Synthesis of Aza Macrocycles by Nucleophilic Ring Closure with Cesium Tosylamides

Bindert K. Vriesema, Jan Buter, and Richard M. Kellogg*

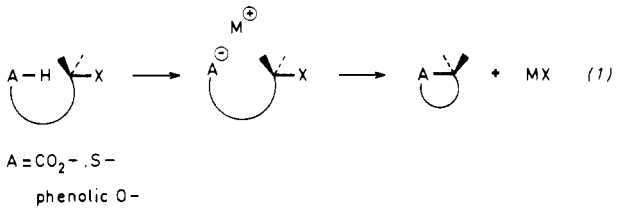
Department of Organic Chemistry, University of Groningen, Nijenborgh 16, Groningen 9747 AG, The Netherlands

Received May 13, 1983

Long-chain diamines as their bis tosylamide derivatives are deprotonated by Cs_2CO_3 in dimethylformamide solution to give the dicesium salts. These react smoothly with various dibromides or dimesylates to afford the cyclic diamines as their tosyl derivatives. The yields, depending on the size of the ring, range between 25% and 95% of isolated product. The largest ring made, 1,12-diazaoctacosane (as the tosylamide derivative) was isolated in 60% yield. The tosyl groups are readily removed with sodium amalgam in Na_2HPO_4-buffered methanolic solution. Chiral macrocyclic amines have also been prepared by using this cesium salt method.

We observed previously that macrocyclizations based on the general route shown in eq 1 are promoted when the cation is Cs^+ and the solvent dimethylformamide (DMF).[1] This approach is especially useful for the preparation of compounds in which the chain components are chiefly or exclusively of hydrocarbon composition.[2] We have suggested an explanation for this behavior on the basis of the ion-pairing properties of cesium salts in DMF.[1a,3]

The few methods available for the synthesis of macrocyclic amines are all subject to restrictions. The anionic ring closure approach of eq 1, wherein a sodium or potassium salt of a tosylamide is used as nucleophile under high dilution conditions in a dipolar aprotic solvent (DMF), has been examined extensively by Stetter.[4] In a modification of this approach various (tosyl substituted) aza crown ethers can be obtained in excellent yield without the use of high-dilution conditions when preformed sodium salts of the tosylamides are used, again in the dipolar aprotic solvent DMF.[5] We find (see below), in agreement with Richman[5] and Stetter,[4] that this method succeeds less well when long hydrocarbon chains must be coupled.



Other methods have also been used. The various approaches to the numerous classes of important naturally occurring aza macrocycles[6] have usually involved formation in some fashion of the carbonyl–nitrogen bond of an *amide*.[7,8] Other methods that have been used include carbon–carbon bond formation under basic conditions (for the synthesis of maytansinoids)[9] and a palladium-catalyzed macrocyclization for the synthesis of spermidine-containing macrocycles wherein cyclization occurs by substitution of an allylic acetate by a primary amine.[10]

Table I. Cyclization of $TsNH(chain)_aNHTs$ (1a-j) with $Br(chain)_bBr$ (2a-g) with Cs_2CO_3 in DMF

compd	$(chain)_a$ (1)	$(chain)_b$ (2)	isolated yield of 3,[a] %
3a	$(CH_2)_5$ (1a)	$(CH_2)_4$ (2a)	25
3b	$(CH_2)_5$ (1a)	$(CH_2)_5$ (2b)	30
3c	$(CH_2)_5$ (1a)	$(CH_2)_{10}$ (2d)	65
3d	$(CH_2)_{10}$ (1b)	$(CH_2)_4$ (2a)	64
3e	$(CH_2)_{10}$ (1b)	$(CH_2)_6$ (2c)	95
3f	$(CH_2)_{10}$ (1b)	$(CH_2)_{10}$ (2d)	76[b]
3g	$(CH_2)_{10}$ (1b)	$(CH_2)_{16}$ (2e)	60
3h	$(CH_2)_5$ (1a)	$CH_2(CH_2OCH_2)_2CH_2$ (2f)	76
3i	$(CH_2)_5$ (1a)	$CH_2(CH_2OCH_2)_3CH_2$ (2g)	66
3j	$(CH_2)_{10}$ (1b)	$CH_2(CH_2OCH_2)_3CH_2$ (2g)	50

[a] Yield is that of analytically pure material. [b] Isolated by preparative plate chromatography with CH_2Cl_2 as the eluent.

