SUPPLEMENTAL MATERIAL

Synthesis of Ibuprofen in the Introductory Organic Laboratory

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Contents:

Hazards (reproduced from the original article):

Care should be taken to avoid inhalation, eye contact, or ingestion of any of the chemicals used in this experiment. Eye protection, rubber gloves, and appropriate protective attire should be worn at all times. Sodium hydroxide, sodium borohydride, and hydrochloric acid are corrosive in cases of skin contact. Hydrochloric acid emits hydrogen chloride gas which presents a serious inhalation hazard. Chloroform-*d* and 1,2-dibromoethane are carcinogenic in cases of chronic exposure. Methanol, petroleum ether, diethyl ether, THF, and 4-isobutylacetophenone are flammable. THF tends to form peroxides more readily than diethyl ether and these peroxides are explosive. Responsibility for the handling of this solvent, including drying and dispensing as well as overseeing the fate of any leftover portion until it is either used or disposed of, should be given only to someone who has the necessary knowledge and experience.

Student procedure:

First Day.

1-(4-Isobutylphenyl)ethanol. Dissolve 1.00 mL of *p*-isobutylacetophenone in 3 mL of methanol in a separatory funnel. Weigh out 0.25 g $NaBH_4$ and then very quickly add it to the separatory funnel. Allow it to sit 10 minutes. While working in a fume hood, add 10 mL of 10% HCl and then extract the product from this mixture (CAUTION: considerable pressure buildup!) using 3 x 5 mL of petroleum ether. Remove the solvent by rotary evaporation from a 50-mL roundbottomed flask. Place one drop of the product into an NMR tube and add about 0.5 mL of $CDCl_3$. Record the ^1H NMR spectrum.

1-Chloro-1-(4-isobutylphenyl)ethane. While working in a fume hood, use a pipet to carefully transfer the 1-(4-isobutylphenyl)ethanol from the previous step into a separatory funnel and then use two 5-mL portions of 12 M HCl to help transfer any that remains in the flask and the pipet. Shake this mixture about 2 minutes. Extract the product from this mixture with 3 x 5 mL of petroleum ether, and then dry it with Na_2SO_4. Remove the solvent by rotary evaporation from a pre-weighed 50-mL round-bottomed flask, and then weigh to determine the yield. Record the ^1H NMR spectrum of one drop of this product in about 0.5 mL $CDCl_3$. Stopper the flask. Use a marker to write your name on it, and then hand it in on a cork ring.

Second Day.

1-(4-Isobutylphenyl)ethylmagnesium chloride. To an oven-dried 50-mL round-bottomed flask add 0.5 g of oven dried magnesium, 0.25 mL of 1-chloro-1-(4-isobutylphenyl)ethane, 10 mL of THF, and three drops of 1,2-dibromoethane. Attach a reflux condenser (with the bottom joint greased) and attach a drying tube to the top of this. Begin heating under reflux. When Grignard formation has begun, as evidenced by a large amount of foaming, continue heating under reflux for an additional 30 minutes. Cool with a water bath, disassemble the apparatus, and wipe the grease from the joints.

2-(4-isobutylphenyl)propanoic acid ("ibuprofen"). While working in a fume hood, bubble about a liter of CO_2 into the reaction mixture. Decant the solution into a separatory funnel. Use 5 mL of diethyl ether to rinse the flask and magnesium and then decant this ether into the separatory funnel. Add 8 mL of 10% HCl and mix. Remove the organic phase and set it aside. Extract the aqueous phase with 2 x 5 mL diethyl ether. Combine the three organic layers and extract with 2 x 4 mL 5% NaOH. Acidify this new 8-mL aqueous layer by adding 5 mL 10% HCl. Use litmus or pH paper to make sure the mixture is acidic. Extract ibuprofen from this aqueous layer with 2 x 5 mL diethyl ether and then dry with Na_2SO_4. Remove the solvent by rotary evaporation from a pre-weighed 25-mL round-bottomed flask, and then use a gentle stream of air through a pipet to remove any remaining traces of the solvent. Weigh the flask to determine the yield. Use about 0.6 mL of $CDCl_3$ to transfer the entire sample to an NMR tube, but if the solution is cloudy, use a plug of cotton in a pipet to filter it directly into the NMR tube. Record the ^1H NMR spectrum.

List of required chemicals and equipment:

Chemicals (amount per student):
p-isobutylacetophenone (1.00 mL but could be scaled down to 0.50 mL)
methanol (3 mL)
Sodium borohydride (0.25)
10% HCl (23 mL)
Petroleum ether 30-60 (30 mL)
Sodium sulfate anhydrous (to dry a 15-mL pet ether solution and a 10 mL ethyl ether solution)
Chloroform-*d* (1.6-2.0 mL)
12 M HCl (10 mL)
Magnesium turnings (oven dried, 0.5 g)
Calcium sulfate anhydrous (as needed for drying tube)
Product from 1st day (needed on 2nd day, 0.25 mL)
Tetrahydrofuran—very dry and peroxide free (10 mL)
1,2-dibromoethane (3 drops)
Carbon dioxide gas (in a gas cylinder with regulator, 1 liter)
Diethyl ether (25 mL)
5% NaOH (8 mL)
Litmus or pH paper (less than ½ inch)

