Multistep Synthesis of 5-isopropyl-1,3-cyclohexanedione

The purpose of this experiment was to synthesize 5-isopropyl-1,3-cyclohexanedione from commercially available compounds. To do this, acetone and isobutyraldehyde were combined by aldol addition. The product of this reaction then underwent dehydrative elimination to form an α,β-unsaturated ketone, which reacted by conjugate addition with diethyl malonate, immediately followed by a Dieckmann-type annulation to form a cyclic compound. The ester part of this compound was hydrolyzed, and then the compound underwent decarboxylation to give the desired product. This is summarized in the following reaction scheme:

Background:

The procedure for this synthesis was taken from “A Multistep Synthesis Featuring Classic Carbonyl Chemistry for the Advanced Organic Chemistry Laboratory” by David B. Duff, Tyler G. Abbe, and Brian C. Goess.

The synthesized compound, 5-isopropyl-1,3-cyclohexanedione, is available from Sigma-Aldrich for $150.50 for 5 grams. The starting materials of this synthesis – isobutyraldehyde, acetone, and diethyl malonate – are readily available, inexpensive compounds and the reactions involved in the synthesis are all standard carbonyl reactions that have been studied extensively. Therefore, this synthesis demonstrates the value of synthesizing compounds rather than buying them from a chemical supplier.

Synthesis:

The procedures for each of the steps of the lab were very similar. For steps 1, 2, 3, and 4 labeled above on the reaction scheme, the organic reactants were combined with the inorganic catalysts or reactants in a round-bottom flask and stirred or refluxed for a specified amount of time. For steps 1, 2, and 4, the intermediate was isolated after the mixture was done reacting. This required a detailed workup. First,
the reactive mixture was brought to a neutral pH and was extracted with diethyl ether, collecting the organic layer. The aqueous layer was extracted two more times with diethyl ether, and the three organic extracts were combined in a flask. This was then washed with saturated aqueous sodium chloride to remove water, and anhydrous sodium sulfate was added to remove the last traces of water. The sodium sulfate was filtered out by pouring through a Buchner funnel, and the solvent was removed by rotary evaporation. For Step 1 and 2, the product was so volatile that the flask was not heated during the rotary evaporation. The flask was then weighed, and a sample was submitted for NMR analysis. For step 3, the product was not isolated but instead brought to a neutral pH and left in solution until Step 4 was performed.

In Step 1, 1.25 mL acetone was combined with aqueous sodium hydroxide in a round bottom flask and stirred for 15 minutes. Then, 0.62 mL isobutyraldehyde dissolved in 1.25 mL acetone was added to the flask, and the mixture was stirred for 60 minutes. This effected an aldol addition between the two organic reactants. Afterwards, the workup described above was done, resulting in 0.683 g of a clear oil, a 77.1% yield.

In Step 2, the product from Step 1 was added to a flask containing p-toluenesulfonic acid monohydrate and anhydrous sodium sulfate, rinsing with benzene. The mixture was brought to reflux. In this and following reflux setups, the procedure called for the top of the condenser to be lightly stoppered, due to the high volatility of the desired product. The solution reacted at reflux for 90 minutes to complete the dehydration of the reactant to form an α,β-unsaturated ketone. Following the workup, 0.244 g of a light yellow oil was obtained, a 41.4% yield from the previous step.

In Step 3, 0.7 mL of diethyl malonate was added to a flask containing sodium ethoxide in absolute ethanol. This mixture was brought to reflux and allowed to react for 15 minutes. This allowed the sodium ethoxide to deprotonate the diethyl malonate. Then, the α,β-unsaturated ketone from the previous step, dissolved in absolute ethanol, was added to the reaction dropwise through the top of the condenser. This mixture then reacted for a further 30 minutes. This allowed the deprotonated diethyl malonate to add to the α,β-unsaturated ketone by conjugate addition. This set up the molecule perfectly for an intra-molecular Dieckmann-type annulation, which resulted in a cyclic compound. At the end of the 30 minutes, a sample was taken and compared to the α,β-unsaturated ketone from Step 2 by a TLC analysis. This showed that the most of the α,β-unsaturated ketone had reacted and given a product with a much lower Rf value. Also at that time, aqueous potassium hydroxide was added to the reaction, and the solution was allowed to react for an additional 75 minutes. The hydroxide anion replaced the ethoxide of the ester of the cyclic compound in a saponification reaction, giving a carboxylic acid, which reacted with the hydroxide to form the anion. After 75 minutes, hydrochloric acid was added to give the carboxylic acid again. The solution was then stored until Step 4.

