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ETHERIFICATION OF HETEROCYCLIC COMPOUNDS BY NUCLEOPHILIC AROMATIC SUBSTITUTIONS UNDER GREEN CHEMISTRY CONDITIONS

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Abstract - Solid-liquid phase transfer catalysis coupled with microwave irradiation was shown to be an efficient method for S_NAr reaction of halogenated quinoline and pyridine with alkoxides and phenoxides. Whereas for phenoxylation there is no need for any solvent, the addition of small amount of non-polar solvent is necessary during methoxylation for accurate monitoring of temperatures. Yields and conditions involved here constitute a noticeable improvement over classical methods within the frame of Green Chemistry. Specific MW effects were evidenced for phenoxylation and interpreted in terms of late position of the transition state along the reaction coordinates.

INTRODUCTION

Aryl halides are characterized by their low reactivity toward nucleophilic reagents. Therefore, nucleophilic aromatic substitution (S_NAr) is less used in synthesis than either nucleophilic substitution (S_N2) or electrophilic aromatic substitution (S_EAr).[1] Generally, long reaction times or harsh conditions are required to achieve acceptable yields under conventional heating.

Several derivatives of heterocyclic compounds are well-known as biologically active compounds. Extensive efforts have been exerted on developing methodology for the synthesis of heterocyclic compounds which are frequently found in natural products and pharmaceuticals.[2] They could be often obtained by S_NAr reaction of nucleophilic species with heteroaryl halides.

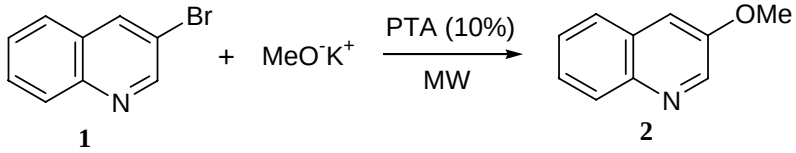
Thanks to the application of microwave irradiation (MW), it was shown that the reaction time of a lot of S_NAr reactions can be dramatically reduced and the yields improved.[3-13] The main conditions in this field are using solvents such as EtOH, DMSO, DMF or HMPA, i.e. highly polar solvents. As these ones are very prone to adsorb MW due to their high polarity, they can mask the possible benefits of MW irradiation during the reaction.[14-16] Unfortunately, no comparisons with conventional heating (Δ) are available under these conditions.

In this study, we can therefore focus our efforts on the etherification by S_NAr reactions through reacting potassium methoxide (MeO^-) or phenoxide (PhO^-) with two representative heterocyclic compounds, halogenated pyridine and quinoline. Taking advantage of this study, we also want to appreciate the effective role of MW activation and to distinguish between thermal and specific (non purely thermal) MW effects.[17] To this purpose, to check this possible influence, we have to compare yields obtained by Δ and MW activation under strictly similar conditions (medium, vessels, reaction, temperature, profiles of raises in temperature).

RESULTS

Etherifications were studied for the significant cases of 3-bromoquinoline and 2- and 3-halopyridines. We especially foresee the behaviour of coupling two non-classical methods, phase transfer catalysis (PTC) + microwave irradiation, the efficiency and potentialities of which being clearly proved.[18,19]

Methoxylation of 3-Bromoquinoline [eq. 1]



1 **2** [eq. 1]

