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Scalability of Microwave-Assisted Organic Synthesis. From Single-Mode to Multimode Parallel Batch Reactors

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Microwave Theory

Microwaves

- Between IR and Radio wave: 0.3 - 300GHz
- In use 2.45GHz (cooking and chemistry)

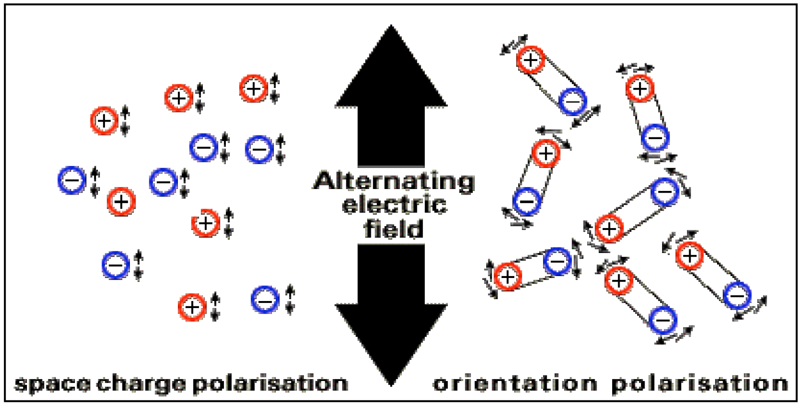
Microwave heating

- Dipolar polarization - rxn mixture must have some polar species (solvent, reactants, additives)
- Conduction

DDT 2002, 7, 373

Dielectric heating

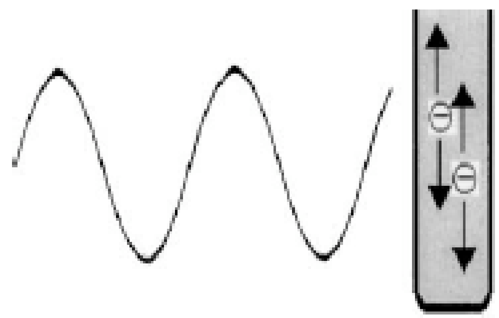
- For a substance in MW to generate heat it must have dipole moment.
- In liquids alignment is affected by viscosity and frequency.
- The dipole reorients to align itself with electric field, the field is already changing and phase difference is generated, causing energy to be lost by molecular friction and collisions giving rise to dielectric heating.



Tetrahedron 2001, 57, 9225

Conductivity heating

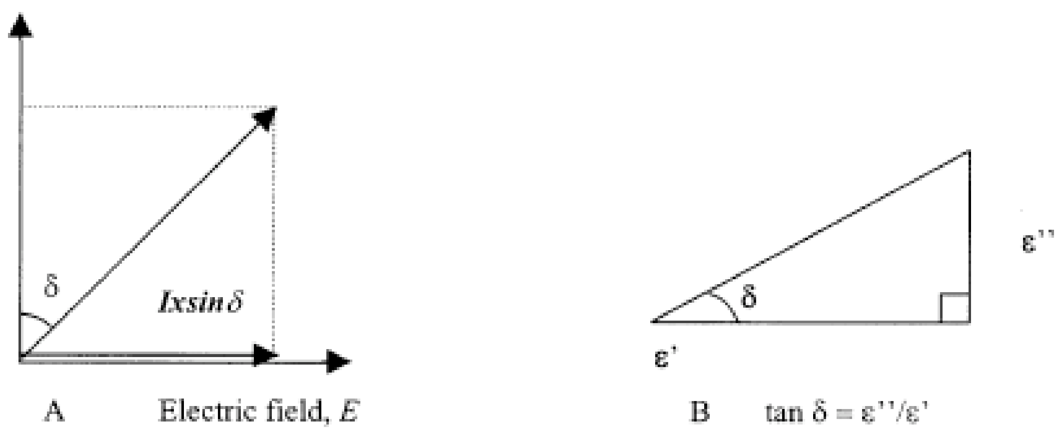
- Ions in the solution follow the electric field resulting in expenditure of energy due to increased collision rate, converting kinetic energy to heat.
- This mechanism gives much stronger heating then dipolar.