Also needed by each student:
10-mL graduated cylinder
Separatory funnel (we use a 125-mL but a 30 or 60 might be better)
25-mL roundbottomed flask
50-mL roundbottomed flask with stopper
Cork ring suitable for a 50-mL roundbottomed flask
NMR tubes (2 per student on day 1 and 1 per student on day 2)
Reflux condenser and hoses
Drying tube with cotton
Small Erlenmeyer flasks (for working up reactions)
Pasteur pipet(s) (1 per student will do, but students prefer more)

Common equipment:
25-mL buret (for dispensing 1.00 mL of starting material to each of 24 students)
100-mL buret (for dispensing 3 mL of methanol to each of 24 students)
Rotary evaporator (at least 2, but preferably 4, for a class of 24 students)
Marker (for students to write their name on their 50-mL flask, one for the whole class)
NMR instrument (60 MHz permanent magnet Fourier transform works fine)
Oven (set a little above 100 °C)
10-mL buret (for dispensing 0.25 mL of the first-day product to each student)
Balloon/stopcock/Pasteur pipet assembly (see drawing in Note #10, ~8 for 24 students)
Pasteur pipet secured to a 3 inch hose attached to an air supply (~4 per 24 students)

Instructors' notes:

(1) *Starting material.* We always dispense the 1.00 mL of *p*-isobutylacetophenone (Alfa Aesar 97%) and the 3.00 mL of methanol each from a buret in a fume hood.

(2) *Glassware*. We use a 125-mL separtory funnel because that is what our drawers are stocked with. A 30-mL or 60-mL would probably be better. We also use glassware with 14/20 ground-glass joints.

(3) *NMR.* We use an Anasazi Eft-60 NMR with a Varian EM360L magnet. Each student runs his/her own samples. The instructor is seated next to the instrument so that on those rare occasions when the alcohol is contaminated with ketone or the alkyl chloride is contaminated with alcohol, the student's attention can be drawn to this, and the student can be instructed to subject the product to the reaction conditions again and then run another NMR. There is plenty of time.

(4) *Pasteur Pipets*: When we first began doing this experiment we were frustrated by the fact that so many student's NMR spectrum of their chloride showed contamination with small amounts of the alcohol. We soon realized that the problem was not that the reaction didn't go to completion. The problem was that so many students would not clean their Pasteur pipet before transferring the chloride to the NMR tube. Their previous use of the pipet was to transfer the alcohol. Although we have changed the procedure to have them now use the two 5-mL portions of 12 M HCl to help transfer any remaining traces of the alcohol from the flask *and the pipet*, it is still a good idea to remind them of the importance of using a *clean dry* pipet when transferring any sample to an NMR tube.

(5) *Hand in the chloride?!* At the end of the first day some students have a lot of product, some have only a little. Some have a dry product and some, in spite of using a drying agent, have a wet product. That's why we have the students hand in the chloride at the end of the first day; this allows us to level the playing field for the day-two procedure. We assign ½ point per 100 mg up to a maximum of 3 points and then subtract ½ pt if the sample is wet (cloudy). The instructor then transfers these samples to another container, adds some petroleum ether, dries this solution with a drying agent, decants or filters, and then removes the solvent by rotory evaporation. We prefer to use a 10 mL buret for dispensing this material to the students (0.25 mL each) on the second day. The instructor also rinses each student's 50-mL round-bottomed flask with acetone and then oven dries it prior to the second day. The students could get their flasks out of the oven, but we prefer to go into the lab about an hour before each lab section meets, remove the flasks from the oven, flush them with dry nitrogen (not essential, but a good idea), stopper them with the students' Teflon stoppers, and set them in the cork rings for the students to pick up. It has been our experience that students tend to drop and break hot glassware.

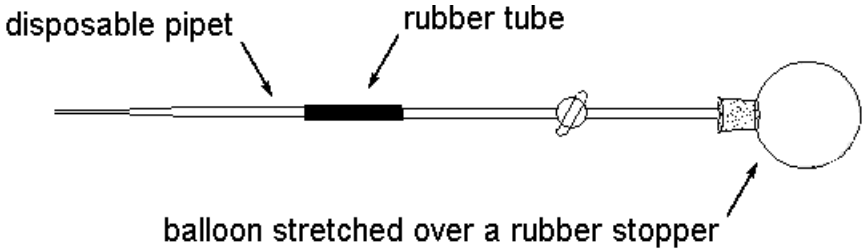
(6) *Magnesium*. In our own hands, "dry-stir magnesium" is convenient and effective for preparing benzylic Grignards in high yield. But for our sophomore organic chemistry lab course, we strongly prefer oven-dried magnesium turnings (Fisher Scientific).

