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PAPER

Microwave role in the thermal induced $S_{RN}1$ reaction for α-Arylation of Ketones

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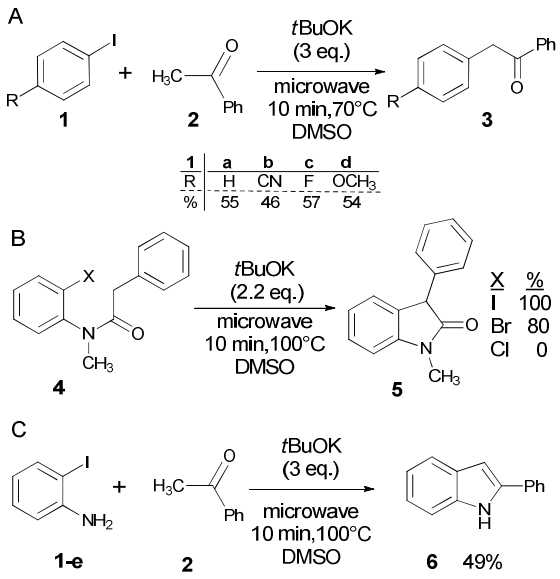
The coupling between iodobenzene and enolate anion from acetophenone is accelerated by microwave irradiation. This increase in reaction rate is only ascribed to thermal effects. The coupling reaction gave the corresponding substitution product 1,2-di-phenylethanone in a 50% yield when microwave irradiation was applied between 15 - 60 sec according to the intensity of the pulse. Moreover, this reaction is effective in a temperature window of 70 -120 °C. The presence of ionic and dipolar species is not involved in the initiation process as molecular radiators. The excess of *t*BuOK in the reaction medium may also act as electron donor helping to generate radicals when the solution temperature increases to 70 °C.

Introduction

The use of modern microwave heating devices proves valuable in pharmaceutical and fine chemistry offering a faster and safer synthetic methodology than conventional heating procedures.[1] Thus, the combination of microwave heating with a process that involves an electron-transfer (ET) step to generate radical anions and radicals to achieve new C-C bonds, such as the Unimolecular Radical Nucleophilic Substitution or $S_{RN}1$, is particularly attractive.[2] The $S_{RN}1$ mechanism is an important route for the synthesis of carbocycles and heterocycles by ring-closure reactions, such as indol derivatives with interesting pharmacological properties, and for a significant number of natural products.[3]

Recently we report the use of microwave irradiation for the formation of new C-C bond in the α-arylation of aromatic ketones and acetamides by the $S_{RN}1$ mechanism (Scheme 1).[4] This was the first report of microwave-induced $S_{RN}1$ reaction in the aromatic system. The microwave-induced reaction showed as many advantages as those related to simplicity, shorter times (10 min of microwave irradiation compared with 120 min of photoirradiation), compatibility with substituents such as CN, F, OCH_3, and a better performance in the intramolecular formation of 2-oxindol derivatives as compared to photoinduced reactions. Accordingly, this process allows the synthesis of 2-aryl-1-phenyletanones (**3**) by α-arylation of the enolate anion of acetophenones (**2**) with different haloarenes (**1**) (Scheme 1 A). The main problem under these reaction conditions concerns the enolate/ketone aldol condensation that reduces the effective concentration of the nucleophile and hinders the purification process. In addition, this methodology provides a simple way to achieve heterocycles such as 1-methyl-3-phenylindolin-2-one (**5**) and 2-phenylindol (**6**) by intra- or intermolecular $S_{RN}1$ reactions, respectively, in a very fast reaction (Scheme 1, B and C). The mechanistic assays showed that these



Scheme1. Microwave induced α-arylation of ketones

reactions proceed by an $S_{RN}1$ mechanism and are thermally induced.[4]

Under microwave irradiation, two phenomena are responsible for the energy transfer from the electromagnetic microwave to the internal energy of the molecules by rotations and collisions. These phenomena involve ionic conduction and dipolar polarization. In the former, the ions move in the solution by the change in the electric field orientation; in the latter, the dipoles try to align through this changing electromagnetic field.[5] Both movements and rotations produce an increase in the collisions of the molecules or ions with their neighborhood. This increment in the internal energy is located around the absorbing species (ionic and dipolar) and the focal point of the microwave. Thus, the so called "molecular Hot

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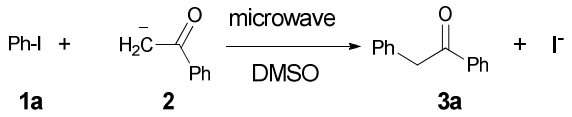
Spots" could undergo a higher local temperature (high internal energy) than the pull solution.[6] In these radical reactions, the initiation step is proposed to take place by a thermal microwave-induced ET. [4]

Nevertheless other theories imply that initial radical formation could be generated by the homolytic C-I bond rupture. This rupture does not come from microwave irradiation itself, but could be promoted in the "Molecular Hot Spots" or by a selective heating produced by molecular radiator as ionic species, i.e. K^+, acetophenone enolate anion, tBuO$^-$ or the neutral molecules with high dipole moments. With the aim of gaining insight into the reaction mechanism under microwave irradiation and of eliminating possible controversial issues about the microwave role in the reaction, we investigate the coupling reaction between acetophenone enolate anion and PhI at different microwave irradiation conditions.

