

# Microwave Chemistry in Organic Synthesis

(By A. Bacher, UCLA, 4-30-2016)

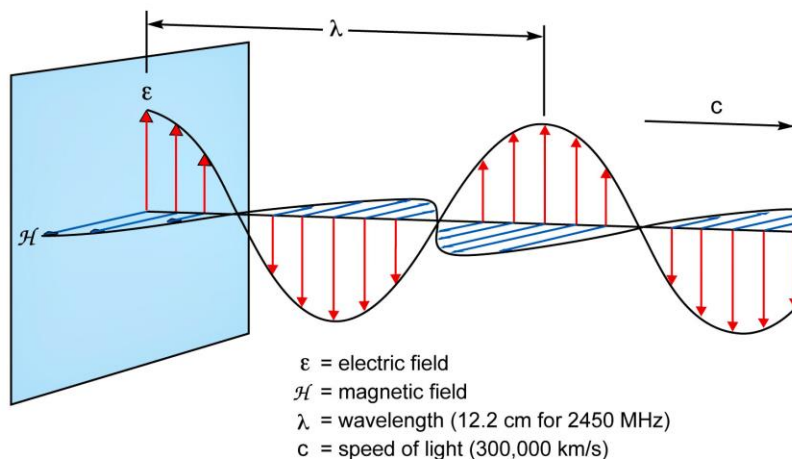
## Introduction

The serendipitous discovery that microwave technology can be used for cooking is based on a melted candy bar in the discoverer's pocket, Percy Spencer, a Raytheon engineer. In 1945, he worked with magnetrons that were supposed to be used as combat radar equipment. Raytheon filed a patent for microwave cooking ovens immediately and started selling the Radarange (6 ft. tall, 750 lbs., see right top) for commercial use in 1947. In 1955, Tappan (belongs now to Electrolux, see right bottom) started to sell the first home microwaves, amid not very successfully probably due of the high cost and the 220 V power requirement. Chemists started to use these kitchen microwaves for synthetic purposes in the mid-1980s. While these multimode domestic microwave ovens can serve as an entry point for this heating technology (as they have been over the past several years in Chem 30BL and Chem 30CL), they have also proven to be problematic due to the lack of safety controls, which does not allow for the use of flammable solvents. Since the exact power output is very difficult to regulate, temperature and pressure control are also challenging resulting in greatly varying outcomes. There is also no protection from explosions resulting from runaway reactions. Due to the increased interest in this approach to perform chemistry, companies like Anton Paar, Biotage, CEM and Milestone, just to name a few, developed monowave and multiwave microwave reactors for synthetic chemistry applications.

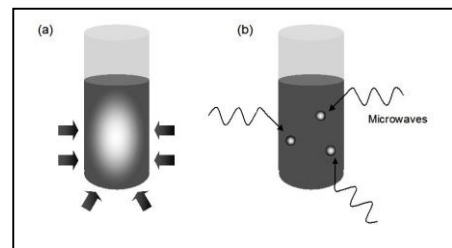


## What makes this technology so interesting to chemists?

While the microwave range is large (1-100 GHz, 300-3 mm), a frequency of 2.450 GHz is preferentially used for conventional microwaves because it provides the right penetration depth for most samples and is also easily available. While it is also important to remember that the electromagnetic radiation consists of an electric and a magnetic field component, there is usually no interaction with the magnetic field during the reaction. Unlike sunlight, the energy of the microwaves is too low ( $\sim 10^{-3}$  kJ/mol) to break chemical bonds (300-500 kJ/mol).