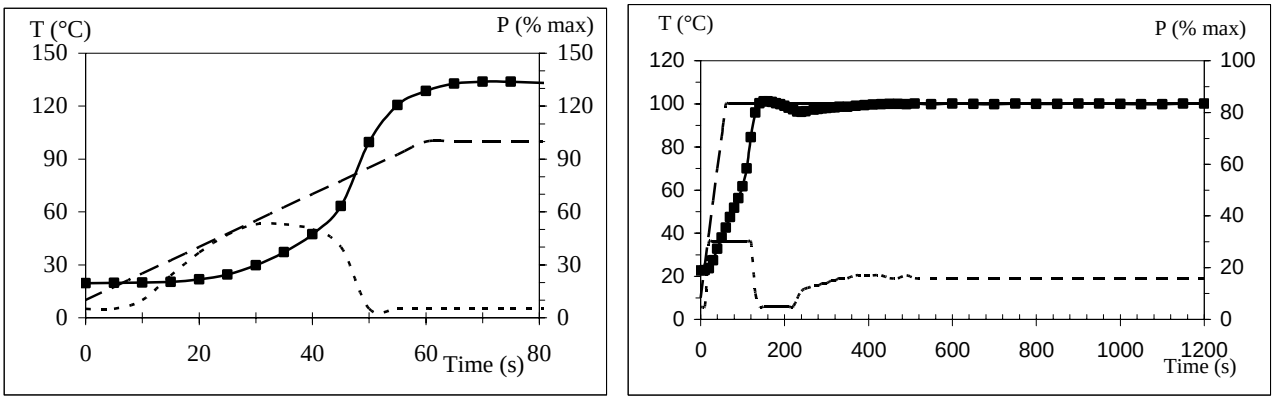
Table 1 : Solvent-free reaction of 3-bromoquinoline (**1)** (5 mmol) with potassium methoxide (1.5 equiv.) under MW for 20 min at 100 °C.

Entry	PTA (10 mol %)	Conversion **1** [a)b)] (%)	Yield **2** [b)] (%)
1	-	0	0
2	Aliquat 336	19	4
3	Bu_4NBr	11	5
4	Bu_4NCl	11	4
5	Bu_4NHSO_4	38	2
6	TDA-1	35	21
7	18-crown-6	100	42
8	18-crown-6 + isooctane [c)]	100	58

a) relative to **1** consumption
b) GC yield and conversion using an internal standard (diethyl phthalate)
c) 1 mL of isooctane

By operating under standard conditions at 100 °C for 20 min, the influence of the nature of the phase transfer agent (PTA) was previously studied. The main results are indicated in Table 1.

Whereas ammonium salts lead to low yields, the best result was obtained with 18-crown-6. However, as control and monitoring of temperature is impossible due to thermal runaway up to 140 °C (Figure Ia) even at the lowest MW emitted power (15 Watts), addition of a small amount of non-polar solvent (isooctane – transparent to MW) is necessary to maintain constant the temperature (Figure Ib).



(a) (b)

Figure I : Profiles of power and raise in temperatures for entries 7 (a) and 8 (b).
(Instruction Temperature[i] Power[ii])

i) imposed instruction by computer for profile of raise in temperature.
ii) emitted power by magnetron expressed in percentage of maximal power (300W).

As it remains a large difference between conversions in **1** and yields in **2**, indicative of some decomposition or loss of materials, reaction time and temperature were next optimized (Table 2).

The best result (73 – 74%, Entries 13 and 14) was obtained at 70 °C for 20 – 30 min. Further experiments indicate that 1.5 equiv. MeOK is an adequate amount of nucleophile as well as 10 mol % of PTA is convenient.

Cation is also of prime importance. After optimization, the reaction of **1** with MeONa in place of MeOK did not exceed 11 – 12% yield even under the reaction conditions for 4 h at 120°C (decane) or for 30 min at 150 °C (nonane) using specific 15-crown-5 catalyst.

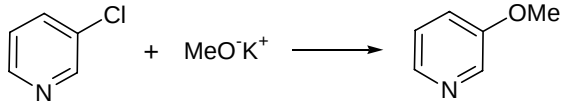
Table 2 : Influence of reaction time and temperature on reaction of **1** (5 mmol) with potassium methoxide (1.5 equiv.) under MW in the presence of isooctane (1 mL).