Tetrahedron 2001, 57, 9225

Loss angle

- The reorientation of dipoles and displacement of charge are equivalent to an electric current. This displacement is 90° when the dielectric follows precisely the field. That is not the case, therefore the resulting ***phase displacement, δ, produces a component I sin δ, in phase with electric field. This causes the energy to be absorbed from the electric field which is converted to heat - dielectric loss.***



. (A) A phase displacement which results when energy is converted to heat. (B) The relationship between ϵ' and ϵ'', $\tan\delta = \epsilon''/\epsilon'$.

Tetrahedron 2001, 57, 9225

Solvents

Table 1. Values of solvent loss tangents

Solvent	Dielectric constant (ε_s)[a]	Loss tangent ($\tan\delta$)[b]
Hexane	1.9	–
Benzene	2.3	–
Carbon tetrachloride	2.2	–
Chloroform	4.8	0.091
Acetic acid	6.1	0.174
Ethyl acetate	6.2	0.059
THF	7.6	0.047
Methylene chloride	9.1	0.042
Acetone	20.6	0.054
Ethanol	24.6	0.941
Methanol	32.7	0.659
Acetonitrile	36.0	0.062
Dimethyl formamide	36.7	0.161
Dimethyl sulfoxide	47.0	0.825
Formic acid	58.0	0.722
Water	80.4	0.123

[a]The dielectric constant, ε_s, equals the relative permittivity, ε', at room temperature under the influence of a static electric field.
[b]Values determined at 2.45 GHz and room temperature.
Abbreviation: THF, tetrahydrofuran.

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Terminology to remember

- ***Magnetron –*** an electromagenetic device that generates microwaves at fixed frequency (2.45GHz).
- ***Multi-mode cavity*** – domestic and large chamber microwaves – large enough to propagate multiple modes of microwave energy (20-30) which interact with each other constructively and destructively and create "hot spots" and "cold spots". To get uniform heating simple stirring (mode stirrer- moving metal vane that continuously changes the instantaneous field pattern inside the cavity) is used or rotation. Field intensity is homogeneous in all directions and all locations throughout the entire cavity.
- ***Mono-mode cavity*** – a small chamber that allows the propagation of one mode of microwaves. This allows a more homogenous energy distribution and higher power density then multimode cavities. The essential characteristic of single-mode cavities is the deliberate creation of a standing wave pattern inside the cavity.

Microwave synthesis, B.L. Hynes, CEM

http://www.milestonesci.com/synth-fund.php

Why do the microwaves speed up reactions?

$$K = A\, e^{-\Delta G/RT}$$

A - describes molecular mobility

ΔG - free energy of activation

T - temperature (the key!)

No magic! More efficient heating!

Superheating and hot spots.

Microwave chemistry is a hot spot!

Supercharged

Most experts now believe that the mysterious effect is the result of nothing more than microwaves' ability to superheat solvents way beyond their normal boiling points — because the even spread of heat through the liquid allows it to reach a higher temperature before bubbles form. Water, for example, reaches 105 °C before boiling in a microwave oven; whereas the solvent acetonitrile boils at 120 °C instead of its usual 82 °C. "There are

Out of the kitchen

Designer microwave ovens that can heat reactants in record time are heralding a quiet revolution in chemical synthesis. David Adam feels the heat.

www.nature.com

What reactions can be done in microwave?

