University of Zagreb
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BASIC TECHNIQUES OF MICROWAVE SYNTHESIS

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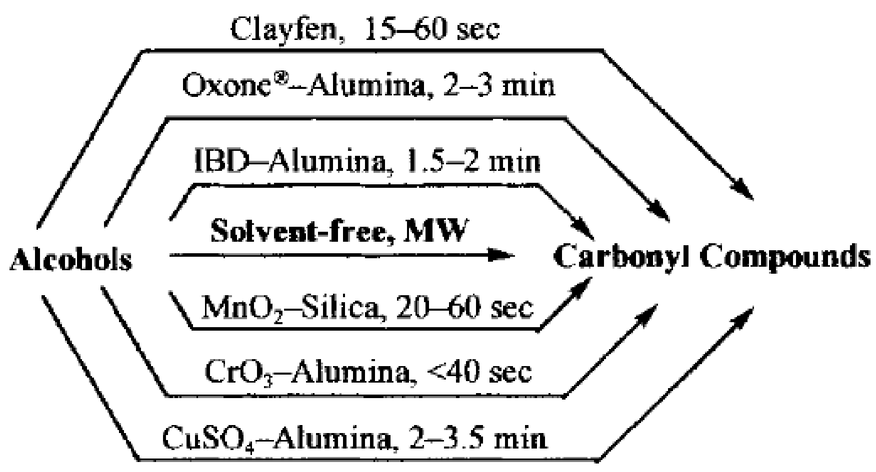
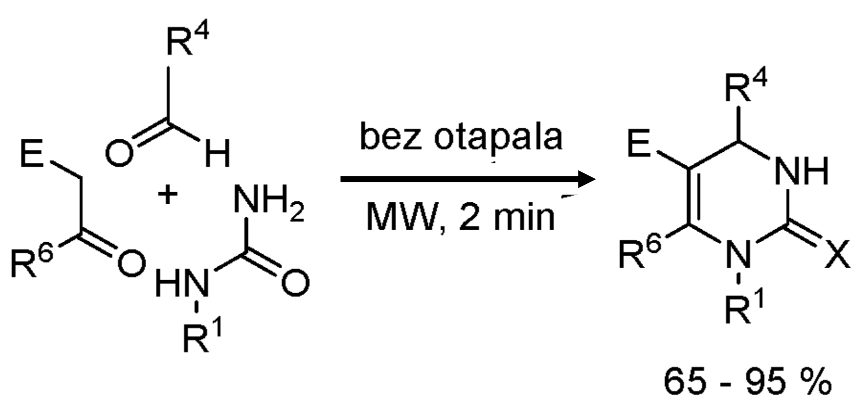
INTRODUCTION

- today, organic synthetic chemistry is geared towards new environmentally friendly methods
- the foundations of green chemistry
- solvent-free reactions are very important - they are also very often carried out in microwave synthesis
- the safety of their implementation in MW reactors is very high
- other synthetic methods commonly used in MW synthesis include reactions on inorganic carriers and reactions with undiluted reagents and reactants



SOLVENT-FREE REACTIONS

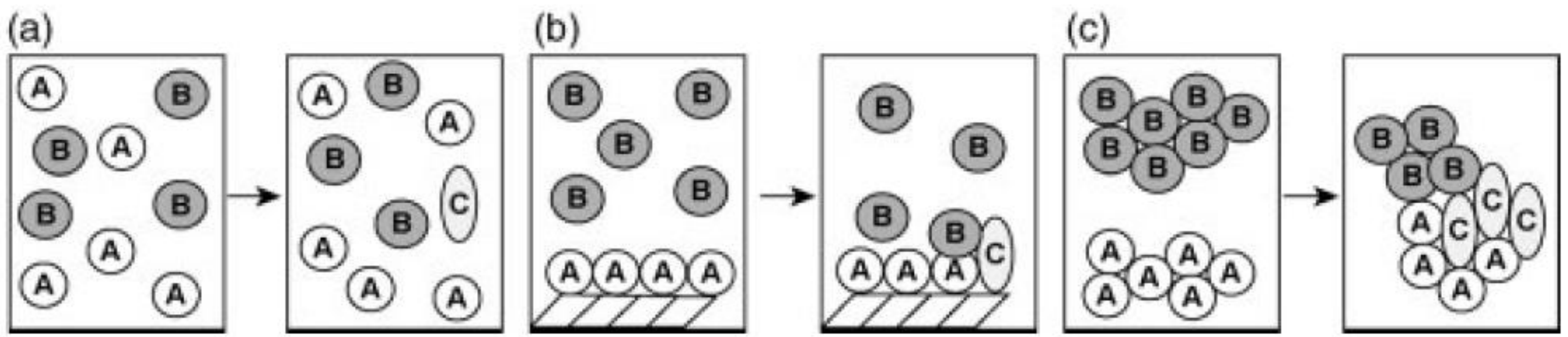
- also called "dry media reactions"
- they have been evolving since the 1990s - the reactants were mixed directly
- pure and dry organic reactants do not absorb the energy of MW radiation - almost no heating
- a small amount of polar solvent is added to the reaction mixture to achieve dielectric heating by MW radiation
- an example of such a reaction is the synthesis of pyrimidone derivatives from β-ketoesters, aldehydes and urea by the assistance of MW radiation



C. O. Kappe, D. Kumar, R. S. Varma, Synthesis (1999) 1799.

SOLVENT-FREE REACTIONS

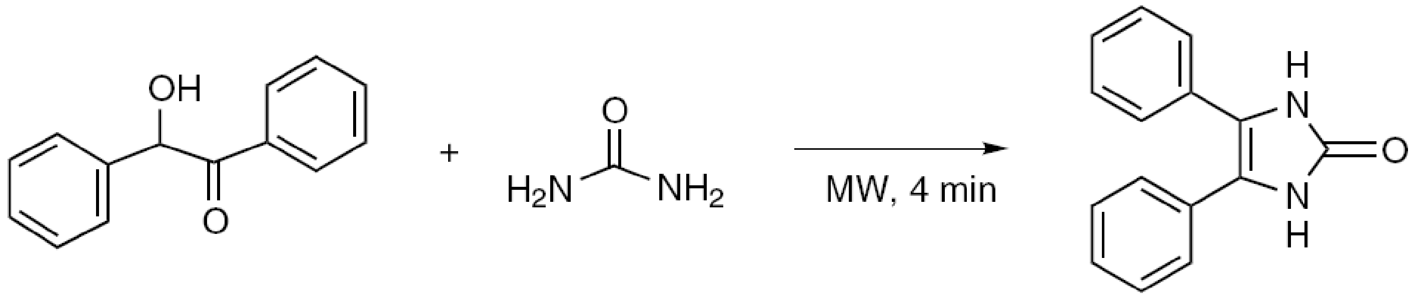
- when talking about reactions between solids, it is necessary to distinguish between "solvent-free" (solvent-free reactions), "solid-phase" (reactions on a solid support) and "solid-state" reactions (solid-state reactions)
- solid reactants and reagents can be polymeric materials, zeolites, graphite, mineral oxides (silica gel, aluminum oxide)
- for reactions requiring high temperature, graphite is used - strong interaction with MW radiation (T> 1300 K)
- in solid state reactions, two solids react to give a product which is also solid



