washed with diisopropyl ether: 0.80 g (32%); mp 137–139 °C. Recrystallization from diisopropyl ether and from ether/petroleum ether (bp 30–40 °C) gave an analytical sample: mp 138.5–140 °C; IR (Nujol) 1580, 1570, 1510, 1380, 1260, 1110, 770, 700 cm^{-1}; UV (CH_3OH) λ_{max} 231 (inflection, ϵ 6580), 335 nm (ϵ 17600) (addition of a few drops of 3.6 M HCl caused a peak to appear at 379 nm, ϵ 10000);NMR ($CDCl_3$) δ 2.85–3.32 (d, 6 H), 7.3 (m, 10 H) (at 55 °C the doublet collapsed to a singlet at 3.08). Anal. Calcd for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.20. Found: C, 71.51; H, 6.48; N, 22.22.

Concentration of the mother liquors and washings led to crystallization of a conglomerate, wt 1.29 g; analysis by IR and UV–vis of a solution gave the composition 0.45 g of **5** and 0.84 g of **2c**. A second crop of conglomerate (0.28 g) was isolated from the liquors; total yield of **5** was 0.56 g (20%) and 1.81 g of **2c** (72%).

Reaction of 1 with Dimethylamine in the Presence of HCN. Hydrogen cyanide (3 mL, 2 g, 70 mmol) was added to a solution of **1** (2.34 g, 10 mmol) in diisopropyl ether (70 mL) prepared as described above. A 2.26 M solution of dimethylamine in diisopropyl ether was added until the color of **1** had disappeared (6 mL required). Gas evolved slowly from the solution, which was seeded with **5** and allowed to stand at 25 °C and then at 5 °C. The large cubes that formed were washed with diisopropyl ether: wt 1.30 g. The mother liquor and washings were concentrated to give 1.40 g of a conglomerate; analysis by IR and UV–vis indicated the composition 0.97 g of **2c** (38%) and 0.43 g of **5** (total yield 63%).

Reaction of 1 with Methylamine. Conditions similar to those for the reaction of **1** with dimethylamine produced mixtures of **2b** and **4a** from **1** and methylamine. Compound **4a** was isolated from the reaction of 2.0 g (8.5 mmol) of **1** added to an excess of a wet solution of methylamine (obtained by adding NaOH pellets to a mixture of ether and commercial 40% aqueous methylamine). The mixture was cooled in ice for about 1 h, and the white product, 2-(methylimino)-2,*N*-diphenylacetamidine (**4a**), was collected, washed with ether, and recrystallized from diisopropyl ether. The somewhat sensitive material was obtained analytically pure after four crystallizations from oxolane/petroleum ether followed by one from acetone: mp 141–141.5 °C with slight dec; NMR ($CDCl_3$) δ 3.25–3.48 (3 H), 5.0 (broad s, 1 H), 7.2–7.85 (m, 10 H) (at 58 °C, the 3.25–3.48 signal collapsed to a singlet at 3.28, and the others appeared at δ 5.4 and 7.3). 3-[α-(Methylamino)-benzylidene]-1-phenyltriazene (**2b**) (or a tautomer) was isolated from a reaction of **1** (2.34 g, 10 mmol) in 15 mL of dimethylacetamide (DMA) treated dropwise with 0.8 g of 40% aqueous methylamine (10 mmol) in an equal volume of DMA. Each drop caused immediate gas evolution and warming. After 15 min, the red solution was saturated with water and scratched, giving a precipitate of fine yellow needles. They were washed sparingly with 1:1 aqueous DMA and triturated twice with water and dried in air: 1.21 g; mp 148–151.5 °C dec. Crystallization from ether at 0 °C gave 0.89 g of yellow crystals, homogeneous by TLC: mp 161–162 °C. The original filtrate yielded an additional 0.15 g of impure **2b**, mp 118–127 °C (total yield 43%). Four recrystallizations from ether gave an analytical sample: mp 162–163 °C; IR (Nujol) 3260, 1615, 1590, 1570, 1535, 1470, 1430, 1110, 780, 775, 710, 700 cm^{-1}; NMR ($CDCl_3$) δ 3.03–3.10 (d, 3 H), 6.22 (broad, 1 H), 7.1–7.6 (m, 10 H); UV (CH_3OH) λ_{max} 230 (inflection) (ϵ 8040), 328 nm (ϵ 16600); UV in presence of HCl, λ_{max} 236 (ϵ 6900), 310 nm (ϵ 11600). Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.57; H, 5.92; N, 23.51. Found: C, 70.52; H, 5.92; N, 23.83.

Oxidation of 2a. A sample of **2a** (0.50 g, 2.1 mmol) was added in portions to a boiling solution of 0.23 g (1.5 mmol) of potassium permanganate in 1.5 mL of 1.0 M sodium hydroxide and 20 mL of water. The color was discharged before all of the **2a** had been added, so further portions of permanganate (3.0 g total) were added. After refluxing for 5 h, the mixture was treated with sodium bisulfite and 300 mL of water was added. The mixture was distilled until about 150 mL of distillate had been collected. The condenser was rinsed with ether to remove product adhering to the walls, and the ether was allowed to evaporate. The dry sticky solid weighed 40 mg (8%). Sublimation (130 °C, 45 Torr) gave colorless needles, mp 101.5–103 °C, not depressed by mixture with authentic 2,5-diphenyltetrazole (**3**) prepared from phenyl azide and benzaldehyde phenylhydrazone.[7]

Hydrolysis of 5. A solution of **5** (0.45 g, 160 mmol), 10 mL of 25% sodium hydroxide solution, and 5 mL of ethanol was refluxed for 36 h, cooled, and filtered from inorganic solids. After standing overnight at 5 °C, it was again filtered and then acidified with aqueous hydrochloric acid to a thymolphthalein end point. Inorganic solids were filtered off, and the filtrate was acidified (HCl) and concentrated slightly (aspirator, steam bath). The solid that formed was collected and washed with water: 90 mg (46%; mp 121.5–122 °C; IR identical with that of benzoic acid).

