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O-Arylation of Iodophenols with 2-Fluorobenzaldehyde Under Microwave Conditions

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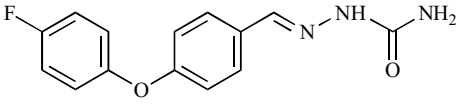
Abstract: The arylation of 4-iodo-, 2-iodo- and 3-iodophenols with 2-fluorobenzaldehyde may be carried out in the presence of K_2CO_3 in DMF as the solvent under microwave conditions. The arylation of 4-iodophenole was promoted by the use of triethylbenzylammonium chloride (TEBAC) as the phase transfer catalyst. In the other model reactions, the use of TEBAC was harmful. By-products formed by isomerization and disproportionation were also detected.

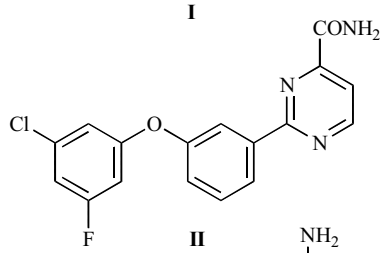
Keywords: 2-Flourobenzaldehyde, Iodophenols, Arylation, Microwave, Phase transfer catalysis.

1. INTRODUCTION

Phenoxyphenyl moieties are useful building blocks in the field of voltage gated sodium channel (VGSC) blockers. For example's sake the well-known analgesic and antiepilepticum **I** was synthesized by the *O*-arylation of 4-fluorophenol with 4-F-benzaldehyde in *N*,*N*-dimethylacetamide heating with K_2CO_3, the next step was the reaction with semicarbazide hydrochloride and NaOAc refluxing in EtOH/H_2O [1, 2]. Ilyin and his coworkers studied **I** as a state dependent blocker of mammalian voltage gated sodium channels [3].



I



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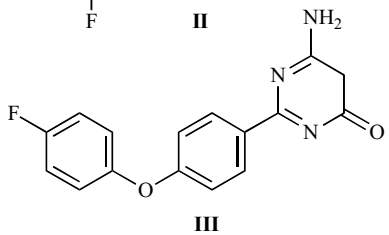
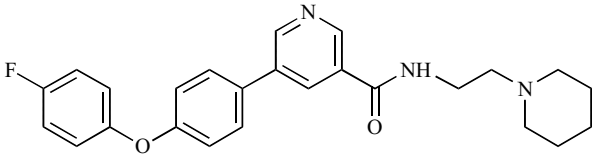


III

Compound **I** became a starting point for further VGSC blockers. Later its ring closed derivatives [4, 5], including the non-opioid analgesic "2-[3-(3-chloro-5-fluorophenoxy)-phenyl]-pyrimidine-4-carboxamide" (**II**) [4] and others (e.g. **III**) [5] were also described. These compounds are NaV1.2 sodium channel blockers. Later further derivatives of VGSC blockers were published, where the phenoxyphenyl moiety was combined with a substituted pyridine unit **IV** and **V** [6, 7] and other derivatives were also described [8-10]. The main diseases areas were ischemic neuronal damage, neurodegenerative problems, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, various types of pain, manic depression.



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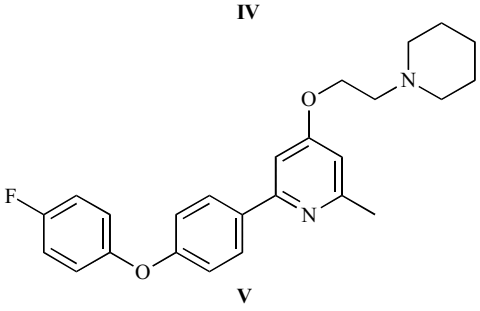
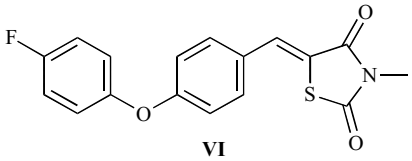


V

Compounds with phenoxyphenyl moiety containing a thiazolodione unit (**VI**) was also introduced [11]. The indications were various types of pain, irritable bowel syndrome (IBS), epilepsy, etc.



