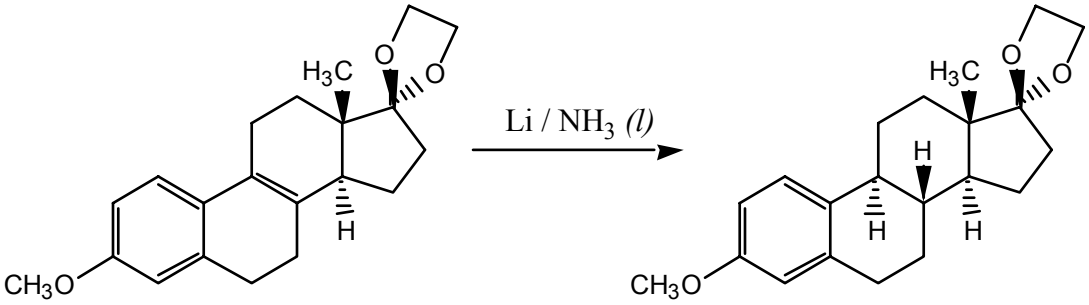
STEP 5:

ESTRONE-3-METHYL ETHER-17-ETHYLENE KETAL



1. Procedure

At least 24 hours in advance: Fill a 250-mL, 3-necked round-bottomed flask equipped with a stirbar with 50 mL acetone. Mark the solvent level with a wax pencil (note 1), decant the acetone, air dry (note 2), then oven dry the flask, stirbar, and a cold-finger condenser overnight. Also dry a 100-mL round-bottomed flask.

As quickly as possible, assemble the warm reaction apparatus as shown in Figure 5, omitting the cannula and the 100 mL round-bottomed flask. The 3-necked flask is fitted with the cold-finger condenser in the middle neck, a septum on a side neck, and a vacuum adapter on the other neck. Cool the apparatus under a stream of dry nitrogen. When cool, submerge the flask as deeply as possible in a dry ice-acetone bath. Also fill the cold-finger trap with dry ice and acetone (note 3). With nitrogen flowing, carefully turn on the ammonia tank so that the gas begins to condense in the dry ice-cooled flask (note 4). When approximately 50 mL of ammonia has condensed, stop the ammonia flow while maintaining nitrogen flow. Disconnect the ammonia tank, replacing the vacuum adapter on the side neck with another septum. Briefly remove the septum on either side neck and add lithium metal (10 equiv, in small pieces). **Caution: Before handling**

lithium metal, see note 5. Replace the septum, stop the nitrogen flow, and stir until all the metal dissolves. The reaction solution should be deep blue.

Cool an oven-dried, septum-sealed 100-mL, round-bottomed flask and cannula under a stream of dry nitrogen by blowing nitrogen in through a needle and out through the cannula. When cool, remove the septum briefly to add the starting material, 3-methoxy-1,3,5(10),8(9)-estratetraene-17-ethylene ketal. Replace the septum, purge further with dry nitrogen, then add dry THF by syringe (sol'n ~ 0.04 M). Swirl the flask gently to dissolve the starting material. Slowly transfer this solution by cannula to the cold solution of lithium in liquid ammonia (note 6). When the transfer is complete, quantitate the addition with more dry THF (5 mL). During the addition, add dry ice to the condenser and cooling bath as necessary. The reaction should be complete after 1 hour.

Because an excess of lithium was used, the reaction solution should remain deep blue. If the color fades, add more lithium. To quench the excess lithium, remove the septum and add isoprene (about 0.5 mL) by pipette; the blue color should rapidly dissipate (note 7). Remove the condenser and the cooling bath to allow the ammonia to evaporate. When ammonia can no longer be detected (note 8), dilute the reaction mixture with an equal amount of ether. Wash sequentially with small portions of 5% HCl (1x) and distilled water (2x). Dry the organic layer over sodium sulfate, filter, and evaporate the solvent on the rotary evaporator. The resulting oily product may solidify under vacuum. Take a TLC of this crude product. Purify the crude reaction product via column chromatography.

2. Notes

1. Check that the solvent level mark is not acetone-soluble.
2. Do not put glassware wet with acetone in the oven; the oven could explode.
3. Fill only about 2/3 of the way. Do not let acetone overflow the trap.
4. Ammonia gas (bp –33 ˚C) is strongly basic and corrosive. It is extremely irritating to the airway, eyes, and skin. Avoid breathing vapors. Wear goggles or safety glasses. Do not wear contact lenses in the laboratory, ever, but especially not when handling ammonia. Wear gloves and long sleeves to prevent skin exposure.
5. **Caution:** Lithium, like sodium and potassium, reacts violently with water to form hydrogen. The heat generated in this reaction is sufficient to ignite the hydrogen gas thus produced. In the presence of organic solvents, this could start a terrible fire. Fires involving alkali metals are considered class D fires, and cannot be extinguished by most ordinary fire extinguishers.

Lithium wire is stored in mineral oil to minimize exposure to water in the air. To safely transport and weigh the metal, cut off one piece of wire and immediately place it in a beaker of dry hexane. At the scale, remove the wire from the beaker with forceps, briefly shake to dry, and weigh quickly. (Since such a large excess of lithium is used, getting an exact amount is not important. Try to get close to the required amount.) Put the wire back into the hexane beaker to return to the hood, where it can be cut into smaller pieces for the reaction.