- Almost any reaction that requires heat, but not limited to these…

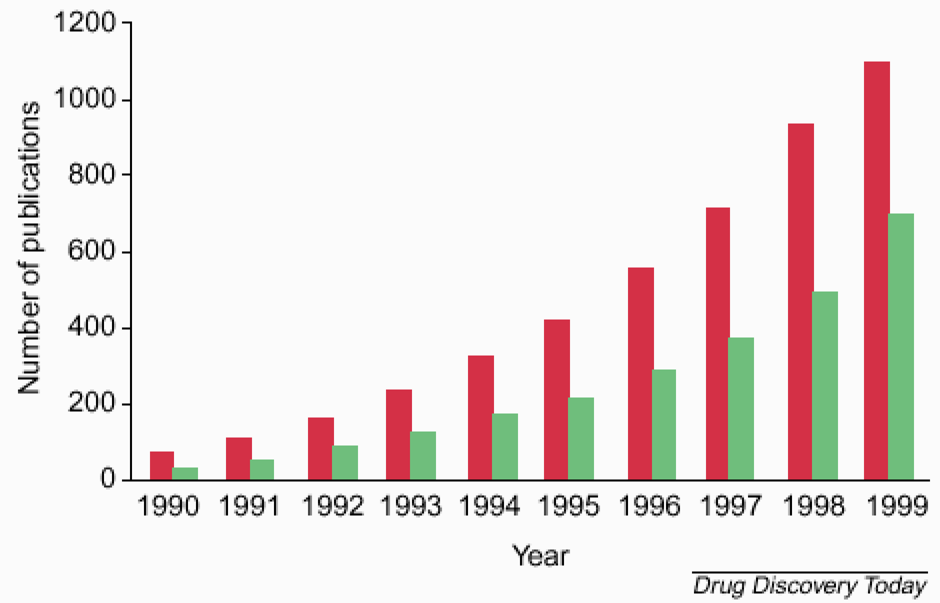

Figure 1. Growth in the number of published papers on microwave-assisted inorganic and organic chemistry. Accumulated number of papers (red) compared with the number of papers on organic synthesis (green).

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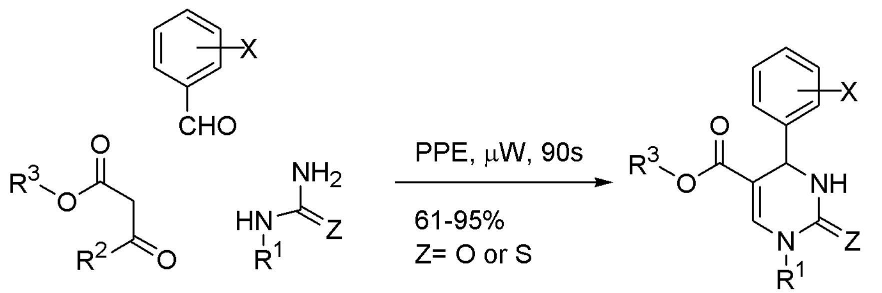
Microwaves in combinatorial synthesis, medicinal chemistry and drug discovery



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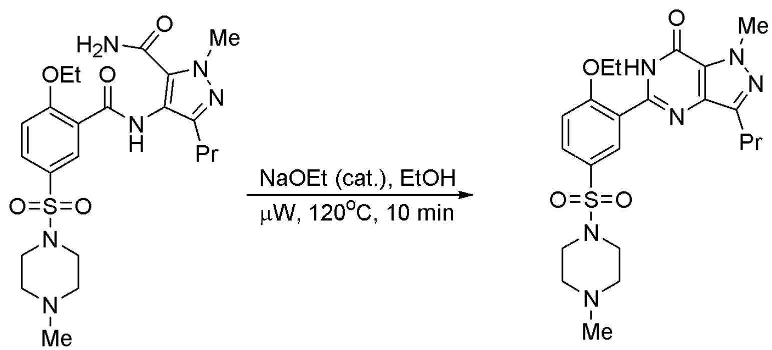
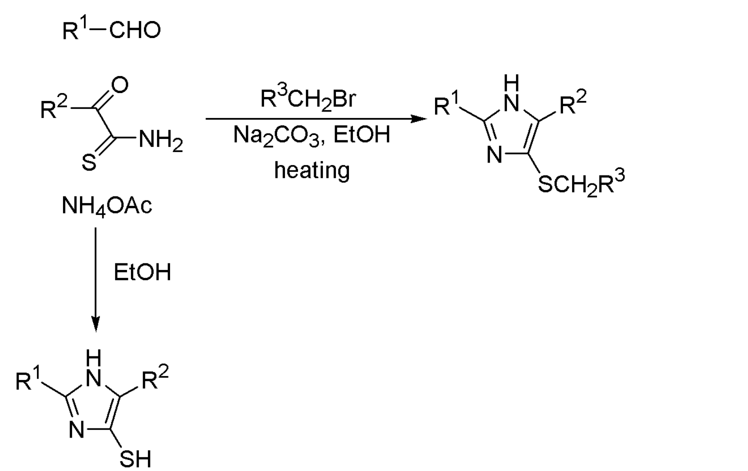