Results

We have examined the general synthetic scheme shown in eq 2, which is analogous in character to routes followed by Stetter[4] and Richman.[5] The reaction of 1^{2-},$[Cs^+]_2$ and **2** to form **3** is assumed to involve a sequence of two nu-

(1) (a) Kruizinga, W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 5183. (b) Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4481. (c) van Keulen, B. J.; Kellogg, R. M.; Piepers, O. *J. Chem. Soc., Chem. Commun.* **1979**, 285. (d) Barbier, M. *J. Chem. Soc., Chem. Commun.* **1982**, 668. (e) Potts, K. T.; Cipullo, M. J. *J. Org. Chem.* **1982**, *47*, 3038. (f) Hosseini, M. W.; Lehn, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 3524. (g) Vögtle, F.; Klieser, B.; *Synthesis* **1982**, 294.

(2) Large-ring crown ethers can be made also by this approach or by the use of CsF. See, for the latter method: Reinhoudt, D. N.; de Jong, F.; Tomassen, H. P. M. *Tetrahedron Lett.* **1979**, 2067.

(3) Accurate determinations of the effective molarity ratio $k_{intra}{\cdot}k_{inter}^{-1}$ (in units of moles per liter) have been made for the anionic ring closure approach to simple macrocyclic lactones: Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591. These data serve as a guide to the kinetic difficulties to be expected in ring closure to form other macrocycles. For comments on this approach, see: Galli, C.; Mandolini, L.; *J. Chem. Soc., Chem. Commun.* **1982**, 251.

(4) (a) Stetter, H.; Roos, E. E.; *Chem. Ber.* **1954**, *87*, 566. (b) Stetter, H.; Roos, E. E. *Chem. Ber.* **1955**, *88*, 1390.

(5) (a) Richman J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, 96, 2268. (b) Richman, J. E.; Atkins, T. J.; Oettle, W. F. *Org. Synth.* **1979**, *58*, 86.

(6) (a) Badawi, M. M.; Bernauer, K.; van den Broek, P.; Gröger, G.; Guggisberg, A.; Johne, S.; Kompis, L.; Schneider, F.; Veith, H.-J.; Hesse, M.; Schmid, H.; *Pure Appl. Chem.* **1973**, *33*, 81. (b) "Advances in Polyamine Research"; Campbell, R. A., Morris, D. R., Bartos, D., Daves, G. D., Bartos, F., Eds.; Raven Press: New York, 1978.

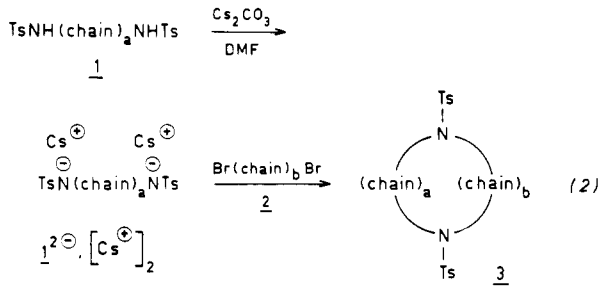
(7) For an early investigation of this general approach, see: Stetter, H.; Mayer, K.-H. *Chem. Ber.* **1961**, *94*, 1410.

(8) (a) Boron-templated amide bond formation: Yamamoto, H.; Maruoka, K.; *J. Am. Chem. Soc.* **1981**, *103*, 6133. (b) Trans amidation approach: Nagao, Y.; Seno, K.; Fujita, E. *Tetrahedron Lett.* **1980**, *21*, 4931. Nagao, Y.; Takao, S.; Miyasaka, T.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1981**, 286. Jenny, C.; Hesse, M. *Helv. Chim. Acta* **1981**, *64*, 1807. (c) Catalyzed amide bond formation: Wälchi-Schaer, E.; Eugster, C. H. *Helv. Chim. Acta* **1978**, *61*, 928. Guggisberg, A.; van den Broek, P.; Hesse, M.; Schmid, H.; Schneider, F.; Bernauer, K. *Helv. Chim. Acta* **1976**, *59*, 3013. Schmidt, U.; Griesser, H.; Lieberknecht, A.; Talbiersky, J. *Angew. Chem., Int. Ed. Engl.* **1981**, 20, 280. (d) ring expansion via an amide (imine ether): Wasserman, H.; Matsuyama, H.; *J. Am. Chem. Soc.* **1981**, *103*, 461.

(9) (a) Meyers, A. I.; Comins, D. L.; Roland, D. M.; Henning, R.; Shimizu, K.; *J. Am. Chem. Soc.* **1979**, *101*, 7104. (b) Meyers, A. I.; Reider, P. J.; Campbell, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 6597.

(10) Trost, B. M.; Cossy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6881.

