School of Industrial and Information Engineering
Course 096125 (095857)
Introduction to Green and Sustainable Chemistry

POLITECNICO DI MILANO

Unusual Forms of Energy in Synthesis: Microwave irradiation.

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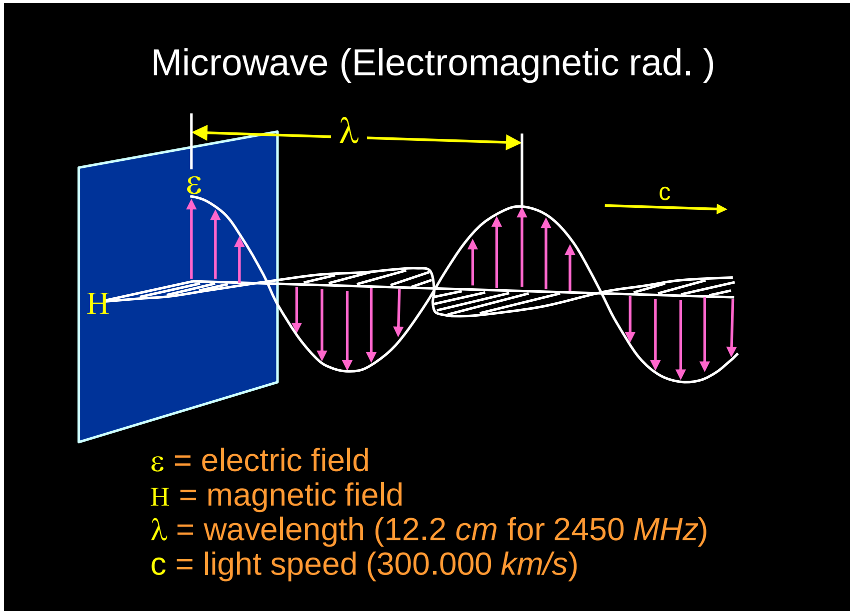
http://iscamapweb.chem.polimi.it/citterio/education/**course-topics/**

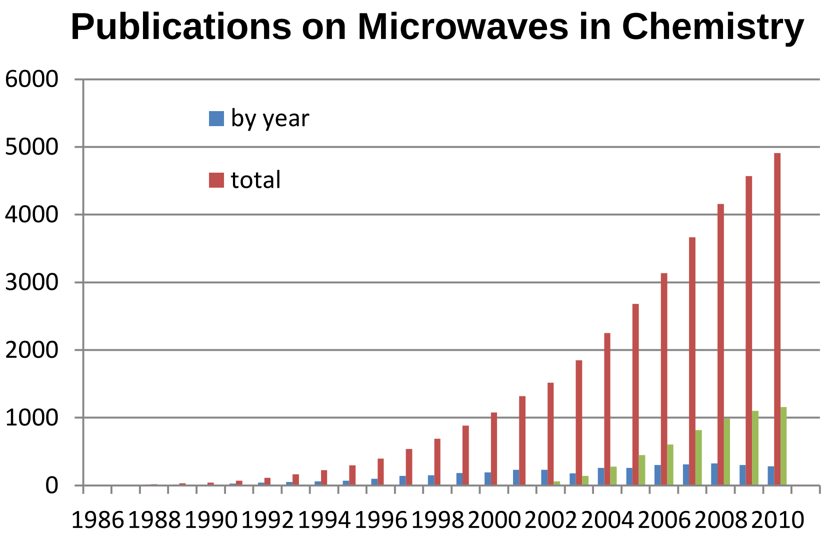
Microwave Irradiation (MW).



Microwave (Electromagnetic rad.)

ε = electric field
H = magnetic field
λ = wavelength (12.2 *cm* for 2450 *MHz*)
c = light speed (300.000 *km/s*)

Microwave Chemistry

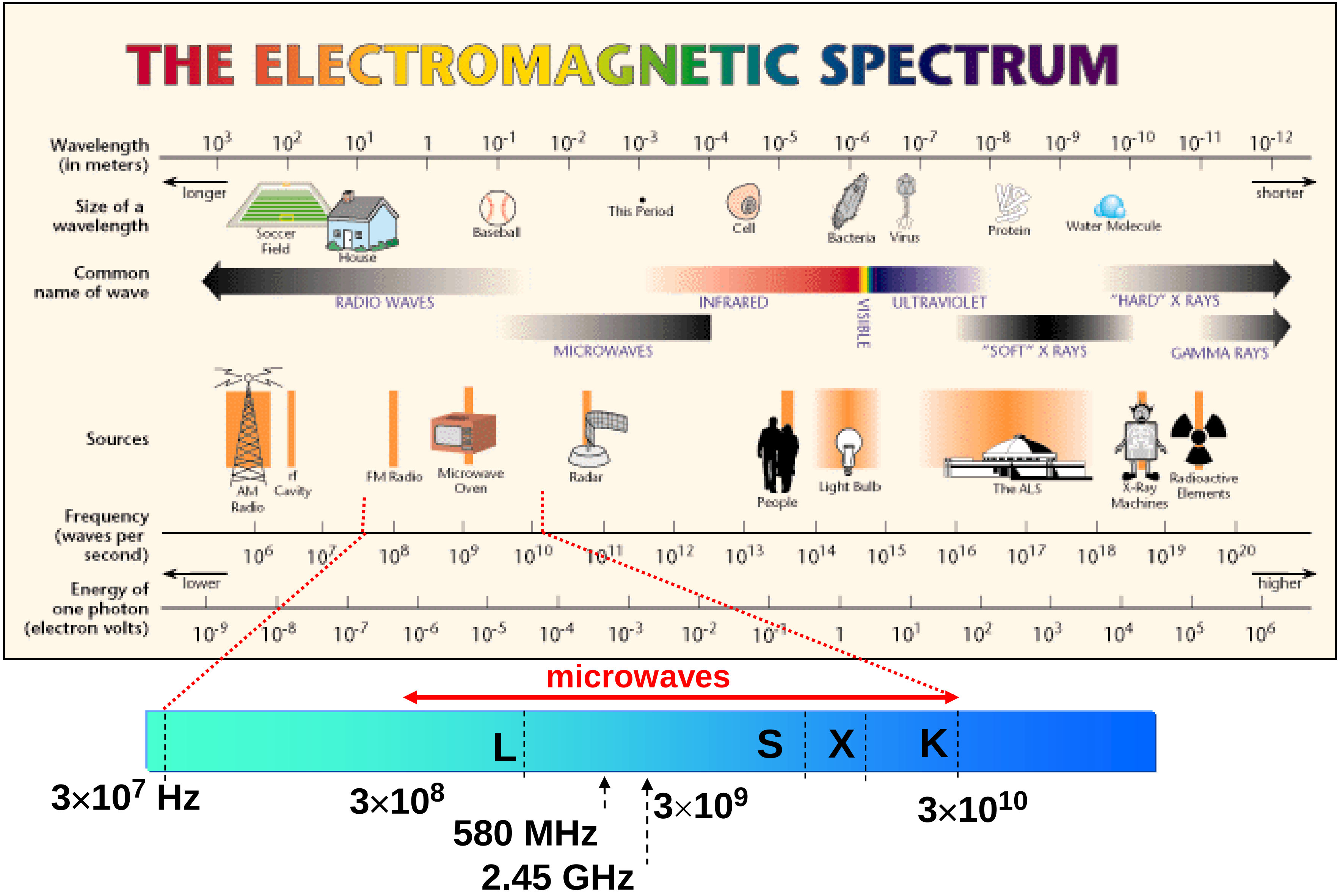


Publications on Microwaves in Chemistry

O. Kappe et al. Microwaves in Organic and Medicinal Chemistry, Volume 52 (2012)

- microwaves (2.45 GHz)
- WWII –radar (magnetron)
- 1950s food industry
- 1984 first application in chemical synthesis

Microwave Irradiation.



microwaves

L **S** **X** **K**

3×10^7 Hz

3×10^8

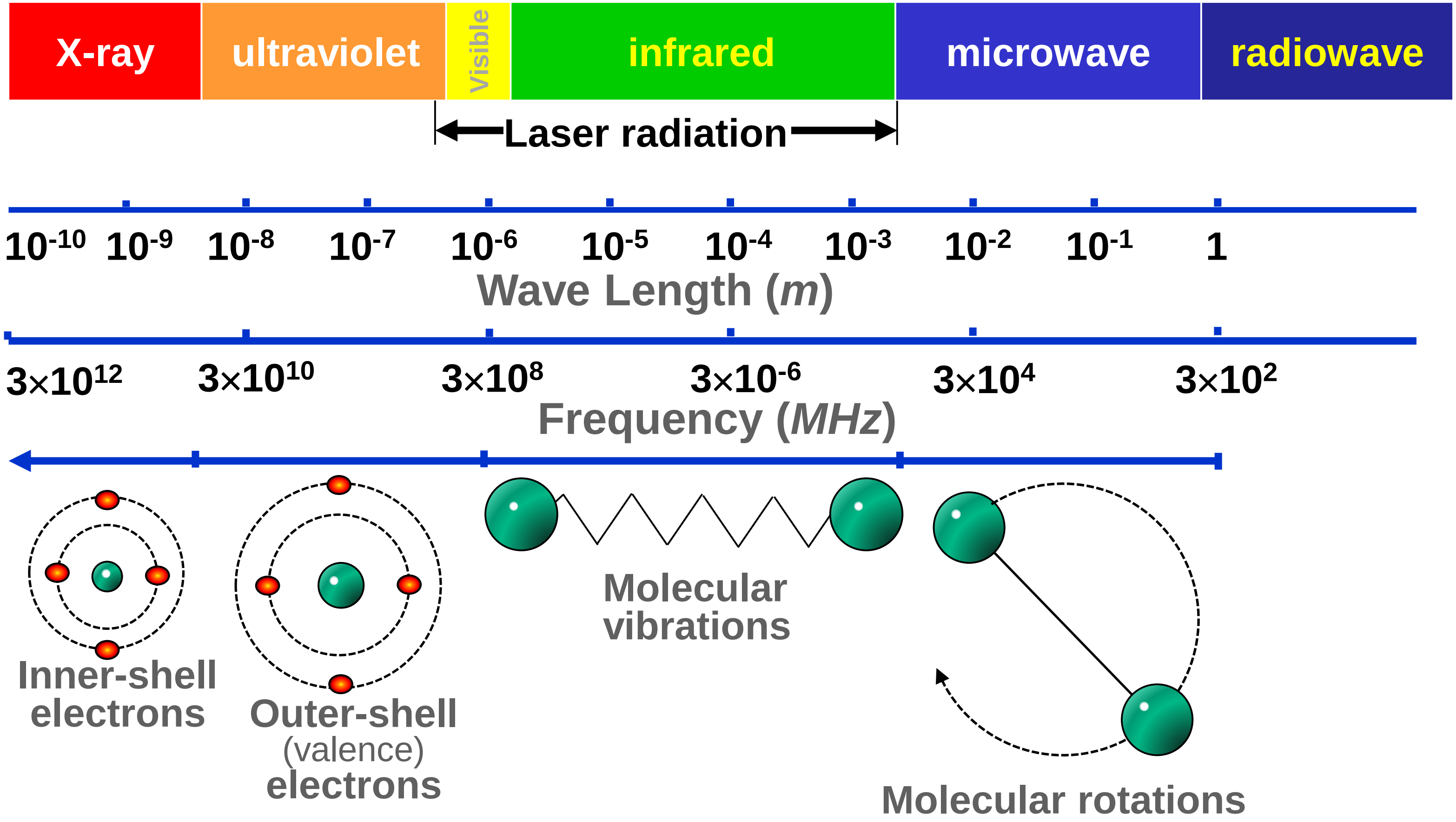
3×10^9

3×10^{10}

580 MHz

2.45 GHz

Electromagnetic Spectrum.



Neas, E.; Collins, M. Introduction to Microwave Sample Preparation: Theory and Practice, **1988**, p. 8.

History or how it all began…

- While fire is now rarely used in synthetic chemistry, it was not until Robert Bunsen invented the burner **in 1855** that the energy from this heat source could be applied.
- There is some controversy about the origins of the microwave power cavity called the **magnetron** – the high-power generator of microwave power.
- The British were particularly forward-looking in deploying radar for air defence with a system called Chain Home which began operation in 1937.
- Originally operating at 22 MHz, frequencies increased to 55 MHz .
- **1921 was published by A.W. Hull the earliest description of the magnetron, a diode with a cylindrical anode**
- **1940 It was developed practically by Randall and Booth at the University of Birmingham in England; they verified their first microwave transmissions: 500 W at 3 GHz.**
- A prototype was brought to the US in September 1940 to define an agreement whereby US industrial capability would undertake the development of microwave radar.
- **1940 the Radiation Laboratory was established at the Massachusetts Institute of Technology to exploit microwave radar.** More than 40 types of tube would be produced, particularly in the S-band (i.e. 300 MHz). The growth of microwave radar is linked with Raytheon Company and P.L. Spencer who found the key to mass production.

History or how it all began (2)…

- **1946 Dr Percy Spencer- the magnetron inventor; he has found a variety of technical applications in the chemical and related industries since the 1950s, in particular in the food-processing, drying, and polymer**
- **surprisingly, microwave heating has only been implemented in organic synthesis since the mid-1980s.**
- Today, a large body of work on microwave-assisted synthesis exists in the published and patent literature.
- Many review articles, several books and information on the world-wide-web already provide extensive coverage of the subject.
- **1969 " Carrying out chemical reactions using microwave energy "** J.W. Vanderhoff – Dow Chemical Company US 3,432,413
- **1986 "The Use of Microwave Ovens for Rapid Organic Synthesis"** Gedye, R. N. et al. *Tetrahedron Lett.* 1986, 27, 279
- **1986** "**Application of Commercial Microwave Ovens to Organic Synthesis"** Giguere, R. J. and Majetich, G. *Tetrahedron Lett.* 1986, 27, 4945

Alternative Heating (old and new).

microwave

oil bath

heating mantle

Bunsen

Energy Calculations in MW.

Hot plate

- Energy = $698\ J\cdot s^{-1} \times 378\ s = 263844\ J = 263.8\ kJ$
- % efficiency = $(42.2\ kJ/263.8\ kJ) \times 100 = 16.0$ %
- Cost = $6.75\ c\cdot kwh^{-1} \times (1\ kwh/3600\ kJ) \times 263.8\ kJ = 0.495\ c$

Microwave

- Energy = $1000\ J\cdot s^{-1} \times 62\ s = 62000\ J = 62.0\ kJ$
- % efficiency = $(42.2\ kJ/263.8\ kJ) \times 62.0 = 68.1$ %
- Cost = $6.75\ c\cdot kwh^{-1} \times (1\ kwh/3600\ kJ) \times 62\ kJ = 0.116\ c$

Charge Oscillation in Matter.