A similar reaction was carried out with 0.64 g of **5**, and the solvents were decanted from a small amount of a red oil at the end of the refluxing. The oil was taken up in ether and kept for 3 days at 0 °C. The liquid was decanted from a small amount of solid and was then extracted with 5 mL of 15% aqueous HCl. Addition of bromine water precipitated a small amount of 2,4,6-tribromoaniline: mp 119–120 °C; IR identical with that of an authentic sample.

Registry No. **1**, 95980-52-2; **2a**, 125879-46-1; **2b**, 125879-53-0; **2c**, 125879-51-8; **3**, 18039-45-7; **3d**, 125879-49-4; **4a**, 125879-52-9; **4b**, 125879-47-2; **4c**, 125879-48-3; **5**, 125879-50-7; $PhCO_2H$, 65-85-0; PhNHMe, 100-61-8; HCN, 74-90-8; 2,4,6-tribromoaniline, 147-82-0.

(7) Dimroth, O.; Merzbacher, S. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 2402.

Preparation of Triaza-, Tetraaza- and Peraza-Crown Compounds Containing Aminoalkyl Side Groups or Unsubstituted Ring Nitrogen Atoms

Krzysztof E. Krakowiak, Jerald S. Bradshaw,* and Reed M. Izatt

Department of Chemistry, Brigham Young University, Provo, Utah 84602

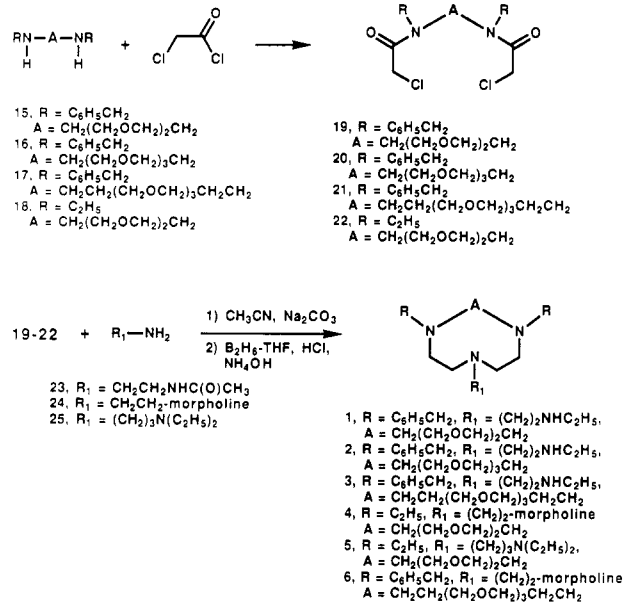
Received September 21, 1989

There is interest in the preparation of functionalized macrocyclic ligands. Much of the interest concerns the medical application of complexed metal ions and new metal ion separation techniques. Medicinal applications include the treatment of kidney stones[1] and as nuclear magnetic resonance contrast agents for antibody labeling in cancer diagnosis and therapy.[2-9] Macrocyclic ligands bonded to silica gel can be used to separate specific groups of metal ions.[10,11] From a synthetic point of view, macrocycles containing reactive functional groups are important for the above-listed applications. For example, the

(1) Kimura, E. *Top. Curr. Chem.* **1985**, *128*, 113.
(2) Lauffer, R. B. *Chem. Rev.* **1987**, *87*, 901.
(3) Kozak, R. W.; Waldmann, T. A.; Atcher, R. W.; Gansow, O. A. *Trends Biotechnol.* **1987**, *4*, 259.
(4) Morphy, J. R.; Parker, D.; Alexander, R.; Bains, A.; Carne, A. F.; Eaton, M. A. W.; Harrison, A.; Millican, A.; Phipps, A.; Rhind, S. K.; Titmas, R.; Weatherby, D. *J. Chem. Soc., Chem. Commun.* **1988**, 156.
(5) Morphy, J. R.; Parker, D.; Kataky, R.; Harrison, A.; Eaton, M. A. W.; Millican, A.; Phipps, A.; Walker, C. *J. Chem. Soc., Chem. Commun.* **1989**, 792.
(6) Craig, A. S.; Helps, J. M.; Jankowski, K. J.; Parker, D.; Beeley, N. R. A.; Boyce, B. A.; Eaton, M. A. W.; Millican, A. T.; Millar, K.; Phipps, A.; Rhind, S. K.; Harrison, A.; Walker, K. *J. Chem. Soc., Chem. Commun.* **1989**, 794.
(7) Cox, J. P. L.; Jankowski, K. J.; Kataky, R.; Parker, D.; Beeley, N. R. A.; Boyce, B. A.; Eaton, M. A. W.; Millar, K.; Millican, A. T.; Harrison, A.; Walker, C. *J. Chem. Soc., Chem. Commun.* **1989**, 797.
(8) Riesen, A.; Kaden, T. A.; Ritter, W.; Mäcke, H. R. *J. Chem. Soc., Chem. Commun.* **1989**, 460.
(9) Moi, M. K.; Meares, C. F. *J. Am. Chem. Soc.* **1988**, *110*, 6266.
(10) Bradshaw, J. S.; Krakowiak, K. E.; Tarbet, B. J.; Bruening, R. L.; Biernat, J. F.; Bochenska, M.; Izatt, R. M.; Christensen, J. J. *Pure Appl. Chem.* **1989**, *61*, 1619.
(11) Bradshaw, J. S.; Bruening, R. L.; Krakowiak, K. E.; Tarbet, B. J.; Bruening, M. L.; Izatt, R. M.; Christensen, J. J. *J. Chem. Soc., Chem. Commun.* **1988**, 812.