0022-3263/84/1949-0110$01.50/0

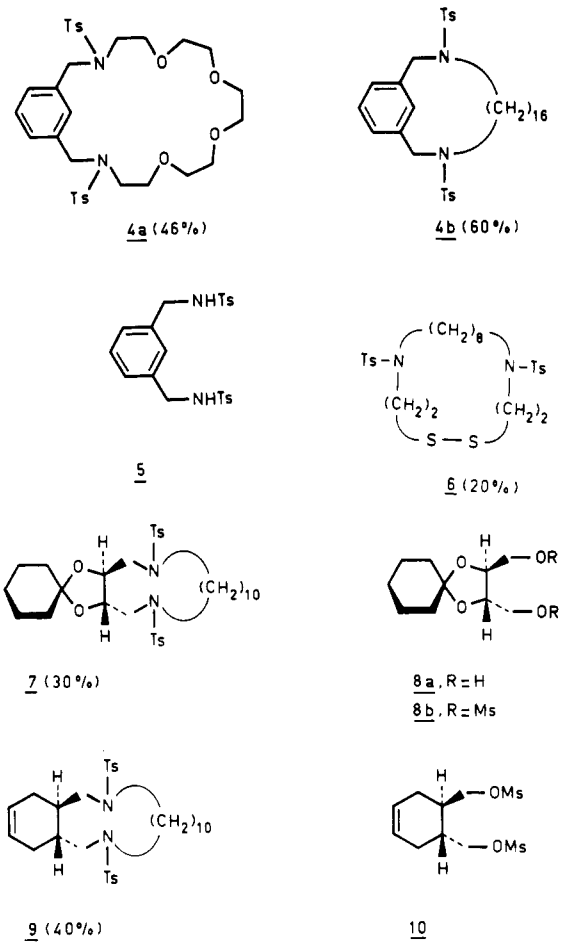


cleophilic substitutions. Readily available Cs_2CO_3 deprotonates 1 quantitatively within a few minutes at room temperature in DMF.[11] Cesium bicarbonate ($CsHCO_3$) is, however, insufficiently basic to deprotonate 1 cleanly or at a reasonable rate. Therefore, one Cs_2CO_3 is required for each tosylamide deprotonated. Although tosylamides reacted readily, Cs_2CO_3 was not found to be basic enough to deprotonate cleanly, either in DMF or methanol, carboxamides and urethanes (*N*-benzyloxycarbonyl-protected primary amines).

Cyclizations were not carried out under high-dilution conditions. A solution or suspension of $1^{2-},[Cs^+]_2$ (2×10^{-2} M) in DMF was allowed to react at 20 °C with an equivalent amount of **2**, added over 2–3 h. The results for a series of model cyclizations are given in Table I. The crude products, with the exception of **3a,b**, are obtained in 95–100% purity as judged from the ^1H NMR spectra. Considerble losses were suffered in some cases during the preparation of analytically pure material. If the recrystallizations are done with extra care, the losses can be reduced. All products reported in Table I as well as elsewhere in this paper have ^1H NMR spectra in accord with expectation, osmometric molecular weights within 5% of the theoretical values for monomeric materials, and elemental analyses or exact masses in accord with theory.

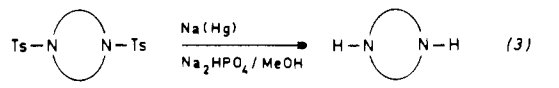
The present method is well suited for the synthesis of aza macrocycles not containing extra heteroatoms in the chains (see **3c–g**). Smaller rings (**3a,b**) are formed less well. The reactions of preformed sodium tosylamides in DMF (obtained by deprotonation with sodium methoxide), as reported by Richman,[5] lead in excellent yields to aza crown ethers. In our hands, however, the synthesis of the 28-membered macrocycle **3g**, when carried out with the sodium salt obtained by deprotonation of the bis tosylamide with sodium methoxide, afforded only a 30–40% yield of crude product, which was not purified. The synthesis of **3c** by the same method gave a 40–50% crude yield of product. An examination of alkali metal carbonates was carried out for the synthesis of **3e**. Li_2CO_3, Na_2CO_3, K_2CO_3, and Rb_2CO_3 were examined as bases in DMF solution. Only with the latter carbonate was a significant conversion (roughly 70%) obtained within 24 h, and the product formed was not clean. Purification was not attempted. With Li_2CO_3 no reaction was observed, and Na_2CO_3 and K_2CO_3 gave only about 10% reaction after 10 days at 20 °C. These alkali metal carbonates are clearly incapable of deprotonating the tosylamide.

Compounds **4a,b** were prepared by the cesium mediated reaction of **5** with the appropriate dibromide. The unusual disulfide **6** was obtained from the reaction of the bis tosylamide of cystamine with 1,8-dibromooctane. This opens a promising route to macrocyclic disulfides. The optically active aza macrocycle **7** was obtained from the (sluggish)

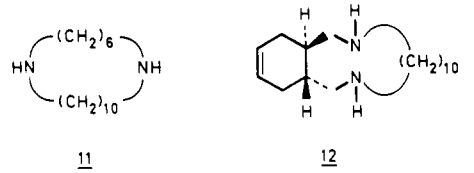


reaction of **8** at 50 °C with the appropriate bis tosylamide. An analogous reaction with racemic **10** provided the aza macrocycle **9**. Compound **8b** is obtained from D-tartaric acid, which is ketalized with cyclohexanone (P_2O_5) and then reduced and mesylated. A similar sequence was followed with the Diels–Alder addition product of 1,3-butadiene and ethyl fumarate to give **10**.