(7) *THF*. Because it is a 2° benzylic Grignard that is being made, it is especially important that the THF be scrupulously dry and peroxide free. We set up a recycling solvent still in one of the fume hoods in the lab. This provides an opportunity for students to see how one of these works. We use benzophenone ketyl and we make sure that the contents of the still pot are purple rather than just blue. Conveniently, our student drawers are equipped with 50 mL roundbottom flasks that have a circle (for writing on with a pencil), and it takes almost exactly 10 mL of liquid to fill the flask up to the bottom of this circle. So, we run THF from the side arm of the still right into the flask up to the bottom of the circle and this is close enough to 10 mL of THF. Although we have not used commercially available pre-dried THF, it should work just as well and this would eliminate the need to have a recycling solvent still. Certainly, however, it would be advisable to dispense the commercially available pre-dried THF with a syringe, and the septum on the bottle should have a needle that is attached to a nitrogen or argon source so that as THF is removed, nitrogen or argon can replace it. Also, the bottle should be very securely clamped to a lattice rod. We have not used THF from a solvent purification system.

(8) *1,2-dibromoethane*. Three drops from a Pasteur pipet is plenty. One would expect that if too much 1,2-dibromethane is used the resulting bromide ion could convert the benzylic chloride to a bromide and this would lead to even more coupling. We tried using additional 1,2-dibromobutane, and indeed, the yield of ibuprofen was lower.

(9) *Foaming*. Realizing that foaming occurs when the Grignard has begun to form was a major breakthrough on this project! Of course right after we realized this we ran across some examples of it in the literature. Actually, once the foaming starts it takes a minute or two for it to go from the "is this what you call foaming?" stage to the "yup, it's definitely foaming now" stage. A 50-mL round-bottomed flask is large enough to contain the foaming without it going into the condenser, but it's a good idea to keep an eye on it, especially near the end of the reflux.

(10) *CO_2*. For 20 students we have several of the apparatus shown below. The teaching assistant runs CO_2 into the balloon through the rubber tube, attaches a disposable pipet, and hands it to the student. We use 12-inch round balloons that we buy at a local scientific supply company called "Dean's Party Mania."



(11) *Stream of air*. THF is notoriously difficult to remove completely by rotary evaporation. For this reason, it is important to have the students use a gentle stream of air through a pipet following rotary evaporation so that any small amounts of THF will be removed before the final weighing and before the final NMR is taken. It is safer to use a plastic pipet because some students turn on

the air full blast and the pipet goes flying off the end of the hose. The stream of air is used to gently push the product (an oil) around the bottom of the flask. Sometimes the ibuprofen solidifies while doing this (lit. m.p. 76° C).

(12) *^{13}C, DEPT and HETCOR*. Whereas ^{1}H and ^{13}C NMR are discussed in every sophomore organic lecture course, DEPT and HETCOR are not even included in some of the textbooks for those courses. The ibuprofen experiment should stand on its own without doing the ^{13}C, DEPT, or HETCOR, but for those who wish to have their students experience the use of DEPT or HETCOR or both, this is an excellent opportunity for the reason given in the article. Perhaps the best way to do this would be to discuss DEPT and HETCOR briefly in the lecture part of the course and then, in the prelab lecture, point out that, with ibuprofen, they should expect to notice some missing signals in the ^{13}C and DEPT but that the HETCOR should reveal the reason for this. The students could be asked to explain this reason in their lab report or, alternatively, one of the assigned questions might ask them about this. That's the easy part. The problem lies in physically running the three spectra with only 200 mg. The three ^{1}H NMR spectra (2 on day 1 and 1 on day 2) require very little time even if the student has as little as 30 mg, but this however is not true for these other three NMR techniques. The data acquisition time alone for the ^{13}C, DEPT, and HETCOR is about 3.5 minutes, 3.5 minutes, and 9 minutes respectively with a 200-mg sample (the combined samples of three students or so). So far, we have incorporated these three techniques with a permanent magnet instrument only during the summer when there is just one section with only about a dozen students. We divided the students into groups of three to combine their samples, rotovap them down, transfer to a clean NMR tube with fresh $CDCl_3$, and then run a ^{13}C, DEPT, and HETCOR (see a sample of each below). Some possible scenarios for acquiring one or more of these spectra with a class of 24 students are given below.

(A) Dovetail the ^{13}C, DEPT, and HETCOR spectra with another experiment the following week. This experiment would have to be one from which the students could take about a 30-minute break at any time to go to the instrument. Dividing 24 students into 6 groups of 4 each would leave plenty of time for each group during a 3-hour lab period.

(B) Give the students the ^{13}C and DEPT results and call their attention to the fact that there are some missing signals. Then have them, in maybe 4 groups of 6, combine samples to acquire just the HETCOR spectrum. In their lab report, the students can use the HETCOR data to explain the missing signals.

(C) Show and discuss the ^{13}C, DEPT, and HETCOR spectra during the lecture and then give extra credit to those students who wish to take the time to run them during another time such as during a "make-up day" at the end of the semester.

(D) Have the students submit their samples to an NMR instrument that is equipped with an autosampler. In some of our other experiments we have students submit their samples to a 400-MHz instrument for their ^{1}H and ^{13}C spectra which are then automatically e-mailed to them.

