Microwave-Assisted Alkylation of Phenols by Quaternary Onium Salts

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Abstract: The alkylation of cresol and its analogues was accomplished by quaternary onium salts under solventless and microwave (MW) conditions using Cs_2CO_3 as the base. The beneficial energy absorbing ability of the onium salts could be clearly observed under MW conditions as compared to the thermal experiments and was relevant in the range of 110–125 °C.

Keywords: Microwave, solventless accomplishment, O-alkylation, phenols, ammonium salts.

1. INTRODUCTION

These days, the utilization of the microwave (MW) technique in organic synthesis has become widespread [1, 2]. A search for specific MW-effects is in focus [3]. Specific MW-effects were observed in the quaternization of phosphines with onium salts [4]. The result is an enhancement in the polarity of the transition state. Onium salt additives were useful in MW-assisted Diels–Alder reactions [5].

Tetramethylammonium chloride and other onium salts could be used successfully in the alkylation of a variety of phenols and naphthols using an alkali carbonate under MW or thermal conditions [6, 7]. It is a drawback that this method requires the use of a solvent. It was observed by us that the outcome of the O- versus C-alkylation in the solvent-free benzylation of phenol derivatives was dependent on the absence or presence of base and catalyst under MW irradiation [8, 9].

We wished to study in detail if the use of commercially available simple quaternary ammonium salts offers advantages in the solvent-free MW-assisted alkylation of phenol derivatives.

2. RESULTS AND DISCUSSION

The MW-assisted benzylation of cresol was carried out using 1.2 eq. of triethylbenzylammonium chloride (TEBAC) under solventless conditions in the presence of 1.0 eq. of K_2CO_3 or Cs_2CO_3 in the range of 110–150 °C. Comparative thermal experiments were also performed.

In general, it can be said that the formation of the 4-methylphenyl benzyl ether (**2**) was quite selective, but in a few cases small quantities or traces of 4-methylphenyl ethyl ether **3**, 2-benzyl-4-methylphenol **4**, 2-benzyl-4-methylphenyl benzyl ether **5** and dibenzyl-4-methylphenol **6** were also formed (Scheme **1**, for details see Table **1**).

Using K_2CO_3 at 125 and 150 °C, the conversions remained below 26%, and there was no significant difference between the results of the MW and thermal accomplishments (Table **1**/Entries 1 vs. 2 and 3 vs. 4). Applying Cs_2CO_3 in the range of 110–150 °C, the conversions were significantly higher. The MW variations took place in conversions of ≥74% toward **2** (and **3**), these being, 10–25% higher as compared to the values of the thermal control experiments (Table **1**/Entries 5/6, 7/8 and 9/10). The best results were obtained by MW irradiation at 150 °C for 5 min. In this case, the conversion was 91% (Table **1**/Entry 10) and the isolated yield of **2** was 74%. After an irradiation time of 10 min, the benzylation was complete. Appearance of the side products **3-6** was relevant when Cs_2CO_3 was used as the base.

Triethylbenzylammonium bromide (TEBAB) was also tested as a MW-absorber benzylating agent. The conditions were similar to those applied above; however, in these cases only Cs_2CO_3 was used. The results listed in Table **2** suggest that the use of TEBAB offers no further advantage over that of TEBAC, as fully comparable results were obtained (Table **2**/Entries 1–6). It can be seen that the most significant difference between the thermal and MW reactions was realized at 110 °C where the proportion of 4-methylphenyl benzyl ether is 40 vs. 77% (Table **2**/Entries 1/2). At the same time, the difference is decreased at higher temperature (At 125 °C it is 24%, while at 150 °C it is only 4%, see Table **2**/Entries 3/4 and 5/6).

One can see that the use of TEBAC and TEBAB as benzylation agents in O-alkylation leads to significantly faster reactions if Cs_2CO_3 is used, as compared to the thermal variations. The increase in the rate is promoted by the special heat absorbing ability of the onium salts.

