Reactivity and selectivity under microwaves in organic chemistry. Relation with medium effects and reaction mechanisms*

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Abstract: Typical applications of solvent-free conditions and microwave activation are described. Non-purely thermal specific effects are evidenced and discussed in terms of reaction medium and mechanisms, taking into account the variations in polarity of the systems.

INTRODUCTION

Accelerations by microwave (MW) have been observed for a wide range of organic reactions [1–4]. They result from material–wave interactions leading to thermal effects (connected to dipolar and charge space polarization) and specific (purely nonthermal) effects. These last ones could result from variations in activation parameters as shown by plotting rate constants against temperature [5] (Fig. 1), enhancements in molecular impact [6], and possibly high localized microscopic temperatures (hot spots) as advocated in sonochemistry [7].
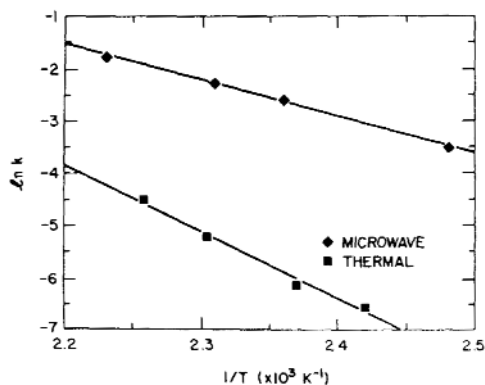
Fig. 1 First-order kinetic plot showing formation of imide [5].

Experimental evidence for microscopic effects needs cautious and reliable results resulting from strict comparisons [2,3,8] between reactions carried out either under MW or conventional heating (Δ) in similar conditions (same reaction medium, temperature, time, pressure, etc.). A monomode reactor has to be preferentially used due to wave focusing (reliable homogeneity in the electric field) and to

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accurate control of the temperature throughout the reaction [2,9] with the possibility of operating with rather similar temperature profiles in both kinds of activation.

MEDIUM EFFECTS

Microwave effects have to be considered according to reaction medium. Solvent effects are especially of great importance. If polar solvents are involved, either aprotic (e.g., DMF) or protic (e.g., alcohols), the main absorption occurs between microwaves and the polar molecules of the solvent. In this case, energy transfer is from solvent to reaction mixtures and reactants. Consequently, the results should be nearly the same under classic heating (Δ). It is, for instance, the case in alcoholic media for the influence of microwaves on the rate of the esterification of propan-1-ol with ethanoic acid (Fig. 2) [10] or of propan-2-ol with mesitoic acid [11]. The absence of MW effects also arised from several experiments carefully carried out in DMF [12].
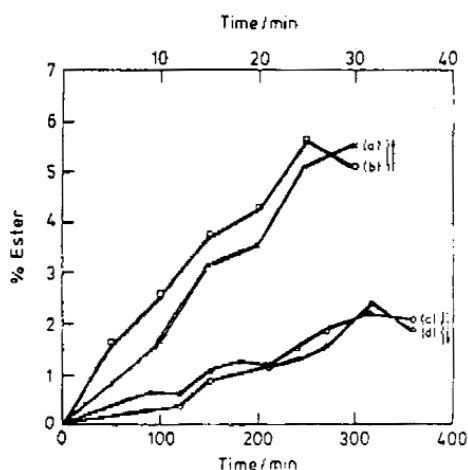
Fig. 2 Concentration of ester as a function of time during heating under reflux at atmospheric pressure [10].
a) H_2SO_4 catalyst, Δ; b) H_2SO_4 catalyst, MW; c) silica catalyst, Δ; d) silica catalyst, MW.

More interesting could be the use of nonpolar solvents (e.g., xylene, toluene, hydrocarbons) as there only exist a very weak solvent–MW interaction (they can be considered as transparent). They thus can allow specific absorption by reactants. Energy transfer can occur from the reactants to the solvent, and the results could be different under MW and Δ and be mechanism dependent (see below). It has thus been shown that the magnitude of specific microwave effects in solution is decreased when the polarity of solvent is increased as advocated in some Diels–Alder reactions [7] and in coumarin synthesis by a Knoevenagel condensation [13].

By far, the best situation concerned solvent-free reactions, as here, absorption of microwave radiation should be limited only to the reacting species.

They can be accomplished according to three methods [14]:

• reactions between neat reagents in quasi equivalent amounts, needing preferentially at least one liquid phase in heterogeneous media and leading to interfacial reactions;
• solid–liquid phase transfer catalysis (PTC) conditions in the case of anionic reactions using the liquid electrophile as both reactant and organic phase and a catalytic amount of tetraalkyl-ammonium salts as transfer agent; and
• reactions using supported reagents impregnated on solid mineral supports (aluminas, silicas, and clays).

These methods are claimed to involve eco-friendly chemistry (called "green chemistry") as no solvents are used for the reactions and as the purity of products is enhanced under very simplified and safe experimental conditions.

Selective phenacylation of 1,2,4-triazole

We have studied the solvent effect on the selectivity of 1,2,4-triazole alkylation by 2,2',4'-trichloroace-tophenone (Scheme 1) according to activation mode (MW or Δ in identical conditions). The main results are given in Table 1.

Ar = 2', 4'-Cl-C$_6$H$_3$ N$_1$ N$_4$ N$_{1,4}$
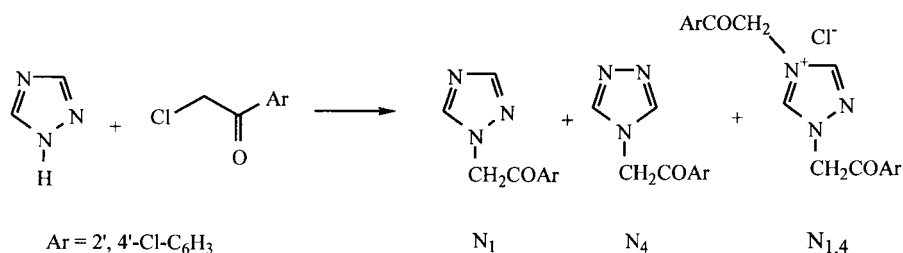
Scheme 1

Table 1 Solvent effect. Irradiation time = 20 min at an imposed temperature of 140 °C.

Solvent	Activation mode	Conversion %	N$_1$ / N$_4$ / N$_{1,4}$ [a]
Pentanol	MW	90	95 / 5 / 0
	Δ	90	95 / 5 / 0
DMF	MW	90	95 / 5 / 0
	Δ	90	95 / 5 / 0
o-xylene	MW	82	100 / 0 / 0
	Δ	95	32 / 28 / 40
No solvent	MW	92	100 / 0 / 0
	Δ	100	36 / 27 / 27

[a] determined by GC and ^{1}H NMR

No microwave effects were observed in polar solvents (pentanol or DMF), whereas in nonpolar xylene the regioselectivity is noticeably affected by activation mode. The reaction became totally regioselective under microwave either in xylene or under solvent-free conditions.

Polar solvent can be therefore advantageously replaced by a polar one or, better, by no solvent, providing the use of microwave irradiation.

REACTION MECHANISM EFFECTS

From material–wave interactions result thermal microwave effects, and, due to dipolar polarization phenomenon, the greater the polarity of a molecule (e.g., a solvent) the more effective the microwave effect when one considers the rising temperature rate [15]. Thus, the specific microwave effect for a given reaction has to be considered according to the reaction mechanism and how the polarity of the system is modified during the reaction progress.

Specific microwave effects could be expected for polar mechanism, when the polarity is increased during the reaction from ground state to transition state. They can thus essentially depend on the medi-

um and reaction mechanism. If the stabilization of the transition state (TS) is more effective than the ground state (GS) the result is an enhancement of reactivity by decreasing activation energy (Fig. 3).
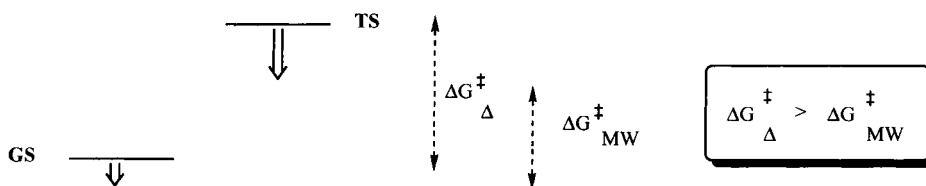
**Fig. 3** Relative stabilization of more polar TS when compared to GS.

