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Synthesis of Ibuprofen in the Introductory Organic Laboratory

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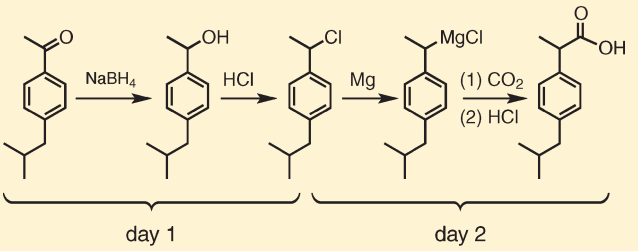
Supporting Information

ABSTRACT: A method for the synthesis of ibuprofen in introductory organic chemistry laboratory courses is reported. This experiment requires two 3-h lab sessions. All of the reactions and techniques are a standard part of any introductory organic chemistry course. In the first lab session, students reduce *p*-isobutylacetophenone to an alcohol and then convert this alcohol to the corresponding chloride. In the second session, students convert this chloride to a Grignard reagent, which is then carboxylated and protonated to give ibuprofen. Although the final yield is modest, this procedure offers both practicability and reliability. Permanent-magnet 60 MHz ^{1}H NMR spectra of the final product and the two intermediates are clean and are easily interpreted by the students. Because, as previously reported, the benzylic methylene and the benzylic methine of ibuprofen have virtually identical ^{13}C NMR chemical shifts and cancel or nearly cancel each other in the DEPT spectrum, this synthesis provides a fitting opportunity for the introduction of HETCOR even with a permanent-magnet Fourier transform instrument.



KEYWORDS: Second-Year Undergraduate, Laboratory Instruction, Organic Chemistry, Hands-On Learning/Manipulatives, Carboxylic Acids, Drugs/Pharmaceuticals, Grignard Reagents, NMR Spectroscopy, Synthesis

The preparation of aspirin has been used in introductory organic laboratory courses for over 80 years.[1] Although it illustrates an important organic reaction—nucleophilic acyl substitution—it is presumably the attraction of making an important pharmaceutical compound that has made the synthesis of aspirin a core experience in the teaching of organic chemistry. Not surprisingly then, student procedures for preparing some other pharmaceutical compounds, including acetaminophen, have appeared.[2] Although there have been articles concerning the separation and analysis of ibuprofen (Advil, Motrin, and Nuprin) for introductory organic laboratory courses,[3] there have been no reports of a student achievable ibuprofen synthesis. We report here a procedure whereby students can, in two 3-h lab periods, make this widely used analgesic, antipyretic, and nonsteroidal anti-inflammatory drug (NSAID) from *p*-isobutylacetophenone (Scheme 1).

EXPERIMENT AND RESULTS

On the first day, students use 0.25 g of sodium borohydride to reduce 1.00 mL of *p*-isobutylacetophenone in methanol. After characterization of the resulting alcohol by ^{1}H NMR, they convert it to the corresponding chloride by shaking with concentrated hydrochloric acid in a separatory funnel, and this, too, is characterized by ^{1}H NMR. The chloride samples are handed in to the instructor who combines and dries the material prior to the next meeting.

On the second day, a 0.25 mL sample of the alkyl chloride that was made on the first day is dispensed to each student. The students convert this to a Grignard reagent by heating under reflux with tetrahydrofuran (THF), oven-dried magnesium turnings, and a small amount of 1,2-dibromoethane. After cooling, approximately 1 L of carbon dioxide gas is bubbled into the reaction mixture by way of a balloon equipped with a stopcock and a disposable pipet. Aqueous workup, including extraction of the product into aqueous sodium hydroxide followed by protonation, another extraction, and then rotary evaporation, gives a clean sample of ibuprofen, which is then characterized by ^{1}H NMR.

The reason for the extraction with sodium hydroxide is that the ibuprofen must be separated, as the sodium salt, from a dimer and any other water-insoluble impurities produced during Grignard formation (Scheme 2). Fortunately, this rather lengthy extraction procedure leads to a reasonably pure product and also provides a valuable learning experience. Unfortunately, it causes students to get yields of only 10−40% on the second day. However, we consider this to be a small consequence in exchange for the practicability and reliability of the procedure. In fact, if a student is given good THF (from a purple-colored benzophenone ketyl distillation pot) and unless a student accidentally discards the product (i.e., "throws out the wrong layer") during the workup, he or she will almost certainly obtain a sample of ibuprofen that gives a very clean ^{1}H NMR spectrum even with just one scan on a 60 MHz permanent-magnet Fourier transform (FT) instrument.