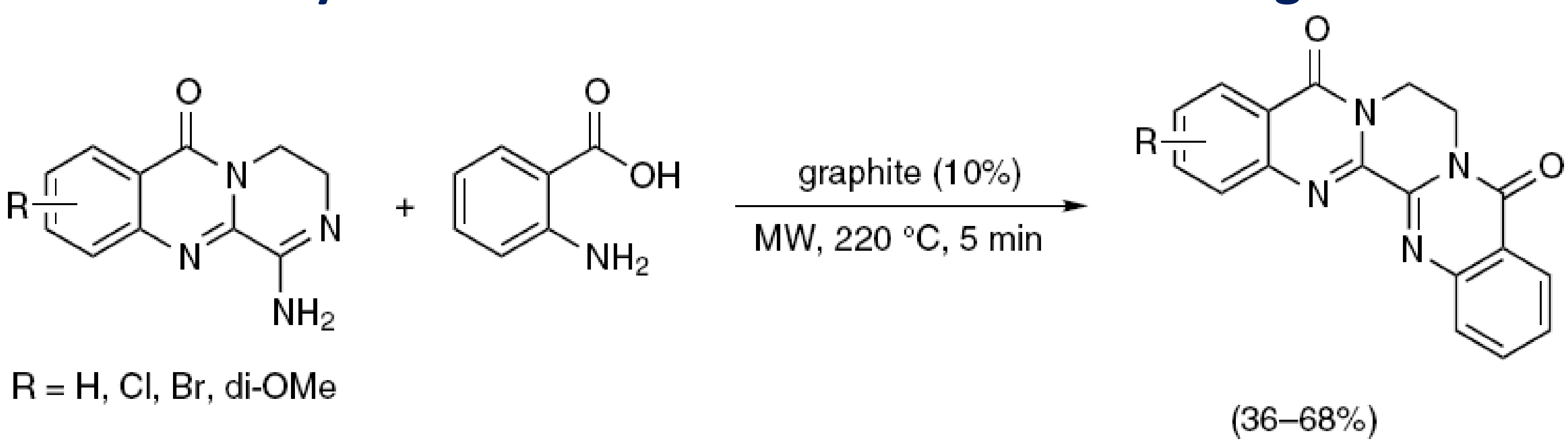
Solvent-free (a), solid-phase (b) and solid-state (c) reactions.

SOLVENT-FREE REACTIONS

- the reaction of benzoin and urea was carried out in a domestic MW oven in a glass vessel which allowed the reaction mixture to be heated to 120-140 °C and the benzoin to melt



- inorganic carriers such as silica gel, aluminum or zeolite are poorly absorbent materials but have a large active surface area
- an eco-friendly method because the carriers can be regenerated



SOLVENT-FREE REACTIONS

Characteristics of dry media reactions.

Advantages

- Easy to handle
- No specialized equipment
- High reactivity due to catalysts/reagents on porous supports
- Safe, since no flammable solvent is involved
- Environmentally benign, "Green Chemistry" (no organic solvent?).

Disadvantages

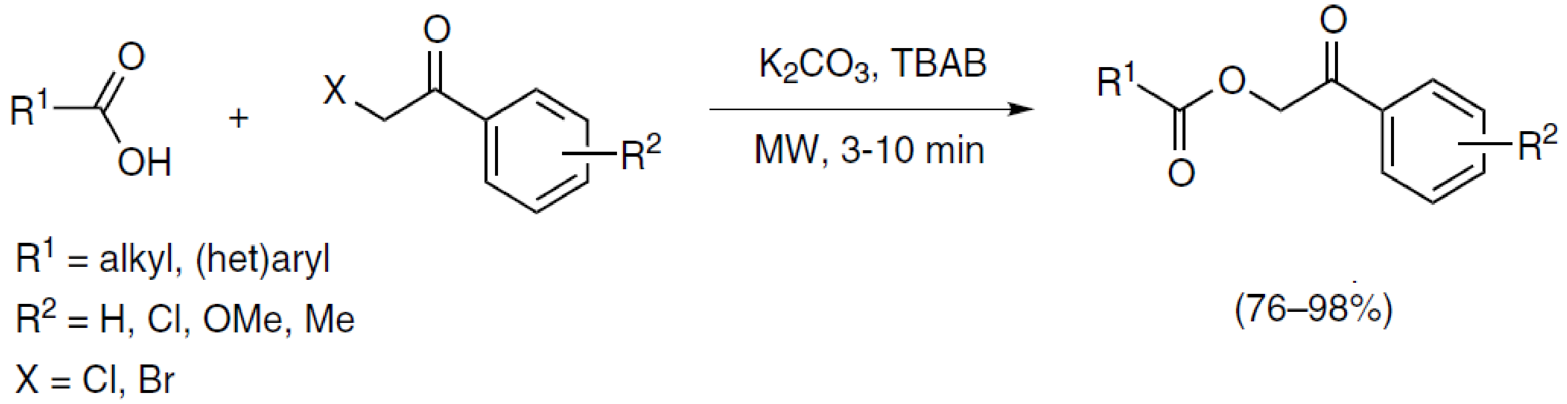
- Temperature measurement difficult
- Localized superheating possible
- Macroscopic hotspots
- Stirring troublesome
- Limited possibilities for scale-up (penetration depth)
- Reproducibility controversial.

