

MICROWAVES IN ORGANIC CHEMISTRY: IS IT JUST A BUNCH OF HOT AIR?

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BACKGROUND AND INTRODUCTION

Although first reported by the groups of Gedye¹ and Giguere/Majetich² in 1986, the use of microwaves (MWs) in organic synthesis was initially hampered by a lack of understanding of the basic principles of MW dielectric heating and the inability to obtain reproducible results with domestic MW ovens. Today over 2000 articles have been published in the area of MW-assisted organic synthesis, including several reviews³⁻⁹ that discuss the scope and benefits of MW heating, and the obstacles first associated with laboratory MW use are beginning to disappear. In addition to improved yields and increased reaction rates, MWs provide the possibility of applying milder and/or less toxic reagents and represent an increasingly popular theme in scientific literature.

MW frequencies range from 0.3 to 300 GHz, but most domestic ovens and chemical reactors operate at a frequency of 2.45 GHz (corresponding to a wavelength of 12.24 cm) in order to avoid interference with telecommunication frequencies. Thus, the energy of a MW photon (0.037 kcal/mol) is too low to break chemical bonds or induce reactivity. (In comparison, the energy of Brownian motion is 0.392 kcal/mol and the energy contained within hydrogen bonds ranges from 0.908 to 10.038 kcal/mol).^{3,10} While conventional heating (CH) transfers energy to reaction vessels via conduction or convection, MW-enhanced chemistry is based on temperature increase by dielectric heating, which operates through two mechanisms: dipolar polarization and ionic conduction. The electric field component of MW irradiation causes dipoles and ions to align, and as the applied electric field oscillates, the dipole-ion field is forced to realign itself. In this process energy is lost as heat through both molecular friction and dielectric loss.⁴

Clearly, MW dielectric heating functions quite differently than CH. MW irradiation enhances reaction rates and increases yields by limiting side reactions.³ While some believe that these results can be explained through thermal influences, others argue that additional nonthermal or specific MW effects are at work. The exact source of MW enhancement is the subject of much controversy.¹¹⁻¹⁵ This seminar will examine detailed results from both sides of the debate in an attempt to discover the true origin of MW effects.

THERMAL EFFECTS

A substance's ability to convert electromagnetic radiation into heat depends on dielectric properties,¹⁶ and is calculated by the loss angle, $\tan\delta$, which is expressed as $\tan\delta = \epsilon''/\epsilon'$. The loss

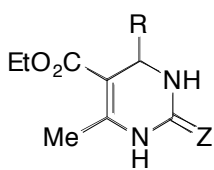
factor ϵ'' quantifies the efficiency with which the absorbed energy is converted into heat, while ϵ' , the dielectric constant, describes the ability of molecules to be polarized by an electric field. A reaction medium with a high $\tan\delta$ value efficiently absorbs electromagnetic radiation and converts it into heat, whereas substances with low $\tan\delta$ values are considered transparent to MWs.³ Thermal effects are accelerations in rate that can not be achieved or duplicated by CH but are essentially the result of dielectric heating. These include the superheating of solvents up to 40°C above their boiling points under MW irradiation at normal atmospheric pressure, as well as the selective heating of strongly MW-absorbing catalysts or reagents in a heterogeneous reaction mixture.^{3,17}

While the multi-component Biginelli dihydropyrimidine synthesis involving the one-pot cyclocondensation of a β -keto ester with an aryl aldehyde and urea (or thiourea) involves reaction times of 2-24 h under CH (80°C, reflux),

MW heating has reduced reaction times to 3-11 min (200-300W).^{18,19} Stadler and Kappe²⁰ probed this reaction to determine if the observed increases were a consequence of a specific MW effect or only a result of more

Table 1. Yield comparison of microwave mediated (80°C, 300 W, 3h) and conventional (80°C, 3h) Biginelli reactions in EtOH

Product R	Z	Yield %	
		MW	CH
phenyl	O	78	80
3,4-dimethoxyphenyl	O	49	54
phenyl	S	29	33
3-nitrophenyl	S	<1	<1



efficient heating. Although the Biginelli synthesis was carried out under several different MW conditions, it was eventually concluded that there was no appreciable difference in reaction rates or yields between syntheses carried out under MW and CH at identical temperatures (**Table 1**). Previously observed differences in reaction rates and yields were attributed to superheating, increased pressures in sealed vessel experiments, and solvent evaporation in open flasks. Substantial MW enhancements were only observed in the absence of solvent, which can be a consequence of hot-spots or the MW-assisted