Depending on the frequency, the electromagnetic field put one or more types of charge association under oscillation:

- Inner electrons tightly bound to the nuclei
- Valence electrons
- Free or conducting electrons
- Bound ions in crystals
- Free ions as in electrolytes and nonstoichiometric crystals
- Multipoles (mainly the quadrupoles and an antiparallel association of two dipoles)

Each association has its own critical frequency above which interaction with the field becomes vanishingly small, and the lower the frequency and more configurations are excited.

At frequency of 0.5-5 GHz molecular dipoles and ionic species (including conducting electrons) are the only absorbing charge associations.

Microwave Irradiation – Heating Effect.

Dielectric polarization:

$$\alpha_t = \alpha_e + \alpha_a + \alpha_d + \alpha_i$$

α_t – total polarization

α_e – electron polarization

α_a – atom polarization

α_i – interfacial polarization (Maxwell – Wagner effect)

α_d – dipolar polarization

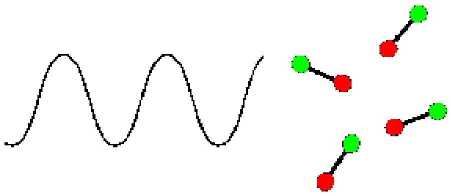
- **MW reactors operate at 2.45 *GHz*.**
- **Electric field oscillates at 4.9×10^9 *Hz* at 10°C/sec heating rate.**

Microwaves – Dipolar Rotation.

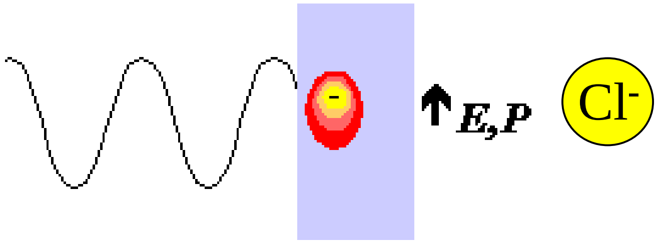
- **Polar molecules have intermolecular forces which give any motion of the molecule some inertia.**
- **Under a very high frequency electric field, the polar molecule will attempt to follow the field, but intermolecular inertia stops any significant motion before the field has reversed, and no net motion results.**
- **At very low frequency of field oscillation molecules will be polarized uniformly and no random motion results.**
- **In the intermediate case, the frequency of the field will be such that the molecules will be almost, but not quite, able to keep in phase with the field polarity.**
- **In this case, the random motion resulting as molecules jostle to attempt in vain to follow the field provides strong agitation and intense heating of the sample.**
- **At 2.45 *GHz* the field oscillates 4.9 × 10^9 *times/s* which can lead to heating rates of 10 °C per second when powerful waves are used.**

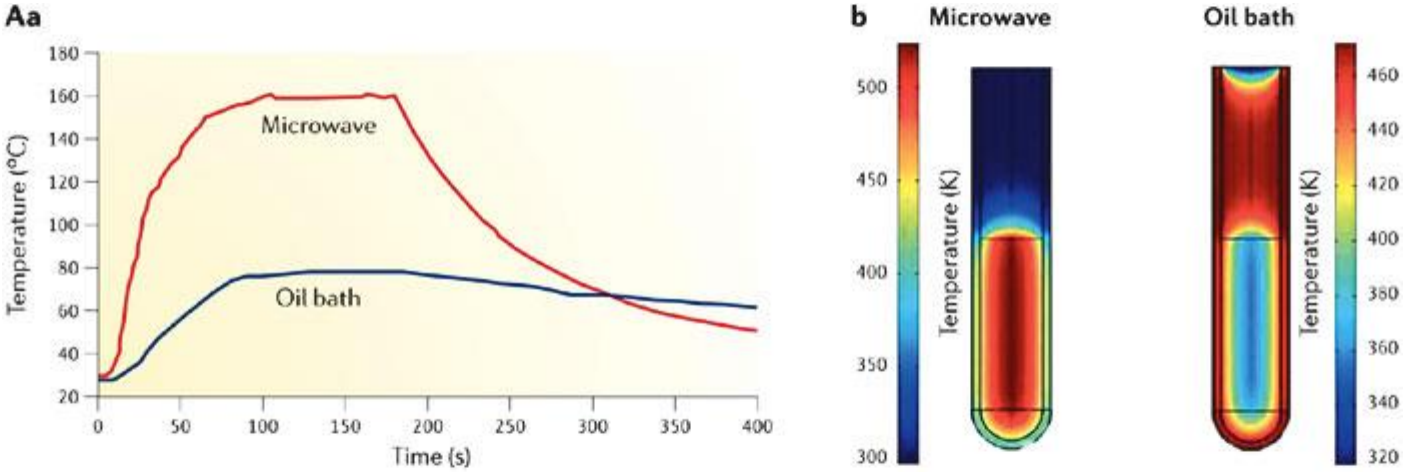
Microwave Irradiation – Heating Effect (2).

Dipole Rotation



Ionic Migration





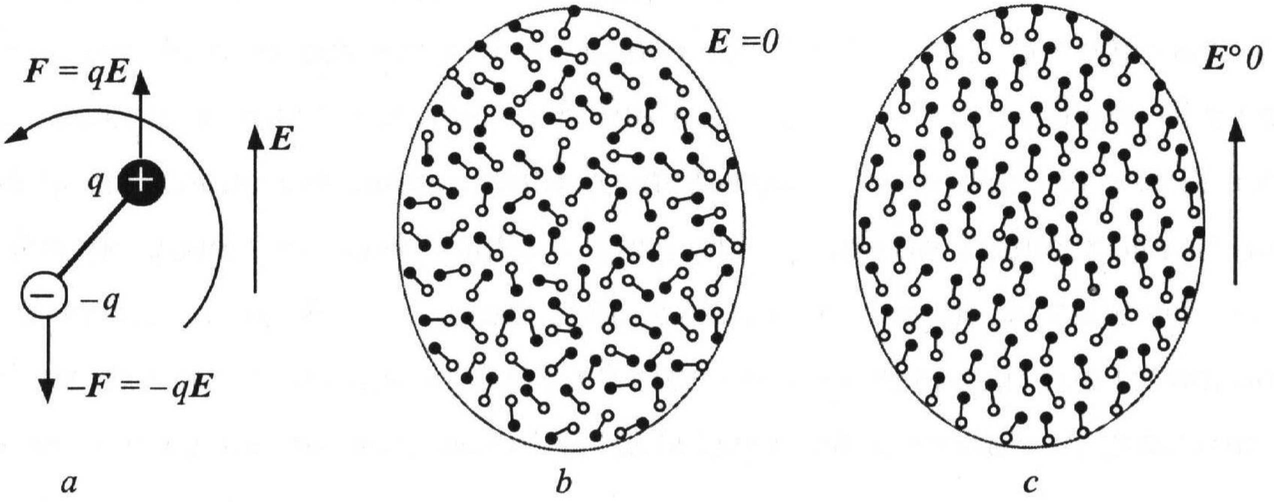
J.-S. Schanche, *Mol. Diversity* 2003, *7*, 293.

Microwave: Effects on Molecules.

Microwaves interacts with permanent and induced dipoles present in molecules inducing:

→ Orientation

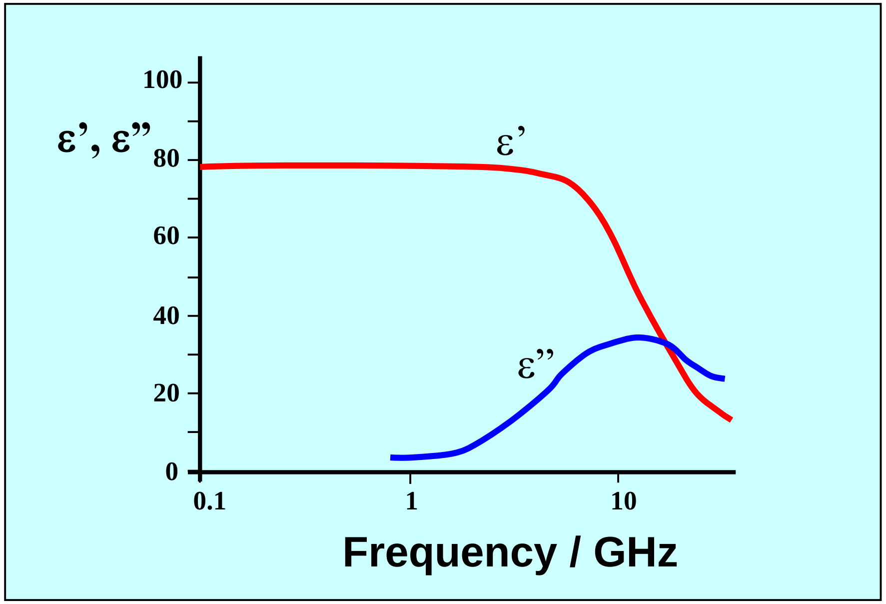
→ Oscillation



Mingos, D. M. P. et al., *Chem. Soc. Rev*. 1991, 20, 1 and 1998, 27, 213

Microwave Irradiation – Heating Effect (3).

Dipolar polarization



Variation of dielectric properties as a function of frequency

$$\tan\delta = \varepsilon''/\varepsilon'$$

ε‘– dielectric constant

ε'' – dielectric loss

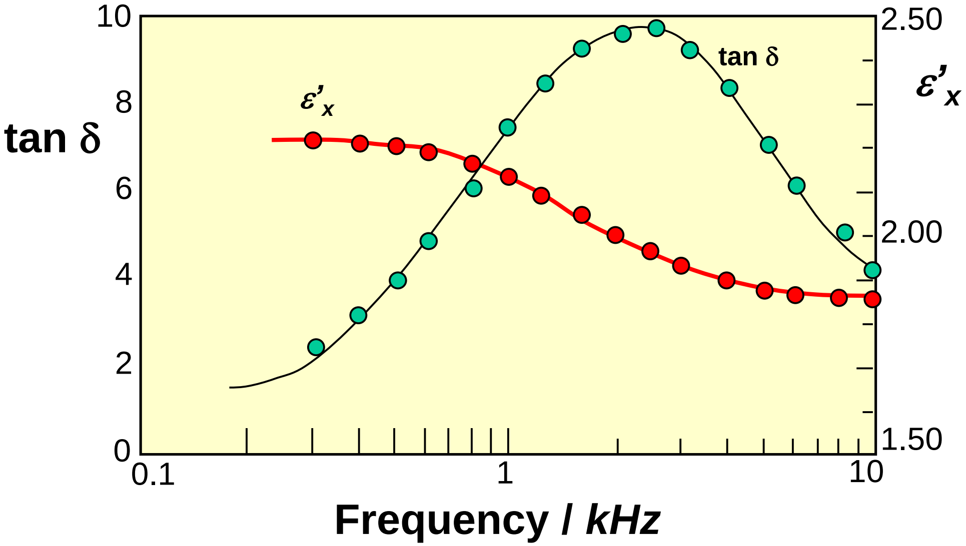
$$D_p \cong \lambda_0 \sqrt{(\varepsilon'/\varepsilon'')}$$

Depth of irradiation

Microwave Irradiation – Heating Effect (4).

Interfacial polarization

$$\varepsilon_i'' \cong \frac{9\upsilon\varepsilon'}{1.8\cdot 10^{10}\sigma}\frac{(\omega\tau)}{(1+\omega^2\tau^2)}$$



