

Protocol 5. Continued

- α -Bromo-*p*-tolunitrile, 12 g, 61 mmol
- Dry dimethylformamide, 60 mL
- Dry ethanol, 300 mL
- Diethyl ether, 500 mL
- Chloroform, 150 mL
- 1,4,7,10-tetraazadecane, 4.18 g, 28.6 mmol
- 1 M Borane-tetrahydrofuran solution, 80 mL, 80 mmol
- Potassium hydroxide pellets, 8 g
- Concentrated hydrochloric acid, 10 mL
- Dry hexane, 20 mL
- Dry methanol, 100 mL

- irritant
- irritant, harmful by inhalation
- flammable
- flammable, irritant
- harmful by inhalation
- irritant
- moisture sensitive
- corrosive
- corrosive
- flammable, irritant
- flammable

1. Take a block of sodium metal out of the paraffin oil in which it is stored, and with a sharp knife cut approximately 1.5 g from it. Wash the block carefully in a beaker containing dry hexane to remove adhering oil and cut the block into three smaller pieces. Dry the shiny blocks with filter papers and weigh out c. 1.4 g accurately.
2. Carefully add the sodium metal (1.4 g, 61 mmol) to a double-necked round-bottomed flask, equipped with an addition funnel, a stirrer and a glass stopper, containing dry ethanol (150 mL), maintained under a gentle stream of nitrogen. Prepare a solution of diethyl malonate (20 g, 125 mmol) in dry ethanol (50 mL) and transfer this solution to the addition funnel.
3. Once the sodium has dissolved completely in the ethanol, add the contents of the addition funnel. Stir the mixture for 20 min. Meanwhile prepare a solution of α -bromo-*p*-tolunitrile* (12 g, 61 mmol) in dry DMF (60 mL) and add this solution from the addition funnel over a period of 20 min. Replace the glass stopper with a water-cooled condenser, and boil the mixture under reflux for 24 h under nitrogen.
4. Cool the mixture to room temperature and filter off the precipitate of the dialkylated malonate derivative. Extract the filtrate with diethyl ether (400 mL). Remove the ether using a rotary evaporator and distil the residue under vacuum using a Kugelrohr apparatus. The monoalkylated product is a colourless oil (b.p. 150°C, 0.1 mmHg), $R_f = 0.26$ (SiO₂, 20% ethyl acetate/petroleum ether), 7.8 g (47%).
5. Prepare a solution of the monoalkylated malonate (7.84 g, 28.5 mmol) in dry ethanol^b (120 mL) in a single-necked round-bottomed flask (250 mL) with a stirrer bar equipped with a condenser. Add 1,4,7,10-tetraazadecane (4.18 g, 28.6 mmol) and boil the mixture under reflux, stirring for 10 d.
6. Cool the reaction mixture to 0°C and filter off a colourless solid on a sintered glass filter funnel. Recrystallise this solid from the minimum volume of dry ethanol (c. 20 mL), and dry the solid under high vacuum, 1.9 g (20%), m.p. 246–8°C (dec.).
7. Dry a double-necked round-bottomed flask (250 mL) and a stirrer bar in an

electric oven (c. 120°C) for 1 h. Equip the flask with a septum and add the macrocyclic diamide (1.3 g, 3.95 mmol) prepared above. Attach a reflux condenser surmounted by a nitrogen inlet adaptor and flush the apparatus with dry nitrogen (or argon) gas.

8. Add slowly by syringe, via the septum inlet, a solution of borane-tetrahydrofuran solution (1 M, 80 mL). Replace the septum with a glass stopper and heat and stir the mixture to reflux under nitrogen for 72 h.
9. Cool the solution in an ice bath and very slowly add dry methanol (5 mL) by pipette down the condenser, to quench the excess borane. After the effervescence has ceased, add hydrochloric acid (1 M, 5 mL) and stir the mixture for 10 min. Evaporate the solvents using a rotary evaporator and to the residue add methanol (10 mL) and evaporate again. Repeat this procedure three times to aid removal of trimethyl borate, which forms a low-boiling azeotrope with methanol, b.p. 55°C.
10. Treat the residue with hydrochloric acid (6 M, 25 mL) and boil the solution under reflux for 3 h.^a Remove the water on a rotary evaporator and dissolve the residue in distilled water (30 mL). Transfer the solution to a separating funnel and wash with ether (3 x 20 mL).
11. Basify the aqueous layer by adding sufficient potassium hydroxide pellets to raise the pH to 13. Extract the aqueous layer with chloroform (4 x 30 mL). Combine the organic extracts, dry over potassium carbonate (c. 1 g), filter and evaporate the solvent to yield a colourless oil (1.2 g, 99%). The carbon-13 NMR spectrum is diagnostic: δ_c (CDCl₃): 140.7 (quat.); 138.8 (quat.); 128.9, 126.8 (aryl C-H); 54.6 (ArCH₂N); 48.8, 47.4, 47.2, 46.0 (CH₂N); 40.2; 38.3 (CH₂Ar + CHC). If necessary the product may be recrystallised as the pentahydrochloride (tetrahydrate) by dissolving the oil in dry ethanol (the minimum of c. 10 mL) and adding 0.5 mL of concentrated hydrochloric acid. The hydrochloride salt crystallises out slowly on standing.

^a Commercially available from Aldrich (14,406-1).