0022-3263/90/1955-3364$02.50/0

Scheme I. Preparation of Triaza-Crown Ethers 1–6

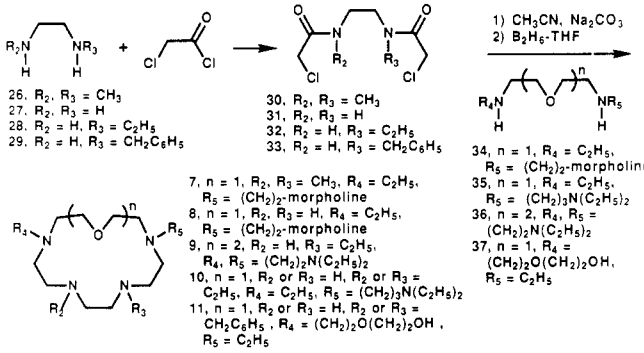


functional groups allow the ligands to be attached to solid supports. The usual substituent functional group has been a secondary amine or a vinyl group.[4,10,11]

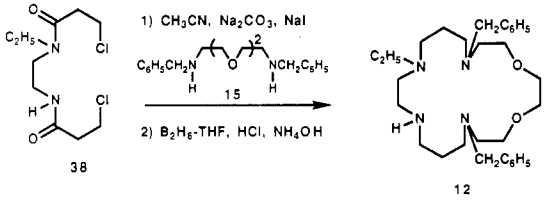
There is a need for simple and inexpensive methods to prepare the monofunctionalized polyaza- and peraza-crowns from inexpensive starting materials. Preparative routes requiring many steps, including protection and deprotection of intermediates, cannot be used in commercial processes. Published methods for the preparation of monofunctionalized polyaza macrocycles include the following. Moi and Meares proposed a route to these compounds via a peptide synthesis.[9] Parker and co-workers used expensive cyclams as starting materials and many steps including tosylation, alkylation, and detosylation to prepare some of their monofunctionalized cyclams.[12,13] Low yield condensations of malonate derivatives and diamines followed by reduction have also been used to prepare the functionalized cyclams.[4,5] Barefield[14,15] and Kaden[16,17] and their co-workers have used template methods to prepare polyaza-crowns. Their methods used metal perchlorates and potassium cyanide, which are not safe.

We have prepared polyaza- and peraza-crowns using only a few steps.[18–21] Some of the methods we have studied are applicable for the preparation of the polyaza macrocycles with monofunctional side groups. Diaza-crowns with an (allyloxy)methyl substituent on a macroring carbon atom have been prepared.[22,23] Polyaza

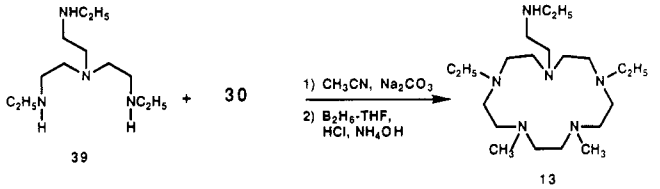
Scheme II. Preparation of Tetraaza-Crown Ethers 7–11



Scheme III. Preparation of Macrocycle 12



Scheme IV. Preparation of Macrocycle 13



macrocycles which contain hydroxyalkyl and secondary aminoalkyl groups substituted on one of the ring nitrogen atoms have also been prepared.[19,24] Each of these new synthetic processes requires only a few steps from easily obtainable starting materials. Our new synthesis of polyaza- and peraza-crowns containing one or two unsubstituted macroring nitrogen atoms likewise required only a few steps using a bis α-chloro amide in the cyclization step.[25]

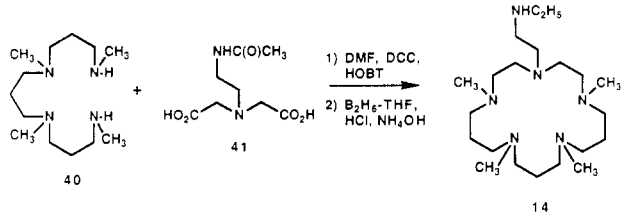
We now report the synthesis of new secondary and tertiary (aminoalkyl)-substituted polyaza macrocycles (the *N*-pivot lariat crowns) using the crab-like preparative method, which has been used to prepare other types of macrocycles.[24,25] Three additional new polyaza macrocycles containing either an unsubstituted macroring nitrogen atom or an attached secondary amine and, in two cases, propylene bridges are also included in this paper.

Results and Discussion

The reactions used to prepare the polyaza macrocycles with (aminoalkyl)-substituted or unsubstituted macroring nitrogen atoms are shown in Schemes I–V. The starting bis α-chloro amides (Schemes I and II) were easy to prepare from chloroacetyl chloride and the appropriate bis *N*-alkyl-substituted secondary amines.[25] The amid portions of the starting materials work as protecting groups for the nitrogen atoms and they increase the reactivity of the chloro-substituted carbon toward nucleophilic substitution without having the blistering effects of the β-