A simple and high-yield method for detosylation is a prerequisite for the utility of the method described here. Various methods for detosylation are available.[5] In our hands the procedure developed by Trost[12] for the desulfonation of sulfones was very effective. The tosyl group is removed under reductive conditions (sodium amalgam) in *buffered* methanol solution (eq 3). By application of



this method compounds **11** (from **3e**) and **12** (from **9**) were



obtained pure in yields of 90% and 85%, respectively. Owing to the limited quantities available, no attempt was made to detosylate **6**.

Work on the application of this macrocyclization method for the synthesis of azamacrocycles with specific ligating

(11) Of the alkali metal carbonates, Cs_2CO_3 is the most basic in aqueous solution and likely also in other solvents. See: "Gmelins Handbuch der Anorganischen Chemie"; Verlag Chemie: Berlin, Germany, 1938; 8th Auflage, Vol. 25, p 234.

(12) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

properties will be described in due course. A search for activating groups other than tosyl that can be removed under even milder conditions is underway.

Experimental Section

General Methods. Melting points were recorded on a Thermopan Reichert Austria apparatus. ^1H NMR spectra (Me_4Si internal standard) were recorded on 60-MHz Varian or JEOL instruments. Mass spectra were measured on an MS-9 mass spectrometer. Elemental analyses were done by the analytical division of these laboratories.

Compounds cited without references were either in stock or were prepared by unexceptional literature procedures. The dibromides, when not commercially available, were prepared by treatment of the corresponding dialcohols with PBr_3, if not otherwise indicated.

General Procedure for Preparation of Macrocyclic Tosylamides. A 250-mL round-bottomed flask is filled with 100 mL of dry DMF, 1 mmol of the bis tosylamide, and 2.1 mmol of Cs_2CO_3 and is stirred magnetically. To this mixture is added 1 mmol of the 1,ω-dibromide (or dimesylate) in 40 mL of DMF dropwise in 2–3 h. After the mixture was stirred for 24 h at room temperature, the DMF was removed under vacuum, and the residue was taken up in CH_2Cl_2, washed with H_2O, and dried over $MgSO_4$. Purification was carried out as indicated by the entries below for the separate compounds.

1,6-Bis(*p*-tolylsulfonyl)-1,6-diazacycloundecane (3a) was prepared from 1,5-bis[(*p*-tolylsulfonyl)amino]pentane and 1,4-dibromobutane. The crude product gave a mass spectrum with a signal at *m/e* 773 which arises from the dimer of **3a** [928 − 155(tosyl) = 773] when heated at 220 °C. After recrystallization from $ClCH_2CH_2Cl$, analytically pure monomer was obtained: white crystals; mp 268–273 °C (lit.[13] mp 270.5 °C); 25% yield; mol wt (osmometric in $CHCl_3$) 488.2, 488.4 (theory 464.6); ^1H NMR ($CDCl_3$) δ 1.57 and 1.83 (br, 10 H), 2.37 (s, 6 H, CH_3), 3.00 (br s, 8 H, CH_2N), 7.33 (2 d, 8 H).

1,7-Bis(*p*-tolylsulfonyl)-1,7-diazacyclododecane (3b) was prepared from 1,5-bis[(*p*-tolylsulfonyl)amino]pentane and 1,5-dibromopentane. The product (**3b**) was obtained in 30% yield as white crystals: mp 242–244 °C (from C_2H_5OH); mol wt (osmometric in $CHCl_3$) 505.2, 502.7 (theory 478.7); ^1H NMR ($CDCl_3$) δ 1.43 and 1.67 (br, 12 H), 2.43 (s, 6 H, CH_3), 3.00 (br, 8 H, CH_2N), 7.53 (br, 8 H); mass spectrum, exact mass *m/e* 478.193 (theory 478.196).

1,7-Bis(*p*-tolylsulfonyl)-1,7-diazacycloheptadecane (3c) was prepared from 1,5-bis[(*p*-tolylsulfonyl)amino]pentane and 1,10-dibromodecane. Material pure by ^1H NMR spectroscopy was isolated in quantitative yield. After recrystallization from C_2H_5OH, analytically pure product was isolated: 65% yield; mp 124–126 °C; mol wt (osmometric in $CHCl_3$) 552.6, 563.3 (theory 548.8); ^1H NMR ($CDCl_3$) δ 1.47 (br, 22 H), 2.38 (s, 6 H, CH_3), 2.93 (br, 8 H, CH_2N), 7.37 (2 d, 8 H). Anal. Calcd for $C_{29}H_{44}N_2O_4S_2$: C, 63.47; H, 8.08; N, 5.11; S, 11.69. Found: C, 63.53; H, 8.20; N, 5.00; S, 11.61.