PHASE-TRANSFER CATALYSIS

- widely used in organic synthesis, biotechnology and material chemistry, industrial chemistry and microwave chemistry
- reactants are in two separate phases (eg liquid-liquid or solid-liquid)
- in liquid-liquid catalysts the phases do not mix; ionic reagents are usually dissolved in water and substrates in organic solvents in solid-liquid catalysis
- ionic reagents are used in the solid state as a suspension in an organic solvent
- transport of anions from the aqueous or solid phase to the organic phase where the reaction takes place is enabled by interfacial catalysts intermediate
- catalysts are typical quaternary salts (eg. tetrabutyl-ammonium bromide) or cationic complexing agents
- the combination of intermediate catalysis and the use of MW radiation gives the best results

PHASE-TRANSFER CATALYSIS

- *o*-alkylation of carboxylic acids solid-liquid by interfacial catalysis - TBAB interfacial catalyst (tetrabutylammonium bromide)



- liquid-liquid interfacial catalysis is widely used in palladium catalyzed reactions (Heck reaction, Suzuki and Sonogashira reaction)
- in these reactions the preferred intermediate catalyst is tetrabutylammonium bromide, and water is used as the solvent

WATER AS SOLVENT IN MW SYNTHESIS

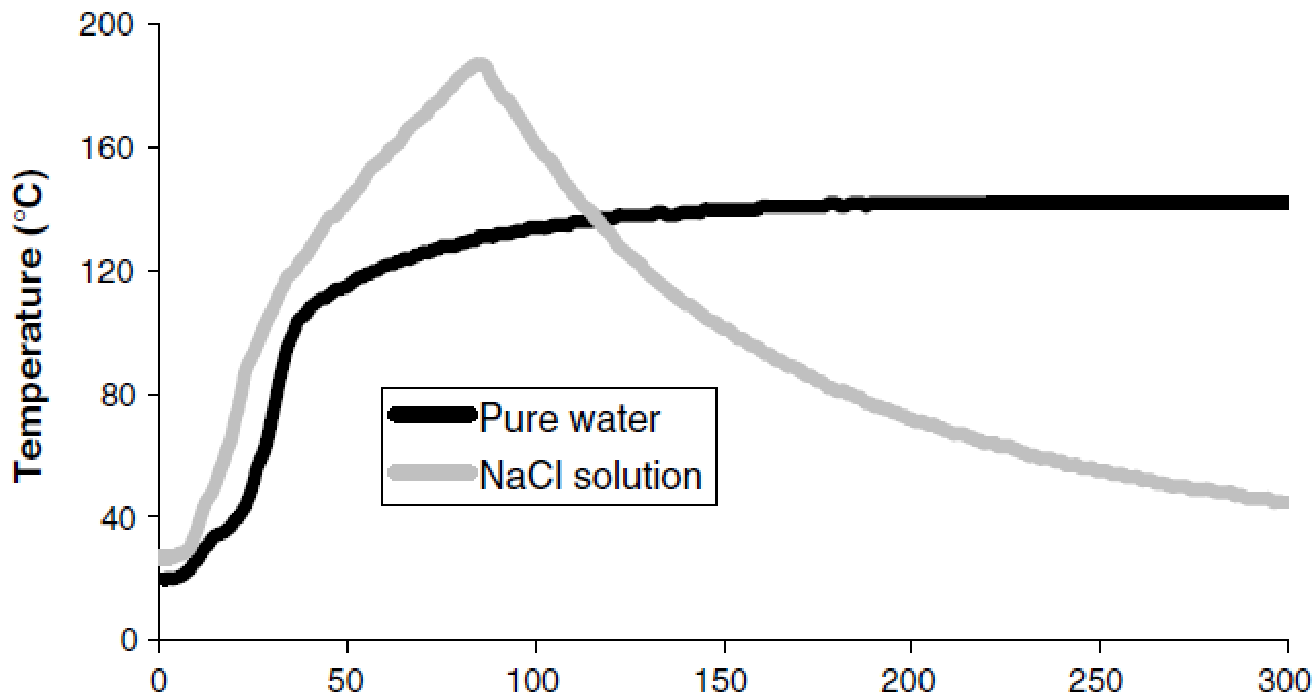
- water as a solvent in organic synthesis often has a unique reactivity and selectivity
- hydrophobic effects in addition to the usual reactions in an aqueous medium in the temperature range of 0 - 100 °C
- reactions at temperatures above 100 °C ("superheated conditions at 384 °C") in closed reaction vessels are also possible
- favorable changes in the physical and chemical characteristics of water at high temperatures, and pressures

Fluid	Ordinary water ($T < 150\,°C$) ($p < 0.4$ MPa)	Near-critical water ($T = 150$–$350\,°C$) ($p = 0.4$–20 MPa)	Supercritical water ($T > 374\,°C$) ($p > 22.1$ MPa)
Temperature (°C)	25	250	400
Pressure (bar)	1	50	250
Density ($g\,cm^{-3}$)	1	0.8	0.17
Dielectric constant ε'	78.5	27.1	5.9
pK_W	14	11.2	19.4

WATER AS SOLVENT IN MW SYNTHESIS

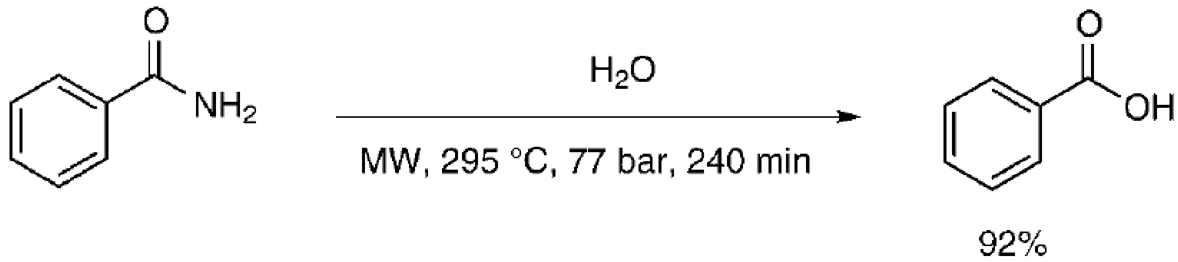
❖ the tangent of water loss can be significantly increased by the addition of a small amount of inorganic salt that will increase the absorption of MW radiation by a conductive mechanism

