



AROMATIC NUCLEOPHILIC SUBSTITUTIONS UNDER MICROWAVE IRRADIATION

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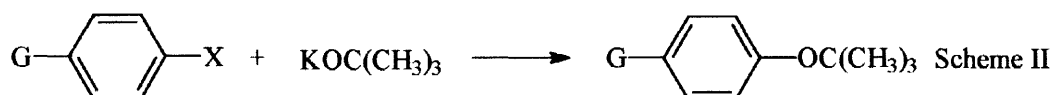
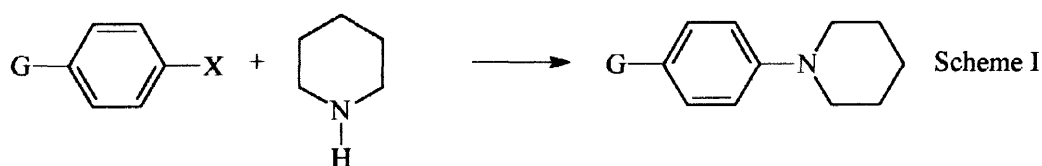
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Abstract: In order to study the effect of microwave irradiation over aromatic nucleophilic substitutions at atmospheric pressure and in a homogeneous medium, experiments with disubstituted-benzenes and the nucleophiles piperidine and potassium t-butoxide, in refluxing DMSO or DMF, were carried out. The aromatic nucleophilic substitutions under microwave irradiation were 2.7 to 12 times faster than under conventional reflux. © 1998 Elsevier Science Ltd. All rights reserved.

Generally, aromatic nucleophilic substitutions are undertaken with difficulty, making them inappropriate for synthesis in the opinion of some authors.^{1,2} Many artifices are used in order to overcome these difficulties: electrochemistry,¹ sonochemistry,³ catalysis by transition metals,¹ more energetic conditions by using stronger nucleophiles, more polar aprotic solvents, and activating effects of electron-withdrawing substituents bonded to the aromatic rings.¹⁻⁵

In order to study the microwave irradiation effect over aromatic nucleophilic substitutions at atmospheric pressure and in a homogeneous medium, experiments with disubstituted-benzenes and the nucleophiles piperidine and potassium t-butoxide, in DMSO or DMF, were carried out (Schemes I and II).



The reactions were run on a Continental 2001 (2.45GHz/500W) adapted with an external reflux system and also under conventional reflux. The products arising were followed using UV-Visible spectroscopy by aliquot withdrawal, and after isolation, the products were characterized by IR and ¹H NMR spectroscopy.

The results showed the same substrate reactivity order^{1,4} (leaving groups: F > Cl \equiv Br > I, activating groups: -NO₂ >> -COCH₃ > -CHO) under microwave irradiation and under conventional reflux. The most reactive substrate was 4-fluoronitrobenzene and the least reactive was 4-iodonitrobenzene (Tables I and II).

Table I: A comparison of reaction time and yield in nucleophilic aromatic substitutions with refluxing piperidine and DMSO as solvent using microwave and conventional heating.

Substrate	Heating*				
	Conventional t _c	Conventional yield %	Microwave t _{mw}	Microwave yield %	t _c /t _{mw}
4-fluoronitrobenzene	30min	94	6min	93	5.0
4-bromonitrobenzene	20h	56	5h	55	4.0
4-iodinenitrobenzene	70h	22	15h	20	4.7
4-fluoroacetophenone	120min	78	25min	80	4.8
4-chloroacetophenone	25h	48	6h	49	4.2
4-bromoacetophenone	50h	23	12h	21	4.2
4-fluorobenzaldehyde	150min	72	35min	74	4.3
4-chlorobenzaldehyde	28h	60	7h	58	4.0
4-bromobenzaldehyde	50h	18	13h	9	3.8

* The results are the mean of three experiments.

Table II: A comparison of reaction time and yield in nucleophilic aromatic substitutions with potassium t-butoxide and refluxing DMSO as solvent using microwave and conventional heating.