1,6-Bis(*p*-tolylsulfonyl)-1,6-diazacyclohexadecane (3d) was prepared from 1,10-bis[(*p*-tolylsulfonyl)amino]decane and 1,4-dibromobutane. Material pure by ^1H NMR spectroscopy was isolated in quantitative yield. After recrystallization from C_2H_5OH, analytically pure product (**3d**) was isolated: 64% yield; mp 130–132 °C (lit.[13] mp 132.5 °C); mol wt (osmometric in $CHCl_3$) 573.5, 576.3 (theory 535.8); ^1H NMR ($CDCl_3$) δ 1.43 (br, 20 H), 2.37 (s, 6 H), 2.97 (br, 8 H), 7.37 (2 d, 8 H). Anal. Calcd for $C_{28}H_{42}N_2O_4S_2$: C, 62.77; H, 8.09; N, 5.23; S, 11.97. Found: C, 62.70; H, 7.82; N, 5.17; S, 11.85.

1,8-Bis(*p*-tolylsulfonyl)-1,8-diazacyclooctadecane (3e) was prepared from 1,10-bis[(*p*-tolylsulfonyl)amino]decane and 1,6-dibromohexane. Material pure by ^1H NMR spectroscopy was again isolated in quantitative yield. After recrystallization from C_2H_5OH, analytically pure product (**3e**) was isolated: 72% yield; mp 114–116 °C (lit.[13] mp 123 °C); mol wt (osmometric in $CHCl_3$) 571.8, 581.0 (theory 562.8); ^1H NMR ($CDCl_3$) δ 1.37 (br, 24 H), 2.35 (s, 6 H), 2.90 (br, 8 H), 7.37 (2 d, 8 H). Anal. Calcd for $C_{30}H_{46}N_2O_4S_2$: C, 64.02; H, 8.24; N, 4.98; S, 11.39. Found: C, 64.11; H, 8.25; N, 5.04; S, 11.37. When the recrystallization was carried out more carefully, the yield of analytically pure product was raised to 95%.

1,12-Bis(*p*-tolylsulfonyl)-1,12-diazacyclodocosane (3f) was prepared from 1,10-bis[(*p*-tolylsulfonyl)amino]decane and 1,10-dibromodecane. Material pure by ^1H NMR spectroscopy was isolated in quantitative yield. The product (**3f**) was purified by preparative plate chromatography with CH_2Cl_2 as the eluent to afford **3f**: 76% yield; mp 149–151 °C; mol wt (osmometric in $CHCl_3$) 619.6, 620.1 (theory 618.9); ^1H NMR ($CDCl_3$) δ 1.40 (br s, 32 H), 2.37 (s, 6 H), 2.97 (br t, 8 H), 7.37 (2 d, 8 H).

1,12-Bis(*p*-tolylsulfonyl)-1,12-diazacyclooctacosane (3g) was prepared from 1,10-bis[(*p*-tolylsulfonyl)amino]decane and 1,16-dibromohexadecane. Material pure by ^1H NMR was isolated in 95% yield. After recrystallization from C_2H_5OH analytically pure product (**3g**) was isolated: 60% yield; mp 98 °C; mol wt (osmometric in $CHCl_3$) 696.8, 692.5 (theory 703.1); ^1H NMR ($CDCl_3$) δ 1.37 (br s, 44 H), 2.37 (s, 6 H), 3.00 (br t, 8 H), 7.37 (2 d, 8 H). Anal. Calcd for $C_{40}H_{66}N_2O_4S_2$: C, 68.33; H, 9.46; N, 3.99; S, 9.12. Found: C, 68.18; H, 9.38; N, 3.96; S, 8.98.

1,10-Bis(*p*-tolylsulfonyl)-1,10-diaza-4,7-dioxacyclopentadecane (3h) was prepared from 1,5-bis[(*p*-tolylsulfonyl)amino]pentane and 1,8-dibromo-3,6-dioxaoctane. Material pure by ^1H NMR was isolated in quantitative yield. After recrystallization from CCl_4 analytically pure product (**3h**) was isolated: 76% yield; mp 152–154 °C; mol wt (osmometric in $CHCl_3$) 514.1, 517.5 (theory 524.7); ^1H NMR ($CDCl_3$) δ 1.53 (br, 6 H), 2.40 (s, 6 H), 3.12 (m, 8 H, CH_2N), 3.53 (s, 4 H, CH_2O), 3.63 (t, 4 H, CH_2O), 7.50 (2 d, 8 H). Anal. Calcd for $C_{25}H_{36}N_2O_6S_2$: C, 57.22; H, 6.92; N, 5.34; S, 12.22. Found: C, 56.93; H, 6.83; N, 5.36; S, 12.44.

