Pedagogical Comparison of Five Reactions Performed under Microwave Heating in Multi-Mode versus Mono-Mode Ovens: Diels–Alder Cycloaddition, Wittig Salt Formation, E2 Dehydrohalogenation To Form an Alkyne, Williamson Ether Synthesis, and Fischer Esterification

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Supporting Information

ABSTRACT: Five reactions were rate-accelerated relative to the standard reflux workup in both multi-mode and mono-mode microwave ovens, and the results were compared to determine whether the sequential processing of a mono-mode unit could provide for better lab logistics and pedagogy. Conditions were optimized so that yields matched in both types of microwave ovens for a Diels–Alder cycloaddition, Wittig salt formation, Fischer esterifications, an E2 alkyne formation, and Williamson ether synthesis. Typically, a 10-fold rate acceleration was observed under mono-mode heating versus multi-mode heating, reducing the total run-time between 1.5 and 3.0 min per sample, which rivals the batch run-time of a multi-mode unit in ~16 student lab sections. Thus, the mono-mode microwave oven required a similar quantity of total reaction time in the lab, allowing students to run their experiments individually with less wait-time, competition for chemicals, equipment, and instrumentation and to complete the experiments in the lab period.

KEYWORDS: Second-Year Undergraduate, Organic Chemistry, Hands-On Learning/Manipulatives, Alkynes, Elimination Reactions, Esters, Ethers, Nucleophilic Substitution, Laboratory Instruction

In this Journal, the rate acceleration afforded under microwave heating for three reactions was recently reported: a Diels–Alder cycloaddition, a Wittig salt formation and a Williamson ether synthesis.1 These reactions were promoted in a multi-mode microwave oven. Reactions that took hours of reflux were completed in high yields within 10 min under elevated temperature and pressure. The multi-mode oven had exchangeable carousels that held 14 or 24 vessels; thus, the ability to run many samples simultaneously made it appropriate for the undergraduate organic chemistry lab. With heat-up (ramp), time at reaction temperature (cook), and cool-down, all samples were held within the oven for 25–35 min, so they were run together in one batch. Students’ sample preparation times varied widely as they waited for balances and reagents. The most efficient students waited the longest time since the batch was not started until all samples were collected. Thus, students received their reaction mixtures at the same time for workup and analysis, which resulted in competition for rotary evaporators and analytical instrumentation.

The microwave field within multi-mode units is diffuse and uneven with “hot and cold” spots, requiring rotation of the carousel to try to even-out energy to all samples. There is another style of microwave oven, mono-mode ovens, utilized in research labs primarily for smaller scale method development and discovery. Mono-mode ovens possess a small reactor cavity in which a sample is placed at the crest of the microwave where the field is densest and energy the greatest. Only one sample is run at a time, which has minimized its regular use in the undergraduate lab. However, each vessel receives identical energy for greater reproducibility. If a mono-mode oven’s denser field translates into a more efficient energy transfer and corresponding shorter reaction time (~2 min) so that the overall time required to run an entire section’s samples sequentially rivals the time frame of a multi-mode oven’s batch run, then there are logistical and pedagogical benefits. Foremost is a steady stream of students placing their vessels in the oven and retrieving them for workup. This reduces student frustration, wait-time, and congestion on equipment and instrumentation. Sequential processing also permits each sample to be run under different reaction conditions, affording experimental flexibility.
REACTIONS

Five reactions (Scheme 1) were investigated using a mono-mode microwave oven: Diels–Alder cycloaddition and Wittig salt formation were reported previously using a multi-mode oven; E2 dehydrohalogenation and Fischer esterification were new reactions that were also investigated using a multi-mode oven for comparison. Although a Williamson ether synthesis was reported previously using a multi-mode oven, Williamson ether synthesis of a new product was investigated also using a multi-mode oven for comparison. Each reaction, its purification and analyses were completed within a 3-h lab period.

Diels–Alder and Wittig Reactions

Please refer to ref 1 for the justification of the Diels–Alder and Wittig salt forming reactions.