v – volume

f_{max} – frequency at max loss

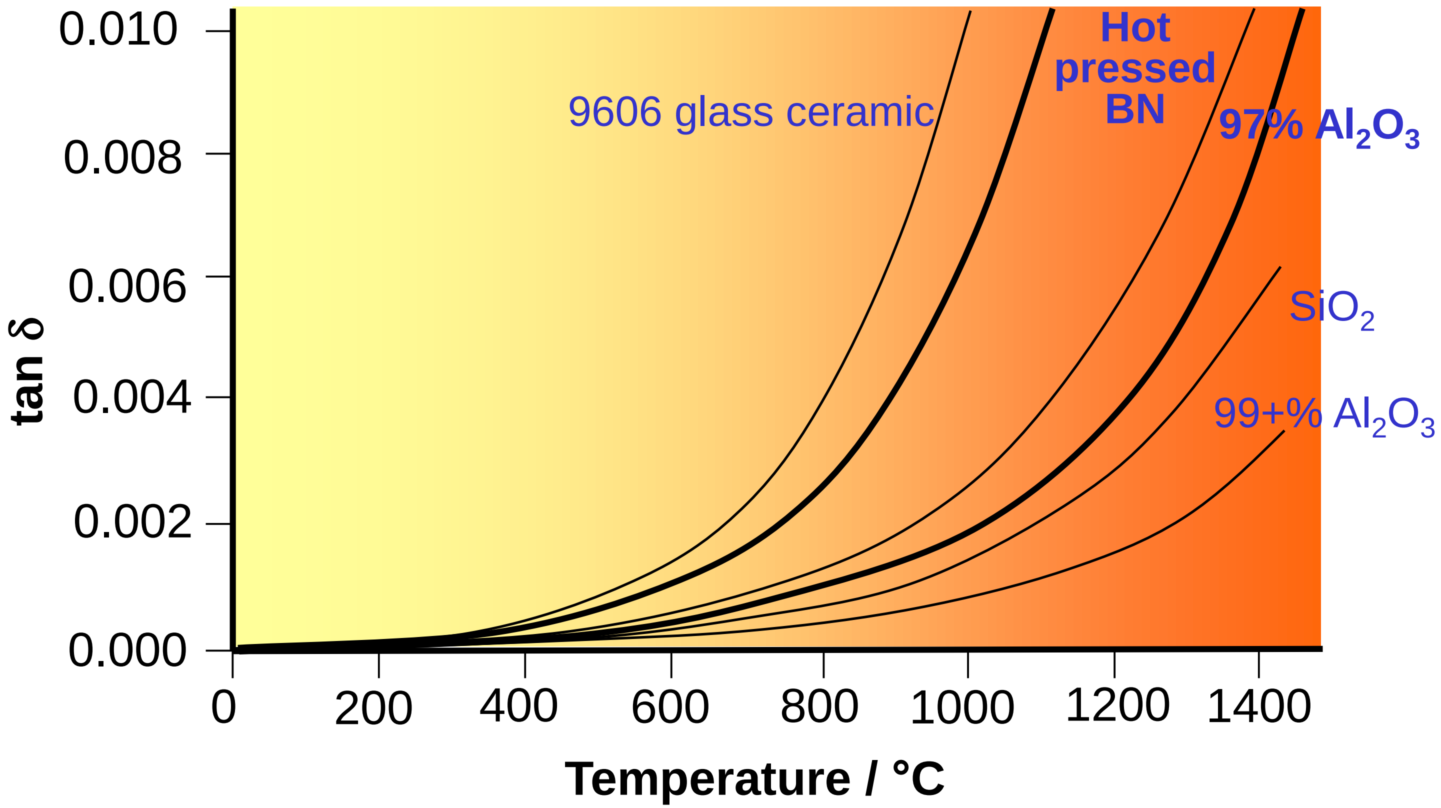
σ - conductivity

ω – frequency of relaxation

τ – time of relaxation

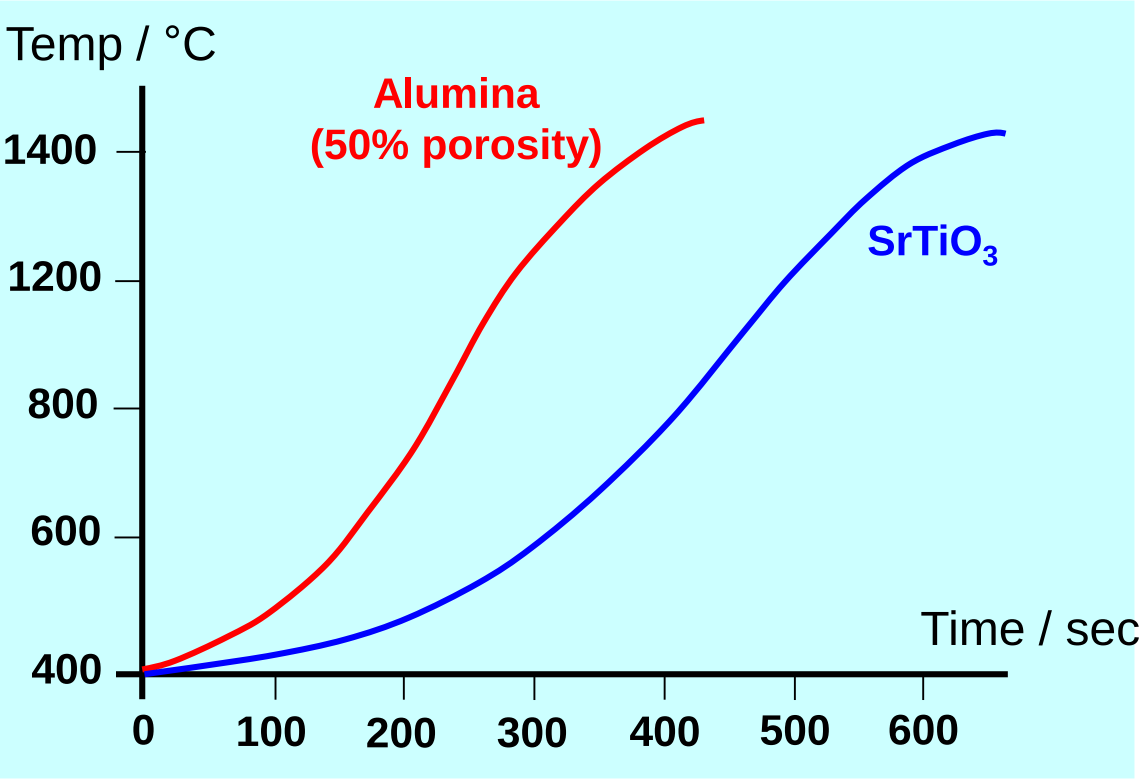
Microwave Irradiation – Heating Effect (5).

Interfacial polarization



Microwave Irradiation – Heating Effect (6).

Interfacial polarization



Dielectric Properties of Solvents.

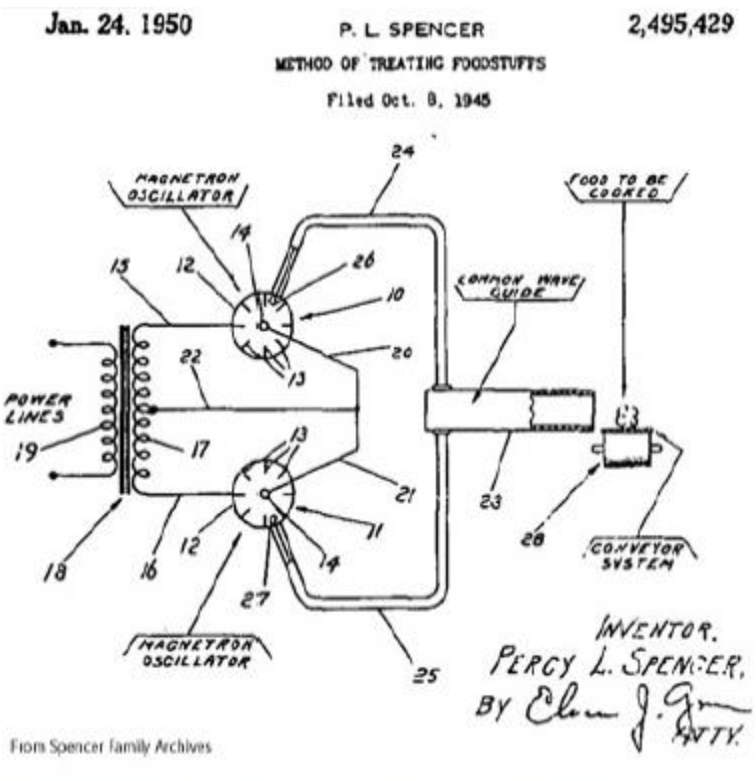
Solvent	Frequency					
	$3 \cdot 10^8$ *Hz*		$3 \cdot 10^9$ *Hz*		$1 \cdot 10^{10}$ *Hz*	
	ε'	ε"	ε'	ε"	ε'	ε"
water	**77.5**	**1.2**	**76.7**	**12.0**	**55.0**	**29.7**
0.1 M NaCl	**76**	**59**	**75.5**	**18.1**	**54**	**30**
heptane	**1.97**	**-**	**1.97**	**0.0002**	**1.97**	**0.003**
methanol	**30.9**	**2.5**	**23.9**	**15.3**	**8.9**	**7.2**
ethanol	**22.3**	**6.0**	**6.5**	**1.6**	**1.7**	**0.11**
1-propanol	**16.0**	**6.7**	**3.7**	**2.5**	**2.3**	**0.20**
1-butanol	**11.5**	**6.3**	**3.5**	**1.6**	**0.2**	**-**
ethylene glycol	**39**	**6.2**	**12**	**12**	**7**	**5.5**
CCl_4	**2.2**	**-**	**2.2**	**0.0009**	**2.2**	**0.003**

Microwave Irradiation – Heating Effect (7).

Sample	P(W)	t(min)	T (°C)	Sample	P(W)	t(min)	T(°C)
water	560	1	81	Al	1000	6	577
methanol	560	1	56	C	1000	1	1283
ethanol	560	1	78	Co_2O_3	1000	3	1290
acetic acid	560	1	110	$FeCl_3$	1000	4	41
$CHCl_3$	560	1	49	NiO	1000	6.2	1305
CCl_4	560	1	28	CaO	500	30	83
Acetone	560	1	56	CuO	500	0.5	701
DMF	560	1	131	WO_3	500	0.5	532
hexane	560	1	25	V_2O_5	500	9	701

Temperature change of materials after 2.45 *GHz* frequency microwave irradiation (*RT* samples, 50 cm^3 liquid, or 25 *g* (1000 *W*) or 5-6 *g* (500 *W*) solids).

Microwaves Application in Heating Food.



Jan. 24, 1950 P. L. SPENCER 2,495,429

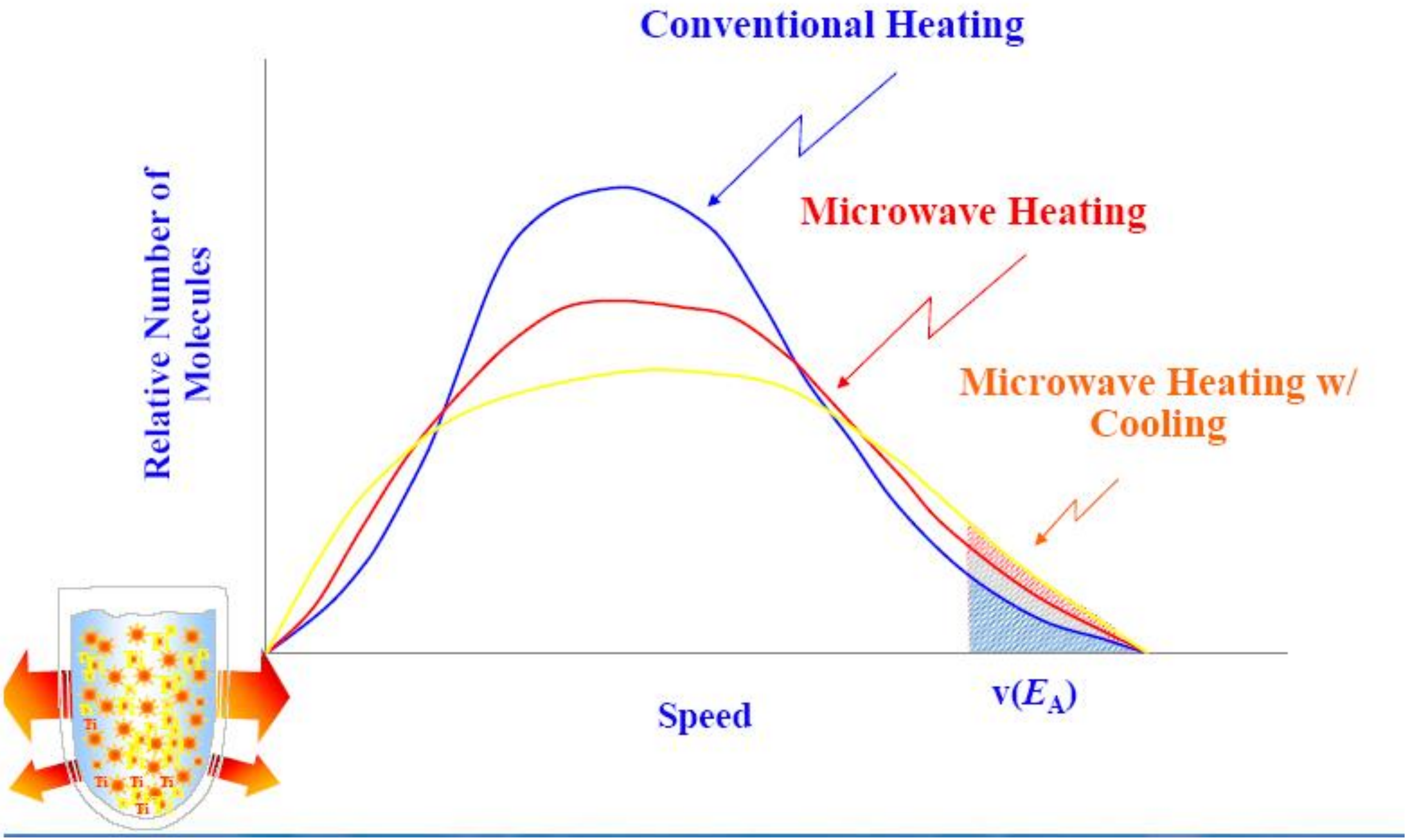
METHOD OF TREATING FOODSTUFFS

Filed Oct. 8, 1945

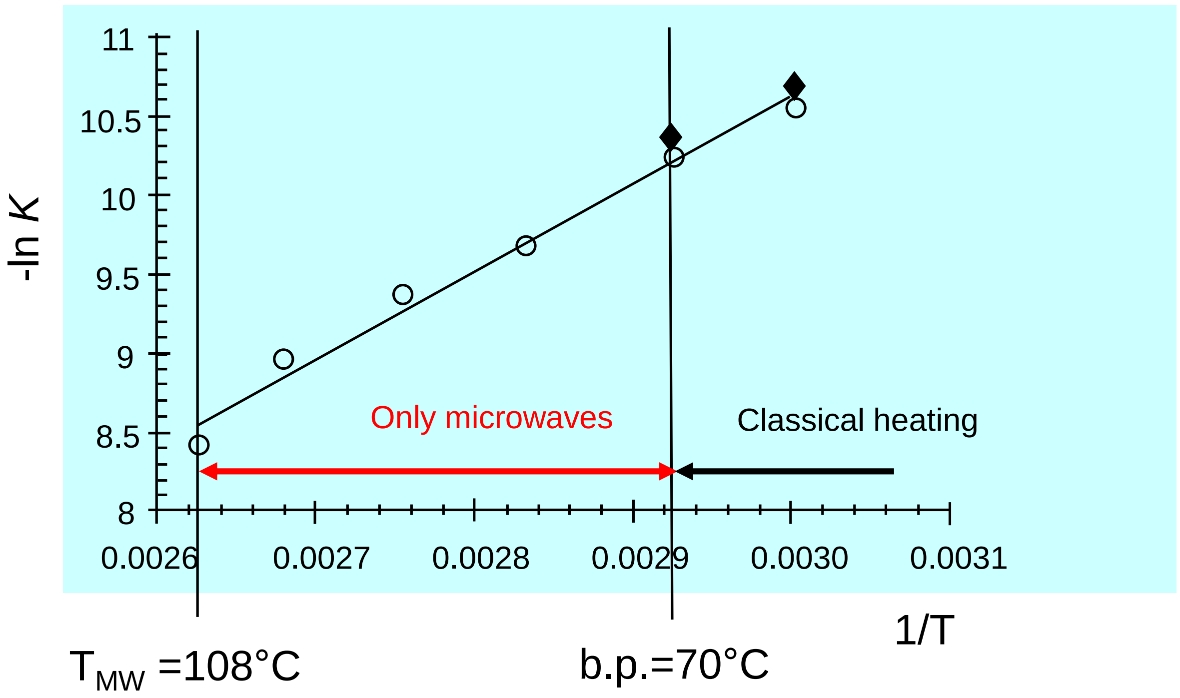
From Spencer family Archives

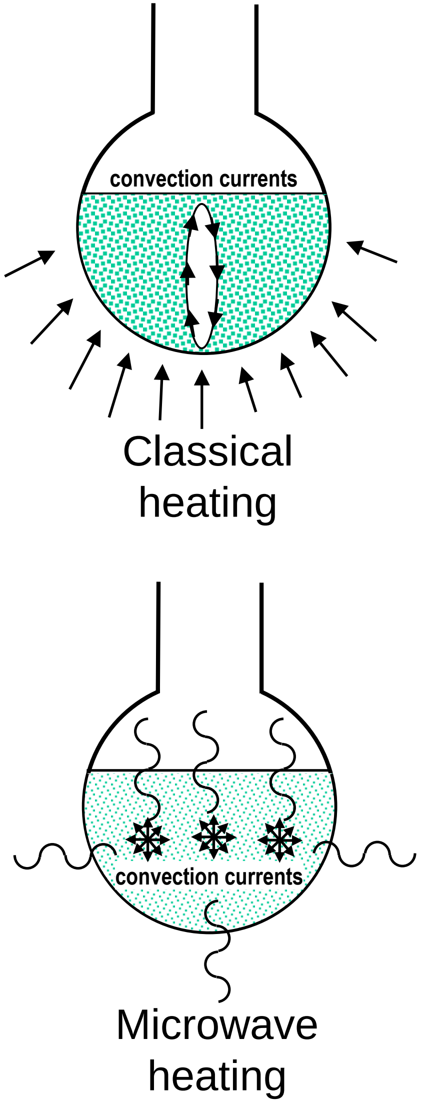
1946: Original patent (P. L. Spencer)
1947: First commercial oven
1955: Home models
1967: Desktop model
1975: U.S. sales exceed gas ranges
1976: 60% of U.S. households have microwave ovens

Molecular Speeds.