Entry	Temperature (°C)	Time (min)	Conversion **1** (%)	Yield **2** (%)
8	100	20	100	58
9	100	10	100	59
10	100	5	100	62
11	100	2	88	57
12	80	20	99	66
13	**70**	**20**	**87**	**73**
14	**70**	**30**	**89**	**74**
15	60	20	51	38

Halopyridines

Methoxylation of 3-chloropyridine [eq. 2]

This reaction was described under conventional conditions by reacting 4 equiv. of sodium methoxide in DMSO at 120 °C for 4 h (yield = 70%).[20]



[eq. 2]

3.Cl **4**

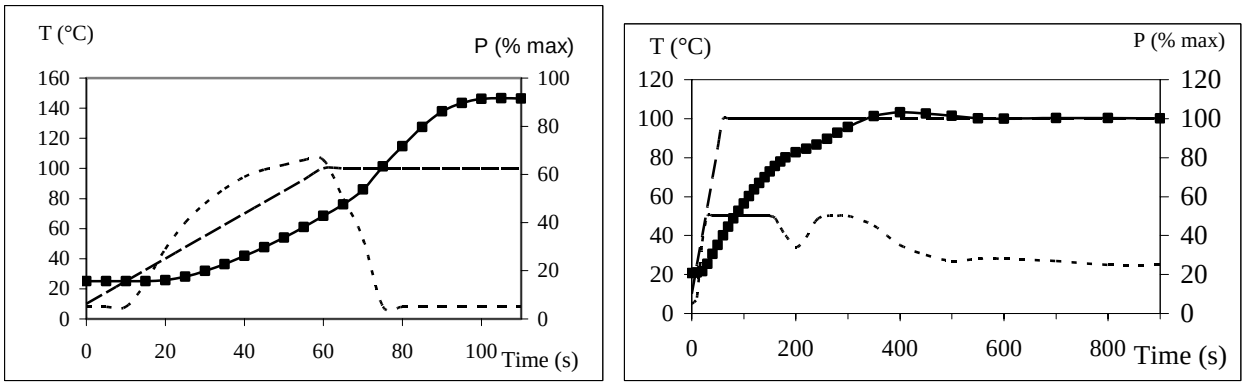
In Table 3 are given the main results obtained in our conditions for screening of PTA catalysts.

Table 3 : Reaction of **3.Cl** (5 mmol) with potassium methoxide (1.5 equiv.) under MW for 15 min at 100 °C.

Entry	PTA (10 mol %)	Conversion **3.Cl** [a)] (%)	Yield **4** [a)] (%)
16	-	4	0
17	Aliquat 336	6	0
18	Bu_4NBr	11	0
19	Bu_4NCl	3	0
20	Bu_4NHSO_4	3	0
21	TDA-1	1	0
22	Kryptofix [2,2,2]	82	48
23	18-crown-6	89	72
24	18-crown-6 + nonane [b)]	69	60

a) GC yield and conversion using an internal standard (ethyl benzoate)
b) 1 mL of nonane

The best catalyst is again 18-crown-6 with a better yield in the absence of nonane. However, the presence of a non-polar solvent is necessary for a reliable control and monitoring of temperature to avoid the thermal runaway around 150 °C (Figure IIa).



(a) (b)

Figure II: Profiles of power and raise in temperature for Entries 23 (a) and 24 (b).

(– – – – Instruction —□— Temperature[i] - - - - - - Power[ii])

i) imposed instruction by computer for profile of raise in temperature.
ii) emitted power by magnetron expressed in percentage of maximal power (300W).

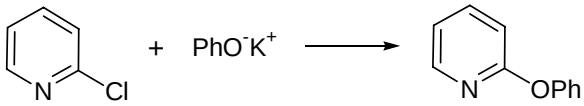
Reaction time and temperature were next optimized to allow enhancement in yield up to 95%. The main results are given in Table 4.

Table 4 : Influence of reaction time and temperature on reaction of **3.Cl** (5 mmol) with potassium methoxide (1.5 eq.) and 18-crown-6 (10 mol %) under MW in the presence of nonane (1 mL).