Results and Discussion

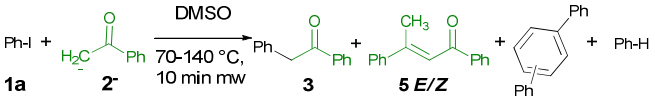
Microwave-induced reactions

The reaction between PhI (**1a**) and the enolate anion of acetophenone (**2**) was taken as a model to explore the effectiveness of microwave irradiation as heating method for thermal initiation, in DMSO (Scheme 2). Table 1 shows the results obtained.



Scheme 1 Microwave-induced α-arylation of acetophenone with phenyl iodide in DMSO.

We reported that a mixture of 0.5 mmol of **1a**, 3 equivalents of acetophenone and 3.1 equivalents of tBuOK after microwave irradiation at 70°C for 10 min in DMSO afforded the substitution product 2-phenylacetophenone (**3a**) in 55% yield, with a conversion of 78% determined by iodide ion quantification (Table 1, entry 1).[4] A similar result was found at 5 and 30 min. Increase in time to 30 min or rise in temperature to 100°C did not show a substantial increase in the yield of substitution product **3a**; however, an increase in the reduction product was shown by the higher iodide ion yield. Furthermore, product **3a** proved to be stable under the reaction conditions. Thus, GC-MS analysis did not show any side-product generated by thermal decomposition at 70-80°C under microwave heating for 10 min., and **3a** was recovered in 84% isolated yield. All attempts to detect the reduced product benzene were unsuccessful.[4] In addition, when the reaction temperature exceeded 120 °C, the presence of terphenylenes was detected and a lower yield of **3a** was achieved, Scheme 3. Terphenylenes are probably produced by further reaction of the phenyl radicals generated in a high local concentration (Scheme S1, Supporting information).[7] As mentioned above, the main reaction side-product **5** derives from the self-condensation of acetophenone enolate anion.



Scheme 3. α-Phenylation of acetophenone enolate anion and side-products.

Table 1. Effect of Base/Nucleophile ratio on **3** yield.[a]

Entry	**2**[b]	tBuOK[b]	Base/**2**	Product **3a**%[c]	I⁻%[d]	**5**
1	3	3.1	1.0	55	78	d
2	10	10.1	1.0	32	nq	d
3	3	5	1.7	52	95	nd
4	3	10	3.3	40	87	d
5	1.5	5	3.3	27	94	nd
6	1	3	3.0	19	88	nd
7	1	2	2.0	25	76	nd

[a]Reactions heated to 70°C by microwave irradiation (150 W_{max}) under N_2 atmosphere for 10 min. Nucleophile = acetophenone (**2**), base = tBuOK, and PhI (0.5 mmol) in 2 mL of DMSO.. [b]Equivalents relative to PhI. [c]Quantified by NMR with internal standard. [d]Determined potentiometrically using a Ag/Ag(I) electrode. d: detected. nd: no detected. nq: no quantified.

Deprotonation of acetophenone (pKa_{DMSO} = 24.7)[8] by the tBuOK (pKa_{DMSO}= 32.2)[9a] is highly favored ($K = 5 \cdot 10^7$); however, 3 equivalents of the base lead to a particularly low amount of remaining ketone that allows the self aldol condensation process at temperatures higher than 60°C. In order to avoid this undesirable side-product, the concentration of tBuOK was increased to favor equilibrium displacement to anion enolate formation (Table 1, entries 2 to 5). In the first attempt, the nucleophile relation was increased to 10 equivalents, with a similar base/nucleophile ratio (Table 1, entry 2). A significant decrease in the yield of product **3** to 32% was found and side-product **5** was clearly detected together with traces of unreacted PhI. The best results were obtained with 5 equivalents of the base, (2.5 mmol), and a base/nucleophile ratio of 1.7 (Table 1, entry 3). In this condition, side- product **5** was not detected and the final purification of the products proves easier than the previous method using **3** equivalents of the base.[10] By increasing the concentration of tBuOK with a base/nucleophile ratio to 3.3, product yield was not improved (Table 1, entry 4). When acetophenone was reduced to 1.5 eq, but not tBuOK (5 eq), in a base/nucleophile ratio of 3.3, the yield of product **3** decreased to 27%; yet, iodide anion reached 94% yield (Table 1, entry 5). A similar behavior was observed for acetophenone 1 eq and tBuOK 3 and 2 equivalents with 88 and 76% yield of iodide anion, respectively (Table 1, entries 6 and 7). These results support the idea of an electron transfer process from both tBuO$^-$ and acetophenone enolate anions.[11] Nevertheless, these anionic species are always present with their cationic counter ion K^+ that could act as an ionic radiator and generate the superheated molecular hot spot (See below for a discussion).

