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Green Chemistry: Three Step Synthesis of Acetaminophen

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Title and Authors:

A Three-Step Synthesis of Acetaminophen

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Abstract (with new/different green chemistry):

Acetaminophen was synthesized from phenol in three steps. In this synthetic route the solvent from step two was kept to help maximize atom economy. The first step was an electrophilic aromatic substitution on phenol with nitric acid to create p-nitrophenol. Next, p-nitrophenol was used to synthesize p-aminophenol through hydrogenation using an iron catalyst. Lastly, acetaminophen was synthesized by the acylation of the aminophenol. This new method including the green step minimized chemical waste.

Scheme: (on chem draw)

Introduction:

In this investigation, the synthesis of acetaminophen was attempted using a three step experiment. Acetaminophen is a well known drug that is used to relieve headaches, fever, and aches and pains in joints and muscles. It is also a main ingredient in many cold and flu medications and prescriptions. It is considered a safe and effective drug when used in the recommended dosages.

The acetaminophen compound counteracts the enzyme cyclooxygenase which synthesizes prostaglandins. Prostaglandins serve many different protective functions within the human body, such as producing pain and raising body temperature. By hindering this synthesis of prostaglandins, the body's response to elevating temperature and increasing pain can then be reduced. Acetaminophen is different from other pain-controlling drugs, such as aspirin or ibuprofen, because it has no anti-inflammatory properties. It is unlike other non-steroidal anti-inflammatory drugs (NSAIDs) because it seldom irritates the lining of the stomach, and does not affect blood clotting, or the kidneys.

Acetaminophen can be synthesized via traditional one or two-step syntheses but three step syntheses are not as common. To begin the synthesis, an electrophilic aromatic substitution on phenol with nitric acid was completed to create p-nitrophenol. P-Nitrophenol was then hydrogenated using an iron catalyst to produce p-aminophenol. Benzene, the solvent in this reaction, is typically discarded, although in this synthesis it was kept as a recyclable solvent, thus maximizing our atom economy. Benzene was separated and characterized by Nuclear Magnetic Resonance (NMR) and Infrared Spectroscopy (IR) to be pure and reusable. P-aminophenol was selectively acetylated using acetic anhydride and the reaction was completed within 10 minutes compared to other protocol using chloroform as the acylated reagent which would have taken 15 hours.

Experimental Week 1:

Acetonitrile was added to phenol (0.401g, 4.27mmol) until it completely dissolved. Nitric acid (0.269g, 4.27mmol) was then added to the solution. A solution of cetrimonium bromide (CTAB) (0.389g, 1.067mmol) was added and the reaction mixture was stirred at room temperature for two hours. A color change and thin layer chromatography (TLC) analysis indicated that the reaction had reached completion. The acetonitrile was evaporated by being rotovapped. The product was diluted with dichloromethane and washed with water (3 x 5 ml). The organic layer was dried over anhydrous sodium sulfate, and dichloromethane was removed.

Silica-gel chromatography with ethyl acetate:hexane (3:7) was used to purify and collect the crude product, p-nitrophenol. The solution was then rotovapped and allowed to sit overnight for orange crystals to form. The final yielded 50.1mg of major product with a percent yield of 35.7%. IR: 3342 cm^{-1} (O-H stretch), 3119-2921 cm^{-1} (C-H aromatic stretch), 2851 cm^{-1} (C-H stretch), 1589-1331 cm^{-1} (N-O nitro stretch). ^1NMR (CDCl_3 , 400 MHz): δ 5.56 (s, 1H), 6.91-6.93 (d, 2H), 8.18-8.20 (d, 2H).

Experimental Week 2:

Activated iron was prepared by slowly adding concentrated HCl (2 ml, 81.7 mmol) to granulated iron(10g, 179 mmol).

P-nitrophenol (1.00g, 7.19 mmol) was dissolved in benzene (40 ml) in a round bottom flask and was heated almost to boiling before the activated iron was added. Once activated iron was introduced to the benzene solution, it was refluxed for seven hours. Small quantities of water were added to the reaction mixture throughout the reflux period of seven hours (3 x 1.5ml additions), overall an addition of 4.5ml of water were added.

After the reaction was complete the excess iron was removed by filtration while the solution was still hot. The iron was washed three times with hot benzene and the extracts were added to the original filtrate. Benzene was removed by distillation to attain the free amine and purification was attempted through recrystallization with hot methanol, but was unsuccessful. The experiment had a low yield of 30.2 mg, 3.8%. IR: inaccurate results

Experimental Week 3:

Neutral aluminum oxide (1.67 g, 12.1mmol) was added to the aniline (1 ml, 10.97mmol). Acetic anhydride (1.14ml, 16.46mmol), the acylating agent, was then added and the mixture was left unstirred and stoppered at room temperature (25 °C). TLC was used to monitor the progress of the reaction until it had reached completion. Following completion, ethyl acetate: hexane (3:7) was used to wash the solution (2 x 10 ml) and then filtered via vacuum filtration. The remaining solvent was then removed via rotovap to obtain the desired product, acetaminophen. IR: 3331 cm^{-1} (N-H stretch), 3241-2981 cm^{-1} (C-H aromatic stretch), 1652 cm^{-1} (C=O stretch). ^1NMR (CDCl_3 , 400 MHz): δ 1.57 (s, 3H), 2.20 (s, 1H), 7.08-7.16 (t, 2H), 7.33 (t, 2H), 7.46-7.54 (d, 1H).