The MW-absorber ability of a few onium salts such as TEBAC, TEBAB and tetrabutylammonium bromide (TBAB) was investigated in solution. It was found that by irradiating 0.37 mol/L onium salt solutions at 5–8W, their temperature was ≥40 °C higher, as compared to the control experiment

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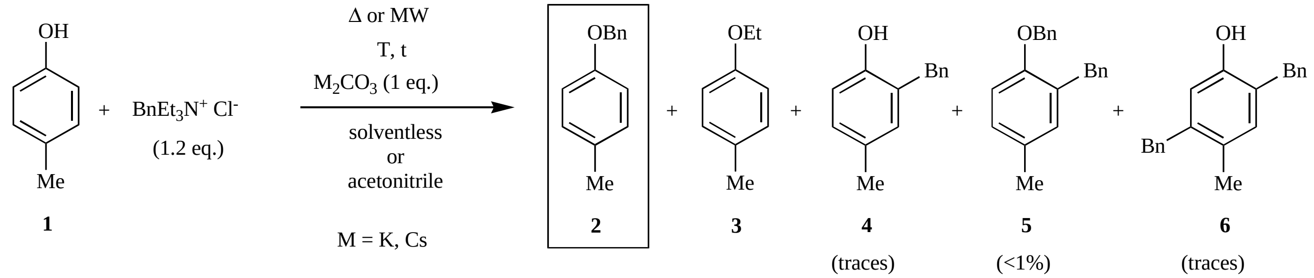


Scheme 1.

Table 1. The Benzylation of Cresol with TEBAC under Solventless Conditions

Metal of the carbonate	Mode of heating	T (°C)	t (min)	1	2	3	Entry
				(%)[a]			
K	Δ	125	20	81	19	0	1
K	MW	125	10[b]	83	17	0	2
K	Δ	150	10	74	26	0	3
K	MW	150	< 5[b]	74	26	0	4
Cs	Δ	110	20	51	48	1	5
Cs	MW	110	20[b]	26	73	1	6
Cs	Δ	125	20	31	68	1	7
Cs	MW	125	15[b]	14	83	3	8
Cs	Δ	150	10	20	79	1	9
Cs	MW	150	5[b]	9	89[c]	1	10

[a] At least from two independent measurements.
[b] There is no significant change on further irradiation.
[c] The reaction mixture comprised < 1% of 2-benzyl-4-methylphenyl benzyl ether.

Table 2. The Benzylation of Cresol with TEBAB using Cs_2CO_3 under Solventless Conditions

Mode of heating	T (°C)	t (min)	1	2	3	Entry
			(%)[a]			
Δ	110	20	56	40	4	1
MW	110	10[b]	18	77	5[c]	2
Δ	125	20	39	58	3	3
MW	125	10[b]	14	82	3[c]	4
Δ	150	10	19	80	1	5
MW	150	5[b]	12	84	3[c]	6

[a] At least from two independent measurements.
[b] There is no significant change on further irradiation.
[c] The reaction mixture comprised <1% of 2-benzyl-4-methylphenyl benzyl ether.

(acetonitrile alone). Applying 5 W, the acetonitrile was warmed to 70 °C, while the temperature of the TEBAC, TEBAB and TBAB solutions increased to 110, 107 and 112 °C, respectively (Fig. **1**). In this case, the most efficient onium salt was TBAB. An irradiation of 8 W warmed the acetonitrile to 86 °C, while the onium salt solutions rose to ca. 130 °C (Fig. **2**). Applying 10 W, both the acetonitrile and the onium salt solutions were warmed to ca 135 °C regardless of the composition (Fig. **3**). It is obvious that at lower energy irradiation, the presence of an onium salt is beneficial in acetonitrile. TBAB seems to be the most efficient.

The MW-assisted benzylation was also investigated in acetonitrile solution (Table **3**). The benzylations were definitely slower in acetonitrile (Table **3**/Entries 3 and 4), but using K_2CO_3 as the base, the conversions were, eventually, significantly higher as compared to those obtained in the absence of solvent. See the conversions of 28 and 16%, obtained after 1 h in solvent and 20 min under solventless