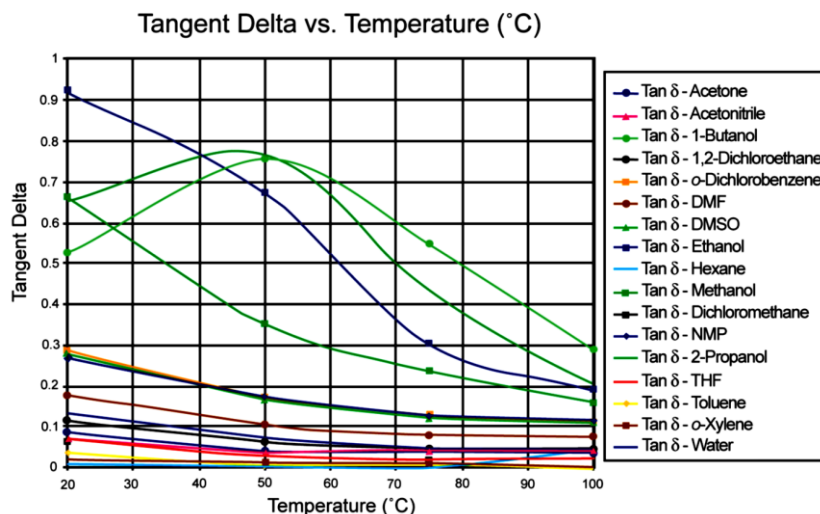


What makes microwave heating interesting then? Usually, the reaction vessel is heated from the outside to the inside (a) like in cooking (i.e., this is important when you prepare a steak or a roast). The internal temperature is usually significantly lower than the outside temperature, which results in a temperature gradient in the reaction vessel and poor control over the conditions. Mixing can help overcome this problem but thermal equilibrium can take a lot of time to attain.



In microwave heating (b), the microwaves couple directly with the molecules because the reaction vessels are generally transparent to microwaves. This will help to minimize wall effects, as the vessel wall is not directly heated. It will result in a more rapid increase in temperature in the system and localized superheating that will lead to dipolar polarization or ionic conduction. In order for a molecule to be able to generate heat when irradiated with microwaves (dielectric heating), it must have a permanent dipole, which will align with the oscillating field. The alignment will cause rotation, which results in friction between the molecules that is ultimately converted to heat. Ionic conduction is based on dissolved charged particles that oscillate back and forth under the influence of microwave radiation. The collisions with other molecules or atoms creates heat as well. Subsequently, heating gases is impossible because the distance between rotating molecules is too large (note that the rotation can be observed in the infrared spectrum of a molecule in the gas phase). In solids, this rotation is hindered because the dipoles are bound in the crystal and cannot move as freely as in the liquid state. This does not mean that reactions cannot be carried out in the solid state, but often a thermally conductive material like silicon carbide, which is excellent microwave absorber, are added as heat transfer medium.

In dielectric heating, the material has to have certain dielectric properties. The heating characteristic of a compound (i.e., solvent) are dependent on its ability to convert microwave radiation into heat, which is described in the so-called loss tangent ( $\tan \delta = \epsilon''/\epsilon'$ ). It is defined as the ratio of the dielectric loss (=efficiency with which electromagnetic radiation is converted to heat,  $\epsilon''$ ) and the dielectric constant (=polarization of molecules in the electric field,  $\epsilon'$ ). It is important to note that the loss tangents of most solvents decreases at higher temperatures making it more difficult to heat hot solvents than cold solvents.



While a solvent with a high  $\tan \delta$  should be used for rapid heating in the microwave field, a solvent with low loss  $\tan \delta$  can be used as well because the other components in the reaction mixture will often increase the overall polarity of the solution. However, the vapor pressure increases very quickly if a solvent is heated above its boiling point (see table below). For instance, ethanol has a normal boiling point of 78 °C but reaches a pressure of 20 bar, a safe pressure in most microwave reactors, at 181 °C. Many higher-boiling solvents reach this safe pressure at higher temperatures due to their inherently higher boiling point (i.e., ethylene glycol: b.p.: 197 °C, 20 bar at 314 °C).

Solvent	$\tan \delta$	b.p. (°C)	Temp. @ 20 bar
Ethylene glycol	1.350	197	314
Ethanol	0.941	78	181
DMSO	0.825	189	
2-Propanol	0.799	82	187
Formic acid	0.722	101	230
Methanol	0.659	64	166
Nitrobenzene	0.589	210	397
1-Butanol	0.571	118	231
2-Butanol	0.447	99	210
1,2-Dichlorobenzene	0.280	180	375
NMP	0.275	204	
Acetic acid	0.174	118	249
DMF	0.161	154	323
1,2-Dichloroethane	0.127	84	221
Water	0.123	100	213
Chlorobenzene	0.101	132	294
Chloroform	0.091	61	193
Acetonitrile	0.062	81	214
Ethyl acetate	0.059	77	208
Acetone	0.054	56	180
THF	0.047	65	200
Dichloromethane	0.042	40	163
Toluene	0.040	111	263
Hexane	0.020	69	207

Many common vessel materials are infrared transparent as can be seen by their low loss tangent values. Thus, they heat up very slowly in the microwave, which makes their heating contribution during the reaction very low. SiC has a much higher  $\tan \delta$  than all the other materials resulting in an uptake of heat during the microwave process. Thus, SiC vessels are often used in cases where the reaction mixture does not absorb the heat efficiently enough.