VI

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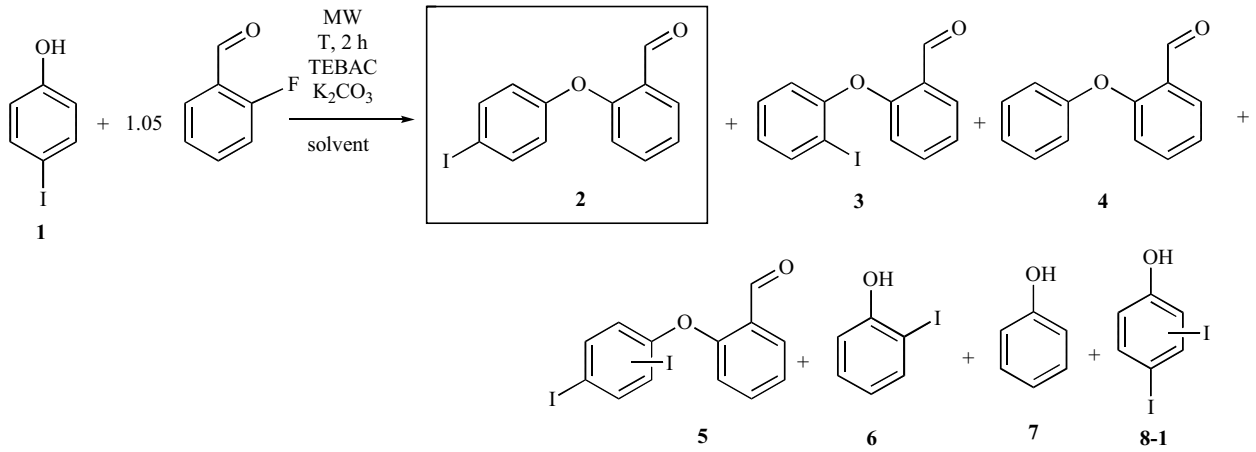


Scheme (1). *O*-Arylation of 4-Iodophenol (**1**) Under MW Conditions.

Microwave (MW) irradiation [12–14] and phase transfer catalysis (PTC) [15] represent attractive methods in environmentally friendly chemistry. A few *O*-alkylations of phenol derivatives were described, where there was no need to use a phase transfer catalyst under MW irradiation [16–19]. It is noted that MW-assisted heterogeneous phase *C*-alkylations did not require the use of phase transfer catalyst either [20-24]. However, in most cases, the combination of the MW and phase transfer catalytic techniques offered additional advantages [25]. Both S–L and L–L two phase alkylations of phenols were performed under combined MW–PTC techniques, the former using K_2CO_3/KOH [26] or K_2CO_3/NaOH [27] without any solvent, the latter utilizing NaOH/H_2O [28]. We found that in the S–L phase alkylation of phenols applying K_2CO_3 under solvent-free conditions, MW and PTC synergized each other [29, 30]. This was also true for other *O*-alkylations [31, 32]. Applying alkyl halides, the situation was similar for the *O*-alkylation of naphtholes. However, the benzylations could be performed best in acetonitrile solutions in the absence of phase transfer catalyst [33].

In this paper, the arylation of 4-, 2- and 3-iodophenols is studied with 2-fluorobenzaldehyde under MW and PTC conditions.

2. RESULTS AND DISCUSSION

The first model reaction was the arylation of 4-iodophenol (**1**) with 2-fluorobenzaldehyde in the presence of K_2CO_3 with or without triethylbenzylammonium chloride (TEBAC) in the absence or presence of solvent under MW conditions. In general, it was found that beside the expected 4-iodophenyl 2-formylphenyl ether (**2**), the 2-iodo isomer (**3**), the dehalogenated ether (**4**) and variations of the diiodo ethers (**5**) were also formed (Scheme **1**). The unreacted 4-iodophenol (**1**) appeared also as 2-iodophenol (**6**), phenol (**7**) and, in a few cases, as diiodophenols (marked generally by structure **8**).