Viagra

Three - Component Synthesis of Substituted 4(5)-Sulfanyl-1*H*-imidazoles



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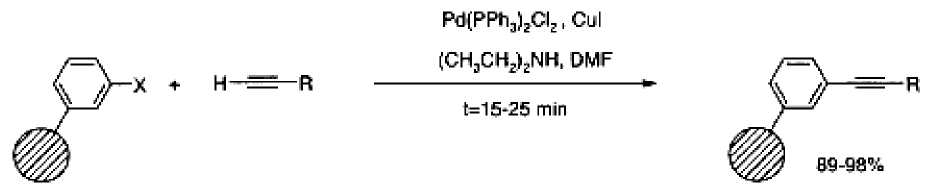
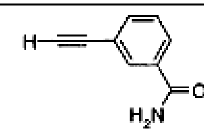
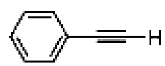
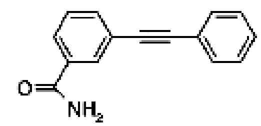
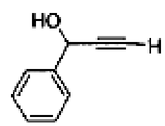
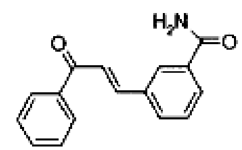
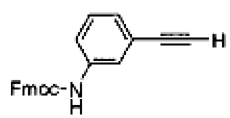
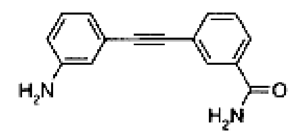
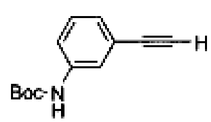
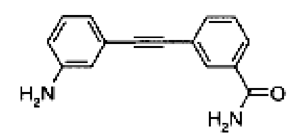
Coleman et al, J. Comb. Chem. **2002,** *4,* 87-93

Sonogashira Coupling of Arylacetylenes on Iodophenyl and Bromophenyl Resins



	R-C≡CH	3-iodophenyl resin yield[A]	3-bromophenyl resin yield[B]	product
1[C]		94%	97%	
2		89%	92%	
3		92%	98%	
4[C]		-	95%	
5[C]		98%	94%	

Method A, 120 °C, 15 min, 5% Pd, 10% Cu.
Method B, 120 °C, 25 min, 10% Pd, 20% Cu, 20% PPh3.

J. Org. Chem. ***2003****, 68, 6431-6434*

Small scale gets big!

Major concerns:

Restricted penetration depth of microwave irradiation into reaction mixtures. At the typical operating frequency of most microwave reactors of 2.45 GHz, the *penetration depth* is generally in the order of *a few centimeters*, depending on the dielectric properties of the medium.

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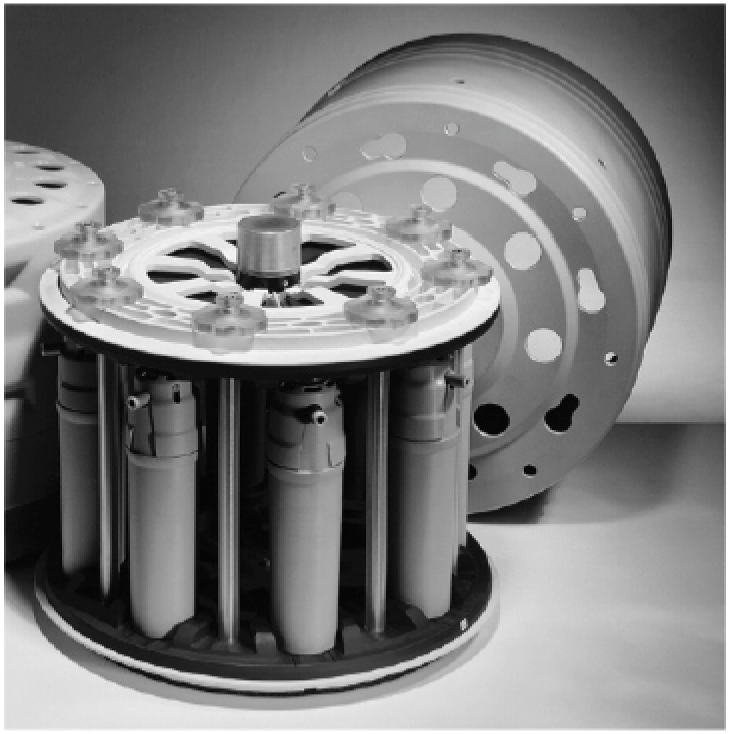
Prototype multimode batch reactor (Anton Paar GmbH, Graz)