Table 2. Yield comparison of microwave mediated and conventional Suzuki coupling reactions²²

Aryl halide	Yield %			
	MW	CH	MW	CH
	73	77	86	73
	86	92	86	92
	80	86	80	86
	62	5	62	5

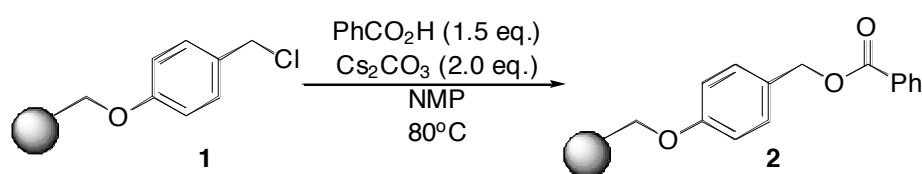
removal of the water generated in the course of the reaction.²⁰

Palladium-catalyzed cross coupling of aryl halides with boronic acids is one of the most useful reactions

for formation of carbon-carbon bonds. As early as 1996, the first high yielding MW-assisted Suzuki couplings were reported with reaction times of 3-4 minutes. In contrast, CH produced similar conversions only after 6 hours.²¹ In order to ascertain whether these improved reaction rates were simply due to efficient thermal heating under MW irradiation or a specific MW effect, Leadbeater and Marco²² monitored temperatures, pressures, and reaction times in a series of aqueous Suzuki couplings completed with Pd(OAc)₂ catalyst and the additive Bu₄NBr. It was revealed that this reaction can be performed equally well using CH or MW conditions (**Table 2**). Previously observed increases in reaction rates were associated with improved heating efficiency under MW irradiation.

Significant rate accelerations and higher loadings have been observed for the attachment of aromatic and aliphatic carboxylic acids to Wang resins under MW irradiation (**Scheme 1**). MW flash heating at 200°C has reduced reaction times to 5-15 min. In comparison, the analogous CH method took 2-48 h at 50-80°C,²³ and degradation of the polymer support was often observed. Although the benefits

Scheme 1. Coupling of benzoic acid to Wang resin

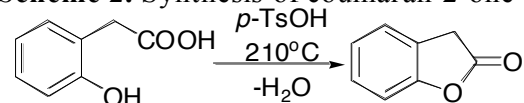


of MW-enhanced chemistry in solid-phase synthesis can not be denied, Stadler and Kappe²⁴ were interested in rationalizing these dramatic

rate improvements in terms of a thermal or specific MW effect. A kinetic comparison between the thermal and MW-assisted couplings of benzoic acid to resin **1** was completed at both 80 and 200°C. While the MW-enhanced process proceeded at a slightly faster rate in the early stages of the experiment, it was discovered that the overall reaction rates and yields were the same for both processes. The small rate and yield enhancements observed under MW irradiation were attributed to the rapid heating of the solvent rather than specific MW effects.²⁴

Goncalo and coworkers studied the lactonization of 2-hydroxy-phenylacetic acid under both MW and CH (**Scheme 2**).²⁵ Although direct irradiation of the starting acid failed to produce the dehydrated product, upon placement in an alumina

Scheme 2. Synthesis of coumaran-2-one



bath, 85% conversion to product was observed after 6 min of irradiation (210°C). A similar experiment completed with CH under identical conditions (210°C, 6 min) produced the lactone with yields of only 63%, indicating the possibility of a non-thermal MW effect. Comparisons between MW and CH were subsequently invalidated by measurement of the temperature distribution within the monomodal MW oven. Initially an IR pyrometer was used to measure and control the temperatures of the MW-mediated reactions. Unfortunately this technique only measures surface temperatures, and an optical fluorescence

Table 3. Temperature distribution in a microwave oven after 240 s²⁵

x ^a (mm)	y ^b (mm)	T (°C)
0	0	259
0	1.5	256
0	3	262
3	0	245
3	3	265
6	0	275
6	3	290