(12) Helps, I. M.; Parker, D.; Chapman, J.; Ferguson, G. *J. Chem. Soc., Chem. Commun.* **1988**, 1094.
(13) Helps, I. M.; Parker, D.; Morphy, J. R.; Chapman, J. *Tetrahedron* **1989**, 219.
(14) Wagner, F.; Barefield, E. K. *Inorg. Chem.* **1976**, *15*, 408.
(15) Barefield, E. K.; Foster, K. A.; Freeman, G. M.; Hodges, K. B. *Inorg. Chem.* **1986**, *25*, 4663.
(16) Tschudin, P.; Basak, A.; Kaden, T. *Helv. Chim. Acta* **1988**, *71*, 100.
(17) Basak, A. K.; Kaden, T. A. *Helv. Chim. Acta* **1983**, *66*, 2086.
(18) Krakowiak, K. E.; Bradshaw, J. S.; Izatt, R. M. *Tetrahedron Lett.* **1988**, *29*, 3521.
(19) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Tetrahedron Lett.* **1989**, *30*, 803.
(20) Krakowiak, K. E.; Bradshaw, J. S.; Forsnes, E. V.; Izatt, R. M. *J. Heterocycl. Chem.* **1989**, *26*, 661.
(21) Krakowiak, K. E.; Bradshaw, J. S.; Izatt, R. M.; Zamecka-Krakowiak, D. J. *J. Org. Chem.* **1989**, *54*, 4061.
(22) Bradshaw, J. S.; Krakowiak, K. E.; Bruening, R. L.; Tarbet, B. J.; Savage, P. B.; Izatt, R. M. *J. Org. Chem.* **1988**, *53*, 3190.
(23) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *J. Heterocycl. Chem.* **1989**, *26*, 565.
(24) Krakowiak, K. E.; Bradshaw, J. S.; Dalley, N. K.; Jiang, W.; Izatt, R. M. *Tetrahedron Lett.* **1989**, *30*, 2897.
(25) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *J. Heterocycl. Chem.* **1989**, *26*, 1431.

Scheme V. Preparation of Macrocycle 14



chloro amines. The majority of the cyclization reactions to form the intermediate cyclic bis amides did not require high dilution techniques and gave yields of 40–50% at room temperature. In two cases (preparation of the cyclic diamides for **1** and **2**), high temperatures were used. It is important to note that we have recently determined that a careful, simultaneous addition of the two starting materials using syringe pumps increased the cyclization yields for these types of reactions by 25–30%.[26] Reduction of the cyclic diamides gave polyaza macrocycles **1–11** in good overall yields.

In contrast to the ease of reaction of the bis α-chloro amides, bis β-chloro amide **38**, used to prepare **12**, reacted with the diamine only in refluxing acetonitrile and in the presence of sodium iodide (Scheme III). The yield for this cyclization step was lower than those in which the bis α-chloro amides were used to prepare **1–11**. The resulting cyclic bis amide was purified by column chromatography on alumina before the reduction step to form **12**.

Two routes to prepare peraza-crowns containing secondary aminoalkyl substituents were carried out (Schemes IV and V). As shown in Scheme IV, dichloride **30** was reacted with tris[2-(ethylamino)ethyl]amine (**39**) followed by reduction to give **13** in a 24% yield. [2-(Ethylamino)ethyl]-substituted peraza-crown **14** was prepared by first reacting tetraamine **40** with (2-acetylamino)-ethyl-substituted diacid **41** using dicyclohexylcarbodiimide and 1-hydroxybenzotriazole to form the cyclic diamide. This latter compound was reduced to give **14** (Scheme V).

The final macrocyclic polyamines were purified by chromatography on a short column of silica gel. A major problem with this purification method was complete removal of the product from the gel since polyamines have a great affinity for silica gel. To overcome this problem, we used a mixture of methanol and ammonium hydroxide as the final eluant on a short silica gel column. Care must be taken when evaporating the solvents because of the relatively low boiling points of some of the products. In general, it is better to avoid chromatographic purification. In some cases, reduction of the purified cyclic diamide intermediate gave a macrocyclic polyamine, which was 95–98% pure. This purity may be good enough for many applications of these compounds. Of course, avoidance of the chromatography step increases the overall yield. These compounds probably could be purified by reverse-phase, ion-exchange chromatography on Amberlite.

We have shown three convenient methods to prepare the (aminoalkyl)-substituted polyaza macrocycles as shown in Schemes I, II, IV, and V. The cyclization method shown in Schemes I and II is superior to other procedures for preparing these compounds because of the ease of preparation of the new intermediates, usually in one step, and their increased reactivity toward primary amines (Scheme I) or bis secondary amines (Scheme II). Many other methods for the preparation of the peraza-crowns generally give lower yields in the cyclization step. For example, a recently published process to make 16-membered pentaaza-crowns similar to those in this paper by reacting malonyl diazide or dichloride with terminal diamines gave only 16% and 7% of the cyclic diamide, respectively.[27] Our new process will allow a faster and more efficient synthesis of a variety of polyaza- and peraza-crowns n good yields as we have shown in this and previous papers.[24,25]

(26) Krakowiak, K. E.; Bradshaw, J. S. Unpublished results.

Experimental Section

^{1}H NMR spectra were obtained at 200 MHz in deuteriochloroform. Molecular weights were determined by electron-impact HRMS. Amines **23–29**, **40**, tris(2-aminoethyl)amine (to prepare **39**), chloroacetyl chloride, β-chloropropionyl chloride, diethylene glycol bis(2-chloroethyl ether), diethylene glycol bis-(3-aminopropyl ether), and 1,2-bis(2-chloroethoxy)ethane were used as purchased from either Aldrich, TCI, Kodak, Fluka, Sigma, or Alfa Chemical Companies. The following starting materials were prepared as reported: **15**,[28] **18**,[29] **19**,[25] **30**,[30] **31–33**,[25] **34**, **35**, **37**,[31] and **41**.[32] Starting materials not previously reported were prepared as follows. Elemental analyses were not made on these starting materials, but satisfactory analyses were obtained on all macrocycles prepared from these materials.

