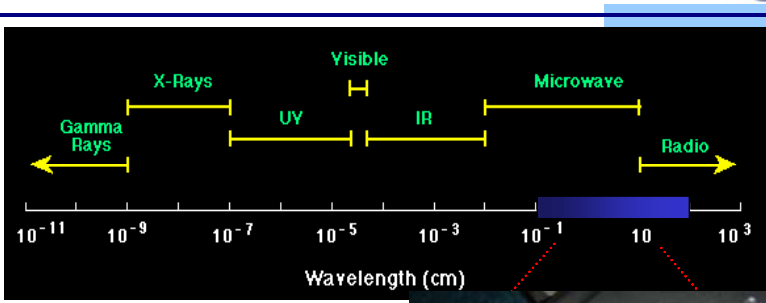
Chemie mit Mikrowellen

C. Oliver Kappe
Christian Doppler Laboratory for Microwave Chemistry (CDLMC)
Institute of Chemistry, University of Graz
Heinrichstrasse 28, A-8010 Graz, Austria
oliver.kappe@uni-graz.at
www.maos.net

Outline

1. **What are Microwaves?**
2. **Microwave Reactors**
3. **How do Microwaves Interact with Matter**
4. **Chemistry Examples**
5. **Scale-Up**
6. **“Specific” Microwave Effects**

Microwaves and the Electromagnetic Spectrum



Permitted Frequencies for Industrial, Scientific and Medical Uses (ISM):

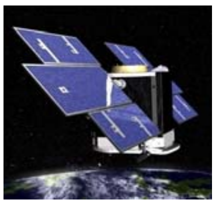
915 MHz
2450 MHz
5800 MHz
27120 MHz

Application of Microwaves in Transporting Information

Communication
+ satellites
+ cable TV/internet (coaxial cables)
+ mobile and cordless phones (GSM)
+ WLAN, bluetooth
+ space exploration

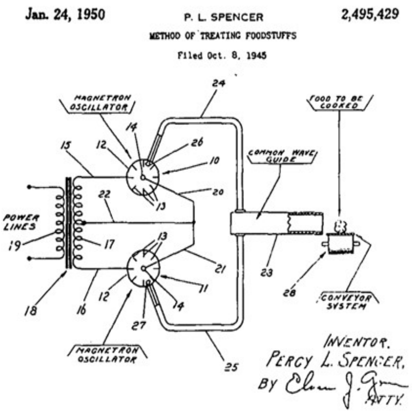
Radar etc.
+ air traffic control, missile guidance
+ speed detection, road pricing
+ GPS

Miscellaneous
+ RFID
+ microwave imaging
+ nondestructive testing



Source: Microwaves and Metals, Gupta, M.; Wong Wai Leong, E., John Wiley & Sons, **2007**

Application of Microwaves for Heating Foodstuff



A Brief History

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

Industrial / Chemical Applications of Microwave Heating

Food Processing
+ defrosting / tempering
+ drying / roasting / baking
+ pasteurization / sterilization

Drying Industry
+ wood, fibers, textiles, books
+ pharmaceuticals
+ brick / concrete walls

Polymer Chemistry
+ rubber curing, vulcanization
+ polymerization

Ceramics/Materials
+ alumina sintering
+ welding, melting, gluing
+ mining/oil industry
+ nanoparticles, zeoliths

Waste Remediation
+ sewage treatment

Microwave Plasma
+ nuclear fusion

Analytical Chemistry
+ digestion
+ extraction
+ ashing

Biochemistry / Pathology
+ protein hydrolysis
+ PCR, proteomics
+ tissue fixation, histoprocessing

Medical
+ diathermy, tumor detection
+ blood warming
+ sterilization (Anthrax)
+ drying of catheters

Large Scale Microwave Processing Applications

Rubber Curing

MW Dryers

Plasma Source

Material Science

www.industrielle-mikrowelle.de www.sairem.com

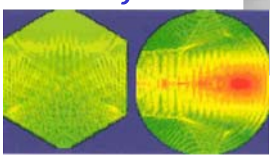
Largest Microwave System Known

HEPHAISTOS-CA3

High Electromagnetic Power
Heating Automated Injection
Structure Oven System

+ 750 or 4200 L volume
+ 10-30 kW MW power, 2.45 GHz
+ heating, drying, hardening
(carbon fiber-reinforced composite materials)

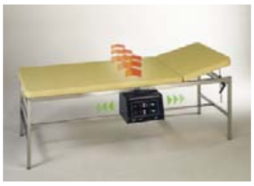
Field Distribution Hex Vs Cyl



Vötsch Industrietechnik GmbH: http://www.v-it.com

Exposure of Humans to Microwaves

Microwave Diathermy



+ use of MW to produce heat
+ used to either cut or destroy tissue
+ frequency range 300 kHz to 3 MHz

Microwave Weapons, ADS (Active Denial System)

+ high power microwave irradiation
+ frequency 95 GHz
+ heats skin to cause pain

http://en.wikipedia.org/wiki/Active_Denial_System

Sacrifice Fixation Microwave

+ used to sacrifice lab animals (brain dead)
+ 2.45 GHz frequency, 5 kW
+ “from live to brain fixed in less than one second“

Microwaves in Organic Synthesis

Seminal 1986 Publications by the Gedye and Giguere/Majetich Groups

“The Use of Microwave Ovens for Rapid Organic Synthesis”
Gedye, R. N. et al. (Laurentian University, Canada)
Tetrahedron Lett. **1986**, *27*, 279.

“Application of Commercial Microwave Ovens to Organic Synthesis”
Giguere, R. J. (Mercer Univ) and Majetich, G. (Univ Georgia)
Tetrahedron Lett. **1986**, *27*, 4945.

up to 1000 fold rate increases for several reactions reported !

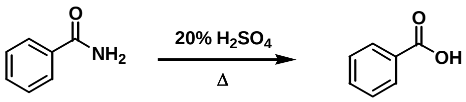
Earlier Patent Literature

“Carrying Out Chemical Reactions Using Microwave Energy”
Vanderhoff, J. W. (Dow Chem Co), US 3,432,413 (1969)

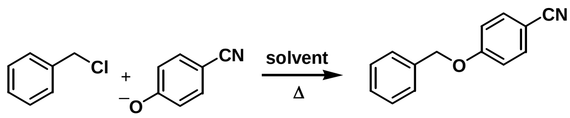
see also: US 4,210,593 (1981), DE 3,018,321 (1981)