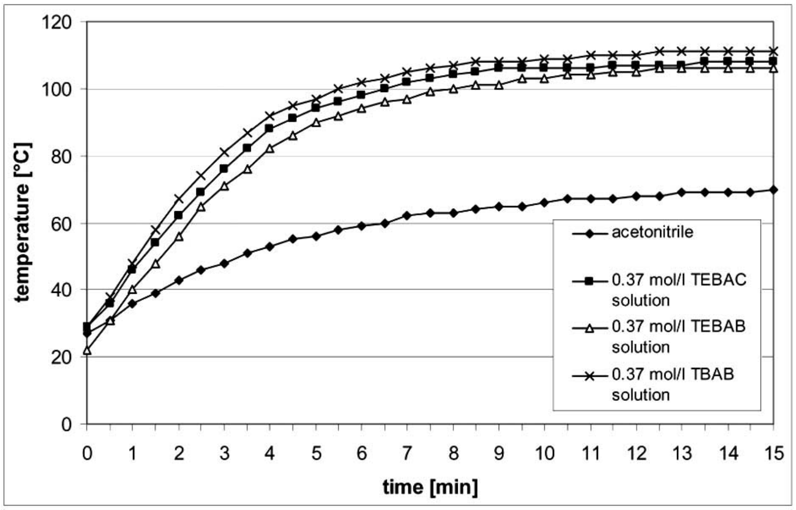


Fig. (1). Heat uptake of acetonitrile and acetonitrile/onium salt mixtures measured at an irradiation of 5 W in a CEM Discover reactor.

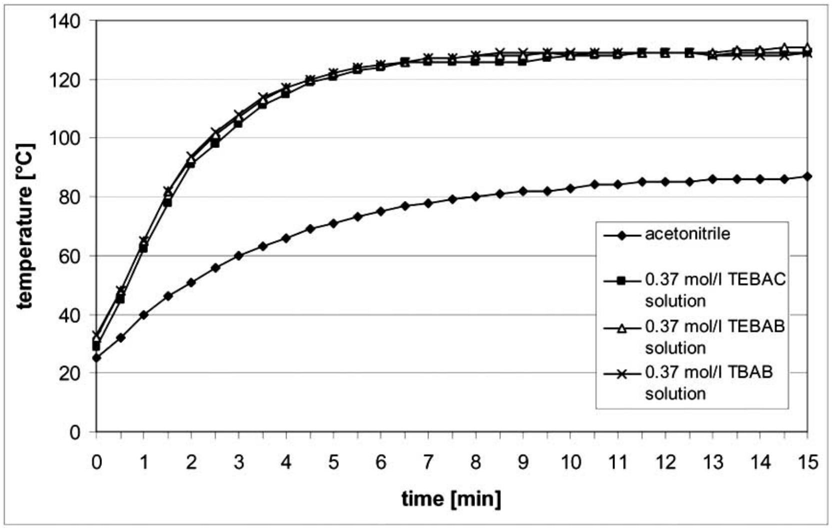


Fig. (2). Heat uptake of acetonitrile and acetonitrile/onium salt mixtures measured at an irradiation of 8 W in a CEM Discover reactor.

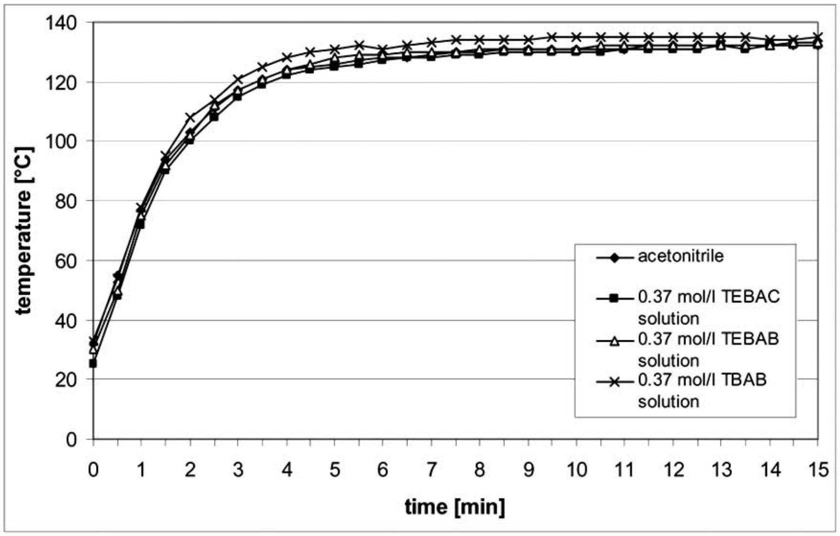


Fig. (3). Heat uptake of acetonitrile and acetonitrile/onium salt mixtures measured at an irradiation of 10 W in a CEM Discover reactor.