E2 Dehydrohalogenation of meso-Stilbene Dibromide to Diphenylacetylene

Alkynes are typically made via two sequential E2 dehydrohalogenations of a dibromide prepared from the bromination of an alkene. This experiment affords a review of bimolecular elimination geometry requirements of alkyl halides to form alkenes and revisits the reduced reactivity of vinyl halides. Although vinyl halides can possess the necessary geometry to participate in either an antiperiplanar or a synclinal transition state, the C–H and C–X bonds being broken involve sp², not sp³, carbons. These bonds are shorter and stronger than those within alkyl halides; thus, they require higher temperatures to promote the elimination.

Few laboratory textbooks include this type of reaction due to the high temperature demands achieved via sand or oil baths. Open baths heated to 200 °C present a significant burn hazard and the harsh conditions lead to low yields and charred alkyynes. Also, high boiling solvents, such as triethylene glycol, are used that are difficult to remove during purification. The specific multistep sequence starting from E-stilbene and producing diphenylacetylene was reported, but utilized a sand bath as the heat source. Microwave heating can reach high temperatures safely within seconds in a closed, pressure-resilient vessel placed inside a steel reinforced oven. This closed system allows the use of lower boiling solvents, such as ethanol, which are easier to remove.

Williamson Ether Synthesis

The Williamson ether synthesis is the preferred method for synthesizing asymmetrical ethers and an excellent example of an S_N2 mechanism. Ether preparation experiments appear in many lab texts and this Journal, but they require long refluxes and do not produce the highest yields. For example, Neuzil describes the synthesis of ethyl 2-naphtholate, or nerolin, a perfume fixative with a 1.5-h reflux, which was only a fraction of the time required for the reaction to go to completion. This experiment was performed under microwave acceleration that doubled the yield, but suffered from poor recovery (∼40%) following recrystallization, mostly due to oiling out of the low melting ether (37 °C). Other alkyl aryl ethers that should have higher melting points were investigated. p-Bromobenzyl bromide was chosen as the alkylating agent for the following reasons, even though the expected ether product was not known in the literature. The alkylating agent contained two different types of carbons bearing leaving groups; one bromine was on a benzylic, sp³ carbon and the other was on an aryl, sp² carbon. This afforded an opportunity to reinforce lecture material concerning the mechanistic geometry requirements for an S_N2 reaction, the nucleophile’s accessibility to a carbon bearing the leaving group.

Scheme 1. Reactions Rate-Accelerated in Both Mono- and Multi-Mode Microwave Ovens

Diels–Alder Cycloaddition

Wittig Salt Formation

E2 Dehydrohalogenation of meso-Stilbene Dibromide to Diphenylacetylene

Williamson Ether Synthesis

Fischer Esterification

CH₃(CH₂)nCO₂H + ROH → CH₃(CH₂)nCO₂R + H₂O
Laboratory Experiment

There was no possibility for a competing E2 reaction. It also provided the opportunity to emphasize the difference in acidity of aromatic versus alkyl alcohols; 2-naphthol was deprotonated to form a better nucleophile in methanol’s presence. This was the first report of the product, p-bromobenzyl 2-naphthyl ether (mp 120 °C); it was very fragrant and could be used like nerolin in perfumery.

Fischer Esterifications

Fischer esterification is a mechanistically important reaction and an excellent way to introduce students to key biological molecules that also have significant commercial applications. Esterifications were among the first reactions successfully accelerated under microwave heating. Leadbeater and McGowan compared ester preparation in both mono-mode and multi-mode ovens. They prepared three acetate esters in 5 min at either 120 °C (multi-mode) or 130 °C (mono-mode) and reported similar yields. Interestingly, they did not report a rate increase in the mono-mode oven.

