Tetrahedron Letters 49 (2008) 5039–5042

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Chemoselectivity in the microwave-assisted solvent-free solid–liquid phase benzylation of phenols: O- versus C-alkylation

György Keglevich [a,*], Erika Bálint [a], Éva Karsai [b], Alajos Grün [c], Mária Bálint [b], István Greiner [d]

[a] Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary
[b] Bálint Analytics, H-1116 Budapest, Fehérvári Street 144, Hungary
[c] Research Group of the Hungarian Academy of Sciences at the Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary
[d] Gedeon Richter Plc., H-1475 Budapest, Hungary

ARTICLE INFO

Article history:
Received 3 April 2008
Revised 2 June 2008
Accepted 10 June 2008
Available online 14 June 2008

Keywords:
Microwave heating
Phase transfer catalysis
Alkylation
Selectivity

ABSTRACT

The outcome of the solvent-free benzylation of phenol and 4-substituted phenols (such as 4-cresol and 4-chlorophenol) under MW irradiation was found to depend on the absence or presence of the base (K_2CO_3) and catalyst (triethylbenzylammonium chloride (TEBAC)). Reaction of benzyl halides at 80–120 °C in the presence of K_2CO_3 and TEBAC resulted in O-alkylation in high (89–96%) chemoselectivities. In the absence of TEBAC, the proportion of C-alkylation was considerable (16–34%). Omitting also K_2CO_3 from the reaction mixture, C-alkylation became predominant. In the case of 4-*tert*-butylphenol, the presence of TEBAC promoted C-alkylation. The selectivity of the alkylations can be fine-tuned by choosing the appropriate conditions.

Phase transfer (PT) catalysis[1] and microwave (MW) techniques[2] have become powerful tools in environmentally friendly ('green') chemistry. It was a logical extension to combine PT catalysis and the MW technique, and to date, many publications have disclosed the advantages of MW assisted PT catalytic reactions.[3]

We found that the MW-promoted solid–liquid (S–L) phase PT catalytic alkylation of active methylene-containing substrates can also be carried out in the absence of any PT catalyst, in a solvent-free manner.[4] This also means that in certain C-alkylations the onium salts can be replaced by MW irradiation. This is a 'green' modification of the reaction under discussion, as there is no need of a catalyst or a solvent. The former typically forms a waste unless it is bound to a solid support.

Evaluation of the role of PT catalysts in MW-assisted liquid–liquid (L–L) or S–L phase reactions may bring further surprises. We have studied the effect of catalysts on heterogeneous phase O-alkylations carried out under MW conditions. The alkylation of phenols was chosen as a model to be investigated.

Surveying the literature, alkyl halides were used mostly as the alkylating agents and onium salts applied as the catalysts. Literature examples demonstrate that the rate of the PT catalytic alkylation of phenols can be synergistically enhanced by MW irradiation. In a few instances, the reactions were carried out in S–L phase using organic solvents and alkali hydroxides as the base.[5,6] Solvent-free alkylations in the presence of K_2CO_3 or K_2CO_3/NaOH are also known.[7,8] In one case, a sodium phenolate formed the solid phase,[9] while in another example a L–L phase alkylation applying aq NaOH was described.[10] In the latter two cases, benzyl chloride was the reagent and toluene was the solvent. It is noteworthy that a few O-alkylations were carried out in the absence of a PT catalyst. This was possible when K_2CO_3 was used in methanol,[11] or in acetone.[12] In the former case, in particular, the slight solubility of the potassium salt in the solvent made the alkylation possible. Another catalyst-free example is the combined MW and ultrasound promoted L–L phase alkylation of phenols.[13]

The combination of the PT catalytic and MW techniques is advantageous from the rate enhancement point of view, but no other details, such as effect on the selectivity and yield have been disclosed. In the above O-alkylations, the yields ranged between 52% and 99%, but comparison and even reproduction of the data is rather difficult, as the early experiments were carried out in domestic MW ovens, where detection of the exact temperature was not possible. Moreover, the role of the PT catalysts in MW-assisted O-alkylations has not yet been clarified.

In the present Letter, we evaluate the impact of the PT catalysts on the course of the MW-assisted S–L phase benzylation of phenols. The effect of the presence or absence of the onium salt on the rate and especially on the selectivity, and also the role of the base applied were studied.