Even though we do not ask the students to recover the NMR sample of either the alcohol or the chloride during the first day, the average size of the chloride sample handed in at the end of the first lab period is about 0.75 g. Therefore, the instructor could

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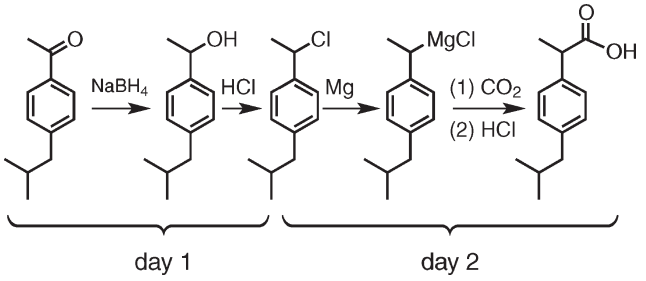
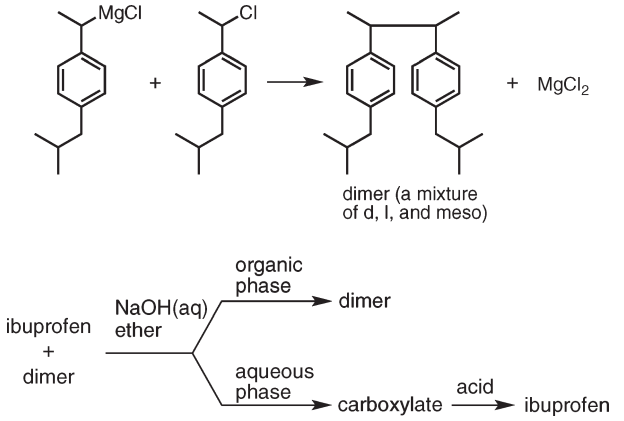
Scheme 1. A Sequence To Synthesize Ibuprofen from *p*-Isobutylacetophenone



Scheme 2. Formation (top) and Separation (bottom) of the Dimer Formed while Making the Grignard Reagent



either scale down the first-day procedure or scale up the second-day procedure.

During the summer of 2010, we had an opportunity to put the difficult part of this experiment to the ultimate test. That is, we had a group of 16 high school students carry out the second day procedure. Their previous experience with a separatory funnel was limited to the extraction of caffeine from coffee. All 16 students successfully made at least some ibuprofen as indicated by the formation of a cloudy mixture when they acidified the aqueous NaOH extract. However, the extensive workup proved to be too much for this inexperienced group; only about half of them were able to successfully isolate enough ibuprofen to give a suitable ^{1}H NMR spectrum with a 60 MHz permanent-magnet FT instrument. We do not recommend the experiment for high school students.

HAZARDS

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.

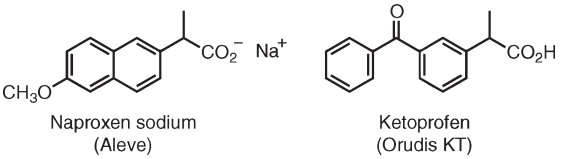
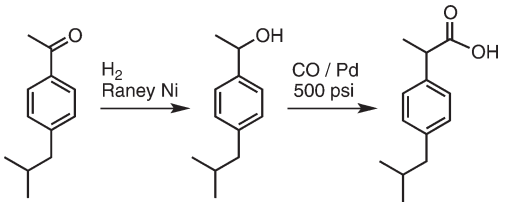


Figure 1. Two well-known α-arylpropanoic acid NSAIDs other than ibuprofen.

Scheme 3. The BHC Procedure for Making Ibuprofen on an Industrial Scale



DISCUSSION

Ibuprofen is one of the α-arylpropanoic acid NSAIDs. Two of the others that are sold in the United States include naproxen (sold as the sodium salt) and ketoprofen (Figure 1). The synthesis and use of ibuprofen were both patented by Boots Pure Drug Company in the 1960s.[4] The synthesis involved several steps and led to the production of a considerable quantity of chemical waste. A more efficient procedure (Scheme 3) was later developed by BHC, which was a joint venture of Boots and Hoechst Celanese.[5] This "BHC" procedure is now owned by BASF and is a model of "atom economy".[6,7] It was awarded the 1997 Presidential Green Chemistry Challenge Award given by the U.S. Environmental Protection Agency. This very "green" procedure is used at a BASF plant in Bishop, Texas, where about 7.7 million pounds of ibuprofen are produced each year. This represents about 20−25% of the world production of this important pharmaceutical.[7]

Unfortunately, the BHC procedure (Scheme 3) is not suitable for use in the introductory organic lab. Many other methods for making ibuprofen have been reported,[8] but after carefully examining and even trying some of them in our own lab, we concluded that none of them are suitable. To employ techniques and reactions that are standard in most introductory organic chemistry lab courses, we chose to pursue the Grignard route described in Scheme 1.