A “new twist” was put on this classic esterification experiment, making it more interesting with greater intellectual challenge and shifting the focus from a tedious reflux to a mechanism review coupled with solving an NMR problem. This was accomplished by making the identity of the ester a “mystery.” There were several goals for this experiment: (a) to utilize microwave heating to shorten heating time from hours to minutes, so the entire experiment could be completed in 1 lab period; (b) to develop a short workup that gave pure esters ready for spectral interpretation; and (c) to select esters whose 1H and 13C NMR spectra were challenging, yet unambiguous.

Unlike the 4 previously discussed reactions where every student prepared the same compound, each student was assigned a different combination of carboxylic acid and alcohol for the Fischer esterification. Although there were concerns about performing different reactions together in a multi-mode oven due to varying sample absorbance, the similarity in reagents minimized this issue. There was no such concern with the mono-mode unit.

EXPERIMENT

Diels–Alder Cycloaddition Reaction

A Diels–Alder cycloaddition reaction between N-phenylmaleimide and 1,3-cyclohexadiene in ethanol was heated to 130 °C (40 s ramp at 100 W fixed power and 1 min cool-down), at which time the reaction was over. Each sample was in the oven for less than 2 min; the last student in a 16-student lab section retrieved the vessel in about 30 min, which matched the time frame for a multi-mode oven. The rate acceleration in a mono-mode oven was 10-fold that in a multi-mode oven with identical yields.

Wittig Salt Formation

Wittig salt formation from triphenylphosphine and benzyl chloride in acetonitrile required a temperature of 190 °C (1 min 10 s ramp at 100 W fixed power and 1 min 45 s cool-down) to achieve complete reaction. Each reaction vessel was in the oven for a total of 3 min. The last student retrieved the sample in about 48 min as compared to ~32 min for a multi-mode oven. The additional time of about 15 min was used by students for a lab briefing, lab quiz, or preparing for workup. The acceleration in a mono-mode oven was 10-fold that in a multi-mode oven with identical yields.

E2 Dehydrohalogentation of meso-Stilbene Dibromide To Form Diphenylacetylene

Dehydrohalogentation of meso-stilbene dibromide to diphenylacetylene was achieved in a multi-mode oven heated to 160 °C for 10 min with ramp (~2 min), cook time and cool-down (~13 min); the entire process required about ~25 min. In a mono-mode oven, the reaction was completed with 1 min of heating to 160 °C (100 W fixed power), a 30 s heat time, and a 1.5 min cool-down. Each sample required ~3 min; thus, the 16th sample was retrieved in about 48 min. Most students (~200) reported a yield of 85% of an off-white to light tan powder that melted within error of the literature value of 59–61 °C and within a narrow 2 °C range.

Williamson Ether Synthesis

Williamson ether synthesis of potassium 2-naphtholate and p-bromobenzyl bromide to p-bromobenzyl naphthyl ether was achieved in a multi-mode oven heated to 130 °C and held for 10 min. With ramp, hold and cool-down, samples were in the oven for 25–30 min. By increasing the temperature to 160 °C in a mono-mode oven, the cook time was reduced to 1 min at 100 W fixed power; samples were available every 3 min, so the last student in a 16-student section received the sample in ~48 min. The reaction worked well in both types of ovens to produce ~30% of very fragrant white crystals (recrystallized) that melted at 120–122 °C.

Fischer Esterification

Reaction of an alcohol and a carboxylic acid to produce an ester in a multi-mode oven involved a 10 min cook at 130 °C; with ramp and cool-down, the samples were in the oven for 25–30 min. Reaction in a mono-mode oven was achieved by heating to 130 °C with no hold at 100 W (fixed power); the total run time was 2 min. Thus, even with the sequential sample processing, the last sample came available in 32 min, which matched the interval required by a multi-mode oven. Table 1 gives a list of the esters prepared. Average yields are reported with the multi-mode runs. For the more recently performed mono-mode runs, ranges are provided. Students obtained 1H and 13C APT NMR spectra. [Note: The NMR spectra of all starting materials and all other products are available online from either www.sigma-aldrich.com or www.aist.go.jp.com.]