Microwaves in Chemistry - Organic Synthesis

Seminal 1986 Publications by Gedye and Coworkers



classical: 1 h 90%
microwave: 10 min 99%

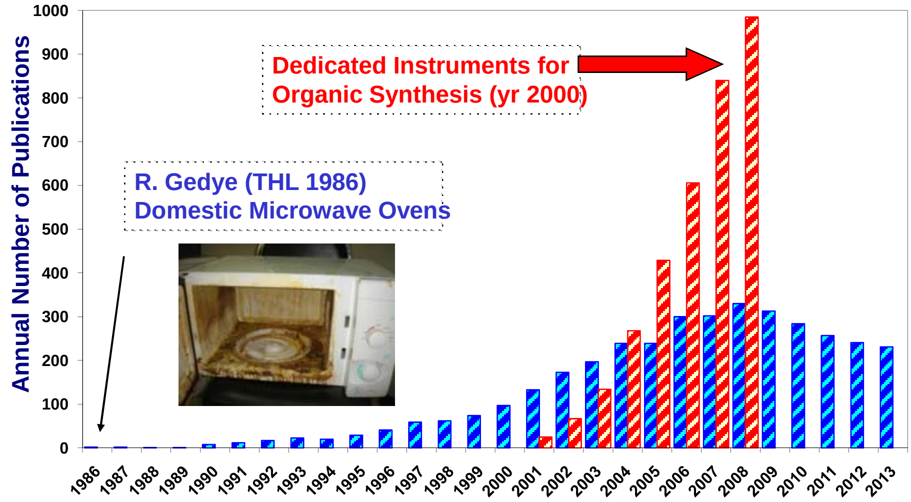


classical: 16 h 89%
microwave: 4 min 93%

sealed *teflon vessels in domestic microwave oven*

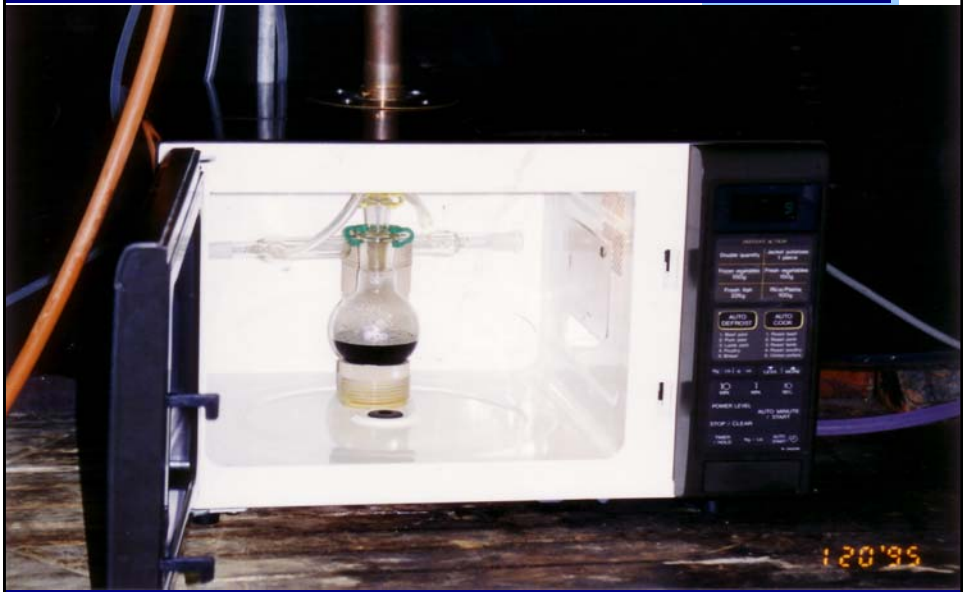
"The Use of Microwave Ovens for Rapid Organic Synthesis"
Gedye, R. N. et al. (Laurentian University, Canada)
Tetrahedron Lett. **1986**, *27*, 279.

Number of Peer-Reviewed Publications in Microwave-Assisted Organic Synthesis (MAOS)



Keywords: 1986-2013, 7 synthetic chemistry journals (domestic and dedicated reactors)
Full Text: 2001-2008, all journals (dedicated reactors only)

Modified Domestic Microwave Ovens



13

Dedicated Microwave Reactors

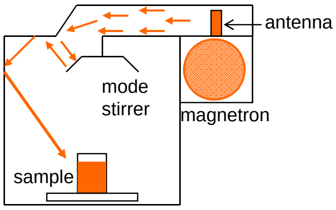



"Microwaves in Organic and Medicinal Chemistry, 2^{nd} Ed.
Kappe, C. O.; Stadler, A.; Dallinger, D.
Wiley-VCH, **2012** (Chapter 3)



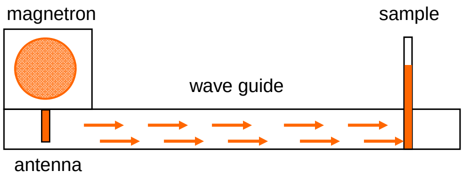

Modern Microwave Reactors: Multimode and Monomode Instruments

Multimode Cavity



Chaos

Monomode (Single Mode) Cavity
(rectangular waveguide)



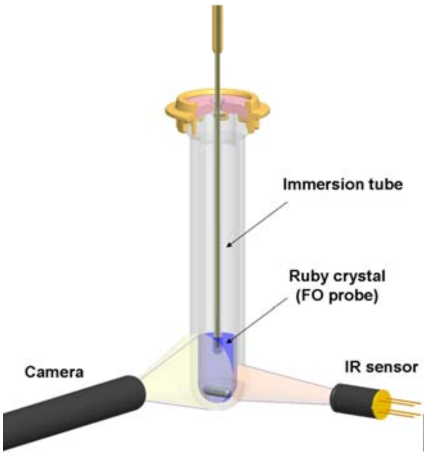
Standing Wave

2nd Generation Single-Mode Microwave Reactor (Monowave 300, Anton Paar, 2009)

Instrument Features

- dual IR/FO temperature control
- 300 °C, 30 bar
- 850 W power
- 3 vessel sizes (0.5-20 mL)
- SiC vessel, built-in camera
- magnetic stirring (0-1200 rpm)

Simultaneous IR/FO Temperature + Camera

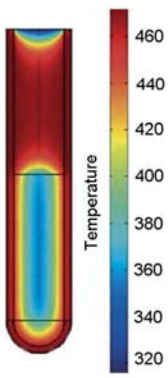


Hayden, S.; Damm, M.; Kappe, C. O.
Macromol. Chem. Phys. **2013**, *214*, 423

Advances in Heating Techniques in Chemical Laboratories

Conventional Heating by Conduction

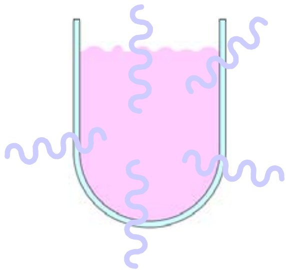
- conductive heat
- heating by convection currents
- slow and energy inefficient process
- wall effects

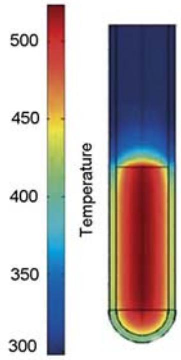


temperature on the outside surface is in excess of the boiling point of liquid

”Direct” Heating by Microwave Irradiation

- solvent/reagent absorbs MW energy
- vessel wall transparent to MW
- direct in-core/ volumetric heating
- instant on-off
- remote, non-contact heating

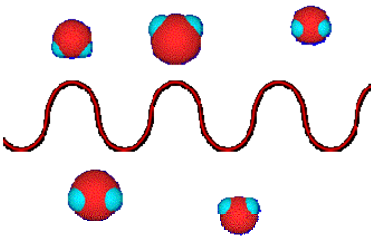




vessel wall transparent to microwave energy

Microwave Dielectric Heating Mechanisms (1)

Dipolar Polarization Mechanism

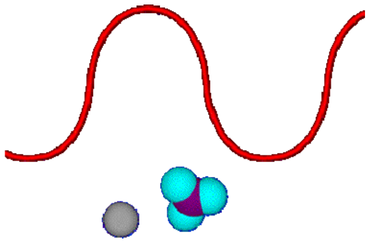


- Dipolar molecules try to align to an oscillating field by rotation
- Energy lost through molecular friction and dielectric loss
- If dipole has insufficient time to realign or reorients too easily no heating occurs

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

Microwave Dielectric Heating Mechanisms (2)

Ionic Conduction Mechanism



Ions in solution will move by the applied electric field

heat produced by ionic conduction is greater than that from the dipolar polarization mechanism