❖ pure water can be heated to 130 ° C and NaCl solution to 190 °C

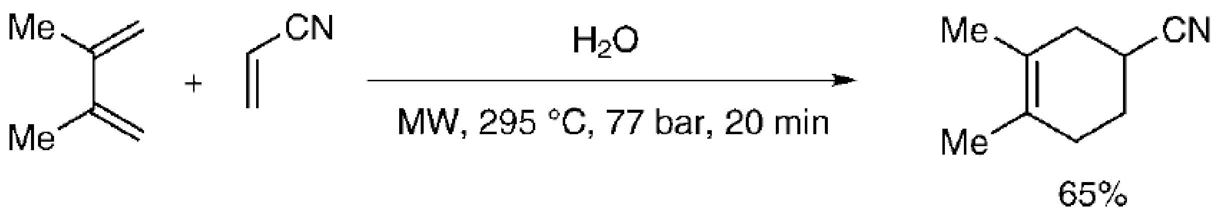


WATER AS SOLVENT IN MW SYNTHESIS

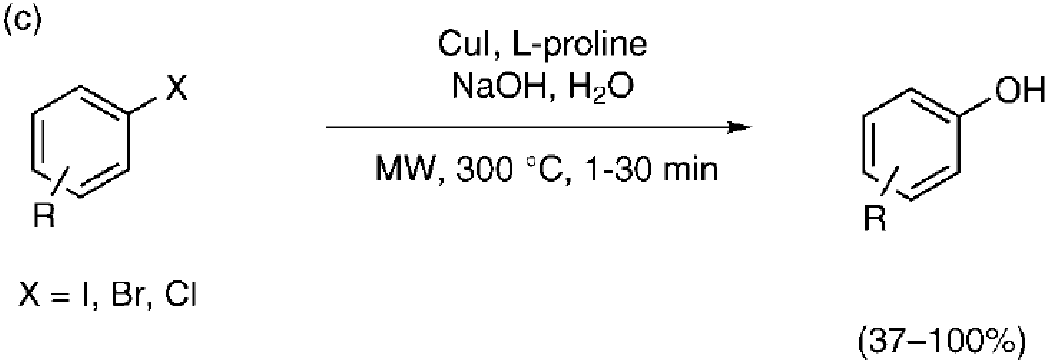
(a)



(b)



(c)



IONIC SOLUTIONS (LIQUIDS)

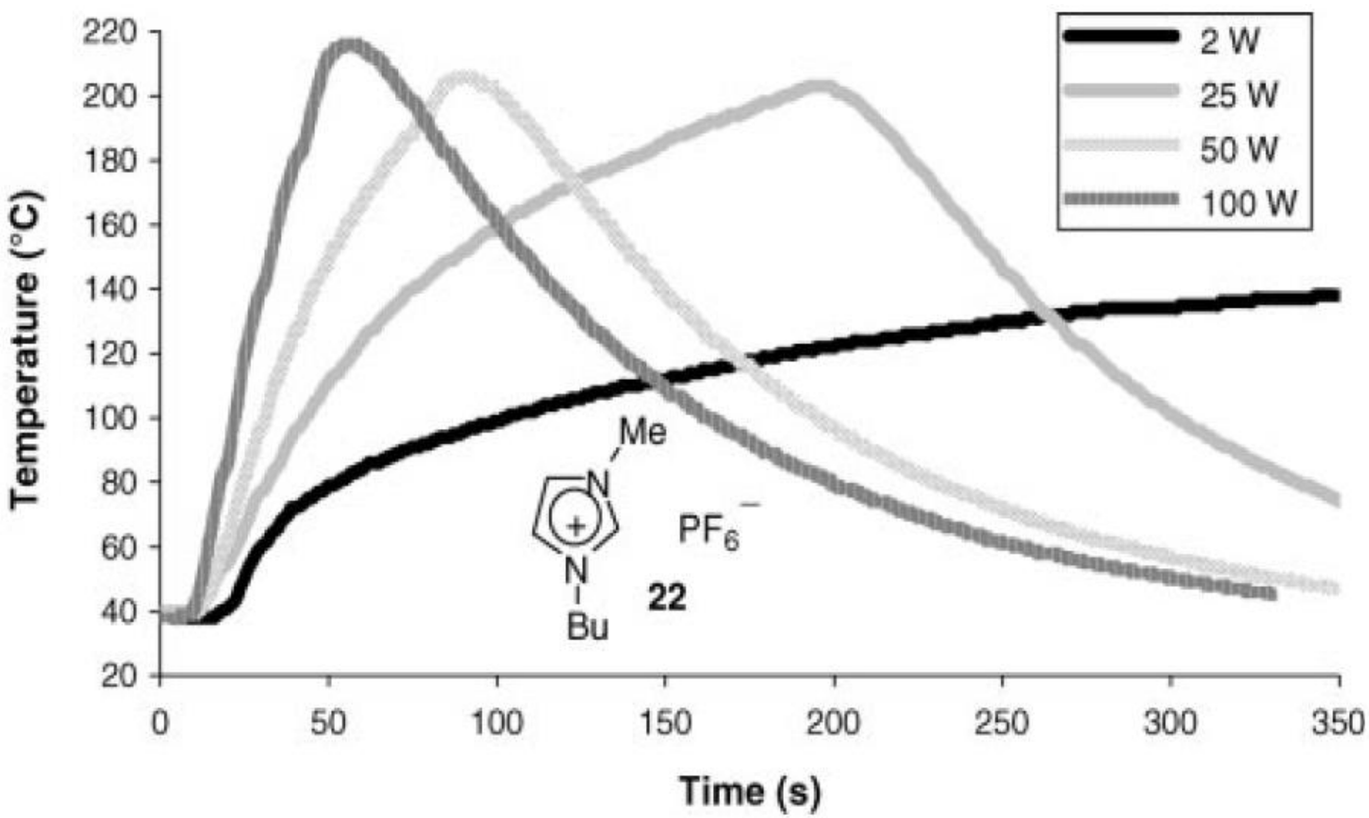
- a new type of solvent consisting entirely of ions
- they usually have an organic cation (mostly a quaternary N atom) and an inorganic or organic anion
- in the structure at room temperature are solutions or have a melting point below 100 °C
- are not flammable, they do not mix with non-polar solvents so organic products are easily removed by extraction
- ionic solutions could be regenerated
- wide temperature range > 300 °C, very low toxicity

Characteristics of ionic liquids.

- Organic salts that are liquids at room temperature
- Large liquid temperature range (300 °C)
- Polar, non-volatile
- Dissolve organic and inorganic compounds
- Environmentally benign?
- Couple very effectively with microwaves (ionic conduction).