^aHorizontal coordinate from axis of reactor. ^bVertical coordinate from bottom of reactor

device indicated that temperatures within the MW reactor ranged from 245-290°C (**Table 3**). When the synthesis of benzofuran-2(3H)-one was completed with CH at 245°C, product was obtained in 85% yield, indicating the absence of any specific MW effect.²⁵

Finally, ene reactions involving carbonyl enophiles have been carried out under controlled MW irradiation.²⁶ In this case, the ene reaction provided a good model because the required experimental conditions are homogeneous and permit a comparative kinetic study with CH. Additionally, it was proposed that the polar carbonyl group of the enophile

would serve as an “antenna” for MW effects through its direct interaction with the electromagnetic field. Rates and yields of the reactions of diethyl mesoxalate with 1-decene and β-pinene as well as the cyclization of (+)-citronellal were independent of the heating mode, thus eliminating the possibility of a specific MW effect in this case (**Scheme 3**).

SPECIFIC MW EFFECTS

On the other hand, some have suggested the possibility of specific MW effects, which are characterized as rate accelerations, yield improvements, or selectivity changes that can not be explained by thermal effects. The existence of nonthermal MW effects is often explained in the literature by consideration of the terms in the Arrhenius equation, $k = Ae^{-E_a/RT}$. The pre-exponential term, A , describes molecular mobility and depends on the frequency of vibrations at the reaction interface.^{28,27} Since MWs induce an increase in molecular vibrations,¹⁶ it was proposed that this could also cause an increase in the A factor of the Arrhenius law. Others have predicted that MWs might increase the overall organization of a reaction, decrease ΔG^\ddagger , and increase reaction rate, especially if polarity increases from reactant to transition state (TS) during the course of a reaction.²⁹

Scheme 3. Ene reactions with carbonyl enophiles

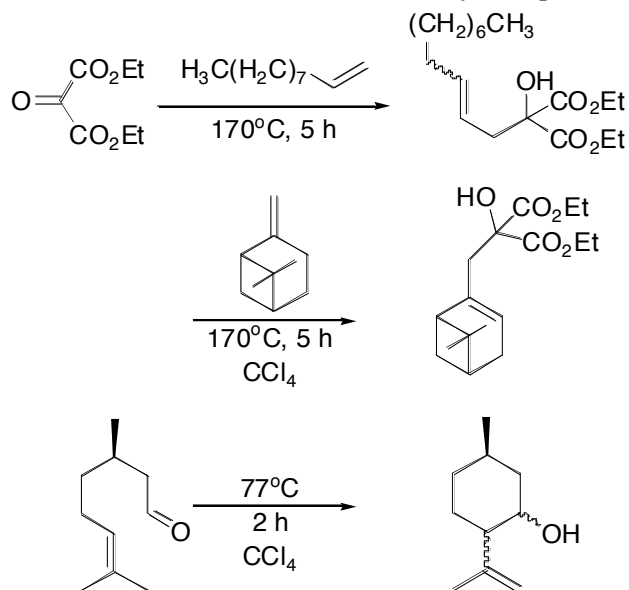


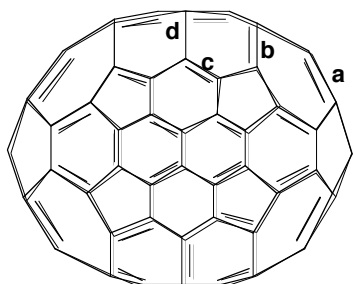
Table 4. Effects of X and R groups in the synthesis of phosphonium salts³⁰

PR ₃ + PhCH ₂ X → PhCH ₂ ⁺ PR ₃ X ⁻		Yield %	
R	X	MW	CH
Ph	Br	99	99
Ph	Cl	78	24
Ph	N ⁺ Me ₃ Cl ⁻	70	0
<i>n</i> -C ₄ H ₉	Br	94	92
<i>n</i> -C ₄ H ₉	Cl	92	87
<i>n</i> -C ₄ H ₉	N ⁺ Me ₃ Cl ⁻	100	0

reactions with benzyl bromides exhibited a negligible specific MW effect, benzyl chlorides and BTAC seemed to be more prone to specific MW effects. This behavior is compatible with the consideration of the position of the TS along the reaction coordinate, as it is proposed that for a polar reaction mechanism, a later TS corresponds to an increase in potential MW effects.^{15,31} Additionally, larger MW effects were observed in reactions with the less nucleophilic triphenylphosphine as compared to reactions involving tributylphosphine. Reactions involving triphenylphosphine proceed through a later and thus more product-like (more polar) TS, allowing for increased specific MW interactions.³⁰