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

21

Microwave Heating Depends on Dielectric Properties (Loss Tangent tan $\delta = \varepsilon''/\varepsilon'$)

"High" (> 0.5)

Solvent	Tan δ
ethylene glycol	1.350
EtOH	0.941
DMSO	0.825
2-propanol	0.799
formic acid	0.722
MeOH	0.659
nitrobenzene	0.589
1-butanol	0.571

"Medium" (0.1-0.5)

Solvent	Tan δ
dichlorobenzene	0.280
NMP	0.275
$bmimPF_6$	0.185
acetic acid	0.174
DMF	0.161
dichloroethane	0.127
water	0.123
chlorobenzene	0.101

"Low" (< 0.1)

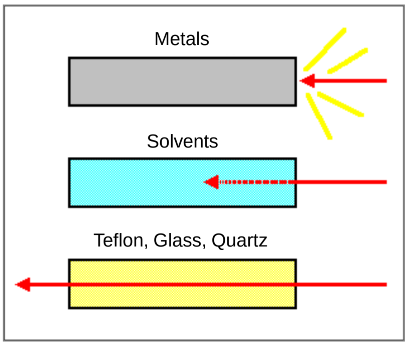
Solvent	Tan δ
chloroform	0.091
MeCN	0.062
EtOAc	0.059
acetone	0.054
THF	0.047
DCM	0.042
toluene	0.040
hexane	0.020

MW transparent solvents: CCl_4, benzene, dioxane

Temperature dependence: tan δ $bmimPF_6$ at 100 °C: 1.805; at 200 °C: 3.593

a reaction medium with a higher tan δ will have a higher susceptibility to MW heating

Materials Interaction with Microwaves



Reflective
(Conductor)

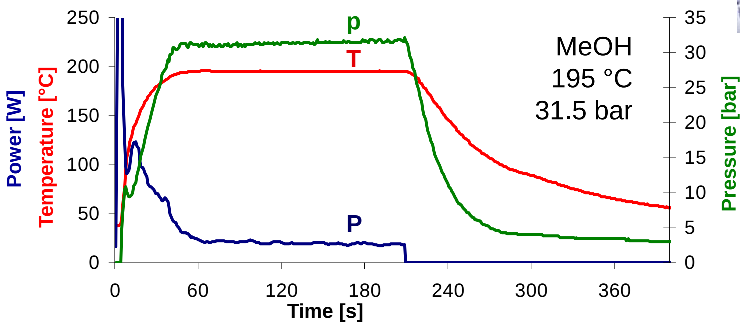
Absorptive (tan δ 0.05 - 1)
(Dielectric)

Transparent (tan δ < 0.01)
(Insulator)

penetration depth is critical !

Controlled Microwave Heating in <u>Sealed</u> Vessels

Temperature-Time-Pressure Diagram
(MeOH, boiling point at atm. pressure: 65 °C)



Relationship Between Temperature and Reaction Time

Arrhenius Equation (1889)

$k = A\,e^{-Ea/RT}$

$E_a = 100$ kJ mol^{-1}
$A = 4 \times 10^{10}$ mol^{-1}s^{-1}

Temperature (°C)	rate constant (k/s)	t 90% conv
27	1.55×10^{-7}	68 days
77	4.76×10^{-5}	13.4 hours
127	3.49×10^{-3}	11.4 min
177	9.86×10^{-2}	23.4 s
227	1.43	1.61 s

"increase of temp by 10 °C leads to a halving of reaction time"

Mingos, D. M. P., Bagurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1

Pressure Cooking (Denis Papin, 1679)

Pressure cooking is a method of cooking in a sealed vessel that does not permit air or liquids to escape below a preset pressure.

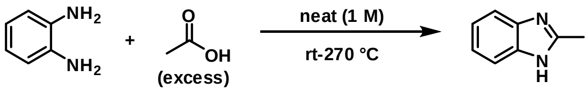
Because the boiling point of water increases as the pressure increases, the pressure built up inside the cooker allows the liquid in the pot to rise to a higher temperature before boiling.

- Typical pressure: ~1.8 bar
- Boling point of water: ~120 °C
- Reduces cooking time to ~30%

Pressure Cooker ("Kelomat")

One Illustrative Example

Rate Enhancement in the Synthesis of Benzimidazoles



Temperature (°C)	t >99% conv (HPLC)
25	9 weeks
60	5 days
100	5 h
130 (2 bar)	30 min
160 (4 bar)	10 min
200 (9 bar)	3 min
270 (29 bar)	“1 s“

$k = A\ e^{-Ea/RT}$

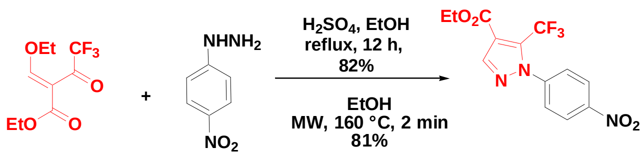
$E_a = 73.4\ kJ\ mol^{-1}$
$A = 3.1 \times 10^8$

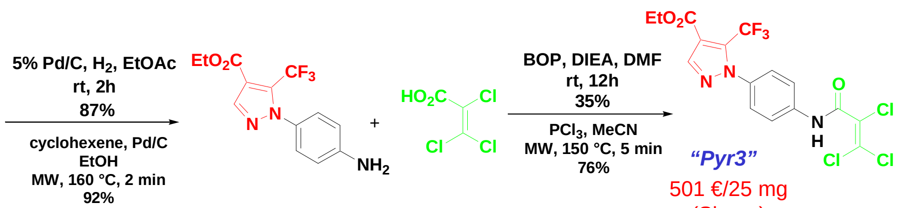
M. Damm

Org. Process Res. Develop. **2010**, *14*, 215

One Real Life Example Out of Thousands….

Synthesis of TPRC3-Inhibitors for Cardiac Hypertrophy Prevention



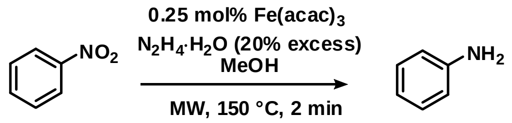


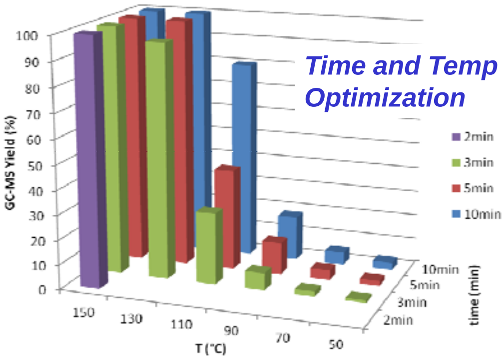
“Pyr3”
501 €/25 mg
(Sigma)

Conventional: Kiyonaka, S. et al. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 5400
Microwave: Glasnov, T. N.; Groschner, K.; Kappe, C. O. *ChemMedChem* **2009**, *4*, 1816
Analog Synthesis: Obermayer, D.; Glasnov, T. N.; Kappe, C. O. *J. Org. Chem.* **2011**, *76*, 6657

Develop New Highly Efficient Chemistry - Increase Speed and Reduce Catalyst Loading

