Advanced Organic Chemistry/ Organic Synthesis – CH 621

Microwave Assisted Organic Synthesis (MAOS)

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Microwave Irradiation – Historical Overwiev

Microwave Chemistry

- microwaves (2.45 GHz)

- WWII – radar (magnetron)

- 1950s food industry

- 1984 first application in chemical synthesis

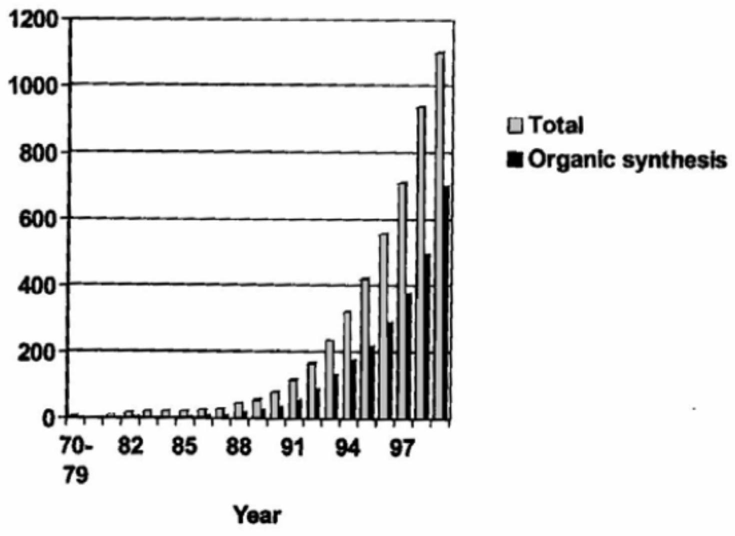


Fig. 1 Published articles involving microwave irradiation since 1970[41]

Microwave Irradiation – Historical Overwiev

- Microwave Ovens: domestic use
- Chemical Reactions – usually requires activation energy
  - Conductive energy transfer
  - Microwaves (dielectric heating)

- First instrument - Hull
- Reliable magnetron – Randall and Both (WVII)
- USA, 1950s food industry
- 1970s-1980s reliable domestic istruments

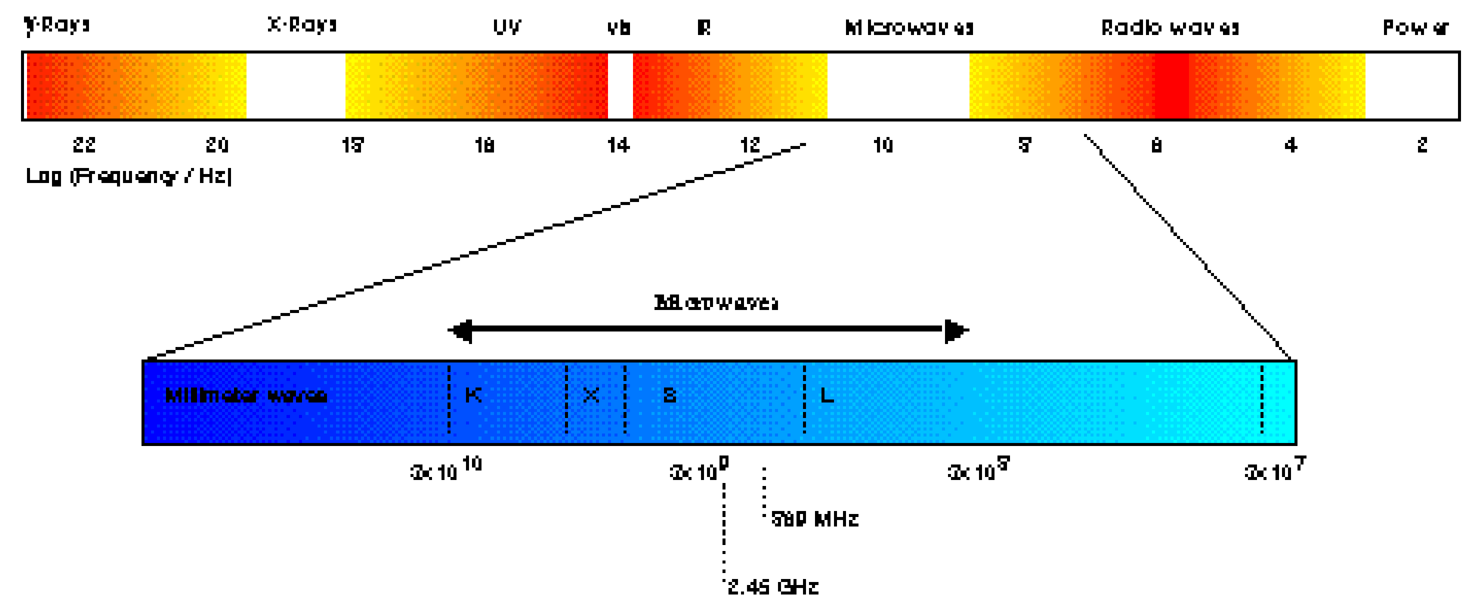
Microwave Irradiation – Historical Overwiev

- First application 1969
    - Aqueous emulsion polymerization
    (acrylic acid, butyl acrylate, methacrylic acid)
- Biological geological samples
- Water treatment
- “Real” synthetic applications
    - Gedye
    - Giguerre

Microwave Irradiation – Historical Overwiev

Frequency (GHz)	Tolerance ()	Area permitted
0.434	0.2%	Austria, Netherlands, Portugal, Germany, Switzerland
0.896	**10MHz**	**United Kingdom**
0.915	13MHz	North and South America
2.375	50MHz	Albania, Bulgaria, CIS, Hungary, Romania, Czech /Slovak Republics,
2.450	**50MHz**	**World-wide, except where 2.375 is used**
3.390	0.6%	Netherlands
5.800	**5MHz**	**World-wide**
6.780	0.6%	Netherlands
24.150	**25MHz**	**World-wide**
40.680	**25MHz**	**United Kingdom**

Microwave Irradiation –



The electromagnetic spectrum

Microwave Irradiation – Heating Effect

Dielectric polarization

α_t – total polarization

α_e - electron polarization

α_a - atom polarization

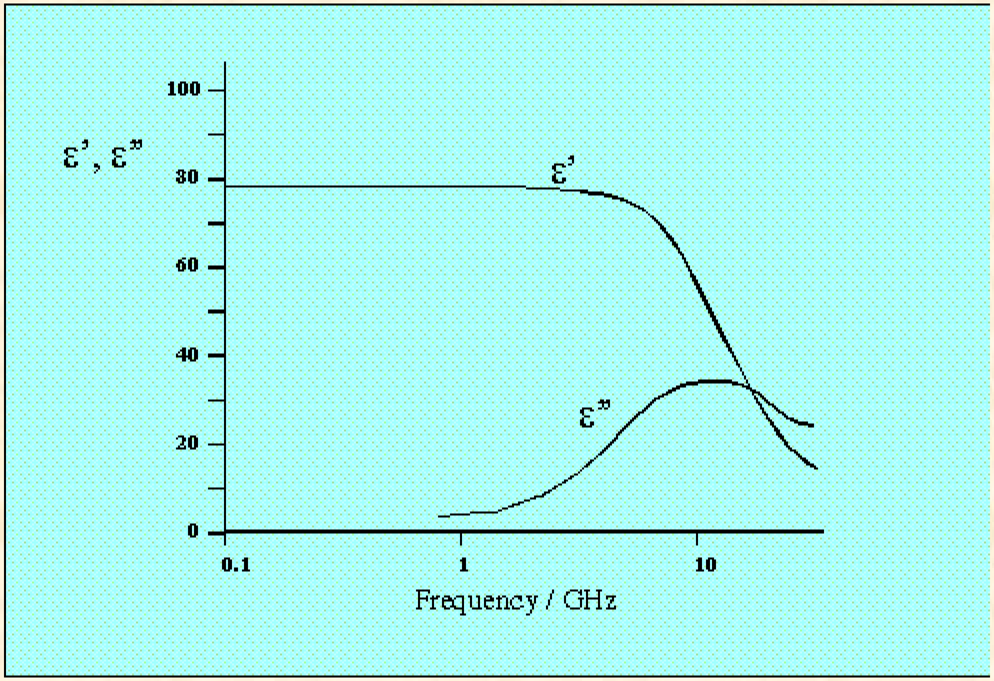
α_i - interfacial polarisation
(Maxwell – Wagner effect)

α_d – dipolar polarization

$$\alpha_t = \alpha_e + \alpha_a + \underline{\alpha_d} + \underline{\alpha_i}$$

Microwave Irradiation – Heating Effect

Dipolar polarization



tgδ=ε''/ε'

ε' – dielectric constant
ε'' – dielectric loss

Variation of dielectric properties as a function of frequency

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

Depth of irradiation

Microwave Irradiation – Heating Effect

Interfacial polarization

$$\varepsilon_{\mathrm{i}}'' \cong \frac{9 v \varepsilon' f_{\max}}{1{,}8\ .\ 10^{10}\,\sigma}\,\frac{(\omega\tau)}{(1+\omega^{2}\tau^{2})}$$

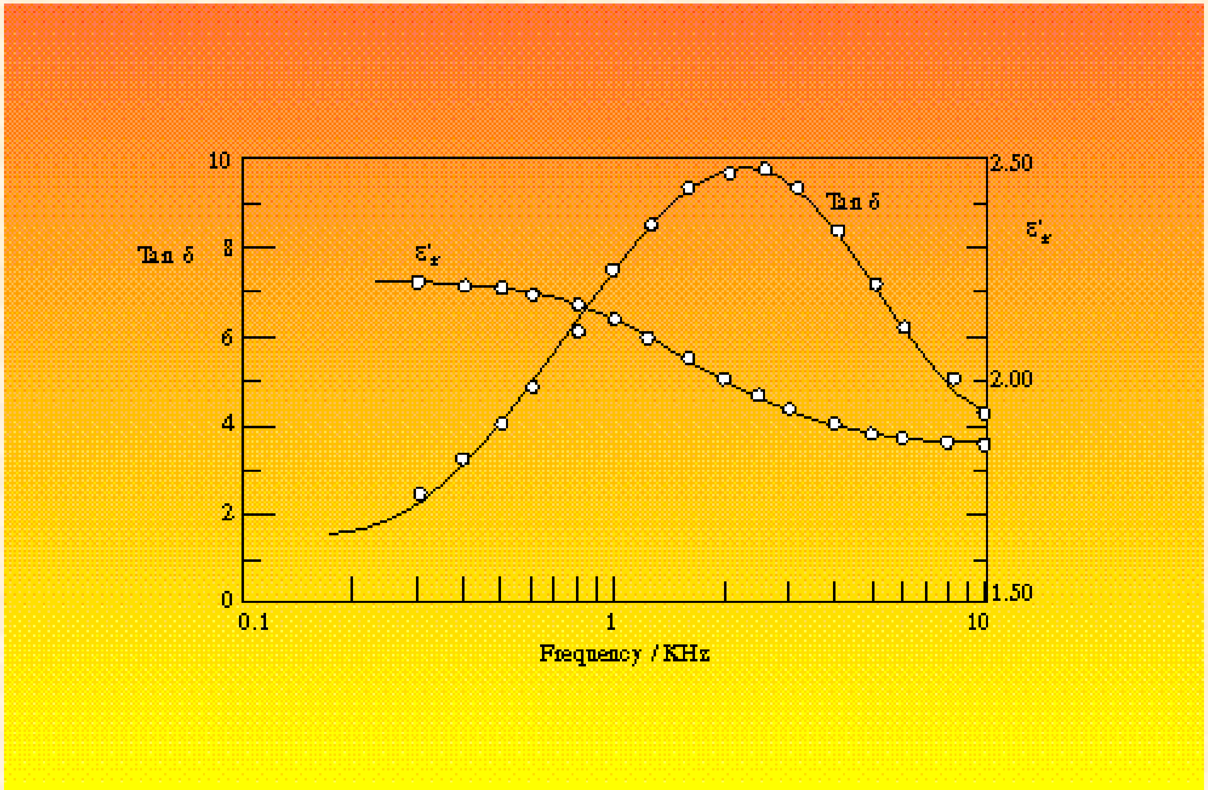
v – volume

f_{max} – frequency at max loss

σ- conductivity

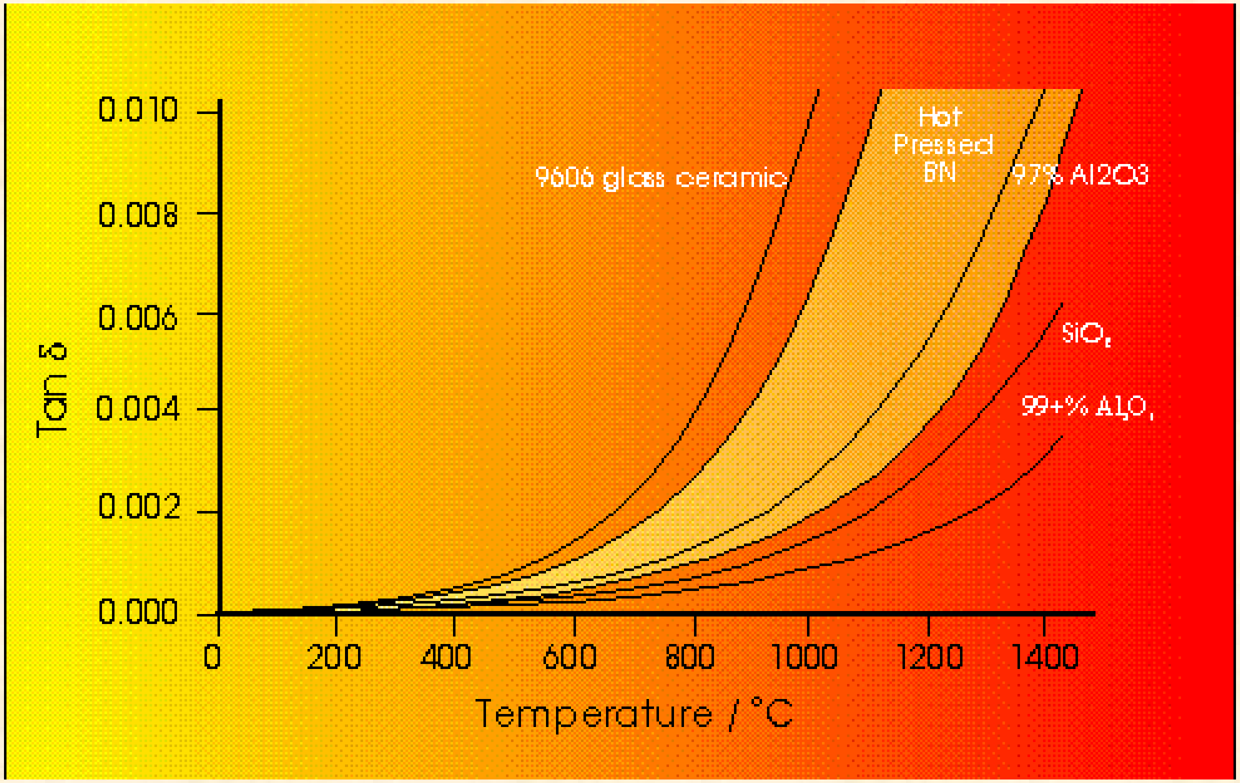
ω – frequency of relaxation

τ – time of relaxation



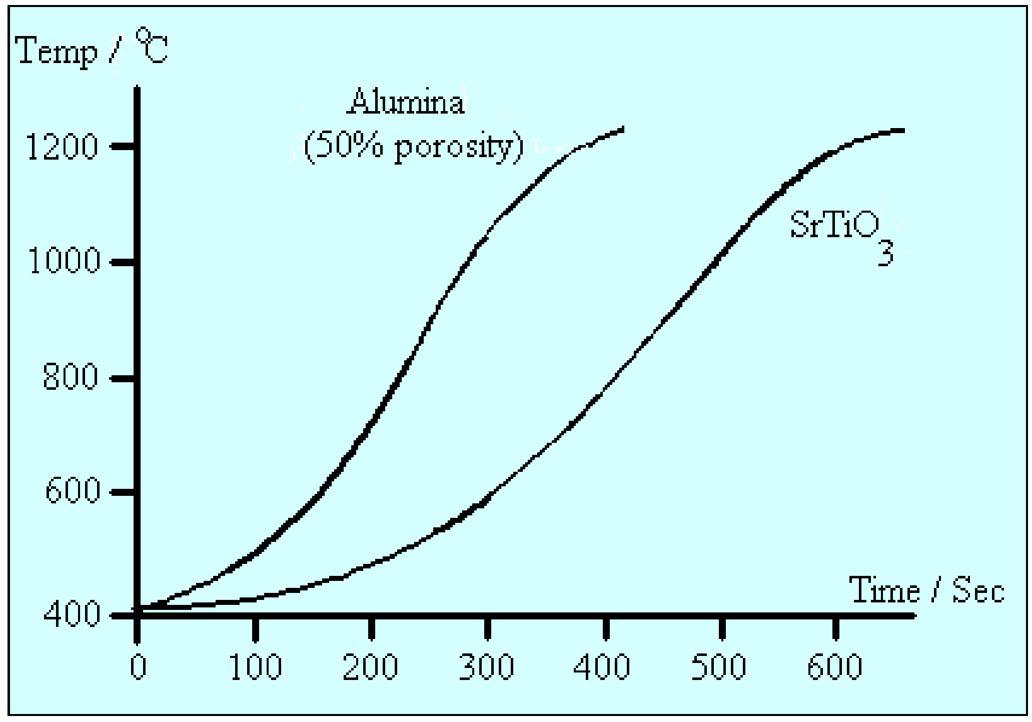
Microwave Irradiation – Heating Effect

Interfacial polarization



Microwave Irradiation – Heating Effect

Interfacial polarization



Microwave Irradiation – Heating Effect

	Frequency					
Solvent	3.10^8 Hz		3.10^9 Hz		1.10^{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	-
Ethyleneglycol	39	6.2	12	12	7	5.5
CCl_4	2.2	-	2.2	0.,0009	2.2	0.003

Dielectric properties of solvents

Microwave Irradiation – Heating Effect

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

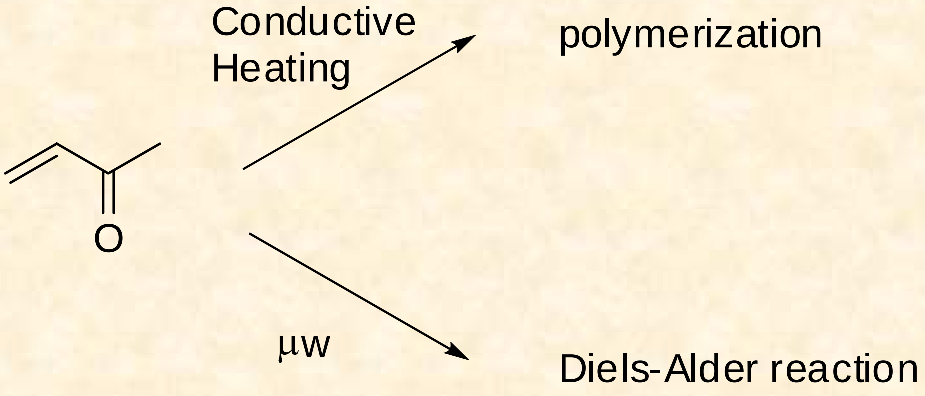
Temperature change of materials after 2.45 GHz frequency microwave irradiation (RT samples, 50 cm^3 liquid, or 25 g (1000 W) or 5-6 g (500 W) solids)

Microwave Irradiation – Heating Effect

Specific microwave effect ? Yes and No

No - Molecular rotations only, no bond cleavage

Yes - The temperature dependence of E_A of different reactions could be significantly different – change in selectivities



Microwave Irradiation – Heating Effect

Summary:

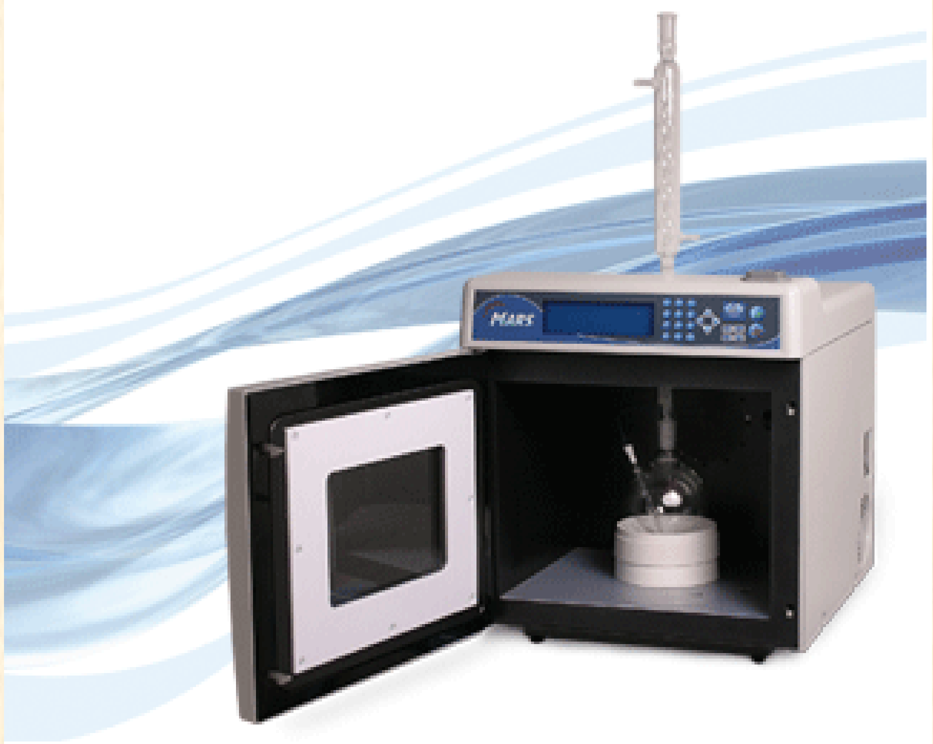
Internal (and very fast and effective) heating of the reaction mixtures

There is no specific (black magic) microwave effect.

Microwave Irradiation – Synthetic Applications

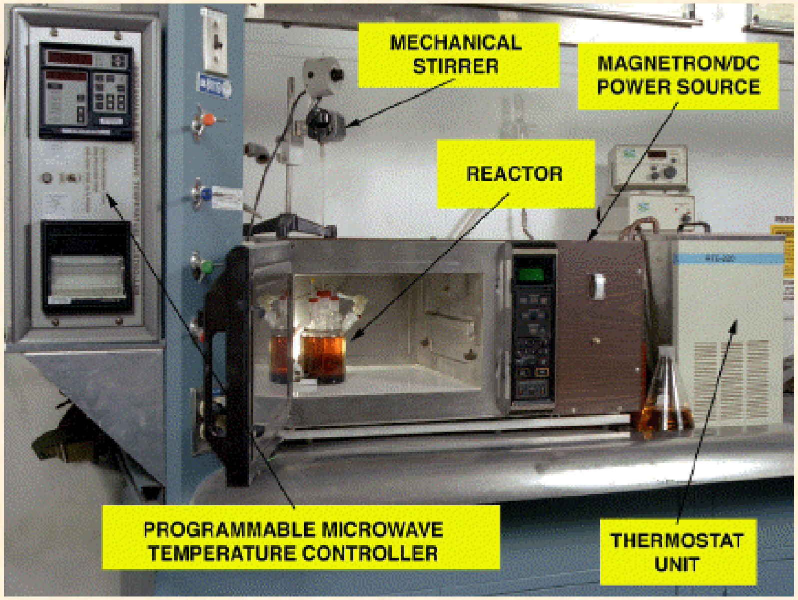
1. Reactions in Solvents

Reactions under reflux conditions



Microwave Irradiation – Synthetic Applications

- The microwave oven



- Synthetic instruments
  - Milestone, Prolabo, Berghof, CEM

Microwave Irradiation – Synthetic Applications

1. Reactions in Solvents   Reactions in closed systems



Microwave Irradiation – Synthetic Applications

1. Reactions in Solvents   Reactions in closed systems

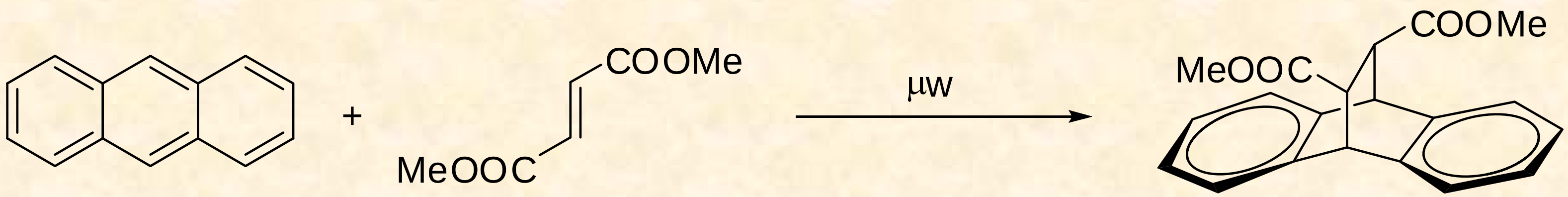
Microwave Irradiation – Synthetic Applications

1. Reactions in Solvents

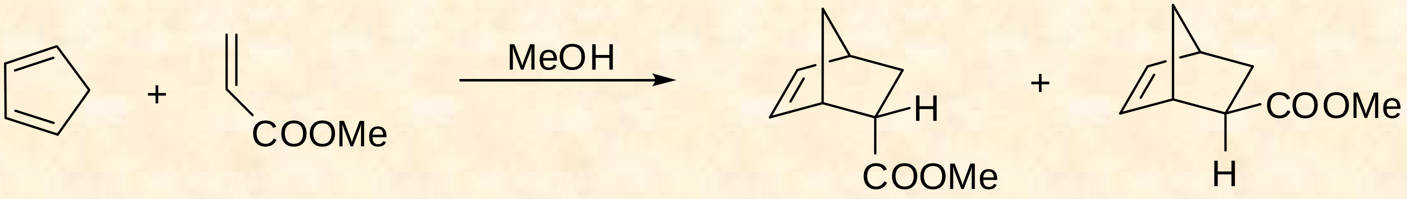
Reactions in continuous system

Microwave Irradiation – Synthetic Applications

1.1. Pericylic Reactions



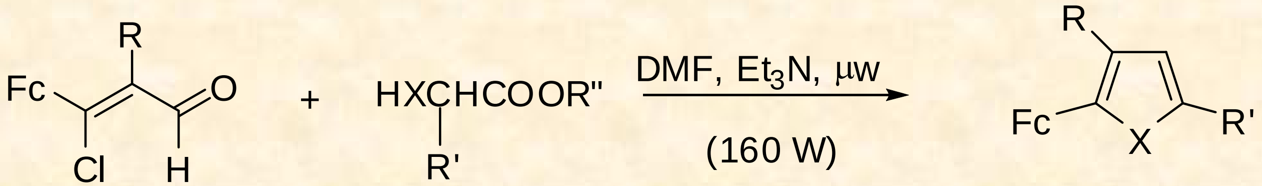
chlorobenzene (5 min)	< 5%
1,2-dichlorobenzene (5 min)	15-25%
1,2,4-trichlorobenzene (5 min)	70%



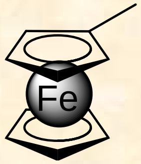
Conventional (0 °C, 67 h)	88 %	12%
Conventional (56°C)	85 %	15%
mw (110°C, 2-5 min)	79 %	21%

Microwave Irradiation – Synthetic Applications

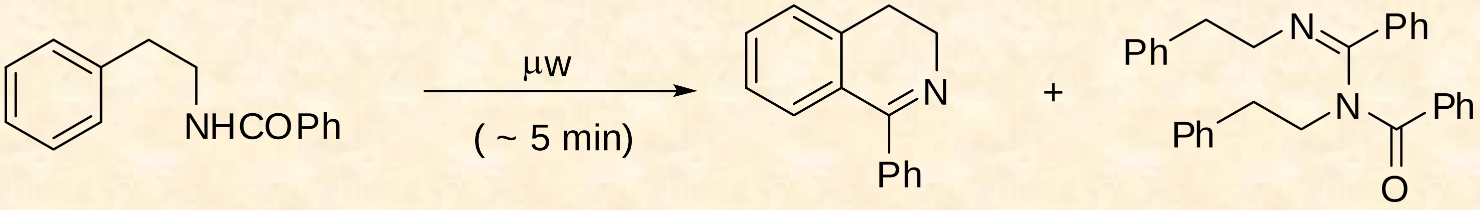
1.2. Synthesis of Heterocycles



Fc - ferrocenyl



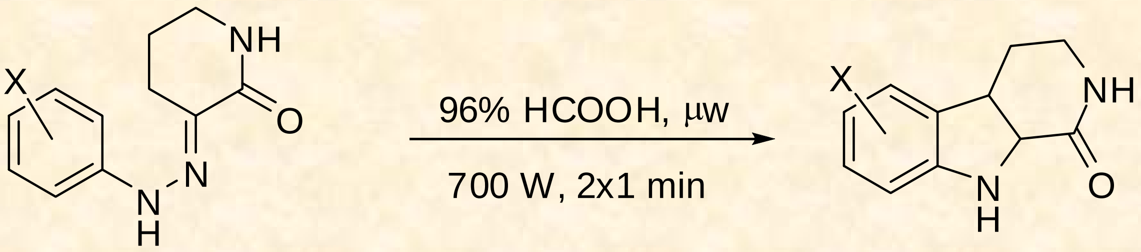
35 - 87 %



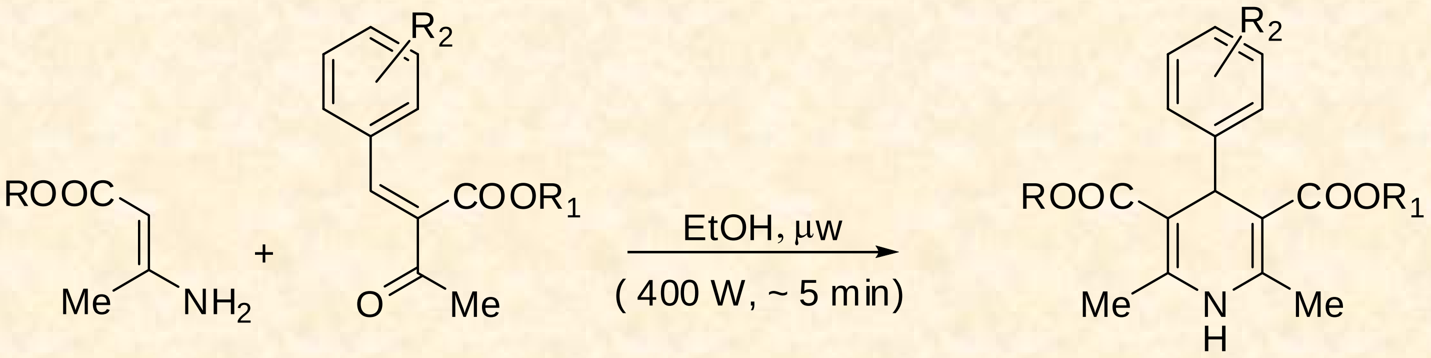
1,2-dichloroethane, P_2O_5 (80 °C)	traces	major product
toluene, $POCl_3$ (80 °C)	traces	major product
chlorobenzene (110-120 °C)	40%	60%
1,2-dichlorobenzene (140-150 °C)	90%	10%

Microwave Irradiation – Synthetic Applications

1.2. Synthesis of Heterocycles



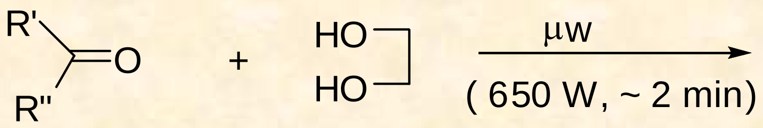
73 - 88 %



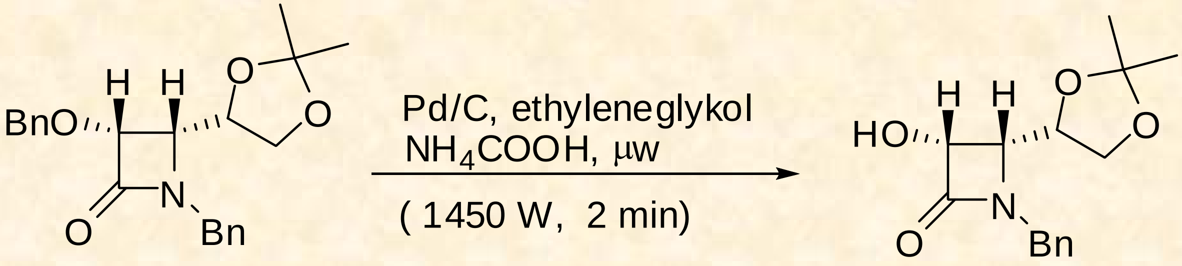
58-98%

Microwave Irradiation – Synthetic Applications

1.3. Protection/Deprotection



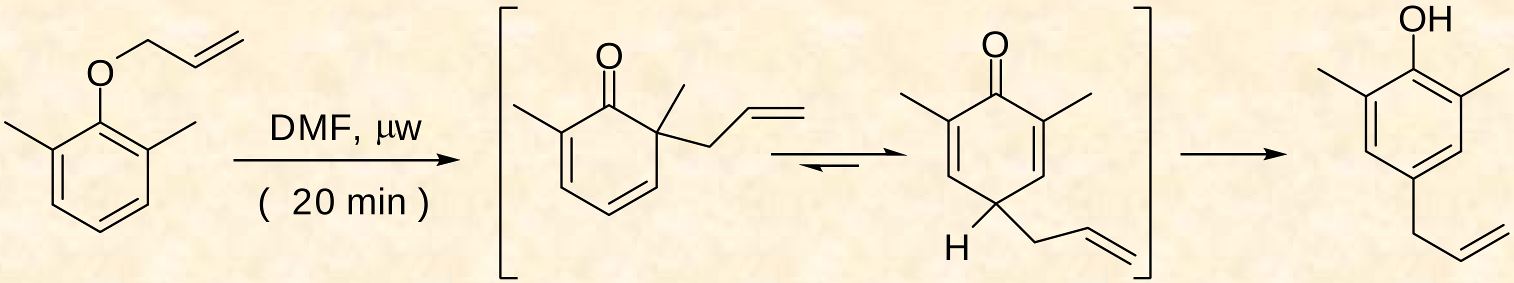
Acid Catalyst



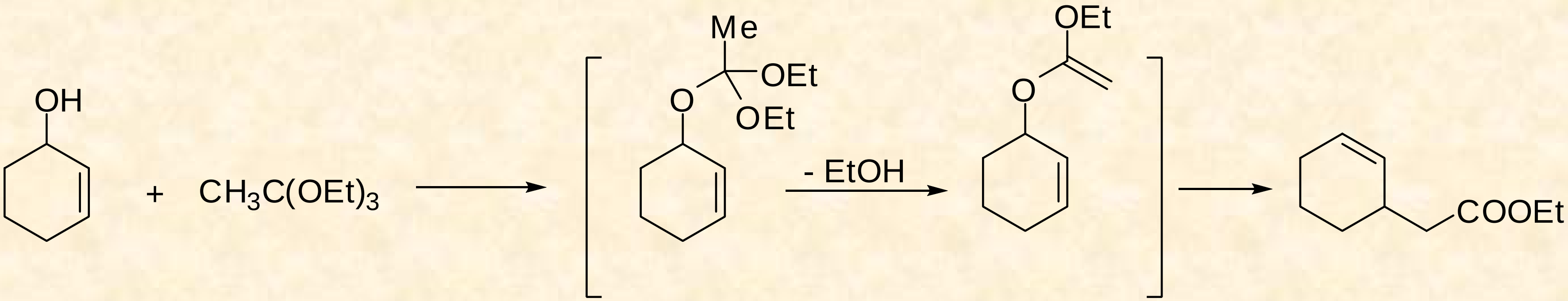
90%

Microwave Irradiation – Synthetic Applications

1.4. Rearrangements/Isomerization



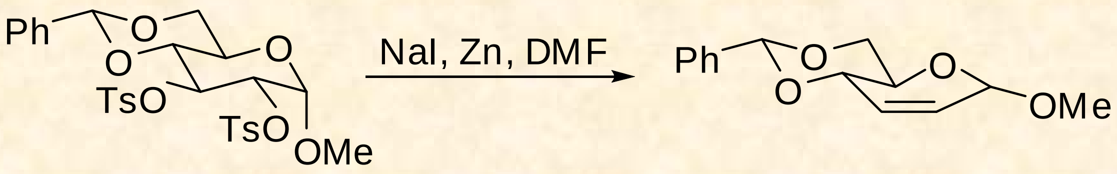
91%



140 °C, propionic acid, 12.5h	73%
μw, DMF, 450 W, 4+4 min	80%

Microwave Irradiation – Synthetic Applications

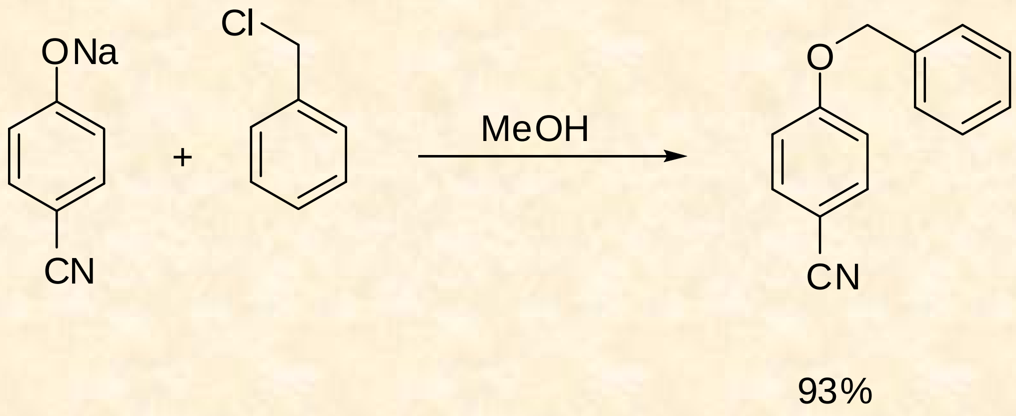
1.5. Elimination



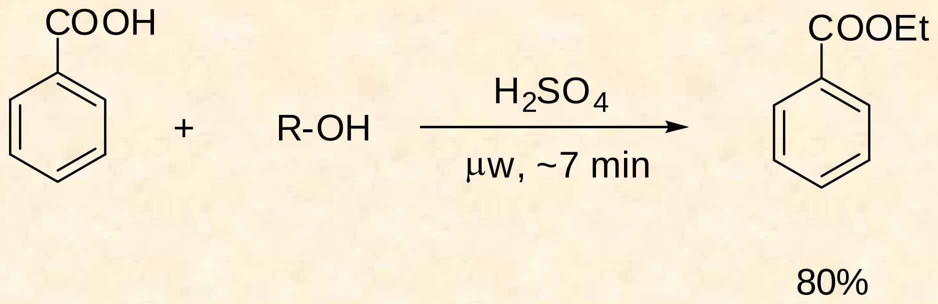
conventional, 2h	53%
4h	40%
μw, 700 W, 14 min	88%

Microwave Irradiation – Synthetic Applications

1.6. Alkylation/Acylation

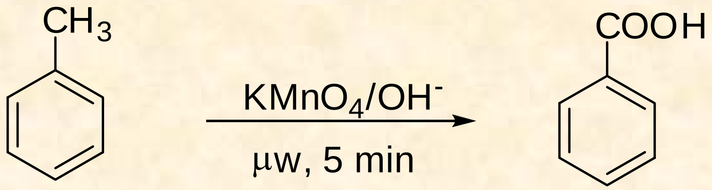


conventional, 12h	65%
μw, 560 W, 35 s	65%



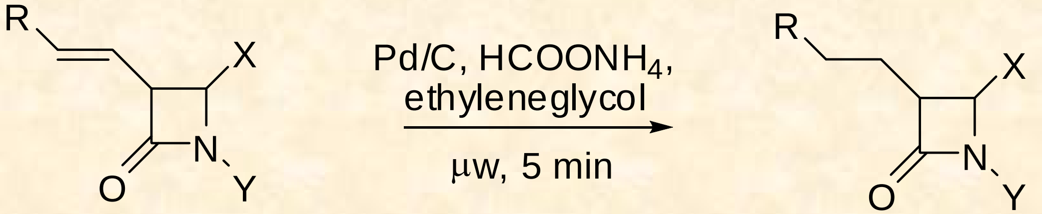
Microwave Irradiation – Synthetic Applications

1.7. Oxidation/Reduction



(high pressure!)

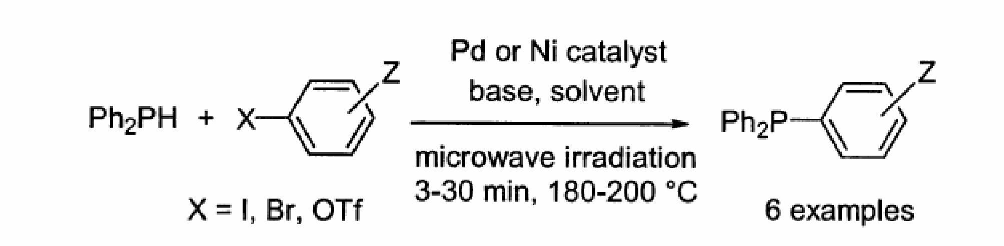
40%



up to 100%

Microwave Irradiation – Synthetic Applications

1.8. Coupling/Arylation



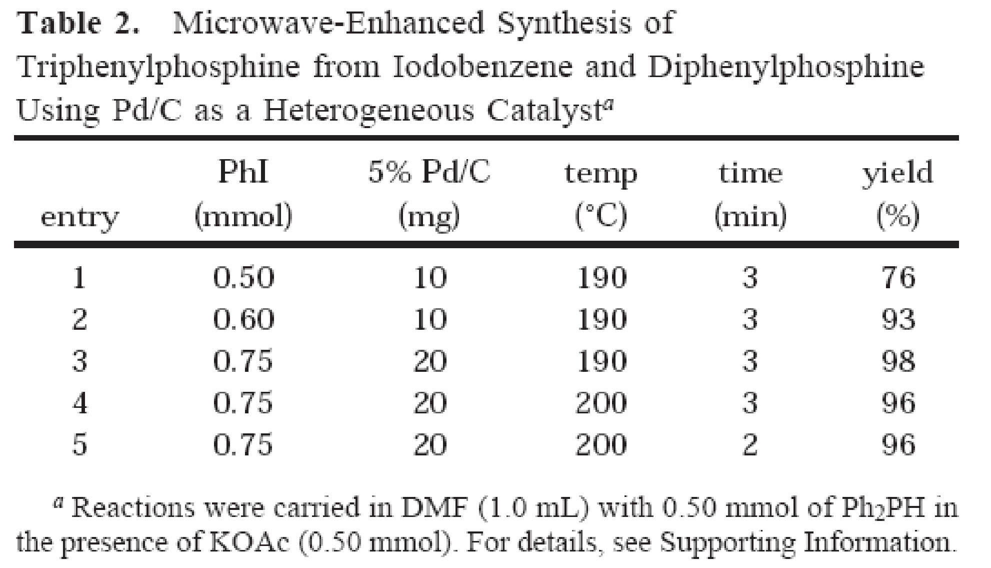


Table 2. Microwave-Enhanced Synthesis of Triphenylphosphine from Iodobenzene and Diphenylphosphine Using Pd/C as a Heterogeneous Catalyst[a]

entry	PhI (mmol)	5% Pd/C (mg)	temp (°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

[a] Reactions were carried in DMF (1.0 mL) with 0.50 mmol of Ph$_2$PH in the presence of KOAc (0.50 mmol). For details, see Supporting Information.

Microwave Irradiation – Synthetic Applications

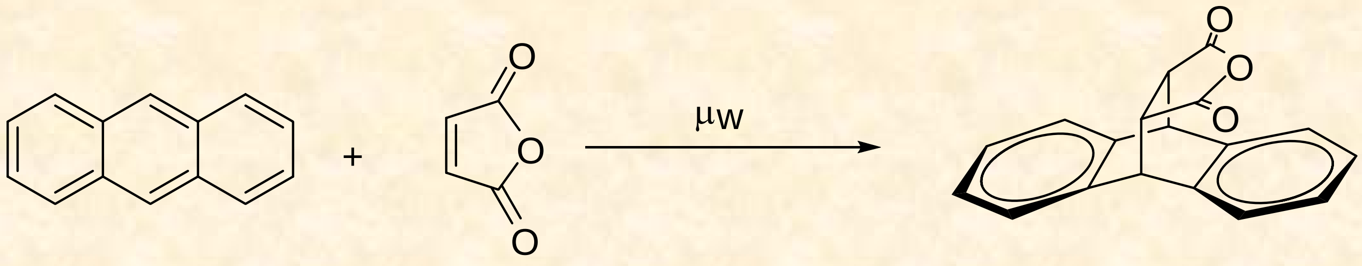
2. Reactions without Solvents

Reactions can be carried out in different ways:

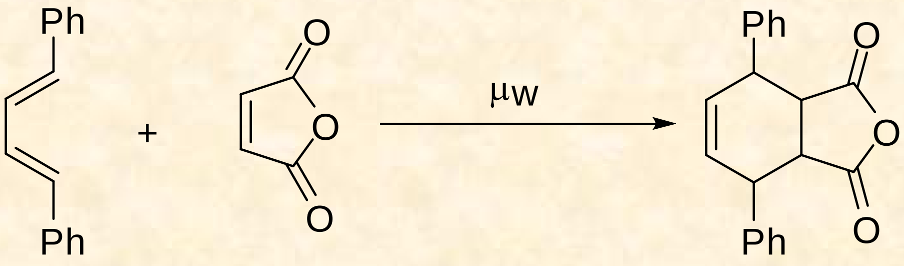
- neat
- on surfaces: support only
  on a catalytic surface

Microwave Irradiation – Synthetic Applications

2.1. Pericylic Reactions



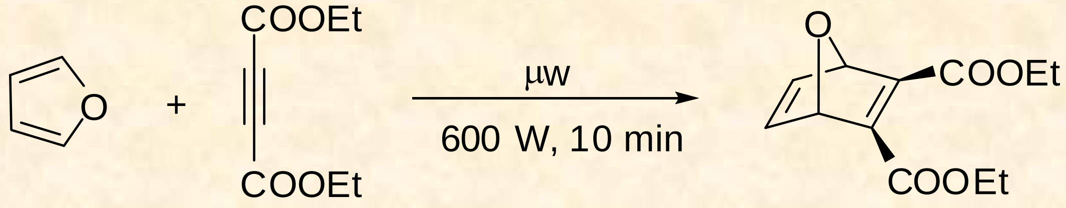
dioxane (60 h)	90%
mw (graphite, 30W, 3x1min)	75%



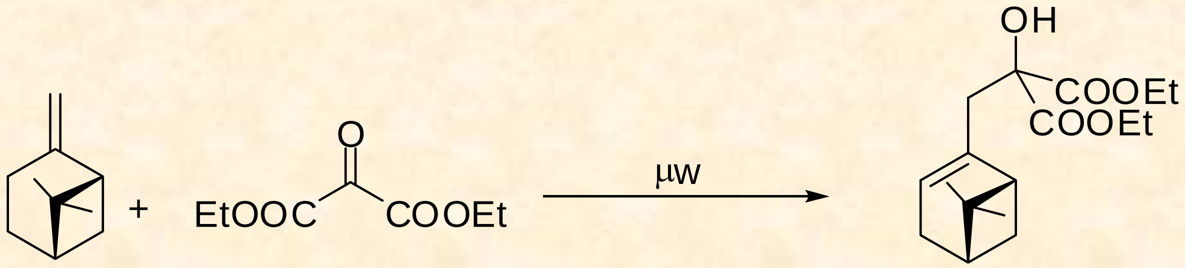
xylene (7 h)	88%
μw (chlorobenzene, 10min)	27%
μw (no solvent, 3min)	85%

Microwave Irradiation – Synthetic Applications

2.1. Pericylic Reactions



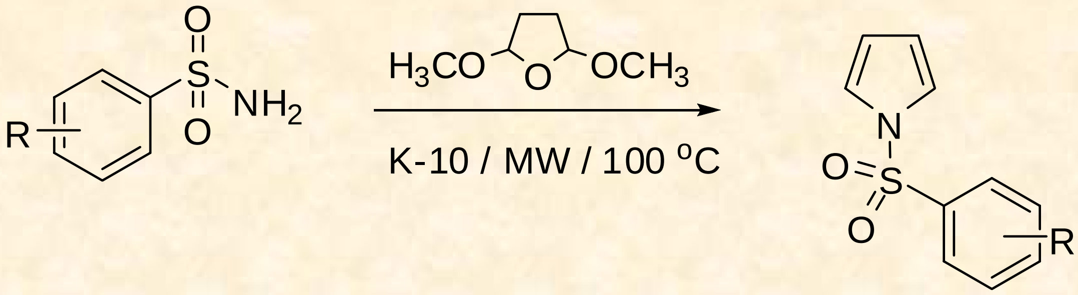
66%



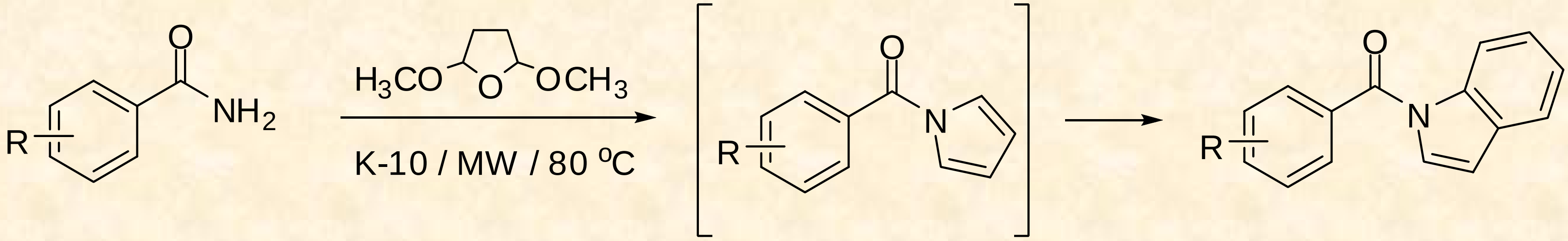
CCl_4, 5h	92%
μw, graphite	70%

Microwave Irradiation – Synthetic Applications

2.2. Synthesis of Heterocycles



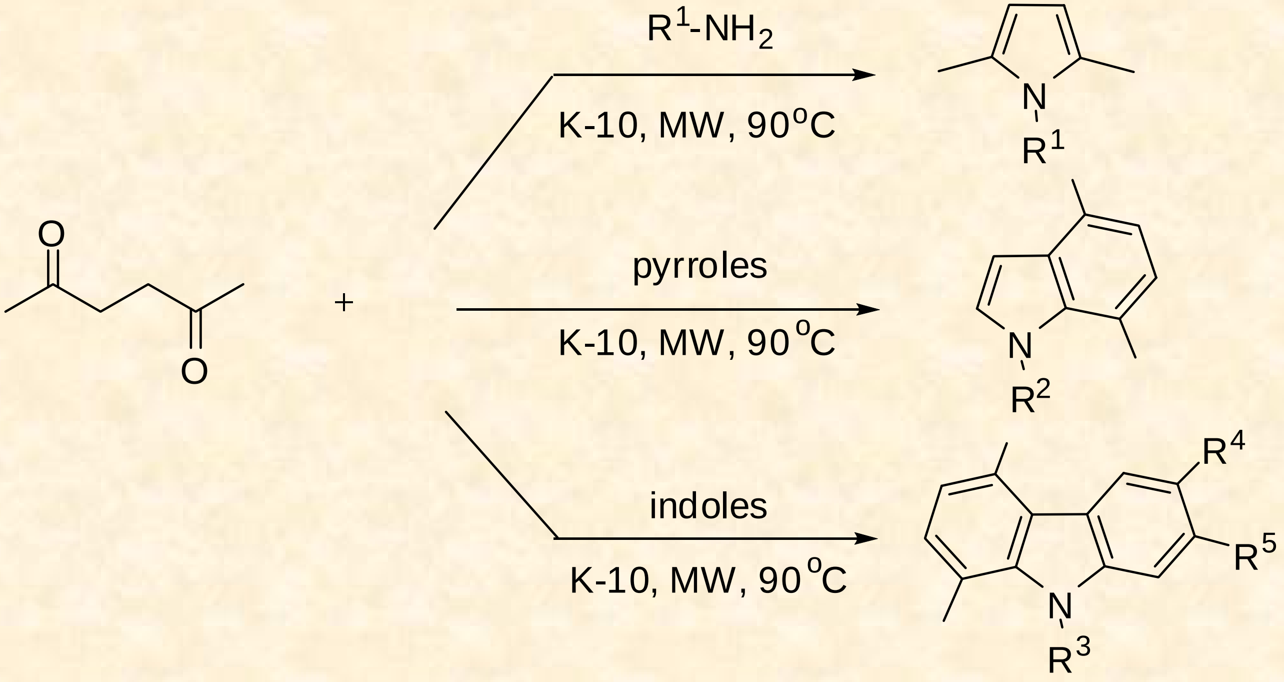
yields 86-95%



yields 85% (5-30 min)

Microwave Irradiation – Synthetic Applications

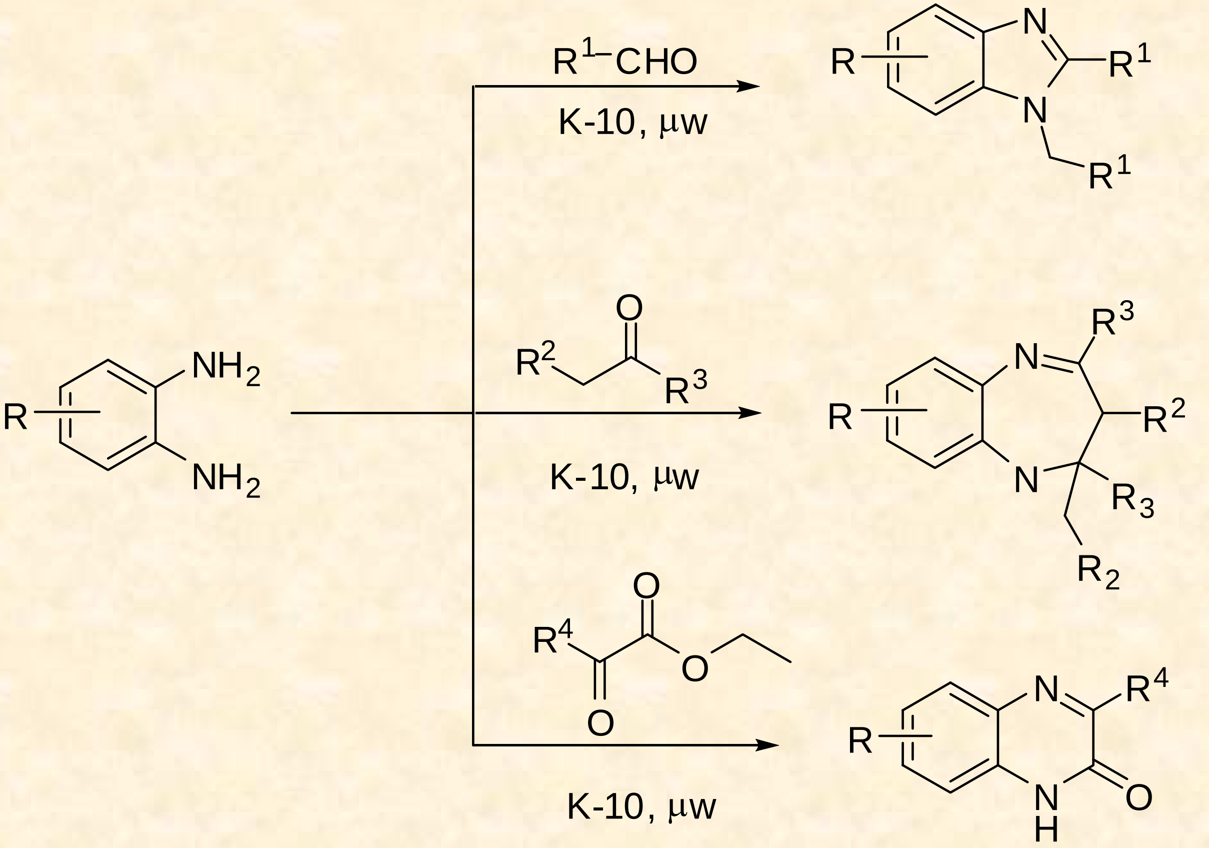
2.2. Synthesis of Heterocycles



Yields up to 98%

Microwave Irradiation – Synthetic Applications

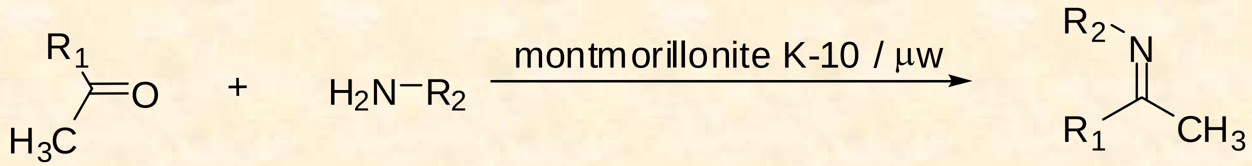
2.2. Synthesis of Heterocycles



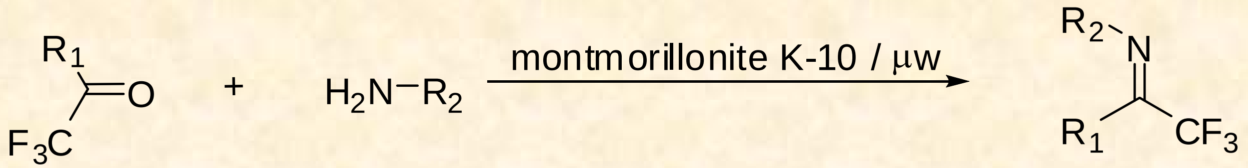
75-98% (2-15 min)

Microwave Irradiation – Synthetic Applications

2.3. Condensation



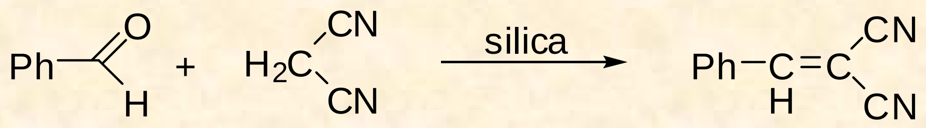
95% (5-10 min)



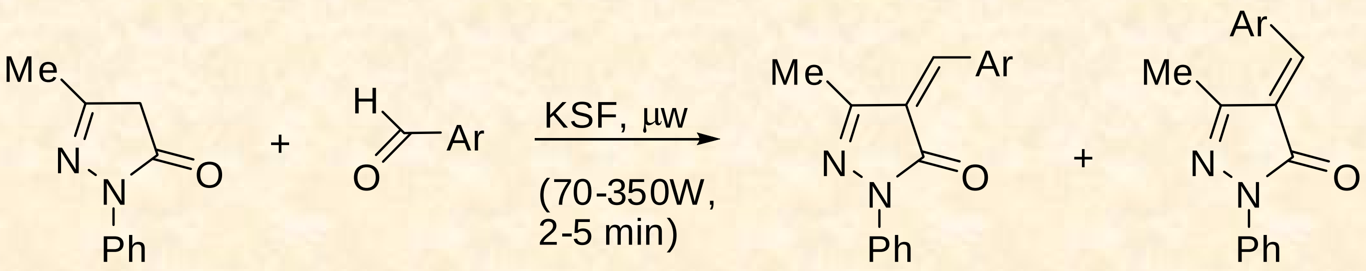
PTSA, toluene, reflux	70% (7 days)
K-10, μw	75-98% (5-35 min)

Microwave Irradiation – Synthetic Applications

2.3. Condensation



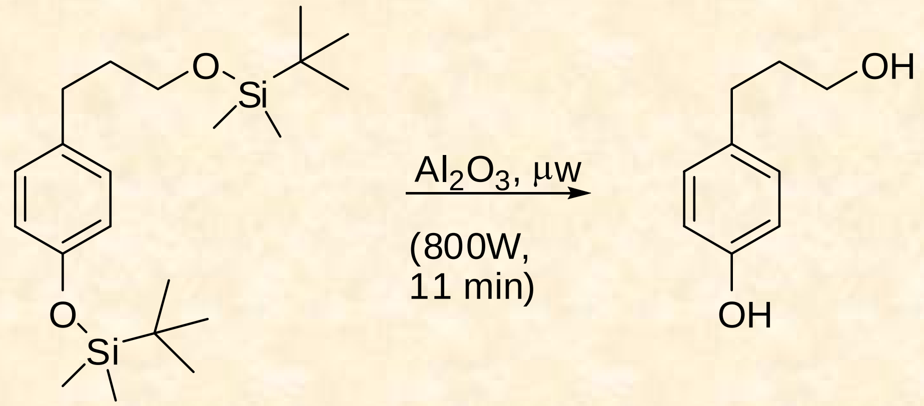
conventional (120 °C, 30 min)	48%
μw (150W, 3 min)	79%



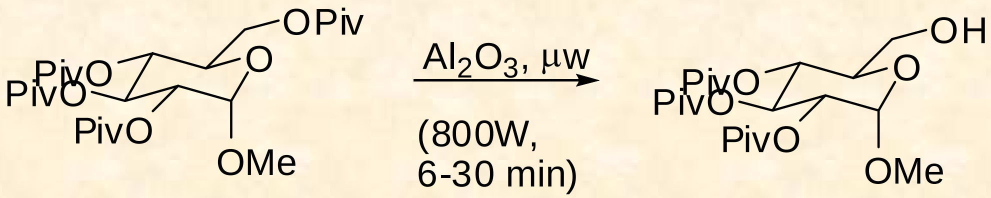
68 - 92%

Microwave Irradiation – Synthetic Applications

2.4. Protection/Deprotection



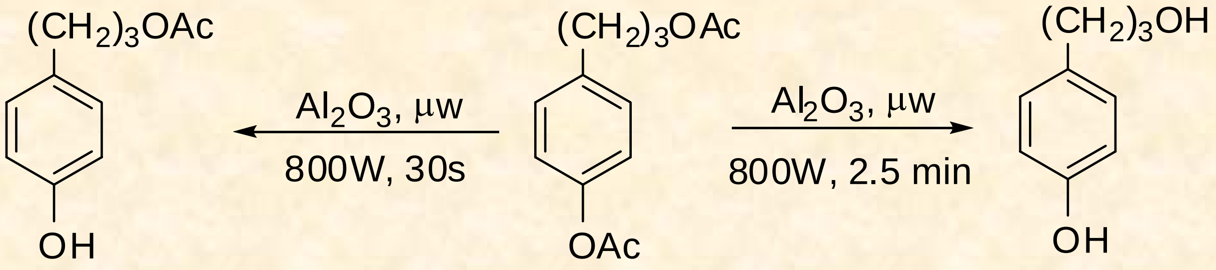
78%

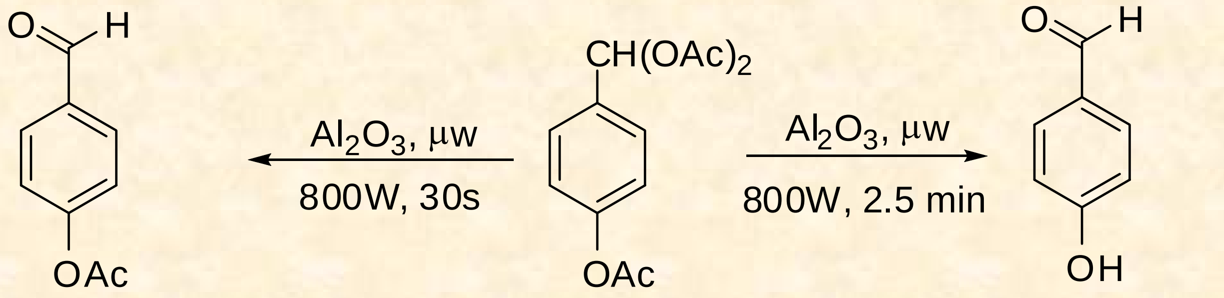


89-91%

Microwave Irradiation – Synthetic Applications

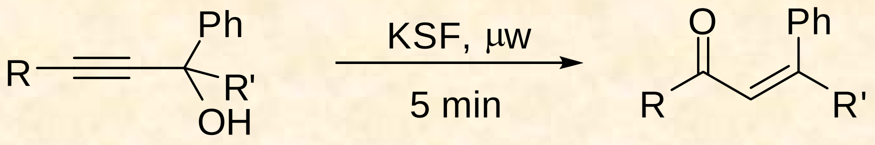
2.4. Protection/Deprotection

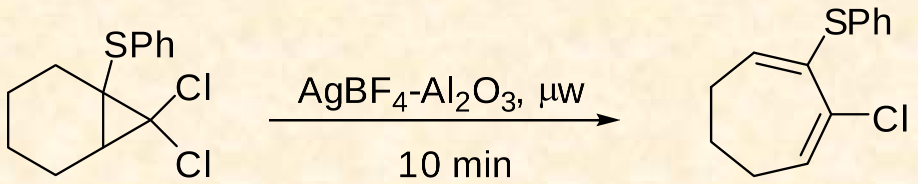




Microwave Irradiation – Synthetic Applications

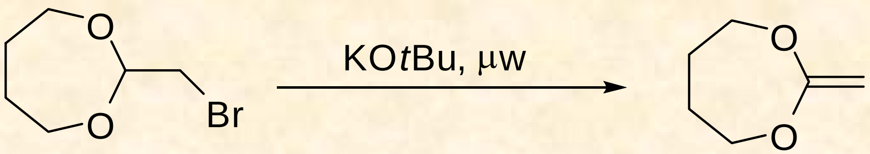
2.4. Rearrangements/Isomerization



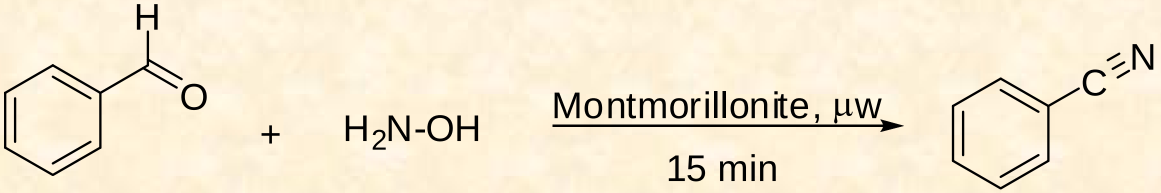


Microwave Irradiation – Synthetic Applications

2.5. Elimination



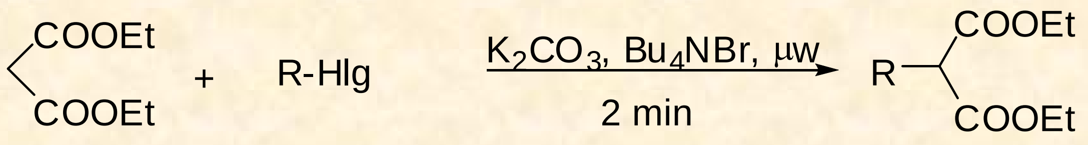
conventional (64 C, 5 min)	41%
mw (64 C, 5 min)	97%



