Solvent-Free Microwave-Assisted Aromatic Nucleophilic Substitution – Synthesis of Aromatic Ethers

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Specific (not purely thermal) microwave effects are shown to be highly dependent on the nature of the nucleophilic ion pairs and on the substituents and leaving groups on the aromatic substrates. This can be interpreted in terms of a polarity enhancement during the progress of the reaction and a shift of the position of the transition state along the reaction coordinates.

Industrially important aromatic nucleophilic substitutions (S_NAr) generally afford only moderate yields under harsh conditions.[1] They are most commonly carried out on activated aromatic substrates bearing electron-withdrawing groups.

A considerable improvement was achieved through the use of solvent-free solid/liquid phase-transfer catalysis (PTC) conditions, which gave promising results but often at elevated temperatures with rather long reaction times.[2,3] A new case of solvent-free PTC, for instance, has recently been published, demonstrating *N*-arylation of pyrrolidinofullerene at 150 °C with K_2CO_3 in the presence of $n\mathrm{Bu}_4\mathrm{NBr}$ as phase-transfer agent.[4]

Also recently, a few publications exploiting microwave activation for S_NAr reactions with activated aromatic halides have appeared. The authors described the use of polar solvents in several reactions:

a) Ethoxylation of *o*-chlorophenol or *p*-nitrochlorobenzene in ethanol[5,6]

b) Reactions with *tert*-butoxide and *p*-fluorobenzaldehyde in DMSO[7]

c) Coupling of amino acids with 2,4-dinitrofluorobenzene in water in the presence of sodium bicarbonate.[8]

Only one case of solvent-free S_NAr on basic alumina as support has been described; for reactions between cyclic amines and activated (*p*-CHO, *p*-NO_2) chlorobenzenes. Unfortunately, however, there was deficient temperature control and no comparison with conventional heating.[9]

In this study, we developed some S_NAr reactions involving different alkoxide anions (RO^- with R = alkyl, phenyl) by combining two complementary technologies: solvent-free PTC conditions and microwave activation, with noticeable effectiveness.[10,11] The aim of these experiments was twofold: i) improvement over classical reaction conditions, and ii) explanation of microwave effects in terms of substituents, halides and nucleophiles.

In order to check for a possible specific (not purely thermal) microwave effect, a monomode reactor involving focused waves and accurate temperature measurement by IR detection was used in preference over a multimode domestic oven.[12] Comparisons between microwave activation and conventional heating (Δ) could thus be made under similar conditions of time, temperature, pressure etc., and with identical temperature rise profiles.

Regarding the goal of a general interpretation of specific microwave effects, we can assume that these will be favourable if the polarity of the transition state is increased during the reaction (microwave–materials interactions are enhanced with polarity).[13] This should therefore be the case for reactions in which the transition state (TS) is more polar than the ground state (GS) (Figure 1).[24a]

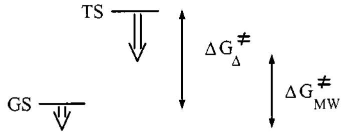

Figure 1. Relative stabilization of transition state (TS) and ground state (GS) by dipole–dipole interactions with electromagnetic field if TS is more polar than GS

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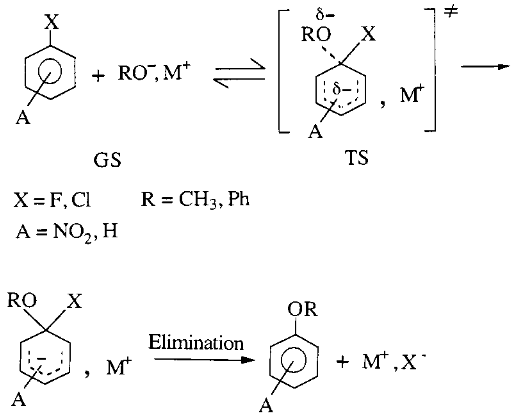
We selected some S_NAr cases in which it can be assumed that the mechanism involves an addition/elimination, and in which the addition is the rate-determining step (Scheme 1).[1a,14] This must effectively be the case when a fluorinated compound is more reactive than a chlorinated one.



