A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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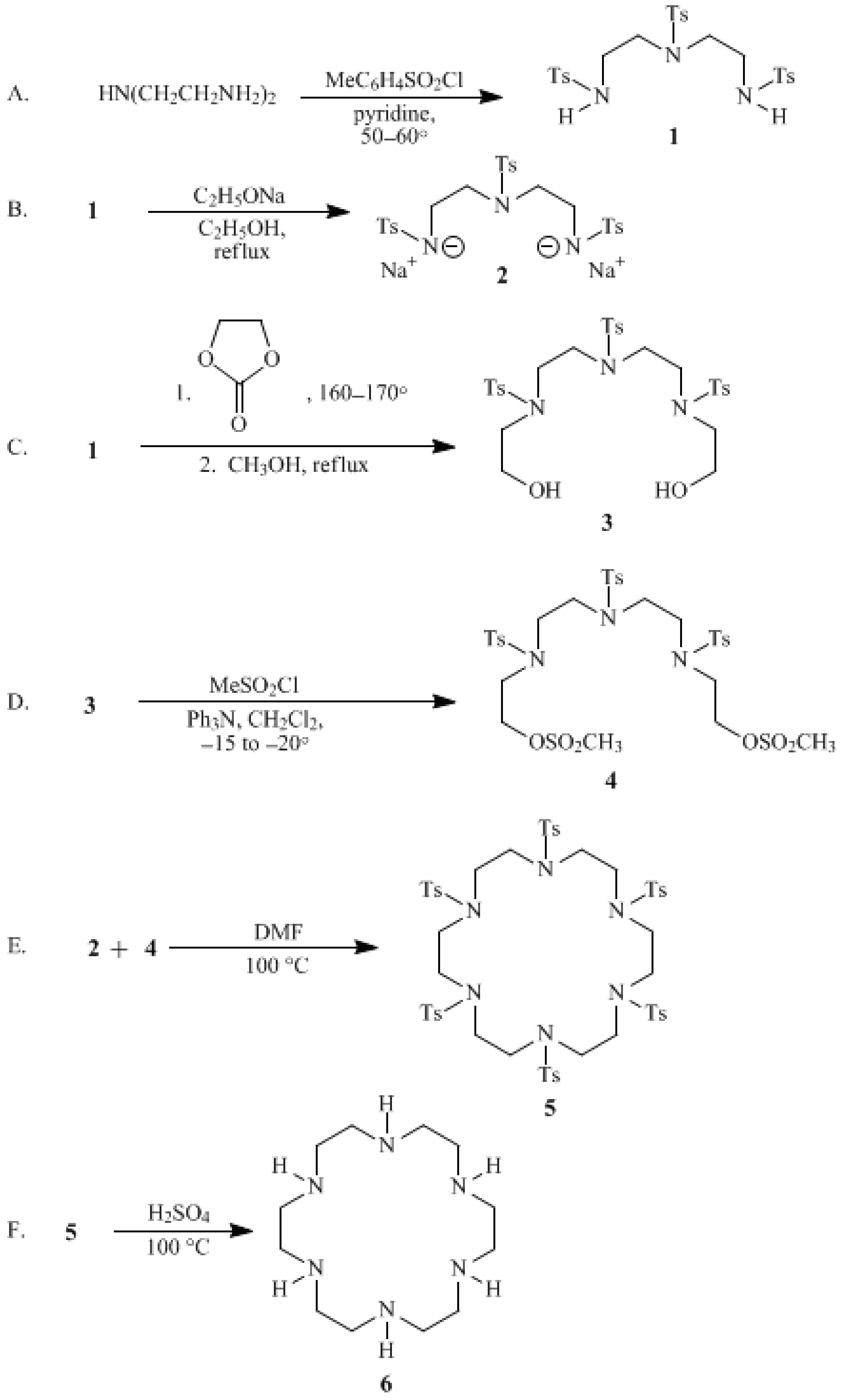
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.058.0086

Organic Syntheses, Coll. Vol. 6, p.652 (1988); Vol. 58, p.86 (1978).