1,13-Bis(*p*-tolylsulfonyl)-1,13-diaza-4,7,10-trioxacyclooctadecane (3i) was prepared from 1,5-bis[(*p*-tolylsulfonyl)amino]pentane and 1,11-dibromo-3,6,9-trioxaundecane. Material pure by ^1H NMR was isolated in 95% yield. After recrystallization from C_2H_5OH analytically pure product (**3i**) was isolated: 66% yield; mp 114–116 °C; mol wt (osmometric in $CHCl_3$) 579.6, 575.8 (theory 568.7); ^1H NMR ($CDCl_3$) δ 1.43 (br, 6 H), 2.37 (s, 6 H), 3.11 (m, 8 H, CH_2N), 3.53 (s, 8 H, OCH_2), 3.54 (t, 4 H, CH_2O), 7.34 (2 d, 8 H). Anal. Calcd for $C_{27}H_{40}N_2O_7S_2$: C, 57.02; H, 7.09; N, 4.93; S, 11.28. Found: C, 56.85; H, 7.15; N, 4.80; S, 11.17.

1,13-Bis(*p*-tolylsulfonyl)-1,13-diaza-4,7,10-trioxacyclotricosane (3j) was prepared from 1,10-bis[(*p*-tolylsulfonyl)amino]decane and 1,11-dibromo-3,6,9-trioxaundecane. Material pure by ^1H NMR was obtained in 95% yield. After recrystallization from C_2H_5OH, analytically pure product (**3j**) was isolated: 50% yield; mp 107–109 °C; mol wt (osmometric in $CHCl_3$) 657.9, 657.6 (theory 638.9); ^1H NMR ($CDCl_3$) δ 1.33 (br, 16 H), 2.37 (s, 6 H), 3.11 (m, 8 H, CH_2N), 3.53 (s, 8 H, OCH_2), 3.54 (t, 4 H, CH_2O), 7.37 (2 d, 8 H). Anal. Calcd for $C_{32}H_{50}N_2O_7S_2$: C, 60.16; H, 7.89; N, 4.39. Found: C, 60.00; H, 7.80; N, 4.32.

1,3-Bis[[(*p*-tolylsulfonyl)amino]methyl]benzene (5). To a solution of 1.36 g (0.01 mol) of *m*-xylylenediamine (Aldrich) and 0.8 g (0.02 mol) of NaOH in 100 mL of water, under a nitrogen atmosphere, was added a solution of 3.8 g (0.02 mol) of tosyl chloride in 100 mL of CH_2Cl_2. After the mixture was stirred for one night, the CH_2Cl_2 layer was separated. The water layer was extracted three times with 50 mL of CH_2Cl_2. The CH_2Cl_2 layers were washed with water and dried on $MgSO_4$. After filtration and evaporation the crude product (**5**) was recrystallized from C_2H_5OH which gave 3.2 g (72%) analytically pure product **5**: mp 151–153 °C; ^1H NMR ($CDCl_3$) δ 2.37 (s, 6 H), 3.97 (d, 4 H, CH_2–N), 5.00 (t, 2 H, NH), 7.03 (m, 4 H), 7.50 (2 d, 8 H). Anal. Calcd for $C_{22}H_{24}N_2O_4S_2$: C, 59.43; H, 5.44; N, 6.30; S, 14.43. Found: C, 59.43; H, 5.42; N, 6.32; S, 14.50.

18,20-Benzo-1,16-bis(4-tolylsulfonyl)-1,16-diaza-4,7,10,13-tetraoxacyclouncosane (4a) was prepared from **5** and 1,14-dibromo-3,6,9,12-tetraoxatetradecane at 60 °C. After half of the DMF was removed, water was added and the crude precipitate filtered. After recrystallization from C_2H_5OH analytically pure product (**4a**) is obtained: 46% yield; mp 105 °C; mol wt (osmometric in $CHCl_3$) 640.8, 651.9 (theory 646.8); ^1H NMR ($CDCl_3$) δ 2.37 (s, 6 H), 3.40 (m, 20 H), 4.39 (s, 4 H), 7.03 (m, 4 H), 7.50 (2 d, 8 H).

3,5-Benzo-1,7-bis(*p*-tolylsulfonyl)-1,7-diazacyclotricosane (4b) was prepared from **5** and 1,16-dibromohexadecane as described for **4a**. After recrystallization from C_2H_5OH, analytically

(13) Stetter, H.; Marx, J. *Justus Liebigs Ann. Chem.* **1957**, *607*, 59.

pure material was obtained: 60% yield; mp 85–87 °C; mass spectrum, m/e 666 (theory 666); ^{1}H NMR ($CDCl_3$) δ 1.17 (br, 28 H), 2.37 (s, 6 H), 3.00 (br, 4 H), 4.20 (s, 4 H), 7.03 (s, 4 H), 7.50 (2 d, 8 H); mass spectrum, exact mass m/e 666.346 (theory 666.352).