---

[*] Corresponding author. Tel.: +36 1 463 1111/5883; fax: +36 1 463 3648.
E-mail address: keglevich@mail.bme.hu (G. Keglevich).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.06.051

The alkylation of phenol and 4-substituted phenols with 1.2 equiv of benzyl bromide or benzyl chloride in the presence (or in a few cases, in the absence) of 1.0 equiv of K_2CO_3 under solvent-free conditions served as the model reaction. The benzylations were carried out in the range of 80–120 °C isothermally, under MW irradiation in the presence of 0–5% of triethylbenzylammonium chloride (TEBAC)[14] and the reactions were monitored by GC and GC–MS.

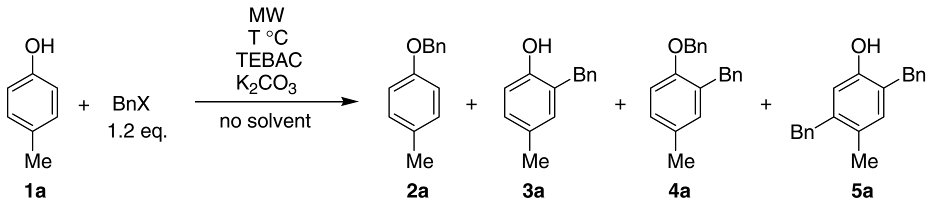
Carrying out the alkylation of cresol with benzyl bromide at 100 °C without the use of K_2CO_3 and TEBAC, the reaction was reluctant but selective with regard to C-alkylation, as mostly 2-benzylcresol **3a** was formed (Table 1, entry 1). In the presence of K_2CO_3 at 80 °C, 45% of the expected benzyl cresyl ether **2a**, 27% of 2-benzylcresol **3a**,[15] 4% and 7% of doubly benzylated derivatives **4a**[16] and **5a**,[17] along with 17% of unreacted cresol were present in the reaction mixture according to GC–MS (Table 1, entry 2). The composition did not change after 50 min. At 120 °C, the situation was similar (55% of **2a** and 27% of **3a** were present), but no cresol remained in the mixture (Table 1, entry 4). The experiment carried out at 100 °C represented an intermediate case (Table 1, entry 3). The addition of 5% of TEBAC to the reaction mixture resulted in a dramatic change in favour of benzyl aryl ether **2a**: 94% and 96% of product **2a** was formed after 45 min at 80 °C or 35 min at 100 °C, respectively (Table 1, entries 5 and 6). The isolated yield of **2a**[18] was 86% after column chromatography. The reaction with benzyl chloride led to rather similar results (Table 1, entries 7 and 8). It can be seen that the MW promoted, solvent-free, S–L phase benzylation of cresol takes place chemoselectively only in the absence of K_2CO_3 or in the case of the combined use of K_2CO_3 and a PT catalyst. In the latter instance, MW irradiation and the presence of the onium salt result in a synergic effect. 2-Benzylcresol **3a** must be formed by aromatic electrophilic substitution, as benzyl cresyl ether **2a** cannot undergo rearrangement to **3a**. This was proved by separate experiments. It is, however, known that alkenyl aryl ethers undergo the Claisen rearrangement at 180–240 °C to furnish a 2-alkenylphenol.[19–22]

Control experiments carried out by traditional heating at 100 °C for 45 min also revealed the effect of K_2CO_3 and a PT catalyst on the chemoselectivity of the alkylation. In the absence of K_2CO_3 the benzylation became C-selective, but the reaction was reluctant (Table 2, entry 1). In the presence of K_2CO_3 and in the absence of TEBAC, 52% of the O-alkylated product (**2a**) and 26% of the C-alkylated species **3a** were formed, while in the presence of 5% of the catalyst, the relative quantities of **2a** and **3a** were 84% and 4%, respectively (Table 2, entries 2 and 3). The cresol was not, however, consumed on further heating. At room temperature, without the use of TEBAC, the O-benzylation was significantly selective, but the reaction was slow (Table 2, entry 4). For the above reasons, thermal heating is not a good alternative to MW heating in the PT catalyzed alkylation under discussion.