Table 3. The Benzylation of Cresol with TEBAC under MW Conditions

Metal of the carbonate	Solvent	T (°C)	t (min)	1	2	Entry
				(%)[a]		
K	–	110	20[b]	84	16	1
K	acetonitrile	110	60	72	28	2
Cs	–	110	20[b]	26	73	3
Cs	acetonitrile	110	20	68	32	4
Cs	acetonitrile	110	45	25	75	5
K	–	125	10[b]	83	17	6
K	acetonitrile	125	45	54	46	7
Cs	–	125	15[b]	14	83[c]	8
Cs	acetonitrile	125	45	28	70[c]	9

[a] At least from two independent measurements.
[b] There is no significant change on further irradiation.
[c] The reaction mixture comprised 2-3% of 4-methylphenyl ethyl ether.

Table 4. The Butylation of Cresol with TBAB under Solventless Conditions

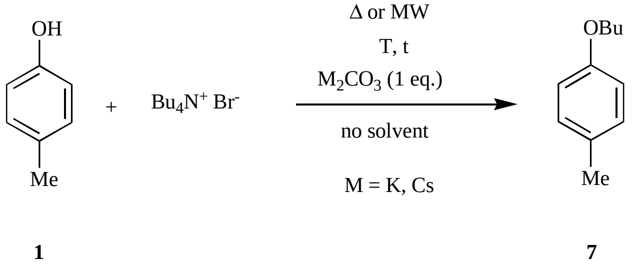
Metal of the carbonate	Mode of heating	T (°C)	t (min)	1	7	Entry
				(%)[a]		
K	Δ	150	10	93	7	1
K	MW	150	10	90	10	2
K	MW	150	30	84	16	3
K	Δ	170	10	90	10	4
K	MW	170	10	83	17	5
Cs	Δ	125	20	89	11	6
Cs	MW	125	20	69	31	7
Cs	Δ	150	20	71	29	8
Cs	MW	150	20	13	87	9

[a] At least from two independent measurements.

conditions, respectively, both at 110 °C (Table **3**/Entries 1 and 2), or the conversions of 46 and 17% detected after 45 min (in solvent) and 10 min (solventless), respectively, at 125 °C (Table **3**/Entries 6 and 7). Applying Cs_2CO_3 as the base, the conversions obtained under solventless conditions could be reproduced in acetonitrile (at 110 °C) (Table **3**/Entries 3 and 5) or were approached (at 125 °C) (Table **3**/Entries 8 and 9). One can see that no solvent should be used in the benzylation under discussion unless K_2CO_3 is used as the base.

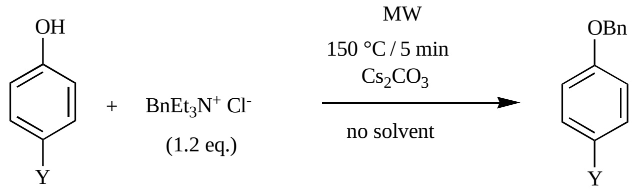
The butylation of cresol was also attempted using TBAB under solventless conditions (Scheme **2**). With the addition of K_2CO_3 at 150 or 170 °C, the conversions remained below 17%, no matter if traditional heating or MW irradiation was used (Table **4**/Entries 1–5). The use of Cs_2CO_3 led to variable conversions. Under thermal conditions at 125 °C, the conversion was 11% (Table **4**/Entry 6), while under MW irradiation at 150 °C, the conversion was 87% (Table **4**/Entry 9). MW at 125 °C and heating at 150 °C led to intermediate states ((Table **4**/Entries 7 and 8). 4-Methylphenyl buthyl ether **7** was isolated from the best experiment (Entry 9) in a yield of 47%.