Boiling Point Extension.

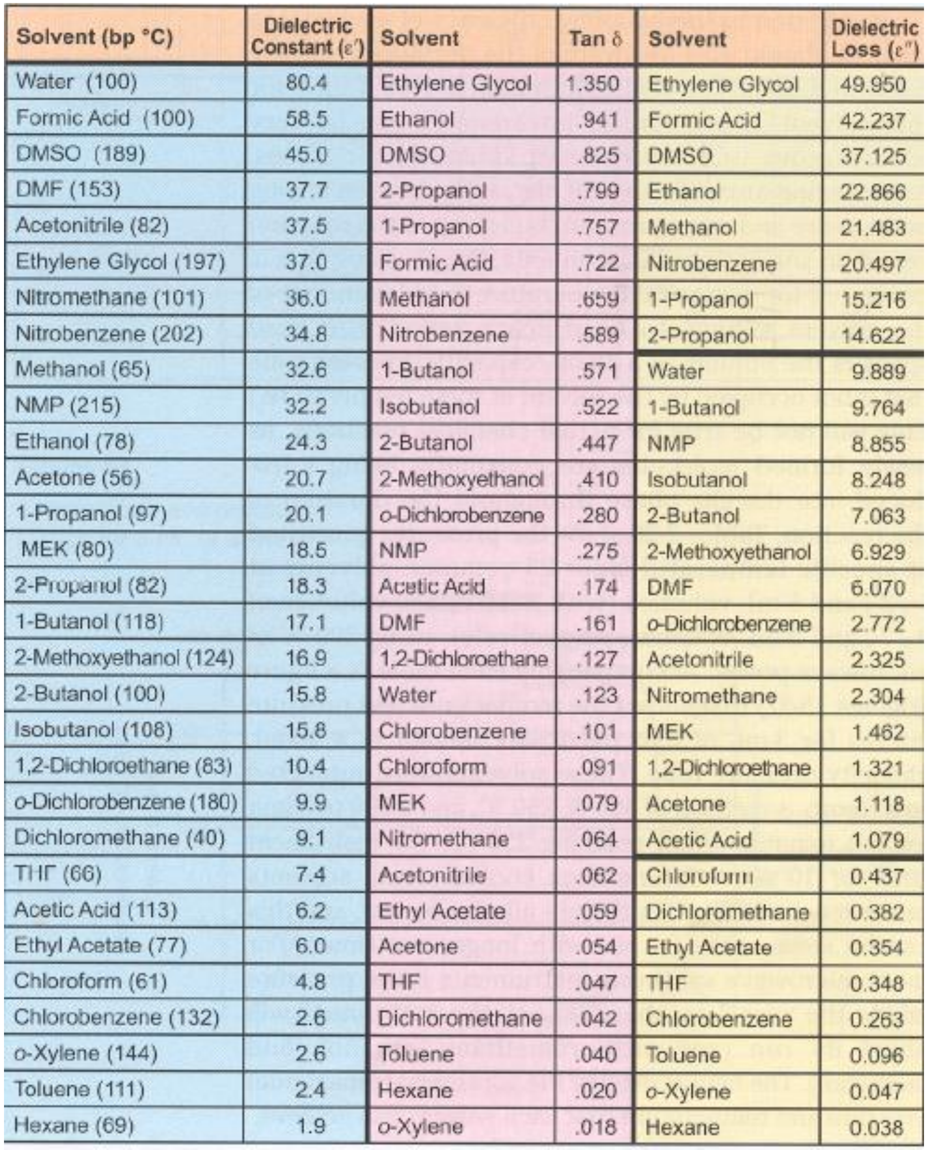




Thermal Effects.

- More efficient energetic coupling of solvent with microwaves promotes higher rate of temperature increase
- Inverted heat transfer, volumetric
- “Hot spots” in monomode microwaves
- Selective on properties of material (solvents, catalysts, reagents, intermediates, products, susceptors)

$$\tan\delta = \varepsilon''/\varepsilon'$$

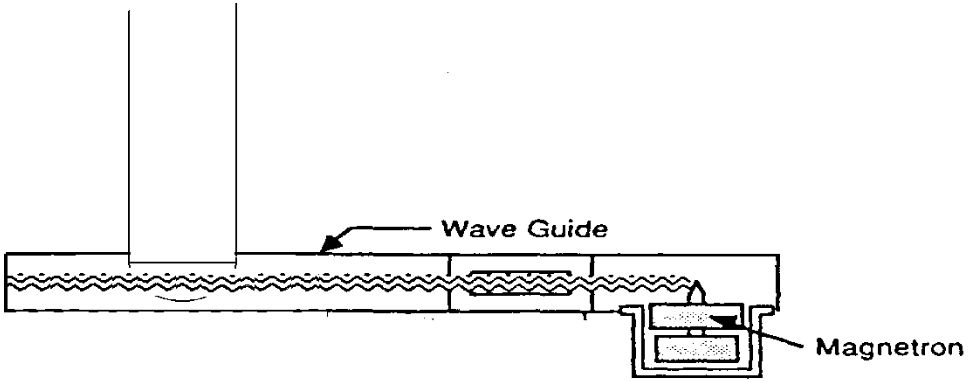


Solvent (bp °C)	Dielectric Constant (ε')	Solvent	Tan δ	Solvent	Dielectric Loss (ε'')
Water (100)	80.4	Ethylene Glycol	1.350	Ethylene Glycol	49.950
Formic Acid (100)	58.5	Ethanol	.941	Formic Acid	42.237
DMSO (189)	45.0	DMSO	.825	DMSO	37.125
DMF (153)	37.7	2-Propanol	.799	Ethanol	22.866
Acetonitrile (82)	37.5	1-Propanol	.757	Methanol	21.483
Ethylene Glycol (197)	37.0	Formic Acid	.722	Nitrobenzene	20.497
Nitromethane (101)	36.0	Methanol	.659	1-Propanol	15.216
Nitrobenzene (202)	34.8	Nitrobenzene	.589	2-Propanol	14.622
Methanol (65)	32.6	1-Butanol	.571	Water	9.889
NMP (215)	32.2	Isobutanol	.522	1-Butanol	9.764
Ethanol (78)	24.3	2-Butanol	.447	NMP	8.855
Acetone (56)	20.7	2-Methoxyethanol	.410	Isobutanol	8.248
1-Propanol (97)	20.1	o-Dichlorobenzene	.280	2-Butanol	7.063
MEK (80)	18.5	NMP	.275	2-Methoxyethanol	6.929
2-Propanol (82)	18.3	Acetic Acid	.174	DMF	6.070
1-Butanol (118)	17.1	DMF	.161	o-Dichlorobenzene	2.772
2-Methoxyethanol (124)	16.9	1,2-Dichloroethane	.127	Acetonitrile	2.325
2-Butanol (100)	15.8	Water	.123	Nitromethane	2.304
Isobutanol (108)	15.8	Chlorobenzene	.101	MEK	1.462
1,2-Dichloroethane (83)	10.4	Chloroform	.091	1,2-Dichloroethane	1.321
o-Dichlorobenzene (180)	9.9	MEK	.079	Acetone	1.118
Dichloromethane (40)	9.1	Nitromethane	.064	Acetic Acid	1.079
THF (66)	7.4	Acetonitrile	.062	Chloroform	0.437
Acetic Acid (113)	6.2	Ethyl Acetate	.059	Dichloromethane	0.382
Ethyl Acetate (77)	6.0	Acetone	.054	Ethyl Acetate	0.354
Chloroform (61)	4.8	THF	.047	THF	0.348
Chlorobenzene (132)	2.6	Dichloromethane	.042	Chlorobenzene	0.263
o-Xylene (144)	2.6	Toluene	.040	Toluene	0.096
Toluene (111)	2.4	Hexane	.020	o-Xylene	0.047
Hexane (69)	1.9	o-Xylene	.018	Hexane	0.038

Instrumentation – Mono Mode.

Two Types

- Multimode
- Domestic Microwaves
- Mono Mode



Small processing volumes

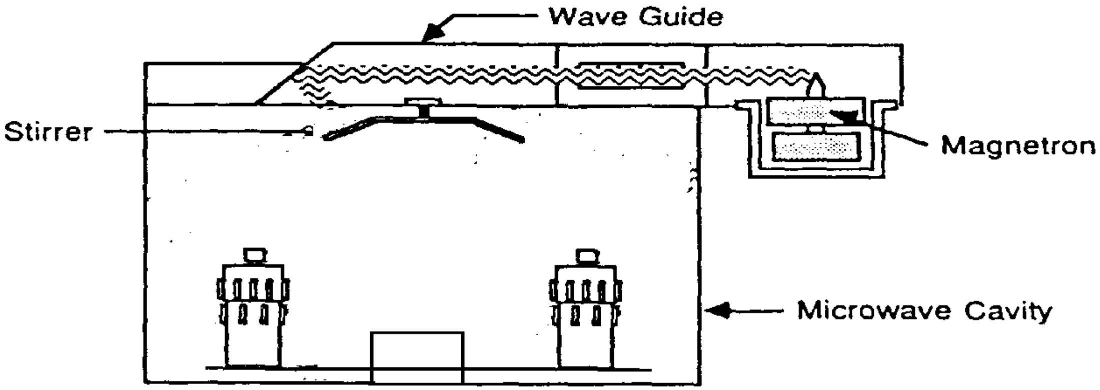
- Stationary waves (Hot Spots)

- Difficulty in Scale-up

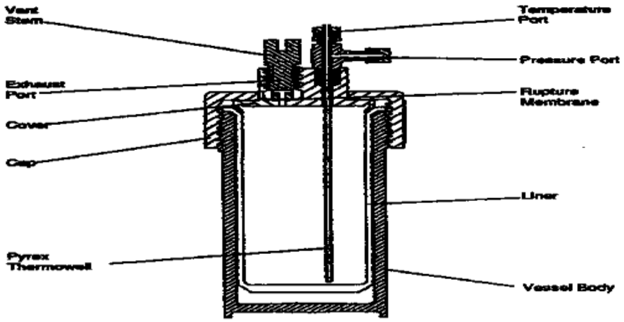
+ High energy density

C.O. Kappe, A. Stadler: Microwaves in Organic and Medicinal Chemistry, Wiley, 2005

Instrumentation – Multi Mode.



Schematic of the microwave cavity, wave guide, and magnetron.

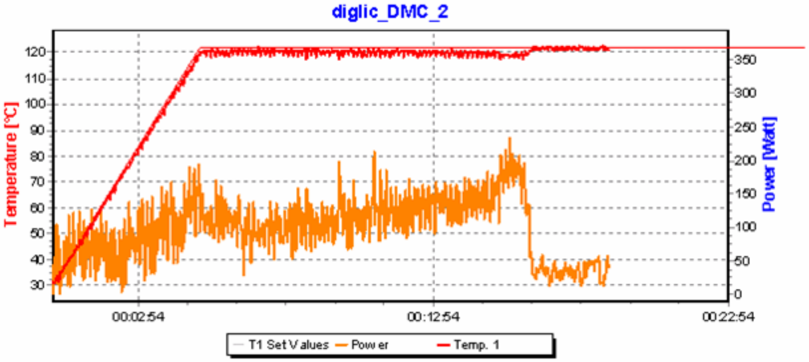


+ High energy density (higher available power)
+ Wider processing volumes (bigger MW cavity)
+ No stationary waves (no hot-spots)
+ Simple scale-up
- Minimum volume

Lab. Equipment.

ETHOS 1600 by Milestone (Bg)

- (35 × 35 × 35 *cm*); power max 1000 *W*
- 2 industrial magnetrons (800 *W*) cooled by high flow air coolers.
- MW introduced in a mixing chamber and distributed through a metal diffuser on the backside of the instrument.



Power control via software

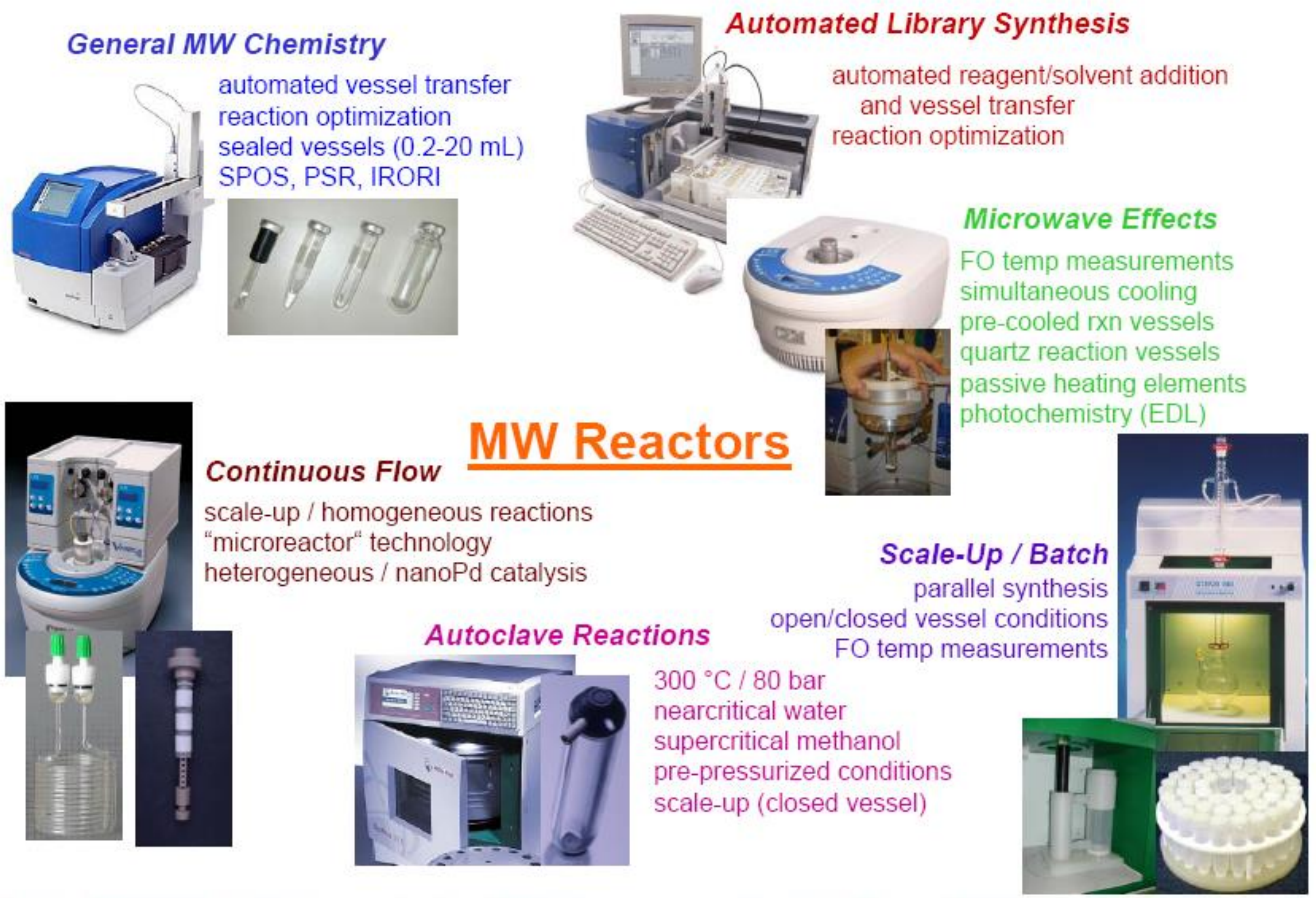
Optimization Equipments.