Entry	Temperature (°C)	Time (min)	Conversion **3.Cl** (%)	Yield **4** (%)
25	100	10	41	39
24	100	15	64	60
26	100	30	90	88
27	**100**	**45**	**98**	**95**
28	120	15	80	76
29	130	15	91	87
30	**130**	**20**	**95**	**92**

Good yields can be obtained either at 100 °C for 45 min (95%) or at 130 °C for 20 min (92%). It was shown here also that 1.5 equiv. MeO^-K^+ is the best adapted amount of nucleophilic species.

Phenoxylation of 2-chloropyridine [Eq. 3]



5.Cl **6** [eq. 3]

This reaction was previously studied in our laboratory [21] by conventional heating under solvent-free conditions (yield is limited to 10% - but can be improved with fluoropyridine up to 69%) or in DMSO or HMPA under MW (yield = 38 – 45%).[9d]

In Table 5 are given the main result for this reaction under our conditions.

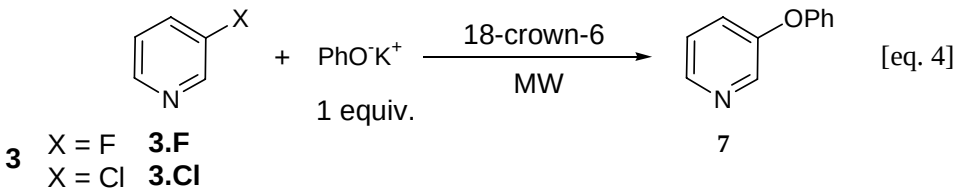
Table 5 : Solvent-free reaction of **5.Cl** (5 mmol) with potassium phenoxide (1 equiv.) under MW. Temperature = 150 °C.

Entry	PTA (10%)	Time (min)	Conversion **5.Cl** [a)] (%)	Yield **6** [a)] (%)
31	Aliquat 336	30	22	20
32	Bu_4NBr	30	32	26
33	Bu_4NHSO_4	30	54	50
34	TDA-1	30	55	54
35	Kryptofix [2,2,2]	30	46	44
36	18-crown-6	30	95	95
37	**18-crown-6**	**20**	**95**	**95**
38	18-crown-6	10	65	65

a) GC yield and conversion using an internal standard (ethyl benzoate)

An excellent yield (95%) is obtained within 20 min at 150 °C under solvent-free conditions. No addition of solvent is necessary as the profile of raising of temperature is very regular and accurately monitored.
Encouraging by the excellent results obtained with 2-chloropyridine, we next have studied the more difficult case of 3-halopyridines.

Phenoxylation of 3-halopyridines [Eq. 4]



3 X = F **3.F**
X = Cl **3.Cl**

7

The main results obtained in this case are given in Table 6.

The efficiency of phenoxylation of 3-halopyridines is strongly dependent on halogen atom, from 85% with F (30 min, 180 °C) to 55% yield with Cl (45 min, 200 °C).

Table 6 : Solvent-free reaction of **3** (5 mmol) with potassium phenoxide (1 equiv., 5 mmol) under MW irradiation (PTA = 18-crown-6).

Entry	X	Time (min)	Temperature (°C)	Conversion **3** [c)] (%)	Yield **7** [c)] (%)
39	F [a)]	20	180	57	57
40		**30**	**180**	**85**	**85**
41		45	180	92	87
42		60	180	90	85
43	Cl [b)]	45	180	49	34
44		30	200	60	45
45		**45**	**200**	**75**	**55**
46		60	200	89	58
47		45	220	86	55

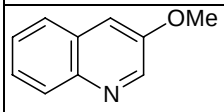
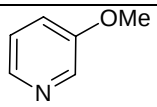
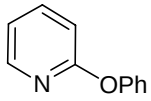
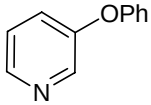
a) PTA = 10 mol % b) PTA = 20 mol %
c) GC yield and conversion using an internal standard (ethyl benzoate)

DISCUSSION

Comparison with literature data

From comparative purposes with the recent methods available from literature, and to appreciate the improvements in yields and (or) conditions, we have collected the main results in Table 7.

