Malonic Ester Synthesis of Cyclobutanecarboxylic Acid


The malonic and related aceoacetic ester syntheses have proven to be versatile methods for building the desired carbon skeletons of carbonyl-containing molecules. Both methods rely on the alkylation of an enolate stabilized by two neighboring carbonyl groups, followed by hydrolysis of one or two ester groups and decarboxylation of the resulting carboxylic acid.

The overall reaction scheme of a malonic ester synthesis is given below.

A carboxylic acid group with a carbonyl group in the β position can undergo decarboxylation on heating, through a cyclic transition state. The net result is that a –CO₂H group β to the carbonyl is replaced with a hydrogen.

Special Hazards
Sodium methoxide is strongly basic and corrosive. Avoid contact with skin and eyes and rinse copiously with water immediately if contact should occur.

In a vacuum distillation, never use glassware that is cracked or damaged, since the apparatus could implode with the danger of cuts from broken glass and burns, both physical and chemical.

Procedure A: Preparation of Dimethyl Cyclobutane-1,1-dicarboxylate

Assemble a 250-mL round-bottomed flask (containing two or three boiling chips) with a Claisen head, condenser, and addition funnel (equipped with a rubber septum). Place a CaCl₂ drying tube on top of the condenser. (Have the TA check your set-up.)

Make sure that all flammable chemicals are at least 15 feet away and flame dry the apparatus with a Bunsen burner for about 3 minutes. Move the burner around the round-bottomed flask, condenser, and addition funnel to dry the glass as thoroughly as
possible. Heating the glass above the boiling point of water is sufficient. Keep the heat away from Teflon stopcocks or rubber stoppers.

As the apparatus is cooling, check that no flames are still in use, then place 10 mL of anhydrous methanol into a dry 125-mL Erlenmeyer flask. Stopper the flask and cool it in an ice bath. You will need 140 mmol of sodium methoxide; syringe out as many mLs as you need from the bottle of 25% NaOMe in MeOH that is on the Advanced Shelf; you will need to calculate the volume needed taking into account the 25% NaOMe in MeOH. When dispensing from this bottle, replace the bottle cap with a rubber septum. Introduce nitrogen to the bottle via Tygon tubing equipped with a needle-tipped disposable 1 mL syringe (ask TA for demo). Use a gas-tight syringe to syringe out the desired volume of NaOMe in solution and add it to the Erlenmeyer flask. Add 70 mmol of dimethyl malonate to the flask and swirl. In a separate dry 50-mL Erlenmeyer flask, dissolve 1,3-dibromopropane (70 mmol) in anhydrous methanol (15 mL).

Check that the flame-dried setup has cooled to room temperature. Syringe in the solution of 1,3-dibromopropane into the addition funnel and allow it to run into the round-bottomed flask. Close the stopcock, then add the solution of dimethyl sodiomalonate to the addition funnel. Bring the solution to reflux. After the solution boils, turn the heat down and begin dropwise addition of the methanolic solution of dimethyl sodiomalonate at the rate of about 1 drop per second, so that the addition is complete in about 20-30 minutes. The reaction is somewhat exothermic, so be cautious to maintain heating at a low level and not to add the reagent too fast. Be ready to shut off the heat and lower the heating mantle if the boiling becomes too vigorous. Continue refluxing the solution for 1 hour, then cool the flask in an ice bath. Disconnect the Claisen head and seal the flask with a septum; store in your hood until the next lab period.

Procedure B: Purification of Dimethyl Cyclobutane-1,1-dicarboxylate

Pour the contents of the 250-mL round-bottomed flask into a 400-mL beaker, add some fresh boiling chips, and place it on a hot plate. Boil it until most of the methanol is gone. Caution: Bumping may occur. The volume should decrease by about 65 mL. Add ice-cold water (50 mL) and swirl to dissolve the salts. Transfer the solution to a separatory funnel and remove the lower (aqueous) layer. Wash the remaining organic layer with water (10 mL) and saturated aqueous NaCl (10 mL), then dry it over Na2SO4. When dry (about 5-10 minutes), decant the product into a 50-mL round-bottomed flask, add boiling chips, and set up for vacuum distillation using the house vacuum. Collect the product, dimethyl cyclobutane-1,1-dicarboxylate, reported bp 116-117°C at 20 mmHg and 174-176°C at 165 mmHg). Record its mass and report a % yield. Take a 1H NMR of this intermediate.

Procedure C: Hydrolysis and Decarboxylation of Dimethyl Cyclobutane-1,1-dicarboxylate

In a 50-mL round-bottomed flask, place KOH (8 g), ethanol (15 mL), and dimethyl cyclobutane-1,1-dicarboxylate (25 mmol). Add some boiling chips and set up for a reflux by adding a condenser and heating mantle. Heat to reflux for 1 hour. Swirl periodically.
Set up for a simple distillation. Remove most of the ethanol, being careful not to distill to dryness. Add water (10 mL), stir and heat if necessary to dissolve the residue, then cool the flask in an ice bath until the solution is below 15°C. Cautiously acidify with concentrated HCl (about 7 mL), then pour the contents into a separatory funnel and extract with three 25-mL portions of ether. Dry the combined ether extracts over CaCl2, filter, and evaporate to dryness on a rotary evaporator. Recrystallize the crude 1,1-cyclobutaneedicarboxylic acid from a minimum of ethyl acetate, then record the mass, report % yield for this step; get a melting range (lit. mp 156-158°C). Get a 1H NMR of this intermediate.

Place this product in a 50-mL round-bottomed flask set up for simple distillation. Heat strongly and observe evolution of CO2. Collect the resulting cyclobutanecarboxylic acid in the boiling range of 191-196°C. Record the mass; report % yield for this step. Take a 1H NMR, 13C NMR, and an IR to confirm its identity.

**Final Report**

Report the overall yield of the synthetic route as well as the yield for each individual step. Annotate all spectral data.
Discuss any possible by-products that may have been produced during this synthesis.
Include the complete mechanism of this whole transformation. Include all items in the Discussion section of your final report.