CEM Voyager SF (SF 80 *mL*)

Multiwave 3000 (8 x 100 *mL*)

Emrys Optimizer EXP.

MW Reactors.



MW Reactors

General MW Chemistry

automated vessel transfer
reaction optimization
sealed vessels (0.2-20 mL)
SPOS, PSR, IRORI

Automated Library Synthesis

automated reagent/solvent addition
and vessel transfer
reaction optimization

Microwave Effects

FO temp measurements
simultaneous cooling
pre-cooled rxn vessels
quartz reaction vessels
passive heating elements
photochemistry (EDL)

Continuous Flow

scale-up / homogeneous reactions
“microreactor“ technology
heterogeneous / nanoPd catalysis

Scale-Up / Batch

parallel synthesis
open/closed vessel conditions
FO temp measurements

Autoclave Reactions

300 °C / 80 bar
nearcritical water
supercritical methanol
pre-pressurized conditions
scale-up (closed vessel)

Industrial /Chemical / Applications of Microwave Heating.

Food Processing
- Defrosting
- Drying / roasting / baking
- Pasteurization

Drying Industry
- Wood, fibres, textiles
- Pharmaceuticals
- Brick / concrete walls

Polymer Chemistry
- Rubber curing, vulcanization
- Polymerization

Ceramics/Materials
- Alumina sintering
- Welding, smelting, gluing

Plasma
- Semiconductors

Waste Remediation
- Sewage treatment

Analytical Chemistry
- Digestion
- Extraction
- Ashing

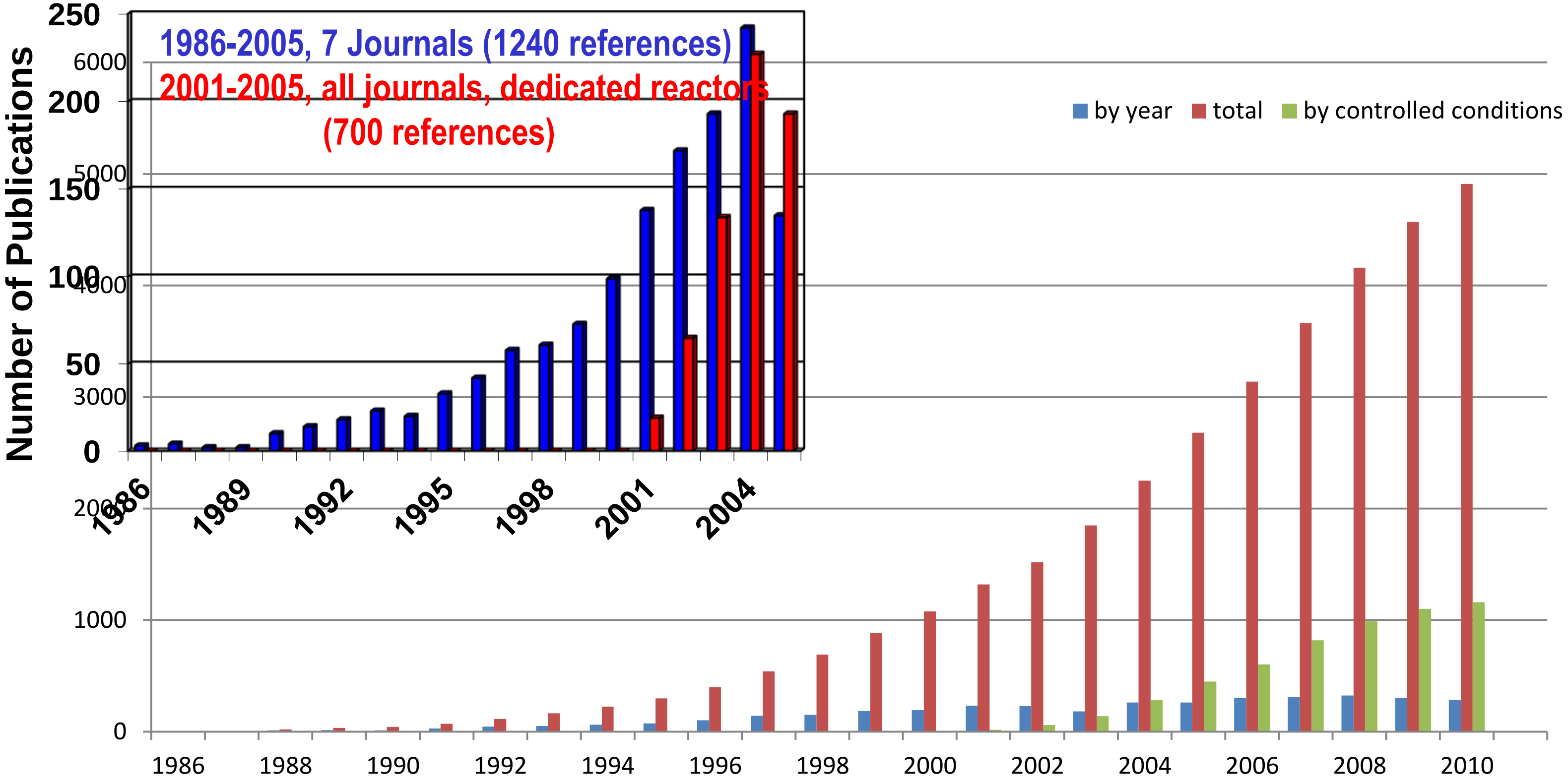
Biochemistry / Pathology
- Protein hydrolysis
- PCR, proteomics
- Tissue fixation
- Histoprocessing

Medical
- Diathermy, tumour detection
- Blood warming
- Sterilization (Anthrax)
- Drying of catheters

Microwave irradiation – Applications in Synthesis.

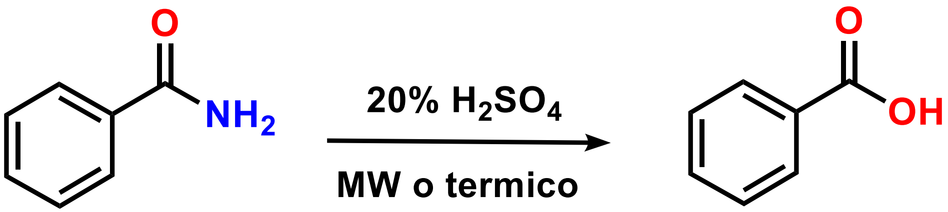
- In some cases different selectivity/reactivity compared to conventional heating
- Extension of boiling points of solvent
- Productivity increase (more effective energy transfer in reduced time, stages compaction)
- Reduction of energy costs (?)
- More clean manufacture and more effective space use (process intensification)
- Automated optimization (parallel and combinatorial syntheses)
- Product post treatment (drying, etc.)

Publications on MW-Assisted Organic Synthesis.



7 Synthetic Journals: *J.Org.Chem.,Org.Lett.,Tetrahedron Lett.,Tetrahedron, Synth.Commun., Synlett, Synthesis*
All Journals (Full Text): Dedicated instruments only (Anton Paar, Biotage, CEM, Milestone, Prolabo)

Hydrolysis of Benzamide.

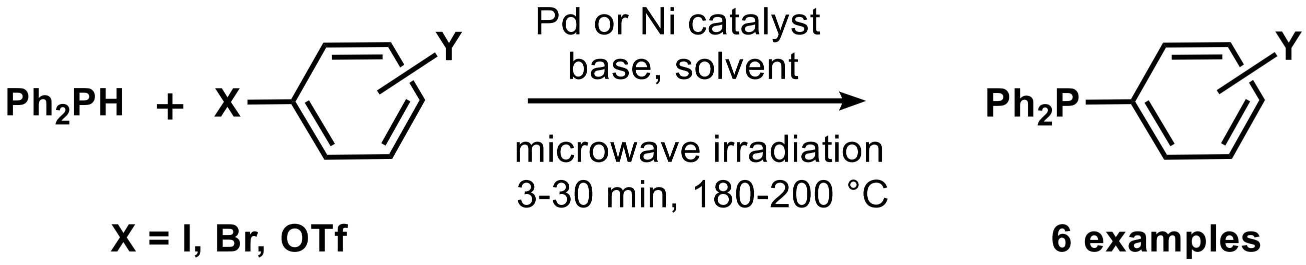


thermal: 1 *h*, 90 % yield (reflux)
MW: 10 *min.*, 99 % yield
(sealed vessel)

R. Gedye, et al. Tetrahedron Lett. ***1986,*** *27, 279–282.*
R. J. Giguere, et al. Tetrahedron Lett. ***1986****, 27, 4945–4958.*

The first reports on the use of microwave heating to accelerate organic chemical transformations (MAOS) were published by the groups of Gedye and Giguere in 1986. In those early days, experiments were typically carried out in sealed Teflon or glass vessels in a domestic household microwave oven without any temperature or pressure measurements. The results were often violent explosions due to the rapid uncontrolled heating of organic solvents under closed-vessel conditions.

Microwave Irradiation – Applications.



X = I

entry	PhI (*mmol*)	5% Pd/C (*mg*)	T (°C)	time (*min*)	yield (%)
1	0.50	10	190	3	76
2	0.60	10	190	3	93
3	0.75	20	190	3	98
4	0.75	20	200	3	96
5	0.75	20	200	2	96

Reactions carried out in DMF (1.0 ml) with 0.50 mmol of Ph_2PH in the presence of KOAc (0.50 mmol)

Syntheses without Solvents.

- Reactions on solid supports (M_xO_y, etc.)

$$CH_3COO^- + n\text{-}C_6H_{17}X \xrightarrow[-X^-]{Al_2O_3} CH_3COOn\text{-}C_8H_{17}$$

98% 2 min. (186°C)

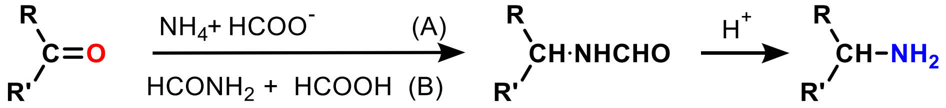
yield <2% 2 min. 186°C

- Phase transfer catalysis ($R_4N^+X^-$, $R_4P^+X^-$, PEG)

$$CH_3COO^- + n\text{-}C_{16}H_{33}X \xrightarrow{\text{5\% Aliquat 336}} CH_3COOn\text{-}C_{16}H_{33}$$

75 sec

- Reactions without catalysts otherwise essentials

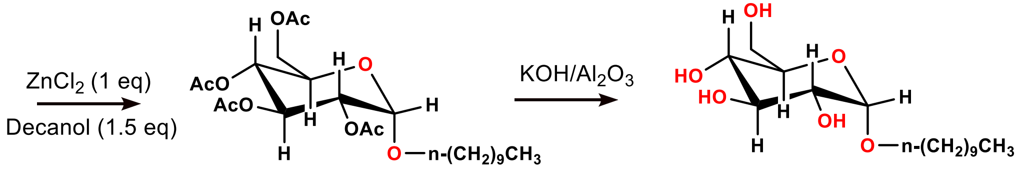


R = R' = Ph (A) 120 W 20 min. 187°C 80% (Δ→2%)

(B) 60 W 30 min. 202°C 99% (Δ→3%)

- Reactions with viscous liquids

- Reactions on natural products
  (also solid biomass)



MW 60-20W 3 min 74%.

110°C

Δ **5 h 25%.**

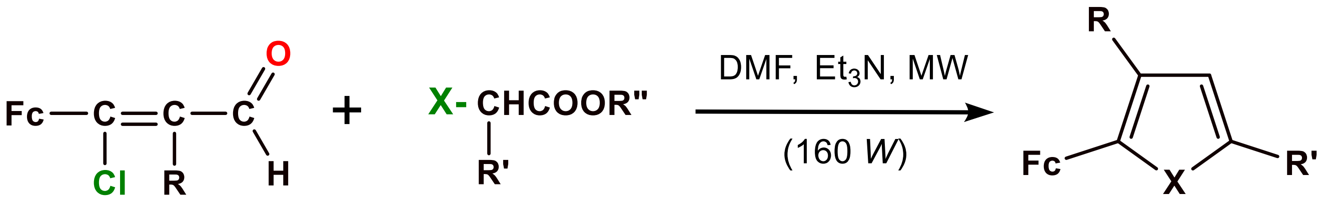
MW 100-20W 96%.

2 min 100°C

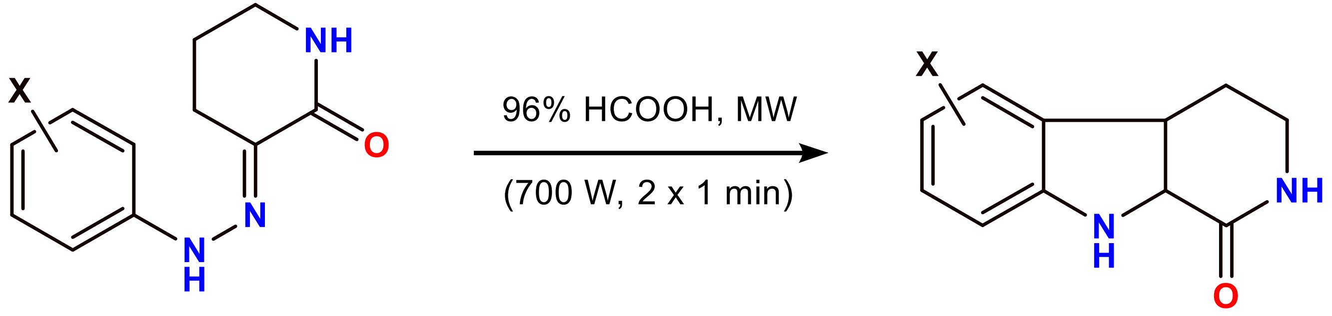
Δ **0%.**

Kappe, O.; Stadler, A.; Yuosefi, B.; Dallinger, D. *Org. Process Res. Dev.* **2003**, *7*, 707.

