ORGANIC

UNDERGRADUATE EXPERIMENT

The Classic Synthesis of Aspirin

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INTRODUCTION

Aspirin belongs to the salicylate family, a group of compounds derived from salicylic acid which are known for their prevention of fevers.[1] Aspirin, also known as acetylsalicylic acid was synthesized in the 1890s and continues to be a pivotal medicinal compound in combating various diseases.[1] The goal of this experiment is to introduce students to fundamental and practical concepts of organic chemistry (*e.g.* organic synthesis, stoichiometry, percent yield, sample preparation, recrystallization[2], and vacuum filtration) used in academia and industry via nuclear magnetic resonance (NMR) spectroscopy. By evaluating the synthesis of a well-known pharmaceutical, students can assess the purity of their own synthesized crude and recrystallized product via proton (^{1}H) NMR spectroscopy.

Procedure

Materials

Salicylic acid, acetic anhydride, and sodium acetate were purchased from Sigma Aldrich. Note that it is recommended to use anhydrous sodium acetate. Deuterated chloroform (99.8%) was purchased from Deutero GmbH. Distilled water was purchased from a local grocery store and ethanol (95%) was purchased from Acros Organics. All reagents were used without further purification.

Instrumentation

All NMR data were collected using both a Nanalysis 60 MHz and 100 MHz instruments. The ^{1}H NMR experiments were performed using the following parameters: spectral width: 20 ppm, spectral center: 5 ppm; number of points: 8192; number of scans: 4; dummy scans: 0; interscan delay: 1 second; pulse angle: 90°; and receiver gain: auto. Note that 4096 points is preferred for a 60 MHz instrument. All the spectra presented were manually corrected for phase and baseline distortions using MestReNova software (v15.1.1).

Synthesis

Aspirin - Crude

A 400 mL beaker filled with ~300 mL of water was placed on a hotplate magnetic stirrer. A 50 mL Erlenmeyer flask was charged

with 1.00 g of salicylic acid, 2 mL of acetic anhydride, 0.20 g of sodium acetate, and a stir bar. The Erlenmeyer flask, partially submerged in a water bath, was heated and stirred for 15 minutes until all solids dissolved. After removing heat and stopping the stirring, 11 mL of distilled water was added to hydrolyze excess acetic anhydride. The flask was then cooled in an ice bath for 20 minutes to promote crystallization. The crude product was washed with cold water and isolated via vacuum filtration.

25 mg of the crude was dissolved in 0.6 mL of deuterated chloroform. The solution was filtered through cotton wool and transferred to an NMR tube for ^{1}H NMR analysis.

Aspirin - Recrystallized

The remaining crude was placed in a clean 50 mL Erlenmeyer flask. Minimal hot ethanol was added to dissolve the crude, followed by 10 mL of warm distilled water. The mixture was cooled to room temperature and then the flask was placed in an ice bath until recrystallization was complete. The crystals were washed with cold water and isolated by vacuum filtration.

25 mg of the recrystallized product was dissolved in 0.6 mL of deuterated chloroform. The solution was filtered through cotton wool and transferred to an NMR tube for ^{1}H NMR analysis.

Results and Discussion

The ^{1}H NMR spectra of the crude and recrystallized products were collected and compared with the spectra of the starting materials and by-product. These spectra are shown in **Figures 1** and **2**.

The recrystallized and crude aspirin samples differ in one key aspect: the presence of acetic acid as a by-product in the crude sample. This difference helps assess the purity of the final product. Both samples show analogous NMR signals for the methyl group of the O-acetyl group, splitting patterns of the aromatic protons, and broad signal for the hydroxy group. Thus, the absence of acetic acid in the recrystallized sample indicates its higher purity compared to the crude aspirin.

Conclusion

The incorporation of Benchtop NMR to the synthesis of aspirin provides "hands-on" training that covers fundamental concepts of organic chemistry. Further, it trains students in the most prevalent characterization method available to a chemist, NMR. The information provided by the NMR data gives students greater insight into the type of impurities that may be present in their crude product. Additionally, this insight can be used to consider both the reaction and possible by-products that could form in side-reactions. Taken together, this approach enhances students' analytical skills and deepens their understanding of processes in organic chemistry.

