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A Greener Approach to Aspirin Synthesis Using Microwave Irradiation

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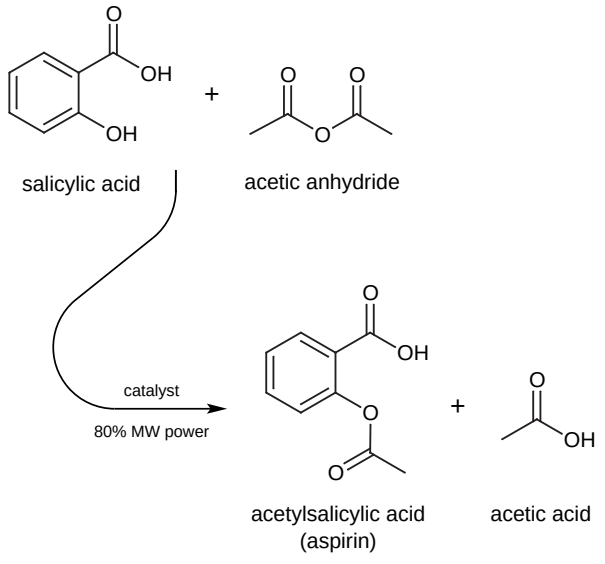
Ingrid Montes,* David Sanabria, Marilyn García, Joaudimir Castro, and Johanna Fajardo
Department of Chemistry, University of Puerto Rico, San Juan, Puerto Rico 00931-3349; **imontes@uprrp.edu*

The synthesis of aspirin has been a popular experiment in organic chemistry teaching laboratories and even in some introductory chemistry laboratories *(1)*. Many laboratory textbooks have included procedures for aspirin synthesis to study carbonyl nucleophilic substitution reactions under acidic or basic conditions *(2, 3)*. However, these traditional experiments use a cookbook recipe approach that does not allow the student to use critical reasoning to thoroughly understand the reaction.

Recently, there has been a growing interest in the use of microwave technology for organic synthesis. The use of microwave induced heating offers certain advantages, such as shorter reaction times, controlled heating and cooling (by placement of an in-line heat exchanger adjacent to the microwave heating zone or by direct contact between a cold finger and the reaction mixture), and reduction of secondary products *(4–11)*. Microwave ovens offer a clean and sometimes cheaper alternative to oil baths for many organic reactions. The popularity of microwave heating has been extended to research applications and recently even to academic teaching laboratories *(6, 12–14)*. It has been proven that microwave heating is effective in solvent-free reactions as well as in reactions that do not utilize catalysts *(5, 6, 10, 11, 15)*. In addition, reactions under solvent-free conditions offer the additional advantage of avoiding the use of solvents that can sometimes be expensive, toxic, or difficult to remove and dispose. Recently, the synthesis of analgesic drugs has been employed to demonstrate the advantages of microwave-assisted synthesis in terms of purity, yield, and reaction time *(6)*. For this reason, an experiment was designed so that the students could determine the best conditions for synthesizing aspirin under microwave irradiation (Scheme I).



Scheme I. Preparation of acetylsalicylic acid.

As opposed to the previously cited experiments *(2, 3, 6, 12)*, this experiment helps the student determine the effect of the catalyst in terms of reaction time, purity, yield, and secondary products formation under microwave conditions. The use of microwave heating instead of conventional heating is a green-chemistry aspect that will be introduced to the student in this synthesis. This experiment also attempts to familiarize the student with the process of searching reference materials related to origin, status, and future challenges of green chemistry. In addition, this experiment has an appendix[W] that includes some important concepts about microwave irradiation, such as overheating effects, dielectric heating, and the role that a catalyst plays when using this technology *(5, 10)*.

Experimental Procedure

The experiment is conducted over two laboratory periods, where the student works individually in the preparation of aspirin from salicylic acid and acetic anhydride. As a safety precaution, the reaction is carried out in a fume hood using a domestic microwave oven (Kenmore Elite Model 565.61582, 1200 W) as a heat source, which is also located inside the fume hood. A different catalyst for the reaction is assigned to each student: there are four acid catalysts, four basic catalysts and one student works without a catalyst. In this way, nine students work individually, but they need to pool their results to reach a conclusion regarding the catalysts' effect.