Scheme 1. Addition-elimination S_NAr mechanism

Microwave effects may be dependent on the polarity increase between TS and GS, but also on the position of the TS along the reaction coordinates.[24b] If it is a reactant-like TS, as in "easy" reactions, microwave effects should be lessened. If, however, a product-like TS, for "difficult" reactions is involved, they will be more important. They might be affected by:

a) Ion-pairing between RO^- and M^+: If tight ion pairs (involving hard anions, such as CH_3O^-) are involved, modification of ion pairs in the TS (loose ion pairs) will be accompanied by a large increase in polarity and therefore a rather large microwave effect. If loose ion pairs (with soft anions, such as PhO^-) are involved, modification in polarity up to the TS will be limited, and microwave effects should consequently be less important.

b) Halide effects: Fluoro compounds are much more reactive than the corresponding chloro derivatives, and consequently need less activation energy. The transition state therefore occurs early along the reaction coordinates (reactant-like), and so microwave effects could be less effective than chloro compounds.

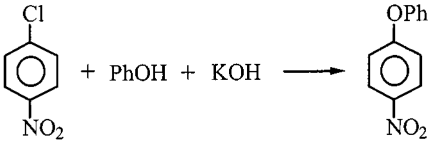
c) Aromatic substituent: Electron-withdrawing and activating groups, such as NO_2, should induce a more reactant-like TS than H would. As some model substrates, we selected 4-nitrophenyl halides and α-naphthyl halides, on the assumption that specific microwave effects might be increased in the latter case.

However, we have to take into account that the reactivity of naphthalene derivatives may sometimes be considered as borderline in nucleophilic substitutions, with possible competition between electron transfer and S_NAr pathways.[15,16]

Results

Reaction of the Phenoxide Anion with *p*-Chloronitrobenzene

The effects of several phase-transfer catalysts, including tetraalkylammonium salts ($Bu_4N^+Br^-$ = TBAB and $MeOct_3N^+Cl^-$ = Aliquat 336), a crown ether and TDA-1,[17] were investigated (Table 1).



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(1)

Table 1. Synthesis of 4-nitrophenyl phenyl ether (**1**) by microwave irradiation (MW) or by conventional heating in an oil bath (Δ) under otherwise identical conditions

Entry	Catalyst	Reaction time [min]	*T* [°C]	Yield (MW) (%)	Yield (Δ) (%)
1	–	2	150	38	24
2		3		43	26
3		5		57	40
4		10		87	64
5	Aliquat	2	150	49	33
6		3		71	40
7		5		84	60
8		7		85	88
9	TDA-1	2	140	83	37
10		5		87	61
11	18-crown-6	2	140	83	61
12		5		93	86

The positive effect of catalysts was evident after 2 min (Entries 1, 5, 9 and 11). When the reaction time was extended to 10 min, though, the yields were essentially the same even in the absence of catalyst. TDA-1 and 18-crown-6 appeared to be the most efficient catalysts (Entries 1, 9, 11), while Aliquat 336 required extended reaction times to give equivalent yields (Entry 7).

When, for comparison with microwave activation (Entry 3), similar reactions were performed at 150 °C with a thermostatted oil bath for the same time interval, with similar temperature rise profiles (Figure 2) and in the absence of a catalyst, the yields were only 40%. This suggested the intervention of a specific microwave effect, which also seemed to be of similar intensity in the presence of catalysts (Entries 3, 7, 10 and 11).

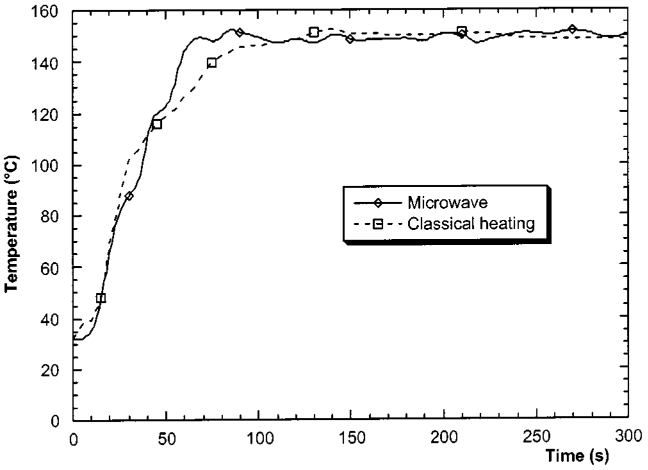
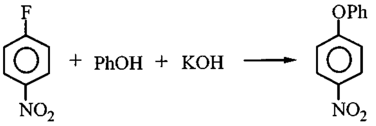