MACROCYCLIC POLYAMINES: 1,4,7,10,13,16-HEXAÄZACYCLOÖCTADECANE



Ts = *p*-$CH_3C_6H_4SO_2$-

Submitted by T. J. Atkins[1], J. E. Richman, and W. F. Oettle.
Checked by K. Bernauer, F. Schneider, and A. Brossi.

1. Procedure

A. N,N',N"-*Tris*(p-*tolylsulfonyl*)*diethylenetriamine* **(1)**. A 5-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, thermometer, and addition funnel is charged with 1150 g. (6.037 moles) of *p*-toluenesulfonyl chloride (Note 1) and 3 l. of pyridine. The mixture is stirred and warmed to 50°, dissolving the solid; the flask is immersed in a 30° water bath; and a solution of 206 g. (2.00 moles) of diethylenetriamine (Note 1) in 300 ml. of pyridine is added through the addition funnel at a rate that maintains a reaction temperature of 50–60° (1 hour). The reaction mixture is kept at 50–60° for 30 minutes longer, cooled, and divided into two equal portions in 4-l. Erlenmeyer flasks. The pyridine solutions are mechanically stirred as 1000 ml. of water is slowly poured into each. After stirring overnight and cooling in an ice bath for 2 hours, the white solid is collected by filtration, thoroughly washed with ice-cold 95% ethanol, and dried in a vacuum oven at 100°, yielding 950–1015 g. (84–90%) of triamine **1**, m.p. 173–175°.

B. N,N',N"-*Tris*(p-*tolysulfonyl*)*diethylenetriamine*-N,N"-*disodium salt* **(2)**. A 3-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel is charged with 1 l. of absolute ethanol and 425 g. (0.752 mole) of triamine **1** under nitrogen. The stirred slurry is heated to reflux, the heat source is removed, and 1000 ml. of 1.5 *N* sodium ethoxide solution (Note 2) is added through the addition funnel as rapidly as possible. The solution is decanted from any undissolved residue into an Erlenmeyer flask. The disodium salt **2**, which crystallizes on standing overnight, is filtered under nitrogen, washed with absolute ethanol, and dried in a vacuum oven at 100°, yielding 400–440 g. (87–96%).

C. 3,6,9-*Tris*(p-*tolylsulfonyl*)-3,6,9-*triazaundecane*-1,11-*diol* **(3)**. A 2-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, reflux condenser, and heating mantle is charged with 226 g. (0.400 mole) of triamine **1**, 77.5 g. (0.881 mole) of ethylene carbonate (Note 1), and 0.7 g. of powdered potassium hydroxide. The stirred mixture is heated at 160–170° for 4 hours (Note 3). The reaction mixture is then allowed to cool to 90°, and 500 ml. of methanol is added through the condenser as rapidly as possible. The solution is refluxed for 30 minutes, treated with 5 g. of activated carbon, and filtered through Celite. Water (120–140 ml.) is added dropwise to the stirred filtrate until the cloud point is reached. After crystallization is complete, diol **3** is collected and washed with 3 : 1 water–ethanol and dried in a vacuum oven at 50°, yielding 225–240 g. (86–92%) of colorless product, m.p. 108–112° (Note 4).

D. 3,6,9-*Tris*(p-*tolylsulfonyl*)-3,6,9-*triazaundecane*-1,11-*dimethanesulfonate* **(4)**. A 3-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, addition funnel, nitrogen inlet, and low-temperature thermometer is charged with a dried solution of 200 g. (0.306 mole) of diol **3** and 100 ml. of triethylamine in 1500 ml. of dichloromethane (Note 5). The stirred solution is held at −15 to −20° in an acetone-dry ice bath as 74 g. (50 ml., 0.65 mole) of methanesulfonyl chloride (Note 1) is added over 10 minutes. The dry-ice bath is replaced with an ice bath, and the solution is stirred for 30 minutes, poured into a mixture of 1 l. of crushed ice and 500 ml. of 10% hydrochloric acid, and shaken. The layers are separated, and the organic layer is washed with two 500-ml. portions of water and 500 ml. of saturated salt solution, then dried over anhydrous magnesium sulfate. The solution is filtered and evaporated to dryness under reduced pressure giving a white solid, which is dissolved in 250 ml. of dichloromethane and crystallized by addition of 500 ml. of ethyl acetate and cooling in an ice bath, yielding 215–235 g. (87–95%) of methanesulfonate **4**, m.p. 146–148.

