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PAPER

An Expedient Route to Heterocycles through α -Arylation of Ketons and Arylamides by Microwave Induced Thermal $S_{RN}1$ Reactions

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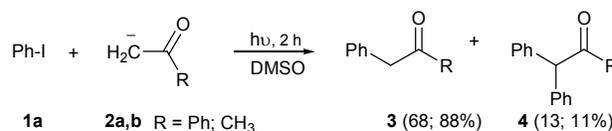
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Microwave irradiation promotes a quick aromatic nucleophilic substitution by a thermally induced electron transfer process to form new C-C bonds by the coupling of aryl radicals and enolate nucleophiles. Diverse 2-aryl-1-phenylethanones can be prepared by the direct α -arylation of acetophenone with different haloarenes. The ketone enolate anion is generated by deprotonation with *t*BuOK in DMSO and the reaction is carried out in a closed microwave vessel at 70-100 °C for 10 min. This simple procedure also allows the synthesis of deoxybenzoin and indol heterocycle derivatives by inter- or intramolecular ring closure reactions, from moderate to excellent substitution yields.

Introduction

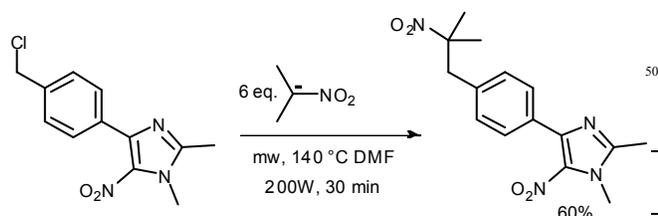
Radical reactions provide a powerful method to achieve new C-C bonds in organic synthesis.¹ The process that involves an electron-transfer (ET) step to generate radical anions and radicals, as the Unimolecular Radical Nucleophilic Substitution or $S_{RN}1$, has proven to be a versatile mechanism for replacing a suitable leaving group by a nucleophile at the ipso position.² This reaction affords substitution in non-activated aromatic (ArX) compounds, with an extensive variety of nucleophiles derived from carbon, nitrogen and oxygen to form new C-C bonds. In addition, 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.² On the other hand, 2-phenyl acetophenones, also known as deoxybenzoin, is a motif present in anti-inflammatory,³ anti-convulsant, analgesic,⁴ and antimicrobial drugs.⁵ These aryl acetophenone structures are also suitable precursors of other interesting compounds, such as oxazoles, pyrazoles, indoles, and fire retardants in polymeric matrixes.^{4,6} This deoxybenzoin (3, R = Ph) and its derivatives can be easily achieved by α -arylation of carbonyl compounds by the $S_{RN}1$ reaction. For example, the reactions of non-activated haloarenes with enolate anions from both aliphatic and aromatic ketons afford substitution under photostimulation in DMSO or liquid ammonia as solvent (Scheme 1).⁷ These reactions had good yield; yet, two or more hours of photochemical induction or the use of chemical radical initiators are required.



Scheme 1. Photostimulated $S_{RN}1$ α -arylation of ketone enolate anions.

The selection of liquid ammonia as solvent requires distillation prior to use, which is energy costly and entails a particular careful manipulation.⁸ The development of new synthetic procedures, which implies simple and safer reaction conditions, is always a challenge for organic chemists. Alternatively, there are some examples of thermally induced $S_{RN}1$ α -arylation of different aliphatic ketone enolate anions with ArI heating at 25 °C for 60 min in DMSO with moderate to good yield.⁹ Nevertheless, under these conditions the enolate anions from aromatic ketons did not react.⁹ In addition, thermal or spontaneous initiated reactions need about 60 min to proceed at room temperature. We consider that this synthetic pathway could be improved by microwave irradiation and be applied to heterocycles synthesis.

In the last decade microwave-assisted organic synthesis (MAOS) has proved an attractive heating method since this system reduces reaction time, increases yields, and in some cases increases selectivity in comparison with traditional oil bath heating.¹⁰ There are a few cases of thermally induced $S_{RN}1$ reactions by microwave irradiation for the substitution of activated nitro benzyl derivatives. Thus, *Vanelle et al* have reported that $S_{RN}1$ reaction of *p*-nitrobenzyl chloride with 2-nitropropane anion under microwave irradiation with a domestic microwave oven affords very good coupling yields.¹¹



Scheme 2. Fast thermal long distance $S_{RN}1$ reaction of 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1H-imidazole with 2-nitropropane anion.