Figure 2. Temperature rise profiles under microwave or classical heating conditions for the reaction depicted in Equation (1) in the absence of catalyst (Entry 2)

Reaction of the Phenoxide Anion with *p*-Fluoronitrobenzene

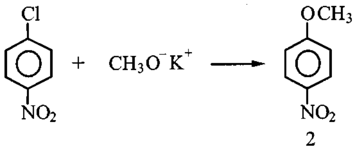
The reaction was performed in the absence of any catalyst. At 150 °C, we obtained a 98% yield under microwave conditions and 73% by conventional heating both within 30 s.



(2)

Reaction of the Methoxide Anion with *p*-Chloronitrobenzene

The effects of the nature of the catalyst were studied under microwave conditions for reactions at 125 °C over 30 min. The key results are given in Table 2.



(3)

Table 2. Synthesis of *p*-nitroanisole (**2**); microwave (MW), 125 °C, 30 min

Entry	Phase-transfer agent	Yield (MW) (%)
13	–	38
14	18-crown-6	58
15	Aliquat	68
16	TDA-1	78

TDA-1 was shown to be the most efficient catalyst (Entry 16), presumably because of its high thermal stability.[17] The best yield obtained after optimization was 90%, after microwave irradiation for 20 min at 170 °C. With conventional heating (oil bath), the yield was only 37% under similar conditions and with broadly matching temperature rise profiles (Figure 3).

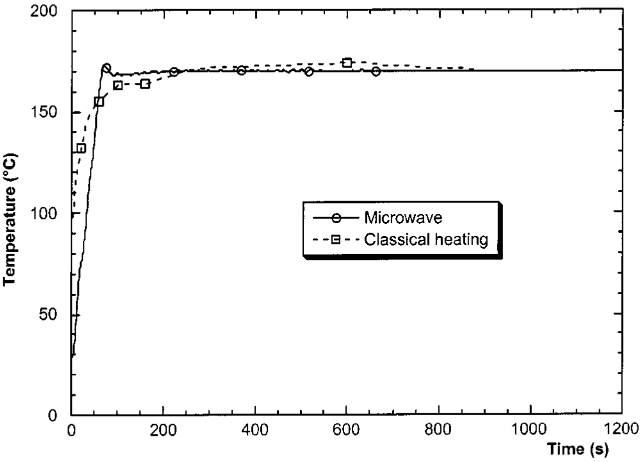
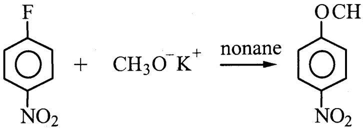


Figure 3. Temperature rise profiles under microwave (MW) or classical heating (Δ) conditions for the reaction of Equation (3); catalyst = TDA-1

Reaction of the Methoxide Anion with *p*-Fluoronitrobenzene

This reaction needed to be performed in the absence of a phase-transfer agent in order to prevent denitration,[18] which was observed even at room temperature in the presence of TDA-1.

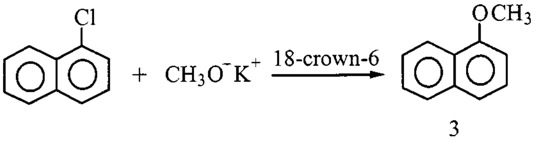


(4)

Under microwave irradiation conditions, the presence of a nonpolar solvent (nonane) was essential for accurate control and constancy of the temperature. A quantitative yield was obtained within 3.5 min at 80 °C, against only 81% by conventional heating under the same conditions.

Reaction of the Methoxide Anion with 1-Chloronaphthalene

This reaction was studied under microwave irradiation conditions over a wide temperature range for purposes of optimization (Table 3).