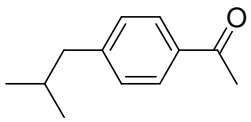
(E) Schedule some times on nonlab days for groups of 3 students to come in and run the ^{13}C, DEPT, and HETCOR spectra.

CAS Registry Numbers:

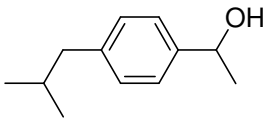
p-Isobutylbutylacetophenone	[38861-78-8]
Methanol	[67-56-1]
Sodium borohydride	[16940-66-2]
Hydrochloric acid	[7647-01-0]
Petroleum ether (30-60)	[68476-50-6]
Chloroform-*d*	[865-49-6]
1-(4-Isobutylphenyl)ethanol	[40150-92-3]
Sodium sulfate	[7757-82-6]
1-Chloro-1-(4-isobutylphenyl)ethane	[62049-65-4]
Tetrahydrofuran	[109-99-9]
Magnesium	[7439-95-4]
1,2-Dibromoethane	[106-93-4]
Carbon dioxide	[124-38-9]
Diethyl ether	[60-29-7]
Sodium hydroxide	[1310-73-2]
2-(4-Isobutylphenyl)propanoic acid (ibuprofen)	[15687-27-1]

^{1}H NMR spectra (Anasazi Eft-60, 1 scan)

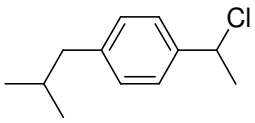
p-isobutylacetophenone
(commercial sample)



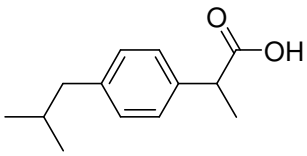
1-(4-isobutylphenyl)ethanol
(student preparation)



1-chloro-1-(4-isobutylphenyl)ethane
(student preparation)

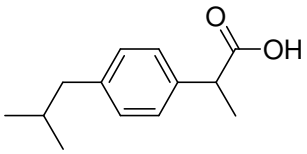


ibuprofen
(student preparation)

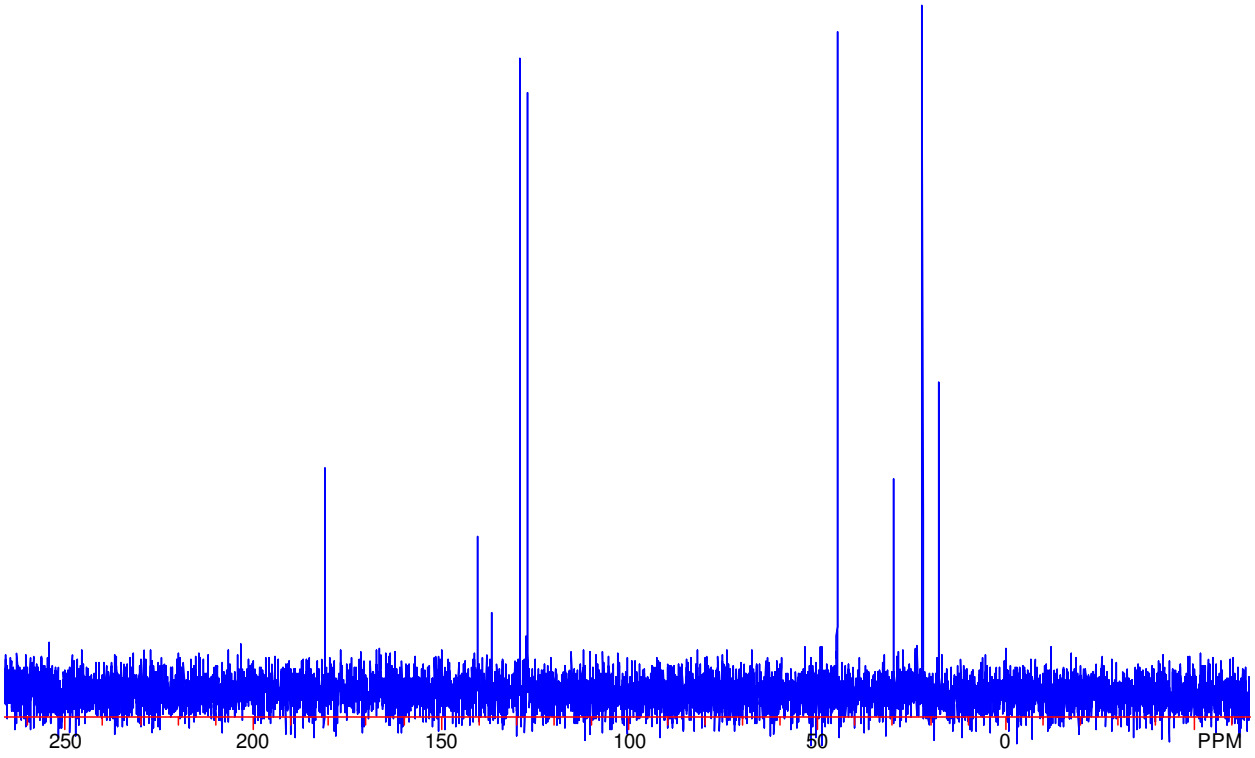


^{13}C NMR spectra (Anasazi Eft-60)

Sample size: about 200 mg (three combined student samples of 60-70 mg each)
Solvent: $CDCl_3$ (approximately 0.5 mL)
Data acquisition and processing: about 6½ minutes (but half that time works fine)

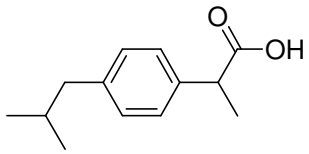


Notice that there appears to be only nine resonances rather than ten. Notice also that DEPT does not clear up this dilemma, but HETCOR does.