Nano-Fe_3O_4 Catalyzed Nitroarene Reduction





Time and Temp Optimization

1.5 mL MeOH, 2 mmol $PhNO_2$, 3.6 mmol N_2H_4 H_2O

Conventional Reflux Conditions

0.5 mol%, 65 °C (MeOH): 6 h

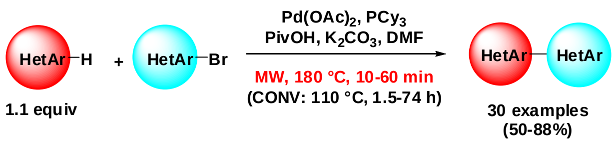
1.0 mol%, 65 °C (MeOH): 3 h
1.0 mol%, 80 °C (EtOH): 1 h

3.0 mol%, 80 °C (EtOH): 25 min

Cantillo, D.; Baghbanzadeh, M.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2012**, *51*, 10190

Difficult Chemistry: C-H Activation

Pd-Catalyzed Direct Arylation of Heterocycles (Fagnou)

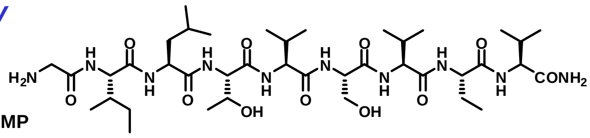


M. Baghbanzadeh

J. Org. Chem. **2011**, *76*, 8138

Difficult Chemistry: Solid Phase Peptide Synthesis

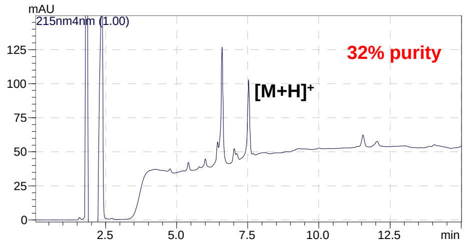
9-mer Peptide GILTVSVAV



Coupling: 5 eq Fmoc-AA, DIC, HOBt, NMP
Deprotection: 30% piperidine/DMF

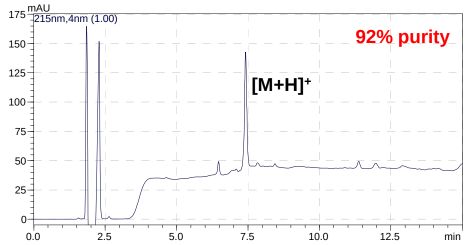
Gly-Ile-Leu-Thr(tBu)-Val-Ser(tBu)-Val-Ala-Val-Tentagel S RAM

SPPS at Room Temperature



Coupling: 25 °C, 1h
Deprotection: 25 °C, 2+20 min

Microwave-Assisted SPPS



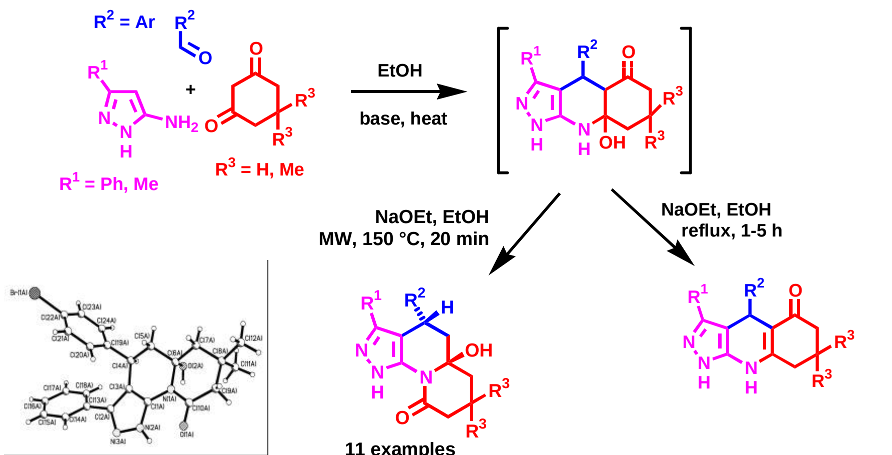
Coupling: MW: 86 °C, 10 min
Deprotection: MW: 86 °C, 0.5+2.5 min

B. Bacsa

J. Org. Chem. **2008**, *73*, 7532; *J. Org. Chem.* **2010**, *75*, 2103

Find Novel Reaction Pathways

Multicomponent Reactions



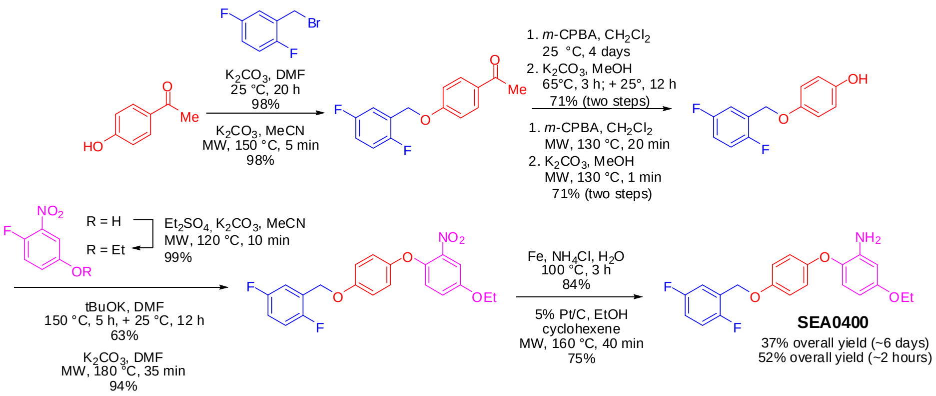
11 examples
(40-75%)

V. Chebanov, T. Glasnov

Org. Lett. **2007**, *10*, 1691
J. Org. Chem. **2008**, *73*, 5110

"First Choice", not "Last Resort"

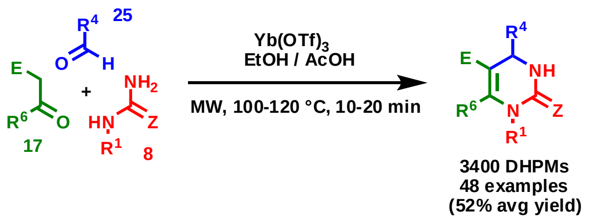
Five-Step Synthesis of SEA0400 (Selective Inhibitor of the Na^+/Ca^{2+} Exchanger)



T. Glasnov | *Tetrahedron Lett.* **2012**, *53*, 3731

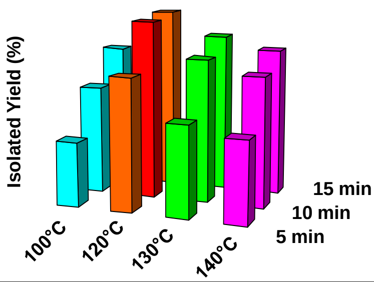
Automated Compound Synthesis (Libraries)

Multicomponent Reactions



Z = O, S
R^1 = H, alkyl, aryl
R^4 = aryl, alkyl, heterocycle
E = ester, acyl, amide nitro
R^6 = alkyl, aryl

Time & Temp Optimization

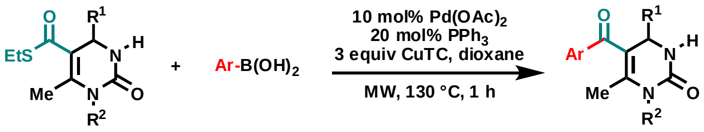


A. Stadler

J. Comb. Chem. **2001**, *3*, 624
Nature Protoc. **2007**, *2*, 1713

Automated Sequential Versus Parallel Library Synthesis (Rotors)