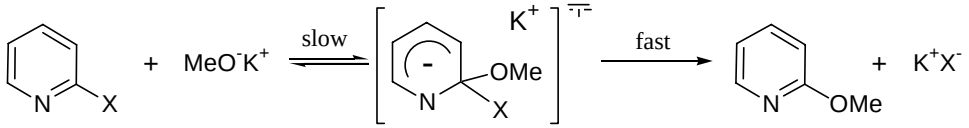
Table 7 : Comparative results between our datas and literature.

Product	Reagents	Our conditions (PTA + MW)	Literature
 **2**	**1**	Entry 14 **74%**	MeONa / HMPA - MW 30 sec 90 °C **72%** [9c]
 **4**	**3.Cl**	Entry 30 **92%** Entry 27 **95%**	MeONa (4 equiv.) / DMSO 4 h – 120 °C **70%** [20]
 **6**	**5.Cl**	Entry 37 **95%**	PhOH + *t*-BuOK + Aliquat 336 (6 mol %) no solvent 4 h 120 °C **10%** [21] from **5.F** *Idem* **69%** [21] PhONa / HMPA MW 2 min 110 °C **45%** [9d]
 **7**	**3.F**	Entry 40 **85%**	

Clearly, PTC + MW conditions are by far the best ones in terms of yields and conditions. They avoid the use of polar toxic solvent (ex : carcinogen HMPA) and minimize pollution under more safe conditions. They need to use crown ether as catalyst, which can be simply recycled after use [22] and, in some case, small amounts of non-polar solvents for homogeneity purpose and to allow an accurate monitoring of temperature.

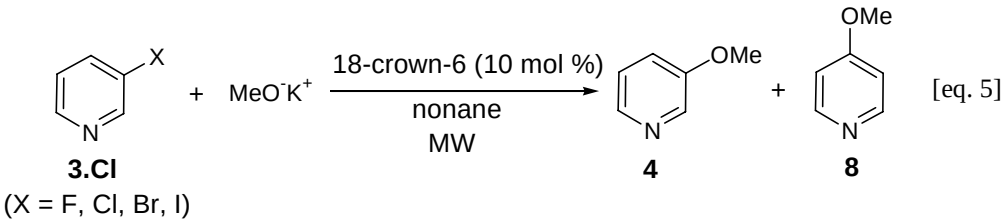
Halide effect – Mechanistic considerations

When we have checked the halogen influence during phenoxylation of 3-halopyridines (Table 6), fluorine is evidently more prone than chlorine to give the best results under milder conditions. This observation is consistent with an addition-elimination S_NAr mechanism,[23] the first step being the rate determining one as governed by the electronegativity of X (Scheme 1).



Scheme 1 : S_NAr addition-elimination mechanism

As an extension, we have next examined the halogen effect during the methoxylation of 3-halopyridines from reactivity and regioselectivity points of view (Equation 5).



The main results are given in Table 8.

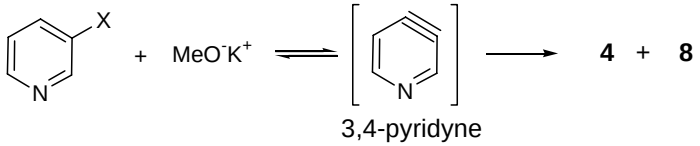
Table 8 : Methoxylation of 3-halopyridines **3.X** (5 mmol) under MW + PTC conditions. MeO^-K^+ (5 mmol) – 18-crown-6 (10 mol %) –nonane (1 mL) – Time = 20 min.

Entry	X	Temperature (°C)	Conversion **3,X** (%) [b]	Yield **4** + **8** (%) [b]	Selectivity **4** / **8**
48	F	100	100	100	100 / 0
49	Cl	130	95	92	100 / 0
50	Br	100	83	49	80 / 20
51	I	100	69 [a]	5	33 / 67

a) 20% of pyridine has been characterized
b) GC yield and conversion using an internal standard (ethyl benzoate)

If the mechanism concerned with F and Cl is presumably a S_NAr addition-elimination process as only regioisomers in position 3 are obtained, it is clearly not the case for Br and I.