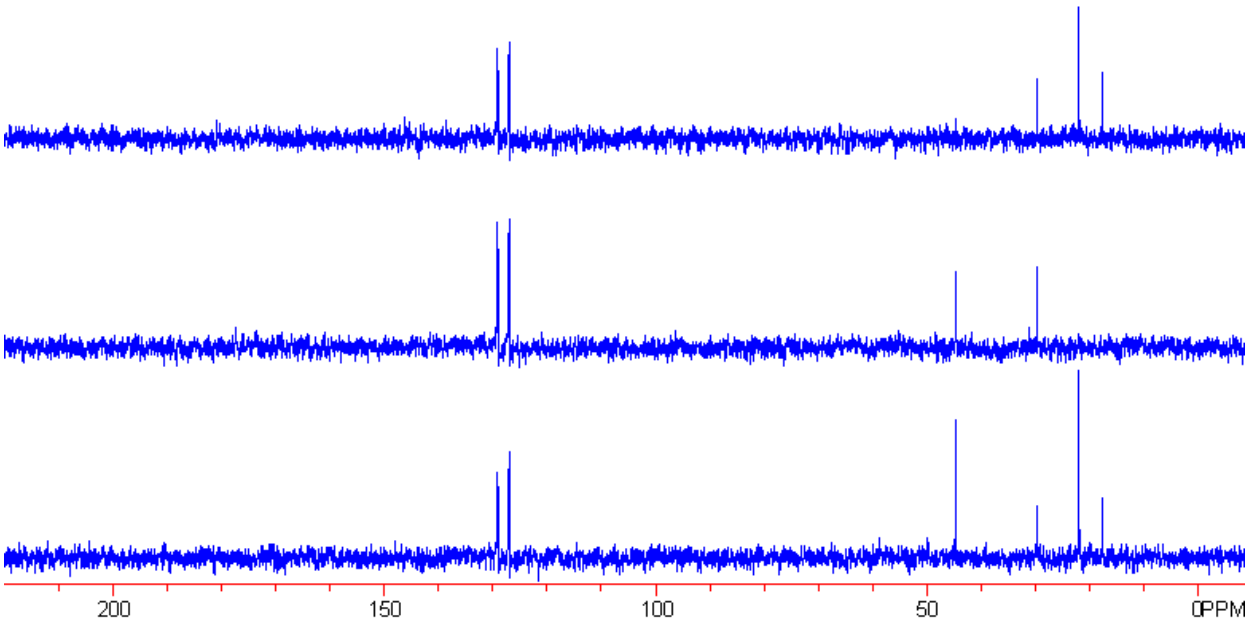
^{13}C DEPT (Anasazi Eft-60)

Sample size: about 200 mg (three combined student samples of 60-70 mg each)
Solvent: $CDCl_3$ (approximately 0.5 mL)
Data acquisition and processing: about 3.5 minutes



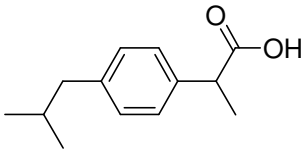
Top: DEPT-135 (CH_3 and CH up, CH_2 down)
Middle: DEPT-90 (CH up)
Bottom: DEPT-45 (CH_3, CH_2, and CH up)

Notice that the DEPT-135 spectrum appears to be missing two signals—one of them positive (up) and one of them negative (down). That would be only one missing signal if you count what appears to be a very small positive signal at 45 ppm; however, in some runs there is no signal at all at 45 ppm, and in some there is a very small negative signal at 45 ppm instead of the very small positive one seen here.