5,14-Bis(4-tolylsulfonyl)-1,2-dithia-5,14-diazacyclohexadecane (6) was prepared from *N,N'*-[(ethanodithio)ethano]bis-[*p*-toluenesulfonamide][14] and 1,8-dibromooctane by the general method except that stirring was continued for 90 h. After the workup the crude product (oil) gave an ^{1}H NMR spectrum as expected. When the oily product was heated with ethanol (96%), a white precipitate was derived from the cooled mixture. The isolated crystals were analytically pure product **6**: 20% yield (procedure is not optimized); mp 132–135 °C; mol wt (osmometric in $CHCl_3$) 586.5, 589.0 (theory 570.8); ^{1}H NMR ($CDCl_3$) δ 1.40 (br, 12 H), 2.38 (s, 6 H), 3.07 (br, 12 H, N–CH_2 and CH_2–S), 7.43 (2 d, 8 H). Anal. Calcd for $C_{26}H_{38}N_2O_4S_4$: C, 54.70; H, 6.71; N, 4.91. Found: C, 54.51; H, 6.87; N, 4.90.

Cyclohexanone Ketal of (2*S*,3*S*)-1,4-Bis(4-tolylsulfonyl)-1,4-diaza-2,3-dihydroxycyclotetradecane (7). This was prepared from 1,10-bis[(*p*-tolylsulfonyl)amino]decane and **8b**. Because considerable amounts of dimer were formed when the general conditions were used, the dropwise addition was extended from 3 to 10 h. The mixture was stirred for 90 h at 55 °C. After the workup the product was purified by preparative plate chromatography over silica gel with (distilled) methylene chloride/ethyl acetate (96:4) as the eluent to give in 30% yield the monomer **7** as a colorless oil: $[\alpha]^{20}_D$ +0.44° (*c* 1, $CHCl_3$): mass spectrum, m/e 646 (theory 646); ^{1}H NMR ($CDCl_3$) δ 1.35 (br s, 16 H, $(CH_2)_8$), 1.55 (br s, 10 H, cyclohexyl), 2.41 (s, 6 H), 3.22 (m, 8 H, CH_2–N), 4.20 (br m, 2 H), 7.53 (2 d, 8 H); mass spectrum, exact mass m/e 646.312 (theory 646.311).

Cyclohexene Ketal of (2*S*,3*S*)-Butane-1,4-diol (8a). This was prepared by adding diethyl cyclohexylidenetartrate in ether to a suspension of $LiAlH_4$ in ether followed by reflux for 1 h and a workup with 20% H_2SO_4.[15] The crude product was distilled at 0.025 mmHg (bp 125 °C) to give **8a**: 74% yield; $[\alpha]^{20}_D$ −4.49° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.47 (br s, 10 H), 2.99 (t, 2 H), 3.80 (m, 6 H).

The corresponding mesylate **8b** was prepared by addition of **8a** (2.06g, 10.2 mmol) to 14 mL of pyridine. To this mixture was added mesyl chloride (2.63 g, 23 mmol). After being stirred for 3 h, the mixture was poured in 230 mL of 1 N HCl and extracted two times with 115 mL of CH_2Cl_2. The CH_2Cl_2 is washed with water and dried over $MgSO_4$. After filtration and evaporation the crude product was recrystallized from MeOH to give 3.2 g (87%) analytically pure product **8b**: mp 86–88 °C; $[\alpha]^{20}_D$ −9.7 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.55 (br s, 10 H), 3.08 (s, 6 H, CH_3SO_2), 4.23 (br m, 2 H), 4.38 (br, 4 H, CH_2–O). Anal. Calcd for $C_{12}H_{22}O_8S_2$: C, 40.21; H, 6.19; S, 17.89. Found: C, 39.85; H, 6.16; S, 17.91.

Racemic 3,14-bis(4-tolylsulfonyl)-3,14-diazabicyclo[14.4.0]eicos-18-ene (9) was prepared from **10** and 1,10-bis[(*p*-tolylsulfonyl)amino]decane by following general methods except that the mixture was heated for 72 h at 55 °C. After the workup, the product was purified by preparative plate chromatography over silica gel with (distilled) methylene chloride/ethyl acetate (97:3) as the eluent to give the monomer: 40% yield; mass spectrum, m/e 586 (theory 586). Recrystallization from C_2H_5OH gives white needles: mp 189 °C; mol wt (osmometric in $CHCl_3$) 571.4, 575.7 (theory 586.8), ^{1}H NMR ($CDCl_3$) δ 1.40 (br s, 16 H), 2.03 (br, 6 H), 2.40 (s, 6 H), 3.07 (br d, 8 H), 5.52 (s, 2 H), 7.47 (2 d, 8 H); mass spectrum, exact mass m/e 586.291 (theory 586.290).