(5)

Table 3. Synthesis of 1-methoxynaphthalene (**3**) under microwave (MW) conditions [Equation (5)]

Entry	Reaction time [min]	*T* [°C]	Conversion (%)	Yield (MW) (%)
17	30	170	100	27
18	30	150	98	38
19	30	120	91	52
20	60	100	80	71
21	90	100	86	74

The best result was obtained at 100 °C (Entries 20, 21) with a 74% yield of **3** (conversion 86%) and a reaction time of 90 min. At higher temperatures, conversions were nearly quantitative (Entries 17, 18) but yields were rather poor (27, 38 and 52% at 170, 150 and 120 °C, respectively), indicative of secondary or subsequent reactions. Some by-product formation was observed under these conditions:

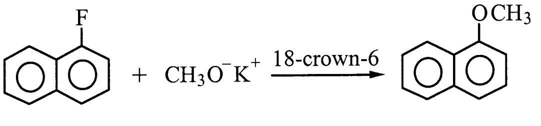
− α-naphthol, which resulted from a demethylation of **3**, which has already been reported to be favoured under these microwave solvent-free conditions[19]

− naphthalene, presumably originating from a radical mechanism

The same reaction as in Entry 20 (1 h at 100 °C) was performed under similar conditions but provided only a 27% yield of **3** under classical heating conditions with identical temperature rise profiles (conversion 41%). Reaction times were extended to 12 h at 100 °C in the oil bath. Although the degree of conversion was now 90%, the yield of **3** was limited to 69%. It thus appeared that secondary reactions were slightly suppressed under microwave irradiation conditions, since differences between conversions and yields were lessened in this case.

Reaction of the Methoxide Anion with 1-Fluoronaphthalene

The optimal conditions for this reaction were found to be at 80 °C for 1 h, (conversion and yield of **3** 94%). Under conventional heating conditions, the conversion was 74% and the yield of **3** only 52%, with some unidentified by-products. It was also obvious in this case that microwave conditions afforded purer products than classical heating, during which some secondary by-products were formed.



(6)

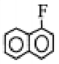
Discussion

Improvements in the Experimental Conditions in Comparison with Classical Procedures

The results that we obtained with a solvent-free/microwave procedure clearly constitute a noticeable improvement over previous conditions. In general, highly polar solvents such as DMF, NMP or HMPA have previously been used.[20] Although the results were sometimes satisfactory, the problem here lies in the use, cost, purification and removal of these solvents. Polar solvents can therefore advantageously be replaced by a solvent-free method and the use of microwave irradiation.

Another classical method consists of the addition of copper salts or copper oxides[21,22] to aromatic bromo compounds in the Ullmann synthesis of aryl ethers by a radical process. With solvent-free PTC, noticeable improvements were observed in comparison of microwave-assisted reactions with classical heating. Comparative results for the reactions depicted in Equations (1), (4) and (5) are given in Table 4.

Table 4. Solvent-free PTC S_NAr reactions

Reaction	Catalyst	Mode of activation	Reaction conditions	Yield (%)
 + PhOH + KOH	TDA–1	Δ	4 h 120°C	99 [2]
	"	MW	5 min 140°C	87
	18-crown-6	MW	"	93
 + $CH_3O^-K^+$	TDA–1	Δ	24 h 150°C	24 [2]
	18-crown-6	MW	1 h 100°C	71
 + $CH_3O^-K^+$	TDA–1	Δ	24 h 100°C	93 [2]
	18-crown-6	MW	1 h 80°C	94

Phase-Tansfer Agent Effect

The addition of a phase-transfer agent is highly beneficial in the case of reactions involving tight ion pairs (with hard anions, such as CH_3O^-) (cf. Table 2) because it results in more dissociated and lipophilic species after cation complexation or ion pair exchange with tetraalkylammonium salts [Equation (7)].

$$CH_3O^-,K^+ \;+\; \bigcirc \;\rightleftharpoons\; CH_3O^-,\textcircled{K^+}$$

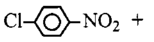
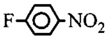
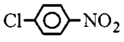
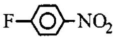
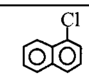
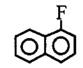
$$CH_3O^-,K^+ \;+\; NR_4^+,X^- \;\rightleftharpoons\; NR_4^+,OCH_3^- \;+\; K^+,X^- \tag{7}$$

TDA-1 and 18-crown-6 were shown to be the most efficient phase-transfer agents (Tables 1 and 2). Tetraalkylammonium salts could be used under limited conditions, although these were less thermally stable due to Hofmann degradation when subjected to rather high temperatures.[23]

The enhancement was less significant with the ion pair PhO^-,K^+. The reaction with activated substrates was able to go to completion even in the absence of catalyst, the soft anion PhO^- and the already loose ion pair PhO^-,K^+ being sufficiently lipophilic and soluble in the organic phase (the aromatic halide) as to promote the reaction.