Finally, phenol and *p*-chlorophenol were alkylated by TEBAC under the conditions found to be optimal for the benzylation of cresol. According to this the MW-assisted alkylation of these phenols were carried out at 150 °C for 5 min without the use of solvent, in the presence of Cs_2CO_3 (Scheme **3**). It was found that the benzylation of phenol took place similarly to that of cresol, but the alkylation of 4-chlorophenol was somewhat slower. Isolated yields of aryl benzyl ethers **9a** and **9b** amounted to 75 and 63%, respectively.



Scheme 2.

In conclusion, the onium salts may be suitable alkylating agents under MW and solventless conditions using Cs_2CO_3. Due to the MW absorbing ability of the onium salts, these alkylations take place relatively fast.



8 Y = H (**a**), Cl (**b**) **9**

Scheme 3.

3. EXPERIMENTAL

3.1. General

The alkylations were carried out in a CEM Discover [300 W] microwave reactor equipped with a pressure controller using 5-15 W irradiation. The length and diameter of the vial used was 8.8 and 1.3 cm, respectively.

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 H_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.

3.2. General Procedure for the Benzylation of Phenol Derivatives with Quaternary Onium Salts Under Solventless and MW Conditions

A mixture of 1.0 mmol of phenol derivative (0.11 g of cresol, 0.13 g of 4-chlorophenol or 0.09 g of phenol), 1.0 mmol of alkali carbonate (0.14 g of K_2CO_3 or 0.33 g of Cs_2CO_3) and 1.2 mmol of the quaternary onium salt (273 mg of TEBAC, 327 mg of TEBAB or 387 mg of TBAB) in a closed vial was irradiated (5–15 W) in the microwave reactor at the appropriate temperature for the appropriate time (see Tables **1**, **2**, **4**, **5**). 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 cm) layer of silica gel using ethyl acetate as the eluant to give an oil that was analysed by GC–MS or GC. The results are listed in Tables **1**, **2**, **4**, **5**.

Similar reactions were carried out in 3 mL of acetonitrile as the solvent (see Table **3**). The work-up was similar to that described for the solventless alkylations, but in this case ethyl acetate did not have to be added.

Table 5. The Benzylation of Phenol and 4-Chlorophenol with TEBAC using Cs_2CO_3 under Solventless and MW Conditions at 150 °C for 5 min

Y	4-YC_6H_4OH	4-YC_6H_4OBn	Entry
	(%)^{a,b}		
H	9 (8a)	90 (8a)	1
Cl	20 (8b)	78 (8b)	2
Me	9 (1)	89 (2)	3

^{a}At least from two independent measurements.
^{b}The missing quantity (1-2%) covers by-products.

Compound 2: yield: 74 %^{1}H NMR ($CDCl_3$) δ 2.28 (3H, Me), 5.03 (2H, CH_2), 6.86–7.09 (4H, ArH-1), 7.29–7.43 (5H, ArH-2); the data are identical with those described for an authentic sample [8]; $(M+H)^+_{found}$ = 199.1118, $C_{14}H_{15}O$ requires 199.1123.

Compound 7: yield: 47%; ^{1}H NMR ($CDCl_3$) δ 0.88–0.98 (3H, CH_2CH_3), 1.41–1.54 (2H, CH_2CH_3), 1.69– 1.78 (2H, OCH_2CH_2), 2.26 (3H, $ArCH_3$), 3.89–3.93 (2H, OCH_2), 6.78 (2H, ArH-1), 7.05 (2H, ArH-2); the compound was described [10], but no ^{1}H NMR data were found in the literature; $(M+H)^+$ = 165.

Compound 9a: yield: 75%; ^{1}H NMR ($CDCl_3$) δ 5.17 (2H, CH_2), 7.06–7.57 (10H, ArH); the data are identical with those described for an authentic sample [11]; (M+H) = 185.

Compound 9b: yield: 63%; ^{1}H NMR ($CDCl_3$) δ 5.08 (2H, CH_2), 6.95 (2H, ArH-1), 7.29 (2H, ArH-2), 7.38–7.46 (5H, ArH-3); the data are identical with those described for an authentic sample [11]; $(M+H)^+$ = 219 (for the ^{35}Cl isotope).

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