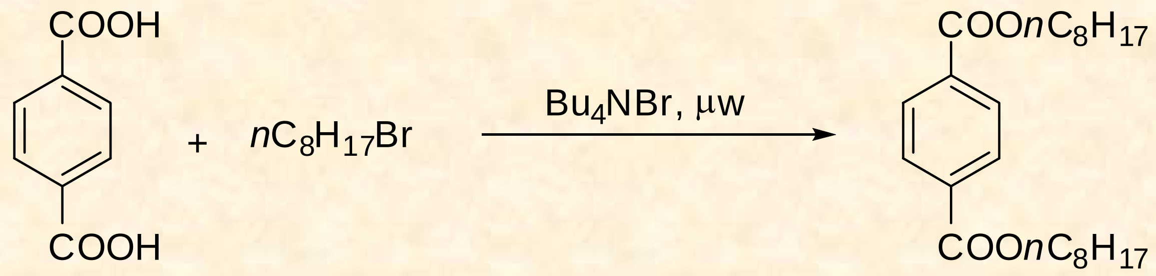
85%

Microwave Irradiation – Synthetic Applications

2.6. Alkylation



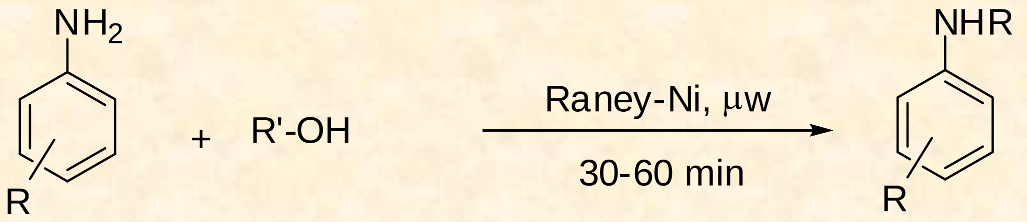
86%



K2CO3, 175 C	20%
K2CO3, mw, 6 min	84%
K-salt, mw, 7 min	92%

Microwave Irradiation – Synthetic Applications

2.6. Alkylation



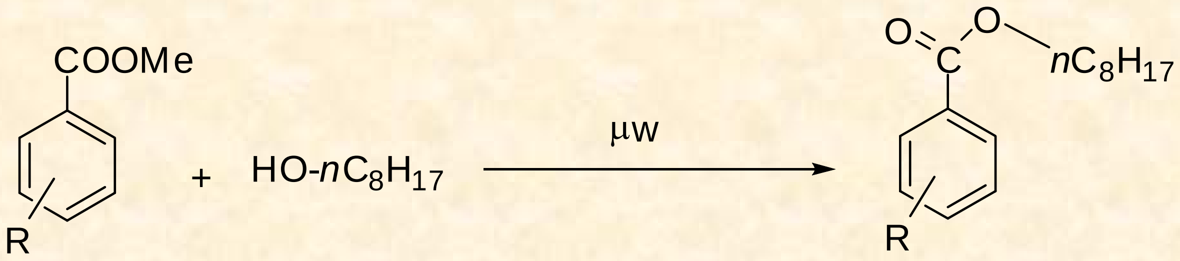
60-91%

$$RCH_2\text{-}Hlg \quad + \quad Ph\text{-}SO_2^- \ Na^+ \xrightarrow[5\ \text{min}]{Al_2O_3,\ \mu w} RCH_2\text{-}SO_2\text{-}Ph$$

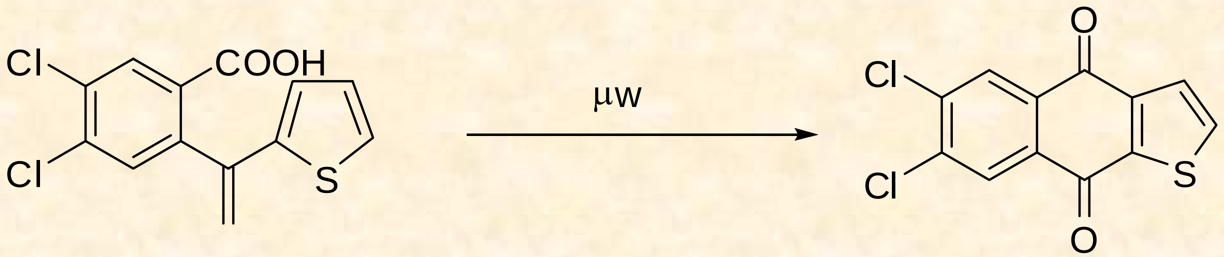
45-99%

Microwave Irradiation – Synthetic Applications

2.7. Acylation



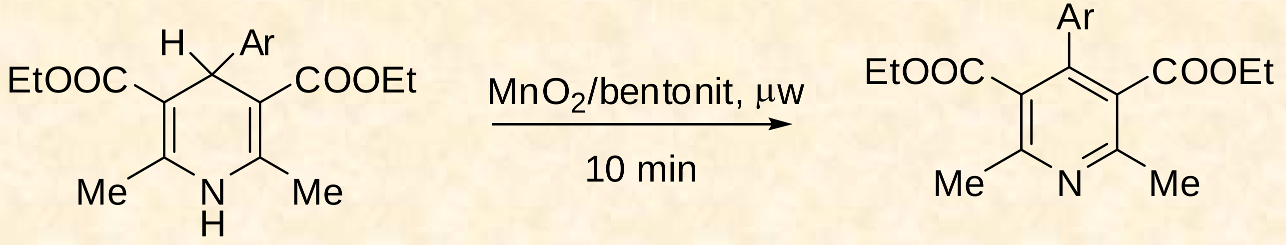
Amberlyst 15, 1 min	61%
TsOH, 2 min	97%
KF-Al_2O_3, 3 min	71%
K2CO3+Aliquat, 2.5 min	90%



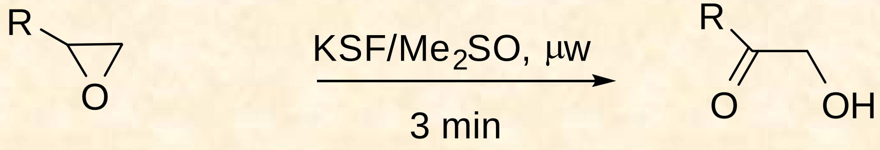
traditional, 320 C, 1h	61%
µw, 780 W, 3 min	92%

Microwave Irradiation – Synthetic Applications

2.8. Oxidation/dehydrogenation



47-100%



55-90%

Microwave Irradiation – Synthetic Applications

2.8. Organometallic compounds

Reaction Mixture	Solvent	Product	*t* (s)	Yield (%)	*t* (h) (conventional)
$CrCl_3.3H_2O$, carbamide, dipivaloylmethane	EtOH–H_2O	$[Cr(dpm)_3]$	40	71	24
$IrCl_3.xH_2O$, PPh_3	DMF	$[IrCl(CO)(PPh_3)_2]$	45	70	12
$IrCl_3.xH_2O$, 9S3	MeOH	$[IrCl_3(9S3)]$	16	98	2
K_2PtCl_4, tpy	H_2O	$[PtCl(tpy)]Cl.3H_2O$	2x30	47	24-100
$HAuCl_4$, tpy	H_2O	$[AuCl(tpy)]Cl_2.3H_2O$	2x30	37	24
$RuCl_3.xH_2O$, bpy	DMF	$[RuCl(CO)(bpy)_2]Cl$	3x20	70	168
$RuCl_3.xH_2O$, 9S3	MeOH	$[Ru(9S3)_2](PF_6)_2$	6x25	49	*

dpm: 2,2,6,6-tetramethyll-3,5-heptadionato; 9S3: 1,4,7-trithiacyklononane; tpy: 2,2',2"-terpyridin; bpy: 2,2'-bipyridyl * cannot be synthesized directly

Microwave Irradiation – Synthetic Applications

2.8. Organometallic compounds

Reaction Mixture	Solvent	Product	*t* (min)	Yield (%)
$[Mo(CO)_6]$ acetyl-acetone	$AcOH–Ac_2O$	$[Mo_2(acac)_4]$	30	65
Mo_6Cl_{12}, AcOH, Ac_2O		$[Mo_6Cl_8][OAc]_2Cl_2$	8	79
$RuCl_3.3H_2O$, 9S3	MeOH	$[Ru(9S3)_2](PF_6)_2$	70	96
$RuCl_3.3H_2O$, bpy	MeOH, Et_3N	$[Ru(bpy)_3](PF_6)_2$	10	87
$RuCl_3.3H_2O$, cycloheptatriene	EtOH	$[Ru\{(C_7H_8)Cl_2\}_2]$	9	66
$RhCl_3.3H_2O$, cyclooctadiene	$EtOH–H_2O$ (4:1)	$[\{Rh(COD)Cl\}_2]$	0,5	84

acac: acetyl-acetone; 9S3: 1,4,7-trithiacyclononane; bpy: 2,2'-bipyridyl; C_7H_8: cycloheptatriene; COD: cyclooctadiene

Microwaves/Sonochemistry – References

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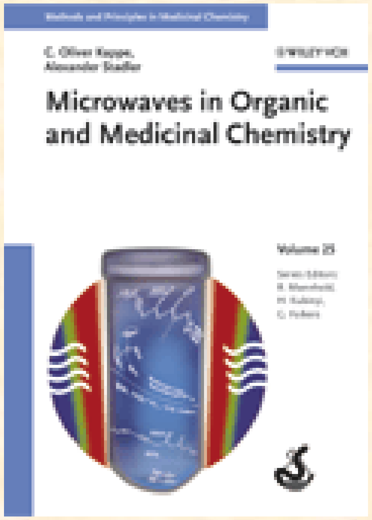
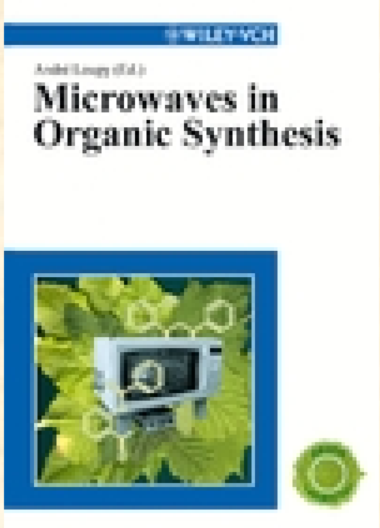

Microwaves in Organic and Medicinal Chemistry


Microwaves in Organic Synthesis