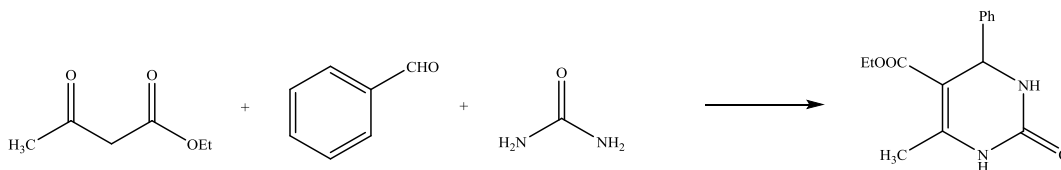
Compound	$\tan \delta$
Quartz	$6.0 \cdot 10^{-5}$
Porcelain	$1.1 \cdot 10^{-3}$
Borosilicate glass	$1.0 \cdot 10^{-3}$
Plexiglass	$5.7 \cdot 10^{-3}$
Polystyrene	$3.3 \cdot 10^{-4}$
Teflon	$1.5 \cdot 10^{-4}$
SiC	0.02-1.05

Microwave reactions can be carried out in an open vessel (i.e., beaker and Erlenmeyer flask as being used in the conventional microwave) or in a closed vessel. The microwave heating of an open vessel will not result in any rate enhancement because the maximum temperatures will be similar to the conventional heating because in solution-based reactions, the boiling point of the solvent will be the upper limit. The closed vessel allows superheating of the solvent to a certain degree because the vessel is able to withstand some pressure (typically up to 20 bar, see table above for individual temperatures). This is the main reason why it is possible to accelerate reactions using microwave heating, similar to a pressure cooker in the kitchen, which can withstand about 2 bar (b.p.(water): 121 °C).



SiC, 4 mL, 10 mL and 30 mL vessel and cap with septum

For instance, the Biginelli reaction with urea, benzaldehyde and ethyl acetoacetate can be carried out in ethanol using hydrochloride acid as a catalyst. The conventional reaction requires three hours of reflux (80 °C, 1 bar) and produces a 78 % yield of the dihydropyrimidinone. The same yield can be obtained by heating a sealed vessel in a microwave (120 °C, 5 bar) for 10 minutes, about twenty times faster.



*How can the reaction conditions from a traditional reaction be transferred to a microwave reaction?*

In order to understand the necessary changes, one has to go back to the Arrhenius equation, which predicts that an increase of temperature by 10 °C results in 2-fold rate increase for many reactions (the exact rate change depends on the activation energy of the reaction). For instance, a reaction that requires eight hours to complete at 80 °C, has the potential to be completed in about one hour at 110 °C, in about seven minutes at 140 °C and in two minutes at 160 °C (shown in bold in the table below). However, limiting factors like thermal stability of the reagents, the catalyst, the solvents and the products have to be considered in the choice of conditions as well. In addition, one has to keep in mind that a higher temperature during the reaction can lead to more byproducts as well. In some cases, it is necessary to carry the reaction out under an inert gas to reduce oxidation at the higher temperatures.

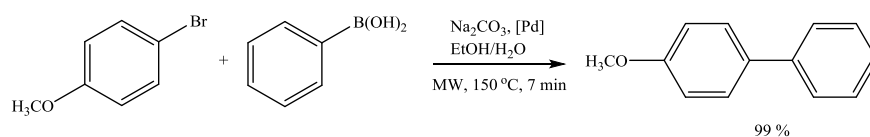
### Conversion Table (excerpt)

<i>Temp</i>	<i>Time</i>									
20 °C	1	2	4	6	8	12	24	48	96	168
30 °C	30	1	2	3	4	6	12	24	48	84
40 °C	15	30	1	1.5	2	3	6	12	24	42
50 °C	8	15	30	45	1	1.5	3	6	12	21
60 °C	4	8	15	23	30	45	1.5	3	6	10.5
70 °C	2	4	8	11	15	23	45	1.5	3	5
80 °C	56	2	4	6	8	11	23	45	1.5	3
90 °C	28	56	2	3	4	6	11	23	45	1.4
100 °C	13	28	56	1.5	2	3	6	11	23	40
110 °C	7	13	28	42	56	1.5	3	6	11	20
120 °C	4	7	13	21	28	42	1.5	3	6	10
130 °C	2	4	7	11	13	21	42	1.5	3	5
140 °C	1	2	4	5	7	11	21	42	1.5	3
150 °C		1	2	3	4	5	11	21	42	1.5
160 °C			1	1	2	3	5	11	21	42
170 °C					1	1	3	5	11	21
180 °C							1	3	5	11
190 °C								1	3	5
200 °C									1	3
210 °C										1