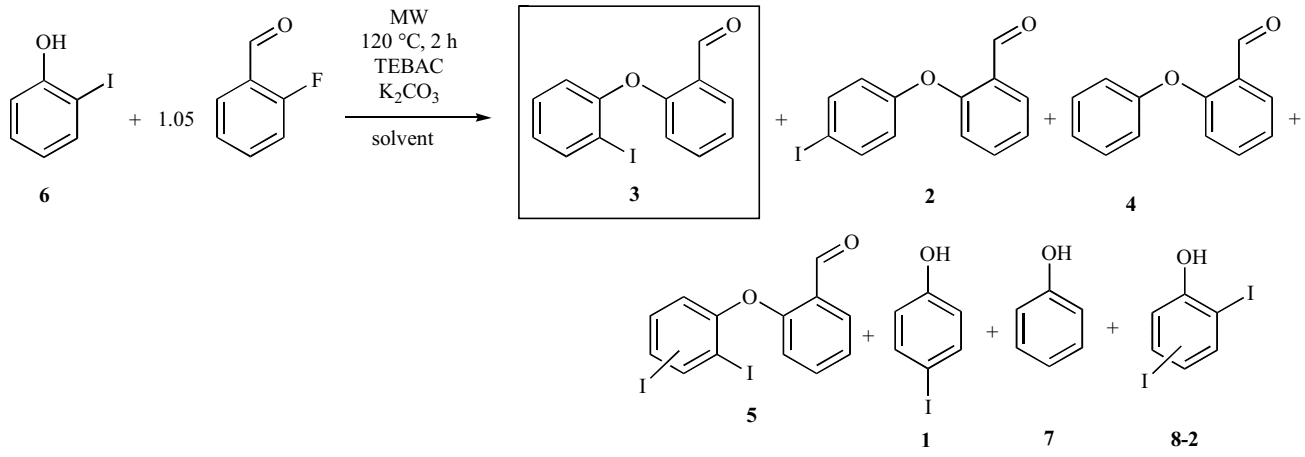
The composition of the reaction mixtures depended on the conditions: the use of catalyst and solvent, as well as temperature (Table **1**). Carrying out the arylation at 120 °C for 2 h without TEBAC and solvent, a quite complex mixture was formed including 42% of the expected product (**2**), 4% of the 2-iodo isomer (**3**), 8% of the dehalogenated product (**4**) and 8% of the diiodo components (**5**). The ethers **2-5** all together represented 62%. The remaining 38% covered 19% of unreacted 4-iodophenol (**1**), 8% of 2-iodophenol (**6**) and 11% of phenol (**7**) (Table **1**/Entry 1). The use of 5% or 10% of TEBAC, on the one hand, increased the proportion of the desired diaryl ether (**2**) to 46% and 65%, respectively, on the other hand led to "cleaner" reactions. The different mono- and diiodo isomers **3** and **5** represented only 6/7%, and no dehalogenated product (**4**) could be detected (Table **1**/Entries 2 and 3). However, the conversions remained incomplete. The thermal comparative experiment led to a lower conversion (41%), but in respect of the diaryl ethers, the reaction was more selective: beside the 41% of **2**, only 7% of the diiodo components (**5**) were formed (Table **1**/Entry 4). Elevation of the reaction temperature to 140 °C led to a complex mixture containing almost all possible components (**2-5**, **1**, **6** and **7**) in quantities of 6-36% (Table **1**/Entry 5). Then, we performed the arylations in solvents. In acetonitrile, again a complex mixture was obtained, no matter if 5% of TEBAC was added in or not. The only positive observation was that the proportion of the diaryl ether products (**2-5**) amounted to 85% (Table **1**/Entry 6). The use of DMF as the solvent, especially in the presence of increasing amount of TEBAC was very efficient (Table **1**/Entries 7-9). The proportion of the expected product **2** in the presence of DMF as the solvent was 67% (Table **1**/Entry 7). Adding 5% and 10% of the catalyst, the proportion of iodophenyl 2-formylphenyl ether **2** was 80% and 92%, respectively (Table **1**/Entries 8 and 9). In the latter case, only 8% of the 2-iodo isomer (**3**) was present as an additional component meaning that the best option is to carry out the reaction in the presence of K_2CO_3 and 10% of TEBAC in DMF at 120 °C. The thermal control experiment gave ether (**2**) in a conversion of 76%. It is noteworthy that only 24% of unreacted 4-iodophenol (**1**) was present beside product **2** (Table **1**/Entry 10). However, the conversion remained unchanged even after a prolonged heating.