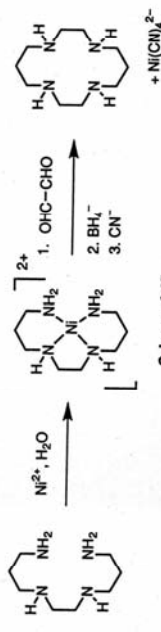
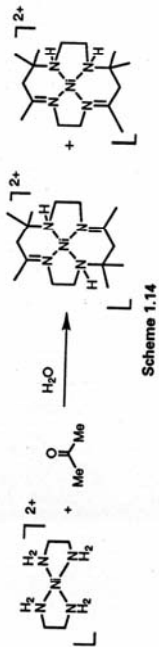
^b Distil ethanol and methanol from the corresponding magnesium alkoxide.

3. Templated reactions

The cyclisation reactions that are used to generate medium-ring and large-ring cyclic polyamines suffer from an unfavourable entropy term to the overall free energy change. Indeed this effect often limits the temperature at which the reaction can be carried out, because heating gives rise to an even more unfavourable ΔS term and competing reactions (e.g. oligomerisation) may be favoured at the expense of the desired cyclisation. Such effects may be obviated if an ion can be used to act as a template for the cyclisation step. Such an effect was first reported (for poly-aza 'crown' syntheses) by Curtis²⁶ in the reaction of [Ni(1,2-diaminoethane)]²⁺ with dry acetone (Scheme 1.14), to generate a

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[14]-N₂ ring system in which the carbon–nitrogen double bonds may be subsequently reduced by borohydride. Many such metal templated syntheses have now been reported (a further example is in Chapter 3, Protocol 7), not only involving condensation reactions but also alkylation or acylation at metal-bound nitrogens.²¹ Subsequent demetalation may be effected either by adding acid, by a ligand exchange process (e.g. adding CN⁻, sulfide or EDTA) or following reduction of the metal if it has a suitable redox couple. A classic example is the synthesis of [14]-N₂ or cyclam, **2**, where the nickel ion is removed following cyanide addition (Scheme 1.15).²²

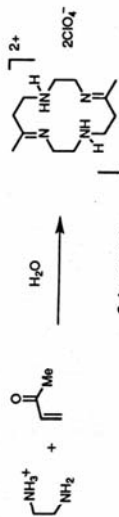


A limited number of syntheses are templated by one or more protons wherein a hydrogen-bonding network may function as a template, correctly predisposing the electrophilic and nucleophilic components for the cyclisation step.

Protocol 6.

Synthesis of 5,12-dimethyl-,9-diaza-4,11-diazotetradeca-4,11-diene bis(perchlorate) (Scheme 1.16)

Caution! Amine perchlorate salts are potentially explosive and should not be heated to dryness under vacuum. Manipulations should be carried out in a well-ventilated hood, transfers of perchlorate salts carried out with ceramic or glass spatulas, and latex or vinyl gloves and chemical-resistant safety goggles should be worn.



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1: Aza crowns

The following procedure is representative of a proton-templated cyclisation reaction.

Equipment

- Erlenmeyer flasks, 100 mL and 500 mL
- Sintered filter funnel (porosity 2)
- Buchner flask (500 mL)
- Pressure-equalising addition funnel (50 mL)
- Thermometer
- Vacuum desiccator containing P₂O₅

- Double-necked round-bottomed flask, 500 mL
- Nitrogen inlet adaptor
- Magnetic stirrer
- Stirrer bar
- Thermometer inlet adaptor

Materials

- Aqueous perchloric acid (70%), 17.2 mL
- Ethylenediamine (12 g, 200 mmol)
- Methyl vinyl ketone (14 g, 200 mmol)
- Dry methanol, 200 mL
- Diethyl ether, 50 mL

corrosive
irritant
harmful by inhalation
flammable
flammable, irritant

1. Prepare a solution of ethylenediamine (12 g, 0.2 mol) in distilled water (10 mL) in a ice-cooled conical flask (100 mL), and slowly add aqueous perchloric acid^a (70%, 17.2 mL) with gentle swirling. Remove the water on a rotary evaporator, periodically adding distilled methanol (5 × 10 mL) to aid azeotropic removal of the solvent. Once a white solid forms, carefully transfer^b the contents of the flask on to a crystallising dish, and place in a vacuum desiccator overnight.

2. Transfer the dried solid to a double-necked round-bottomed flask (500 mL) equipped with a stirrer bar and a thermometer and add dry methanol (150 mL), breaking up the solid gently with a glass rod. Purge the flask with nitrogen and attach a pressure-equalising addition funnel (50 mL) containing a solution of methyl vinyl ketone (14 g, 0.2 mol) in dry methanol (25 mL). Add the contents of the addition funnel slowly, over a period of 2 h, to the vigorously stirred cooled reaction flask, maintaining the temperature of the solution below 0°C during the addition period.

3. Allow the stirred mixture to warm up slowly to room temperature and stir for an additional 3 h. Filter off the abundant white precipitate which forms on a sintered glass filter funnel attached to a Buchner flask. Wash the solid product on the filter funnel with cold methanol (3 × 5 mL), diethyl ether (2 × 25 mL) and dry the product under vacuum (0.1 mmHg) at room temperature. The product (13.4 g, 63%), m.p. 109°C, is sufficiently pure to be used directly, but may be recrystallised from hot methanol if appropriate.

^a 70% aqueous perchloric acid is commercially available (Aldrich 24,425-2).

^b Use all glass or ceramic spatulas for solid transfers: do not use nickel spatulas.

A more rational approach to the synthesis of cyclic polyamines involves the cleavage of a common bond between two or more normal rings (i.e. five-,