4-Cyclohexene-1,2-dimethanol dimethanesulfonate (10) was prepared analogously to the method described by Walborsky:[16] mp 93–94 °C (lit. mp 90–92 °C); ^{1}H NMR ($CDCl_3$) δ 2.13 (br s, 6 H), 3.03 (s, 6 H), 4.25 (br s, 4 H), 5.67 (br s, 2 H).

1,8-Diazacyclooctadecane (11). A mixture of the bis tosylamide **3e** (563 m, 1 mmol), Na_2HPO_4 (600 mg, 4.2 mmol), and finely ground 6% sodium amalgam (6 g) in methanol (10 mL) was stirred rapidly and heated to a gentle reflux for 20 h. After cooling to room temperature, the mixture was poured into water, extracted three times with ether, and dried over $MgSO_4$. After filtration and evaporation, the product **11** remains as a white solid: 90%; mass spectrum, m/e 254 (theory 254); ^{1}H NMR ($CDCl_3$) δ 1.33 (br, 26 H), 2.62 (br, 8 H, CH_2–N); mass spectrum, exact mass m/e 254.272 (theory 254.272).

Racemic 3,14-Diazabicyclo[14.4.0]eicos-18-ene (12). Treatment of the bis tosylamide **9** (240 mg, 0.4 mmol) in a similar manner to that described for the preparation of **11** afforded the desired product **12**: 85%; mass spectrum, m/e 278 (theory 278); ^{1}H NMR ($CDCl_3$) δ 1.37 (br s, 16 H), 1.97 (br, 8 H), 2.63 (br s, 8 H), 5.63 (br s, 2 H); mass spectrum, exact mass m/e 278.271 (theory 278.272).

Acknowledgment. The Dutch National Science Foundation (Z.W.O.), administered by the Office for Chemical Research (S.O.N.), has provided a fellowship for B.K.V.

Registry No. **1a**, 67508-30-9; **1b**, 79130-37-3; **2a**, 110-52-1; **2b**, 111-24-0; **2c**, 629-03-8; **2d**, 4101-68-2; **2e**, 45223-18-5; **2f**, 31255-10-4; **2g**, 31255-26-2; **3a**, 87338-06-5; **3b**, 87338-07-6; **3c**, 87338-08-7; **3d**, 87338-09-8; **3e**, 87338-10-1; **3f**, 87338-11-2; **3g**, 87338-12-3; **3h**, 87338-13-4; **3i**, 87338-14-5; **3j**, 87338-15-6; **4a**, 87338-16-7; **4b**, 87338-17-8; **5**, 87338-18-9; **6**, 87338-19-0; (±)-(*S,S*)-**7**, 87338-20-3; (−)-(*S,S*)-**8a**, 60989-82-4; (−)-(*S,S*)-**8b**, 87338-21-4; (±)-**9**, 87338-22-5; (±)-**10**, 87338-23-6; **11**, 296-27-5; (±)-**12**, 87338-24-7; Cs_2CO_3, 534-17-8; *m*-xylylenediamine, 1477-55-0; 1,14-dibromo-3,6,9,12-tetraoxatetradecane, 57602-02-5; *N,N'*-(dithiodiethylene)bis[*p*-toluenesulfonamide, 23516-74-7; 1,8-dibromooctane, 4549-32-0; (*R,R*)-diethyl cyclohexylidenetartrate, 73069-00-8.

(14) Hermer, N. E.; Field, L. *J. Org. Chem.* **1970**, *35*, 1668.
(15) Tsuzuki, Y. *Bull. Chem. Soc. Jpn.* **1937**, *12*, 487.
(16) Walborsky, H. M.; Barash, L.; Davis, T. C. *Tetrahedron*, **1963**, *19*, 2333.

Approaches to the Synthesis of Aza Analogues of the β-Lactam Antibiotics: Some Anomalous Rhodium(II)-Catalyzed Carbene Insertion Reactions

Edward C. Taylor* and Huw M. L. Davies

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

Received July 6, 1983

An attempt to apply the "normal" α-diazo ketone carbene insertion reaction to the aza-β-lactams **6a–c** gave products derived from interception of the intermediate carbene by N-1, followed by ring expansion or ring fragmentation.

There is intense current interest in the preparation of diverse carbapenems since the discovery of the potent β-lactam antibiotic thienamycin (1). One of the most efficient procedures developed thus far for the construction of the bicyclic ring system found in the carbapenems is the rhodium(II) acetate catalyzed insertion reaction outlined

0022-3263/84/1949-0113$01.50/0