We have previously established that the reaction follows an $S_{RN}1$ mechanism [4], based on the presence of radical intermediates in the reaction assessed by the use of a radical clock[12] and by the inhibition of the reaction in the presence of a strong electron

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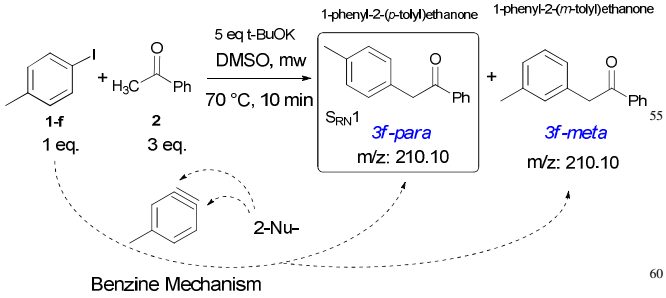
acceptor like *m*-dinitrobenzene,[3] affording 14% yield of product **3a** and 21% conversion yields.

In order to evaluate whether a benzyne mechanism can compete with $S_{RN}1$ in the presence of an excess of base, the reaction was performed using 0.5mmol of 4-methyl iodobenzene (**1f**) as substrate with 3 equivalents of acetophenone and 5 equivalents of *t*BuOK (Scheme 4). A benzyne mechanism will afford equal amounts of *meta* and *para* 1-phenyl-2-(tolyl)ethanone **3f**. A GC-MS analysis of the organic extract of the reaction crude showed two signals with m/z 210.10 with a relative integration of 99% (t_r = 10.4 min) and 1% (t_r = 10.3 min). After purification in a short silica gel column and then by identification and quantification by NMR using an internal standard, only one product was found. NMR reveals a 42% yield of 1-phenyl-2-(*para*-tolyl)ethanone. Taking into account both assays we can assume that the *meta* product represents less than 0.4% (see SI for more details). These results indicate that the $S_{RN}1$ mechanism is the main mechanism involved in product formation.



Scheme 2: Test for benzyne mechanism using 4-methyl iodobenzene (**1f**). The benzyne mechanism affords equals amounts of *meta* and *para* products **3f**, while $S_{RN}1$ mechanism gives ipso-substitution, with formation of only **3f**-*para* product.

Reaction time

In our previous reports we observed a slight difference between 5, 10 and 30 min of reaction times (49%, 55% and 54% yields respectively), and 10 min was selected as standard reaction condition.[4] Now we aim at testing the optimized base/nucleophile ratio of 1.7 vs reaction time at 70°C. After several experiments with microwave heating, any appreciable difference was found in the yields after 1, 3, 5, 10 or 30 min at 70° C (Figure 1). In these cases, the microwave reactor was set at 150 W maximum, 70°C and the corresponding selected time. Hence, in the "dynamic mode", the equipment applies a pulse to reach the setting temperature. Once the reaction reaches 70°C, the timer starts countdown and then, sometimes, ~1W is applied to maintain temperature at 70°C. Figure 1 shows the typical power curve (black solid line) applied for reactions at 1, 3, 5, 10 and 30 min. Notice that similar yields of **3** (light grey) and iodide anion (dark gray) were achieved in all cases. In this way it is possible to reduce the reaction time to less than 1 min. Nevertheless we speculate that all radical reaction could occur during the ~22 sec microwave pulse with a maximum power of ~100W, or in other words, under the application of 1300J to the 2 mL reaction mix in DMSO.

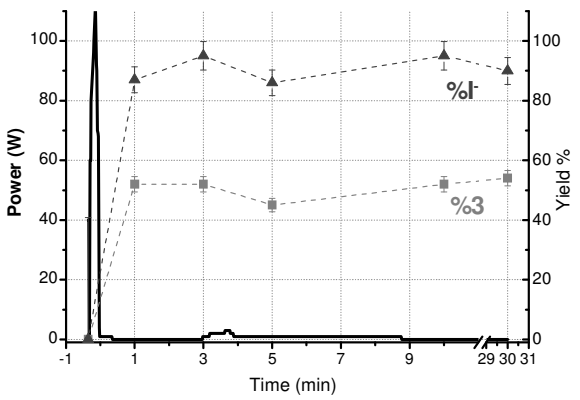


Figure 1. Reactions under N_2 atmosphere heated by microwave irradiation (150 W max) for 30, 10, 5, 3 and 1 min after irradiation. Acetophenone (1.5 mmol), *t*BuOK (2.5 mmol) and PhI (0.5 mmol) in 2 mL of DMSO. In light gray squares, yield of product **3** quantified by NMR with internal standard; in dark gray triangle % I-, determined potentiometrically using a Ag/Ag(I) electrode. Typical power applied to these experiments from the CEM discover Microwave reactor in solid black line.

