



Microwave effects in solvent-free esters aminolysis

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Abstract—Solvent-free ester aminolysis was studied under microwave or conventional heating either in the absence of base or induced by KO^tBu with or without a phase transfer agent. The specific microwave effects were shown to be dependent on the conditions and discussed in terms of relative polarities of ground and transition states. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Amides are among the most important functions in organic chemistry, naturally occurring or synthetic.¹ The direct transformation of carboxylic esters to amides, of potentially important synthetic interest, is generally carried out under harsh conditions requiring high temperatures and extended reaction times.¹ Earlier reported conditions for such direct ester aminolysis involve strongly basic catalysis [alkoxides,² hydrides,³ amides,⁴ alkyllithium^{4b}], metallic catalysts [Grignard reagents,⁵ aluminum⁶ or tin complex⁷] or even high pressure.⁸

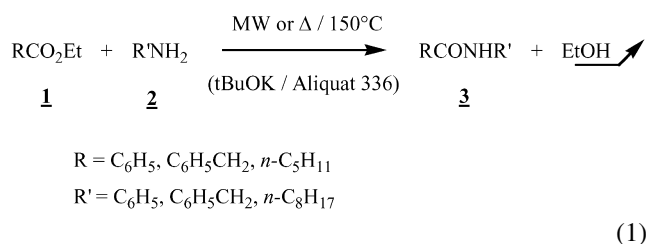
Within the framework of 'Green Chemistry',⁹ a noticeable improvement was provided by the association of solvent-free techniques and microwave activation (MW).^{10–12} Thus, Varma and Naicker¹³ described the solid state synthesis of amides from non-enolizable esters and amines using potassium *tert*-butoxide under microwave irradiation in an unmodified domestic microwave oven. The temperature was not controlled but was certainly rather high as the reaction vessel was placed in an alumina bath, most likely providing an important external temperature increase.¹⁴

We decided to further explore such a procedure to control the possibility of specific (not-purely thermal) microwave effects using different substituted esters and amines. As advocated to be the most efficient and reliable conditions,¹¹ the reactions were performed under microwave irradiation with accurate control and power-enforced temperature, as measured by infrared detection throughout the reaction¹⁵ using a monomode reactor (focused waves) Prolabo Synthwave S402.¹⁶ For the sake of comparison, the reactions were also performed with conventional heating

(Δ) using a thermostated oil bath under the same conditions (pressure, time, temperature,...) including similar profiles of temperature increase using both activation modes (MW or Δ).

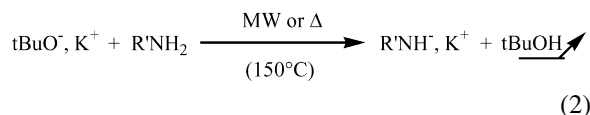
2. Results

Ester aminolysis (Eq. (1)) was studied under microwave irradiation in the absence of base or induced by potassium *tert*-butoxide in the presence (or not) of a phase transfer agent (Aliquat 336) under solvent-free conditions.



Reactions were performed at rather high temperature (150°C) to:

- prevent reaction from reversibility (EtOH removal)
- ensure potassium amide formation (*t*BuOH removal) [Eq. (2)]:



We have successively studied:

- the influence of the amine substituent (R') in its reaction with ethyl benzoate in the presence of KO^tBu (Table 1)
- the influence of base and phase transfer agent for the

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Table 1. Reaction of ethylbenzoate (**1**, R=C₆H₅) with several amines **2** (1.5 equiv.) in the presence of KO^tBu (2 equiv.) for 10 min at 150°C

Entry	R'	Aliquat 336	Yield 3 (%) ^a	
			MW	Δ
1	C ₆ H ₅	–	88	73
2		+	90	83
3	C ₆ H ₅ CH ₂	–	84	42
4		+	98	85
5	<i>n</i> -C ₈ H ₁₇	–	80	22
6		+	87	70

^a Yield in isolated product.

reaction of *n*-octylamine (which led to the large effects in Table 1) with several esters (Table 2)

- the influence of the ester substituent (R) in its reaction with aniline (which led to the smaller effects in Table 1)
- the influence of temperature in the case of ethyl caproate (**1**, R=*n*-C₅H₁₁) with aniline (Table 3), as only very weak or no effects were observed at 150°C (Table 4).

The microwave effects are rather important and noticeably depend on the nature of amine substituent R': *n*-C₈H₁₇ > C₆H₅CH₂ > C₆H₅ (entries 1, 3, 5). They are shown to be strongly lowered in the presence of a phase transfer agent (entries 2, 4, 6).

In the absence of base, an important specific microwave effect was observed with ethyl phenylacetate (entry 10/MW:Δ=63:13). The effect was largely decreased when KO^tBu and Aliquat 336 were involved (entry 11).

Table 2. Reaction of *n*-octylamine (**2**, R'=*n*-C₈H₁₇, 1.5 equiv.) with several esters **1** for 10 min at 150°C

Entry	R	KO ^t Bu (2 equiv.)	Aliquat (10%)	Yield 3 (%) ^a	
				MW	Δ
7	C ₆ H ₅	–	–	0	0
8		+	–	80	22
9		+	+	87	70
10	C ₆ H ₅ CH ₂	–	–	63	13
11		+	+	70	50
12	<i>n</i> -C ₈ H ₁₇	–	–	25	20
13		+	+	83	70

^a Yield in isolated product.**Table 3.** Reaction of aniline (**2**, R'=C₆H₅, 1.5 equiv.) with several esters **1** in the presence of KO^tBu (2 equiv.) at 150°C

Entry	R	Time (min)	Aliquat (10%)	Yield 3 (%) ^a	
				MW	Δ
14	C ₆ H ₅	10	–	88	73
15		10	+	90	83
16	C ₆ H ₅ CH ₂	2	+	98	33
17	<i>n</i> -C ₅ H ₁₁	2	–	92	73
18		2	+	84	83

^a Yield in isolated product.**Table 4.** Temperature effect for the reaction of ethyl caproate (**1**, R=*n*-C₅H₁₁) with aniline **2** (R'=C₆H₅, 1.5 equiv.) in the presence of KO^tBu (2 equiv.) within 2 min

Entry	Temperature (°C)	Aliquat (10%)	Yield 3 (%) ^a	
			MW	Δ
19	150	–	92	73
20	120	–	82	73
21	90	–	79	53
22	150	+	84	83
23	120	+	87	52
24	90	+	74	45

^a Yield in isolated product.

Excellent yields were obtained in all cases. The most important specific microwave effect was observed in the case of ethyl phenylacetate (entry 16). They were relatively moderate when the reaction was carried out in the absence of a phase transfer agent (entries 14 and 17) and decreased in its presence (entries 15 and 18).

Both in the presence or absence of Aliquat 336, the microwave effect was enhanced when the temperature was decreased from 150 to 90°C.

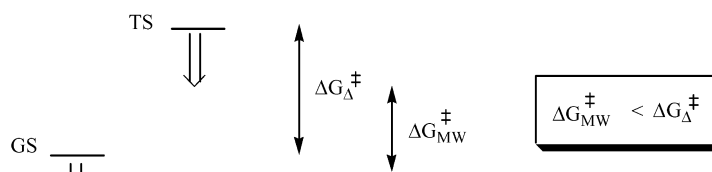
The microwave specific effect shows an increased magnitude when the temperature is decreased. This fact, previously described in the literature^{17–19} is logically connected to a high temperature level which may lead to good yields under conventional heating. To show any effect (catalyst, microwave), it is necessary to reduce the temperature under classical conditions. Those cases can be revealed by lowering temperature to allow the observation of the microwave effect.

3. Discussion

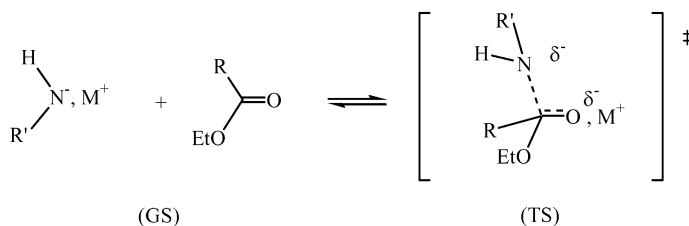
Microwave effects result from material-wave interactions and, due to the dipolar polarization phenomenon, the greater the polarity of a molecule (such as the solvent) the more pronounced the microwave effect when the rise in temperature²⁰ is considered. In terms of reactivity and kinetics, the specific effect has therefore to be considered in relation to the reaction mechanism, and particularly with regard as to how the polarity of the system is altered during the progress of the reaction.

Specific microwave effects can be expected for polar mechanisms, when the polarity is increased during the reaction from the ground state towards the transition state (as more or less implied by Abramovitch in the conclusion of his review in 1991²¹). The outcome is essentially dependent on the medium and the reaction mechanism.²² If stabilization of the transition state (TS) is more effective than that of the ground state (GS), this results in an enhancement of reactivity by a decrease in the activation energy (Scheme 1).

All of these results can be tentatively rationalized considering the mechanisms involved:



Scheme 1. Relative stabilization of a more polar TS when compared to the GS (polar mechanism).



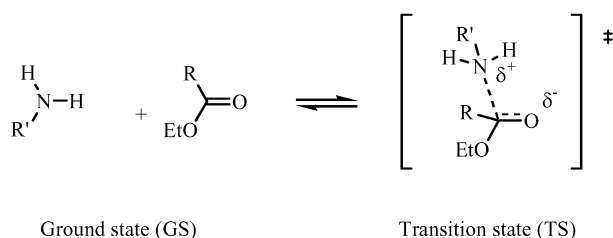
Scheme 2. Mechanism for base induced ester aminolysis.

(1) *In the presence of base* (Scheme 2). The TS for anionic S_N2 reactions involves loose ion pairs as in a charge delocalized (soft) anion. On the other hand, the GS could involve a neutral electrophile and either tight or loose ion pairs depending on:

- the anion structure (hard or soft). When the substituent R' is able to delocalize the negative charge on the amine anion ($R'=\text{Ph}$), the ion pairs $R'\text{NH}^-, \text{M}^+$ exist in a looser association. Consequently, a decrease in microwave effect is expected as the evolution from the $\text{GS} \leftrightarrow \text{TS}$ occurs with only a slight modification of polarity in the ion pairs. Conversely, the microwave effect is optimal with the tighter ion pair ($n\text{-OctN}^-, \text{K}^+$)
- the cation nature. The microwave effect disappears when a bulky cation ($\text{MeN}^+(n\text{-Oct})_3$) is concerned. The effect of the cation and phase transfer is better understood as tight ion pairs $R'\text{NH}^-, \text{K}^+$ gave a far more important effect when compared to loose ion pairs $R'\text{NH}^-, \text{MeN}^+(n\text{-Oct})_3$.

In a parallel study,²² it was shown that formamide, primary and secondary amines react with esters in the presence of potassium *tert*-butoxide under microwave irradiation. Substituted amides are formed in yields (generally more than 70%) much higher than under conventional heating.

(2) *Under neutral conditions* (Scheme 3). The case drawn in Scheme 3 is the most propitious to reveal specific microwave effects as the polarity is evidently increased during the reaction from a neutral ground state to a dipolar transition state which is more prone to microwave interaction than the neutral GS by dipole–dipole interactions.²³



Scheme 3. Mechanism for neutral ester aminolysis.

Alternative reasons for the phenomenon could be possibly advanced dealing with: –the intervention of microscopic localized ‘hot spots’²⁴ as yet advocated to justify sonochemical effects—enhanced interfacial mass transfer—enhancement in collision probabilities (pre-exponential factor in Arrhenius law) due to previous mutual orientation of dipoles along the electromagnetic field (entropic effects).²⁵

To rationalize the polarity enhancement along the reaction processes, we measure the dielectric characteristics (ϵ' and ϵ'') by the method of resonant cavity little perturbations²⁶ and the temperature increase profiles of different mixtures realized under microwave activation. In fact, this behavior gave a good indication of the polarity of these systems characterized by their sensitivity to an electric field. We chose to study the reaction of *n*-octylamine with ethyl phenylacetate under neutral conditions (Table 2). It is first necessary to study the behavior of each species involved in the reaction (Fig. 1).

All of the reactants were heated under microwave irradiation. The amide most strongly interacted with the electromagnetic field. A similar behavior was observed with

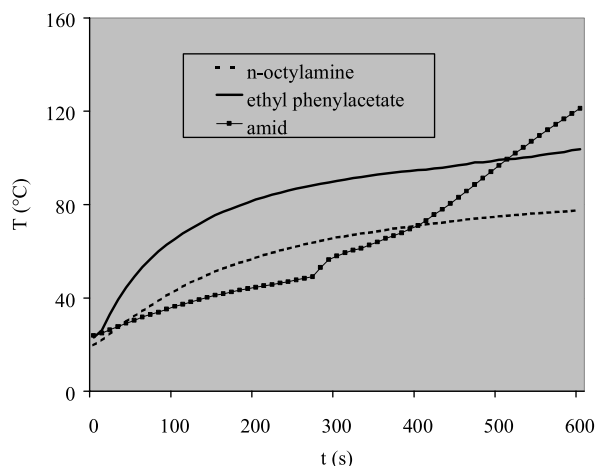


Figure 1. Temperature increase profiles of reactants under microwave irradiation (power=300 W).

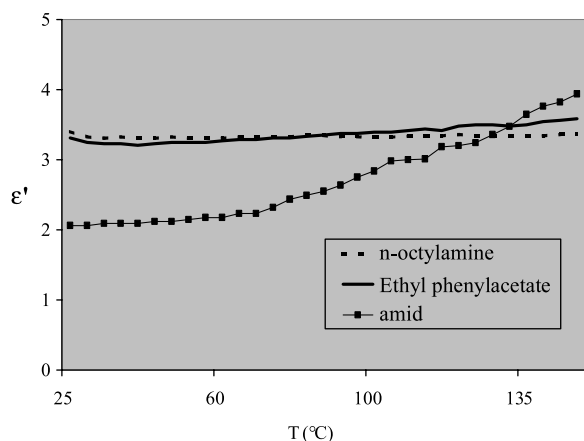


Figure 2. Permittivity ϵ' versus temperature.