This early use of a domestic microwave oven did not allow an accurate control of temperature, pressure and power applied to the sample. Today, strict reaction conditions could be set and controlled by specific laboratory microwave devices. In consequence the experiment conditions can be easily reproduced. Recently, *Vanelle et al* reported the C-alkylation of 2-nitropropane anion with 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1H-imidazole at 140 °C (DMF) or 170 °C (DMSO) for 30 min in 25 mL using an accurate multimode microwave reactor with 200 W of applied power, with 60% yield¹² (Scheme 2).

In this work, we revisited the thermal initiated- $S_{RN}1$ reactions of ArX with enolate nucleophiles, using for first time a controlled microwave heating to promote the reaction. Here we present a new method to produce the α -arylation of arylketones and aryl acetamides induced by thermal initiation under microwave irradiation. This methodology has also been successfully applied to the one-pot synthesis of heterocycles.

Results and Discussion

Microwave-induced reactions

The reaction between PhI (**1**) and the enolate anion of acetophenone (**2a**) was taken as a model to explore the effectiveness of microwave irradiation as heating method for thermal initiation, as a simple alternative to photo-induction in liquid ammonia or DMSO. Table 1 shows the results yielded.

When a mixture of **1** and anion **2a** was stirred at 25 °C for 60 min in DMSO, the detection of only a trace of α -arylation product **3a** by GLC was reported (Table 1, entry 1).⁹ In view of this preliminary result we first tested the reaction between PhI with acetophenone enolate anion by heating under microwave irradiation for 10 min at different temperatures. No reaction at 40 °C under microwave irradiation was observed; however, by increasing the temperature to 50-60 °C, the substitution product **3a** occurred in moderate yields and only traces (<4%) of di-arylation product **4a** were observed (Table 1, entries 2-4).

Following this examination, the best result in this system was obtained at 70 °C in DMSO, irradiated with microwave, substitution product 1,2-diphenylethanone **3a** was quantified in 55% yield in just 10 min, with a conversion of 78% determined by iodide ion quantification (Table 1, entry 5). A similar result was found at 5 min; yet the GC-MS analysis showed presence of unreacted PhI (Table 1, entry 6). Increasing time to 30 min,

Table 1. Temperature effect on microwave-induced α -arylation of acetophenone with phenyl halides in DMSO.^a

Entry	X	Time (min)	Temp. °C	Product 3a % ^b	X-% ^c
1 ^d	I	60	25	<1	<1
2	I	10	40	trace	n.q.
3	I	10	50	34	n.q.
4	I	10	60	45 ^e	n.q.
5	I	10	70	55 ^e	78
6	I	5	70	49 ^e	70
7	I	30	70	54 ^e	72
8	I	10	100	58 ^e	92
9 ^f	I	10	70	7	<10
10 ^g	I	10	70	8	<10
11	I ^h	10	70	--	0
12	I ⁱ	10	70	14	21
13	I ^j	10	70	-- ^k	80
14	Br	10	70	trace	4

^aReactions heated by microwave irradiation (150 W_{max}) under N₂ atmosphere for 10 min. Acetophenone (1.5 mmol), *t*BuOK (1.55 mmol), and PhI (0.5 mmol) in 2 mL of DMSO, otherwise indicated. ^bQuantified by NMR with internal standard. ^cDetermined potentiometrically using a Ag/Ag(I) electrode. n.q.: no quantified. ^dThermostated in water bath, from ref 9. ^eTraces (<4%) of di-arylation product **4a** were observed. ^fDMF as solvent. ^gMeCN as solvent. ^hWithout acetophenone enolate. ⁱWith 10 mol% *m*-dinitrobenzene. ^jWith *t*BuOK as nucleophile and base ^kPhOC(CH₃)₃ was quantified by NMR in 4% yield.

or raising temperature to 100 °C did not show a substantial rise in the yield of substitution product **3a**; however, an increase in the reduction product was shown through the higher iodide ion yield (Table 1, entries 7 and 8). The 1,2-diphenylethanone **3a** was stable under the reaction conditions. After GC-MS analysis it did not show any by-product produced by thermal decomposition at 70-80 °C, under microwave heating for 10 min; it was recovered in 84% isolated yield. All attempts to detect the reduced product benzene were unsuccessful.¹³ Another solvents such as DMF or MeCN were also tried without success (Table 1, entries 9 and 10). In addition, the main reaction by-product was the auto-condensation of acetophenone present in excess in the basic reaction media.