Microwave Applied Power

Several tests were performed to establish how the microwave power influenced the reaction course. In these experiments a continuous pulse of a fixed power for different times was applied; the sample reached a temperature higher than 70°C. Thus over the pulse application, the temperature reached ~110°C for the 100W pulse and ~90°C for 50W pulse. When the microwave pulse ended, the cooling device started and the temperature slowly decreased to 50°C (the safe release temperature from device). This process took approximately 1.3 min, and the reaction lasted 1 min up to 70°C (Figure 2), the temperature set for the reaction to take place.[4]

A proportional relation between power and temperature increase was obtained using 30 second pulses (Figure 3, red dots line). When we applied more than 50 W by 30 seconds, or 1500J to 2mL DMSO, temperature increased but the yield of product **3**, decreased, probably due to thermal decomposition at more than 140°C. In these conditions terphenylenes were also found. On the other hand, the dehalogenation was near to quantitative at 1500J for 2 mL reaction. At 25 W the temperature reached almost 50°C, and a low yield for **3** and I- was found.

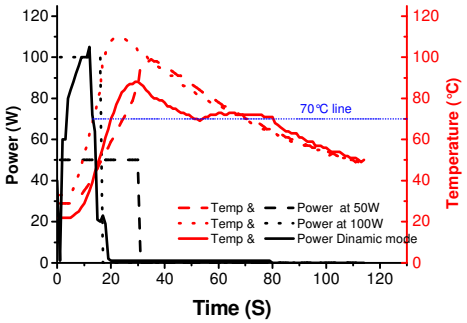


Figure 2: Comparison of temperature (red) and power (black) profiles for dynamic mode heating (solid) and experiments at fixed power at 50W (dash) and 100W (dots).

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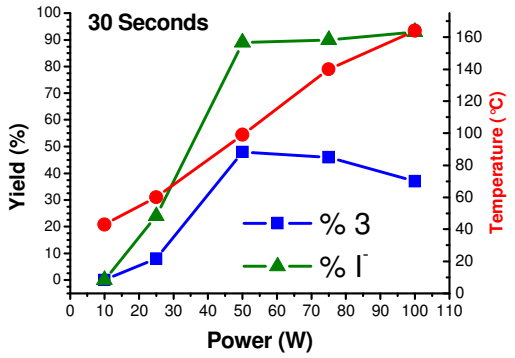

Figure 3: Reaction yields and temperature variation vs. applied microwave power for 30 seconds. Yield of product **3** (%) in blue squares (■) quantified by NMR with internal standard, in green (▲) % I^- determined potentiometrically with Ag/Ag^+ and in red dots (●), maximum temperature reaction determined by IR sensor of the CEM Discover reactor

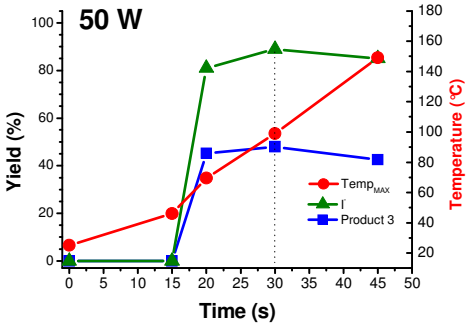

Figure 4. Yield and temperature profiles in the coupling reaction of 0.5 mmol PhI, 1.5mmol acetophenone and 2.5 mmol *t*BuOK heated by microwave with pulses of 50 W vs time. Blue squares (■), product 3 % yield, quantified by NMR with internal standard, % I^- determined potentiometrically with Ag/Ag^+ in green ▲, and temperature by IR sensor inside the CEM Discover reactor in red ●.Doted lines indicate 1500 J point.

With the aim of determining whether the yield of coupling product 3 was related to temperature or power applied, the model reaction was tested with fixed pulses of 100, 50, 25 and 10 W, by different times (Figure 4, and Figure S2 in the Supporting Information). It is noteworthy that **3** yield is always near ~50% when the microwave energy applied is 1500J, similar to the ~1300J applied in the fixed 70°C experiments. In each case when the reaction temperature exceeded 120°C, the yield of **3** decreased; however if the reaction did not reach 70°C, the yield was much lower than 50%. These results suggest that the reaction conversion depends more on the temperature reached than in the microwave pulse intensity. It should also not exceed 120°C to avoid thermal decomposition of the product and side reactions.

The model reaction was then studied by varying the microwave irradiation method in order to establish a relation between the energy and the yield of **3** (Table 2). A comparison between the different irradiation methods did not show a clear relation with the energy applied. It should be noted that total energy refers to the emitted pulse by the reactor, and not to the accurate microwave energy absorbed. The total energy applied to reach 70°C depends on the reaction volume used. As mentioned before, in the dynamic mode, all samples received between 1000 – 1859 J; yet, this did not depend on the full reaction time. The total energy was commanded by the IR temperature sensor to modulate the microwave power applied. However, in all cases 70°C were achieved and the yields of product **3** and I^- were similar. (Table 2, entries 1-4)

Considering that some problems with the IR temperature sensor were previously reported,[13] a power fix method for more reproducible assays was selected. Using similar microwave energy of 1500J, independent of intensity and time pulse irradiation, the reaction gave the same global results (Table 2, entries 5-8).

The same reaction model carried out at 70°C in sealed tubes heated by regular oil bath, pre-heated to 70°C bath, after 10, 30 and 60 min, revealed for product **3** yield of 23, 33 and 50% respectively, (Table 2, entries 9-11). As observed in our previous report no pressure effect was noted, because the reaction carried out at 1 atm. gave similar results.

Apparently at temperatures up to 70°C, 50% of product is the maximum obtained by thermal initiation. Figure 5 shows a collection of several experiments running with different microwave methods. In those cases when temperature reaches 70°C, the coupling yields are near 50%. Lower temperatures produce the decrease of product yield and temperatures higher than 120ºC affect product yield by thermal decomposition. A similar correlation of yield vs. energy makes a more disperse plot (data not shown).

Table 2. Comparison between the reactions heated in an oil bath at 70°C and with microwave under different irradiation methods.

Ent	Method	P (W)	E (J)	t_I (s)	t_R (s)	T_{max} (°C)[a]	**3** %[b]	I^- %[c]
1	dinamic	105[d]	1187	22	1	88	52	87
2	dinamic	100[d]	1215	21	3	84	52	95
3	dinamic	90[d]	1000	23	5	81	45	86
4	dinamic	110[d]	1859	21	10	98	52	95
5	Fixed power	100	1500	15	1	110	49	97
6	Fixed power	50	1500	30	1	99	48	89
7	Fixed power	25	1500	60	1	114	49	87
8	Fixed power	10	1200	120	1	100	53	100
9	oil bath		ϕ		10	70[e]	23	49
10	oil bath		ϕ		30	70[e]	33	58
11	oil bath		ϕ		60	70[e]	50	100

For the coupling reaction of PhI (0,5 mmol) and 3 eq acetophenone, 5 eq *t*BuOK in 2 mL DMSO. P: power. E: energy. t_I: irradiation time.t_R: reaction time. [a] Temperature measured by IR sensor inside the CEM Discover reactor except, unless otherwise indicated. [b] Product **3** % yield, quantified by NMR with internal standard. [c] % I^- determined potentiometrically with Ag/Ag^+. [d]Maximum power setting 150W. [e]Temperature determined by standard lab thermometer.

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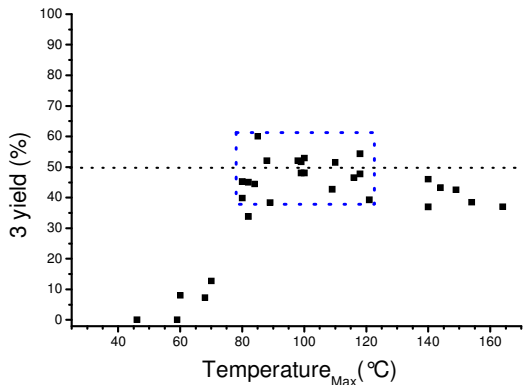
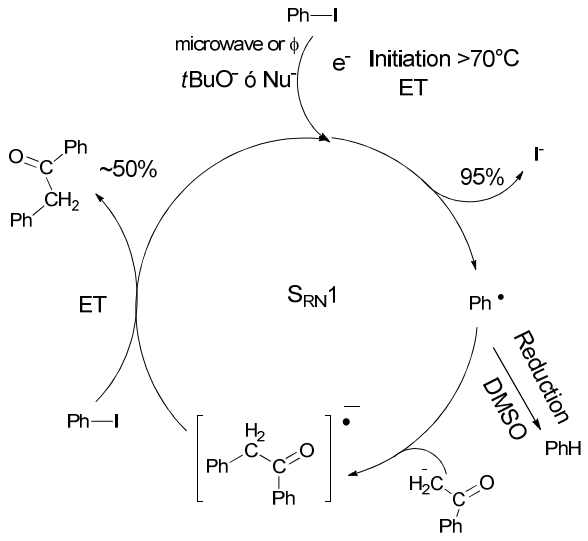


Figure 5: Product **3** yield vs maximun temperature reaction distribution in the coupling reaction of 0.5 mmol PhI, 1.5 mmol acetophenone and 2.5 mmol *t*BuOK heated by microwave. Product **3** % yield (■), quantified by NMR with internal standard. The blue rectangle indicates the 70-120°C temperature window with ~50% yield of **3** and ~90% of I⁻.