Microwave Irradiation – Applications (2)



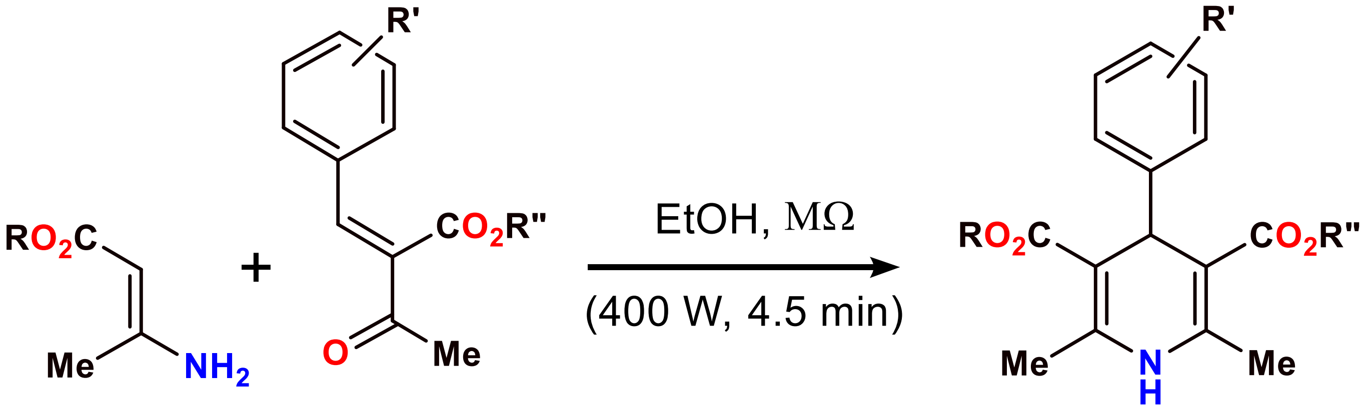
R	R‘	R“	X	
H	H	H	S	87%
Ph	H	H	S	79%
H	H	Et	O	35%
H	Ph	H	O	15%



X = H, 2-Me, 4-MeO,
4-Br, 4-NO$_2$

72.8-88 %

Microwave Irradiation – Applications (3).

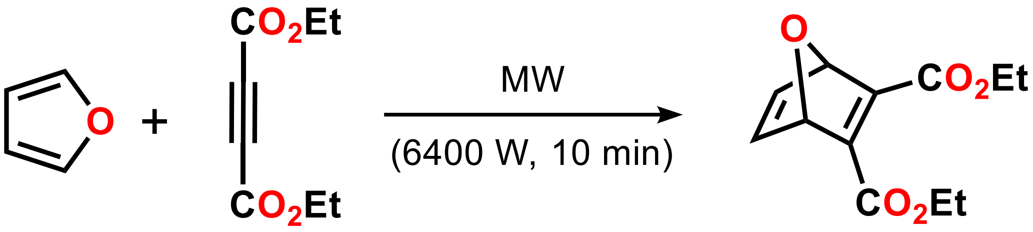


R = Me, iPr, $MeOCH_2CH_2$

R' = 2-es 3-Cl, 2,3-diCl, 3-Br, 2-es 3-NO_2

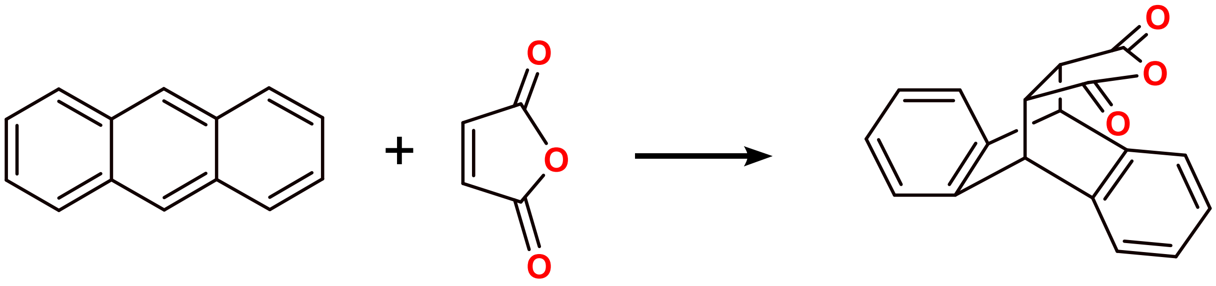
R" = Me, Et, 4-Me-furyl

58-98 %

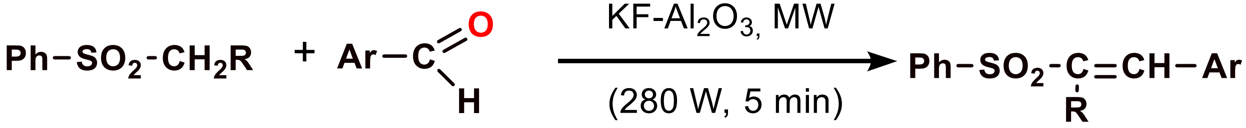


66 %

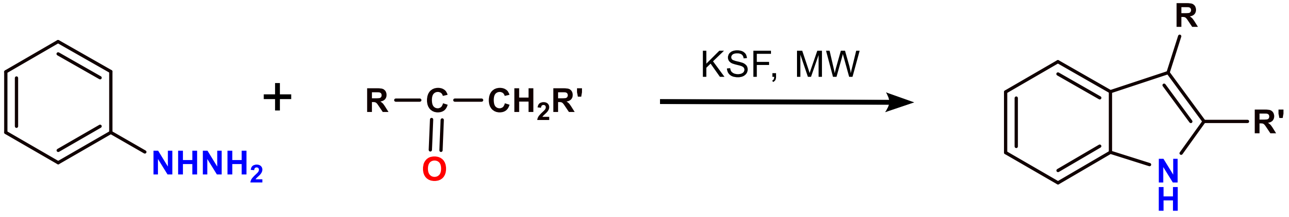
Microwave Irradiation – Applications (4).



dioxane (60 h)	90%
MW (graphite, 30 W, 3x1 min)	75%



$$\mathrm{Ph{-}SO_2{-}CH_2R + Ar{-}CH{=}O \xrightarrow[(280\ W,\ 5\ min)]{KF\text{-}Al_2O_3,\ MW} Ph{-}SO_2{-}\underset{R}{C}{=}CH{-}Ar}$$



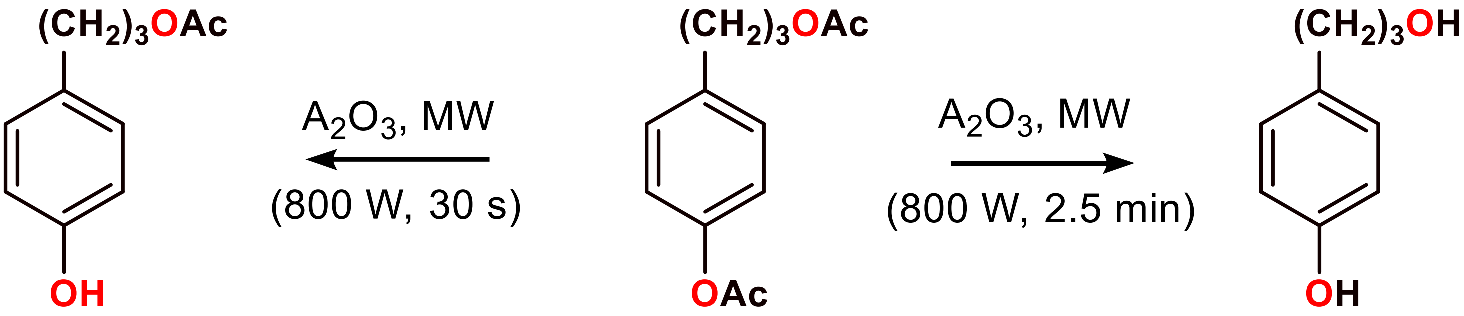
KSF, MW

R = H, Me, Ph   R' = H, Ph

R,R' = $(CH_2H_3$ $(CH_2)_4$, $CHMe(CH_2)_3$

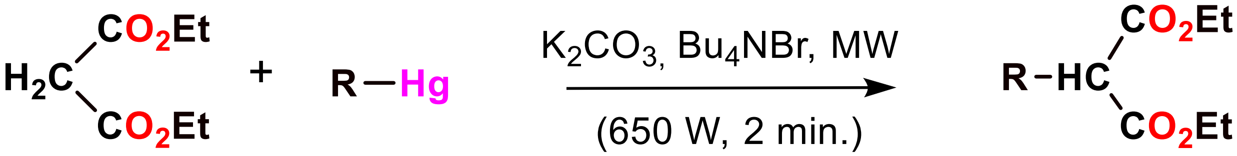
72-90 %

Microwave Irradiation – Applications (5).



93 %

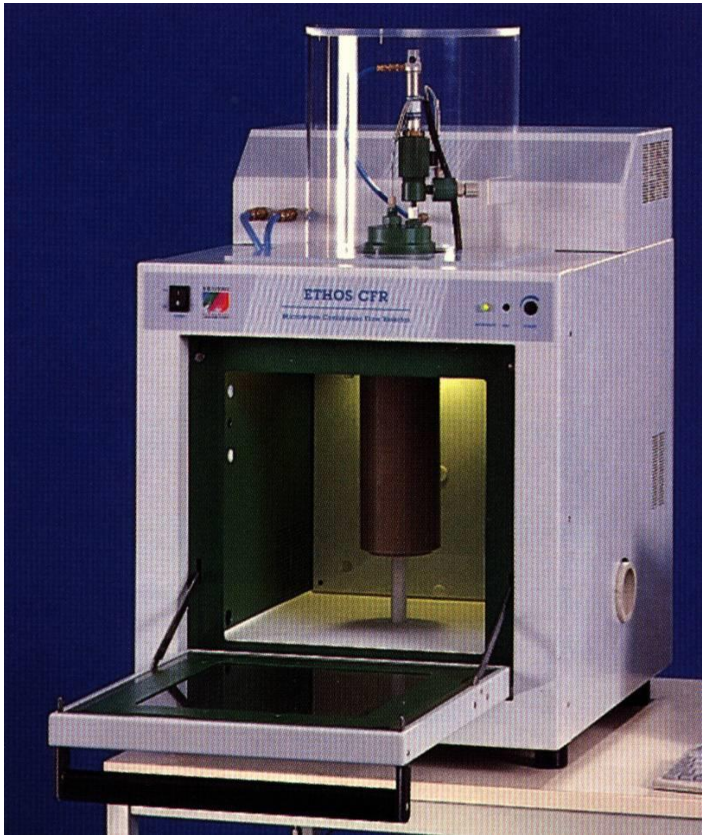
92 %

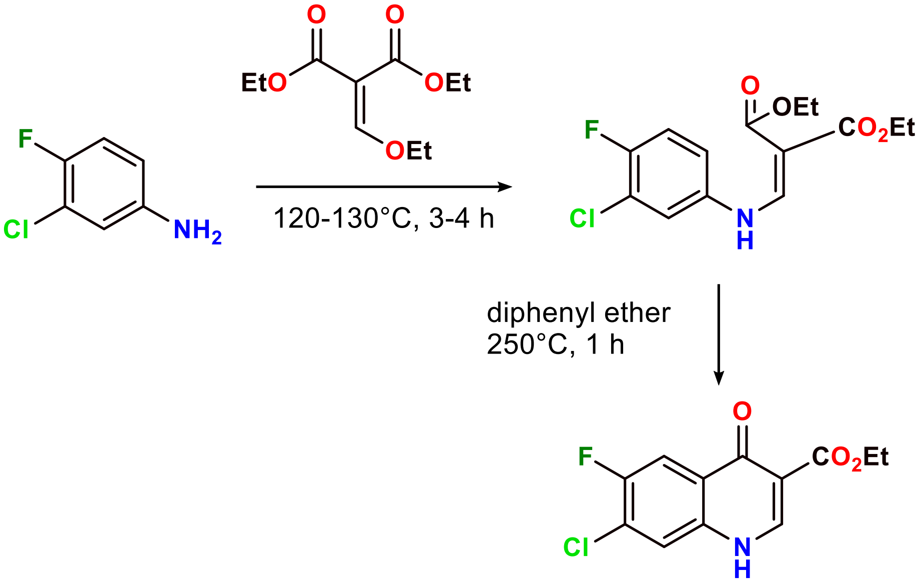


R = Bu, allyl, Bn
4-MeO-benzyl

71-86 %

Continuous Flow Syntheses (CMWR).

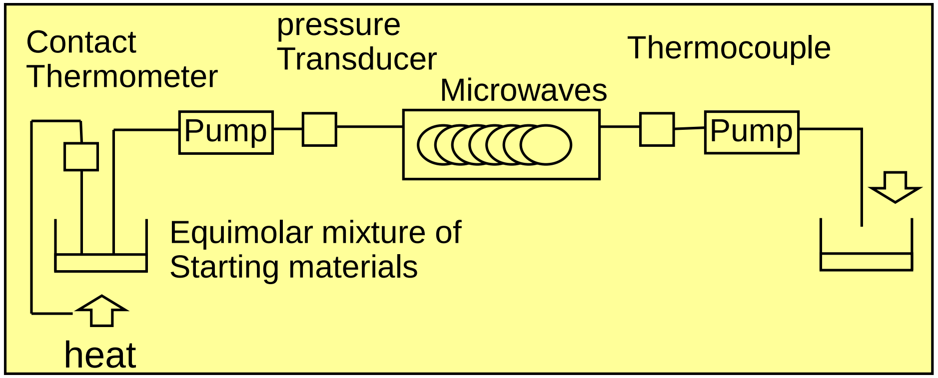




120-130°C, 3-4 h

diphenyl ether
250°C, 1 h

interested intermediate



Contact
Thermometer

pressure
Transducer

Microwaves

Thermocouple

Pump

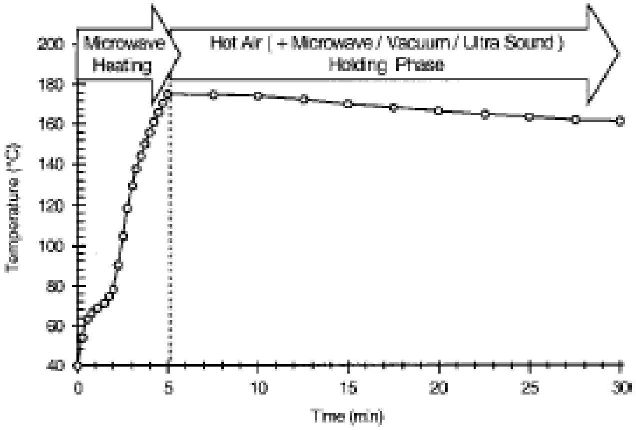
Pump

Equimolar mixture of
Starting materials

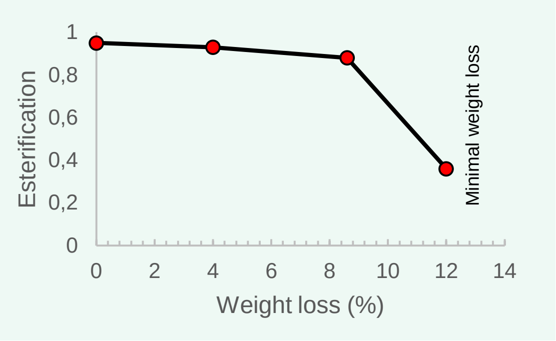
heat

Condensation Reactions.