HAZARDS

KOH pellets, subsequent methanolic solution, 3 M HCl, and concentrated H2SO4 are corrosive. All other chemicals

Table 1. Fischer Esterification Results in Multi-Mode versus Mono-Mode Microwave Ovens

<table>
<thead>
<tr>
<th>Ester</th>
<th>Multi-Mode Oven Average Yields, %</th>
<th>Mono-Mode Oven Ranges of Yields, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl hexanoate</td>
<td>71</td>
<td>72–86</td>
</tr>
<tr>
<td>Isopropyl hexanoate</td>
<td>82</td>
<td>71–77</td>
</tr>
<tr>
<td>Methyl hexanoate</td>
<td>74</td>
<td>67–91</td>
</tr>
<tr>
<td>Ethyl heptanoate</td>
<td>90</td>
<td>73–87</td>
</tr>
<tr>
<td>Isopropyl heptanoate</td>
<td>85</td>
<td>72–82</td>
</tr>
<tr>
<td>Methyl heptanoate</td>
<td>82</td>
<td>82–97</td>
</tr>
<tr>
<td>Ethyl octanoate</td>
<td>79</td>
<td>61–89</td>
</tr>
<tr>
<td>Isopropyl octanoate</td>
<td>88</td>
<td>88–94</td>
</tr>
<tr>
<td>Methyl octanoate</td>
<td>73</td>
<td>69–90</td>
</tr>
<tr>
<td>Ethyl nonanoate</td>
<td>79</td>
<td>70–79</td>
</tr>
<tr>
<td>Methyl nonanoate</td>
<td>81</td>
<td>67–81</td>
</tr>
</tbody>
</table>
Laboratory Experiment

Table 2. Summary of Five Reactions Performed under Microwave Heating in Multi-Mode versus Mono-Mode Ovens

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Oven Type</th>
<th>Power, Watts</th>
<th>Target T/°C</th>
<th>Heat-Up Time/min</th>
<th>Hold Time/min</th>
<th>Cool-Down Time/min</th>
<th>Total Time in Oven/min</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diels−Alder cycloaddition</td>
<td>Multi-Mode</td>
<td>800</td>
<td>130</td>
<td>~2.0</td>
<td>10.0</td>
<td>~13.0</td>
<td>25–30</td>
<td>80–90</td>
</tr>
<tr>
<td></td>
<td>Mono-Mode</td>
<td>100</td>
<td>130</td>
<td>0.5</td>
<td>0.0</td>
<td>~1.5</td>
<td>&lt;2</td>
<td>80–90</td>
</tr>
<tr>
<td>Wittig salt formation</td>
<td>Multi-Mode</td>
<td>800</td>
<td>190</td>
<td>6.5</td>
<td>10.0</td>
<td>~15.0</td>
<td>~32</td>
<td>90–100</td>
</tr>
<tr>
<td></td>
<td>Mono-Mode</td>
<td>100</td>
<td>190</td>
<td>1.5</td>
<td>0.0</td>
<td>1.5</td>
<td>3</td>
<td>90–100</td>
</tr>
<tr>
<td>Dehydrohalogenation of dibromide</td>
<td>Multi-Mode</td>
<td>800</td>
<td>160</td>
<td>~2.0</td>
<td>10.0</td>
<td>~13.0</td>
<td>25–30</td>
<td>85–100</td>
</tr>
<tr>
<td>to alkyne</td>
<td>Mono-Mode</td>
<td>100</td>
<td>160</td>
<td>0.5</td>
<td>1.0</td>
<td>1.5</td>
<td>3</td>
<td>85–100</td>
</tr>
<tr>
<td>Williamson ether synthesis</td>
<td>Multi-Mode</td>
<td>800</td>
<td>130</td>
<td>~2.0</td>
<td>10.0</td>
<td>~13.0</td>
<td>25–30</td>
<td>30*</td>
</tr>
<tr>
<td></td>
<td>Mono-Mode</td>
<td>100</td>
<td>160</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>3</td>
<td>30*</td>
</tr>
<tr>
<td>Fischer esterification</td>
<td>Multi-Mode</td>
<td>800</td>
<td>130</td>
<td>~2.0</td>
<td>10.0</td>
<td>~15.0</td>
<td>25–30</td>
<td>70–90*</td>
</tr>
<tr>
<td></td>
<td>Mono-Mode</td>
<td>100</td>
<td>130</td>
<td>0.5</td>
<td>0.0</td>
<td>1.3</td>
<td>2</td>
<td>70–90*</td>
</tr>
</tbody>
</table>

*Wattage varied with number of vessels within oven that affected heat-up and cool-down times. Includes heat-up, cook and cool-down. Recrystallized. See Table 1 for specific esters.