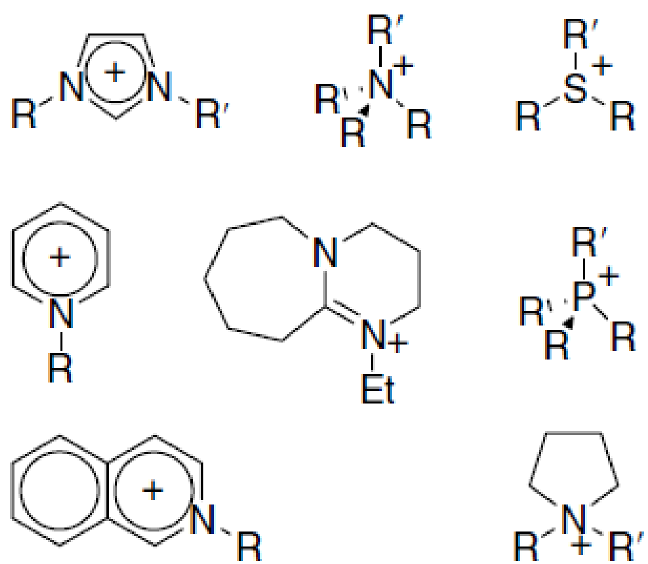
IONIC SOLUTIONS (LIQUIDS)

- they heat up very quickly and a power of 2W very efficiently heats the reaction medium to 140 ° C in 5 minutes



IONIC SOLUTIONS (LIQUIDS)

❖ **most commonly used ionic solutions**

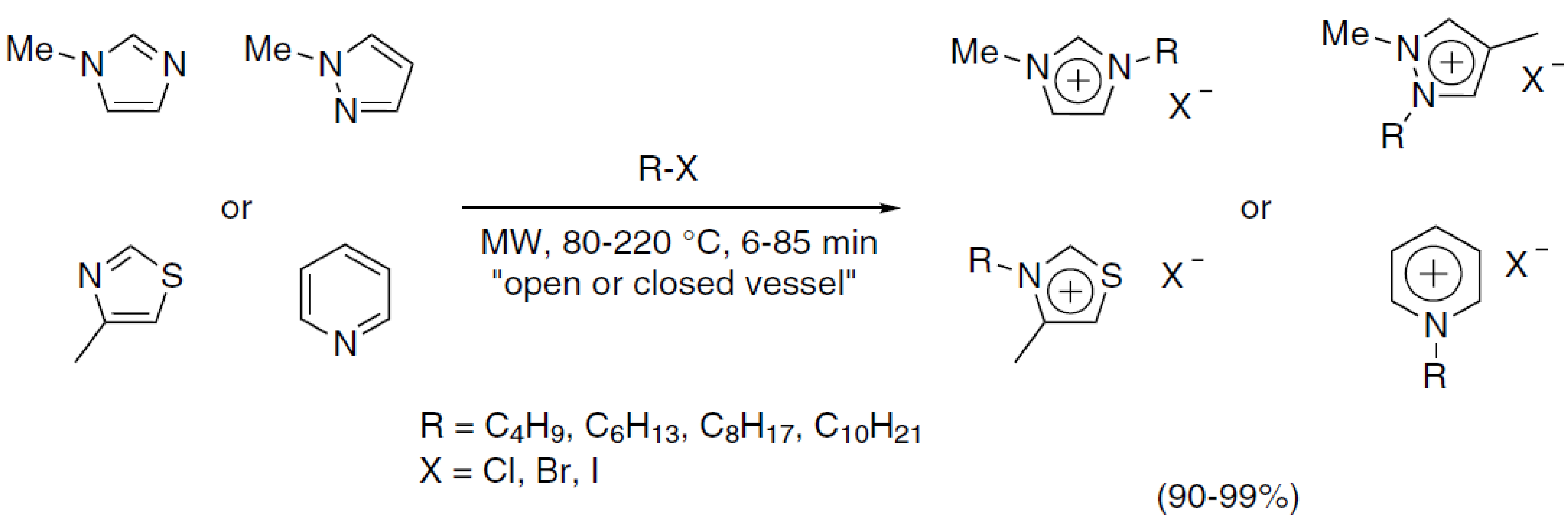


halide$^-$	$AlCl_4^-$	$Al_2Cl_7^-$
IBr_2^-	$CuCl_2^-$	$Cu_2Cl_3^-$
NO_3^-	SO_4^{2-}	$CH_3CO_2^-$
L-lactate$^-$		$^nC_8H_{17}OSO_3^-$
PF_6^-	BF_4^-	SbF_6^-
Tf_2N^-	Tf_3C^-	$N(SO_2C_2F_5)_2^-$
OTf^-	$N(CN)_2^-$	$Co(CO)_4^-$

IONIC SOLUTIONS (LIQUIDS)

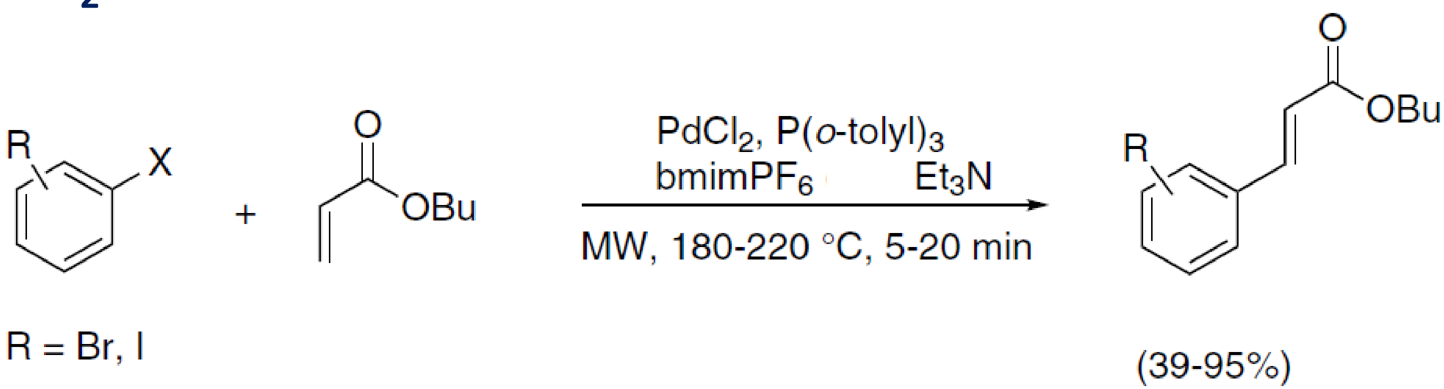
In three main ways related to MW radiation:

- ❖ use of MW radiation for the synthesis of ionic solutions; they are used as solvents, reagents or catalysts in microwave-assisted synthesis as an additive to solvents that poorly absorb MW radiation
- ❖ are considered an environmentally friendly reaction medium but their synthesis is not because their purification requires a large amount of organic solvents