The directing role of the reaction components such as K_2CO_3 and quaternary onium salt is noteworthy. It seemed to be interesting to investigate if the chemoselectivity (O-alkylation versus C-alkylation) observed is of general value or not. For this, reactions were carried out with additional model compounds, such as 4-chlorophenol (**1b**) and 4-*tert*-butylphenol (**1c**) without and with K_2CO_3 and TEBAC, using the conditions established for the alkylation of cresol (**1a**) using benzyl bromide. Carrying out the alkylation of **1b** with BnBr in the absence of K_2CO_3 and in the presence of K_2CO_3 and 5% of TEBAC at 120 °C for 35 min, the proportion of the O- (**2**) and C-alkylated (**3**) products was 0/43 and 96/0, respectively (Table 3, entries 1 and 3). Repeating the latter benzylation in the absence of TEBAC, the above ratio was 73/14 (Table 3, entry 2). It was found that the benzylation of 4-*tert*-butylphenol at 120 °C in the absence of K_2CO_3 yielded only C-alkylated products **3c** and **5c** (44% combined) (Table 3, entry 4). In the presence of K_2CO_3, the ratio of **2c** and **3c** was 59:20 (Table 3, entry 5). It is noteworthy that the use of TEBAC resulted in an even slower reaction (only a 71% conversion and selective formation of the C-benzylated products (**3c** and **5c**, 62% combined) (Table 3, entry 6). In all the three cases, the reaction was reluctant to proceed. The increased proportion of the C-alkylated product (**3a**) is due to the *tert*-butyl group activating the phenyl ring to aromatic electrophilic substitution. With the lack of a suitably acidic hydroxy group in 4-*tert*-butylphenol, formation of the potassium salt is suppressed and as a consequence of the lipophilicity due to the *tert*-butyl group on the aromatic ring, the salt formed and anchored on the surface of K_2CO_3 can enter the organic phase without the assistance of the phase transfer catalyst. Moreover, the presence of TEBAC in the organic phase prevents the transfer of the phenolate from the surface of K_2CO_3 as the onium salt content may result in decreased solubity.

Finally, the S–L phase benzylation of phenol was investigated. Three products, benzyl phenyl ether (**7**) along with 4- and 2-benzylphenol (**8** and **9**, respectively) may be formed as a result

Table 1
The reaction of cresol with benzyl halides under MW irradiation



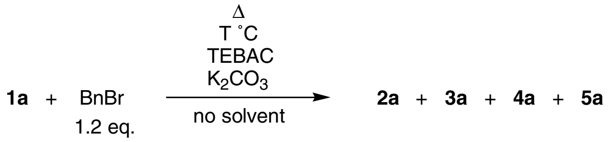
Entry	X	K_2CO_3 (equiv)	TEBAC (%)	*T* (°C)	*t* (min)	**1a**[a] (%)	**2a**[a] (%)	**3a**[a] (%)	**4a**[a] (%)	**5a**[a] (%)
1	Br	–	–	100	35	58	0	32	0	7[b]
2	Br	1	–	80	50	17[c]	45	27	4	7
3	Br	1	–	100	40	9[c]	52	27	6	6
4	Br	1	–	120	35	0	55	27	9	9
5	Br	1	5	80	45	0	94	0	6	0
6	Br	1	5	100	35	0	96	0	4	0
7	Cl	1	–	120	40	17[c]	53	22	4	4
8	Cl	1	5	100	40	0	91	4	5	0

[a] Determined by GC–MS or GC.

[b] 3% others.

[c] Does not disappear on further irradiation.

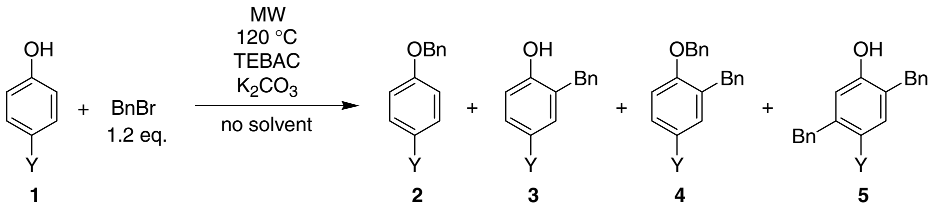
Table 2
The alkylation of cresol with benzyl bromide under thermal conditions



Entry	K$_2$CO$_3$ (equiv)	TEBAC (%)	*T* (°C)	*t*	**1a**[a] (%)	**2a**[a] (%)	**3a**[a] (%)	**4a**[a] (%)	**5a**[a] (%)
1	–	–	100	45 min	78	1	16		[b]
2	1	–	100	60 min	10[c]	52	26	6	6
3	1	5	100	60 min	8[c]	84	4	4	0
4	1	–	26	2.5 days	0	91	2	7	0

[a] Determined by GC.
[b] 5% others.
[c] Does not disappear on further heating.

