Improving the Grignard Reaction for the Synthesis of Ibuprofen by creating an Organozinc Reagent

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Experiment 4

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Introduction

Ibuprofen is a common over-the-counter, non-steroidal, and anti-inflammatory drug. Its structure is shown in Figure 1. It has been shown to have many uses, most notably, in the medical field. One particular common use that it has been shown to have is that it can relieve pain from arthritis, fever, and headaches.\(^1\) It can also prevent blood clots.\(^1\) A potential use of ibuprofen in the medical field as a treatment for tuberculosis.\(^2\) This could potentially be safer than other current methods of treatment. A third use of ibuprofen is as an anti-blushing drug when applied directly to the skin in a cream.\(^3\)

The purpose of this experiment was to synthesize ibuprofen. There are multiple methods used to synthesize ibuprofen. The main method employed in this experiment to synthesize ibuprofen was the Grignard reaction. A Grignard reaction uses a metal to create a nucleophillic carbon atom in an organometallic compound that could then react with an electrophilic carbon to create a new carbon-carbon bond.\(^4\) Grignard reactions have been very common among several syntheses of common products such as naproxen and tramadol.\(^5\)

While the Grignard reaction may be useful, it does have some disadvantages. On a large scale, the reaction can be hard to control due to its strong exothermic tendency both during the synthesis and the actual reaction.\(^5\) Also, the solvents of the reaction, EtO\(_2\) and THF, have relatively low boiling points and could form a peroxide that could then ruin the Grignard reaction.\(^5\) One problem that needed to be addressed for this experiment was Wurtz coupling which is the formation of the symmetrical by-product of the Grignard reaction.\(^5\) Wurtz coupling is frequently a competitor with a Grignard reaction and is especially prevalent in alkyl halides, one of which was used in this experiment.\(^6\)

\(^1\) Ahmad, Khan I., Anjum Kahkashan, Koya P. Ajmal, and Qadeer Atiytul. "Cloud Point, Fluorimetric and 1H NMR Studies of..."
\(^3\) Drummond, Peter D., Kate Minosora, Greeta Little, and Wendy Key. "Topical Ibuprofen Inhibits Blushing during Embarrassment and Facial Flushing during Aerobic Exercise in People with a Fear of Blushing." European Neuropsychopharmacology 23.12 (2013): 1747-753.
The original synthesis is shown in figure 2. It was hypothesized that Wurtz coupling would cause a need to change the Grignard step for the formation of ibuprofen. This is due to the Grignard reaction with an alkyl halide. The proposed modification of the synthesis is shown in figure 3. The proposition engages zinc chloride and lithium chloride to form an organozinc compound that will act as a stronger nucleophile to make the attached carbon more electrophilic. It has been hypothesized that this change would improve the percent yield of ibuprofen and decrease the Wurtz coupling. It was found that this change in the Grignard reaction could increase the yield of ibuprofen in the overall synthesis as well as reduce the Wurtz coupling that occurs in the unmodified Grignard reaction in the synthesis of ibuprofen.

Figure 2: The original synthesis of ibuprofen: p-isobutylacetophenone (2) reduces to 1-(4-isobutylphenyl)ethanol (3) by reaction with NaBH₄. The 1-(4-isobutylphenyl)ethanol (3) is then reacted with HCl to form 1-chloro-1-(4-isobutylphenyl)ethane (4). The 1-chloro-1-(4-isobutylphenyl)ethane (4) can then undergo the Grignard reaction in the presence of carbon dioxide and hydrogen peroxide to form ibuprofen (1).

Experimental: General

All solid reagents used in this experiment were anhydrous. All liquid reagents were prepared by the organic chemistry stock room in the needed concentrations. The tetrahydrafuran (THF) was anhydrous and stored in argon gas. For the modified reaction, the solution containing LiCl and ZnCl\textsubscript{2} dissolved in THF was prepared by Curtis Siezert to be added to the reaction as 1 mL of solution/mmol of substrate. All reactions were carried out under atmospheric pressure and 20 °C unless otherwise stated. Formation of 3, and 4 was carried out twice, once for the original synthesis using the Grignard reaction, and the second for the modified procedure.