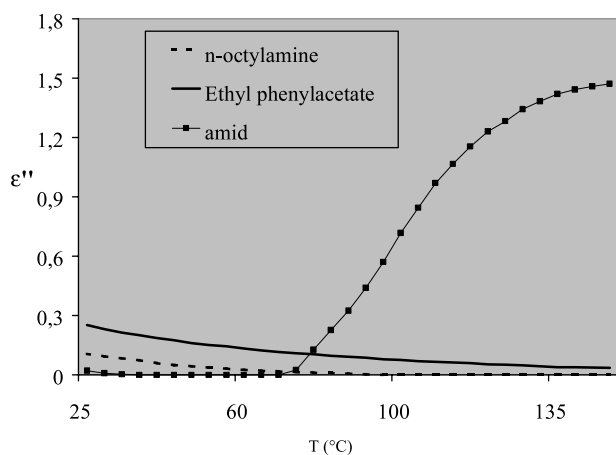


Figure 3. Characteristic of absorption ϵ'' versus temperature.

the dielectric characteristics during temperature increase (Figs. 2 and 3).

The increase of the ϵ' and ϵ'' values with temperature indicated a polarity exaltation in the case of the amide.

On the contrary, in the case of the reactants, the dielectric characteristics varied in small extent. Consequently, the appearance of amide during the reaction promotes a polar

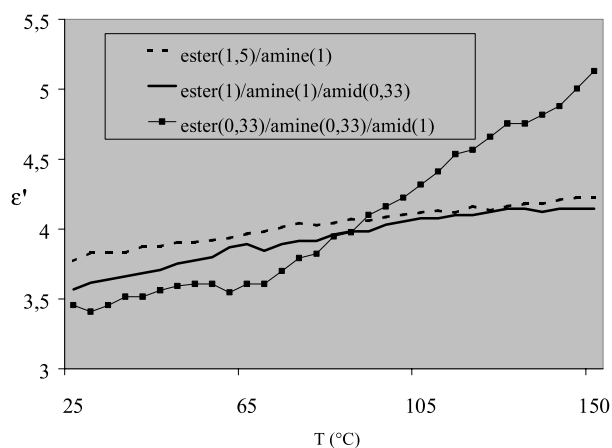


Figure 4. Permittivity ϵ' versus temperature of several mixtures.

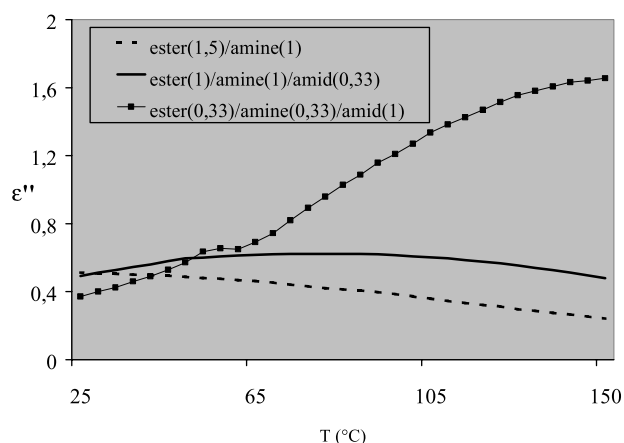


Figure 5. Characteristic of absorption ϵ'' versus temperature of several mixtures.

medium. This is effectively the case when we studied different mixtures (Figs. 4 and 5).

All of these measurements gave a good indication as to the evolution of the polarity between the ground and final states. At the beginning, the reactants are not very polar. When the amide appears in the medium, a polarity exaltation is observed and, consequently, an important effect of microwave activation (Table 2).

This approach is quasi consistent with all the results contained in Tables 1–3. Many rather similar observations can be rationalized in the same way.²² However, there remains the particular behavior of a benzyl group either on the ester or the amine. This could eventually be due to possible π -stacking intervention.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on Brücker AC-250 instruments and IR spectra were recorded on Perkin–Elmer instruments.

4.1.1. Aminolysis of esters. The synthesis of benzanilide is representative of the typical procedure employed. Potassium *tert*-butoxide (2 mmol) was added to a pre-mixed mixture of aniline (1 mmol) and ethylbenzoate (1.5 mmol) in a glass test tube which was placed in a monomode microwave and irradiated for the specified time. The reaction mixture was extracted with dichloromethane. The combined extracts were dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to afford a residue which recrystallized from *n*-pentane: mp 162–165°C; IR 3344, 2924, 1670, 1620, 1545, 745 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.85–7.15 ppm (m, 11H, ArH), ^{13}C NMR (CDCl_3) δ 165, 139, 137, 131–120 ppm.

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