Thiol Ester-Boronic Acid Couplings



H. Prokopcova

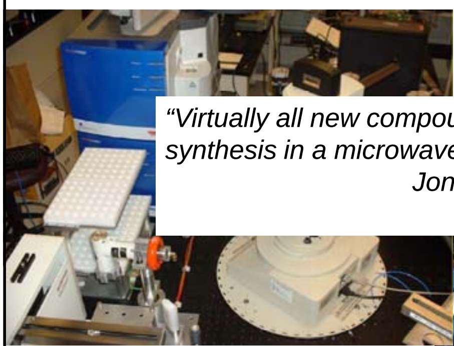
Synlett **2007**, 43

48 vessel rotor
200 °C, 20 bar
6-25 mL

L. Pisani *J. Comb. Chem.* **2007**, *9*, 415

R^1	R^2	Ar	Sequential Yield [%]	Parallel Yield [%]
Ph	H	Ph	86	80
Ph	H	3-OMe-Ph	74	71
3-Br-Ph	H	3-Cl-Ph	64	62
2-CF_3-Ph	H	3,4-$(F)_2$-Ph	66	63
2-CF_3-Ph	H	3-Cl-Ph	70	69
3,4-$(OMe)_2$-Ph	H	4-Me-Ph	63	64
3,4-$(OMe)_2$-Ph	H	3,4-$(F)_2$-Ph	74	72
thiophen-2-yl	Me	Ph	82	86
thiophen-2-yl	Me	4-Me-Ph	68	66

High Throughput "Microwave Synthesis Factories" in Big Pharma



"Virtually all new compounds now have their first synthesis in a microwave"

Jonathan Moseley, AstraZeneca UK

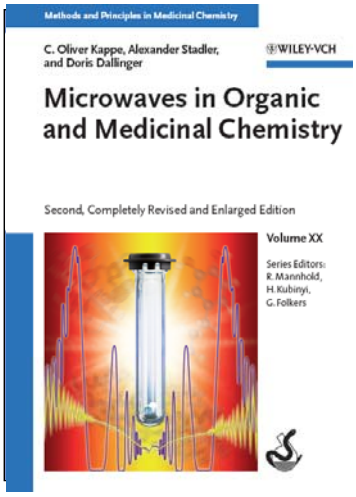
Chemistry World **2008**, *5(10)*, 40

Courtesy of D. R. Sauer, Abbott, USA

Dallinger, D.; Kappe, C. O.
Nature Rev. Drug Discov. **2006**, *5*, 51

Courtesy of S. Chamoin, Novartis, Switzerland

From Laboratory Curiosity to Standard Practice (>10000 References, 250 Reviews, 12 Books)



Applications in Organic Synthesis

- Transition Metal Catalyzed C-X Bond Formation
- Other Metal-Mediated Processes
- Metathesis, CH-Bond Activation
- Cycloaddition Reactions
- Rearrangements
- Enantioselective Reactions
- Organocatalysis, Biocatalysis
- Radical Reactions
- Oxidations, Reductions
- Heterocycle Synthesis
- Total Synthesis
- Solid- /Fluorous Phase Synthesis
- Immobilized Reagents, Scavengers and Catalysts
- Solid Phase Peptide Synthesis

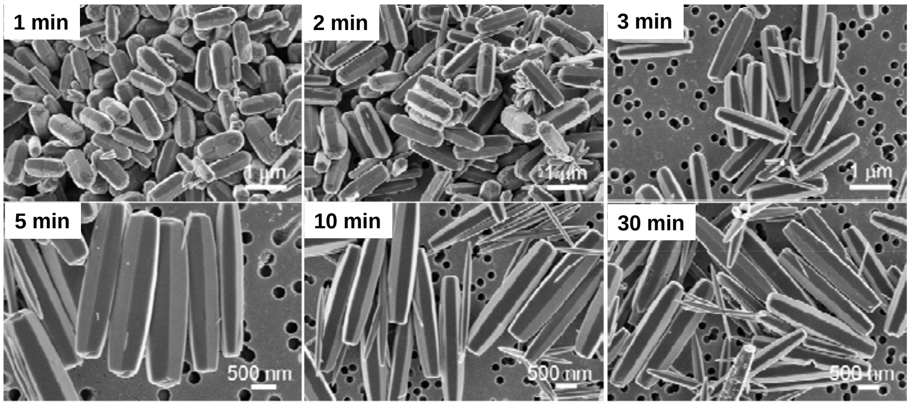
Kappe, C. O.; Stadler, A.; Dallinger, D. "*Microwaves in Organic and Medicinal Chemistry*" Wiley-VCH, 2012

Emerging Applications

- **Material / Nano sciences**
- **Polymer chemistry**
- **Peptide synthesis**
- **Biomass Processing**
- **Platform Molecules/Biofuels**

Synthesis of ZnO Nanocrystals

ZnO Synthesis – Effect of Hold Time at 150 °C
(Zn nitrate/urea in ethylene glycole/water 3:1)



Baghbanzadeh, M et al. *Chem. Eur. J.* **2012**, *18*, 5724

Research in the CDLMC (2006-2013)

- **Applications in Organic/Medicinal, Peptide, Polymer Nano/Materials and Biochemical Research**
- **Scale-Up/Continuous Flow**
- **Microwave Effects**
  (Thermal, Specific and Nonthermal Effects)

Anton Paar | ThalesNano | micro innova efficient processing | BASF The Chemical Company
piCHEM research & development | Lonza

One Problem: Scale-Up (Penetration Depth)

$$PD = \frac{\lambda}{2\pi} \cdot \frac{\sqrt{\varepsilon'}}{\varepsilon''}$$

depth at which power density has decreased to 37% of its initial value

PD's at 2.45 GHz

MeOH (25 °C):	0.66 cm	glass (25 °C):	35 cm	SiC (20 °C): 0.97 cm
water (25 °C):	1.4 cm	Paper (25 °C):	16 cm	Al_2O_3 (25 °C): 633 cm
water (95 °C):	5.7 cm	PVC (20 °C):	210 cm	Al (25 °C): 1.7 µm
beef (30 °C):	1.13 cm	Teflon (25 °C):	9200 cm	Au (25 °C): 1.5 µm
ice (-12 °C):	1100 cm	quartz (25 °C):	16000 cm	

PD's at 915 MHz

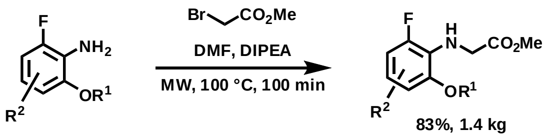
water (25 °C): 38 cm

Microwave Scale-Up in Parallel Multimode Reactors to the Kilogram Scale

Multiwave Pro

16 vessel Rotor (100 mL filling volume)

Case Study, Novartis (Basel)

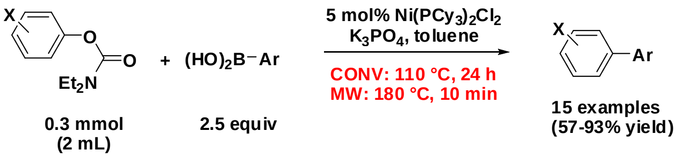


- **16 x 80 mL each, 1.28 L/run**
- **6 runs, 7.68 L reaction volume**
- **good reproducibility**
- **1.4 kg product isolated**
- **2 runs per day, 4 days in total (incl. work-up)**

Lehmann, H. J.; LaVecchia, L. *Org. Process Res. Dev.* **2010**, *14*, 650

Scale-Up from Monowave to Masterwave

Ni-Catalyzed Suzuki-Miyaura Cross-Coupling (Garg, Shi, Snieckus)