One can see that especially the solvent-free and MW-assisted arylations were complicated by isomerization and disproportionation side reactions. The 4-iodophenyl product (**2**) could be isomerized to the 2-iodo species (**3**) and the expected product (**2**) could be disproportionated to

Table 1. *O*-Arylation of 4-Iodophenol (1) Under MW and Thermal Conditions.

Entry	Mode of Heating	TEBAC	Solvent	T (°C)	Composition of the Reaction Mixtures (%)[a]									
					2	**3**	**4**	**5**	**∑ ethers**	**1**	**6**	**7**	**8-1**	**∑ phenols**
1	MW	–	–	120	42	4	8	8	62	19	8	11	0	38
2	MW	5%	–	120	46	3	0	3	52	21	8	12	7	48
3	MW	10%	–	120	65	2	0	5	72	15	2	5	6	28
4	Δ	10%	–	120	41	0	0	7	48	30	4	8	10	52
5	MW	–	–	140	36	6	12	6	60	8	8	24	0	40
6	MW	–	MeCN	120	48	14	18	5	85[b]	2	8	5	0	15
7	MW	–	DMF	120	67	1	9	1	78	14	2	4	2	22
8	MW	5%	DMF	120	80	2	7	2	91	4	2	2	1	9
9	MW	10%	DMF	120	92	8	0	0	100	0	0	0	0	0
10	Δ	10%	DMF	120	76	0	0	0	76[c]	24	0	0	0	24

[a]On the basis of GC and GC-MS measurements.
[b]No change in the presence of 5% of TEBAC.
[c]No change after a prolonged reaction time of 3 h.



Scheme (2). *O*-Arylation of 2-Iodophenol (**6**) Under MW Conditions.

dehalogenated ether **4** and to diiodo derivatives **5**. The same kind of side reactions occurred with 4-iodophenol (**1**) to form by-products (**6-8**). It is also obvious that the presence of TEBAC, and what is more important, the use of DMF as the solvent promoted a clear-cut, quite selective arylation. Without MW irradiation no complete conversion could be attained. The thermal experiments were more selective, but led to incomplete conversions. Hence, the positive role of MW irradiation is unambiguous.

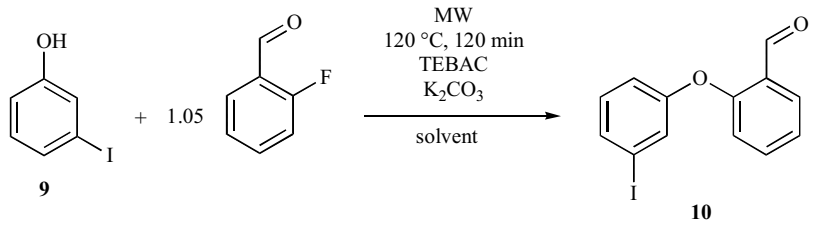
The next model reaction was the arylation of 2-iodophenol (**6**) with the same arylating agent, 2-fluorobenzaldehyde. The situation was similar to the previous case: beside the expected product of 2-iodophenyl 2-formylphenyl ether (**3**), the 4-iodo derivative (**2**), the dehalogenated and the diiodo products (**4** and **5**) were also formed as a result of isomerization and disproportionation (Scheme **2**). The 4-iodophenol (**1**), phenol (**7**) and diiodophenols (**8**) were also formed.

The results are listed in Table **2**. Regarding the solvent-free accomplishments, the composition was more favourable in the absence of TEBAC as compared to the case when it was present. In the absence of catalyst, 50% of the expected product (**3**) was formed along with a 29% portion of the other diaryl ethers (**2**, **4** and **5**) (Table **2**/Entry 1). At the same time, in the presence of TEBAC, 32% of product **3** and 11% of diaryl ethers **2**, **4** and **5** were formed (Table **2**/Entry 2). It can also be seen that without the catalyst, the ratio of the phenolic components (**6**, **1**, **7**, and **8**) was 21%, while with TEBAC, the proportion of phenols was 57%. All these experiences suggests that in contrast with the reaction of 4-iodophenol (**1**), in the case of the arylation of 2-iodophenol (**6**), the presence of TEBAC is harmful, as less of the expected diaryl ether (**3**) was formed. In acetonitrile without TEBAC, the 2-iodophenyl aryl ether **3** was formed in 55%, while the other diaryl ethers (**2**, **4** and **5**) only in a small quantity (5%) (Table **2**/Entry 3). In DMF, the arylation was

Table 2. *O*-Arylation of 2-Iodophenol (6) Under MW Conditions.