E. 1,4,7,10,13,16-*Hexakis*(p-*tolylsulfonyl*)-1,4,7,10,13,16-*hexaäzacycloöctadecane* **(5)**. A 5-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and an addition funnel is charged with 151 g. (0.248 mole) of sodium salt **2** and 2000 ml. of *N,N*-dimethylformamide. The stirred solution is held at 100° as a solution of 200 g. (0.247 mole) of sulfonate **4** in 800 ml. of *N,N*-dimethylformamide is added dropwise over 3 hours. After 30 minutes the heat source is removed, and 500 ml. of water is added through the addition funnel. After cooling to room temperature and stirring overnight, the cyclic hexamine **5** is collected by filtration, washed with 95% ethanol, and dried in a vacuum oven at 100°, yielding 206–225 g. (70–77%), m.p. 260–290° (Note 6).

F. 1,4,7,10,13,16-*Hexaäzacycloöctadecane* **(6)**. A 3-l., three-necked, round-bottomed flask equipped with mechanical stirrer, nitrogen inlet, and addition funnel is charged with 200 g. (0.169 mole) of cyclic hexamine **5** and 500 ml. of concentrated (97%) sulfuric acid. The stirred mixture is held at 100° for 70 hours, then cooled in ice as 1300 ml. of anhydrous diethyl ether is slowly added. The precipitated polyhydrosulfate salt is filtered under nitrogen and washed with anhydrous ether (Note 7). The salt is then stirred in 200 ml. of water and cooled in ice as 71 ml. of aqueous 50% sodium hydroxide is added to neutralize the solution. Activated carbon (3 g.) is added, and the solution is heated to 80° and filtered through Celite. The filtrate is cooled in ice and reacidified to pH 1 by adding 42 ml. of concentrated sulfuric acid. The white, nonhygroscopic tris(sulfuric acid) salt of **6** that precipitates is collected and washed with 95% ethanol.

To the salt and 200 ml. of water in a 1-l., round-bottomed flask equipped with an efficient magnetic stirrer and cooled in ice is added 400 ml. of 50% sodium hydroxide solution. The resulting mixture is continuously extracted with tetrahydrofuran for 4 days (Note 8). The extract is concentrated to dryness at reduced pressure, and 1,4,7,10,13,16-hexaäzacycloöctadecane **(6)** is recrystallized from acetonitrile (30 ml. per g.), giving 19–22 g. (49–50%) of long, white needles, m.p. 147–150° (Note 9).

2. Notes

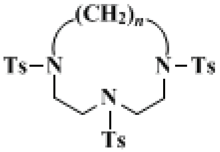
1. This reagent was purchased from Aldrich Chemical Company, Inc.
2. Sodium ethoxide was prepared under nitrogen just prior to use by dissolving 34.5 g. of sodium metal in 1000 ml. of absolute ethanol.
3. At 100–120° the solid begins to dissolve and carbon dioxide evolution commences.
4. Pure diol **3**, m.p. 110–112°, may be obtained by recrystallization from toluene (10 ml. per g.), but further purification is unnecessary for use in Step D.
5. This solution should be dried over 4-Å molecular sieves overnight.
6. The submitters obtained a yield of 190–210 g. (65–71%), m.p. 290–315° (dec.).
7. At this stage the grayish salt is quite hygroscopic and should be carefully kept from air to prevent difficulty in filtering.
8. A large excess of base is needed to reduce the water solubility of the amine. The precipitated solids contain product; any lumps should be broken up and the aqueous slurry efficiently stirred during the extraction.
9. The submitters found m.p. 154–156°.