As two regioisomers (**4** and **8**) are formed, an elimination-addition process via aryne intermediate can be certainly involved as favoured when strong bases (ex ; MeO^-K^+) and good leaving groups (I > Br) are concerned (Scheme 2). Quantum chemical calculations [24,25] indicate that this intermediate is more plausible than its 2, 3 analog and can lead to two regioisomers by reaction with nucleophiles.



Scheme 2 : elimination-addition pyridyne mechanism

The important loss of materials with Br and I (Entries 50, 51) can also be indicative of a contribution of a radical chain mechanism $S_{RN}1$ leading to a lot of non-identified and recovered coupling products and justifying the presence of pyridine in entry 51.

Comparison between Microwave and Conventional Heating : about non-thermal MW effects

Being established that the mechanism involved is certainly as addition-elimination S_NAr process, we finally foresee the possible specific (non-purely thermal) MW effects. To this purpose, we have

compared the yields obtained under strictly similar conditions by conventional heating (Δ) as under MW, even including same profiles of raise in temperature (Figure III).

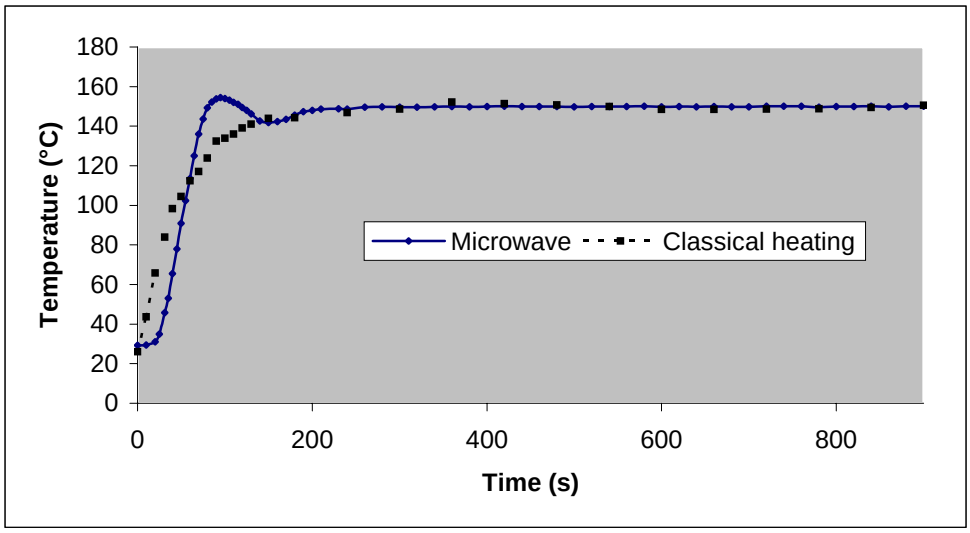


Figure III : Profiles of raises in temperature for entries 57, MW and Δ.

The main results are given in Table 9.

Table 9 : Influence of activation mode (Δ or MW).

Entry	Reagents	Exp. Conditions		Yields (%)	
		t_{min}	$T_{°C}$	MW	Δ
52	**1** + MeO^-K^+	30	70	74	75
53	**1** + MeO^-Na^+	120	150	36	22
54	**3.Cl** + MeO^-K^+	20	130	95	98
55	**3.Cl** + PhO^-K^+	45	200	55	1
56	**3.F** + PhO^-K^+	20	180	57	15
57	**5.Cl** + PhO^-K^+	15	150	65	34
58	**5.F** + PhO^-K^+ a)	15	150	80	70

a) in closed vessels (discover CEM reactor)

No specific MW effects were observed for methoxylation of 3-bromoquinoline (**1)** and 3-chloropyridine **3.Cl**, the most reactive systems. However, in the case of **1**, some MW specific effects appeared by reacting MeO^-Na^+ instead of MeO^-K^+ relatively with harder conditions (150 °C instead of 70 °C).