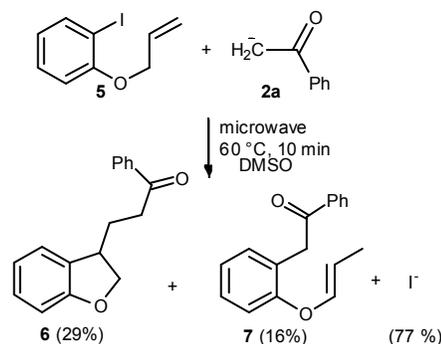
Comparison between microwave and oil bath heating

The same model reaction was tested using a sealed microwave tube on a pre-heated (to accurate temperature) oil bath, and after 10 min at 70 °C only 10% yield of product **3a** was quantified by GC-MS. In addition, product **3a** was obtained in 17% yield after 60 min at 70 °C. When the reaction was performed under microwave irradiation in an open vessel (at atmospheric pressure), a comparable yield of **3a** and unreacted PhI were found in relation to those observed in Table 1, entry 5. Under microwave irradiation it is possible that significant and localized overheating is produced in the solution since DMSO is a strongly microwave absorbing solvent. This overheated spots, will help to accelerate reaction rate in relation to conventional heating.¹⁴ In addition, the pressure conditions of 1.7 atm did not seem to be required; however, microwave irradiation was needed to accelerate the reaction. This

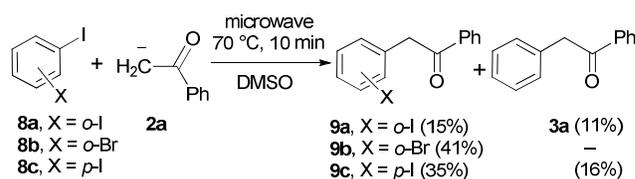
reaction effectively proceeds faster under microwave irradiation in an open or closed vessel; for security issues, however, the latter was adopted as a standard methodology. Further research into these microwave induced thermal ET reactions is currently in progress in our lab.

Reaction Mechanism

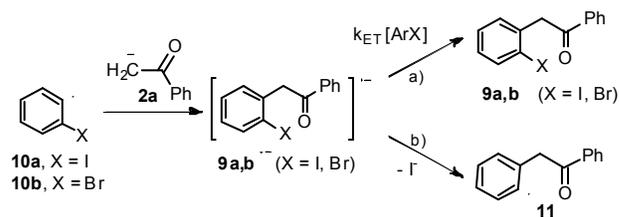
To evaluate the mechanism involved in this reaction, some experiments were performed. First we checked the presence of radical intermediates in the reaction by using 1-(allyloxy)-2-iodobenzene (**5**) as radical clock (Scheme 3).¹⁵ To reduce the base promoted isomerization of the double bond in **5**, the reaction was conducted at 60 °C.¹⁶ Thus, the reaction of **5** with the enolate anion of acetophenone in a ratio 1:3, after 10 minutes under microwave irradiation at 60 °C, gave 29% and 16% of the cyclized (**6**) and straightforward (**7**) substitution products, respectively. This result clearly indicates that aryl radicals are reactive intermediates in the microwave reaction.¹⁵ Formation of product **6** must involve the intermediacy of the 2-(allyloxy)phenyl radical and its 5-exo ring closure followed by addition to the enolate anion **2a**. On the other hand, direct coupling between the 2-(allyloxy)phenyl radical and the anion **2a** followed by ET and isomerization of the double bond affords product **7**. Isomerization of **5** prior to ET step would also account for the formation of product **7**, but would not allow 5-exo cyclization to yield derivative **6** after coupling with the nucleophile.⁶⁵ In fact, when the reaction between **5** and anion **2a** was performed at 80 °C, the only product obtained was **7** in 45% yield. Moreover, PhI showed to be thermally stable under the reaction conditions. After 10 min of microwave irradiation of PhI in DMSO, either benzene or iodide ion was not detected, (Table 1, entry 11). This fact allows discarding a homolytic rupture of the C_{Ar}-I bond as the radical initiation process. Furthermore, when the reaction between PhI and the enolate anion of acetophenone was conducted in the presence of 10 mol % of *m*-dinitrobenzene, which is a strong electron acceptor inhibiting the ET step,² a 14% yield of product was obtained with 21% conversion yields (Table 1, entry 12). These assays suggest that the reaction proceeds through an S_{RN}1 mechanism thermally initiated¹⁷ with radicals and radical anions as intermediates. 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} (Scheme 5). In this case, the increase in temperature or the direct microwave energy applied to the substrate could provide the necessary energy to the initial ET from the nucleophile to the ArX. Alternatively, the slightly excess of *t*BuO⁻ anion could also act as the electron donor in an entrainment reaction.¹⁹ This later statement was confirmed by the reaction between PhI and *t*BuOK in the absence of acetophenone, which gave 80% of I⁻ anions after 10 min of microwave irradiation (Table 1, entry 13). As in the above reactions, benzene could not be detected after microwave irradiation. In addition only a low amount of the substitution product with the *t*BuO⁻ anion was observed (4%), according to the low reactivity of the alkoxide anions toward aryl radicals attributed to their very positive oxidation standard potentials, being hard nucleophiles.^{2, 20}