3. Discussion

Macrocyclic polyamines and amine-ethers can be readily prepared without high-dilution techniques by this improved, general procedure.[2] Previous methods employed high-dilution techniques[3] [4] [5,6,7] or transition metal templates.[8] By adapting the present procedures, macrocycles of up to 24 members may be designed and directly synthesized in high yields from readily available starting materials.[2,9,10,11]

The critical cyclization step gives 50–85% yields when hydrocarbon segments between heteroatoms are short (see Table I) and when relatively equal segments of the target macrocycle are condensed. Methane- and di-*p*-toluenesulfonate esters[12,13] give markedly better yields than dihalides (see Table II). Cyclizations in *N,N*-dimethylformamide solvent are generally more convenient, although comparable yields are obtained in dimethyl sulfoxide and hexamethylphosphoric triamide [see *Science*, **190**, 422 (1975) for a toxicity warning concerning the latter compound]. Ether linkages or selectively substituted nitrogens may replace *N*-tosyl groups along the chain without seriously affecting cyclization yields. Other macrocyclic amines and amine-ethers[2,9,10,11,14] prepared by these methods are listed in Tables III and IV.

TABLE I
CONDENSATIONS OF
TERMINAL ALKANE
DITOSYLATES, TsO-$(CH_2)_n$-OTs



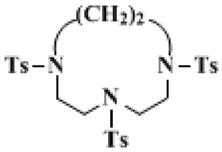
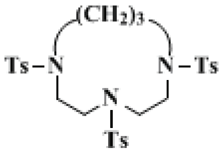
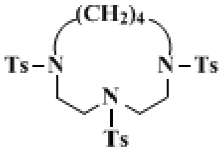
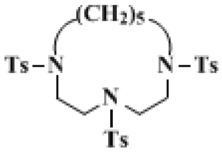
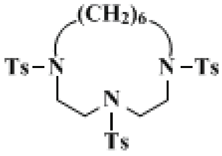
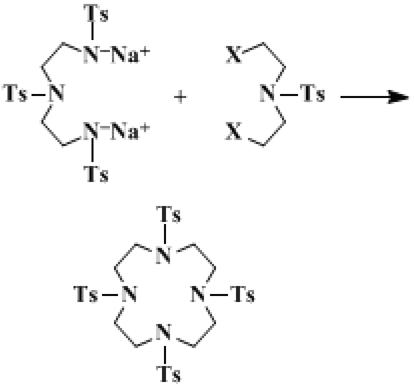
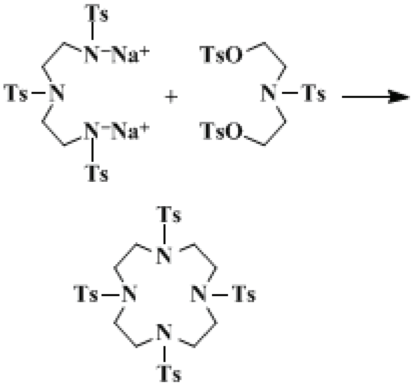
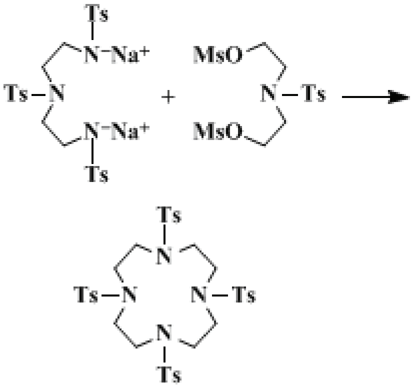
n	Yield (%)
2 	71
3 	84
4 	81
5 	55
6 	40–50

TABLE II
Yields of Cyclization for Various Leaving Groups



X	Yield (%)
 -OTs	80
 -OMs	66
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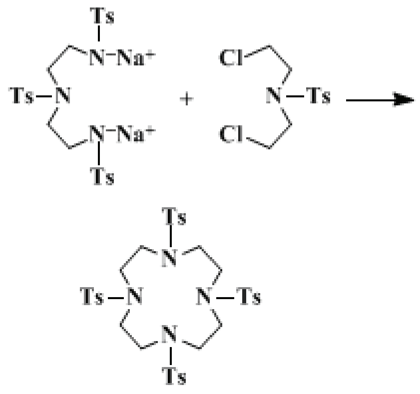
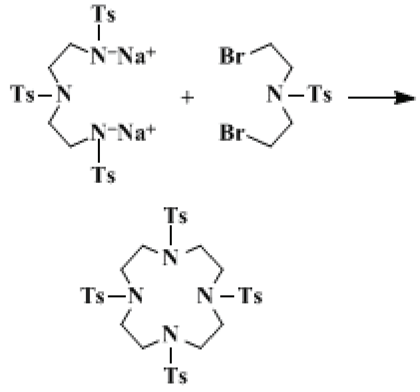