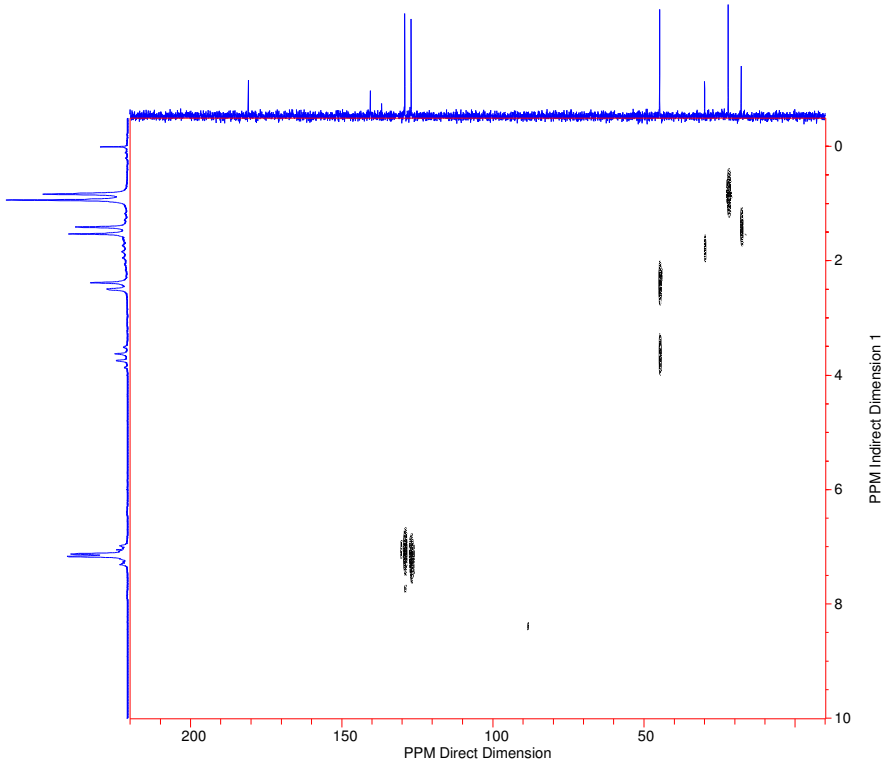


^{13}C HETCOR (Anasazi Eft-60)

Sample size: about 200 mg (three combined student samples of 60-70 mg each)
Solvent: $CDCl_3$ (approximately 0.5 mL)
Data acquisition and processing: less than 9 minutes

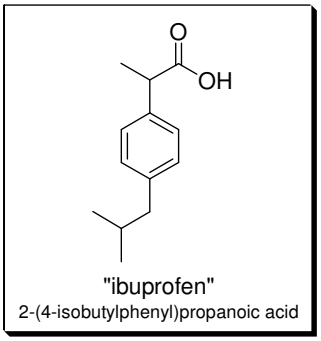


Notice that the two benzylic resonances (CH_2 and CH) are both at 45 ppm. This explains the apparent missing resonance in the ^{13}C and the DEPT-45 and the two missing resonances (one up and one down) in the DEPT-135.



Synthesis of Ibuprofen—Part 1

Background Information:



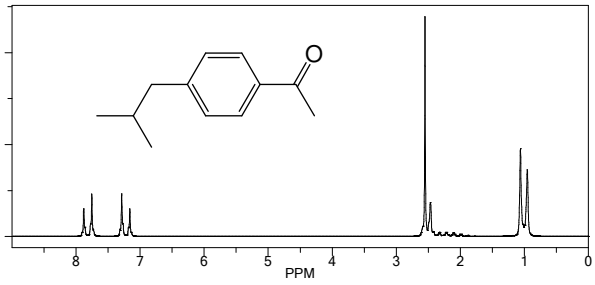
"ibuprofen"
2-(4-isobutylphenyl)propanoic acid

Ibuprofen was developed by the Boots Pure Chemical Company and then patented in 1961. It is a non-steroidal anti-inflammatory drug (NSAID) and is marketed under a wide variety of trade names including Advil® and Motrin®. Ibuprofen is one of several 2-aryl propanoic acids that are currently on the market. Others include ketoprofen, flurbiprofen, and naproxen.

The name "ibuprofen" originally came from the name isobutylpropanoicphenolic acid, but this nomenclature has not been used for many years and, in fact, virtually all chemists today are unfamiliar with it. Fortunately, however, the name is still a reasonably good match for the currently accepted name 2-(4-isobutylphenyl)propanoic acid.

Many methods for making ibuprofen have been published, but the one that is currently used for large scale production is one developed jointly by Boots and Hoechst Celanese. This method leads to very little chemical waste and, because of this, it earned the "Presidential Green Chemistry Challenge Award" in 1997. Currently, BASF uses this process to manufacture 7.7 million pounds of ibuprofen per year in Bishop, Texas. Unfortunately, this very efficient method requires the use of carbon monoxide at 500 psi. For this reason, we will use another route to make it.

Our route will employ only reactions that are traditionally taught in most two-semester introductory organic chemistry courses. We will begin with commercially available *p*-isobutylacetophenone which is also what the Hoechst process begins with. Today you will reduce this ketone to an alcohol and then convert the alcohol to an alkyl chloride. You will record the 60 MHz ^{1}H NMR spectrum of both of these products. The 60 MHz ^{1}H NMR spectrum of the starting material is shown here for comparison. Next week you will convert this alkyl chloride to ibuprofen by way of carboxylation of a Grignard reagent.