Scheme 3. 1-(allyloxy)-2-iodobenzene as radical clock



Scheme 4. Microwave-induced reaction of acetophenone anion (**2a**) with ortho-haloiodobenzene (**8a,b**) and para-diiodobenzene (**8c**) in DMSO



Scheme 5. Propagation steps for the S_{RN}1 mechanism of the reaction of acetophenone anion (**2a**) with ortho-haloiodobenzene (**8a,b**) in DMSO

Additionally, PhBr was unreactive toward the anion of acetophenone after 10 min of microwave irradiation at 70 °C, with low conversion (<5%) and traces of the substitution product **3a** (Table 1, entries 14). Similar results were observed at 100 or 140 °C.

Furthermore, the reactivity of dihalobenzenes toward the anion of acetophenone was studied under microwave induction and the results compared with the photoinduced reactions in order to get further insights into the mechanism. The microwave-irradiated reactions of ortho-haloiodobenzenes (**8a,b**; X = I, Br) with anion **2a** gave mono-substitution with retention of halide (**9a,b**) and mono-substitution with reduction of the second halide (**3a**), the later only observed for X = I (Scheme 4). The reaction of the para-diiodobenzene (**8c**) with anion **2a** afforded both the *p*-iodo substituted derivative (**9c**) and the mono-substituted reduced product **3a** with only trace of the *p*-disubstituted derivative observed by GC-MS. Similar results were previously obtained in the photoinduced reactions of **8a,b** with anion **2a**.²¹ The agreement between the reactions performed under photochemical and

microwave irradiation strongly supports that both reactions proceed by the same $S_{RN}1$ mechanism as follows. After the initial ET, the radical anion of the substrate (**8a,b^{•-}**) fragments into iodide anion and radical **10a,b**. The radical anions **9a,b^{•-}** formed by the coupling of radical **10a,b** with anion **2a** can afford the mono-substituted products **9a,b** after inter-ET to the substrate (Scheme 5, pathway a) or can fragment at the C-halogen bond to give radical **11** (Scheme 5, pathway b). The unpaired spin distribution in the most stable radical anion intermediate (**9a,b^{•-}**) is localized in the benzoyl moiety (π -system), which is separated from the *ortho*-halophenyl moiety by a sp^3 carbon atom; the intra-ET is favored only when X = I to afford radical **11** after C-X fragmentation.

Finally, disubstitution was not observed, even with the *ortho*-diiodobenzene (**8a**). This can be attributed to the low excess of the acetophenone anion present in the reaction media, since disubstitution was previously observed for the ketone enolate anion under photostimulation in liquid ammonia.²² An unfavorable coupling reaction due to steric constraints can also be responsible. On the other hand, trace of disubstitution was detected by GC-MS for the reaction of *para*-diiodobenzene (**8c**) in the presence of 3 equivalents of anion **2a**, under both microwave and photo-induced reactions.