Baghbanzadeh, M.; Pilger, C.; Kappe, C. O. *J. Org. Chem.* **2011,** *76*, 1507

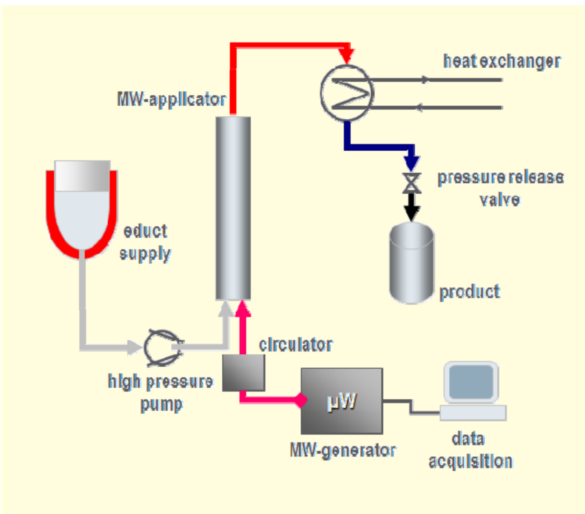
Linear Scale Up (Masterwave BTR)

1 L PTFE vessel
Max. 250 °C, 30 bar (1700 W)
Stirring: adjustable integrated agitator (0-700 rpm)

2-Chlorobenzonitrile – p-Tolylboronic Acid Coupling:
0.375 mol (~700 mL): 76.25 g of product

Production Scale Continuous Flow Microwave Reactor

Hybrid Reactor Equipment - General Setup for Continuous Processing



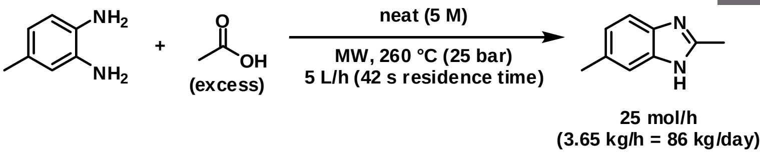
Clariant
Exactly your chemistry.
PÜSCHNER
MicrowavePowerSystems

Clariant Unit:
- frequency: 2.45 GHz
- max power: max 6 kW

Border Conditions for Lab Use:
- max temp: 300°C
- max pressure: 70 bar
- max flow 20 l/h

Scale-Up to Production Scale in Large Scale Microwave Flow Reactor

Process Intensification for Benzimidazole Synthesis



- cylindrical ceramic flow tube (75 cm length, 10 mm i.d., 60 mL volume)
- single-mode microwave cavity (6 kW, 2.45 GHz)
- max temperature 300 °C, max pressure 70 bar
- max flow rate 20 L/h
- extremely energy efficient
- advanced safety concept (TüV)

Morschäuser, R. et al. *Green Process. Synth.* **2012**, *1*, 284

Production Scale Continuous Flow Microwave Reactor

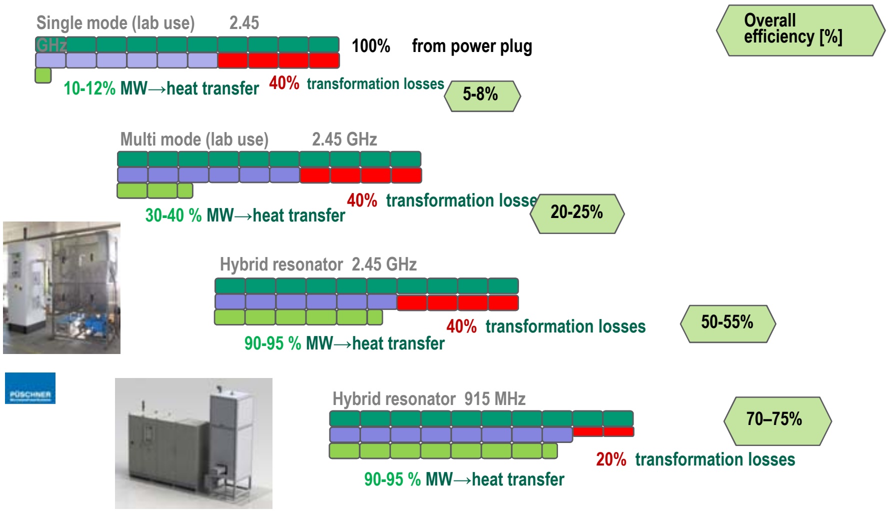
Hybrid Reactor Equipment - General Setup for Continuous Processing of Biodiesel ***(5 tons per day: 170 °C, 18 bar, 10-30 s)***

Clariant's Hybrid reactor

"flow heater"

- 915 MHz continuous flow
- operates at 25 to 300°C
- up to 40 bars tested
- approval under "pressurized equipment guideline" (proved by German TüV)

Appropriate Microwave Reactor Design Allows Significant Savings in Energy Costs



Moseley, J. D.; Kappe, C. O. *Green Chemistry* **2011**, *13*, 794

"Special" Microwave Effects? Nonthermal or Specific Microwave Effects

Angewandte Essays

Microwave Chemistry

DOI: 10.1002/anie.201204103

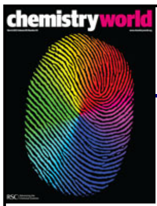
Microwave Effects in Organic Synthesis: Myth or Reality?**

C. Oliver Kappe, Bartholomäus Pieber, and Doris Dallinger*

"……………..We sincerely hope that this Essay will help the scientific community to accept the fact that microwave chemistry is not "Voodoo Science", but in essence an incredibly effective, safe, rapid, and highly reproducible way to perform an autoclave experiment under strictly controlled processing conditions."

Angew. Chem. Int. Ed. **2013**, 52, 1088–1094

Microwave Effects
Still Being Published !



Richards, E. *Chemistry World,* **2012**, *9*, No. 3 (March), p.25
Rosana, M. R. et al. *Chem. Sci.* **2012**, *3*, 1240

Magical microwave effects revived

Microwaves can accelerate reactions without heating

Microwaves have been used to promote organic reactions since the 1980s and can lead to higher yields and shorter reaction times than conventional heating, but why? Conventional wisdom says that it's the heat that promotes the reactions, but new research shows that the waves could be interacting with the reagents directly.

Gregory Dudley and colleagues from Florida State University, Tallahassee, US, discovered a microwave effect occurring during a Friedel-Crafts benzylation reaction in a microwave. The microwave-absorbing polar reactant - a pyridinium - reacted in a non-polar and largely non-microwave-absorbing solvent - toluene. 'Polar molecules interact more strongly with microwaves than non-polar molecules,' explains Dudley. 'So we tried to design a system in which only the reaction substrate would interact with the incident radiation energy.'

The team found that microwave irradiation induces reactivity levels that can't be duplicated by conventional heating, without ever reaching the temperature required in conventional heating. 'It's hard to speculate what exactly is going on,' says Dudley. 'Our focus was to identify an effect.' Dudley adds that there is still much to learn about the differences between activating reactions with microwaves and conventional heating.

The counter-argument - that heat is promoting microwave-assisted reactions - was proved in previous research done by another team. Oliver Kappe, from the University of Graz, Austria, carried out a reaction in a microwave-absorbing silicon carbide vial, which prevents microwaves reaching the reactants inside. They screened 18 reactions and got results identical to those from conventional heating.