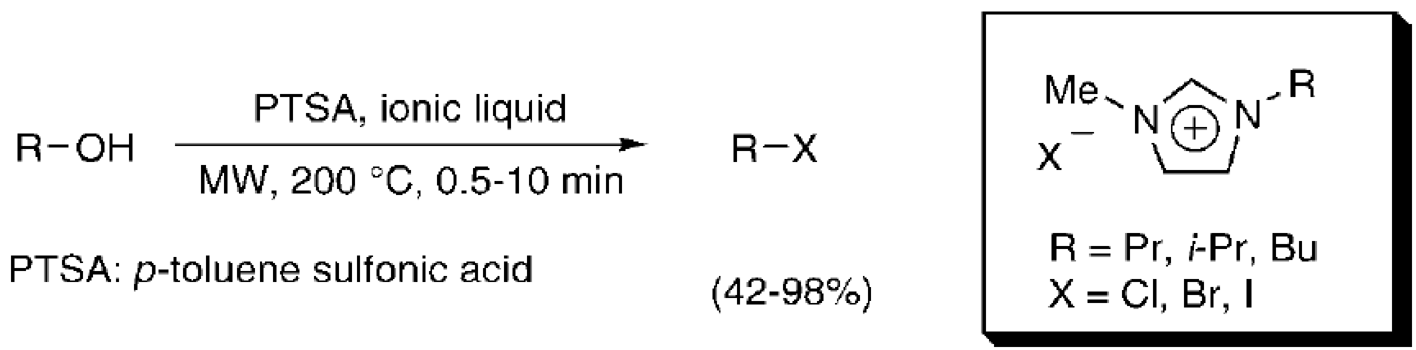


IONIC SOLUTIONS (LIQUIDS)

- ionic solution as solvent - Heck reaction
- the specificity of the reaction is the regeneration of the ionic solution and $PdCl_2$

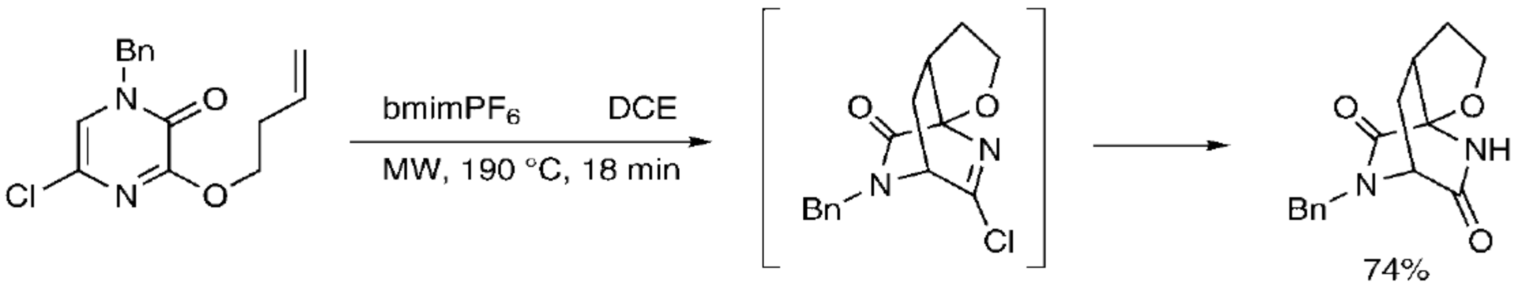


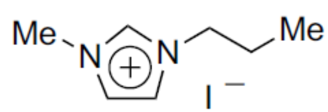
- ionic solution as a reagent and solvent - synthesis of primary alkyl halides



IONIC SOLUTIONS (LIQUIDS)

- **ionic solution as additives to non-polar solvents that poorly absorb MW radiation - toluene, hexane, THF, dioxane**





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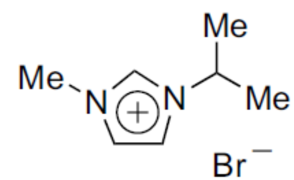

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Solvent	IL added	Temperature attained (°C)	Time taken (s)	Temperature attained without IL (°C)[b]
Hexane	**30**	217	10	46
	31	228	15	
Toluene	**30**	195	150	109
	31	234	130	
THF	**30**	268	70	112
	31	242	60	
Dioxane	**30**	264	90	76
	31	246	60	

IONIC SOLUTIONS (LIQUIDS)

❖ **physico-chemical characteristics**

Advantages	Disadvantages
No vapor pressure	Purification difficult, quality variable
Non-flammable	High viscosity
Highly tunable	Commercially expensive
Easy separation of products and recycling of catalysts	Toxicity not fully understood
Potential for high solubility of gases	Reacts with strong nucleophiles

Property	Applications
Saline structure	New reactions and selectivities possible
High solubility of organic reagents and catalysts	Reactions performed in concentrated conditions
High solubility of gases	Reactions involving gases can be accelerated
Immiscibility with several organic solvents	Catalysts can be recycled and reused; efficient biphasic reactions
High tunability	Solvents can be designed for specific applications

GREEN CHEMISTRY CONCEPT

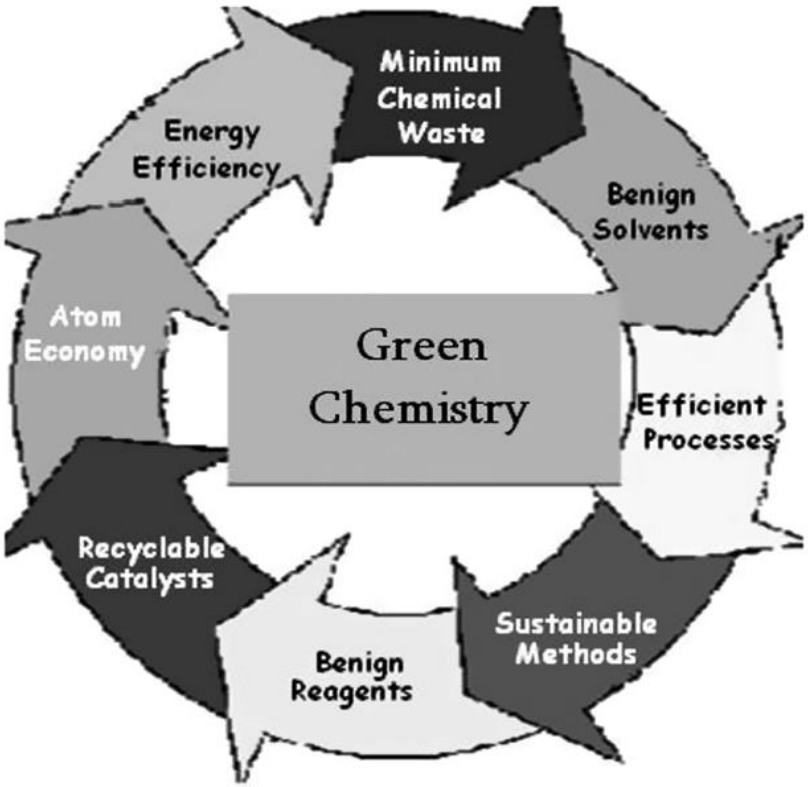
- **the concept of green chemistry - to protect the environment by discovering new chemical processes and reactions that prevent pollution**
- **applies to all aspects of chemistry**
- **pharmaceutical green chemistry - development of new, efficient and environmentally friendly synthetic methods**
- **dispersion of hazardous and harmful chemicals and waste into the environment must be minimal or completely eliminated; material and energy consumption at minimum - maximum efficiency**