Substrate	Heating*				
	Conventional t _c	Conventional yield %	Microwave t _{mw}	Microwave yield %	t _c /t _{mw}
4-fluoroacetophenone	90min	83	7min	81	11.0
4-bromoacetophenone	50h	29	5h	31	10.0
4-fluorobenzaldehyde	120min	79	10min	75	12.0
4-chlorobenzaldehyde	22h	67	120min	68	11.0

* The results are the mean of three experiments.

It is well established that fluoro compounds undergo substitution by various nucleophiles at a rate 100 to 1000 times faster than other halogen analogs,² and the displacement of halogens in 4-haloacetophenones and 4-halobenzaldehydes was found to be 50 to 1000 times slower than in 4-halonitrobenzenes.^{2,4}

The reaction rates of substitutions carried out under microwave irradiation at atmospheric pressure and in a homogeneous medium were 2.7 to 12 times faster than in conventional reflux. This ratio t_c/t_{mw} quantifies the microwave heating effect

For the reactions with piperidine, the rate enhancement magnitudes were modest and substrate-independent (Table I). The best results were for the reactions with potassium *t*-butoxide, an ionic nucleophile, indicating the influence of ionic species concentration in microwave organic reaction enhancement (MORE) due to ohmic effects^{6,7} (Table II).

Table III: A comparison of times and yields in nucleophilic aromatic substitutions with 4-Fluoroacetophenone and piperidine using microwave and conventional heating.

Solvent	Heating*				t_c/t_{mw}
	Conventional t_c	Conventional yield %	Microwave t_{mw}	Microwave yield %	
DMSO	120min	78	25min	80	4.8
DMF	120min	73	45min	75	2.7

* The results are the mean of three experiments.

The microwave induced rate enhancement is also strongly solvent dielectric permittivity dependent. The substitution reaction of 4-fluoroacetophenone with piperidine (Table III) showed a greater ratio in DMSO ($t_c/t_{mw} = 4.8$) than in DMF ($t_c/t_{mw} = 2.7$). The DMSO has higher dielectric permittivity than DMF (Table IV).

Table IV: Static dielectric permittivity of compounds used in aromatic nucleophilic substitutions.^a

Compounds	ϵ_s	Compounds	ϵ_s
4-fluoronitrobenzene	9.48	piperidine ^b	5.80
4-bromonitrobenzene	8.09	DMSO ^b	46.6
4-iodinenitrobenzene	7.12	DMF ^b	36.7
4-fluoroacetophenone	6.05	benzene ^b	2.27
4-chloroacetophenone	5.55	4-piperidinonitrobenzene	48.5
4-bromoacetophenone	4.78	4-piperidinoacetophenone	10.5
4-fluorobenzaldehyde	6.45	4-piperidinobenzaldehyde	11.3
4-chlorobenzaldehyde	5.95	4- <i>t</i> -butoxiacetophenone	8.40
4-bromobenzaldehyde	5.18	4- <i>t</i> -butoxibenzaldehyde	9.12

a) Measured values at 25°C on Dekameter DK03 apparatus; b) Tabled values⁸ at 25°C

The solvent molecules are the majority in the solution, so the solution dielectric permittivity,⁹ ϵ (eq. 1, X is the molar fraction), is almost the solvent dielectric permittivity (eq. 2). The energy dissipation is mainly due to solvent dipolar losses¹⁰⁻¹² in a heterogeneous way,¹³ characterized by the occurrence of carbonizations.

$$\epsilon_{\text{sol}} = \epsilon_1 X_1 + \epsilon_2 X_2 + \epsilon_3 X_3 \dots \text{ (eq. 1) and}$$

$$\epsilon_{\text{sol}} \cong \epsilon_1 \quad \text{(eq. 2)}$$

Ionic reaction rate enhancements induced by microwave heating or by ultrasound irradiation¹⁴ are similar. It suggests that similar forces may be responsible for these enhancements: hot spots are produced due to electromagnetic wave (microwaves)^{6,13,15-17} and mechanical wave (ultrasound)¹⁴ interaction with the reaction solutions.

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