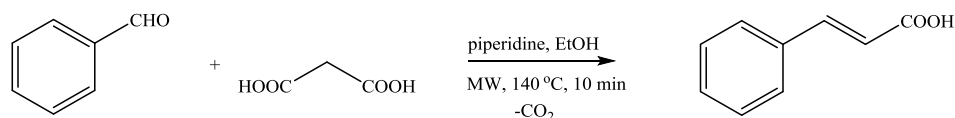
Legend: dark gray (hours), light gray (minutes or hours), no shading in italic (seconds or minutes)

### Examples

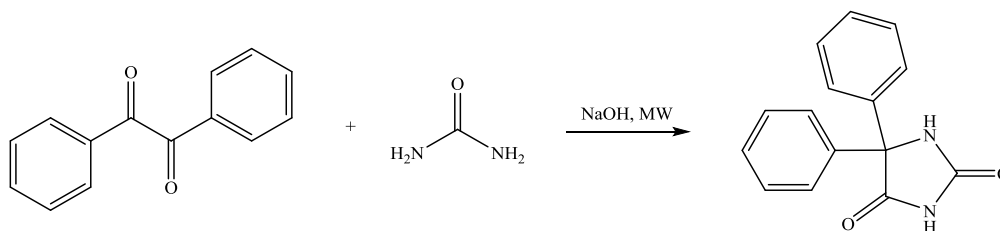
While microwave synthesis was originally mainly of academic interest, it has gained more interest in industrial setting nowadays as well (i.e., medical/pharmaceutical chemistry, material science/preparation of nanoparticles, polymer chemistry, crop protection, cosmetic and fragrances, biotechnology/biomedical chemistry, dye protection). Now about 1000 papers are published annually that involve microwave-assisted synthesis covering a broad range of applications: addition reactions, metal-catalyzed reactions, condensation reactions, substitution reactions, preparation of ionic liquids and nanomaterials. For instance, many palladium-catalyzed carbon-carbon coupling reactions (Heck, Negishi, Suzuki-Miyaura) can be carried out using microwave technology. The reaction below affords a 99 % yield in 1.3 mmol scale while a 96 % yield is observed in 182 mmol scale (conventional: 80 °C, 4 hr, 99 %).



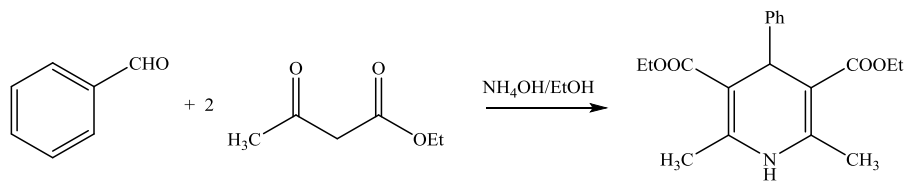
The Knoevenagel condensation of benzaldehyde and malonic acid employing piperidine as base catalyst at 140 °C for 10 min affords a yield of 85 % (5 mmol) and 86 % (0.5 mol) in different scales. However, it is important to note that the pressure in the system increased significantly due to the formation of carbon dioxide (conventional: 85 °C, 24 hr). Thus, additional precautions have to be taken here.



The reaction of benzil with urea using a base catalyst yields phenytoin. The reaction in ethanol using potassium hydroxide yields 66 % of the product at 50-60 °C in two hours. Under solvent-free conditions, using NaOH as base affords a yield of 98 % in 2 min (100 W).