- The maximum amounts of reagents are converted to useful product (atom economy)
- Production of waste is minimised through reaction design
- Non-hazardous raw materials and products are used and produced wherever possible
- Processes are designed to be inherently safe
- Greater consideration is given to using renewable feedstocks
- Processes are designed to be energy efficient

GREEN CHEMISTRY CONCEPT

- preventing the use of easily volatile and toxic solvents
- reuse of catalysts and reagents
- use of benign chemicals, economical synthetic methods with a minimum number of synthetic steps and by-products

- energy efficient and mild reaction conditions
- disposal of generated chemical waste
- synthetic protocol often does not meet all the requirements of green chemistry - the more satisfied the conditions, the "greener" the process is
- substitutes for toxic solvents - bio-solvents, supercritical fluids, ionic solutions...

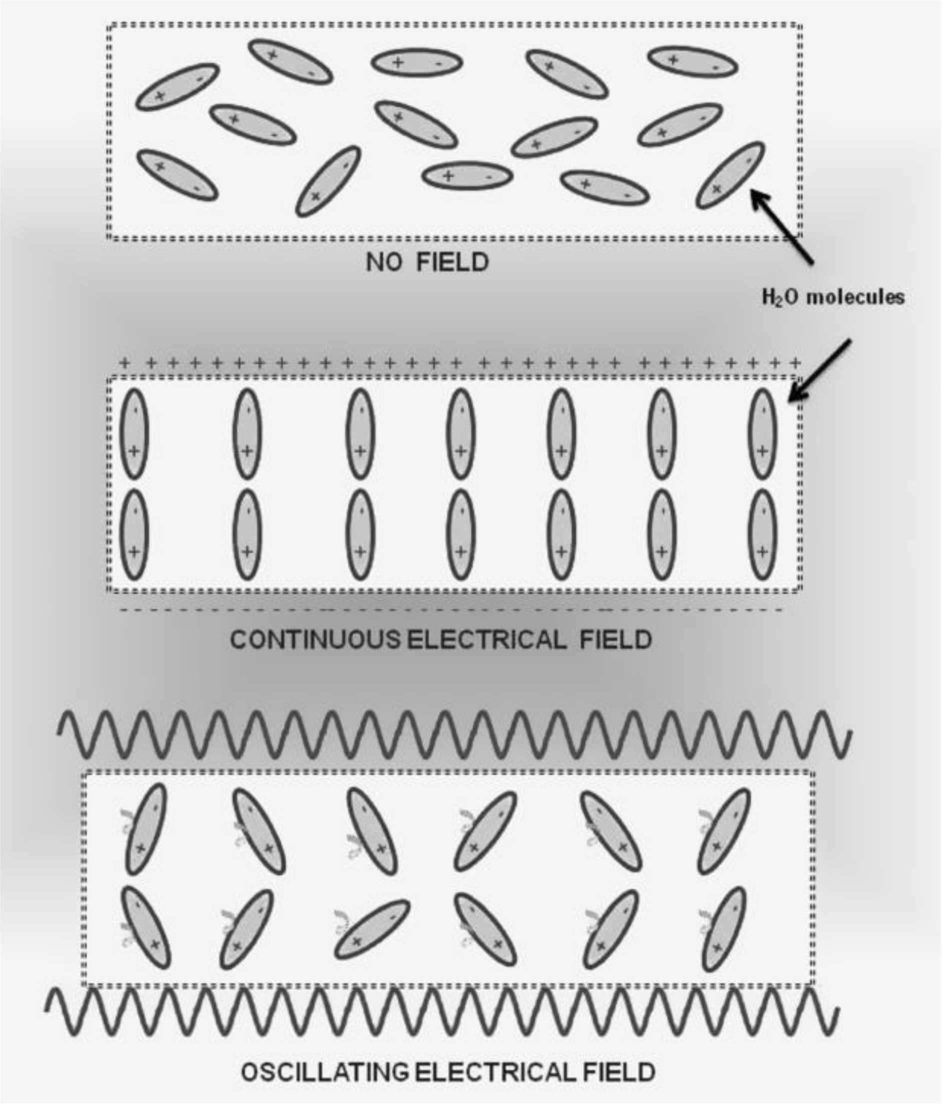


WATER AS GREEN SOLVENT

- one of the most important priorities - the use of green solvents or carrying out solvent-free reactions ("solvent free")
- such a process must be applicable on an industrial scale or at least in pilot plants - "scale up"
- water - large quantities, cheap, non-toxic, non-corrosive and non-flammable, high vapor pressure
- main disadvantages: a) the vast majority of organic compounds are weak and / or insoluble in water - heterogeneous solutions; b) isolation of products - evaporation is not an economically viable process
- bio-solvents, ionic solutions - are not economically viable, toxic
- use of MW heating technique - water is polar and absorbs MW radiation well
- acceleration of chemical reactions optimizing energy consumption

WATER AS GREEN SOLVENT

- mechanism of dipolar polarization and ionic conductivity of water molecules
- heterogeneous solutions without intermediate catalysts
- water is a pseudo organic solvent
- high temperatures
- synthesis of new organic molecules, polymeric materials, nanomaterials, enzymatic and nanocatalysis



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MICROWAVE SYNTHESIS – SCALE UP PROCESS CHEMISTRY

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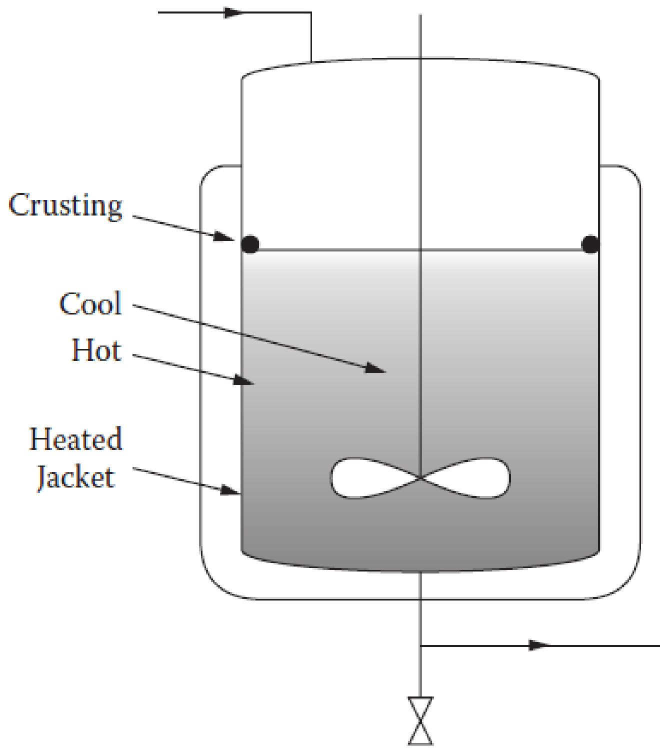
Academic year 2023/2024

INTRODUCTION

- based on pilot plants and "scale-up"
- refers to large-scale production mostly in industry
- MW radiation is most often used for purification, drying, polymerization, analysis and analytical methods, organic synthesis, environmental chemistry, food production
- In the 1990s the first publications on scale-up of organic reactions using MW radiation
- Strauss - the first continuous flow MW reactor for large scale synthesis
- special importance and application of MW reactors since 2000
- in medical and pharmaceutical chemistry
- the need to develop and design MR reactors adapted for scale-up

INTRODUCTION

- scale-up MW chemistry has been particularly evolving in the last 5 years
- temperature gradients - a big problem when conducting reactions on a large scale
- decomposition; the need for large quantities of samples for biological testing



heating effects in a scale-up reactor heated in a conventional manner

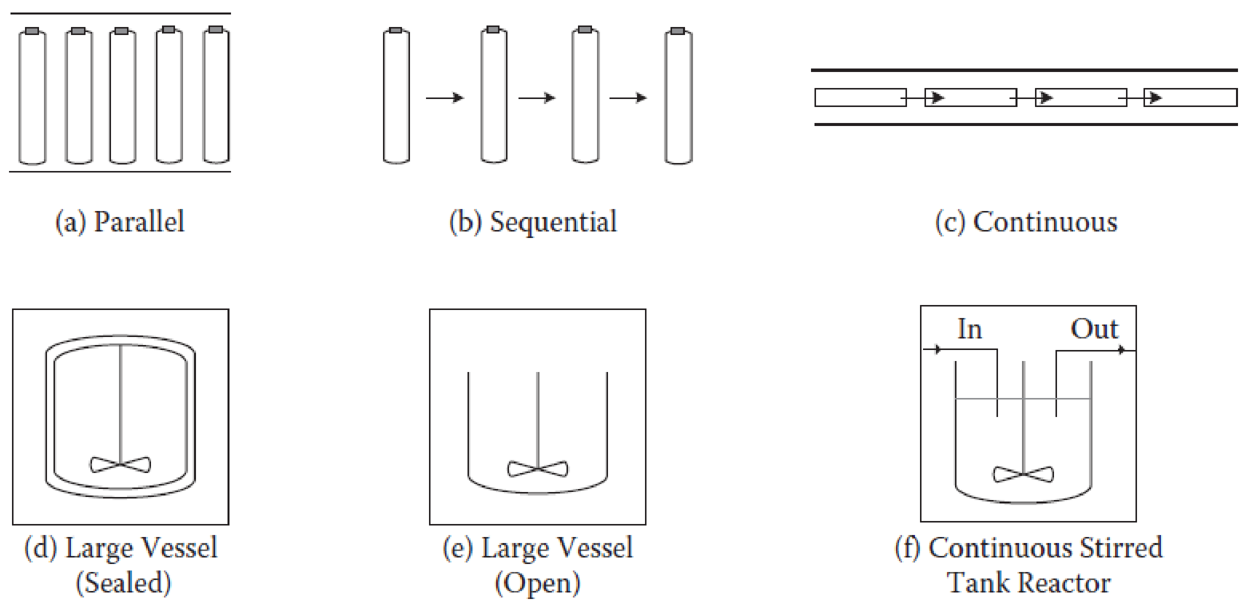
INTRODUCTION

General Summary of Reaction Classes Suitable for Microwave Scale-Up

	Beneficial/Suitable	No Benefit/Unsuitable
Major reaction classes	Additions condensations Alkylations/acylations Heterocycle formation Hydrogenations S_NAr reactions	Amide bond formation Deprotections (excluding hydrogenations) Functional group additions Functional group interconversions Protection reactions
Minor reaction classes	Cycloadditions Friedel–Crafts reactions Metal-catalyzed reactions (e.g., Heck and Suzuki couplings) [Peptide synthesis][a] [Polymer synthesis][b] Thermal rearrangements	Grignard reactions Low-temperature organometallic reactions (e.g., lithiation) Oxidations Reductions (metal hydrides, excluding hydrogenations)
Other reaction parameters	Autoclave/pressure reactions Reactions with gases Reactions with solid-support reagents Reactions with water as solvent Where thermodynamic product required	

PROBLEMS WITH SCALE-UP

- short penetration length (a few centimeters for most organic solvents at 2.45 GHz)
- no efficient heating of the reaction mixture
- the reaction mixture in the central part of the reactor does not absorb enough MW of radiation
- the length of the penetration depends on the frequency
- the few allowed frequencies that can be worked with efficient MW reactors for scale up from 10 g to 1 kg



PARALLEL SCALE-UP

- 6-20 cylindrical reaction vessels
- continuous heating, max up to 1 L of volume and 100 g of product
- good reproducibility of experiments
- disadvantage: filling and emptying of reaction vessels
- used in small and medium pharmaceutical industries

SCALE-UP USING A LARGER REACTION VESSEL

- the larger the reaction vessel, the greater the problem of penetration length and homogeneous heating with MW radiation - safety problem - high vapor pressure during solvent superheating

- due to very high pressures and temperatures - special materials - quartz, ceramics, teflon - must be used for the housing and reaction vessel
- cooling problems - compressed air or solvents are used
- the cooling time is often much longer than the total reaction time
- increasing the total cycle time
- closed and open reaction vessels - volumes of 1 - 3.5 L can be used

SCALE-UP IN SEQUENCE

- **the cycle time is fast - smaller reaction vessels so there are no problems with heating and absorption of MW radiation**
- **the reaction mixtures must be homogeneous in order to be pumped out several hundred grams of product per day**

CONTINUOUS SCALE-UP

- rapid synthesis in medical and pharmaceutical chemistry
- kilograms of product per day
- cooling time is short
- suitable for exothermic reactions higher temperatures are harder to achieve