References

[1] Montinari, M. R.; Minelli, S.; De Caterina, R. *Vascul Pharmacol.* **2019**, *113*, 1-8.

[2] Recrystallization Paired with Benchtop NMR. (blogpost) (Accessed September 5, 2024)

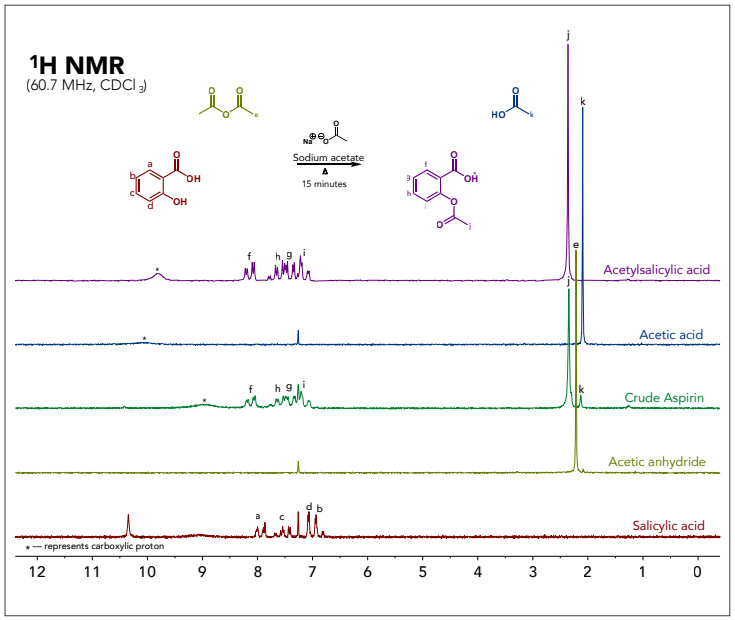

Figure 1. *^{1}H (60.7 MHz) NMR spectra of recrystallized aspirin, acetic acid, crude aspirin, acetic anhydride, and salicylic acid.*

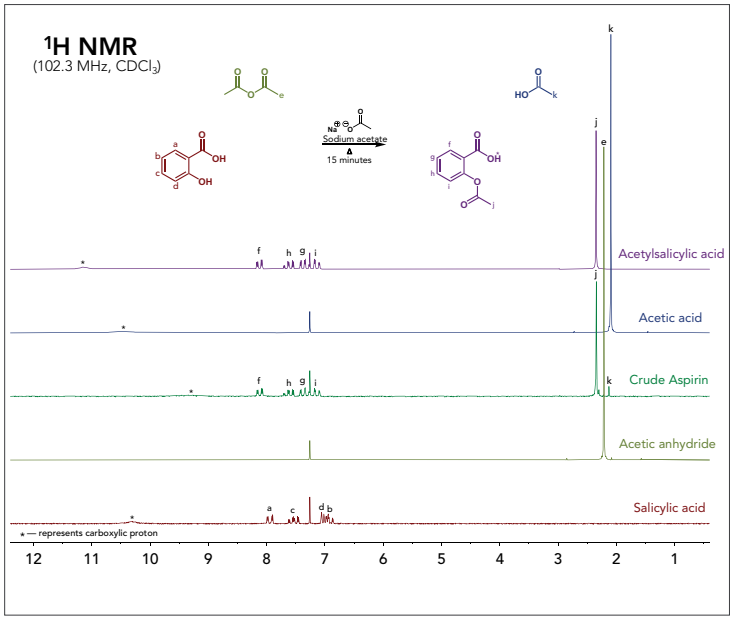

Figure 2. *^{1}H (102.3 MHz) NMR spectra of recrystallized aspirin, acetic acid, crude aspirin, acetic anhydride, and salicylic acid.*

Bay 1, 4600 – 5 Street NE
Calgary, Alberta, Canada
T2E 7C3

Tel: +1.403.769.9499

nanalysis.com

sales@nanalysis.com