Scope of the microwave induced α -arylation reaction

We subsequently studied the reactivity of different aryl halides to determine the scope of the microwave α -arylation reaction; results are found in Table 2. In general, the reaction of aryl iodides bearing electron-donor and -acceptor substituent gave the substitution product in moderate to good yields (49-57%, Table 2, entries 1-4). Using 4-iodobenzonitrile, anion **2a** was mono-arylated in 46% yield. The α -arylation of 4-iodobenzonitrile has not been previously reported under photoinduced $S_{RN}1$ conditions.² Furthermore, attempts to α -arylation of anion **2a** by Pd-catalysis failed; instead of the desired product, β -enaminones were obtained by condensation of the acetophenone with the nitrile moiety of the substrate.²³ On the other hand, it is known that the fragmentation rates of the radical anions of nitro-substituted aryl halides determined electrochemically²⁴ or by pulse radiolysis²⁵ are slow and range from 10^{-3} to 10^2 s⁻¹. As a consequence such substrates have not been suitable for electrochemical or photoinduced $S_{RN}1$ reactions.² In this context, it should be noted that under microwave irradiation 19% of the nitro derivative is obtained (Table 2, entry 5). Nevertheless, a classical aromatic nucleophilic substitution cannot be disregarded. In addition, 1-iodonaphthalene, 1-bromonaphthalene, 2-bromonaphthalene and 2-iodopyridine, by reaction with anion **2a** gave substitution products in moderate yield (Table 2, entries 6-9).

Besides, *p*-substituted acetophenone enolate anions (**2j-m**) were also investigated as nucleophiles in the reaction with PhI (Table 3). As expected for an ET-initiated reaction (Scheme 5), the presence of an electron donor group such as CH₃ in anion **2j** afforded comparable yield of substitution product relative to anion **2a** (Table 3, entries 1 and 2). The amino group is also deprotonated in the reaction media and the yield of α -arylation decreased (Table 3, entry 3). On the other hand the presence of electron withdrawing groups such as Cl and NO₂ in the enolate anion strongly inhibits or avoids ET pathways (Table 3, entries 4 and 5). The formation of **3a** in the α -arylation of anion **2m** supports the participation of **3m^{•-}** as intermediate (Table 3, entry 5).

Table 2. Microwave-induced substitution reactions of ArX by the enolate anion of acetophenone in DMSO

Entry	ArX	Product 3	%Yield ^a
1			55 (53) ^b
2			46
3			54
4			57
5			19
6			59
7			55
8			35
9			44

^aReactions heated to 70 °C by microwave irradiation (150 W_{max}) under N₂ atmosphere for 10 min. Acetophenone (1.5 mmol), *t*BuOK (1.55 mmol), and ArX (0.5 mmol) in 2 mL of DMSO, otherwise indicated. ^bQuantified by NMR with internal standard. ^cIsolated yield from a preparative scale reaction: Acetophenone (7.5 mmol), *t*BuOK (7.75 mmol), and PhI (2.5 mmol) in 10 mL of DMSO.

In addition, we have performed some experiments using the enolate anion of cyclohexanone as nucleophile under microwave irradiation to compare with the thermal induced reaction previously reported.⁹ To our surprise at 70°C only 10% of the α -arylated product, 2-phenylcyclohexanone (**12**) was observed and most IPh remained unreacted (Table 3, entry 6). The yield of **12** was not improved by increasing the temperature to 100°C, except for the ketone condensation product. Further attempts to reproduce the previous reported results⁹ were unsuccessful. In our hands, IPh did not react with the enolate anion of cyclohexanone in DMSO after 60 min heating at 25 °C.

Table 3. Microwave-induced substitution reactions of PhI by ketone enolate anions in DMSO

Entry	Anion	Product	%Yield ^a
1			55 (53) ^b
2			40
3			34
4			0
5			14 ^c
6			10

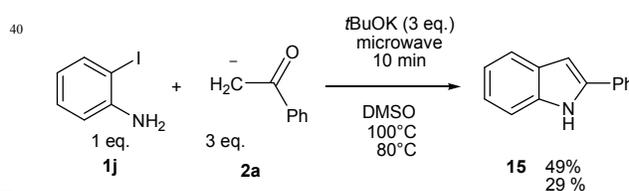
Reactions heated to 70 °C by microwave irradiation (150 W_{max}) under N₂ atmosphere for 10 min. Ketone (1.5 mmol), *t*BuOK (1.55 mmol), and PhI (0.5 mmol) in 2 mL of DMSO. ^[a]Quantified by NMR with internal standard. ^[b]Isolated yield from a preparative scale reaction. ^[c]Together with 7% of **3a**.

As it has been well established, the photoinduced S_{RN}1 reaction provides a good alternative to the synthesis of heterocycles². Therefore, two different approaches were explored to achieve target compounds under microwave irradiation: 1) intramolecular S_{RN}1 reaction and 2) intermolecular S_{RN}1 reaction, followed by a polar ring closure reaction. Initially, the synthesis of indolinone derivatives was performed by intramolecular cyclization of *N*-(2-halophenyl)phenyl acetamides (**13**) under microwave irradiation⁵⁰ (Table 4). Thus, the reaction of the iodo derivative **13a** in the presence of *t*BuOK gave 90% yield of the cyclized compound 1-methyl-3-phenylindolin-2-one (**14**) and 10% of the reduced product *N*-methyl-*N*,2-diphenylacetamide at 70 °C in DMSO (Table 4, entry 1). Quantitative yield was achieved by increasing temperature to 100 °C (Table 4, entry 2). The bromo derivative **13b**, afforded 80% of substitution at 100 °C, while the chloro derivative **13c** required increasing temperature to 130 °C to observe only 14% of product **14** (Table 4, entries 3-6). The reactivity order I > Br > Cl is according to the reduction potential of the aryl halides and with the average fragmentation rate constant for their radical anion intermediates.² Finally, this methodology was extended to the “one-pot” synthesis of indole derivatives (**15**) by two consecutive reactions, an intermolecular nucleophilic substitution of *ortho*-iodo aniline with the enolate anion **2a** induced by microwave irradiation³⁰ followed by a condensation. The best isolated yield (49%) of indole **15** was obtained at 100 °C (Scheme 6). This result agrees with that found in the previous examples in Table 2, for intermolecular process.

Table 4. Synthesis of 1-methyl-3-phenylindolin-2-one (**14**) by intramolecular cyclization of *N*-(2-halophenyl)phenylacetamides by microwave heating

Entry	Substrate 13	X	Temp. °C	Product 14 yield % ^a
1	13a	I	70	90 ^b
2	13a	I	100	100
3	13b	Br	70	30
4	13b	Br	100	80
5	13c	Cl	100	0
6	13c	Cl	130	14

^aQuantified by GC by the internal standard method. ^bTogether with 10% *N*-methyl-*N*,2-diphenylacetamide.

Scheme 6. “One-pot” synthesis of 2-phenylindole (**15**)

Conclusions

The use of modern microwave heating devices proves valuable in the fine chemist and pharmaceutical chemistry offering a faster and safer synthetic methodology. In this report new C-C bonds were obtained by α -arylation of aromatic ketones and acetamides by a thermally induced S_{RN}1 reaction by microwave irradiation at moderate temperatures. This is the first report of microwave-induced S_{RN}1 reaction in the aromatic system. The initiation step is proposed to take place by a microwave-induced thermal ET.

By comparison with the photoinduced procedures, the main disadvantage of the microwave-initiated reaction is the competitive reduction observed for intermolecular process, consequently the best substitution yields is about 60%. On the other hand, the microwave-induced reaction shows as many advantages as simplicity, short times (10 min of microwave irradiation compared with 120 min of photoirradiation), compatibility with substituents like NO₂, CN, F, Br, and a better performance in intramolecular reactions.

Thus, this process allows the synthesis of 2-aryl-1-phenyletanones (**3a-k**, **3m**) by α -arylation of the enolate anion of acetophenones (**2**) with different haloarenes (**1a-i**). In addition, this methodology provides a simple way to achieve heterocycles as 1-methyl-3-phenylindolin-2-one (**14**) and 2-phenylindole (**15**) by intra- or intermolecular S_{RN}1 reactions, respectively, in a very fast reaction.