Procedure:

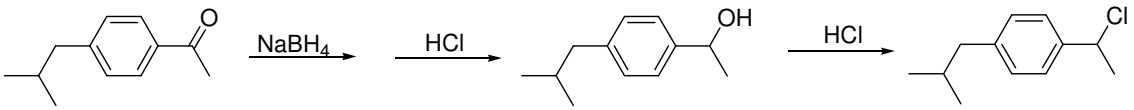
1-(4-Isobutylphenyl)ethanol. Dissolve 1.00 mL of *p*-isobutylacetophenone in 3 mL of methanol in a separatory funnel. Weigh out 0.25 g $NaBH_4$ and then very quickly add it to the separatory funnel. Allow it to sit 10 minutes. While working in a fume hood, add 10 mL of 10% HCl and then extract the product from this mixture (CAUTION: considerable pressure buildup!) using 3 x 5 mL of petroleum ether. Remove the solvent by rotary evaporation from a 50-mL round-bottomed flask. Place one drop of the product into an NMR tube and add about 0.5 mL of $CDCl_3$. Record the ^{1}H NMR spectrum.

1-Chloro-1-(4-isobutylphenyl)ethane. While working in a fume hood, use a pipet to carefully transfer the 1-(4-isobutylphenyl)ethanol from the previous step into a separatory funnel and then use two 5-mL portions of 12 M HCl to help transfer any that remains in the flask and the pipet. Shake this mixture about 2 minutes. Extract the product from this mixture with 3 x 5 mL petroleum ether, and then dry it with Na_2SO_4. Remove the solvent by rotary evaporation from a pre-weighed 50-mL round-bottomed flask, and then weigh to determine the yield. Record the ^{1}H NMR spectrum using one small drop of this product in about 0.5 mL of $CDCl_3$. Stopper the flask. Use a marker to write your name on it, and then hand it in on a cork ring.

Name_____

Synthesis of Ibuprofen—Part 1

Complete the following table. The only density needed is given. Show your calculations (except the calculation of formula weights) in the space below the table. Each calculation should be done in a neat and easy-to-follow manner. All units should be included and significant figures should be given close attention. T.Y means theoretical yield.



F.W.							
amount	1.00 mL	0.25 g	10 mL 10%		10 mL 12 M		
moles				T.Y.			T.Y.
density	0.952						

Mass of RB flask _____g Mass of RB flask plus product _____g

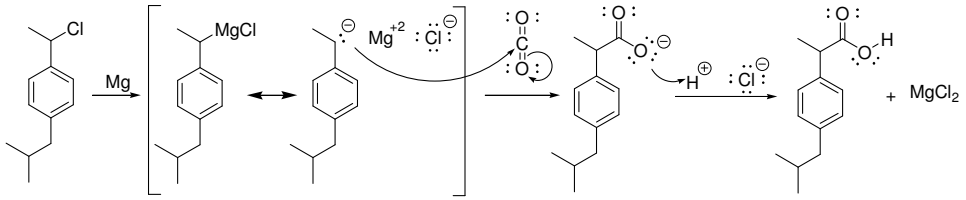
Mass of product _____g % Yield of product_____

Attach the ^{1}H NMR spectra of the alcohol and the alkyl chloride to the back of this sheet. On each one, draw the compound and indicate which protons are responsible for each signal. If there are any impurities, identify them also. On the back of this sheet, answer the questions that were assigned for this experiment.

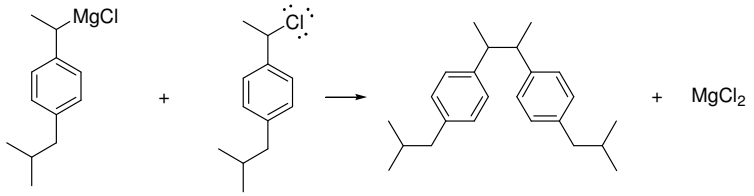
Synthesis of Ibuprofen—Part 2

Background Information:

Last time you made 1-chloro-1-(4-isobutylphenyl)ethane. Today you will convert this benzylic halide into a Grignard reagent and then into ibuprofen.



But there is a major problem with doing this. Benzylic and allylic halides are reactive enough to react easily with Grignard reagents. In other words, in today's experiment a molecule of 1-chloro-1-(4-isobutylphenyl)ethane can react with a molecule of the corresponding Grignard to give a dimer (from the ancient Greek *di* meaning "twice" and *meros* meaning "part;" i.e., a molecule with two identical halves).



By making a *chloride* rather than a *bromide* in the previous step we have already taken one step towards minimizing this unwanted "coupling" to give a dimer. To further minimize coupling we will use tetrahydrofuran (THF) as the solvent instead of diethyl ether. Any dimer that does form can be easily removed. This is possible because the sodium salt of ibuprofen is soluble in water but not in ether, whereas the dimer is soluble in ether but not in water.