To a clean and dry 50-mL beaker, salicylic acid (5 mmol) and acetic anhydride (15 mmol) are added. Then, the assigned catalyst is added. If the assigned catalyst is liquid, add one drop and if it is solid, add 0.02–0.04 g. The catalysts to be used are: H_2SO_4, H_3PO_4, $MgBr_2 \cdot OEt_2$, $AlCl_3$, $CaCO_3$, NaOAc, NEt_3, and 4-*N,N*-dimethylaminopyridine (DMAP). The reaction mixture is placed in a microwave oven for two minutes at 80% power. Then, the mixture is removed from the microwave oven, stirred, and again placed in the microwave for two minutes at 80% power. After this period, microwave irradiation is continued and the reaction mixture is monitored every five minutes using thin-layer chromatography (TLC) with a stationary phase of silica gel and a mobile phase of hexane–ethyl acetate (8:2 v/v). The ferric chloride

($FeCl_3$) test (used to identify the presence of phenols) also is used to identify the presence of salicylic acid in the reaction every five minutes. The initial reaction mixture forms a slurry that after microwave irradiation becomes a homogeneous solution. The formation of solids indicates the presence of the product. Once the solids are formed, the students carry out a procedure for polymer removal, an unwanted side-product, if the catalyst is an acid, or acidify the medium first if the catalyst is a Brønsted base. After this procedure, the students must recrystallize the product using the available solvents, which include acetone, diethyl ether, petroleum ether, and toluene. Solubility tests can be done to determine the best solvents for recrystallization.

Through the solubility tests, and corroborated with the literature, toluene is the best solvent for the recrystallization of aspirin. After recrystallizing the solid product, the students isolate the product using vacuum filtration. The solid product is dried, weighed, and the yield and melting points are determined. Aspirin crystals are characterized using techniques such as NMR, FTIR and UV–vis. The students are encouraged to work with spectral NMR viewers and simulation software, where chemical shifts and multiplicities can be confirmed for aspirin. The suggested software to be used is "^{1}H-NMR VIEWER" version 8.0, a freeware that can be found at the ACD/Labs Web page *(16)*, although any other spectrum visualization package compatible with the jcamp file format and NMR spectral simulation capabilities can be used. Once the student generates the predicted proton spectrum, it can be compared with the experimental proton spectral data obtained for aspirin. The spectroscopic data obtained from this synthesis are available in the Supplemental Material.[W]

To improve the green chemistry aspects of this experiment, the recrystallization step can be eliminated. The crude material obtained for each reaction is washed with 25 mL of cold water to remove the excess acetic anhydride. Then, the product is filtered and dried in a preheated oven at 80 °C. The melting point and yield must be determined. Finally, NMR and other spectroscopic methods are used to characterize the crude product (Table 1).

Table 1. Catalysts Utilized in the Synthesis of Aspirin with Microwave Irradiation Using Recrystallization Procedure and Solvent-Free Approach[a]

Catalyst	Reaction Time/min	Polymer Formation	Yield (%)[b]	Yield (%)[c]
None	10–13	Negative	80	97
H_2SO_4	5	Positive	41	55
H_3PO_4	5	Positive	40	63
$AlCl_3$	6–7	Negative	65	66
$MgBr_2{\cdot}OEt_2$	5	Positive	38	63
$CaCO_3$	5	Negative	77	92
NaOAc	9–10	Negative	52	85
Et_3N	8	Negative	61	90
DMAP	14	Negative	50	67

[a]The melting point ranges of aspirin obtained from recrystallization and solvent-free procedures are comparable: mp 132–135 °C.
[b]Obtained yields from recrystallization procedure.
[c]Obtained yields from solvent-free approach.

Hazards

Some individuals can be allergic to aspirin. Acetic anhydride is a toxic, irritating, and lachrymatory substance. Some of the catalysts used in the experiment (DMAP, H_2SO_4, H_3PO_4, $AlCl_3$ $MgBr_2$, NEt_3) may cause severe skin and eyes burns or are highly corrosive. The solvents that are used in the experiment (toluene, ethyl acetate, diethyl ether, acetone, hexane, petroleum ether) are flammable liquids. Students must consult the Material Safety Data Sheet (MSDS) for each of these reactants before beginning the experiment. Before proceeding with the experiment, the students must be informed of the appropriate disposal of chemical wastes and warned of additional precautions to be taken when working with chemical substances and the microwave oven. These experiments must be carried out inside a fume hood. Home microwave ovens may cause explosions when flammable solvents are heated in open containers or when liquids or solids are heated in closed containers not designed for high pressures. In this experiment the microwave is protected in a hood, but it would be preferable to use a laboratory microwave oven.