Experimental Section

Chemicals:

Potassium *tert*-butoxide (*t*BuOK), iodobenzene, bromobenzene, cyclohexanone, acetophenone, 1-*p*-tolylethanone, 1-(4-aminophenyl)ethanone, 1-(4-nitrophenyl)ethanone, 1-(4-chlorophenyl)ethanone, 1-iodonaphthalene, 1-bromonaphthalene, 2-bromonaphthalene, 2-iodopyridine, 2-iodoaniline, 1,2-diiodobenzene, 1,4-diiodobenzene, 1,2-bromo-iodobenzene, 1,4-fluoro-iodobenzene, 1,4-cyano-iodobenzene, 1,4-methoxy-iodobenzene, and 1,4-iodo-nitrobenzene 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). *N*-Methylanilides **13a-c** were synthesized by standard procedures from the reaction between commercial 2-haloanilines and the corresponding acyl chloride in CH₂Cl₂ in the presence of pyridine.²⁶ *N*-(2-iodophenyl)-*N*-methyl-2-phenylacetamide (**13a**)²⁷, *N*-(2-bromophenyl)-*N*-methyl-2-phenylacetamide (**13b**)²⁸, and *N*-(2-chlorophenyl)-*N*-methyl-2-phenylacetamide (**13c**)²⁷ present spectral data in good agreement with the literature.

The ketone enolate anion or the anion of *N*-methylanilides was generated *in situ* by acid-base deprotonation using *t*BuOK.

General Methods: ¹H and ¹³C 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 Me₄Si, with CDCl₃ 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 (70 eV) 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 with a magnetic stirrer. The tube was dried under vacuum, filled with nitrogen, and then charged with dried DMSO (2 mL) and degassed. Next, for the α-arylation of the haloarene, *t*BuOK (179 mg, 1.55 mmol), acetophenone (1.5 mmol), and aryl halide (0.5 mmol) were added to the degassed solvent under nitrogen. For the intramolecular cyclization reaction halophenylacetamide (0.5 mmol) and *t*BuOK (112 mg, 1.0 mmol) were added to the degassed solvent under nitrogen. Then, the reaction tube was 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. The sample vessels reach the selected temperature in about 30 sec (~2.5 °C/sec). Although, the maximum microwave power was set at 150 W, after the initial heating pulse of maximum 100 W for 30 sec, the average applied power was about 1 W to keep the selected temperature (see supporting information for irradiation details). After 10 min of irradiation the device cooled the tube to 50 °C with compressed air above 1 min. (-0.5 °C/sec).

The average pressure in the vessel was 1.7 atm 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 NH₄NO₃ excess, and the mixture was extracted with methylene chloride (3 × 20 mL). The combined organic extract was dried over anhydrous CaCl₂, and the products were quantified by GC or NMR by the internal standard method or isolated by silica gel chromatography from the crude product reaction mixture. Water layer was recovered to quantify the halide ions by potentiometric titration with an AgNO₃ standard solution.

Product isolation from a preparative scale reaction: this reaction was performed following the representative experimental procedure using acetophenone (7.5 mmol), *t*BuOK (7.75 mmol), and PhI (2.5 mmol) in 10 mL of DMSO. After reaction and usual workup, the combined dried extract was first chromatographed on a silica gel short-column eluted first with *n*-pentane and second with *n*-pentane: ethyl ether (90:10). After evaporation the oily residue was distilled in a kügelrohr to separate the product 1,2-diphenylethanone (**3a**) from acetophenone. The substitution product **3a** crystallizes at 0 °C with a small amount of *n*-hexane: 260 mg (53%); mp 53-55 °C.