Entry	TEBAC	Solvent	Composition of the Reaction Mixtures (%)[a]									
			3	**2**	**4**	**5**	**∑ ethers**	**6**	**1**	**7**	**8-2**	**∑ phenols**
1	–	–	50	4	7	18	79	14	0	7	0	21
2	5%	–	32	3	4	4	43	33	8	8	8	57
3	–	MeCN	55	1	3	1	60	32	1	6	1	40
4	–	DMF	85	-	2	2	89	11	0	0	0	11
5	5%	DMF	59	14	0	0	73[b]	23	0	0	0	23
6	10%	DMF	76	0	0	0	76[b]	15	0	0	0	15

[a]On the basis of GC and GC-MS measurements.
[b]The reaction mixture contained 4-9% of 2-iodophenyl benzyl ether.



Scheme (3). *O*-Arylation of 3-Iodophenol (**9**) Under MW Conditions.

Table 3. *O*-Arylation of 3-Iodophenol (9) Under MW Conditions.

Entry	TEBAC	Solvent	Composition of the Reaction Mixture (%)[a]		
			9	**10**	**Unknown by-product**
1	–	–	14	80	6
2	5%	–	30	66	4
3	–	MeCN	27	73	–
4	–	DMF	9	89[b]	–

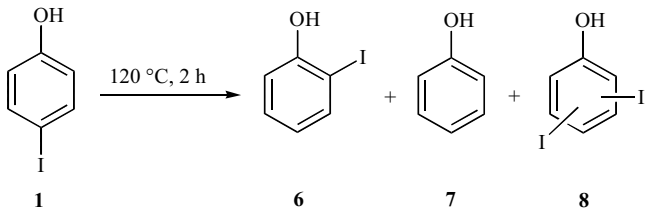
[a]On the basis of GC and GC-MS measurements.
[b]The reaction mixture contained 2% of 2-phenoxy benzaldehyde (**4**).

more selective and the conversion was higher. 85% of product **3** was formed at a conversion of 89% (Table **2**/Entry 4). It was not, however, possible to obtain a complete conversion. It was also observed that performing the *O*-arylation in the presence of TEBAC, the proportion of the main product (**3**) and the conversion were somewhat lower (Table **2**/Entries 5 and 6). Moreover, a new by-product 2-iodophenyl benzyl ether coming from the reaction of 2-iodophenol with TEBAC was also formed. It is again seen that the catalyst does not enhance a complete and clear-cut arylation.

In the above series, the best reaction was when the two reactants met in DMF solution in the absence of TEBAC. It is surprising that while in the arylation of 4-iodophenol (**1**) the use of TEBAC is clearly advantageous, the arylation of 2-iodophenol (**6**) becomes more complex and reluctant in the presence of the catalyst. In the present stage of our work, the reason for this experience is unknown.

The last series of reaction involved the arylation of 3-iodophenol (**9**). As compared to the previous models, this reaction way much simpler (Scheme **3**). Only a few by-products were formed and identified.

In the absence of catalyst and solvent, 80% of the expected product, 3-iodophenyl 2-formylphenyl ether (**10**) was formed. The conversion was 86% (Table **3**/Entry 1). In the presence of TEBAC, the proportion of **10** and the conversion were lower (Table **3**/Entry 2). In acetonitrile solution without catalyst, 73% of diaryl ether **10** was formed without any by-product (Table **3**/Entry 3). The best experiment was, when the arylation was performed in DMF. This occasion, the main product (**10**) was formed in 89%. Beside this, 9% of the starting material (**9**) and 2% of 2-phenoxy



1 **6** **7** **8**

Scheme (4). Disproportionation of 4-Iodophenol (**1**).

Table 4. Disproportionation of 4-Iodophenol (1) at 120 °C for 2 h.

Entry	Mode of Heating	K_2CO_3 (1 equiv.)	TEBAC (5%)	Solvent	1	6	7	8
1	MW	+	–	–	15	29	41	15
2	Δ	+	–	–	17	27	33	23
3	MW	–	–	MeCN	100	0	0	0
4	MW	+	–	MeCN	51	13	21	15
5	MW	+	+	MeCN	53	11	19	17

benzaldehyde (**4**) formed by dehalogenation were present (Table **3**/Entry 4).