1,15-Diphenyl-5,8,11-trioxa-2,14-diazapentadecane (16). Diethylene glycol bis(2-chloroethyl ether) (12.8 g, 0.055 mol) was slowly added to a solution of 50 g (0.47 mol) of benzylamine and 20 g of sodium carbonate in 150 mL of toluene over a 3-h period. The mixture was refluxed in a Dean–Stark apparatus for 20 h to remove water. The inorganic salts were filtered and the filtrate was evaporated under reduced pressure. The residue was distilled to give 14.4 g (70%) of **16** as an oil, bp 205–210 °C/0.1 mm; ^{1}H NMR δ 2.0 (s, 2 H), 2.75 (t, J = 6 Hz, 4 H), 3.55 (m, 12 H), 3.75 (s, 4 H), 7.25 (m, 10 H).

1,15-Diphenyl-6,9,12-trioxa-2,16-diazaheptadecane (17). A mixture of 12.5 g (0.057 mol) of diethylene glycol bis(3-aminopropyl ether) and 12.1 g (0.114 mol) of benzaldehyde in 150 mL of methanol was stirred at 0–5 °C for 15 min. Sodium borohydride (4.32 g, 0.114 mol) was added to the mixture portionwise at 0–5 °C. The mixture was stirred at 0–5 °C for 2 h and the solvent was evaporated under reduced pressure. The residue was thoroughly mixed with 100 mL of saturated aqueous sodium carbonate and 200 mL of ethyl acetate and the mixture was separated. The water phase was extracted twice with 100-mL portions of ethyl acetate. The combined organic layers were dried ($MgSO_4$). The drying agent was filtered and the filtrate was evaporated. The residue was distilled to give 19.3 g (85%) of **17**, bp 210 °C/0.1 mm; NMR δ 1.55 (br, 2 H), 1.8 (quint, J = 6 Hz, 4 H), 2.7 (t, J = 6 Hz, 4 H), 3.5 (m, 12 H), 3.75 (s, 4 H), 7.3 (m, 10 H).

3,18-Diethyl-9,12-dioxa-3,6,15,18-tetraazaeicosane (36). A mixture of 34.8 g (0.6 mol) of 2-(diethylamino)ethylamine, 5.6 g (0.3 mol) of 1,2-bis(2-chloroethoxy)ethane, and 15 g of sodium carbonate in 150 mL of toluene was stirred under reflux for 48 h on a Dean–Stark apparatus to remove water. The mixture was cooled and the inorganic salts were filtered. The filtrate was evaporated and the residue was distilled twice to give 6.2 g (60%) of **36**, bp 138–143 °C/0.1 mm: NMR δ 0.95 (t, J = 6 Hz, 12 H), 1.8 (br, 2 H), 2.45 (quint, J = 6 Hz, 12 H), 2.6 (t, J = 6 Hz, 4 H), 2.75 (t, J = 6 Hz, 4 H), 3.5 (m, 8 H).

Tris[2-(ethylamino)ethyl]amine (39). Acetic anhydride (6.3 g, 0.06 mol) was slowly dropped into 2.92 g (0.02 mol) of tris(2-aminoethyl)amine in 10 mL of ethanol at 5–10 °C. The mixture was then stirred at room temperature for 2 h and evaporated under reduced pressure. Benzene was added during the evaporation step to completely remove any water. The resulting tris acetamide was recrystallized from THF to give 4.5 g (83%), mp 107 °C: ^{1}H

(27) Kimura, E.; Anan, H.; Koike, T.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 3998.
(28) Bradshaw, J. S.; Krakowiak, K. E. *J. Org. Chem.* **1988**, *53*, 1808.
(29) Kikin, T.; Maeda, H.; Nakatsuji, Y.; Okahara, M. *Synthesis* **1984**, 74.
(30) Lin, W. O.; Figueira, J. A. A.; Alt, H. G. *Monatsh. Chem.* **1985**, *116*, 217.
(31) Bradshaw, J. S.; Krakowiak, K. E.; An, H.; Izatt, R. M. *Tetrahedron*. Submitted for publication.
(32) Genik-Sas-Berezowsky, R. M.; Spinner, I. H. *Can. J. Chem.* **1970**, 163.

Table I. Yields and ^{1}H NMR Spectral Data for 20–22 and 36

compd	yield, %	^{1}H NMR
20	75	3.5 (m, 16 H), 4.05 (s, 2 H), 4.3 (s, 2 H), 4.65 (two s, 4 H), 7.25 (m, 10 H)
21	82	1.8 (m, 4 H), 3.5 (m, 16 H), 4 (s, 2 H), 4.25 (s, 2 H), 4.55 (s, 4 H), 7.25 (m, 10 H)
22	78	1.15 (m, 6 H), 3.5 (m, 16 H), 4.05 (s, 2 H), 4.2 (s, 2 H)
38	68[a]	1.15 (t, 3 H), 2.55 (t, 2 H), 2.8 (t, 2 H), 3.4 (m, 6 H), 3.8 (m, 4 H), 6.8 (b, H)

[a] Recrystallized from carbon tetrachloride; mp 66 °C.

NMR δ 2.0 (s, 9 H), 2.5 (t, J = 6 Hz, 6 H), 3.2 (m, 6 H), 6.7 (br, 3 H). The solid tris acetamide was dissolved in hot THF and the hot solution was slowly added to 2 g of lithium aluminum hydride in 30 mL of THF at 5 °C. This mixture was refluxed over night and cooled. Aqueous 5% sodium hydroxide (7 mL) was added and the resulting mixture was stirred for 2 h. The mixture was filtered and the solid was washed with hot THF. The combined THF solutions were evaporated under reduced pressure and the residue was distilled to give 3 g (79%) of **39**, bp 72–74 °C/0.13 mm: ^{1}H NMR δ 1.0 (t, J = 6 Hz, 9 H), 1.3 (br, 3 H), 2.6 (m, 18 H).