On the other hand, important specific effects were evidenced during phenoxylation of halopyridines. They are more important when the halogen lies in position 3 rather than in position 2 and are noticeably increased from F to Cl.

These differences in behaviour can be understood and rationalized by considering the enhancement in polarity during the progress of the reaction which is responsible for MW effects by increased electrostatic (dipole-dipole) interaction (stabilization) from the ground state to the transition state (TS) of the reaction. It thus results a decrease in the energy of activation. MW effects may be dependent on

the position of the TS along the coordinates [10,17] and increase with the difficult of the reaction (later TS) : "slower reacting systems tend to show a greater effect under microwave radiation than faster reacting ones".[26]

With such assumption, one can except and justify the increased sequences for MW effects :

- **3** > **5** > **1** (reaction temperatures : respectively 200, 150 and 70 °C)
- MeO^-Na^+ > MeO^-K^+ (150 versus 70 °C)
- Cl > F (ex : **3.Cl** 45 min, 200 °C versus **3.F** 20 min, 180 °C).

CONCLUSIONS

Solid-liquid phase transfer catalysis coupled with microwave irradiation was shown to be an efficient method for S_NAr reaction of quinoline and pyridine halides with alkoxides and phenoxides. Whereas for phenoxylation there is no need for any solvent, the addition of small amount of non-polar solvent is necessary during methoxylation for accurate monitoring of temperatures. Yields obtained and conditions involved here constitute a noticeable improvement over classical methods within the frame of Green Chemistry. Specific MW effects were evidenced for phenoxylation and interpreted in terms of late position of the transition state along the reaction coordinates.

EXPERIMENTAL

Typical experiment

18-crown-6 (0.5 mmol, 10 mol %) was added to the aromatic substrate (5 mmol) and potassium methoxide (525 mg - 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. S 402 software permitted programming in time and monitoring of the temperature by modulation of the power from 15 to 300 W. When performed under closed vessels (Entry 58), microwave irradiation were carried out in a CEM Discover reactor with both controls of temperature, power and pressure. Irradiation was carried out according to the conditions indicated in the Tables. At the end of the reaction, the organic products were extracted with ether or ethyl acetate and the solution filtrated was next through Celite 545. The products were identified (GC-MS, NMR spectrometry) by comparison with authentic samples and analyzed by GC. Under conventional heating conditions (thermostated oil bath), the same conditions were reproduced (time, pressure, glassware, stirring and identical profiles of raise in

temperatures). Under microwave conditions, the temperature was monitored with an infrared detector and emissivity factor was 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.

GC equipment

Capillary column CP Sil 19 CB, length = 25 m, inside diameter = 0.25 mm, film thickness = 0.20 µm, carrier gas = helium.

GC equipment fitted with a hardware (NCI 900 series interface) and software (Turbochrom) system developed by Perkin Elmer.

GC conditions and retention times for reactants and products are given in Table 10.

Table 10 : GC conditions and retention times for reactants and products.

Products or Reactants	GC Device	GC conditions	RT [a] (min)	Internal standard Products	RT [a] (min)
1	CG 8000 Series Fisons	80 → 250 °C 10 °C / min p_{He} = 50 kPa	11.6	Diethyl phthalate	15.5
2			14.4		
3.F	CG 8000 Series Fisons	80 → 250 °C 10 °C / min p_{He} = 50 kPa	4.6	Ethyl benzoate	14.3
3.Cl			8.1		
3.Br			10.4		
3.I			12.9		
4			6.7		
8			7.1		
5,Cl	GC 5160 Vega Series 2 Carlo Erba	100 → 250 °C 10 °C / min 10 min at 220 °C p_{He} = 70 kPa	4.7	Ethyl benzoate	7.3
6			12.0		
3.F	GC 5160 Vega Series 2 Carlo Erba	100 → 250 °C 10 °C / min 10 min at 220 °C p_{He} = 70 kPa	4.6	Ethyl benzoate	7.3
3.Cl			10.4		
7			12.9		

a) RT = retention time

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