Two cases of more prone ones reveal such specific microwave effects:
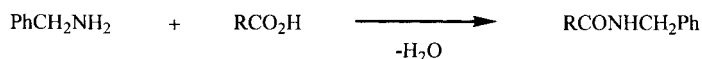1) Reaction of neutral species leading to dipolar TS (Fig. 4):
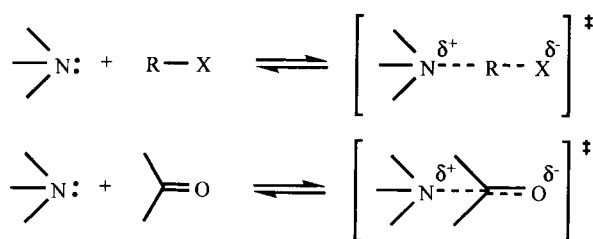
Fig. 4 Amine alkylation and nucleophilic addition mechanisms.

This is, for instance, the case of nucleophilic alkylation (Scheme 2) or addition of amines to carbonyl compounds (Scheme 3, Table 2).
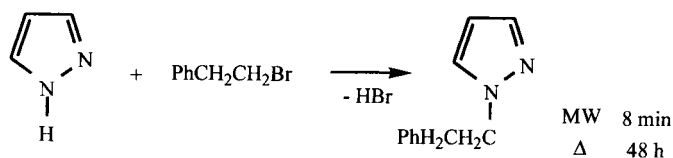
Scheme 2 Alkylation of pyrazole under solvent-free conditions [16].

Scheme 3 Uncatalyzed amidation under solvent-free conditions.

Table 2 Reaction of benzylamine with several carboxylic acids at 150 °C for 30 min.

| R	Amine/acid	Yield %	
		MW	Δ
Ph	1 / 1	10	25
	1.5 / 1	75	17
	1 / 1.5	80	8
$PhCH_2$	1 / 1	80	63
	1.5 / 1	93	72
	1 / 1.5	92	40
$CH_3(CH_2)_8$	1 / 1	85	49

  Microwave specific effects during amine addition to carbonyl group is here of main importance when one considers that at 150 °C, water could be removed equally under both types of activation.

  On the opposite side, small or no microwave effects could be observed when the polarities of GS and TS remain rather the same, i.e., in the case of concerted synchronous mechanisms as described for Diels–Alder cycloadditions [17] and ene-reactions [18].

  2) The reaction of charged nucleophiles, as the anionic species are more delocalized in the transition state and therefore lead to more dissociated (more polar) ion pairs (Fig. 5): A typical example is given in ester aminolysis in basic media (Scheme 4, Table 3).

$$Nu^-, M^+ \quad + \quad \underset{}{\overset{}{C}}{=}O \quad \rightleftharpoons \quad \left[\overset{Nu}{\underset{}{C}}{\equiv}{\cdots}O \;^-, M^+ \right]^{\ddagger}$$

Fig. 5 Mechanism for ion-pair addition to carbonyl compound.

$$\underset{EtO}{\overset{R}{C}}{=}O \quad + \quad CH_3(CH_2)_7NH_2 \quad \xrightarrow[- EtOH]{(base)} \quad RCONH(CH_2)_7CH_3$$
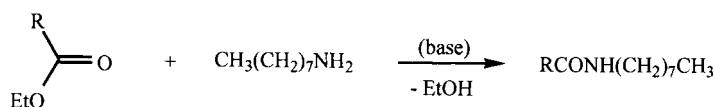
Scheme 4

Table 3 Ester aminolysis with *n*-octylamine at 150 °C for 10 min.

R	base	Yield %	
		MW	Δ
Ph	-	0	0
	KOtBu	80	22
	KOtBu + Aliquat 336	87	70
PhCH$_2$	-	63	6
	KOtBu + Aliquat 336	63	36

  The microwave specific effect is more important when the reaction is performed in the absence of transfer catalyst (Aliquat 336 = nOct3N$^+$Me Cl$^-$), showing thus that the nature of reactive species is of great importance in connection with ionic dissociation (i.e., modifications in polarities).

CONCLUSION

Solvent-free organic synthesis offers a lot of advantages connected to safety, enhancement in reactivity and selectivity, cost saving, and energy and pollution prevention. When coupled with microwave irradiation, nonthermal effects can be developed, thus allowing considerable improvements over classic procedures. These procedures are clearly dependent on the reaction medium and mechanisms involved.

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