General Method for Preparation of Bis α-Chloro Amides 20–22 and 38 (Schemes I and III). Chloroacetyl chloride (or β-chloropropionyl chloride) (0.1 mol) in 50 mL of chloroform and 13 g of potassium carbonate in 500 mL of water were each simultaneously added through dropping funnels to a stirred solution of 0.33 mol of the appropriate diamine in a mixture of 40 mL of chloroform and 20 mL of water at 0–5 °C over a 1-h period. The mixture was stirred an additional 2 h at room temperature. The chloroform layer was separated and washed twice with 50-mL portions of water. The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica gel (**20–22**) or crystallized (**38**). The yields and ^{1}H NMR spectral data are given in Table I.

General Procedure for Preparation of Macrocycles 1–11 (Schemes I and II). A mixture of 0.01 mol of the appropriate bis α-chloro amide (**19–22** or **30–33**), 0.01 mol of the appropriate amine or diamine (**23–25** or **34–37**), and 20 g of sodium carbonate in 300 mL of acetonitrile was stirred at room temperature for 1–5 days and then refluxed for 5–15 h. In the case of the formation of diamides for crowns **1** and **2**, the mixture was immediately refluxed for 36 h. The mixture was filtered, the filtrate was evaporated under reduced pressure, and the resulting crude cyclic bis amide was chromatographed on a short silica gel column using either toluene/ethanol, ethanol, methanol, or methanol/ammonium hydroxide as eluant. The purified bis amide was added to 100 mL of 1 M diborane in THF at 5–10 °C. The resulting mixture was refluxed for 12 to 24 h. After cooling, 10–15 mL of water was carefully dripped into the solution to decompose the excess diborane. The solvent was evaporated under reduced pressure to dryness and 80 mL of 18% aqueous hdyrochloric acid was added. The mixture was stirred overnight at room temperature and then at about 80 °C for about 1 h. The mixture was evaporated under reduced pressure. Water (20 mL) was added to the residue and the mixture was stirred and filtered. Ammonium hydroxide was added to the filtrate until a pH of 12 or 12.5 was reached. The solution was extracted several times with 80-mL portions of chloroform. The combined chloroform extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give the polyaza-crown. In a few cases, the product was chromatographed on 250-mesh silica gel on a short column, using methanol/ammonium hydroxide as eluant. The purified product was dissolved in 10 mL of toluene, filtered to remove any silica gel from the product, and evaporated. The yields and ^{1}H NMR spectral data are given in Table II. Satisfactory elemental analyses were obtained for all new polyaza-crowns.

4,15-Bis(phenylmethyl)-8-ethyl-1,18-dioxa-4,8,11,15-tetraazacycloeicosane (12) (Scheme III). A mixture of 2.4 g (0.01 mol) of **38**, 3.28 g (0.01 mol) of **15**, 3.5 g of sodium iodide, and 15 g of sodium carbonate in 350 mL of acetonitrile was stirred under reflux for 4 days. The mixture was filtered, the solvent was evaporated, and the residue was mixed with 150 mL of chloroform. The chloroform solution was washed with wter, dried, and evaporated. The residue was treated as above for **1–11**, except alumina chromatography (acetonitrile/ethanol) was used to give 1.3 g (26%) of **12** as an oil: ^{1}H NMR δ 0.95 (t, J = 6 Hz, 3 H), 1.65 (m, 4 H), 2.5 (m, 19 H), 3.55 (m, 12 H), 7.25 (m, 10 H). This material gave a satisfactory elemental analysis.

Table II. Yields and ^{1}H NMR Spectral Data for Crowns 1–11[a]

compd	^{1}H NMR	yield overall, % (two steps)
1	1.0 (t, 3 H), 1.6 (b, 1 H), 2.65 (m, 18 H), 3.55 (m, 12 H), 7.25 (m, 10 H)	43
2	1.0 (t, 3 H), 1.7 nb, 1 H), 2.6 (m, 18 H), 3.6 (m, 16 H), 7.2 (m, 10 H)	31
3	1.0 (t, 3 H), 1.7 (p, 4 H), 2.5 (m, 19 H), 3.55 (m, 16 H), 7.25 (m, 10 H)	22
4	1.0 (t, 6 H), 2.5 (m, 24 H), 3.55 (m, 8 H), 3.7 (t, 4 H)	26
5	1.0 (m, 12 H), 1.6 (m, 2 H), 2.6 (m, 24 H), 3.65 (m, 8 H)	34
6	1.75 (m, 4 H), 2.2 (m, 4 H), 2.5 (m, 16 H), 3.6 (m, 20 H), 7.25 (m, 10 H)	25
7	1.0 (t, 3 H), 2.25 (s, 6 H), 2.6 (m, 26 H), 3.5 (t, 4 H), 3.7 (t, 4 H)	40 (crude) 22
8	1.0 (t, 3 H), 2.3 (b, 2 H), 2.5 (m, 26 H), 3.4 (t, 4 H), 3.65 (t, 4 H)	31 (crude) 23
9	1.0 (t, 15 H), 2.0 (b, 1 H), 2.55 (m, 34 H), 3.55 (m, 8 H)	23
10 mixt of crowns	1.0 (m, 12 H), 1.6 (m, 2 H), 2.5 (m, 29 H), 3.5 (m, 4 H)	16
11 mixt of crowns	1.0 (dt, 3 H), 2.35 (m, 2 H), 2.6 (m, 20 H), 3.5 (m, 12 H), 7.25 (m, 5)	18

[a] Satisfactory elemental and MS analyses were obtained for all crowns.