Table 3
The reaction of 4-substituted phenols with benzyl bromide under MW irradiation



Entry	Y	K$_2$CO$_3$ (equiv)	TEBAC (%)	*t* (min)	**1**[a] (%)	**2**[a] (%)	**3**[a] (%)	**4**[a] (%)	**5**[a] (%)
1	Cl (**b**)	–	–	35	46	0	43	0	11
2	Cl (**b**)	1	–	35	0	73[b]	14[c]	10[d]	3[e]
3	Cl (**b**)	1	5	35	0	96	0	4	0
4	^{t}Bu (**c**)	–	–	60	56	0	37	0	7
5	^{t}Bu (**c**)	1	–	60	11[f]	59[g]	20[h]	6[i]	4[j]
6	^{t}Bu (**c**)	1	5	60	29[f]	0	48	0	14[k]

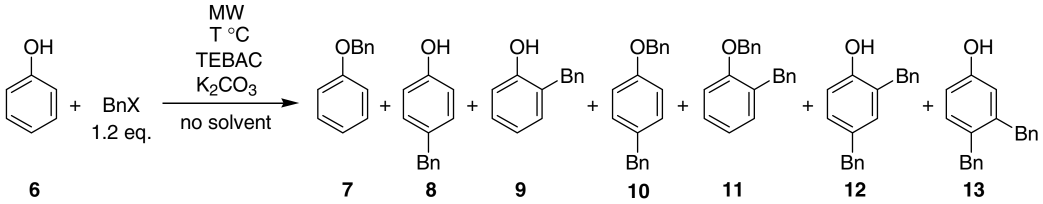
[a] Determined by GC–MS or GC.
[b] For the ^{35}Cl isotope, M$^+$ = 218.
[c] For the ^{35}Cl isotope, M$^+$ = 218.
[d] For the ^{35}Cl isotope, M$^+$ = 308.
[e] For the ^{35}Cl isotope, M$^+$ = 308.
[f] Does not disappear on further irradiation.
[g] M$^+$ = 240.
[h] M$^+$ = 240.
[i] M$^+$ = 330.
[j] M$^+$ = 330.
[k] 9% others.

of monobenzylation. Benzylphenyl benzyl ethers **10** and **11**, as well as dibenzylphenols **12** and **13** are the products of dibenzylation. Applying benzyl bromide at 100 °C, a complex mixture consisting of benzyl phenyl ether **7** (69%), benzylphenol **8** (13%—on this occasion benzylphenol **9** was not formed), as well as benzylphenyl benzyl ethers **10** and **11** (9% combined) and dibenzylphenols **12** and **13** (3% combined) were present in the mixture along with 6% of unreacted phenol (Table 4, entry 1). The selectivity regarding O-alkylation was increased from 69% to 89% in the presence of 5% of TEBAC. In this case, the relative quantities of **7**, **8** + **9** and **10** + **11** were 89%, 4% and 7%, respectively. No compounds **12** and **13** could be detected in the mixture (Table 4, entry 2). At 120 °C, the O-selectivity was decreased to 65% (Table 4, entry 3). Using benzyl chloride, the results were quite similar to those obtained with benzyl bromide (Table 4, entry 4 vs. entry 1, and entry 5 vs. entry 2). Omitting both the catalyst and the base from the reaction mixture led to pronounced C-selectivity. Products **8** and **9** represented 23% and 21% in the reaction mixture (Table 4, entry 6).

To the best of our knowledge, the formation of C-alkylated products in the uncatalyzed benzylation of phenol, 4-cresol and 4-chlorophenol has never been described. The aromatic ring of these phenol derivatives is not reactive enough below or around 100 °C towards electrophilic alkyl halides in the absence of a catalyst.[23] Under solventless conditions, this problem can be partially overcome, as shown by the 16–39% relative quantities of the C-alkylated products.

In summary, the effect of K$_2$CO$_3$ and TEBAC is similar in the MW-promoted solvent-free S–L phase benzylation of cresol and 4-chlorophenol. The absence or presence of the base and the PT catalyst play a crucial role, and the outcome of the reactions regarding O- and C-selectivity can be fine-tuned by choosing the appropriate reaction conditions. Regarding the benzylation of phenol, the situation is quite similar. The pronounced O-selectivity is a consequence of the synergic effect of the PT catalyst and MW irradiation. At the same time, the benzylation of 4-*tert*-butylphenol represents a quite different case due to the effect of the *tert*-butyl group.

Table 4
The reaction of phenol with benzyl halides under MW irradiation



Entry	X	K_2CO_3 (equiv)	TEBAC (%)	T (°C)	t (min)	**6**[a] (%)	**7**[a] (%)	**8**[a] (%)	**9**[a] (%)	**10**[a] (%)	**11**[a] (%)	**12**[a] (%)	**13**[a] (%)
1	Br	1	–	100	40	6[b]	69[c]	13	0	5	4	2	1
2	Br	1	5	100	40	0	89	3	1	2	5	0	0
3	Br	1	5	120	35	0	65	10[d]	10[e]	4[f]	1[g]	7[h]	3[i]
4	Cl	1	–	100	45	3[b]	77	15	0	3	2	0	0
5	Cl	1	5	100	40	0	91	0	0	5	4	0	0
6	Br	–	–	120	30	40	0	23	21	0	0	4	12

[a] Determined by GC–MS or GC.
[b] Does not disappear on further irradiation.
[c] $M^+ = 184$.
[d] $M^+ = 184$.
[e] $M^+ = 184$.
[f] $M^+ = 274$.
[g] $M^+ = 274$.
[h] $M^+ = 274$.
[i] $M^+ = 274$.