Reaction Initiation

Another important issue involved in the reaction mechanism is the initial radical formation step (Scheme 5). In the initiation reaction, a dissociative ET from the present anions *t*BuO⁻ or the enolate anion of acetophenone **2** to PhI generates Ph radical and I⁻ anions. The radical Ph goes into the chain reaction and after coupling with the nucleophile acetophenone enolate anion, a new C-C bond is generated affording the radical anion of 2-phenyl-1-phenyletanone. Then, this radical anion species, by another ET to PhI, gives product **3** and regenerates the Ph radical to continue the chain reaction.[14]

As mentioned before, the maximum yield achieved for this reaction is ~50%, due to a competitive reduction to benzene of Ph radicals mediated by the solvent.[4] Nevertheless, there were some doubts about whether microwave irradiation itself could promote radical formation in this kind of reactions. Is it another case of no-thermal microwave effect? In our previous work, PhI was thermally stable under 10 min of microwave irradiation in DMSO at 70° C (dynamic mode), neither benzene nor iodide ions were detected in those conditions (Table 3, entry 1).[4] Similar results were observed with irradiation at 1 min at 100W by 15 seconds (Table 3, entry 2). This fact allows concluding that homolytic rupture of the C_{Ph}-I bond (67 kcal/mol)[15] is not the radical initiation process. Nevertheless, since PhI and the solvent DMSO have similar dipolar moments (1.8 D), it is possible to consider that both should have a similar microwave absorption (in fact it should be necessary to compare tangent loss[6]; yet, they are not accessible for all the species involved); in addition, in this case there are no ions in the solution to promote the superheated "molecular hot spot". In the model reaction there are various species with high dipolar moment that can act as stronger microwave absorber than DMSO (Figure 6). The *t*BuO⁻ has a dipolar moment of 3.95 D[16] and acetophenone enolate anion has an average dipolar moment of ~8.8 D, considering their resonance forms. Alternatively, the potassium cation K^+ in the solutions could be a strong absorber (by ionic conduction), generating the *molecular superheated hot spots* or receiving a selective microwave heating in relation to the solvent surround. Taking this into account, some tests were conducted. The microwave irradiation of a solution of 0.5 mmol of PhI and 2 mmol of *t*BuOK in 2 mL of DMSO in the absence of acetophenone after 1 min produced dehalogenation at ~85% yield, even when the assay was carried out at 70 or 100°C, (Table 3, entries 4 and 5). When 2 equivalents of KCl or NaCl were used, I⁻ was not found as product by ET dehalogenation of PhI. Potentiometric titration showed only ~2 equivalents of Cl⁻ with a maximum temperature of 97°C and 87°C, respectively (Table 3, entries 6 and 7). These experiments suggest that the ionic species K^+ (or Na^+) and Cl⁻ help the heating process of the solution to raise temperature to 97°C after 15 sec of irradiation at 100W; however, they are not able to initiate the reaction. In addition, when PhBr was employed, the experiment at 70°C produced 27% yield of Br⁻, increasing to 86% at 100°C, Table 3, entries 8 and 9). With MeCOSK, a comparable result was found under similar irradiation conditions. In this reaction the solution reached a higher temperature (125°C) due to the MeCOS- dipole of 4.60 Debye, making it a microwave absorber stronger than *t*BuO-. These results are compatible with the general reactivity pattern of aryl halides in the $S_{RN}1$ mechanism.[3a] In this reaction, the source of initiating electrons could be the nucleophile itself, which transfers an electron to the PhI to generate Ph radical and I⁻ by a dissociative ET.[17,18] In these assays the MeCOS⁻ anion was unable to transfer an electron like *t*BuOK[19], and the radical reaction did not take place because of lack of the initiation step. Any presence of iodide anion was detected and GC-MS analysis also revealed unreacted PhI as the only species present in the organic layer after reaction extraction. Next, the enolate anion of pinacolone was tested as entrainment reactive to initiate the reaction.[3a] When PhI was irradiated in the presence of 2 equivalent of *t*BuOK (pKa = 32.2)[8] with an excess of pinacolone (pKa = 27.7)[7] to ensure the presence of only pinacolone enolate anion and *t*Butanol (K = 31.6 x 10^3), the ionic and dipole species helped the heating process (T_{max} 103°C),



Scheme 5. Main reaction mechanims. For the inter molecular thermal $S_{RN}1$, acelerated by microwave heating.

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but the initiation was poor compared with the reaction being performed by adding an excess of *t*BuOK.

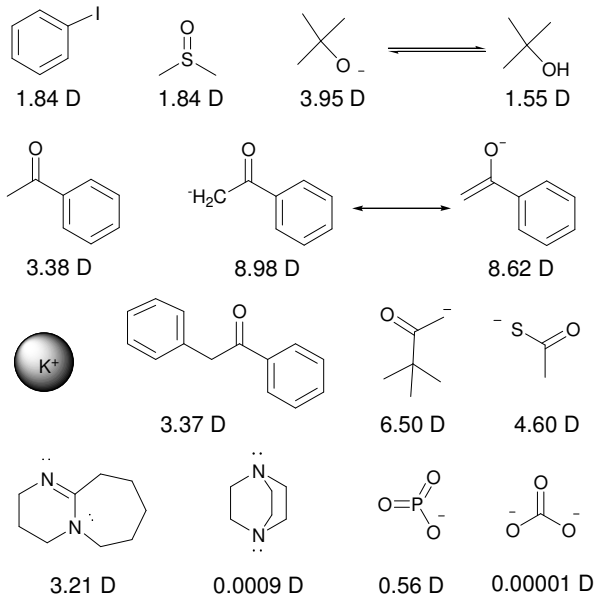
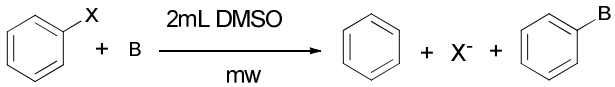


Figure 6: Dipolar moment of the present species in the reaction solution. The values were calculated with GAMESS: Compute Properties RHF/3-21G.