7,10-Dimethyl-4,13-diethyl-1-[2-(ethylamino)ethyl]-1,4,7,10,13-pentaazacyclopentadecane (13) (Scheme IV). Triamine **39** (1.15 g, 5 mmol), 1.21 g (5 mmol) of **30**, and 20 g of sodium carbonate were added to 200 mL of stirred acetonitrile at −40 °C. The mixture was stirred at room temperature for 5 days. The mixture was filtered and treated as above for **1–11** to give 0.45 g (24%) of **13** as an oil: ^{1}H NMR δ 1.0 (m, 9 H), 1.5 (br, 1 H), 2.15 (s, 6 H), 2.6 (m, 30 H). This material gave a satisfactory elemental analysis.

4,8,12,16-Tetramethyl-1-[2-(ethylamino)ethyl]-1,4,8,12,16-pentaazacyclooctadecane (14) (Scheme V). A mixture of 2.18 g (0.01 mol) of diacid **41**, 2.44 g (0.01 mol) of amine **40**, 5 g of 1,3-dicyclohexylcarbodiimide (DCC), and 5.4 g of 1-hydroxybenzotriazole in 200 mL of DMF was stirred at room temperature for 5 days. The mixture was filtered and evaporated. The residue was dissolved in a small amount of THF (~20 mL) and, after standing in the refrigerator for 16 h , was filtered and evaporated. The residue was treated as above for **1–11** except an alumina column (THF/ethanol) was used to give 0.88 g (23%) of **14** as an oil: ^{1}H NMR δ 1.1 (t, 3 H), 1.6 (m, 6 H), 2.15 (s, 6 H), 2.2 (s, 6 H), 2.3 (m, 27 H). This material gave a satisfactory elemental analysis.

Acknowledgment. This work was supported by the Centers of Excellence Program of the State of Utah. We thank Dr. Peter Huszthy for preparing compound **17**.

Registry No. **1**, 126111-74-8; **2**, 126111-75-9; **3**, 126111-76-0; **4**, 126111-77-1; **5**, 126111-78-2; **6**, 126111-79-3; **7**, 126111-80-6; **8**, 126111-81-7; **9**, 126111-82-8; **10** (isomer 1), 126111-83-9; **10** (isomer 2), 126111-97-5; **11** (isomer 1), 126111-84-0; **11** (isomer 2), 126111-98-6; **12**, 126132-96-5; **13**, 126111-85-1; **14**, 126111-86-2; **15**, 66582-26-1; **16**, 66582-27-2; **17**, 126111-87-3; **18**, 90655-88-2; **19**, 126111-88-4; **20**, 126111-89-5; **21**, 126111-90-8; **22**, 124764-03-0; **23**, 1001-53-2; **24**, 2038-03-1; **25**, 104-78-9; **28**, 110-72-5; **30**, 36784-59-5; **31**, 2620-09-9; **32**, 126111-91-9; **33**, 107235-77-8; **34**, 126111-92-0; **35**, 126111-93-1; **36**, 126111-94-2; **37**, 126111-95-3; **38**, 126111-96-4; **39**, 124764-04-1; **40**, 123-67-1; **41**, 25629-30-5;

$Cl(CH_2)_2O(CH_2)_2O(CH_2)_2O(CH_2)_2Cl$, 638-56-2; $PhCH_2NH_2$, 100-46-9; PhCHO, 100-52-7; $H_2N(CH_2)_3O(CH_2)_2O(CH_2)_2O(CH_2)_3NH_2$, 4246-51-9; $Cl(CH_2)_2O(CH_2)_2O(CH_2)_2Cl$, 112-26-5; $H_2N(CH_2)_2NEt_2$, 100-36-7; $H_2N(CH_2)_2N((CH_2)_2NH_2)_2$, 4097-89-6; $AcNH(CH_2)_2N((CH_2)_2NHAc)_2$, 124764-08-5.

Supplementary Material Available: ^1H NMR spectra for compounds **16**, **17**, **20–22**, **36**, and **38** (8 pages). Ordering information is given on any current masthead page.

Triorganothallium Reagents in Organic Chemistry. 1. A Simple, Efficient, and Versatile Preparation of Ketones from Acid Chlorides†

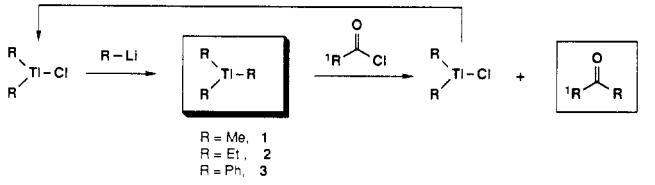
István E. Markó* and J. Mike Southern

Department of Chemistry, The University, Sheffield S3 7HF, U.K.

Received August 23, 1989

Although the transformation of a carboxylic acid into the corresponding ketone is a useful functional group transformation,[1] a simple and versatile procedure is still required. Organometallics[2] usually employed to produce ketones from acid chlorides include organocopper[3] and organocadmium[4] derivatives, but they suffer from limitations.[5]

We now report that triorganothallium derivatives such as trimethylthallium[6] (TMT, **1**), triethylthallium[7] (TET, **2**), and triphenylthallium[8] (TPT, **3**), react cleanly with acid chlorides at room temperature, giving methyl or phenyl ketones in high yields (eq 1, Table I).