Procedure:

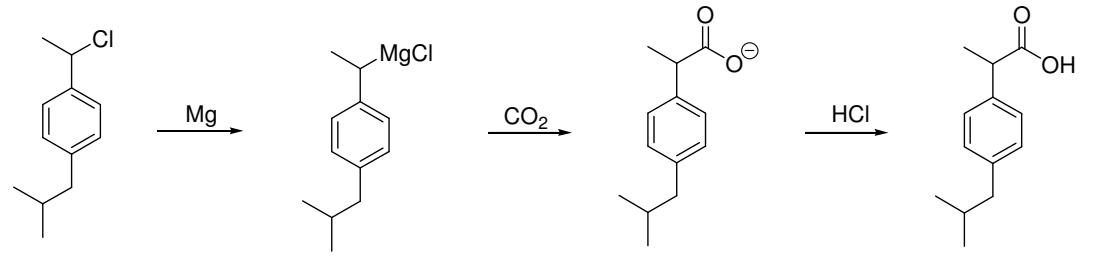
1-(4-Isobutylphenyl)ethylmagnesium chloride. To an oven-dried 50-mL round-bottomed flask add 0.5 g of oven dried magnesium, 0.25 mL of 1-chloro-1-(4-isobutylphenyl)ethane, 10 mL of THF, and three drops of 1,2-dibromoethane. Attach a reflux condenser (with the bottom joint greased) and attach a drying tube to the top of this. Begin heating under reflux. When Grignard formation has begun, as evidenced by a large amount of foaming, continue heating under reflux for an additional 30 minutes. Cool with a water bath, disassemble the apparatus, and wipe the grease from the joints.

2-(4-isobutylphenyl)propanoic acid ("ibuprofen"). While working in a fume hood, bubble about a liter of CO_2 into the reaction mixture. Decant the solution into a separatory funnel. Use 5 mL of diethyl ether to rinse the flask and magnesium and then decant this ether into the separatory funnel. Add 8 mL of 10% HCl and mix. Remove the organic phase and set it aside. Extract the aqueous phase with 2 x 5 mL diethyl ether. Combine the three organic layers and extract with 2 x 4 mL 5% NaOH. Acidify this new 8-mL aqueous layer by adding 5 mL 10% HCl. Use litmus or pH paper to make sure the mixture is acidic. Extract ibuprofen from this aqueous mixture with 2 x 5 mL diethyl ether and then dry with Na_2SO_4. Remove the solvent by rotary evaporation from a pre-weighed 25-mL round-bottomed flask, and then use a gentle stream of air through a pipet to remove any remaining traces of the solvent. Weigh the flask to determine the yield. Use about 0.6 mL of $CDCl_3$ to transfer the entire sample to an NMR tube, but if the solution is cloudy, use a plug of cotton in a pipet to filter it directly into the NMR tube. Record the ^1H NMR spectrum.

Name_____

Synthesis of Ibuprofen—Part 2

Complete the following table. The only density needed is given. Show your calculations (except the calculation of formula weights) in the space below the table. Each calculation should be done in a neat and easy-to-follow manner. All units should be included and significant figures should be given close attention. T.Y means theoretical yield.



F.W.									
amount	0.25 mL	0.50 g			excess			excess	g T.Y.
moles				T.Y.	excess		T.Y.	excess	T.Y.
density	0.96								

Mass of RB flask _____g Mass of RB flask plus product _____g

Mass of product _____g % Yield of product_____

Attach the ^{1}H NMR spectrum of ibuprofen to the back of this sheet. Draw the structural formula on the sheet and then indicate which protons are responsible for each signal. If there are any impurities, identify them also. On the back of this sheet, answer the questions that were assigned for this experiment.

Sample questions for students (day 1):

1. Although we started with a commercially available sample of *p*-isobutylacetophenone in this experiment, we could have started with isobutyl benzene and our first step would have been to convert this to *p*-isobutylacetophenone. Write an equation showing how this could be done and then write a mechanism for the reaction.

2. Actually, we could have started with benzene in our synthesis of ibuprofen; we could have converted this to isobutylbenzene and then proceeded as in question #1. Write equations showing the two step procedure for converting benzene to isobutylbenzene. (Hint: This will involve a Clemmensen Reduction.)

3. Converting an alcohol to an alkyl chloride in this experiment could be achieved by simply shaking in a separatory funnel at room temperature, whereas the last time you converted an alcohol to an alkyl halide, it took much harsher conditions. Why did this one go so fast at room temperature

4. Write a mechanism for each step that was carried out in the conversion of *p*-isobutylacetophenone to 1-(4-isobutylphenyl)-1-chloroethane. When deciding whether or not to show a carbocation in the step involving the alcohol with HCl, keep in mind that this carbocation (if it forms) would be secondary and benzylic.

Sample questions for students (day 2):

1. Suppose a student added water instead of carbon dioxide to the Grignard reagent in this experiment. Draw the product this student would obtain. Include the mechanism.

2. Suppose there was a pain reliever named iproprofen. (In this case, "ipro" stands for isopropyl just as "ibu" stands for isobutyl in ibuprofen.) Show how to make it starting with benzene.

3. Explain the method we used to get reasonably pure ibuprofen from a mixture of ibuprofen and 2,3-di(4-isobutylphenyl)butane (the "dimer").

4. (2 pts) Look up ibuprofen in Wikipedia and study the "stereochemistry" section. Then, *in your own words*, summarize what it says. In particular, address the feasibility of marketing just one enantiomer of ibuprofen.

5. Another pain reliever in the same family as ibuprofen is "naproxen sodium." Draw this compound and then based on this, draw what "ibuprofen sodium" would be.

6. Draw a cut-away view of a recycling solvent still. Explain how it works.