Products characterization: All the products present in Table 2 were obtained following the general procedure, quantified by NMR or GC. Products **3a-k**, **3m**, **9a-c**, **12**, **14**, and **15** are known compounds and present spectral data as shown in the literature, in agreement with the proposed structures. 1,2-diphenylethanone (**3a**)^[29], 4-(2-oxo-2-phenylethyl)benzoxazole (**3b**)³⁰, 2-(4-methoxyphenyl)-1-phenylethanone (**3c**)³¹, 2-(4-fluorophenyl)-1-phenylethanone (**3d**)³¹, 2-(4-nitrophenyl)-1-phenylethanone (**3e**)³², 2-(naphthalen-1-yl)-1-phenylethanone (**3f**)³³, 2-(naphthalen-2-yl)-1-phenylethanone (**3h**)³⁴, 1-phenyl-2-(pyridin-2-yl)ethanone (**3i**)³⁵, 1-(4-methylphenyl)-2-phenylethanone (**3j**)³⁶, 1-(4-aminophenyl)-2-phenylethanone (**3k**)³⁷, 1-(4-chlorophenyl)-2-phenylethanone (**3m**)³⁶, 2-(2-iodophenyl)-1-phenylethanone, 1-(allyloxy)-2-iodobenzene (**5**)¹⁶, (**9a**)²¹, 2-(2-bromophenyl)-1-phenylethanone (**9b**)³⁸, 2-(4-iodophenyl)-1-phenylethanone (**9c**)²¹, 2-phenylcyclohexanone (**12**)³⁹, 1-methyl-3-phenylindolin-2-one (**14**)²⁸, 2-phenyl-1*H*-indole (**15**).³²

3-(2,3-dihydrobenzofuran-3-yl)-1-phenylpropan-1-one (6)

Following the general procedure, using *t*BuOK (179 mg, 0.75 mmol), acetophenone (0.75 mmol), and aryl halide **5** (0.25 mmol), microwave irradiation at 60 °C for 10 min and then purification by radial chromatography (petroleum/ethyl ether, 8/2) provided **6** as light yellow crystals (18 mg, 29% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.94-7.92 (m, 2H), 7.57 (tt, 7.3, 1.3 Hz, 1H), 7.46 (tb, J= 7.6 Hz, 2H), 7.21 (db, J= 7.3 Hz, 1H), 7.14 (tb, J= 7.7 Hz, 1H), 6.87 (td, J= 7.4, 1 Hz, 1H), 6.81 (d, J= 8 Hz, 1H), 4.66 (t, J= 8.9 Hz, 1H), 4.28 (dd, J= 8.9, 5.8 Hz, 1H), 3.61-3.54 (m, 1H), 3.11-2.95 (m, 2H), 2.24-2.16 (m, 1H), 2.11-2.02 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 199.5, 160.0, 136.8, 133.2, 130.1, 128.7, 128.4, 128.0, 124.5, 120.5, 109.7, 41.1, 35.3, 28.9. HRMS ESI⁺ [M+Na⁺] calcd for C₁₇H₁₆O₂Na: 275.1043, found 275.1056

1-phenyl-2-(2-(propen-1-yloxy)1-phenylethanone (7)

Following the general procedure, using *t*BuOK (179 mg, 0.75 mmol), acetophenone (0.75 mmol), and aryl halide **5** (0.25 mmol), microwave irradiation at 60 °C for 10 min and then purification by

radial chromatography (petroleum/ethyl ether, 8/2) provided **7** as light brown crystals, (10 mg, 16% yield).
¹H NMR (400 MHz, CDCl₃) δ 8.08- 8.06 (m, 2H), 7.56 (tt, J = 7, 1 Hz, 1H), 7.56 (tt, J = 7, 1 Hz), 7.46 (tb, J = 7.5 Hz, 1H), 7.27-7.23 (m, 2H), 7.02 (td, J = 7.5, 1 Hz, 1 H), 6.96 (dd, J = 8, 1 Hz, 1H), 6.34 (dc, J = 6, 1.7 Hz, 1H), 4.85 (cd, J = 6.8, 6 Hz, 1H), 4.35 (s, 2H), 1.60 (dd, J = 6.8, 1.7 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 197.7⁰, 155.2, 140.9, 136.9, 133.0, 131.3, 128.6, 128.5, 124.5, 122.6, 114.8, 107.6, 39.9, 9.3. HRMS ESI⁺ [M+Na⁺] calcd for C₁₇H₁₆O₂Na: 275.1043, found 275.1047.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Typical reaction profile under microwave irradiation and spectra (¹H and ¹³C NMR) for products **6** and **7**]. See DOI: 10.1039/b000000x/

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Graphical Abstract and Textual

Quick reaction by Microwave irradiation promotes nucleophilic substitution by thermally induced electron transfer mechanism and allows to synthesize deoxybenzoin and indol heterocycles derivatives by inter or intramolecular ring closure.