- operating at a frequency of 2.45 GHz with continuous microwave output power from 0 to 1400 W.
- dimensions: W D H, 45 42 35 cm3)
- eight-vessel rotor, employing either 100mL PTFE-TFM or 80 mL quartz glass vessels (max filling volume ca. 50-60 mL), both types dedicated for reactions at high pressure (60 or 80 bar controlled pressure) and temperatures (260 and 300 °C).
- PTFE-TFM vessels are inserted into a ceramic vessel jacket, which provides structural strength and dimensional stability.
- vessels are placed in the corresponding rotor
- temperature of all vessels can be monitored by IR
- After irradiation, the rotor is cooled to approximately 40 °C within 20 min by venting air through cooling gaps which are surrounding the reaction vessels.



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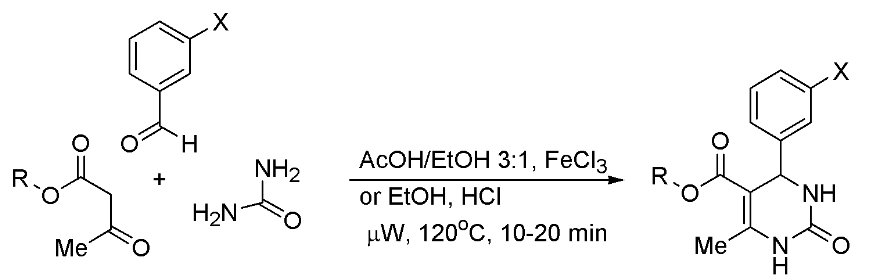
Scaled up reactions using 8 vessel rotor system Biginelli condensation



1a; R=Et, X=H
1b; R=*i*-Pr, X=NO_2

Monomode rxn	Multimode scale up
4.0 mmol scale in AcOH/EtOH 3:1 at 120 °C within 10 min 88 % yield (>98% purity)	80 mmol of reagents each (0.32 mol in total) at 120 °C within 10 min ramp time was programmed for the large-scale run (3 min to 120 °C) individual 4 vessels -(70-74%) yields almost identical.

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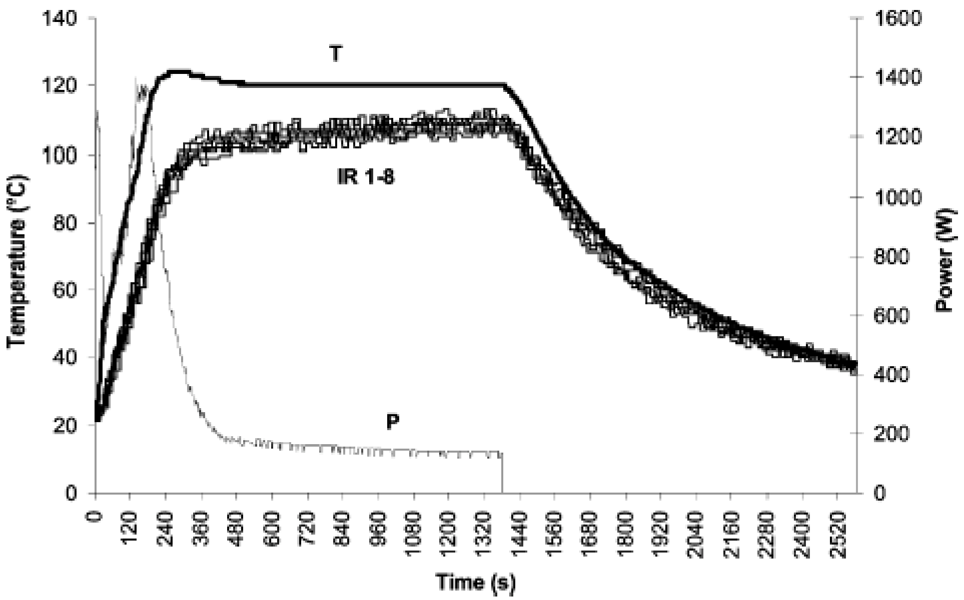
Temperature control

The magnetron power of the reactor (1400 W) sufficient to allow the linear heating from room temperature to 120 °C within 3 min (ramp) of all eight vessels, even when filled with ca. 50 mL each (total of 400 mL) of reaction mixture.