Figure 3: The modified Grignard reaction; 1-chloro-1-(4-isobutylphenyl)ethane (4) is reacted with a solution of Magnesium, LiCl, ZnCl\textsubscript{2} dissolved in THF at 25 °C for 2 hours to create the 1-(4'-Isobutyl-phenyl)ethylzinc chloride (5). This is then reacted with CO\textsubscript{2} for 48 hours to yield ibuprofen (1).
Experimental: Synthesis of 4

Methanol (3 mL; 118 mmol) was used to dissolve 2 (1.00 mL; 5.34 mmol) in a 25 mL round bottom flask with a small stir bar. Then, NaBH₄ (0.258 g; 12.2 mmol) was quickly added to the flask and allowed to stir for 10 minutes. Next, 10% HCl (10 mL; 287 mmol) was added to the solution while working under a fume hood. This reaction was then transferred to a 125 mL separatory funnel where the product was removed using 3 x 5 mL of hexanes. The solvent was removed by rotary evaporation to leave a transparent and colorless oil as shown in figure 4. This product, 3, was analyzed by IR spectrometry in the first version of the synthesis.

To synthesize 4, 12 M HCl (5 mL; 165 mmol) was added to all of 3, the product from the previous step. In this process, extreme bubbling occurred due to the H₂ gas being produced. This solution is shown in figure 5. This solution was then transferred to a 125 mL separatory funnel. The round bottom flask was rinsed with additional 12 M HCl (5 mL; 165 mmol) to retrieve any remaining product left behind. The mixture was shook for 2 minutes and the product was mixed with hexanes 3 x 5 mL to remove the product, 4, from the mixture. This solution was dried with Na₂SO₄ and decanted into a 50 mL round bottom flask. The solvent was then removed by rotary evaporation and the product, 4 (0.084 g; 0.4 mmol [modified and unmodified]), was analyzed by ¹H NMR.
Experimental: Synthesis of Grignard and Ibuprofen Without Modification

Magnesium turnings (0.500 g; 20.6 mmol) were ground with a mortar and pestle. These were placed in an oven dried 50 mL round bottom flask and all of 4 were transferred using 10 mL THF. Three drops of 1,2-dibromoethane were added to the reaction flask. A reflux condenser with a drying tube was attached and the solution was heated and refluxed. Once foaming occurred, the solution remained refluxed for an additional 30 minutes. When finished, the solution was placed in a water bath to cool.

To perform the Grignard reaction, CO₂ (1 L; 44.6 mmol) was bubbled into the reaction mixture in the set-up shown in figure 6. The apparatus is a balloon containing CO₂ attached to a syringe with a rubber stopper and short polyethylene tubing on a 50 mL round bottom flask. Once all of the CO₂ was bubbled through the solution, it was decanted into a 125 mL separatory funnel.

Figure 6: The apparatus used to bubble carbon dioxide into the solution to create 1.
Experimental: Synthesis of Organozinc Reagent and Modified Ibuprofen Synthesis

In a 3-neck 100 mL round bottom flask, magnesium turnings (0.126 g; 5.2 mmol) that had been ground with a mortar and pestle were added. The flask was then flushed with argon gas. The ZnCl$_2$/LiCl (1.1/1.5 M in THF) (2.0 mL; 2.23/3.08 mmol) solution was added by syringe dropwise. A water-cooling bath was used to keep the solution cool during the reaction. The substrate, 4 (0.404 g; 2.05 mmol) was then added to the solution by syringe and was stirred at room temperature. The reaction was stirred for 1 hour as opposed to the desired 2-hour reaction time due to time constraints. Following this reaction, a 1L balloon equipped with CO$_2$ gas was attached with needle and allowed to flow through the solution with a needle attached for gaseous outlet. Once the balloon deflated, the needle was removed and a second balloon was equipped to the reaction flask and continued to stir as shown in figure 7 for 96 hours. The solution was then decanted into a 125 mL separatory funnel.