In Step 4, the organic solvent from the solution from Step 3 was removed by rotary evaporation. Then, the flask was heated to reflux. When it was refluxing, sulfuric acid was added to the reaction dropwise through the top of the condenser. The procedure called for the reaction to continue for 40 minutes, or until no more small bubbles form. It was hard to tell whether the bubbles referred to were forming or not, so the solution was allowed to react for 50 minutes to be safe. This reaction effected the decarboxylation of the carbonyl group, resulting in the final product. After the usual workup, 0.270 of a brownish oil was obtained, an 80.6% yield from the Step 2 product and a 25.7% yield overall.
After Step 4, the synthesis was complete, but the product still contained impurities, as shown by the TLC test done on the crude product. To purify it, a column chromatography was performed. A column was set up with about 40 g of silica, wet-loaded into the column. The crude product was added, and the column was eluted with 4:1 ethyl acetate-hexanes. 28 8-mL fractions were collected, and each fraction was compared by TLC analysis to determine which to collect. The major impurity started to elute in fraction 5, and continued through fraction 9. The product, with an Rf value of about 0.3, started eluting in fraction 7, peaked in 8, 9 and 10, and continued eluting through fraction 21. Fraction 10 was the first to appear free of impurities, so fractions 10-21 were collected. The TLC plates can be seen in Fig. 1 in the Data section below. The solvent was removed by rotary evaporation, resulting in less than 0.001 grams of a clear oil. This was dissolved in deuterated chloroform and submitted for NMR analysis. The purification step gave <0.3% yield from the crude product and a <0.08% yield overall. All of the percent yield calculations are laid out in the Data section below.

Discussion:

The synthesis was in some ways a success, as the desired compound was obtained in each step of the synthesis, and the final product was in fact synthesized. This can be seen in the NMR spectra below, labeled by number in the top right corner. In NMR spectra 1, the spectrum matches very well to the expected compound, the only impurities being solvents. This shows that this step was very successful. In NMR spectrum 2, the spectrum matches fairly well with the expected compound, although the peaks at 6.07 and 6.80 ppm show a double splitting, indicating that the cis isomer as well as the trans isomer had been formed. In NMR spectrum 3, the crude product, most of the compound peaks are very weak, probably because the sample submitted to the NMR was too low in concentration, in an attempt to preserve as much product as possible for the next step. Despite this, the product peaks can be assigned to the expected product. In NMR spectrum 4, the purified product, the peaks are stronger and match the product expected, including the peak at 5.5 ppm: the peak for carbon 9 in the enol tautomer.

However, there were many shortcomings as well. Both the crude product and the purified product had significant impurities. This can be seen in NMR spectra 3 and 4. The peaks near 4 and just below 1 ppm represent major impurities, probably diethyl malonate. The explanation for this is probably as follows: enough diethyl malonate was added in Step 3 to react fully with the expected product from Step 2. However, there was significantly less product from step 2 than expected, and so a significant amount of diethyl malonate was left at the end of the reaction. Since diethyl malonate is organic, it would have been extracted from the aqueous layer as well. And since diethyl malonate is likely very similar in polarity to the product, since they both have two carbonyl groups and several methyl groups, they would have eluted at about the same time from the column, making them very difficult to separate. In addition, all of the percent yields of the reaction steps were moderate to low. This was expected though, because this synthesis was designed for 4-hour lab periods, and the reaction times had to be scaled down to fit into 3-hour lab periods. The yield for the purification step was very low. This was undoubtedly because the impurity eluted too close to the product. As can be seen in Fig. 1 below, most of the product (lower Rf) eluted in fractions 8 and 9, but since the impurity was still eluting, these fractions were not collected.

Overall this lab was moderately successful. The desired compound was synthesized, but with many impurities and at a low yield. In future experiments, the reactions should be allowed to proceed for the full time specified and a different solvent system to give a better separation should be investigated.
NMR spectra:

Intermediate 1

Intermediate 2

CDCl3
5-isopropyl-1,3-cyclohexanedione (crude) 3,4

5-isopropyl-1,3-cyclohexanedione (pure)

Diethyl malonate

H$_2$O
Data:

Yield Calculations:
Step 1: 0.683 g Int 1 / 130.19 g/mol = 5.25 mmol
    Percent Yield: 5.3 mmol/6.8 mmol = 77.1%
Step 2: 0.244 g Int 2 / 112.17 g/mol = 2.17 mmol
    Percent Yield: 2.17 mmol / 5.25 mmol = 41.4%
Step 4: 0.270 g Product / 154.21 g/mol = 1.75 mmol
    Percent Yield: 1.75 mmol / 2.17 mmol = 80.6%
Purification: <0.001 g Product / 154.21 g/mol = <0.0065 mmol
    Percent Yield: <0.0065 mmol / 2.17 mmol = <0.3%
Totals:
    Before Purification: 77.1% x 41.4% x 80.6% = 25.7%
    After Purification: = 20.0% x <0.3% = <0.08%

Reference: