Chemistry Seminar

Microwave Chemistry

(A miracle for organic chemistry!!??)

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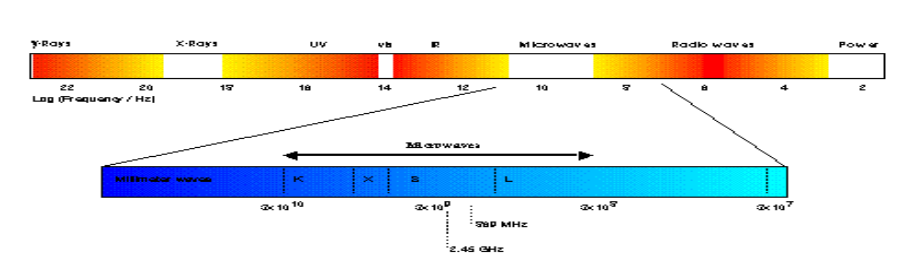
Introduction:

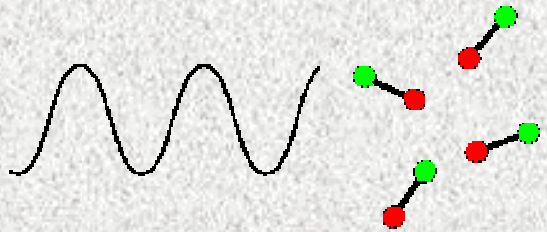
- Microwaves are a form of electromagnetic radiation and lie between IR radiation and radiowaves (0.3 GHz-300GHz or wavelengths bet^{n}.1mm - 1m).



- Form of energy and not heat but manifested as heat through their interactions with materials or medium.
- Used in different applications including organic synthesis.
- Energy delivered by MW is insufficient to break covalent bonds.
- Pharmaceutical industry needs high number of NCE's forcing chemists to produce compounds in less time.
- MW technology a bit rather slowly developed as compared to combichem or computational chemistry.
- In recent times has been popular as it offers a clean, cheap and convenient method of heating resulting in higher yeilds and shorter reaction times.

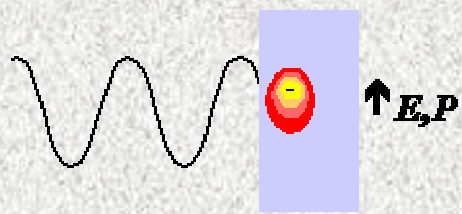
Mechanism of heating:

1. Dipolar polarization mechanism:



- Occurs with polar molecules.
- The polar ends of the molecule tries to align themselves &oscillate in step with oscillating electric field of MW.
- The collisions and friction between moving molecules causes heating.
- i.e more polar the molecule , the more it will couple with the MW field.
- eg. water.

2. Conduction mechanism:



- Seen for the solution containing ionic species(electrons, ions) i.e ionic solution.
- Ions are charged species distributed in a solution and can couple with the oscillating electrical field of MW.
- Rate of MW heating of ionic solution depends on concentration of ions in solution.
- Movement of ions through the solution under influence of an electric field results in expenditure of energy due to increased collision rate, converting KE to heat
- eg:

  Distilled Water and Tap Water.

MAOS

Solvents:

- Polar solvents are the mostly preferred solvents for MAOS
- Non-polar solvents are not preferred but when used in combination with polar solvent shows higher heating rates for whole reaction mixture.
- The energy transfer between polar and non-polar solvent is rapid.
- Addition of salts to the solvent also gives higher heating rates, but problem of solubility?
- Homogenous mixtures preferred in MAOS.
- Ionic liquids(IL) have been recently reported as an alternatives to dipolar aprotic solvents.
- IL absorb MW irradiation efficiently and also gives very low pressure.
- Despite IL being salts they dissolve in wide range of organic solvents.

MAOS techniques:

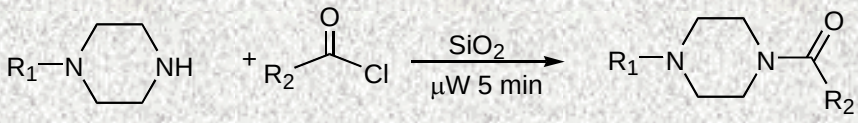
1. Domestic household ovens-'solvent free' open vessel reactions:

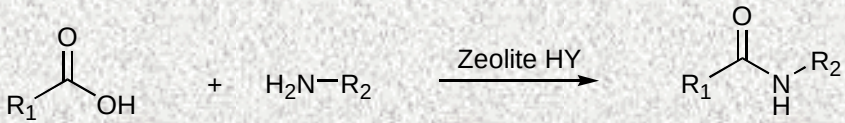
2. Reflux systems.

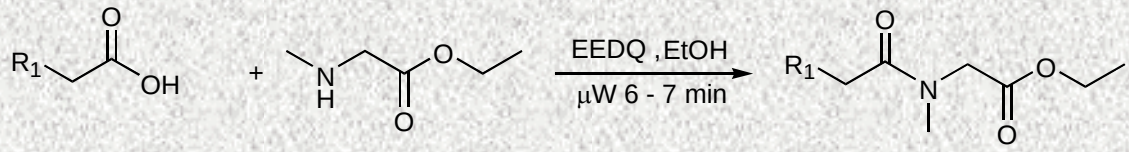
3. Continuous flow systems.

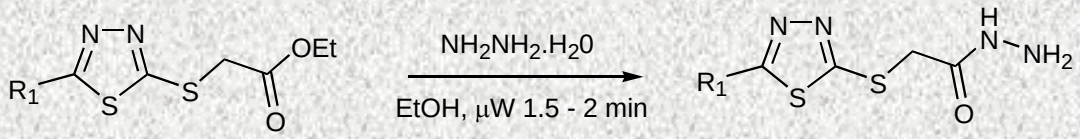
Reactions:

N-Acylation:

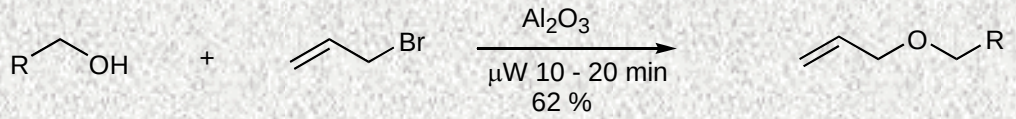


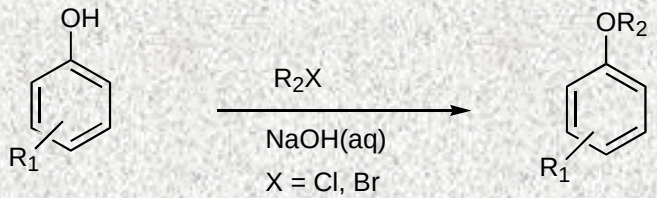


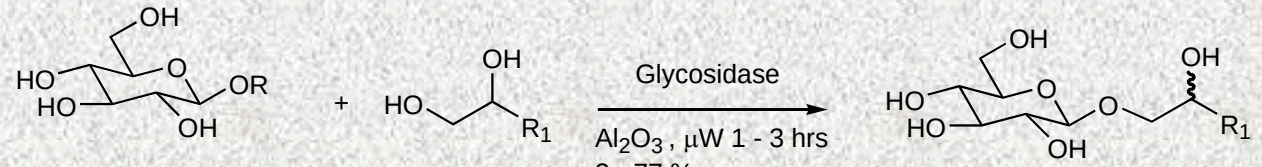


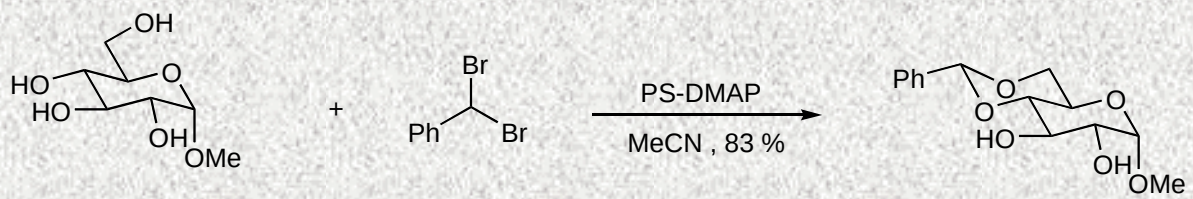


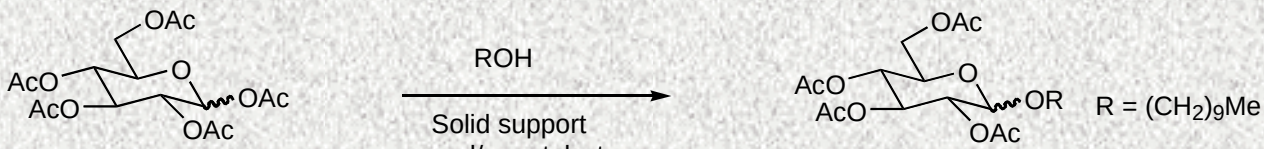
Alkylation:

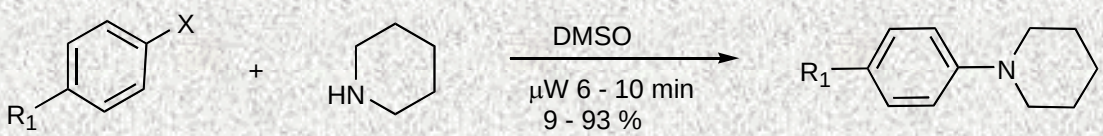

R
OH
+
Br
Al_2O_3
μW 10 - 20 min
62 %
O
R


OH
R_1
R_2X
NaOH(aq)
X = Cl, Br
OR_2
R_1

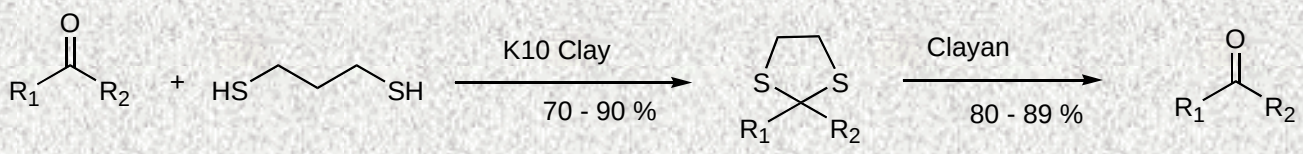

OH
HO
HO
O
OR
OH
+
OH
HO
R_1
Glycosidase
Al_2O_3 , μW 1 - 3 hrs
3 - 77 %
OH
HO
HO
O
O
OH
OH
R_1

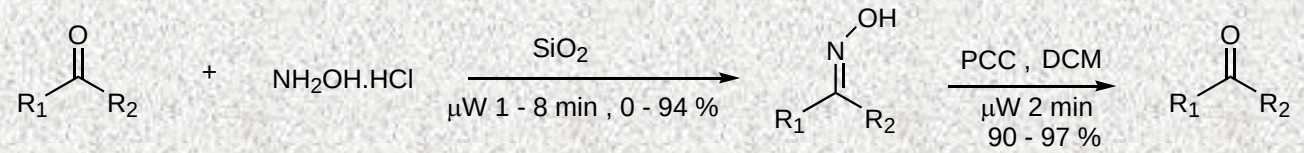

OH
HO
HO
O
OH
OMe
+
Br
Ph
Br
PS-DMAP
MeCN , 83 %
Ph
O
O
O
HO
OH
OMe

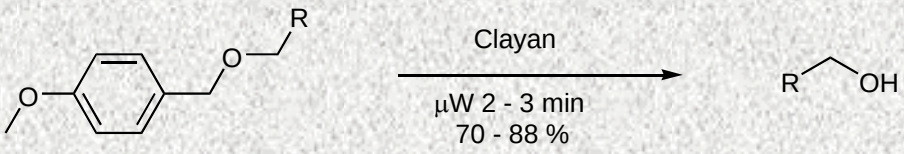

OAc
AcO
AcO
O
OAc
OAc
ROH
Solid support
and/or catalyst
OAc
AcO
AcO
O
OR
OAc
R = $(CH_2)_9Me$

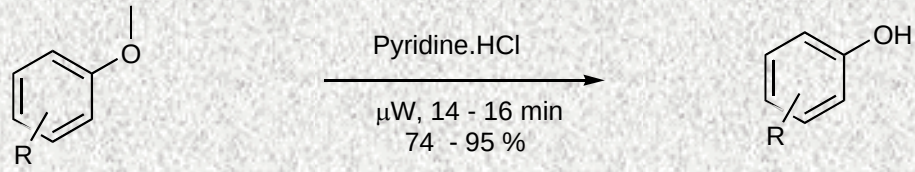

X
R_1
+
HN
DMSO
μW 6 - 10 min
9 - 93 %
R_1
N

Deprotection and protection:

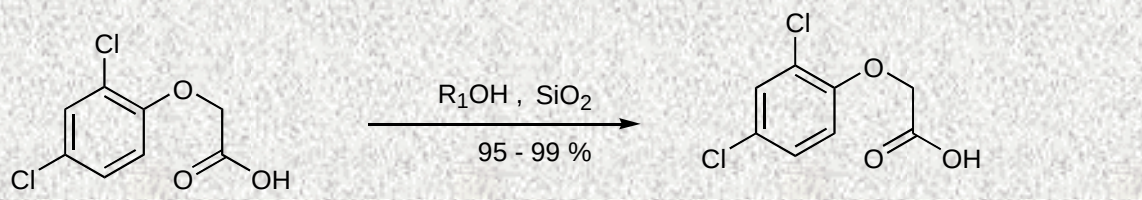


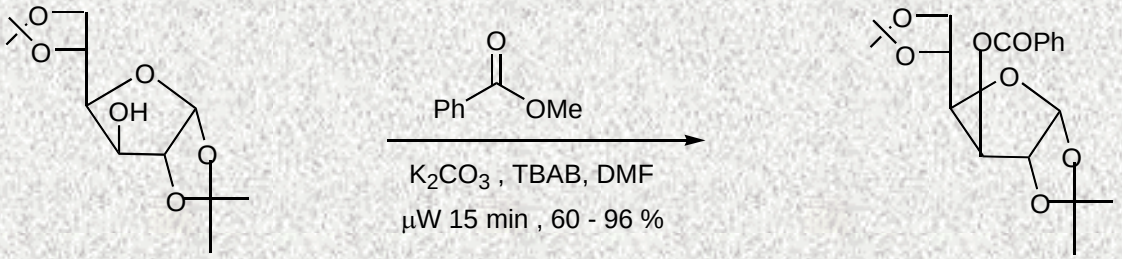


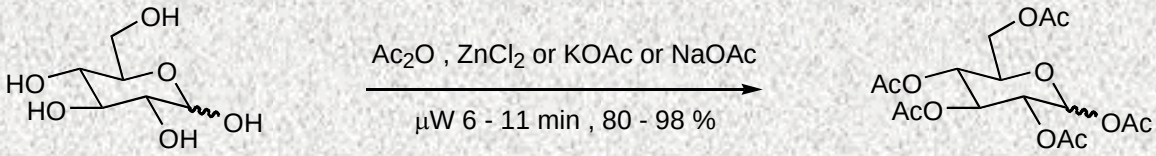


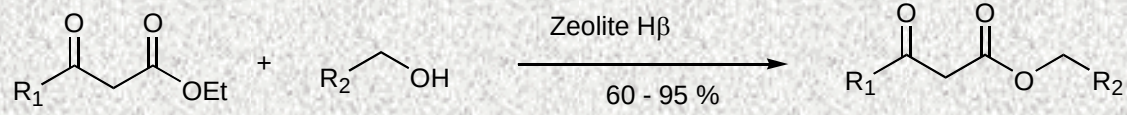


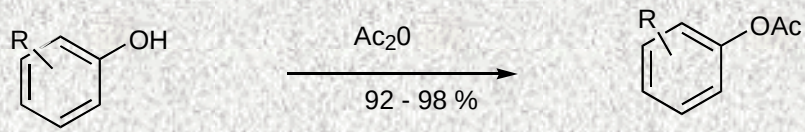
Esterification and transesterification:



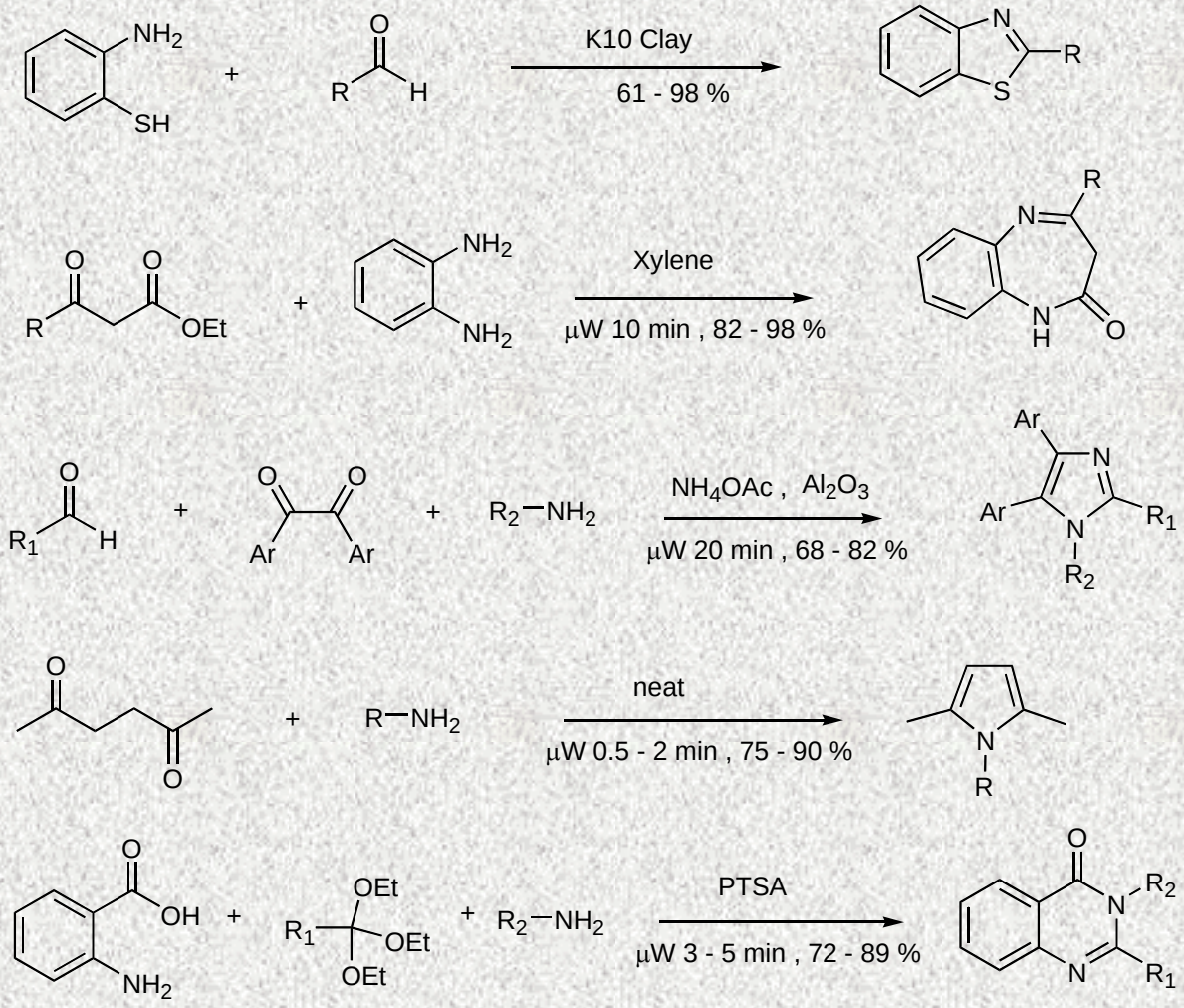




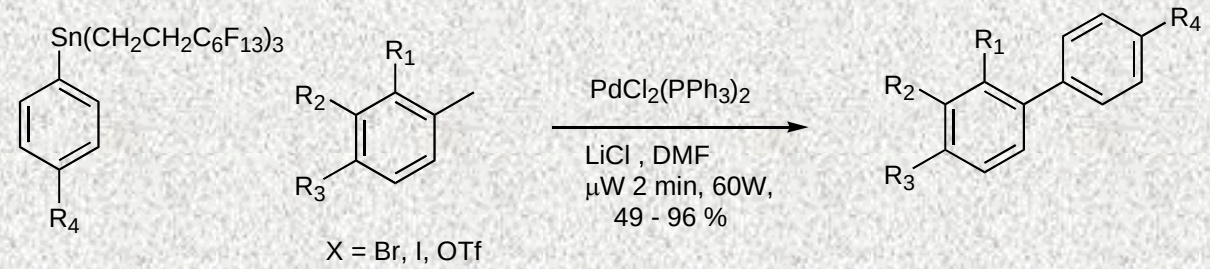




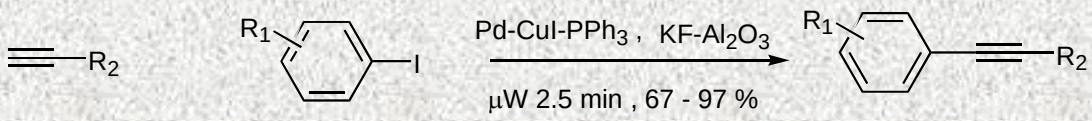
Heterocycles:



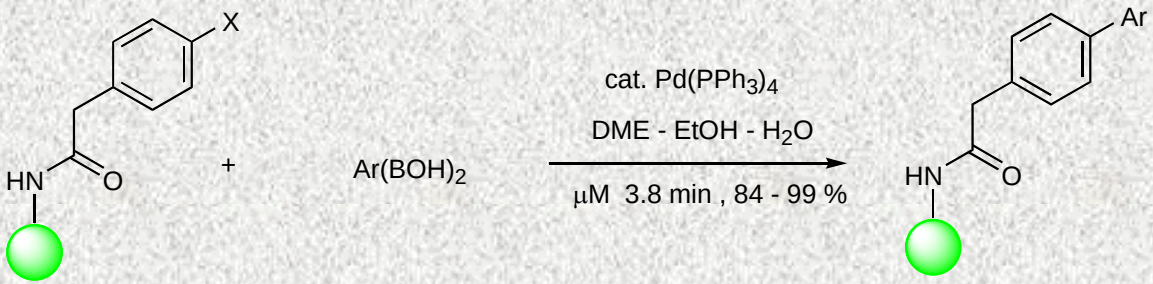
Organometallic reactions:



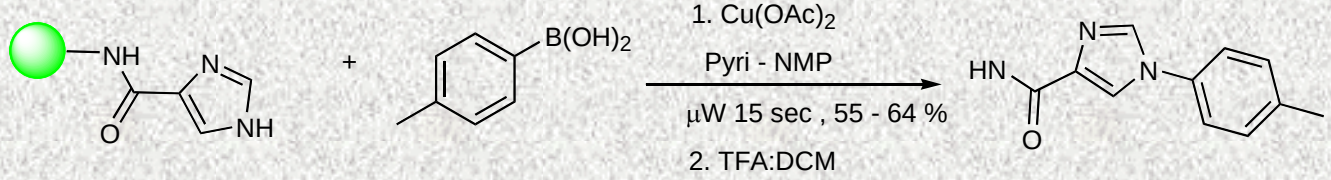
Stille coupling



Sonogashira coupling

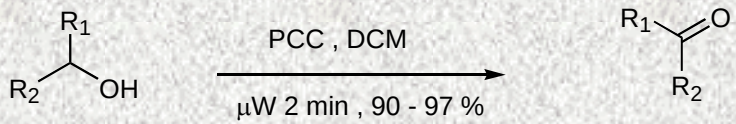


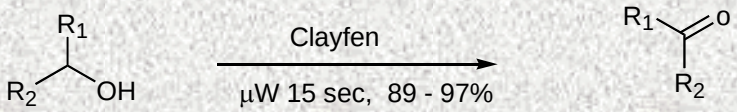
Suzuki coupling

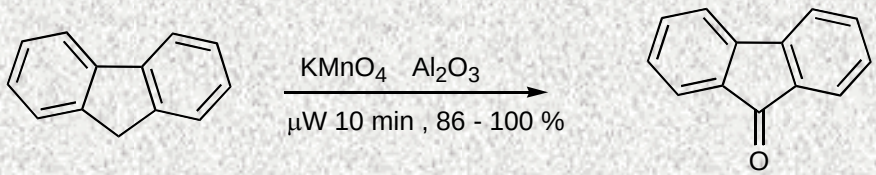


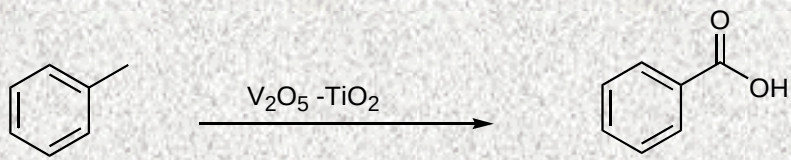
Copper mediated C-N
Cross coupling

Oxidation:

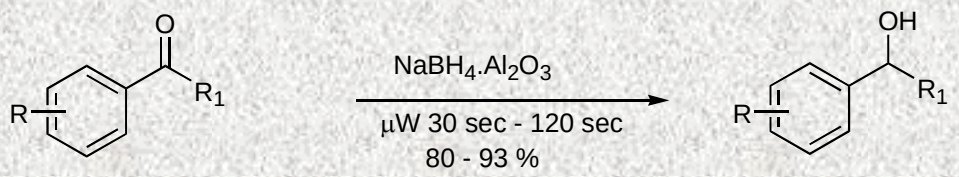

R1
R2
OH
PCC , DCM
μW 2 min , 90 - 97 %
R1
O
R2

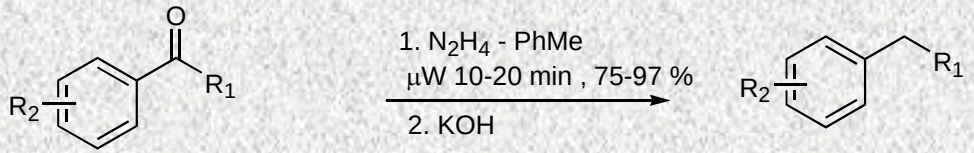

R1
R2
OH
Clayfen
μW 15 sec, 89 - 97%
R1
O
R2

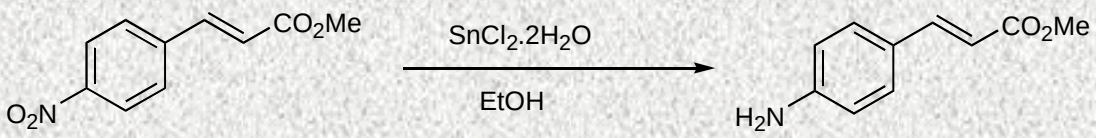

KMnO4 Al2O3
μW 10 min , 86 - 100 %
O

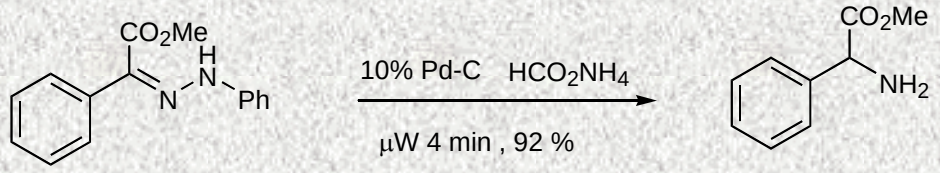

V2O5 -TiO2
O
OH

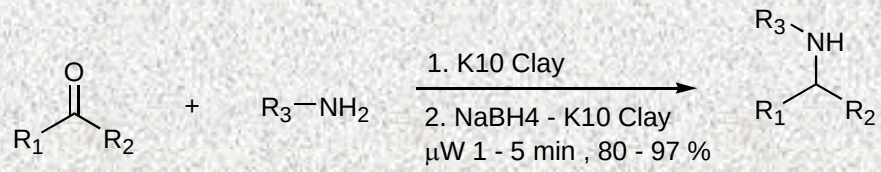
Reduction:


O
R
R1
NaBH4.Al2O3
μW 30 sec - 120 sec
80 - 93 %
OH
R
R1


O
R2
R1
1. N2H4 - PhMe
μW 10-20 min , 75-97 %
2. KOH
R2
R1


CO2Me
O2N
SnCl2.2H2O
EtOH
CO2Me
H2N


CO2Me
H
N
N
Ph
10% Pd-C HCO2NH4
μW 4 min , 92 %
CO2Me
NH2

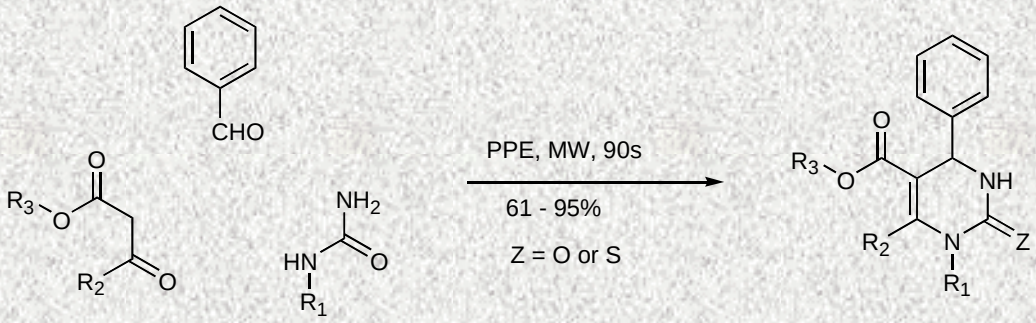

O
R1
R2
+
R3—NH2
1. K10 Clay
2. NaBH4 - K10 Clay
μW 1 - 5 min , 80 - 97 %
R3
NH
R1
R2

MAOS in Drug Discovery:

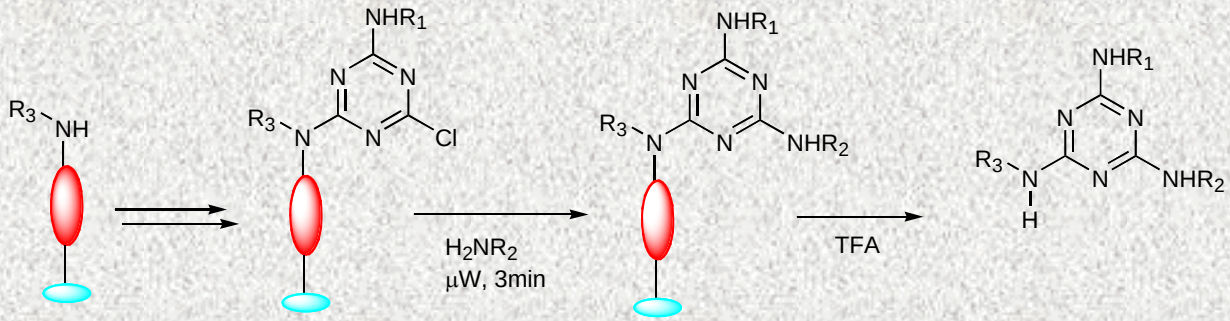
Lead Discovery:

MW assisted combinatorial synthesis. ***(MICROCOS)***

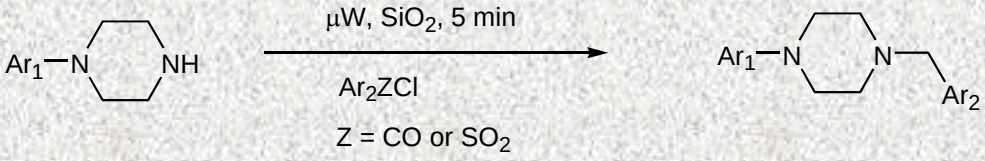
- First described by Khmelnitsky et al who performed reactions in a 96 well plate.
- Produced diverse pyridines by high throughput,automated,single step,parallel synthesis.
- Presently used in multicomponent reactions eg. Biginelli, Ugi.
- Reactions performed in domestic microwave oven.



- 8000 cellulose bound triazines produced by Spot Synthesis.
- Key step was MW assisted nucleophilic substitution of monocholrotraizine

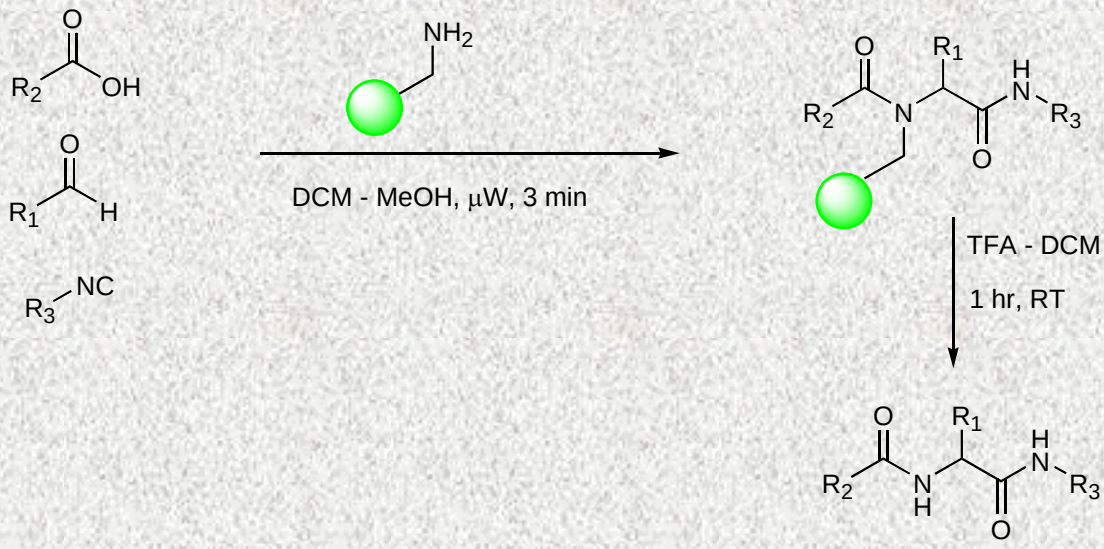


- Used in spot-synthesis by Williams et.al
- Procedure combines synthesis, purification,, analysis and screening of combinatorial libraries on a single TLC plate.
- A library of 40 N-substituted aryl piperazines synthesized and purified for biological screening in 30 min.

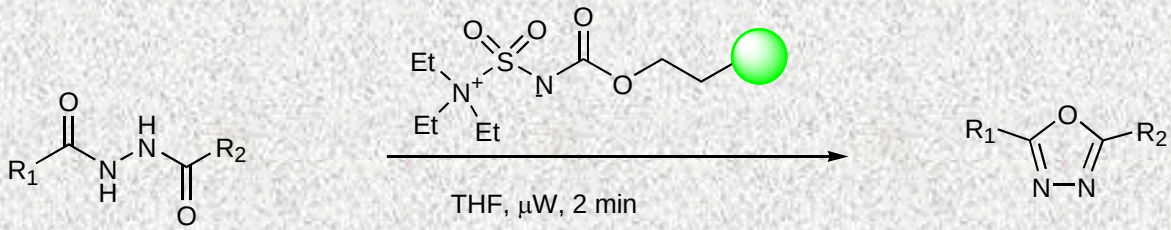


MW assisted solid-phase synthesis: ***(MASS)***

- MASS used to prepare an 18-member array of a-acylamino amides via resin bound Ugi reaction

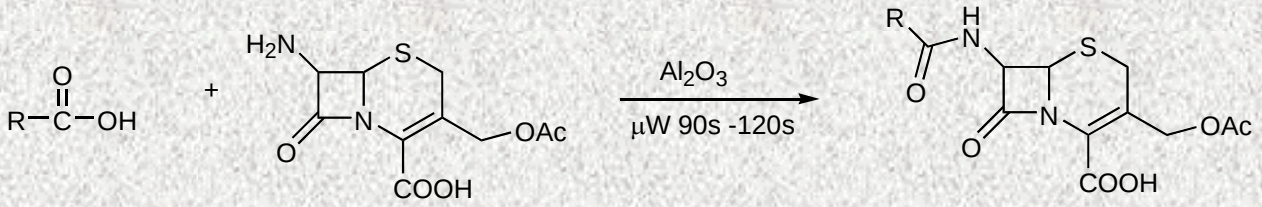


- Brain et.al devised a rapid and efficient synthesis of 1,3,4-oxadiazoles in high yield and purity.
- Involves rapid cyclodehydration of 1,2- diacylhydrazines using burgess reagent under MW.

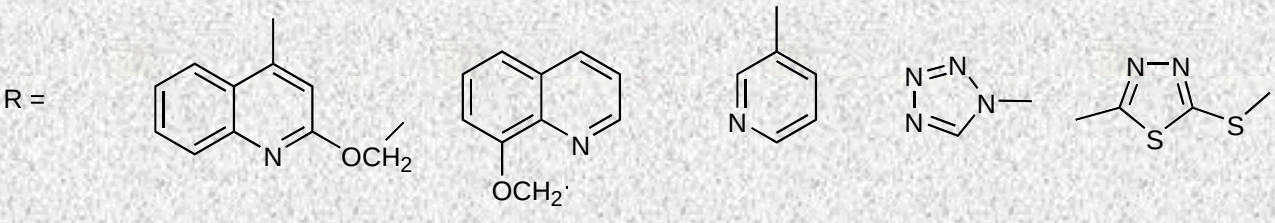


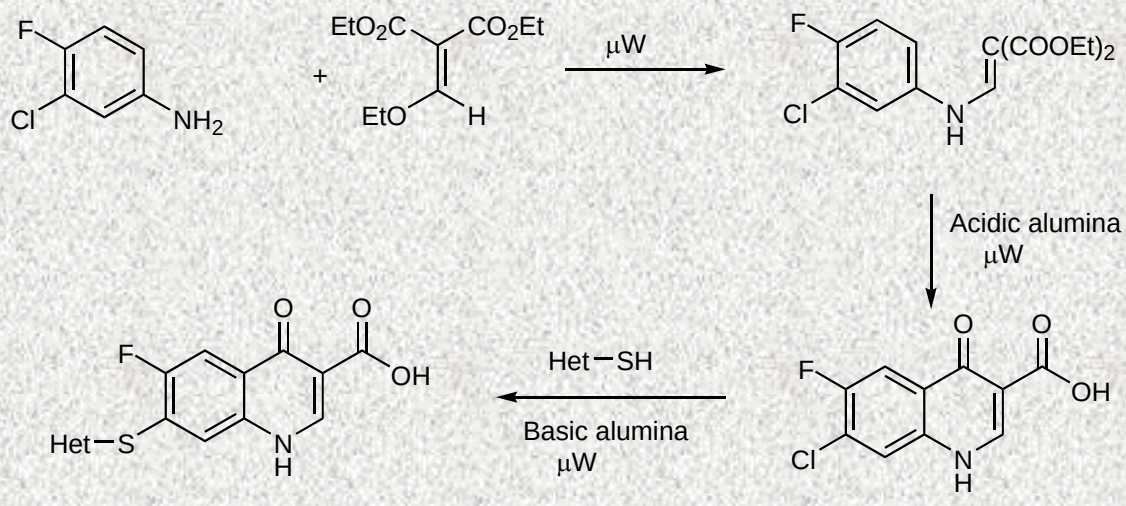
Lead optimisation:

- Kidawi et.al showed MW to effective in synthesis of β-lactams, quinolones, and cephalosporins.

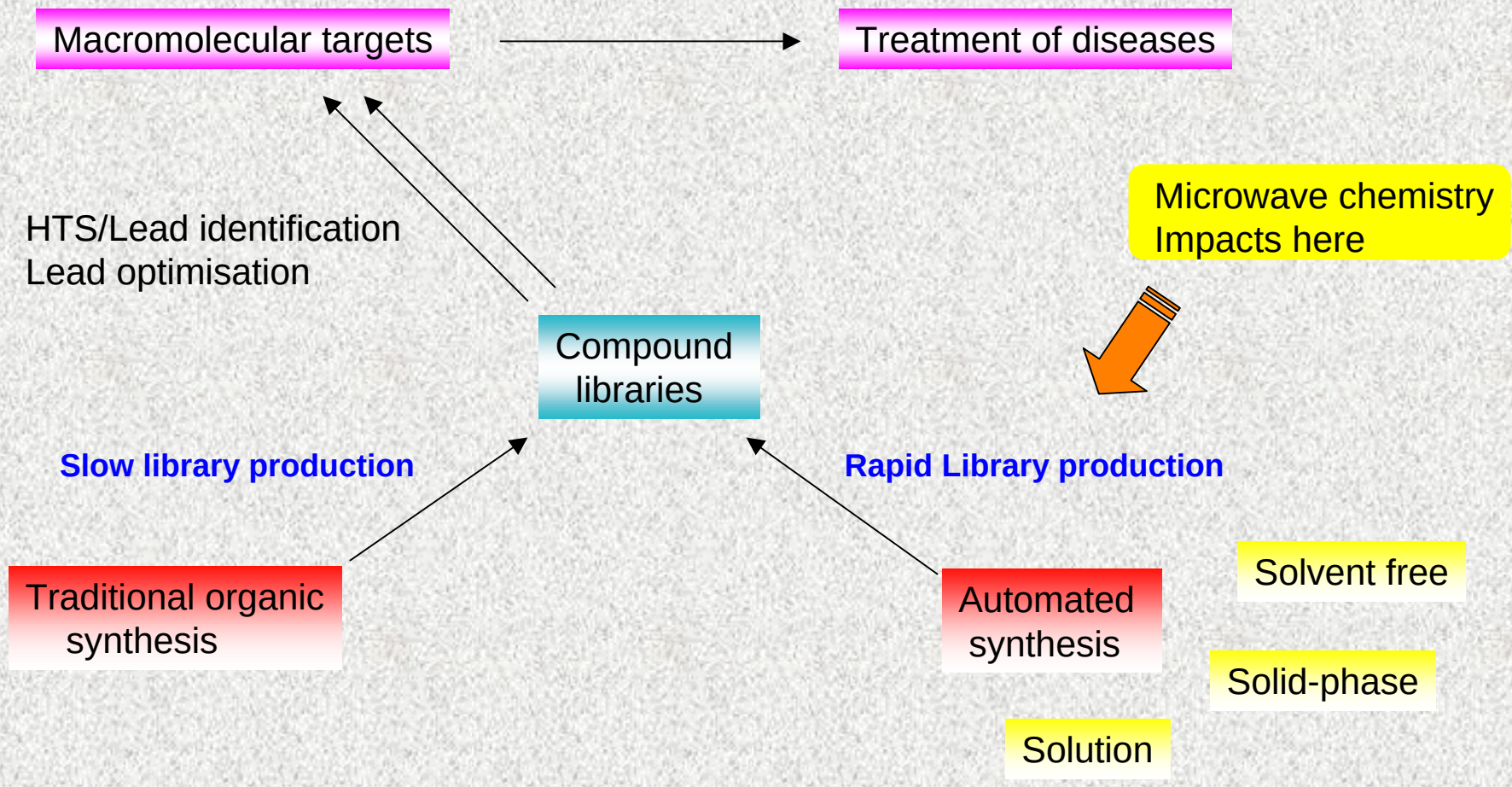


Cephalosporins





Fluoroquinolones


Macromolecular targets
Treatment of diseases
HTS/Lead identification
Lead optimisation
Microwave chemistry
Impacts here
Compound
libraries
Slow library production
Rapid Library production
Traditional organic
synthesis
Automated
synthesis
Solvent free
Solid-phase
Solution

References

- Pelle Lidstrom et. al, *Tetrahedron* **2001**, *57*, 9225 - 9283.
- Mats Larhed and Anders Hallberg, *Drug Discovery Today* **2001**, *6*, Vol.7, 406 - 418
- Bernard Wathey et. al, *Drug Discovery Today* **2002**, *6*, Vol.7, 373 - 380.
- Caddick. S. *Tetrahedron* **1995**, *51*, 10403 - 10432.