for 48 h, CsF (20 equiv) was added and the reaction mixture was heated at 95 °C for 24 h. DMF was removed in vacuo, and the product was isolated after filtration through a column of neutral alumina. The yield was comparable to the two-step procedure.