Interestingly the regioselectivity of the cycloaddition of *N*-methylazomethine ylide to C₇₀ was altered by using MW irradiation as the source of energy.³² While it is known that C₆₀ contains only one type of [6,6] bond, C₇₀ has four distinct [6,6] bonds of varying lengths, and the 1-2(**a**) and 5-6(**b**) exhibit the highest reactivity.³³ Under MW irradiation at 180°C with the polar solvent *o*-dichlorobenzene (ODCB) the 7-21(**c**) isomer was not formed, while under CH it made up 8% of the product mixture. Additionally, the **a:b** product ratio was changed from 50:50 to 45:55 by increasing the incident MW power (**Table 5**). Either a concerted, thermally-allowed [$\pi 2_s + \pi 4_s$] mechanism or a stepwise

Table 5. Reactivity of C₇₀ with *N*-methylazomethine ylide under conventional and microwave heating³²



	conditions		Yield %	isomer distribution		
	solvent	time (min.)		%a	%b	%c
CH	toluene	120	45	46	41	13
MW (120 W)	toluene	120	32	48	44	8
CH	ODCB	120	32	46	46	8
MW (120 W)	ODCB	30	39	50	50	0
MW (180 W)	ODCB	30	37	45	55	0

mechanism involving nucleophilic addition of the ylide to C₇₀ yielding a zwitterionic intermediate which subsequently closes to form the cycloadduct can be imagined. Theoretical calculations indicated that this cycloaddition proceeds in a stepwise manner,^{32,34} suggesting that the regioselectivity under MW heating

Cvengos and coworkers examined the synthesis of phosphonium salts under MW activation in order to study possible specific MW effects in S_N2 reactions.³⁰ While no appreciable specific MW effects were observed in the reactions of benzyl halides with phosphines in the presence of benzyl-trimethylammonium chloride (BTAC) at 150°C, at a reduced temperature (100°C), significant increases in yield were observed under MW irradiation as compared to CH (**Table 4**). The magnitude of this specific MW effect decreased with increasing leaving group ability; whereas

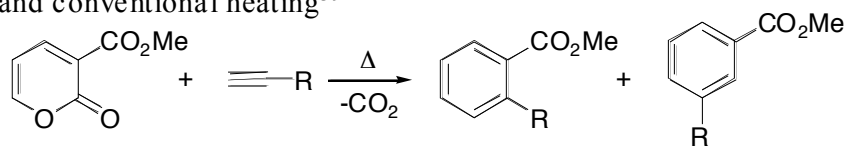
is related to the relative polarities of the TSs involved. Model studies indicated that addition to the **c** bond leads to a nonpolar TS, which can not efficiently interact with the oscillating electric field of the MWs, and therefore is not observed under kinetic control with MW irradiation. A similar explanation was used to rationalize the changes in **a:b** ratios with increasing MW wattage.³²

Studies on the alkylation³⁵ and phenacylation³¹ of 1,2,4-triazole also revealed interesting selectivities which supported specific MW effect arguments. Reaction of benzyl chloride with 1,2,4-triazole under solvent-free conditions gave the 1,4-dialkylated ($N_{1,4}$) product in 13% yield using CH, but with MW irradiation, regioselective benzylation of the 1-position (N_1) was observed in 70% yield. It was assumed that the increased rate of the first benzylation (involving a S_N2 reaction that proceeds through a polar TS) led to the observed selectivity. As an extension of this study, phenylacylation in various solvents was also examined. No MW effects were observed in polar solvents such as DMF and *n*-pentanol, but in nonpolar *o*-xylene, the reaction became totally regioselective under MW irradiation as compared to CH, and produced only the N_1 product. Both reactions were under kinetic control, and this particular MW effect is possibly due to the polarity of the N_1 TS.