Dispose of excess lithium metal in a metal beaker filled with dry methanol. Lithium reacts much less violently with alcohols than with water. When the lithium has reacted completely with methanol, the solution can be poured into the liquid waste container. **Do not place lithium waste in a solid waste container, trash can, or sink.** Organic solvents which may have accidentally been poured into the sink could ignite when the lithium reacts with water.

6. To regulate the flow of the starting material solution through the cannula and into the ammonia solution, inject dry nitrogen from a 50-mL plastic syringe into the 100-mL flask. This gives more control over the flow rate than an active nitrogen stream.

7. Isoprene boils at 34 ˚C and has a pungent odor. When not in the freezer, it should be kept on ice and in the hood.

8. Test for ammonia by holding a piece of moistened pH paper over the neck of the flask.

3. Characterization and Report

Determine the yield of product.

If the product has solidified, determine its melting point.

Characterize the product by IR and ^{1}H and ^{13}C NMR.

Tabulate and assign the spectral data.

List the TLC conditions used and the R_f values of starting material and product.

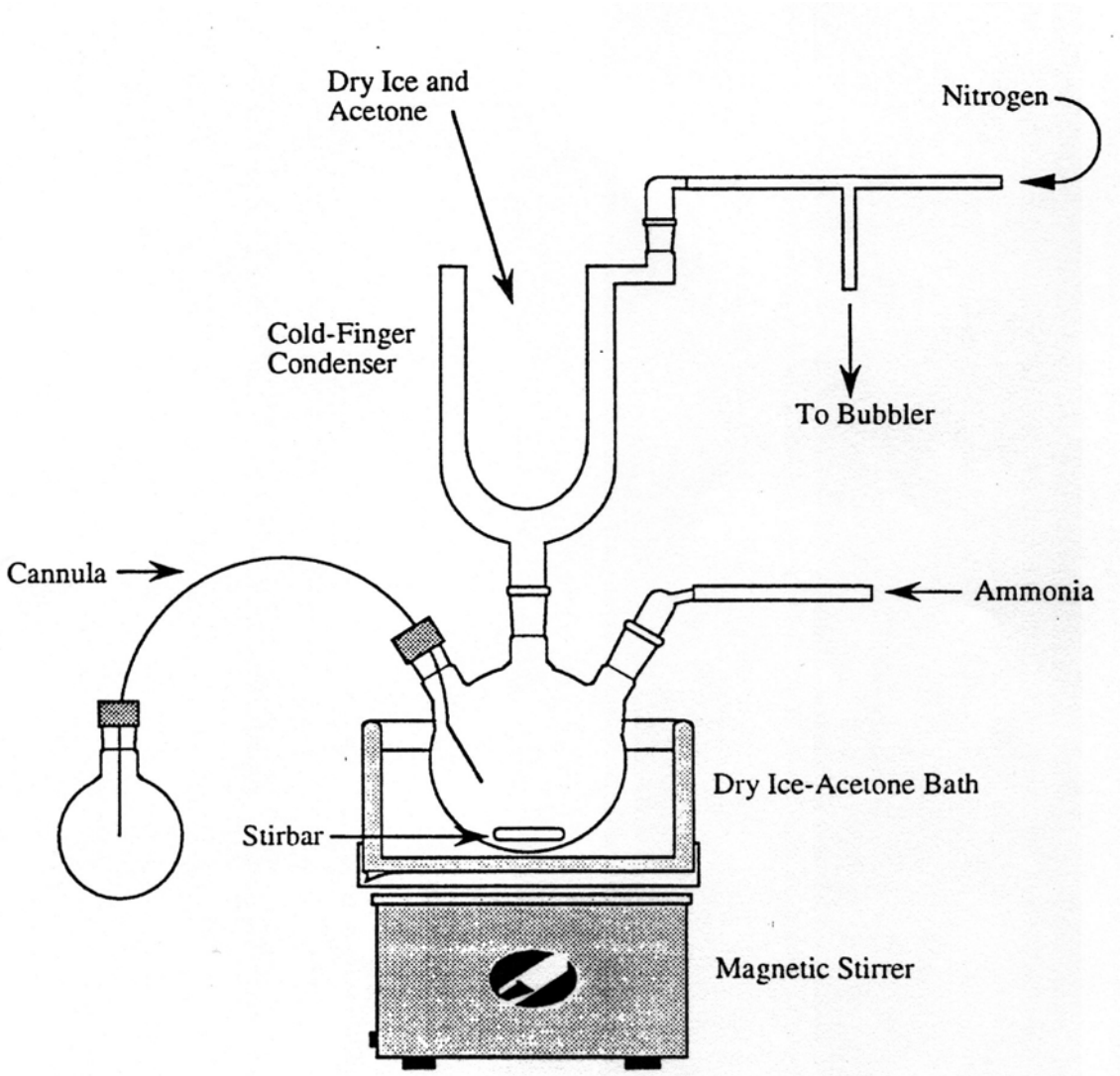


Figure 5. Dissolving Metal Reaction Apparatus