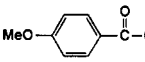
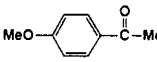


(1)

The thallium(III) compounds are readily prepared from the corresponding diorganothallium halides,[9] which are among the least reactive organometallic reagents known. Diorganothallium halides are usually solids, unaffected by water, oxygen, light, and acids, and insoluble in most organic solvents as well as in water. They can be conveniently handled and stored for months without decomposition. Addition of an organolithium compound to an ethereal suspension of a diorganothallium halide—or of a Grignard reagent to a THF suspension[10]—generates the soluble and highly reactive triorganothallium derivative.[11] When an acid chloride is added to such a solution, rapid (seconds for entries 1–4, 8, and 9, minutes for entries 5–9 and 10) precipitation of the diorganothallium chloride occurs with concomitant formation of the ketone. Filtration of the thallium(III) salt gives in high yields nearly pure ketones, which can be further purified by distillation or chromatography.

The reaction is general (Table I) for both aliphatic and aromatic substrates. It is highly chemoselective. The triorganothallium reagents react selectively with acid chlorides in the presence of other functional groups such as olefins, esters, and ketones.[12] It is noteworthy that no tertiary alcohol, which might conceivably result from overaddition of the triorganothallium derivative to the ketone, could be detected, even in the presence of excess of reagent.

Table I. Synthesis of Ketones from Acid Chlorides Using Triorganothallium Reagents[a]

entry	substrate	reagent	product	yields[g]
1	$C_9H_{19}COCl$ [a]	Me_3Tl[d]	$C_9H_{19}COMe$	85%
2	$CH_2{=}CH(CH_2)_8COCl$ [a]	Me_3Tl	$CH_2{=}CH(CH_2)_8COMe$	73%
3	 [a]	Me_3Tl		76%
4	$CH_3O(CO)(CH_2)_8(CO)Cl$ [c]	Me_3Tl	$CH_3O(CO)(CH_2)_8(CO)Me$	92%
5	$PhCOCl$ [b]	Me_3Tl	$PhCOMe$	78%
6	 [b]	Me_3Tl		82%
7	$PhCOCl$ [b]	Et_3Tl[e]	$PhCOEt$	88%
8	$C_9H_{19}COCl$ [a]	Et_3Tl	$C_9H_{19}COEt$	91%
9	CH_3COCl [b]	Ph_3Tl[f]	CH_3COPh	87%
10	$PhCOCl$ [b]	Ph_3Tl	$PhCOPh$	85%

[a] Prepared from the corresponding carboxylic acid and $SOCl_2$ in refluxing $CHCl_3$. (b) The commercially available acid chloride was distilled before use. (c) Prepared by Fisher esterification, partial saponification with 1 equiv of KOH in MeOH and reaction with $SOCl_2$. (d) Prepared in situ by adding MeLi to a suspension of Me_2TlCl in ether at 20 °C. (e) Prepared in situ by adding EtLi to a suspension of Et_2TlCl in ether at 20 °C. (f) Prepared in situ by adding PhLi to a suspension of Ph_2TlBr in ether at 0 °C. (g) All yields are for isolated, pure material and are based on the starting acid chloride.

† Dedicated fondly to Dr. S. Goldstein.

(1) (a) House, H. O. *Modern Synthetic Reactions*; W. A. Benjamin, Inc.: London, 1972. (b) March, J. *Advanced Organic Chemistry*; J. Wiley and Sons: New York, 1985.

(2) For some leading references discussing the scope and the use of organometallic reagents, other than organocadmium and organocopper, in the transformation of acid chlorides into ketones, see: Collman, J. P., Hegedus, L. S., Norton, J. R., Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.

(3) (a) Posner, G. H. *Organic Reactions*; J. Wiley and Sons: New York, 1975; Vol. 22, p 253. (b) Castro, C. E.; Havlin, R.; Honwad, V. K.; Malte, A.; Moje, S. *J. Am. Chem. Soc.* **1969**, *91*, 6464.

(4) Cason, J.; Fessenden, R. *j. Org. Chem.* **1960**, *25*, 477.

(5) Typical problems associated with this simple transformation are (a) the overaddition of the organometallic reagent, leading to tertiary alcohols, (b) decomposition or racemization of the starting material under the rigorous conditions required for some reagents, e.g., organocadmiums, (c) instability of the organometallic reagent, e.g., organocuprates, (d) difficulties in preparing branched organometallic reagents and therefore in forming branched ketones. Numerous branched triorganothallium compounds have been prepared (ref 9) by classical organometallic reactions. They are much more stable than their copper, cadmium, and zinc counterparts. Ketone synthesis using these branched derivatives will be reported in due course.

(6) (a) Gilman, H.; Jones, R. G. *J. Am. Chem. Soc.* **1946**, *68*, 517. (b) Gilman, H.; Jones, R. G. *J. Am. Chem. Soc.* **1950**, *72*, 1760.

(7) (a) Groll, H. P. A. *J. Am. Chem. Soc.* **1930**, *52*, 2998. (b) Rochow, E. G.; Dennis, L. M. *J. Am. Chem. Soc.* **1935**, *57*, 486. (c) Birch, S. F. *J. Chem. Soc.* **1934**, 1132.

(8) (a) Birch, S. F. *J. Chem. Soc.* **1934**, 1132. (b) Gilman, H.; Jones, R. G. *J. Am. Chem. Soc.* **1939**, *61*, 1513.

(9) (a) Lee, A. G. *The Chemistry of Thallium*; Elsevier: Barking, U.K. 1971. (b) Kurosawa, H. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982; Vol. 1, p 725.

(10) Okhlobystin, O. Y.; Bilevitch, K. A.; Zakharkin, L. J. *J. Organomet. Chem.* **1964**, *2*, 281.

0022-3263/90/1955-3368$02.50/0