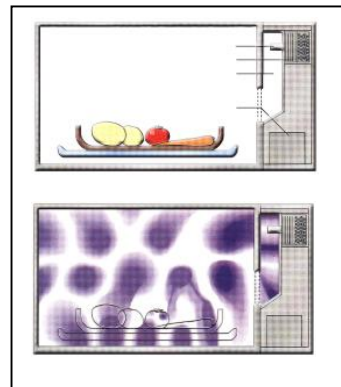
The Hantzsch reaction of benzaldehyde with two equivalents of ethyl acetoacetate in the presence of ammonia in ethanol yields a dihydropyridine. The conventional synthesis affords a 50 % yield after a 12-hour reflux (EtOH, ~80 °C). The microwave-based synthesis in a dedicated reactor uses a higher temperature (140 °C) and is completed after 10 minutes producing an 84 % yield. Interestingly, this reaction was first carried out in a domestic microwave oven about 20 years ago. It only yielded 52 % after 4 minutes of heating due to overheating leading to decomposition of the product (i.e., oxidation to the pyridine).



## Microwave Systems

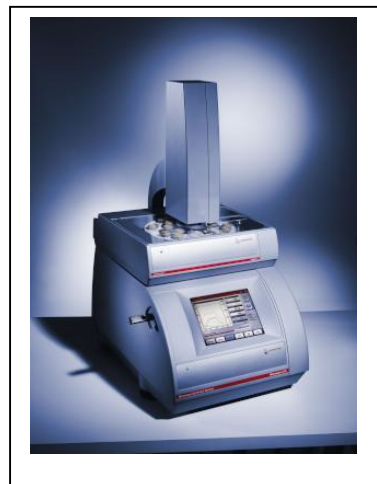
### *Domestic Microwave Oven (Cost: ~\$100-200)*

For the past seven years, a domestic microwave has been used in Chem 30BL and Chem 30CL. While some reactions seem to work well, overheating has often been observed resulting in thermal decomposition of the compound in the reaction mixture (charring). In some cases, the reaction also caught fire due to the local overheating of the reaction mixture. This is a result of hot spots (darker spots in the temperature profile picture on the lower right) in the microwave because domestic microwaves are multimode systems. This means that the temperature in the microwave can be quite different in various parts of the microwave. In addition, the standing wave pattern will change if objects are placed in the microwave making it even more difficult to control the conditions for a larger number of samples. While the microwave oven that was used allowed the control of power output to some extent, dialing in a specific temperature was not possible due to the lack of temperature monitoring features. In addition, since the reactions were carried out in an open vessel, the experimenter could not use a solvent (due to safety reasons). All reactions were carried out solvent-free, which makes the temperature control even difficult because the heating rate and heat distribution in the sample did vary greatly.



### *Dedicated Microwave Reactor (Cost: ~\$30-\$50K)*

Recently, a Monowave 300 with Autosampler MAS24 from Anton Paar was purchased for the undergraduate lab courses. The reactor has one magnetron that provides 850 W microwave power (220 V). The reaction vessel will be a 10 mL (or 30 mL) container. The reactor can reach temperatures up to 300 °C. The temperature in the reaction vessel is monitored using an infrared sensor. The system has a pressure sensor that is based on a non-invasive hydraulic system that provides an immediate pressure feedback up to 20 bar. The system is equipped with a camera, which allows the experimenter to watch the progress of the reaction (i.e., color change, melting, dissolution, and precipitation). The reaction mixture can be stirred as well. The autosampler allows setting up as many as 16 samples (10 mL) and/or 8 samples (30 mL) at a given time, each of which can use different parameters for the run. The software allows monitoring several parameters i.e., pressure, temperature, heating input, etc. The system's safety features shut down the run if an overheating or excessive pressure is observed. These systems can also be used for digestion of samples.



## Summary

What are the benefits of microwave synthesis in dedicated reactors?

1. *Possibility of convenient superheating of the solvent*
  - a. Achieve higher reaction temperatures
  - b. Dramatically shortens the overall process time
  - c. Obtain higher yields and purer compounds (if the reaction is performed correctly)
2. *Excellent parameter control*
  - a. Improved reproducibility
  - b. Utmost handling convenience
3. *Access to automated setups and/or parallel synthesis*
  - a. Improves efficiency
  - b. Time equals money
4. *Possibility of stirring*
  - a. Improves temperature homogeneity
  - b. Increases the scientific validity of the results
5. *Continuous power output*
  - a. Sophisticated reaction control
  - b. Safe and smooth processing
6. *Intuitive user interface via touchscreen*
  - a. Convenient programming and data management
  - b. Automatic data recording
7. *Utmost Safety even under high pressure/temperature conditions*

## References

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