Table 3. Dehalogenation under microwave irradiation.



Entry	X	Method	eq Base	Time min	Temp °C	% X^{-} [a]
1	I	dynamic	--	10	70	0
2	I	fixed power	--	1	89	0
3	I	dynamic	3.3 *t*BuOK	10	70	80
4	I	dynamic	2 *t*BuOK	1	70	82
5	I	dynamic	2 *t*BuOK	1	100	86
6	I	fixed power	2 KCl	1	97	0[c]
7	I	fixed power	2 NaCl	1	87	0[c]
8	Br	dynamic	2 *t*BuOK	1	70	27
9	Br	dynamic	2 *t*BuOK	1	100	86
10	I	fixed power	2 MeCOSK	1	125	0[d]
11	I	fixed power	2 K^{+} $^{-}CH_2COCMe_3$	1	103	44[e]
12	I	fixed power	2 DBU	1	65	0
13	I	fixed power	2 DABCO	1	67	0
14	I	fixed power	2 KCO_3	1	65	0
15	I	fixed power	2 KPO_3	1	68	0

Reaction of 0.5 mmol PhX in 2 mL DMSO with different salts as ionic species in the medium. [a]Determined potentiometrically using an Ag/Ag(I) electrode. [b] From Soria-Castro *et al* ref 4,. [c] 90% of Cl^{-} anions. [d] PhI was detected as the only organic product by GC-MS. [e] With 21% yield of the coupling product with enolate anion of pinacolone.

Other organic bases like DBU and DABCO were employed as possible electron donors in the initiation step, (Table 3, entry 12 and 13). After heating at 100W, the temperature reaches 65°C and 67ºC, respectively, without producing any halogen release. These results are expected if we considered their dipolar moments of 0.0009 for DABCO, and 3.21 for DBU (Figure 6). The last is similar to tBuO^{-} but without the presence of K^{+} counter ion that helps to the heating process. It is important to note that neutral bases like DBU (pKa_{DMSO} 12)[9c] and DABCO (pKa_{DMSO} 2.97, 8.93) [9c], are unable to deprotonate the acetophenone to generate the enolate anion.

Finally, the inorganic bases potassium carbonate and phosphate were also checked (Table 3, entries 14 and 15, respectively). In these examples, cations and anions are present in the reaction mix. In principle, these salts are insoluble in DMSO, but under microwave heating, the solubility would be increased, and the free ions could help to the heating process. Although, for these experiments any traces of dehalogenation were observed, indicating that no ET initial step could be promoted by these bases.

At this point, it is difficult to think of some case of a multiphotonic process in the initial substrate excitation to promote radical formation, because the electromagnetic microwave does not have the necessary energy to break chemical bonds.[6] The required energy jump to break covalent bonds is just so far for these microwave photons. Non radiative process must be involved in the increase of internal energy of the reactive molecules. Microwave irradiation only accelerates the heating process efficiently, but no mysterious or magical microwave effects take place.

This conclusion is in total agreement with that recently reported by Kappe, considering that several no-thermal microwave effects are related to errors in the temperature measurement in the core reaction, leading to misinterpretation of results.[13]

It is possible to conclude that the increment in temperature or in the internal energy of the system by the presence in excess of tBuO^{-} or the nucleophile under microwave irradiation or another heating method could provide the necessary energy to favor electron transfer from the donors to the ArI.[19] Thus, ET from the nucleophile or tBuO^{-} to ArX is produced by a thermal effect. The microwave is a more efficient heating method than conventional heating, and the decrease in reaction time from 60 min to 15 seconds for an oil bath is remarkable.

Conclusions

The use of modern microwave heating devices proves valuable in fine and pharmaceutical chemistry offering a faster and safer synthetic methodology. In this report we studied the process leading to new C-C bonds by α-arylation of aromatic ketones and by $S_{RN}1$ mechanism under microwave irradiation at moderate temperatures. The initiation step is proposed to take place by a thermal microwave-induced ET.

The main disadvantage of microwave-initiated reaction is the competitive reduction observed for the intermolecular process. Consequently, the best substitution yields were about 50%. On the

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other hand, microwave-induced reaction shows as many advantages as simplicity, particularly shorter times, 15 sec of microwave irradiation (plus 1 min to release the sample) compared with 120 min photoirradiation). The ionic and neutral molecules with high dipolar moment in the reaction media could allow a faster heating rate in comparison with that in pure DMSO solvent under microwave. Yet, neither participates in the reaction as catalyst or radical generators initiating the $S_{RN}1$ mechanism. The higher yield was obtained in the 70-100°C temperature windows. 70°C is required to promote the initial ET from the nucleophile or *t*BuO$^-$; however, if temperature exceeds 120°C, the thermal decomposition of substrates and reactives decrease average yields. The use of lower power does not improve product yield and extends reaction time.