'We studied Professor Kappe's work carefully while designing our system,' says Dudley. A fundamental challenge was to separate the effects of penetrating microwaves from the effects of rapid heating. The silicon carbide vials ingeniously enable rapid heating while blocking microwave penetration, he adds. 'We aimed for the extreme opposite. We wanted to avoid rapid volumetric heating, while maximising microwave penetration.'

'This is certainly going to shake up a few things and make people think,' says Nicholas Leadbeater, who studies microwave reactions at Connecticut University in the US. 'These magical microwave effects had essentially been debunked.'

Leadbeater adds that there were some extreme cases where a microwave-absorbing reagent in a non-microwave-absorbing solvent caused unexplained rate accelerations. 'But these were the exception rather than the rule,' he says. In most of those cases, there was a solid catalyst or metal powder in the reaction that was heating up very quickly. 'In this case, it's totally homogeneous and they are still claiming to have seen this special microwave effect,' he says. *Elinor Richards*

REFERENCE
M R Rosana *et al*, *Chem. Sci.*, 2012, DOI: 10.1039/c2sc01003h

Nonthermal Microwave Effects Do Not Exist –
But Special Effects Still Controversial

Angewandte Correspondence

Microwaves in Synthesis

Angew. Chem. Int. Ed. **2013**, *52*, 7918

Correspondence on Microwave Effects in Organic Synthesis

Gregory B. Dudley, Albert E. Stiegman, and Michael R. Rosana*

Microwaves in Synthesis

Angew. Chem. Int. Ed. **2013**, *52*, 7924

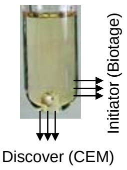
Reply to the Correspondence on Microwave Effects in Organic Synthesis**

*C. Oliver Kappe**

Erroneous Temperature Measurement Using External Infrared Sensors

IR Versus FO Sensors

External Infrared Sensors

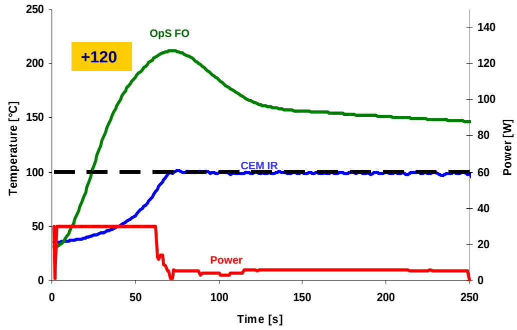


- Measure surface temperature of vessel
- Delay in response
- Extremely dependent on stirring efficiency

Internal Fiber-Optic Sensors

- Probe in immersion well
- Fast response time
- Less dependent on stirring efficiency

Heating Ionic Liquids (100 °C Set Temp, IR + FO Probe)



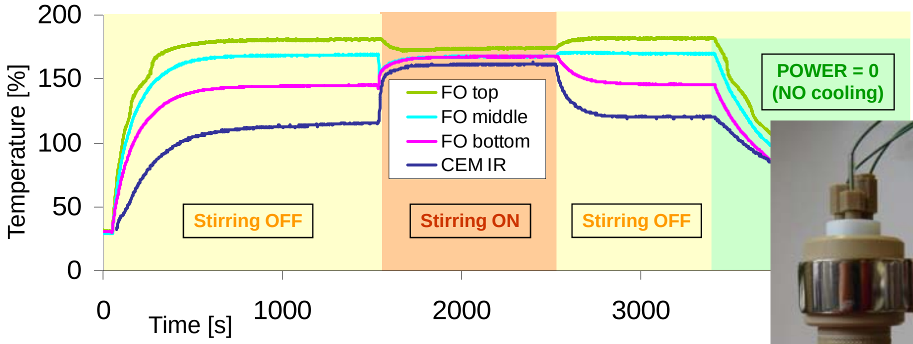
OpS FO OpSens© Fiber Optic Probe
CEM IR CEM Discover Standard Infrared Sensor

D. Obermayer

Org. Biomol. Chem. **2010**, *8*, 114

The Importance of Efficient Stirring

Heating Profile: 5 mL NMP / 50 W / Quartz Vessel (CEM Discover)



triple fiberoptic sensor positioned at different heights in a 10 mL microwave process vial

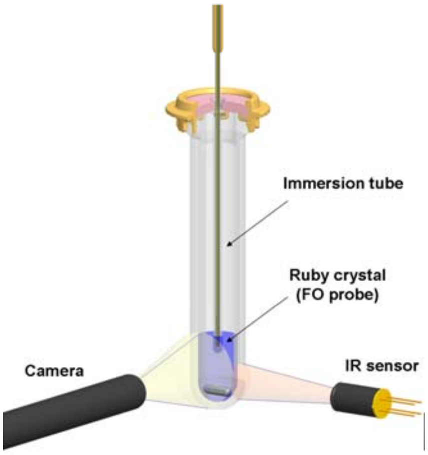
Herrero, M. A. et al. *J. Org. Chem.* **2008**, *73*, 36

2nd Generation Single-Mode Microwave Reactor (Monowave 300, Anton Paar, 2009)

Instrument Features

- dual IR/FO temperature control
- 300 °C, 30 bar
- 850 W power
- 3 vessel sizes (0.5-20 mL)
- SiC vessel, built-in camera
- magnetic stirring (0-1200 rpm)

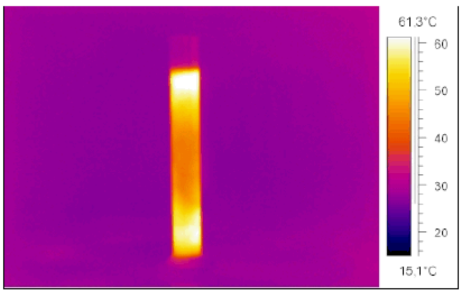
Simultaneous IR/FO Temperature + Camera



Hayden, S.; Damm, M.; Kappe, C. O. *Macromol. Chem. Phys.* **2013**, *214*, 423

Thermal Gradients in Multimode Instruments

Water, MW Irradiation (Domestic Oven)

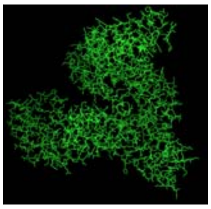


- *Overheated regions in multimode reactors as a result of field inhomogeneities*
- *In chemistry: stirring is necessary to avoid hot spots and temperature inhomogeneity*

Vollmer, M.; Möllmann, K.-P.; Karstädt, D. *Physics Education* **2004**, *39*, 500

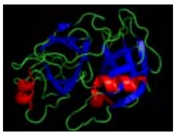
Microwave Effects on Proteins (Proteomics)

Investigation of the Tryptic Digest

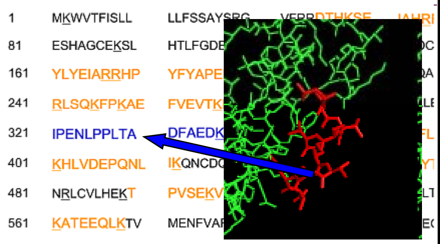


Bovine Serum Albumin
(607 AA residues)

NH_4HCO_3 buffer, $CaCl_2$



Trypsin
(224 AA residues)



Obtained Peptide Sequences

Microwave Digest (37 °C, 50 °C)

vs.