It can be said that similarly to the case of the arylation of 2-iodophenol (**6**), the arylation of 3-iodophenol (**7**) is also disfavored in the presence of TEBAC as the catalyst.

As it was stated above, the reaction mixtures were analyzed by GC and GC-MS. Most of the results listed in Tables **1**–**3** are the average of 2-3 independent experiments. The main and desired iodophenyl 2-formylphenyl ethers **2**, **3** and **10** were obtained by column chromatography from the best experiments that were the runs marked by Table **1**/Entry 9, Table **2**/Entry 4 and Table **3**/Entry 4, respectively. Diaryl ethers **2**, **3** and **10** were obtained in yields of 75-85% in pure forms and were identified by ^{13}C and ^{1}H NMR, as well as mass spectral data. Compound **2** was briefly mentioned in the literature [34] without characterization, while species **10** was characterized only by ^{1}H NMR spectral data [35]. The other components, formed in most of the cases as minor components, were identified on the basis of mass spectrometry.

Finally, the isomerization and disproportionation reaction of 4-iodophenol (**1**) was studied in "blinde probe" experiments. The possible reaction course is shown in Scheme **4**. The results are summarized in Table **4**. It can be seen that disproportionation takes place both under MW irradiation and on conventional heating, no matter if a solvent is used or not. In acetonitrile, the conversion of 4-iodophenol was only 51%. No transformation occurred in the absence of K_2CO_3. The use of 5% of TEBAC did not affect the outcome of the reaction. To the best of our knowledge, we are the first to observe these troublesome side reactions. It is also noted that in case of suitably fast concurrent arylations, the side reactions may be depressed.

In conclusion, the arylations of iodophenols with 2-fluorobenzaldehyde were optimized under MW conditions. DMF as the solvent was advantageous in all cases, but TEBAC as the phase transfer catalyst enhanced the arylation only in the reaction with 4-iodophenol (**1**).

3. EXPERIMENTAL

3.1. General

The chemicals were purchased from Sigma-Aldrich company.

The arylations were carried out in a CEM Discover [300 W] microwave reactor equipped with a pressure controller using 20–30 W irradiation.

GC was carried out on an HP5890 series 2 GC-FID chromatograph, using a 15 m × 0.18 mm Restek, Rtx-5 column with a film layer of 0.20 μm. The temperature of the column was initially held at 40 °C for 1 min, followed by programming at 25 °C/min. up to 300 °C, and a final period at 300 °C (isothermal) for 10 min. The temperature of the injector was 290 °C, and of the FID detector 300 °C. The carrier gas was N_2.

GC-MS was also carried out on an Agilent 6890 N-GC-5973 N-MSD chromatograph, using a 30 m × 0.25 mm Restek, Rtx-5SILMS column with a film layer of 0.25 μm. The initial temperature of column was 45 °C for 1 min, followed by programming at 10 °C/min. up to 310 °C and a final period at 310 °C (isothermal) for 17 min. The temperature of the injector was 250 °C. The carrier gas was He and the operation mode was splitless.

^{13}C and ^{1}H NMR spectra were obtained in $CDCl_3$ solution on a Bruker AV-300 spectrometer operating at 75.5 and 300 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 and TMS.

Mass spectra were obtained using a Q-TOF Premier mass spectrometer in positive electrospray mode.

3.2. General Procedure for *O*-Arylation of Iodophenols with 2-Fluorobenzaldehyde under MW Conditions

A mixture of 0.22 g (1.0 mmol) of 2-, 3- or 4-iodophenol, 0.11 mL (1.1 mmol) of 2-fluorobenzaldehyde, 0.14 g (1.0 mmol) of potassium carbonate and in certain cases 11.4 mg

(0.050 mmol) of TEBAC in a closed vial was irradiated in a CEM Discover microwave reactor at 120-140 °C for 2 hours. The reaction mixture was taken up in 25 mL of ethyl acetate and the suspension was filtered. Evaporation of the volatile components provided the crude product that was passed through a thin (ca. 2–3 cm) layer of silica gel using ethyl acetate as the eluant to give an oil that was analysed by GC–MS or GC.