(results and products) are considered irritants, toxic, and flammable. The usual protection of gloves and goggles should be sufficient. Students work solely in hoods.

RESULTS

Five reactions were successfully rate-accelerated in the same high yield and purity in both multi-mode and mono-mode microwave ovens (Table 2). A 10-fold rate increase was observed for all reactions performed in the mono-mode ovens, which reduced the cook time to 1 min or less. With heat-up and cool-down, the total time within the oven never exceeded 3 min, making the mono-mode oven’s sequential processing feasible for a second-year undergraduate organic chemistry lab. The greater acceleration, energy efficiency, uniform heating conditions, staggered accessing of samples, ability for smaller scale work and to vary reaction conditions, and lower purchase price make a mono-mode oven an option for the undergraduate organic chemistry laboratory. Although not necessary, but advantageous, mono-mode ovens can be outfitted with a computer-controlled robotic arm, which manually exchanges samples. Therefore, students do not need to be present to swap samples every few minutes and are available for other lab activities.

CONCLUSIONS

Students have utilized both types of microwave ovens depending on the chemical reaction. However, they prefer the mono-mode oven because of the quick sample turn around and the automation feature, which allowed them to load their sample and leave to prepare for workup. With the multi-mode oven, the more efficient students were penalized with longer wait-times because the batch run was not started until the last student submitted a sample. There was very little down time with the mono-mode units; students began the purification within minutes of submission. This led to an even-paced lab tempo with less backlog on balances, chemical acquisitions, rotary evaporators, IR and NMR spectrometers, and so on. The more efficient students felt rewarded as they finished the lab early. Students particularly appreciated the ease of repeating the reaction within the same lab period if a problem occurred.

ASSOCIATED CONTENT

Supporting Information

1H and 13C APT spectra for isopropyl heptanoate and octanoate; IR spectrum of ether; student experimental handouts for all five reactions; instructor notes with chemical lists. This material is available via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

William Gammerding and Jonathan Shikora are pursuing Ph.D.s at University of Maryland and University of Buffalo, respectively. Jennifer Leap is pursuing her medical degree at Lake Erie College of Osteopathic Medicine. Michael Weber is a junior chemistry major at Muhlenberg College.

ACKNOWLEDGMENTS

The authors wish to thank Muhlenberg College’s Provost for the Faculty-Student Collaborative Grants that supported Erin, Will, Jon, and Mike’s work. Jen’s research was supported by a generous donation from Carolyn and Robert Buzzard. The multi-mode microwave was CEM Corporation’s MARS oven outfitted with a 24, 20 mL vessel carousel and the mono-mode unit was their Discover SP that can hold 10 or 35 mL reaction vessels. The Discover was equipped with the Explorer robotic arm (48 slot rack).

REFERENCES


(6) Reference 7 describes a dehydrohalogenation of stilbene dibromides to diphenylacetylene in a domestic microwave oven. However, the authors used an ionic liquid, 1-methyl-3-pentylimidazolium tetrafluoroborate, as both the base and solvent. Although their reaction gave excellent results, 92% yield with 3.5 min of...
microwave irradiation, the cost of the ionic liquid, even on a microscale, is prohibitive for most undergraduate budgets.


(12) Fixed power is an option with our monomode oven. The magnetron remains on until the desired temperature is reached, which can lead to overshooting. In standard mode, the magnetron would cycle on and off as it approaches the set temperature to prevent overshooting.