$$RCOOH + RCH_2OH \xrightarrow[\text{KSF cat.}]{\text{170°C, MW,}} RCOOCH_2R + H_2O \qquad R = C_{17}H_{25}$$



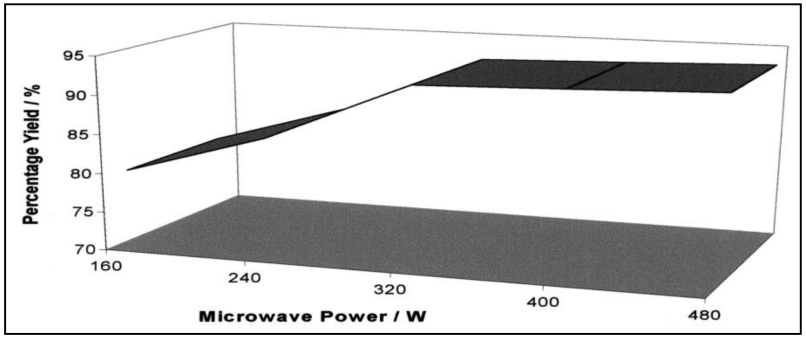
Exp.	Initial stage time (min)	T_{fin} (°C)	Final stage time (min)	T_{fin} (°C)	Yield (%)
I	9 min	141 °C	-	-	33
II	9 min	163 °C	-	-	78
III	6 min	170 °C	24 min	160 °C	92
IV	11 min	203 °C	19 min	130 °C	90
V	7 min	192 °C	23 min	160 °C	84
VI	12 min	170 °C	60 min	210 °C	82

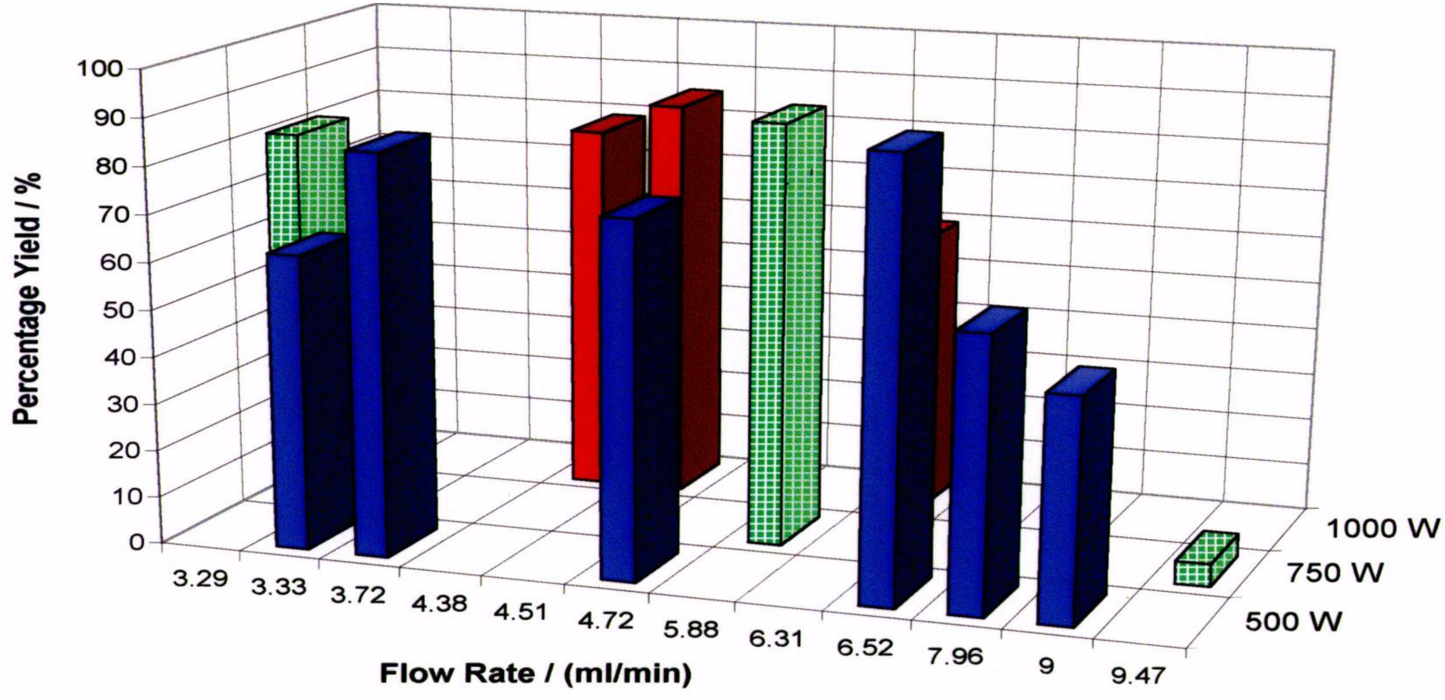


Condition	Acid Excess (%)	Time (min)	Yield (%)
Conventional air heating	0	25	94,6
Conventional air heating	5	25	96,1
Pulsed microwave (0.5 s $s_{\pm1}$)	0	25	95,2
Pulsed microwave e (0.5 s $s_{\pm1}$)	5	25	96.9
Vacuum (150 mbar)	0	25	94,9
Vacuum (150 mbar)	0	360	95,1
Ultrasonic (44 kHz)	0	25	94,0

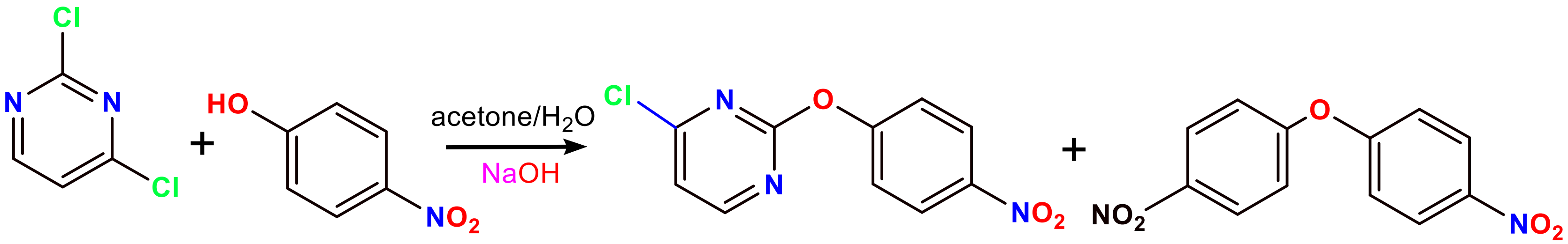
E. Esveld, F. Chemat, J. van Haveren, Chem. Eng. Technol. 23 (2000) 429

CMWR Process Optimization.





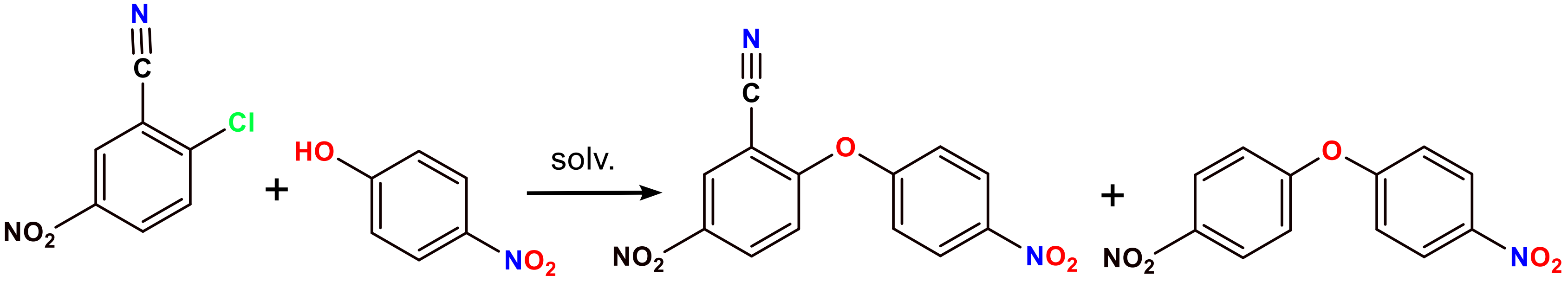
Different Equipment – A Comparison.



Equipment	Dim.Batch (mL)	Reaction Temp., time	work-up time	Isol. Yield (%)	Purity.[a] (%)	Notes
Conv. heating	20	62 °C, 12 h	2 h 30 min	66	80	5% MP, 20% byproducts
µW, Emrys Optimizer	15	120 °C, 5 min	10 min	>83	96	100% conversion, <5% by-product
µW, Multiwave 3000	8 - 50	120 °C, 10 min	30 min	76	90	10% byproducts
µW, Voyager SF	400	120 °C, 15 min	8 x 30 min	81	95	5% byproduct, line bloked by the precipitated products
Autoclave	400	120 °C, 10 min	275 min	74	85	>10% byprodotto

H. Lehmann* L. LaVecchia *JALA* 2005;10:412–7

Different Equipment – A Comparison.



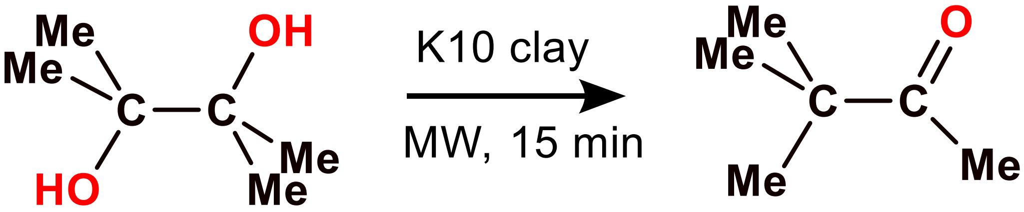
Apparecchiatura	Dim.Batch (mL)	Temp., tempo reazione	tempo lavoraz.	Resa Isol.(%)	Purez.[a] (%)	Note
Riscald. Conv.	20	AN, riflisso, 1h		(86)		**Reazione non completa**
Riscald. Conv.	20	AN, riflusso, 6h	6h 30 min	76		**Completa, crist. porpora scuri**
Riscald. Conv.	20	DMSO, 150°C, 10 min	60 min	57	65	**Miscela di prodotti e sotto-prodotti**
µW, Emrys Optimizer	15	AN,150 °C, 10 min	17 min	98	>96	**cristalli gialli**
µW, Multiwave 3000	4 x 50	AN,150 °C, 10 min	25	78	>96	**Riproducibile**
µW, Voyager SF	300	AN,150 °C, 10 min				**Sospensione non pompabile nella linea**
Autoclave	**200**	**AN,150 °C, 10 min**	**280 min**	**92**	**92**	**8% sotto-prodotto**

Solid-supported Solventless Reactions.

- Microwave irradiation of solventless reactions with inorganic mineral supports such as alumina, silica, or clays have resulted in faster reactions with higher yields with simplified separation.

R. S. Varma, Tetrahedron, 2002, 58, 1235.

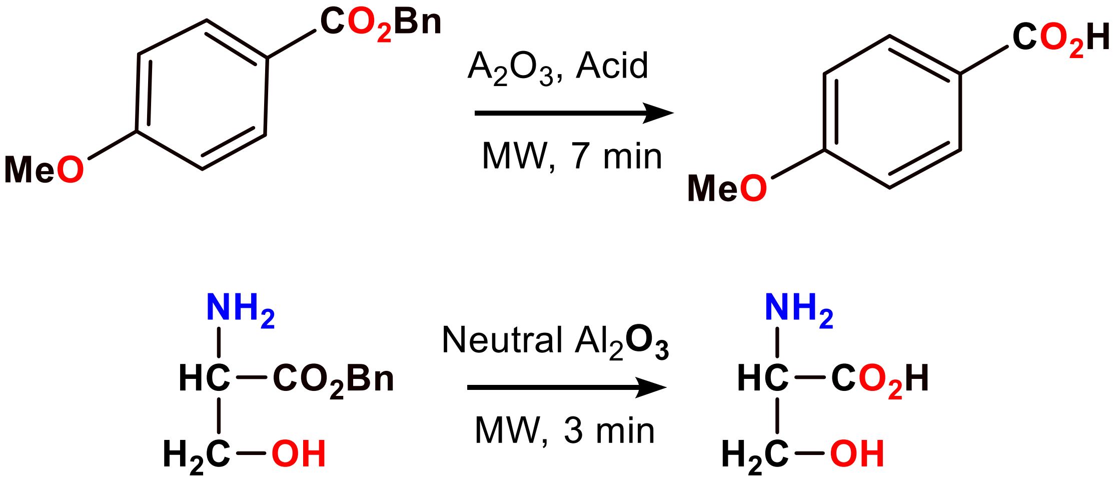
R. S. Varma, Green Chem., 1999, 1, 43.



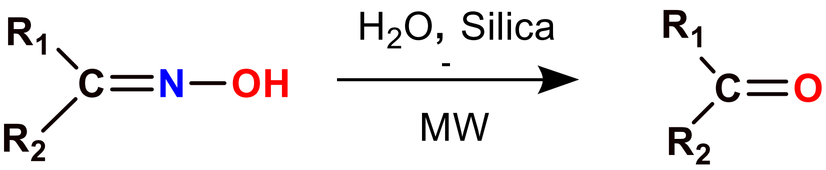
$$\mathrm{AcOK} + \mathrm{C_8H_{17}Br} \xrightarrow[\text{MW, 105 min}]{\text{Alumina or Silica}} \mathrm{AcOC_8H_{17}}$$

E. Gutterrez, A. Loupy, G. Bram, E. Ruiz-Hitzky, *Tetrahedron Lett. 1989, 30, 945.*

Deprotection via Microwave Thermolysis.

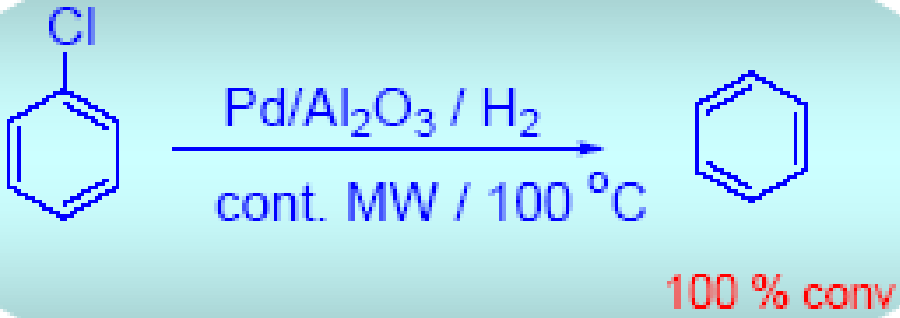


Varma et al.: *Tetrahedron Lett*., 34, 4603 (1993)



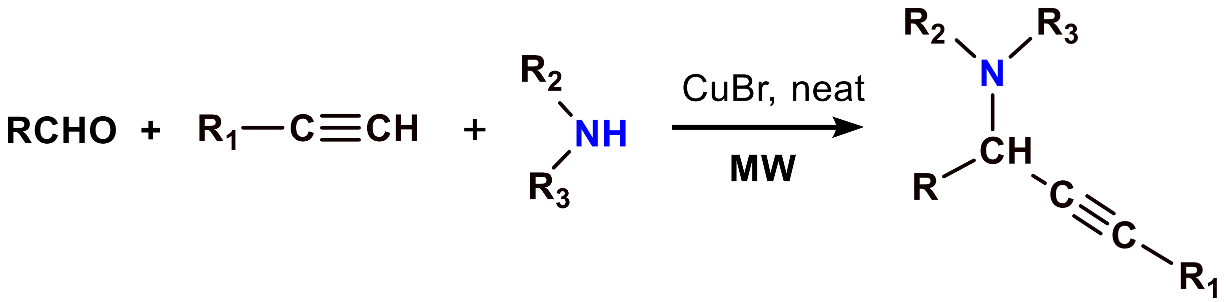
Varma, Meshram: *Tetrahedron Lett*., 38, 5427 (1997)

Hydrodechlorination under Continuous MW.