Similar reactions were carried out in 3 mL of acetonitrile or *N,N*-dimethylformamide as the solvent. The work-up was similar to that described for the solvent-free alkylations above, but in this case, ethyl acetate did not have to be added.

The major components of the above reactions, such as compounds **2**, **3** and **8** were obtained in a pure form by repeated chromatography as above, but using longer columns.

In a few cases, control experiments were performed in a similar way under conventional heating.

The following compounds were thus prepared:

4-iodophenyl 2-formylphenyl ether (2) [34] Yield: 85%; ^{13}C NMR ($CDCl_3$): δ 87.3 ($C_{4'}$), 118.7 (C_3), 121.3 ($C_{2'}$), 123.9 (C_5), 127.1 (C_1), 128.7 (C_6), 135.8 (C_4), 139.1 ($C_{3'}$), 156.6 ($C_{1'}$), 159.2 (C_2), 189.0 (C=O); ^{1}H NMR ($CDCl_3$): δ 6.83 (d, J = 8.6 Hz, 2H, $C_{2'}$H), 6.91 (d, J = 8.3 Hz, 1H, C_3H), 7.23 (t, J = 7.6 Hz, 1H, C_5H), 7.54 (t, J = 7.9 Hz, 1H, C_4H), 7.68 (d, J = 8.6 Hz, 2H, $C_{3'}$H), 7.95 (d, J = 7.7 Hz, 1H, C_6H), 10.46 (s, 1H, C(O)H); $[M+Na]^+_{found}$ = 346.9547, $C_{13}H_9O_2NaI$ requires 346.9545.

2-iodophenyl 2-formylphenyl ether (3) Yield: 75%; ^{13}C NMR ($CDCl_3$): δ 89.2 ($C_{2'}$), 117.3 ($C_{6'}$), 120.5 (C_3), 123.5 (C_5), 126.3 (C_1), 126.5 ($C_{4'}$), 128.6 ($C_{5'}$), 129.9 (C_6), 135.7 (C_4), 140.3 ($C_{3'}$), 155.4 ($C_{1'}$), 159.4 (C_2), 189.3 (C=O); ^{1}H NMR ($CDCl_3$): δ 6.75 (d, J = 8.3 Hz, 1H, $C_{6'}$H), 6.96 (d, J = 7.5 Hz, 1H, C_3H), 6.99 (t, J = 7.9 Hz, 1H, $C_{4'}$H), 7.20 (t, J = 7.4 Hz, 1H, C_5H), 7.37 (t, J = 8.1 Hz, 1H, $C_{5'}$H), 7.50 (t, J = 8.2 Hz, 1H, C_4H), 7.91 (d, J = 7.8 Hz, 1H, $C_{3'}$H), 7.97 (d, J = 7.7 Hz, 1H, C_6H), 10.59 (s, 1H, C(O)H); $[M+Na]^+_{found}$ = 346.9551, $C_{13}H_9O_2NaI$ requires 346.9545.

3-iodophenyl 2-formylphenyl ether (10) Yield: 81%; ^{13}C NMR ($CDCl_3$): δ 94.4 ($C_{3'}$), 118.4 ($C_{6'}$), 118.9 (C_3), 124.0 (C_5), 127.0 (C_1), 128.1 ($C_{2'}$), 128.7 ($C_{5'}$), 131.3 (C_6), 133.3 ($C_{4'}$), 135.8 (C_4), 157.0 ($C_{1'}$), 159.0 (C_2), 188.9 (C=O); ^{1}H NMR ($CDCl_3$): δ 6.92 (d, J = 8.3 Hz, 1H, $C_{6'}$H), 7.00–7.14 (m, 2H, C_3H, $C_{5'}$H), 7.23 (t, J = 8.3 Hz, 1H, C_5H), 7.41 (s, 1H, $C_{2'}$H), 7.52 (t, J = 8.7 Hz, 1H, C_4H), 7.56 (d, J = 7.4 Hz, 1H, $C_{4'}$H), 7.94 (d, J = 7.7 Hz, 1H, C_6H), 10.45 (s, 1H, C(O)H); δ[35] ($CDCl_3$) 6.90-7.96 (m, 8H), 10.48 (s, 1H); $[M+Na]^+_{found}$ = 346.9551, $C_{13}H_9O_2NaI$ requires 346.9545.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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