Benzylic Grignard reagents, especially if they are secondary, are difficult to prepare; that is, they are reluctant to initiate, and they tend to undergo Wurtz-type coupling.[9,10] There are several ways to increase the rate of Grignard formation and thereby minimize or even eliminate coupling. These include the use of magnesium powder,[11] magnesium anthracene,[12] and mechanically activated ("dry-stir") magnesium.[9] A much older method slows down the rate of coupling by using a "cyclic reactor" to

maintain a low concentration of the halide.[13] It is also possible to decrease the degree of coupling by lowering the temperature[9] and by using a chloride rather than a bromide. Additionally, experiments in our own lab with a variety of secondary benzylic halides have shown that better Grignard/dimer ratios are obtained when the solvent is THF rather than diethyl ether.[14] Sonication[15] has been used to initiate the formation of Grignard reagents, but apparently offers little or no further advantage, at least not with benzylic halides.[9,10]

We tried mechanically activated ("dry-stir") magnesium and found it to be unsuitable for a large group of students in an introductory course. Likewise, we felt that neither highly reactive magnesium powder nor magnesium anthracene would be appropriate.[9,10]

Our remaining option was the reaction of a secondary halide (Scheme 1) with unactivated magnesium turnings; a reaction that should give a considerable amount of coupling product, is too slow for a 3-h lab period, and is difficult to initiate at room temperature. Fortunately, however, by using the chloride rather than the bromide, using refluxing THF, and using a very small amount of 1,2-dibromoethane, which is a standard Grignard initiator, students can conveniently, reproducibly, and in a timely manner produce enough Grignard to give acceptable yields of ibuprofen.

There are some modifications that could be employed to either shorten or lengthen this experiment. The two reactions carried out on the first day can be done quickly enough that it would not be unreasonable for the instructor to make a large batch of the chloride to dispense to the students thereby making this a one-day experiment. Alternatively, it should be possible to shorten the procedure by going from the starting ketone directly to the chloride without isolating the alcohol. To lengthen the experiment, it should be possible to have the students make the starting material by carrying out a Friedel−Crafts acylation of *p*-isobutylbenzene. Students could also be asked to acquire the DEPT and HETCOR spectra of their ibuprofen.

It has been previously pointed out[16] that ibuprofen is especially well suited for use in introducing students to HETCOR even with a 60 MHz permanent-magnet FT instrument. The reason for this is that the two benzylic carbons have virtually identical ^{13}C chemical shifts so the students observe only 9 resonances rather than 10. In the DEPT-135 spectrum, the benzylic methylene (expected to be down) and the benzylic methine (expected to be up) cancel or nearly cancel each other. HETCOR solves the problem by clearly showing that the signal at 45 ppm is really two resonances. Because students obtain about 25−100 mg of ibuprofen in the procedure reported here, it takes the combined samples of at least two students—about 200 mg in 0.5 mL of $CDCl_3$ solution is needed—and about 8.5 min of data acquisition to obtain a suitable HETCOR with a 60 MHz permanent magnet instrument.

CONCLUSION

Formation of a secondary benzylic Grignard reagent followed by carboxylation is a reliable method for the preparation of ibuprofen in introductory organic laboratory courses. A considerable degree of dimerization occurs, and this leads to a modest but dependable yield of ibuprofen. Dimerization could be minimized by using specially activated magnesium or carrying out the reaction at a lower temperature, but these types of magnesium would be impractical for a traditional laboratory course and lower temperatures would require excessively long reaction times. The dimer and ibuprofen can be separated from each other completely and easily by extraction of the ibuprofen into aqueous sodium hydroxide followed by protonation. This separation provides a reasonably pure sample of ibuprofen as well as an additional learning experience for the students. Because of two overlapping signals in the ^{13}C NMR of ibuprofen and because these two signals cancel, or nearly cancel, each other in the DEPT spectrum, the synthesis of ibuprofen provides a fitting opportunity for incorporating HETCOR into the introductory organic laboratory even with a permanent magnet FT instrument.

ASSOCIATED CONTENT

Supporting Information

Student procedure; instructor notes; ^1H NMR spectra of the starting material, the two isolable intermediates, and the final product; ^{13}C NMR, DEPT, and HETCOR of the final product; handouts used while testing this experiment; sample questions for the students. This material is available via the Internet at http://pubs.acs.org.

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