Acknowledgement

The above project was supported by Gedeon Richter Plc. and partially by the Hungarian Scientific Research Fund (OTKA T067679). The authors are grateful to Professor Harry R. Hudson (London Metropolitan University) for his advice.

References and notes

1. Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase Transfer Catalysis—Fundamentals, Applications and Industrial Perspectives*; Chapman & Hall: New York, London, 1994.
2. *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002.
3. Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J. L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851–10870.
4. Keglevich, Gy.; Novák, T.; Vida, L.; Greiner, I. *Green Chem.* **2006**, *8*, 1073–1075.
5. Campbell, L. J.; Borges, L. F.; Heldrich, F. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2627–2630.
6. Wang, J.-X.; Zhang, M. L.; Hu, Y. L. *Synth. Commun.* **1998**, *28*, 2407–2413.
7. Bogdal, D.; Pielichowski, J.; Boroń, A. *Synth. Commun.* **1998**, *28*, 3029–3039.
8. Pchelka, B. K.; Loupy, A.; Petit, A. *Tetrahedron* **2006**, *62*, 10968–10979.
9. Yadav, G. D.; Bisht, P. M. *J. Mol. Catal. A—Chem.* **2004**, *221*, 59–69.
10. Yadav, G. D.; Bisht, P. M. *J. Mol. Catal. A—Chem.* **2005**, *236*, 54–64.
11. Sarju, J.; Danks, T. N.; Wagner, G. *Tetrahedron Lett.* **2004**, *45*, 7675–7677.
12. Mitra, A. K.; De, A.; Karchaudhuri, N. *Indian J. Chem.* **2000**, *39B*, 387–389.
13. Peng, Y.; Song, G. *Green Chem.* **2002**, *4*, 349–351.
14. A typical general procedure: A mixture of 1.0 mmol of phenol derivative **1** or phenol **6**, 0.14 g (1.0 mmol) of K_2CO_3, 11.4 mg (0.05 mmol) of TEBAC and 1.2 mmol of benzyl halogenide (0.120 ml of benzyl bromide or 0.115 ml of benzyl chloride) in a closed vial was irradiated in a CEM Discover [300 W] Microwave Reactor at 30–40 W for the appropriate time. 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 which was passed through a thin layer of silica gel using 3% MeOH in $CHCl_3$ as the eluant and then analysed by GC–MS or GC.
15. Compound **3a**: $(M+H)^+_{found} = 199.1118$, $C_{14}H_{15}O$ requires 199.1123.
16. Compound **4a**: $(M+H)^+_{found} = 289.1584$, $C_{21}H_{21}O$ requires 289.1592.
17. Compound **5a**: $(M+H)^+_{found} = 289.1584$, $C_{21}H_{21}O$ requires 289.1592.
18. Compound **2a**: ^1H NMR ($CDCl_3$) δ 2.28 (3H, Me), 5.03 (2H, CH_2), 6.86–7.09 (4H, Ar-1), 7.29–7.43 (5H, Ar-2); $(M+H)^+_{found} = 199.1118$, $C_{14}H_{15}O$ requires 199.1123.
19. Greene, A. E.; Coelho, F.; Barreiro, E. J.; Costa, P. R. R. *J. Org. Chem.* **1986**, *51*, 4250–4253.
20. Benbow, J. W.; Katoch-Rouse, R. *J. Org. Chem.* **2001**, *66*, 4965–4972.
21. van Otterlo, W. A. L.; Ngidi, E. L.; Kuzvidza, S.; Morgans, G. L.; Moleele, S. S.; de Konig, C. B. *Tetrahedron* **2005**, *61*, 9996–10006.
22. Sviridov, S. I.; Vasil'ev, A. A.; Sergovskaya, N. L.; Chirskaya, M. V.; Shorshnev, S. V. *Tetrahedron* **2006**, *62*, 2639–2647.
23. Kamitori, Y.; Hojo, M.; Masuda, R.; Izumi, T.; Tsukamoto, S. *J. Org. Chem.* **1984**, *49*, 4161–4165.