Conventional Digest (37 °C, 50 °C)

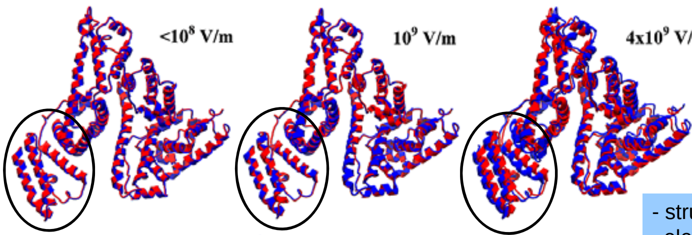
M. Damm

J. Proteom. **2012**, *75*, 5533

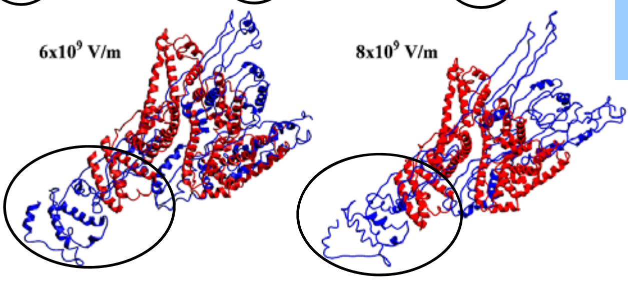
Electric Field Strength Simulations

Effect of Increasing Electric Field on the Structure of BSA

(Molecular Mechanics, Amber all atom force field, Gaussian 09)



- structure for BSA at various electric fields (blue), overlapped with the structure of the native protein (red)



higher field strengths (>10^9 V/m) are strong enough to destroy α-helices

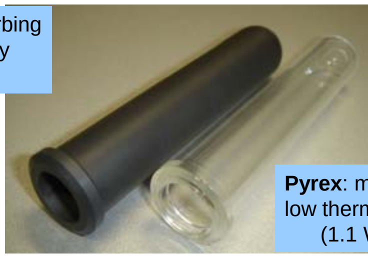
The Silicon Carbide (SiC) Reaction Vessel Concept

Thermal vs Nonthermal /Specific Microwave Effects

SiC: strongly MW absorbing
high thermal conductivity
(150 W/m K at rt)

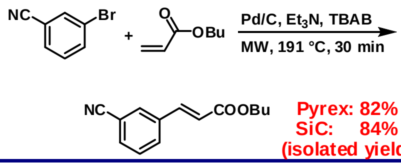
D. Obermayer, B. Gutmann

Angew. Chem. Int. Ed. **2009**, *48*, 8321
(Hot Paper, Highlighted in *Nature, Science, Chem. Eng. News, Chemistry World*)

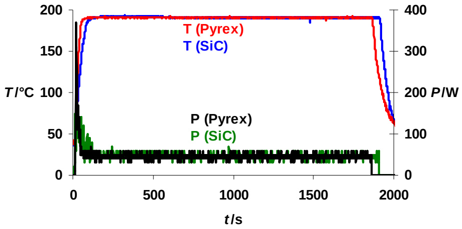


Pyrex: microwave transparent
low thermal conductivity
(1.1 W/m K at rt)

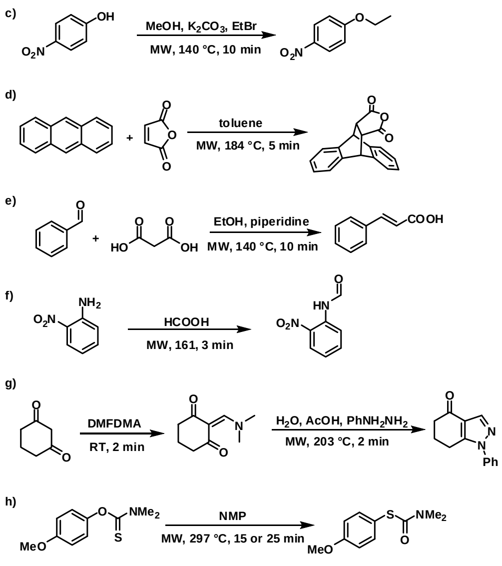
Comparing SiC and Pyrex Data



Pyrex: 82%
SiC: 84%
(isolated yield)



SiC Reaction Vials – Separating Thermal from Specific/Nonthermal Effects



c) Pyrex: 86%
SiC: 78%
(isolated yield)

d) Pyrex: 92%
SiC: 92%
(isolated yield)

e) Pyrex: 88%
SiC: 89%
(isolated yield)

f) Pyrex: 87%
SiC: 86%
(isolated yield)

g) Pyrex: 90%
SiC: 87%
(isolated yield)

h) 15 min: Pyrex: 51%
SiC: 52%
25 min: Pyrex: 73%
SiC: 73%
(HPLC conversion)

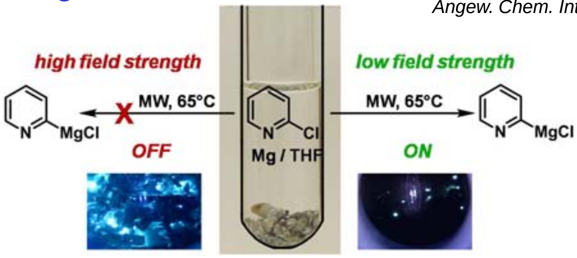
Additional examples
- organic synthesis
- nanoparticles
- protein hydrolysis
- extraction

Obermayer, D.; Gutmann, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 8321; *Chem. Eur. J.* **2010**, *16*, 12182

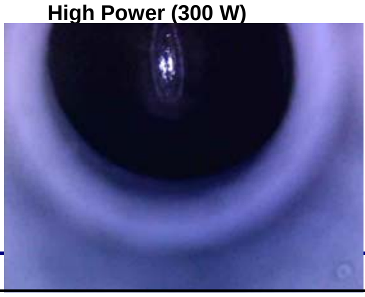
"Specific" Microwave Effects: Arcing in a High Field Density Reactor

Formation of Grignard Reaction

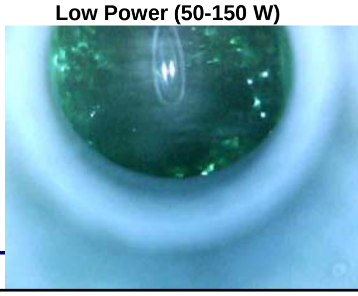
B. Gutmann
Angew. Chem. Int. Ed. **2011**, *50*, 7636



High Power (300 W)



Low Power (50-150 W)



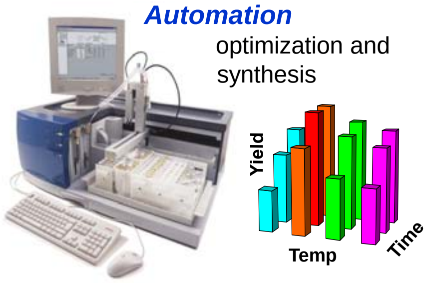
Summary: Microwave-Assisted Chemistry

Characteristics of MW Heating

- direct energy transfer
- rapid dielectric heating (tan δ)
- elimination of wall effects
- volumetric heating
- superheating of solvents (300 °C, 30 bar)

Automation

optimization and synthesis



Processing Techniques

- open/closed vessel
- distillation
- pre-pressurized (autoclave)
- parallel (rotors, plates)
- online monitoring
- limited scale-up (batch and flow)
- ………..

Advantages

- shortening reaction times
- improving yields
- cleaner reaction profiles
- expanded reaction envelop
  - change product distributions
  - new reaction pathways
- …………..

Tutorial Review: Kappe, C. O. *Chem. Soc. Rev.* **2008**, *37*, 1127

Chemie in unserer Zeit Artikel

DOI: 10.1002/ciuz.201300610

Manche mögens heiß

Mikrowellen in der Organischen Synthese

DORIS DALLINGER

MIKROWELLEN | ORGANISCHE SYNTHESE