Green Experimental:

From step two, the excess benzene that was removed via distillation, was tested and characterized using IR spectroscopy and NMR as pure benzene. By reusing this benzene,

waste is reduced and atom economy is maximized significantly. IR: 3090-3035 cm^{-1} (C-H aromatic stretch), 1428 cm^{-1} (C=C stretch), 666 cm^{-1} (C-H stretch). ^1NMR (CDCl_3 , 400 MHz): δ 7.42 (s, 6H).

Data: (spectras)

Green comparison chart:

Comparison Parameter	Benzene	Recovered Benzene
Hazards	Irritant, permeator, carcinogenic, mutagenic.	Irritant, permeator, carcinogenic, mutagenic.
Cost	\$21.12	\$19.20 (saved)
Percent Recovery	100%	90.9%
Experimental Atom Economy	94.4%	85.8%
Rxn temp	20°C	20°C
Ease of separation	Easy	Easy - distillation
Product Purity	100%	Negligible Impurities
Any byproducts	No	No
Waste produced	No	No

Discussion:

In the process of conducting the silica-gel chromatography with ethyl acetate:hexane (3:7) to purify and collect the desired product, p-nitrophenol, there was a lack of the addition of solvent into the column. Due to the deficiency of solvent, the column dried out therefore all of the product was not collected. Although enough test tubes of the desired product was collected, the low percent yield could be due to the error in solvent addition in the silica-gel chromatography purification. Recrystallization was successful with the small yield resulting in p-nitrophenol. Although this yield was low, we were still able to collect our desired product of p-nitrophenol. The

IR spectroscopy showed appropriate peaks, matching similar to those on the standard of p-nitrophenol that was pulled up as the best fit from the IR library. A proton NMR was also ran, also showing very distinct and clear peaks matching the structure of the p-nitrophenol.

Due to low yields from step one, and a need for large amounts to complete step two, the standard p-nitrophenol was used to in hopes of creating a sufficient amount of product, p-aminophenol. Large amounts of reagents were needed for this step in order to get a sufficient amount of product due to the fact that the iron made stirring difficult because of magnetic interference with the stir bar. After recrystallization the end product resulted in a dark brown liquid. An IR spectroscopy was ran, showing indistinguishable characteristics.

Although the desired product was not acquired, the recovery of the majority of the solvent used, benzene was successful. It was noted during distillation that a clear liquid was being collected in the flask, so it was tested using IR and NMR, resulting in a very well fit to pure benzene. The boiling point was also tested and correlated with the standard of benzene, resulting in a range of 79-82 °C, compared to the literature value of 80.1 °C. Being able to recover the majority of benzene allowed for the elimination for a large portion of waste that would have been produced.

Unidentifiable product from the second step synthesis resulted in the incompleteness of the final synthesis of acetaminophen not to be a viable option. To proceed with the scheme of step three, alterations were made so a desirable product would result using the same techniques and molecular additions. Aniline was substituted for p-aminophenol because of its easy accessibility in lab within timeframe of experiment and because of the structural similarities to p-aminophenol. Upon completion of the selective acylation, acetanilide was created. An IR spectroscopy was ran, resulting in a best fit of acetanilide. The peaks that were found matched closely to the standard that was matched from the IR library. A proton NMR was ran as well, showing peaks that correlated with structure of acetanilide as well. The final synthesis was successful in that acylation occurred.

Conclusion:

Overall the experiment conducted was unsuccessful in synthesizing acetaminophen. Complications within the individual steps resulted in low percent yields and some unidentifiable products. To proceed with the scheme some alterations were made so that a similar product could be obtained. Time would not allow for the retrial of individual steps or the development of a new synthesis. Based on the similarities in structure to acetaminophen, acetanilide was chosen as a replacement end product to complete the synthesis. In the final step of the synthesis from aniline to acetanilide, the percent yield obtained was the highest of the overall synthesis, at 64 percent.

The greenest route in this experiment was the recovery of the solvent, benzene, from the second step synthesis. It was isolated, characterized, and compared to standard values, allowing for the recognition of a pure substance. By recollection of the benzene atom economy was maximized, waste was reduced, and money was saved. Keeping the experiment eco-friendly was a success.

Future work:

For future work on this three step synthesis of acetaminophen, an alternate route to the second step would be researched and established. The second procedure was time consuming and resulted in a low yield. Although the benzene was recovered from this step, there was still a lot of waste created and more efficient atom economy would be preferred.

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