Nevertheless, the intramolecular reaction accelerated by microwave irradiation affords good yield and presents a good alternative to photoinduction. The methodology of microwave-induced ET could be applicable to other $S_{RN}1$ examples, mainly in the intramolecular ring closure and in other reactions involving radical rearrangement as well as the addition of radicals to neutral molecules and Homolytic Aromatic Substitution (HAS) reactions.[20] comparative study between photoinduction and microwave in different $S_{RN}1$ ring closure reactions is in progress in our lab.

Experimental Section

Chemicals:

Potassium *ter*-butoxide (*t*BuOK), iodobenzene, bromobenzene, acetophenone, 4-methyl iodobenzene were all high-purity commercial samples used without further purification. DMSO absolute grade was used without further purification and stored over molecular sieves (4 Å).

The ketone enolate anion was generated *in situ* by acid-base deprotonation using *t*BuOK.

General Methods: ^{1}H and ^{13}C NMR spectra were recorded at 400.16 and 100.62 MHz respectively on a 400 spectrometer, and all spectra were reported in δ (ppm) relative to Me_4Si, with $CDCl_3$ as solvent. Gas chromatographic analyses were performed with a flame-ionization detector, on 30 m capillary column of a 0.32 mm x 0.25 μm film thickness, with a 5% phenylpolysiloxane phase. GC-MS analyses were performed employing a 25 m x 0.2 mm x 0.33 μm with a 5% phenylpolysiloxane phase column. HRMS spectra were recorded on a GCT Premie orthogonal acceleration time-of-flight (oa-TOF) GC mass spectrometer. Ionization was achieved by electronic impact (70eV) and detection set up positive mode.

Representative Experimental Procedure: The reactions were carried out in a 10 mL CEM Discover microwave glass vessel, filled with nitrogen and a magnetic stirrer. The tube was dried under vacuum, filled with nitrogen, and then charged with dried DMSO (2 mL) and degassed. For the α-arylation of the haloarene, *t*BuOK (280 mg, 2.50 mmol), acetophenone (1.5 mmol) and aryl halide (0.5 mmol) were then added to the degassed solvent under nitrogen. The reaction tube was subsequently heated by microwave irradiation.

Microwave-induced reactions were performed in a single mode instrument equipped with a noncontact infrared temperature sensor, direct pressure control system for measuring the pressure of the reaction vessel contents and a cooling system by compressed air. Two methods were used. In the first method a temperature controlled reaction at 70°C, with a maximum power of 150 W. Although the maximum microwave power was set at 150W, after the initial heating pulse for 30 sec of maximum 100W, the average power applied was about 1W to keep the selected temperature. Alternatively, the sample vessels were irradiated by microwave at different power settings (100, 50, 25, 10 W) and time (10, 15, 20, 30, 60, 75 seconds) as indicated, and temperature was recorded by the internal IR sensor. After the selected irradiation, the device cooled the tube to 50°C with compressed air above 1 min. (-0.5°C/sec). The average pressure was 1.7 atm in the vessel during the reaction time. After completion of the reaction, the vessel was removed from the microwave cavity and opened to the atmosphere. The reaction was subsequently quenched by addition of water (30 mL) and NH_4NO_3 in excess, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extract was dried over anhydrous $CaCl_2$, and the products were quantified by GC or NMR by the internal standard method. Water layer was recovered to quantify halide ions by potentiometric titration with an $AgNO_3$ standard solution.

Products characterization: All the products in Table 2 were obtained following the general procedure, quantified by NMR or GC. Products **3a** and **3f** are known compounds and present spectral data as shown in the literature, in agreement with the structures proposed. 1,2-di-phenylethanone (**3a**)[21]; 1-phenyl-2-(*para*-tolyl)ethanone (**3f**).[22]

Supporting Information (see footnote on the first page of this article): Typical reaction profile under microwave irradiation and spectra ^{1}H and ^{13}C NMR for **3f**.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Benzyne mechanism evaluation by GC-MS and ^{1}H and ^{13}C -NMR spectra of **3f**. Yield and temperature profiles at different microwave pulses. See DOI: 10.1039/b000000x/

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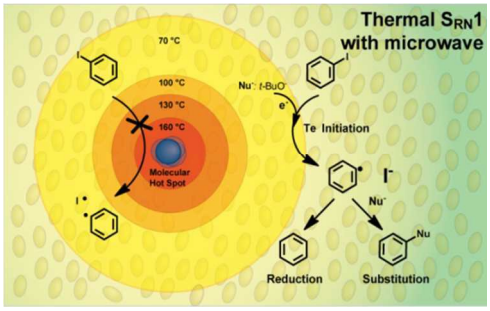
Graphical Abstract and Textual

Microwave irradiation promotes nucleophilic substitution by thermally induced electron transfer mechanism.



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