Use of Microwave Synthetic Reactor in Organic Chemistry Laboratory Curriculum

*Sanjana K. Rana, Dominique Macaluso, Anoosha Banerjee,
Christina Juste, Isabel Hernandez Rodriguez, Jean Vadakkān, Meenakshi Rao*

The bottom of the slide features several overlapping, wavy, horizontal bands in shades of light blue, dark grey, and black, creating a modern, abstract design.

Outline

- Introduction
 - Background
 - Experimental
 - Results
 - Conclusion
-

Organic Chemistry Laboratory Courses at Barnard College

1. Introductory Organic Chemistry Laboratory Course

Students are introduced to most commonly used organic chemistry laboratory techniques

2. Modern Techniques in Organic Chemistry Laboratory Course

Students learn advanced spectroscopic techniques such as NMR and GC/MS. Students also learn to conduct reactions in an inert atmosphere. Synthesis of Dimedone is one of the experiments in this course

Based on previously published results(ref), students in intermediate course had successfully implemented using microwave synthetic reactor for esterification experiment. Hence to try to synthesize dimedone using the microwave synthetic reactor was a natural progression in the course.

3. Advanced Chemical Synthesis Laboratory Course

Students perform experiments that incorporate organic syntheses, inorganic syntheses, and spectroscopy.

Pedagogical Significance of the Synthesis of Dimedone

Complimentary to
Intermediate
Organic
Chemistry Lecture
Course Syllabus

Use of NMR
Spectroscopy for
Kinetics Studies
and Structural
Characterization

Safe and
Student-friendly
Materials and
Procedure

Dimedone; MSDS No. A10140 [Online]; ThermoFischer: Ward Hill, MA, Feb 14, 2020. <https://www.fishersci.com/store/msds?partNumber=AAA1014014&productDescription=DIMEDONE+98%25+25G&vendorId=VN00024248&countryCode=US&language=en> (accessed March 29, 2020).

What is Dimedone?

- Cyclic diketone
- 5,5-dimethyl-1,3-cyclohexanedione
- Undergoes Keto-Enol Tautomerization

Synthesis of Dimedone

- Pedagogical Objective: Sequential one pot synthesis involving listed organic reactions of carbonyl and carboxylic groups.
 - Michael addition
 - Dieckmann-type condensation
 - Ester hydrolysis
 - Decarboxylation

Traditional Synthesis

Enolate Formation

Michael Addition

Ester Hydrolysis

Decarboxylation

4M HCl
reflux, 30 m

Key Notes for Traditional Synthesis

1. Oven-dried RBF
2. Under N₂ until NaOH added
3. Approximately 1h 40 min of reflux time
4. Refluxed in Oil Bath

Mechanism for Synthesis of Dimedone

Mechanism (Continued)

Research Approach

- **Four reactions involved in the synthesis**

- Michael addition
- Dieckmann-type condensation
- Ester hydrolysis
- Decarboxylation

- **Conditions varied**

- Temperature
- Time

Note: Pressure was kept constant at 13.8 atm.

Microwave Assisted Synthesis

- Ester hydrolysis step was the first reaction attempted using the microwave reactor.

Results

Enolate Formation			Claisen condensation			Ester hydrolysis			Decarboxylation			Yield (%)
sodium ethoxide (4.9 mL), diethyl malonate (2.0 mL)			mesityl oxide (1.4 mL)			2 M sodium hydroxide (17 mL)			4 M hydrochloric acid (until pH ~3)			
Pressure (atm)	Temperature (°C)	Time (min)	Pressure (atm)	Temperature (°C)	Time (min)	Pressure (atm)	Temperature (°C)	Time (min)	Pressure (atm)	Temperature (°C)	Time (min)	
13.8	60	5	13.8	80	5	13.8	90	10	13.8	95	5	1
13.8	60	5	13.8	90	5	13.8	80	10	13.8	102	5	0
13.8	60	5	13.8	80	5	13.8	90	10	13.8	95	5	1
13.8	60	5	13.8	85	5	13.8	80	10	13.8	95	5	0
13.8	60	5	13.8	85	5	13.8	80	10	13.8	95	5	0
13.8	60	5	13.8	70	5	13.8	97	10	13.8	95	10	39
13.8	60	5	13.8	60	10	13.8	80	10	13.8	80	5	0
13.8	60	5	13.8	80	5	13.8	90	10	13.8	95	20	0
13.8	60	5	13.8	60	10	13.8	80	10	13.8	80	5	36
13.8	60	5	13.8	80	10	13.8	80	5	X	X	X	0
13.8	60	5	13.8	97	5	13.8	97	10	13.8	90	10	39
									Legend			
									X : did not attempt step			
									dark green: yield >30%			
									light green: yield <30%			

Advantages

- Reduced time
 - Inherently Safer Process-Experience in using Microwave reactor
 - Opportunity to explain alternative heating methods for “Green Chemistry”
 - Now with shorter experiment time, students will have the opportunity to learn more and explore different reactions
-

Advantages (contd.)