Due to the low reactivity of aryl halides, nucleophilic aromatic substitutions are often characterized by long reaction times and harsh conditions, a problem which has been reduced by the use of MW irradiation.^{36,37} Since the etherification of halogenated pyridine derivatives with methoxide has been established as an addition-elimination S_NAr process involving increased polarity from ground state to TS, this reaction was considered ideal to study possible specific MW effects.³⁸ As the authors expected, it was found that when heated under exactly the same conditions, reactions completed with MW irradiation exhibited higher conversions than those under CH. Furthermore, a MW effect was more apparent with chloro- rather than fluoropyridines, and use of 3-chloropyridine as a substrate showed enhanced MW effects when compared to those of 2-chloropyridine. As stated earlier, MW effects are dependent on the position of the TS along the reaction coordinate, and slower reactions should have a greater MW effect, thus explaining the observed results.

Loupy and coworkers have studied the possibility of specific MW effects in irreversible Diels-Alder reactions with acetylenic dienophiles under solvent-free conditions.³⁹ Previous work indicated that with nearly symmetrical reagents, no

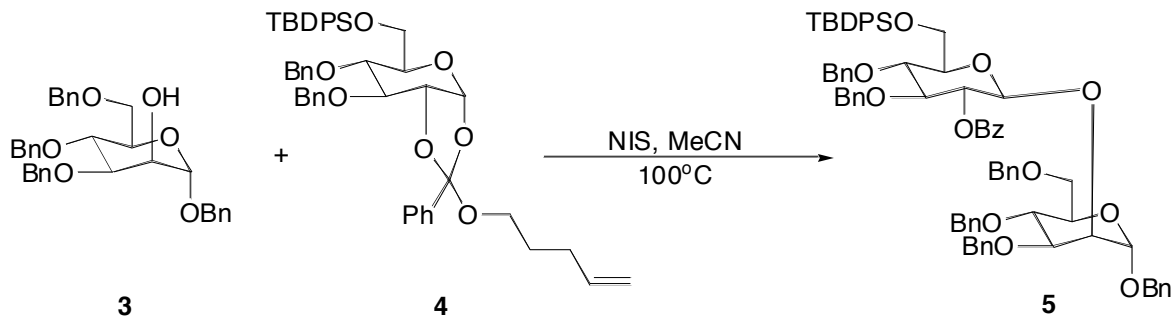
Table 6. Comparison of Diels-Alder reactions under microwave and conventional heating³⁹



	R	time (h)	Yield %	Ratio (X:Y)
MW	CO ₂ Et	2	75	31:69
CH	CO ₂ Et	24	19	42:58
MW	Ph	3	64	100:0
CH	Ph	3	19	100:0

specific MW effects were observed,⁴⁰ but with non-symmetrical and hetero Diels-Alder reactions, MW-enhancement was clearly evident.⁴¹ Strict comparisons between CH and MW heating were carried out, and it was found that the reaction of 3-carbomethoxy-2-pyrone with acetylenic compounds exhibited substantial specific kinetic MW effects (**Table 6**). These were explained in terms of *ab initio* calculations, which indicated an asynchronous mechanism with increasing polarity from ground state to TS.

Finally, development of simultaneous MW irradiation-cooling technology has enabled the effects of MW energy to be studied without substantial increase of the reaction temperature. Coupling of glucoside acceptor **3** with *n*-pentenyl orthoester **4** in the presence of *N*-iodosuccinimide under MW irradiation was investigated at 100°C to test further for thermal versus MW effects.⁴² With only 40-50W of MW power, the coupling product was obtained in only 21% yield; conversely 200W and simultaneous cooling (100°C) provided the desired disaccharide product in 41% yield. The increase in yield can not be attributed to purely thermal effects of MW irradiation, and therefore hints at a possible specific microwave effect.



Scheme 3. Simultaneous irradiation-cooling to form disaccharides

50 W (no cooling)	21%
200 W (with cooling)	41%

CONCLUSION

While MW heating is known to accelerate reaction rates and occasionally lead to altered product distribution compared to CH, the explanation of these MW effects is a source of considerable debate. In many cases, where temperature, pressure and concentration have been carefully monitored, specific microwave effects have not been observed. On the other hand, since the magnitude of the proposed specific microwave effect may be smaller than originally imagined, it is expected that only reactions involving polar transition states completed under low temperature conditions in nonpolar solvents might exhibit such specific effects. Careful research efforts in the future will be necessary to truly understand microwave enhancements in organic synthesis.

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