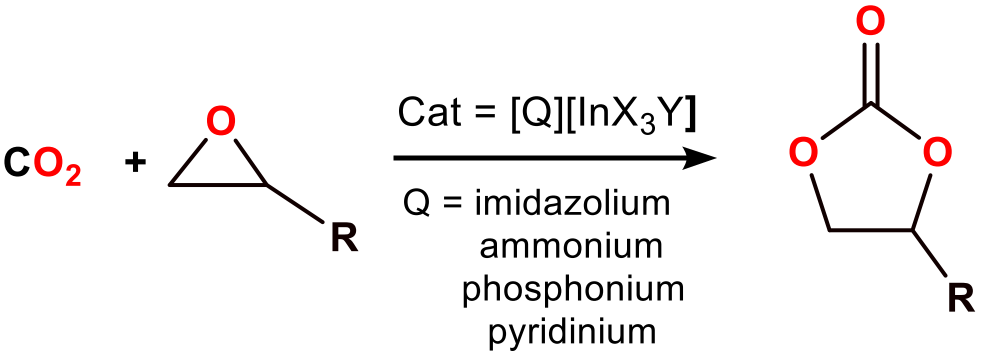
Pillai, Sahle-Demessie, Varma:
Green Chemistry, 6, 295 (2004)

MW-Assisted Solvent-free Three Component Coupling and CO_2 Insertion.



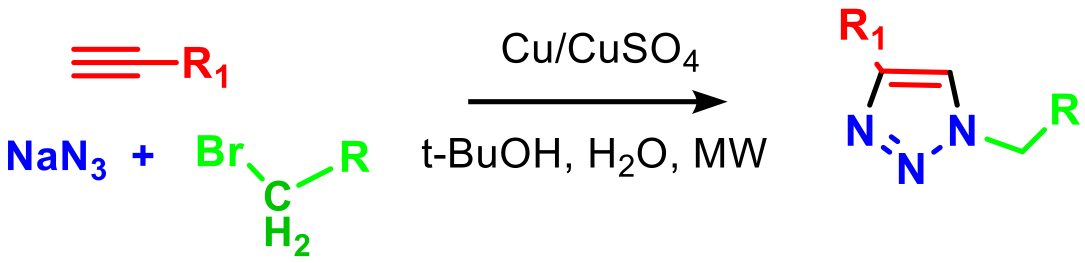
where R = Aryl, alkyl; R_1 = Aryl, alkyl and Et_3Si;
R_2 = Alkyl, allyl, H; R_3 = Alkyl, allyl

Ju, Li; Varma, *QSAR & Combinatorial Science*, 2004, 23, 891

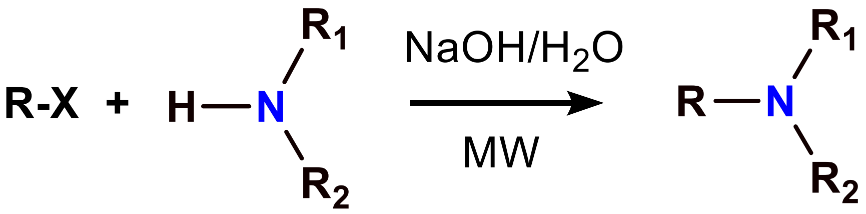


Kim and Varma. *J. Org. Chem.*, 2005, 70, 7882

MW Assisted Synthesis in Water.



P. Appukkuttan, W. Dehaen, V. V. Fokin, E. Van der Eycken. *Org. Lett*. 2004, 6, 4223.



R = Alkyl, allyl; R_1 = H, alkyl, allyl
X = Cl, Br, I; R_2 = alkyl, allyl

Ju, Y.; Varma, R. S., *Green Chem*. 2004, 6, 219-221.

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- O. Kappe, *Angew. Chem. Int. Ed*. 2004, 43, 6250 –6284
- C. O. Kappe, Ed., *Microwaves in Combinatorial and High-Throughput Synthesis* Kluwer, Dordrecht, 2003
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- Metaxas, A. C.; Meredith, R. J. *Industrial Microwave Heating*; IEE Power Engineering Series 4; Peter Peregrinus: London, 1988.
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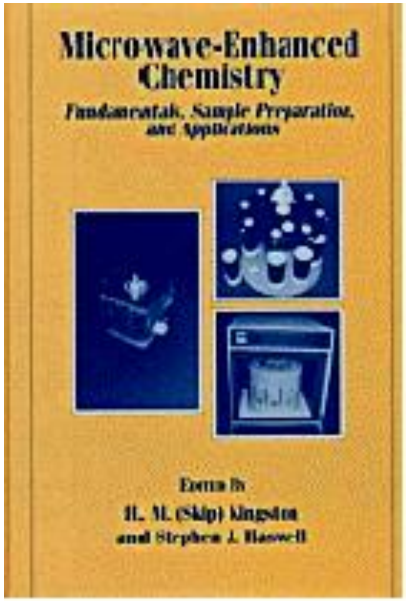
- Wilson, N. S. and Roth, G. P., Curr. Opinion Drug Discov. Develop., 5(4) (2002) 620–629
- Stadler, A. and Kappe, C. O., J. Combinat. Chem., 3 (2001) 624–630.
- M. Nuchter, et al. *Chem. Eng. Technol.* 2005, 28, 871

Books on Microwave-Assisted Synthesis

(ACS Professional Reference Book)
H. M. Kingston, S. J. Haswell (eds.)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Fundamentals, Sample Preparation, and Applications
Edited By
H. M. (Skip) Kingston
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- **Alternative Laboratory Microwave Instruments**
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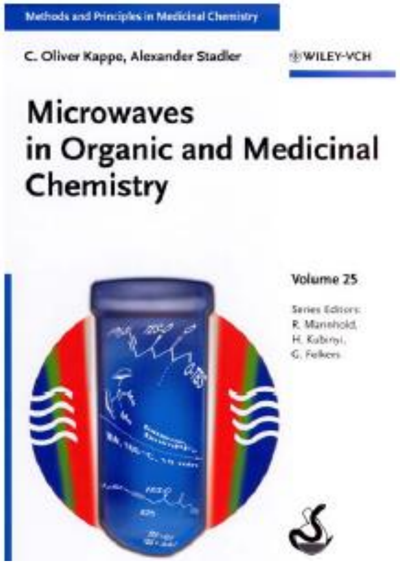
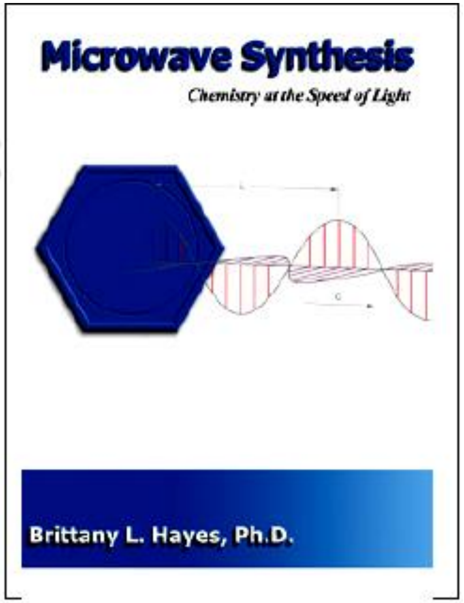
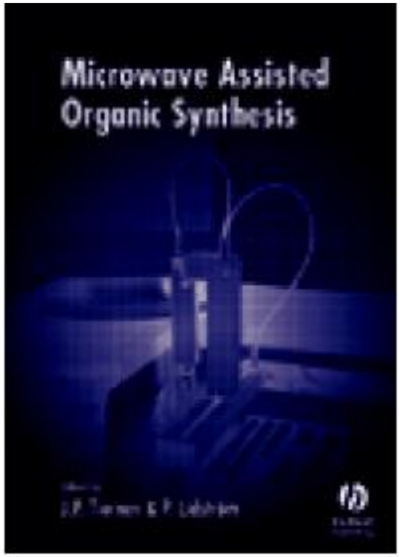

Methods and Principles in Medicinal Chemistry
C. Oliver Kappe, Alexander Stadler
WILEY-VCH
Microwaves in Organic and Medicinal Chemistry
Volume 25
Series Editors:
R. Mannhold,
H. Kubinyi,
G. Folkers

Microwaves in Organic and Medicinal Chemistry
Kappe, C. O. and Stadler, A.
Wiley-VCH, Weinheim, 2005,
ISBN: 3-527-31210-2
410 pages, ca 1000 references,

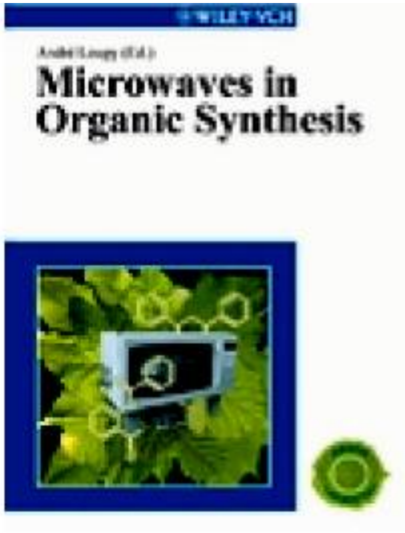

Microwave Synthesis
Chemistry at the Speed of Light
Brittany L. Hayes, Ph.D.

Hayes, B. L., CEM Publishing, Matthews, NC, 2002

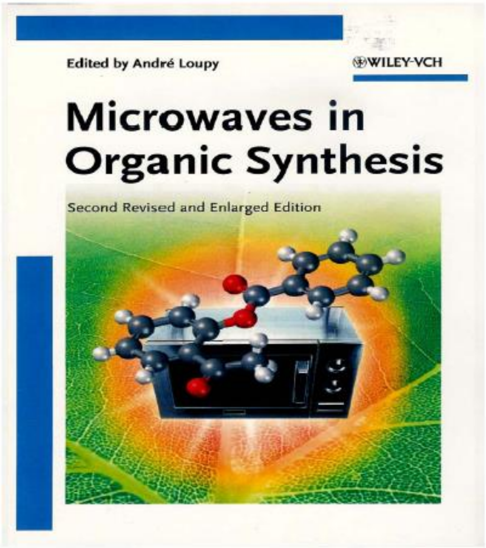
Books on Microwave-Assisted Synthesis (2).



Lidstöm, P.; Tierney, J. P. (Eds.), Blackwell Scientific, 2005



Loupy Andre (Ed.)
Wiley-VCH, Weinheim, 2003,
ISBN: 3-527-30514-9
523 pages, 2000 refs.



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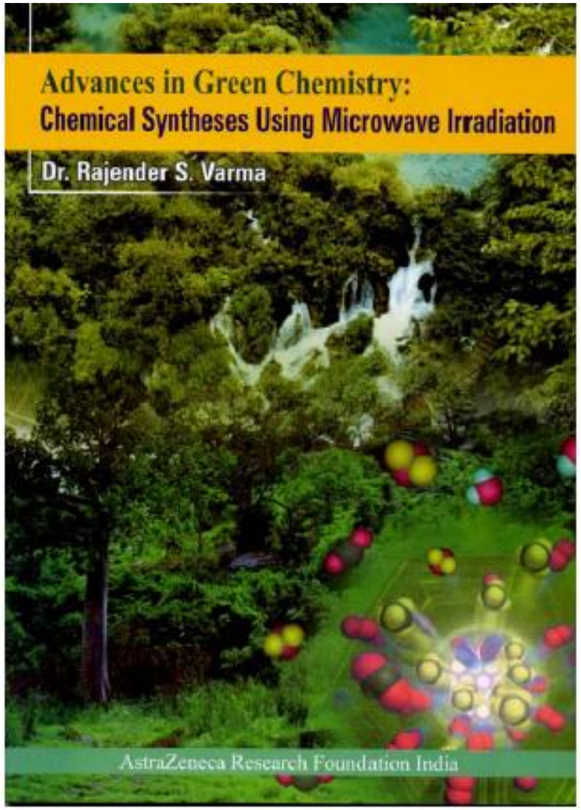

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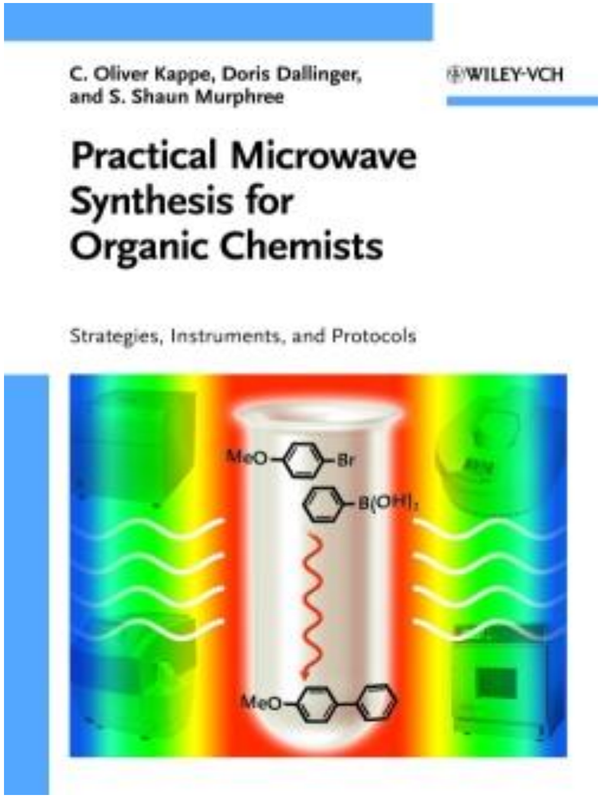
AstraZeneca Research Foundation India

Astra Zeneca Research
Foundation Kavitha Printers,
Bangalore, India, 2002
azrefi@astrazeneca.com



C. Oliver Kappe, Doris Dallinger,
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Strategies, Instruments, and Protocols

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