Figure 7: Set-up for the reaction of CO$_2$ gas with the organozinc substrate.
Experimental: Extracting Ibuprofen

Diethyl ether (5 mL; 47.6 mmol) was used to rinse the round bottom flask that had been used to carry out the Grignard reaction for each respective procedure and decanted into the separatory funnel. 10% HCl (8 mL; 230 mmol) was added to the separatory funnel and mixed. The aqueous phase was rinsed using diethyl ether (2 x 5 mL). The organic layers were combined and mixed with 5% NaOH (2 x 4mL). An additional aliquot of 10% HCl (5 mL; 144 mmol) was added to the aqueous layer and confirmed to be acidic with litmus paper. Ibuprofen was extracted using diethyl ether (2 x 5 mL). This was then dried with Na$_2$SO$_4$, decanted, and the solvent was removed by rotary evaporation. Finally, a pipet was used to remove any remaining solvent by blowing a gentle stream of air. The product, ibuprofen (0.020 g; 0.09 mmol, from the first synthesis was analyzed by $^1$H NMR. The modified synthesis product ((0.064 g; 0.3 mmol) was analyzed the same way. The desired product is shown in figure 8. The expected side product for the original reaction is shown in figure 9. This product would have dissolved in the aqueous layer. The product found in the

Results and Discussion

Figure 9: The mechanism of Wurtz coupling. An electron from magnesium attacks the chlorine on 1-chloro-1-(4-isobutylphenyl)ethane to create a radical. The lone electron on the carbon attacks another carbon with a lone electron to produce 4,4'-(butane-2,3-diyldibis(isobutylbenzene) (7)
Unfortunately, the servers for connecting to the $^1$H NMR data was down and the actual products were not fully analyzed. Therefore it is assumed that all product measured from the organic layer of the experiment was ibuprofen and all product measured from the aqueous layer is assumed to be 7. The reaction of a successful Grignard reaction is shown in figure 10. The reaction mechanism of Wurtz coupling seen in the synthesis of ibuprofen without the modification is shown in figure 9. The resulting side product of the unmodified synthesis was 7. The expected $^1$H NMR for ibuprofen is shown in figure 10. The expected $^1$H NMR spectrum for 7 is shown in figure 11.

The percent yield of the synthesis of ibuprofen with the modification (75.0%) was much higher than the percent yield of the synthesis of the ibuprofen without the modification (22.5 %). This is most likely due to Wurtz coupling that could be observed from the reaction without the modification. The proposed change did work by improving the percent yield of the overall reaction by 52.5 percent. This appears to be a very drastic change in the amount of ibuprofen synthesized. A suggested reason for why the modified reaction worked as well as it did is that the zinc in the organozinc compound served to be more nucleophillic which would then allow it’s corresponding...
carbon to be more electrophilic. As a result of this, the carbon on the Grignard would be more likely to react with the carbon on carbon dioxide as opposed to the carbon on the alkyl halide of other substrates.

To improve the proposed mechanism, it would be useful to let the Grignard be formed for a full two hours so that it would be assured to go to completion. In addition to this, other methods could have been employed and compared to see which method would be most beneficial to improve the overall reaction scheme. In addition to the Grignard reaction, other forms of synthesis could be employed to form ibuprofen such as those used on a large scale. A Grignard reaction is extremely exothermic, so other forms of reactions that are less exothermic would also be helpful.


Conclusion

Based on the experiment the proposed mechanism was useful in improving the Grignard reaction that was originally performed. The modified reaction created an organozinc compound that created a more electrophilic carbon that could then be reacted to synthesize ibuprofen, the desired product. Other methods are used by manufacturers that both yield more and are less tedious.
Original Proposal:

The expected product of the Grignard reaction was not observed for the experiment performed. The proposed mechanism for the reaction obtained is shown in Figure 1. The radical produced due to the radical on the reactant to react with itself.

Figure 1: proposed synthesis of the product obtained.
The proposed new reaction is shown in Figure 2. This is proposed because it makes an organozinc compound that is more likely to react to form ibuprofen. This is because the group is slightly larger and more nucleophilic to create ibuprofen.¹⁰

![Reaction diagram]

Figure 2: Proposed new synthesis of ibuprofen by refining the Grignard Reaction.

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