Discussion

This experiment was initially designed to study the effect of the catalysts on the synthesis of aspirin, refer to the Supplemental Material[W] for these results. For this laboratory experience the results proved that the best catalysts, in terms of reaction time, were the Brønsted acids, similar to the results reported previously *(1, 2).* Subsequently, a procedure for the acid-catalyzed synthesis of aspirin using microwave irradiation was reported in the literature *(6, 12). Based on this finding, it was understood that the original experiment might be modified and extended by applying microwave irradiation, in a research-like approach producing the results in Table 1.*

Analysis of these results reveals the effect of microwave irradiation in relation to the reaction time, polymer formation, product purity and yield. Table 1 shows that under microwave irradiation, the results are similar to those traditionally reported for acid catalysis, in terms of polymer formation and reaction time *(2, 3, 12).* The results under basic catalysis, however, are completely different from those obtained from aspirin synthesis without microwave irradiation, in terms of reaction time, polymer formation, and yield. For example, the reaction using calcium carbonate ($CaCO_3$) did not work with conventional heating (without microwave irradiation), but was completed in five minutes and a 77% yield was obtained under microwave irradiation. The experimental data also show that Brønsted acids produced lower yields when compared to Brønsted bases as catalysts. Initially, this may appear contradictory, because traditional experiments establish that acid catalysts are more effective than basic catalysts, given the nature of the leaving group in the reaction mechanism *(2).* When a carbonyl nucleophilic substitution reaction is carried out in an acidic medium, the leaving group is acetic acid, which is a better leaving group than the acetate ion that is generated in a basic medium *(2, 3).* As can be observed from Table 1, the use of sulfuric and phosphoric acid as catalysts produced low yields owing to the formation of polymers. The polymers must be removed using a saturated

solution of sodium bicarbonate, which is later acidified to recover the aspirin *(2).* In addition, it can be observed from the experimental results that Lewis acids can also be used as catalysts. In the case of $AlCl_3$ the yields were good and no polymer formation was observed.

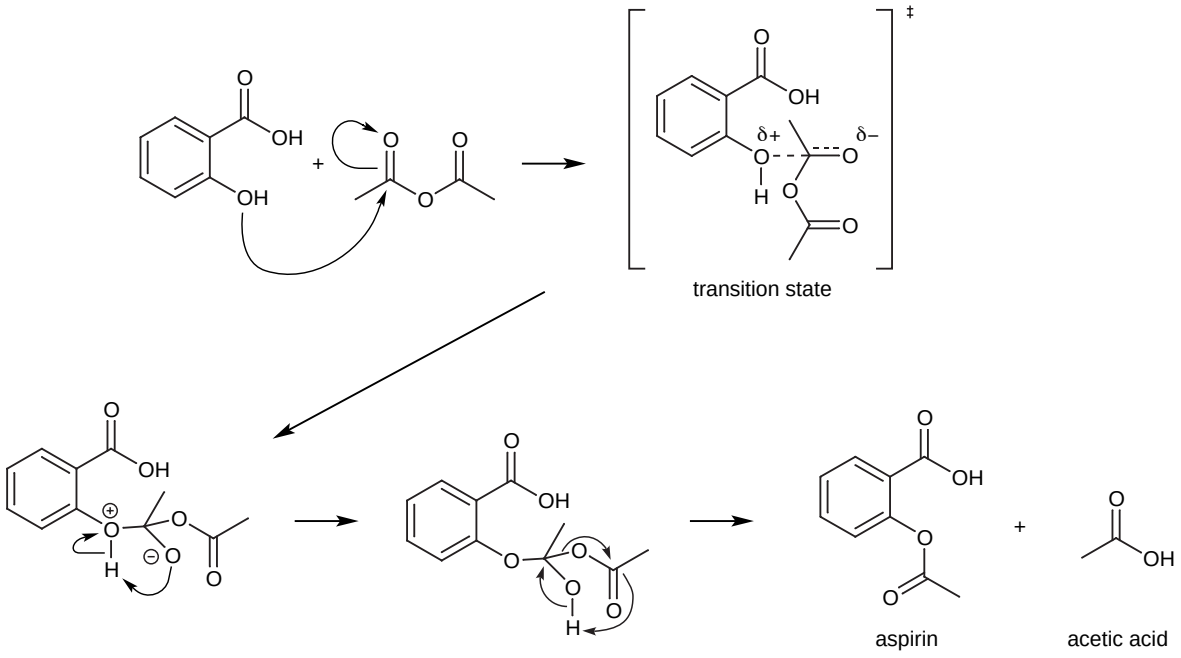
What seems very interesting is the comparison of the results of the reaction without any catalyst. In the absence of catalyst, without microwave irradiation, no reaction is observed. On the other hand, under microwave irradiation the reaction is completed in 10–13 minutes without polymer formation producing the highest yield (80%). This unexpected experimental result provides a good opportunity to introduce green chemistry, emphasizing the importance of the atom economy principle *(17, 18).* By omitting the use of solvents for recrystallization in the previous procedures we can also introduce the solvent-free principle (Table 1). "Green chemistry is the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances *(18, 19).*" The design of environmentally benign products and processes may be guided by 12 principles, among them atom economy and solvent-free reactions. Atom economy stresses that synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product, while the solvent-free reaction principle stresses that the use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used *(19).*