When the less reactive naphthyl halides were used, the addition of a phase-transfer agent was a necessity, as no reaction occurred in its absence.

Table 5. Comparison between classical heating (Δ) and microwave activation (MW) according to the reactions

Entry	Reaction	Catalyst	Reaction conditions	Yield (%) MW	Yield (%) Δ
22	 + PhOH + KOH	–	2 min 150°C	38	24
23	"	–	3 min 150°C	43	26
24	"	18-crown-6	5 min 150°C	93	86
25	 + PhOH + KOH	–	30 s 150°C	98	73
26	 + $CH_3O^- K^+$	18-crown-6	20 min 170°C	90	37
27	 + $CH_3O^- K^+$	–	3.5 min 80°C	100	81
28	 + $CH_3O^- K^+$	18-crown-6	1 h 100°C	71	27
29	 + $CH_3O^- K^+$	18-crown-6	1 h 80°C	94	52

Microwave-Specific Effects

Some comparisons between microwave and conventional heating are summarized in Table 5.

The differences in behaviour can be interpreted by considering the enhancement in polarity of the system during the progress of the reaction and in terms of the structure of the reactants. It appears that specific microwave effects and their magnitude are clearly dependent on:

− the nature of the reactive ion pairs: (i) In the absence of catalyst (Entry 23) − that is, when PhO^- and K^+ are involved − the microwave effect is more important than when crown ether is present (Entry 24). This is consistent with the existence of tighter ion pairs in the first case and, consequently, with an increase in the magnitude of the enhancement of the polarity towards the transition state (TS), which produces looser ion pairs. In the second case, this effect with PhOK (crown ether) is decreased because of the polarity, which remains fairly similar between the ground state and the transition state. (ii) CH_3O^-,K^+ (involving a hard anion) is a tighter ion pair than PhO^-,K^+ (soft anion). Modification of the polarity up to the transition state (loose association), and hence specific microwave effects, is more important (compare Entries 24 and 26).

− the substituents on aromatic substrates: (i) The nature of the halide affects the microwave effect, with Cl > F (Entries 22 and 25, 28 and 29), consistently with a TS later along the reaction coordinates with the less reactive compounds. (ii) The aromatic substituent is responsible for a stronger microwave effect (Entries 28 and 29) in the case of nonactivated substrates.

As to the relative importance of radical and S_NAr pathways, we have here some indications that microwave irradiation is preferable to S_NAr since it minimizes the amount of by-products. As far as competitive mechanisms are concerned, starting from the same ground state, one might thus expect that the more polar transition state − the S_NAr one − would be favoured under microwave conditions.

Experimental Section

Typical Experiment with Potassium Methoxide: 18-Crown-6 (0.5 mmol, 10%) was added to the aromatic substrate (5 mmol) and potassium alkoxide (7.5 mmol). The mixture was introduced into a Pyrex vessel adapted to the microwave equipment (Synthewave 402 monomode reactor from Prolabo) fitted with a mechanical stirrer. S402 software permitted programming in time and monitoring of the temperature by modulation of the power from 15 to 300 W. Irradiation was carried out according to the conditions indicated in the Tables. At the end of the reaction, the organic products were extracted into diethyl ether, and filtration through Celite 545 was carried out. The products were identified (GC-MS, NMR) by comparison with authentic samples and analysed by GC (internal standard = α-naphthol). Under conventional heating conditions (thermostatted oil bath), the same conditions were reproduced (time, pressure, glassware, stirring and identical temperature rise profiles). Under microwave conditions, the temperature was monitored with an infrared detector and calibrated with an optical fibre thermometer inside the reaction medium. Under conventional heating conditions, the temperature was measured with an optical fibre thermometer inside the medium. With nitro aromatic substrates, only 1.2 equiv. of PhOH/KOH was used. GC conditions, equipment: GC 6000 Carlo Erba; capillary column: 12QC2/BP1, 12 m, film thickness 0.1 µm; programming temperature: 80−250 °C, 10 °C/min; carrier gas: helium, $p = 0.70$ bar.

Acknowledgments

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