-Cl



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-Br

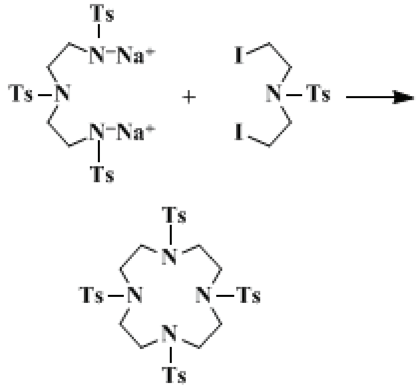

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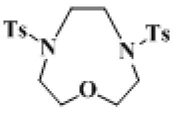
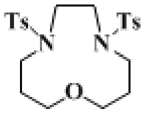
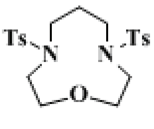
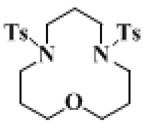
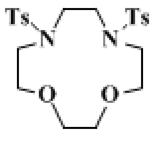
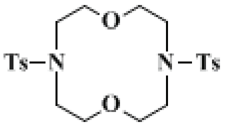
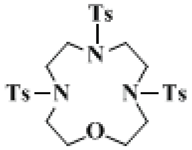
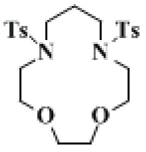
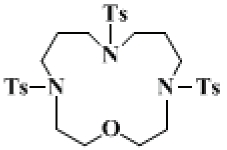
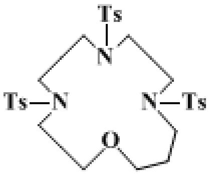
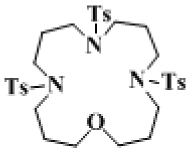
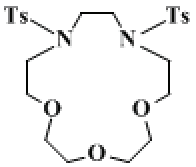
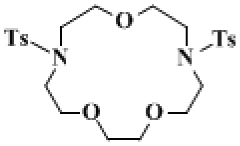
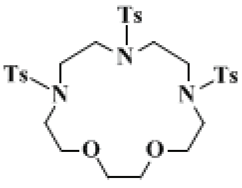
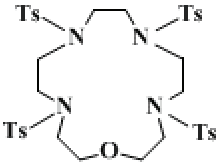
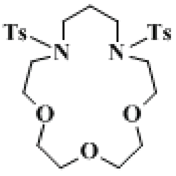
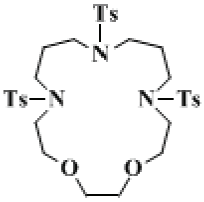
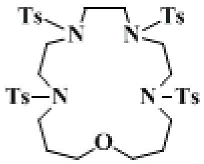
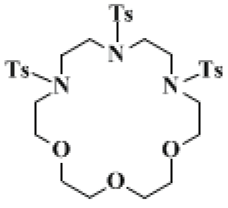
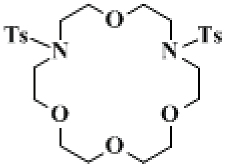
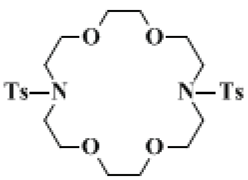
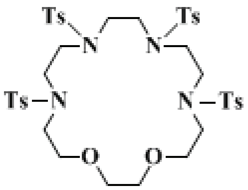
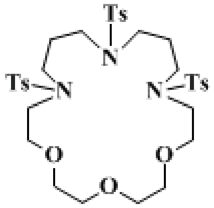
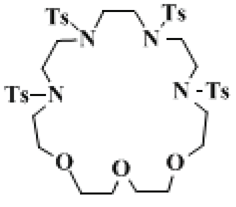
TABLE III
YIELDS OF MACROCYCLIC AMINE–ETHERS