The results obtained from the synthesis of aspirin under microwave irradiation via the solvent-free approach, indicate that the product yield for each catalyst is increased when compared with the recrystallized product yields (Table 1). These differences in yields could be due to the loss of some product during the recrystallization step. When the synthesis of aspirin is carried out in the absence of a catalyst, although the reaction is slower, this condition provides the best reaction medium in terms of purity and yield. In addition, these results show that the yields using Brønsted acids are moderate. This tendency was also observed under microwave irradiation using the recrystallization procedure. Interestingly, calcium carbonate ($CaCO_3$) shows the best yields among the studied basic catalysts.

According to the literature, if there is an increase in the polarity of the medium or charge separation in the reaction transition state, a faster reaction is observed under microwave irradiation, because the transition state is stabilized, decreasing the activation energy *(5, 10, 15).* It is expected that the students will consider a reaction mechanism that proposes a charge separation in the reaction transition state, similar to the one presented in Scheme II.

Once the experiment is completed, the students form groups to discuss results and to explain the effect of the catalyst on the reaction. Discussion questions are provided to the students to guide their reasoning (refer to the Supplemental Material[W]). Using these questions as a guide, the student might conclude that $CaCO_3$ could be the best catalyst, because in just 5 minutes they can obtain aspirin in 77% and 92% yield (Table 1), while without catalyst in 10–13 minutes they can obtain the same product in 80% and 97% yield. This conclusion is correct as long as the reaction time is considered. However, if you want to guide the student to consider some aspects of green chemistry such as solvent-free reaction and atom economy, then the student should arrive at the conclusion that the best practical condition for aspirin synthesis is without catalyst. Students must also explain, in terms of reaction mechanisms, why the formation of the product is favored even when there is no catalyst present, and the role of the microwave radiation in the reaction.

Overall, the experiment affords a good opportunity for groups to compare their experimental results and reach general conclusions that individuals would find difficult to ob-



Scheme II. Reaction mechanism suggested for the synthesis of aspirin under microwave condition without catalyst.

tain. This experience also shows the students that research leads to new findings that can create alternatives to traditional methods. The experiment also presents a good opportunity to emphasize the importance of green chemistry. Moreover, this experiment allows the students to critically assess the advantages and disadvantages offered by the use of microwave technology in the synthesis of aspirin. One of the advantages the students can appreciate is that pure aspirin can be synthesized in short times. On the other hand, because this experiment does not provide the necessary time for the students to optimize their reaction conditions, which is critically important (especially for industry), they must carry out their reaction using a given time, power, and amount of catalyst.

Conclusions

This experiment provides a learning experience for the students because it familiarizes them with the application of new approaches and technologies to a classic experiment in a research-like fashion. It also offers a learning experience and a challenge for the instructor as we continue to develop new experiences to teach the students, including new alternatives and "greener" experimental methodologies for traditional synthetic procedures.

Acknowledgments

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[W]Supplemental Material

Detailed instructions and further discussion of background (including microwave information) for the students and notes for the instructor are available in *JCE Online*.

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