Reduction in Reaction Time: Traditional vs Microwave assisted

Step	Reaction Time Traditional (min.)	Reaction Time using the MSR (min.)
Enolate formation	30	5
Michael addition and Dieckmann type condensation	30	5
Ester Hydrolysis	30	10
Decarboxylation	10-20	10
All the steps combined	100-110	30

MSR = Microwave Synthetic Reactor

Microwave Reactor

- Uses microwave region of Electromagnetic Spectrum
- Microwaves activate molecules in system with:
 - *Dipole*
 - *Ionic*
- Magnetron with anode (containing series of tuned circuits) and directly heated cathode

Figure 1. Multimode system (a) and single-mode cavities (b) (source: the IHPP PAS).

- Two types:
 - Multimode Reactors - electric field due to multiple reflections
 - Monomode - wavebelt and excitations have one mode of propagation

Conventional Heating vs. Microwave Reactor

- Heat passes through vessel
- Less energy to reactants
- Less effective method of energy transfer

- Polarized reactants oscillate
- Not limited by thermal conduction
- More homogenous heating
- More efficient use of energy

Why is Dimedone Important?

Environmental Applications

- Dimedone Assays for detection of biocides
- Hantzsch reaction

Biological Applications

- Anticancer agents
 - Hydrolase substrates and colorimetric esterase/lipase activity detection
 - Terminal labeling of high-molecular weight-ribonucleic acid
-

Anticancer agents

- 5a.** X = H, R = CN
b. X = H, R = COOEt
c. X = Cl, R = CN
d. X = Cl, R = COOEt
e. X = OCH₃, R = CN
f. X = OCH₃, R = COOEt

Dimedone (**1**) was reacted with aryl diazonium salts (**2a-c**) to give aryl hydrazone derivatives (**3a-c**)

Aryl Hydrazone derivatives (**3a-c**) were reacted with elemental sulfur and either malononitrile (**4a**) or ethyl cyanoacetate (**4b**) to give thiophene derivatives (**6a-f**)

Some of these derivatives (**5a,c,e**) then underwent hetero-cyclization reactions giving potentially anticancer agents (**6a-f**)

Anticancer agents (contd.)

- The products were evaluated for in vitro cytotoxic activity against c-Met kinase and six common cancer cell lines
- **Results:**
 - Multiple derivatives showed anti-proliferative activity against human prostate cancer (PC-3 cell line)
 - Many showed Pim-1 kinase inhibition activity
- **Importance:**
 - Dimedone was used as a precursor to create derivatives that inhibit cancer cell growth and proto-oncogene inhibition.

Hydrolase substrates and colorimetric esterase/lipase activity detection

Dimedone esters were used as a substrate for hydrolase-catalyzed reactions to create a colorimetric screen for lipases and esterases

Hydrolase substrates and colorimetric esterase/lipase activity detection (contd.)

- **Importance:**

- High stability lipases are used as prerequisites for biodiesel production through transesterification
- Lipase and esterases are used to make chiral alcohols through hydrolysis
 - Chiral alcohols are crucial in the efficiency and safety of many pharmaceutical products

Terminal labeling of high-molecular weight-ribonucleic acid

- **Importance:**

- Terminal labeling is used in sequence work and to determine heterogeneity of RNA
- End labeling techniques are also used to identify terminal mono and oligonucleotides of RNA

- **Why Dimedone?**

- Dimedone forms derivatives with aldehydes that are saturated at the aldehydic carbon atom and, therefore, not susceptible to beta elimination reactions
- Dimedone also forms stable derivatives so radioactive terminal oligonucleotides can be successfully labeled

Another Example of Microwave assisted reaction: Acid-catalyzed Dehydration of a mixture of *cis*- and *trans*-2-methylcyclohexanols

Microwave Synthetic Reactor was used to convert 2-methylcyclohexanol (mixture of *cis* and *trans*) to 1- and 3-methylcyclohexenes, traditionally done under reflux conditions (Rao, M. *et al.* Barnard College Chemistry Department, Spring 2020).

Conclusion

1. Esterification Reaction

Based on previously published results, students in intermediate course had successfully synthesized esters using the Microwave Synthetic Reactor.

2. Synthesis of Dimedone

As described in this presentation, we successfully developed the synthesis of dimedone using the Microwave Synthetic Reactor.

3. Dehydration of Alcohols

Acid-catalyzed Dehydration of a mixture of *cis*- and *trans*-2-methylcyclohexanols was also successfully carried out using the Microwave Synthetic Reactor with increased regioselectivity.

Future Work

- Modifying organic chemical syntheses using Microwave Synthetic Reactors (MSR) in the current curriculum of Organic Chemistry Laboratory Courses (Introductory, Intermediate and Advanced)
With the focus on:
 - Reducing the reaction time
 - Increasing the percent yield
 - Enhancing both regioselectivity and stereoselectivity

Acknowledgements

Students of Modern Techniques Lab Fall 2018

National Institutes of Health for their generous funding to acquire a Microwave Synthetic Reactor

Barnard College Chemistry Department

Photo: Clockwise from upper left hand corner:

Meenakshi Rao, Sanjana Rana, Isabel Hernandez Rodriguez, Anoosha Banerjee, Jean Vadakkan, and Dominique Macaluso.