Amine-Ether	Yield (%)	Amine-Ether	Yield (%)	Amine-Ether	Yield (%)
	32[b]		63[b]		66[b]

	79[c] 38[b]		52[b] 54[c]		47[c] 80[a]
	90[a] 63[b]		28[b] 69[c]		58[c]
	29[b]		69[b]		23[b] 43[c]
	74[c]		71[b] 88[c]		52[b] 65[c]
	7[b]		85[b]		44[b]
	14[b] 44[c]		69[c]		80[a]
	25[b] 72[a]		83[b]		35[b]

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[a] Reference 2.

[b] Reference 9.

[c] T. J. Atkins, unpublished results.

TABLE IV

YIELDS OF MACROCYCLIC POLYAMINES

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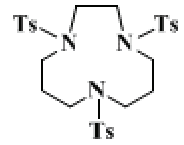
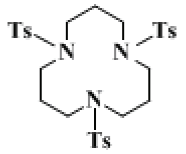
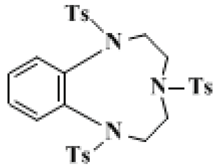
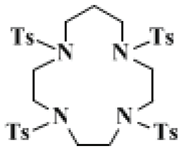
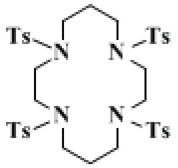
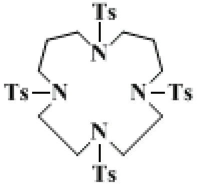
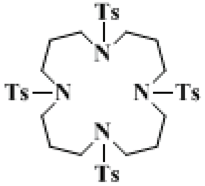
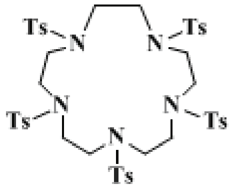
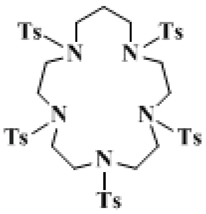
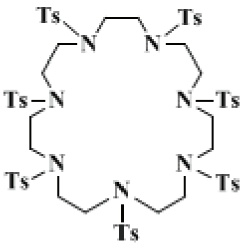
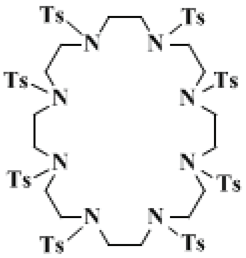
	58		67		24
			77		70
	58		90		83
	51		45		73

The hydroxyethylation of *sec*-sulfonamides has been adapted from Niederprüm, Voss, and Wechsberg.[15] Many new terminal diols for cyclization can be readily prepared by this method.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 10, 667

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N,N',N"-Tris(p-tolylsulfonyl)diethylenetriamine

N,N',N"-Tris(p-tolysulfonyl)diethylenetriamine-N,N"-disodium salt

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

carbon (7782-42-5)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

dichloromethane (75-09-2)

magnesium sulfate	(7487-88-9)
Tetrahydrofuran	(109-99-9)
N,N-dimethylformamide	(68-12-2)
dimethyl sulfoxide	(67-68-5)
triethylamine	(121-44-8)
Methanesulfonyl chloride	(124-63-0)
hexamethylphosphoric triamide	(680-31-9)
ethylene carbonate	(96-49-1)
p-Toluenesulfonyl chloride	(98-59-9)
diethylenetriamine	(111-40-0)
3,6,9-Tris(p-tolylsulfonyl)-3,6,9-triazaundecane-1,11-diol	(74461-29-3)
3,6,9-Tris(p-tolylsulfonyl)-3,6,9-triazaundecane-1,11-dimethanesulfonate	(74461-30-6)
1,4,7,10,13,16-Hexakis(p-tolylsulfonyl)-1,4,7,10,13,16-hexaazacyclooctadecane	(52601-75-9)
1,4,7,10,13,16-Hexaazacyclooctadecane	(296-35-5)