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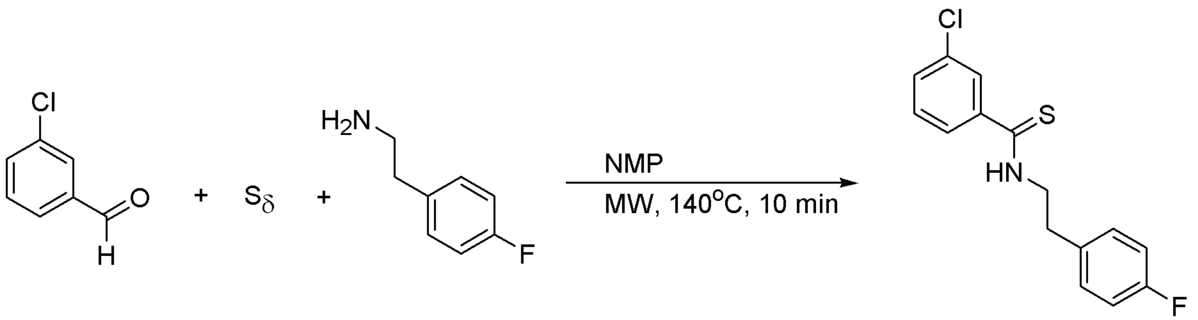
Kindler Reaction.



Monomode rxn – sealed vessel	Multimode scale up
4.0 mmol scale at 140 °C within 10 min 95 % yield	40 mmol of reagents each at 140 °C within 10 min ramp time was programmed for the large-scale run (3 min to 140 °C) individual 8 vessels – 90% yiled

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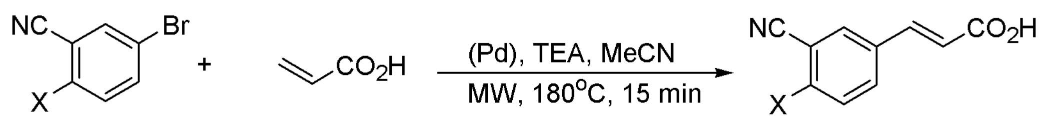
Heck reaction



3a; X=H
3b; X=F

Monomode rxn – sealed vessel	Multimode scale up
2.0 mmol scale 1 mol % Pd(OAc)2/tri(*o*tolyl)phosphine triethylamine (TEA) as base, at 180 °C within 15 min 3a (82%) , 3b (55%)	4 x 20 mmol at 180 °C within 15 min Overall yield 3a (77%) , 3b (56%)

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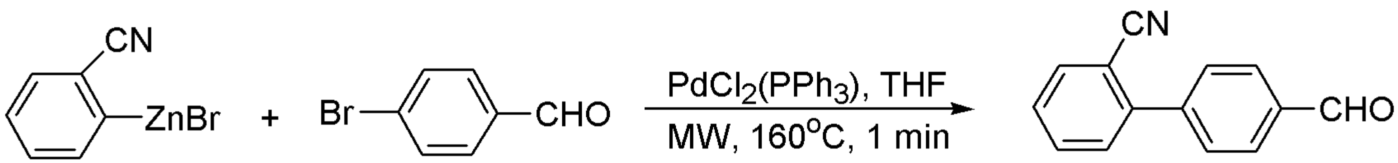
Negishi Reactions.



The large-scale synthesis was carried out in two vessels on a 2 x 20 mmol scale under an argon atmosphere in the multimode batch reactor. The reaction was heated to 160°C, employing a heating ramp of 2 min, and kept at 160 °C for an additional minute - 77% isolated yield.

Organic Process Research & Development ***2003****, 7, 707716*

Are there reactors for scale ups?

The First Prototype of the Batch Reactor

Specifications

- 350 ml
- 260°C
- 100 Bar
- 100-1200W
- Overshoot <3°C
- Stability <0.5°C
- Safety valves, Safety Interlocks

personalchemistry

Milestone's MRS Batch Reactors, designed to work with the MicroSYNTH Labstation, are inserted into the multimode cavity through the top of the labstation.

Conclusions

- Microwave heating becomes more and more popular.
- Major problems with scaling up reactions are being solved
- Scale up in monomode cavity is still an issue.
- Multimode cavity reactors with mode stirrers do provide homogenous field and high control and allow successful scale up.