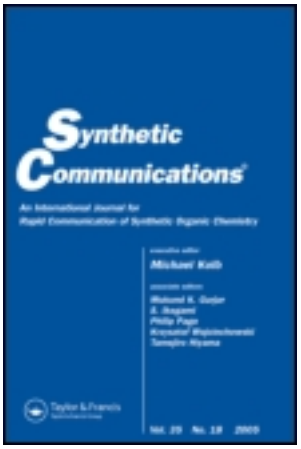

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O-ACYLATION OF SUBSTITUTED PHENOLS WITH VARIOUS ALKANOYL CHLORIDES UNDER PHASE-TRANSFER CATALYST CONDITIONS

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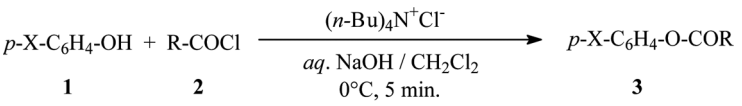
GRAPHICAL ABSTRACT



X- = H-, Me-, Et-, *n*-Pr-, *sec*-Bu-, *i*-Pr-, *t*-Bu-, MeO-, NO_2-, Cl-
R- = H-, Me-, Et-, *n*-Pr-, *n*-Bu-, *i*-Pr-, *t*-Bu-, *cyclo*-C_6H_{11}-, Ph-

Abstract *Esterification of several types of mono- and disubstituted phenols with various mono- and dialkanoyl chlorides was performed in phase-transfer catalysis conditions, using tetrabutylammonium chloride in a mixture of aqueous NaOH and dichloromethane. The process is particularly efficient (almost quantitative yields) as well as rapid (only 5 min reaction time, at a temperature of 0 °C).*

Keywords Hindered phenols; *O*-acylation; phase-transfer catalyst; tetrabutylammonium chloride

INTRODUCTION

The -COOR moiety is a key figure in a large number of organic compounds, both natural and synthetic.[1] Therefore, it is understandable that the esterification reaction is one of the most studied and frequently used organic processes, generating an impressive number of reports each year in a large number of chemical journals.[1,2] Among the various methods used for obtaining esters, one of the most useful and

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This paper is dedicated to the memory of Professor Iwao Hashimoto (1942–2011).

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versatile transformation is the acylation of alcohols and/or phenols.[2] However, some major inconveniences are present: either long duration and harsh reaction conditions are necessary for the direct esterification, or essentially anhydrous conditions when using anhydrides or acyl chlorides instead of the carboxylic acid. A notable exception is the well-known Schotten–Baumann procedure,[3] a reaction that implies acylation of a phenol using an acyl chloride and can be carried out in anhydrous organic solvents as well as in aqueous media.[4] Several variations of the method were proposed to accommodate the sensitivity of acyl chlorides toward aqueous conditions. The 1980s–1990s recorded a first volley of reports dealing with esterification processes under phase-transfer catalyst (PTC) methods,[5] which tend to be replaced nowadays with several types of procedures in solvent-free conditions.[6] A major requirement of these numerous solvent-free methodologies is the use of anhydrides and, quite often, sophisticated and sensitive catalysts. However, we noticed in the past few years a return of interest in practical and useful *O*-acylation method using a PTC in studies of the kinetics of phenol benzoylation.[7] Starting from Direktor and Effenberger's procedure,[5e,h] we developed our own protocol for the *O*-acylation of phenols,[8] with main advantages versus previously PTC esterification process of the use of equimolecular amounts of phenol and acyl chloride (instead of an excess of phenol), the use of sodium hydroxide (instead of $NaHCO_3$, avoiding thus the risk of effervescence), dichloromethane (instead of the more viscous chlorobenzene), less toxic tetrabutylammonium chloride (instead of tetrabutylammonium bromide), low temperatures (0 °C), extremely short reaction time (only 5 min), and kinetical evaluation of the scope and limitations of this process.[8c] We report the extent of our study to various substituted phenols in the *O*-acylation reaction under PTC conditions with different acyl chlorides.

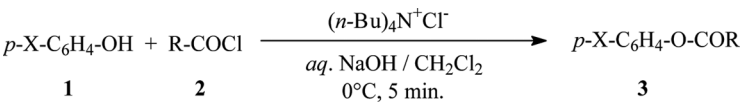
RESULTS AND DISCUSSION

Our aim was to study the effect of the reagents (substituted phenols **1** and acyl chloride **2**) on the *O*-acylation process (Scheme 1).

A series of experiments was conducted using different acyl chlorides in reaction with equimolecular amounts of phenol **1a** at 0 °C for 5 min. The results are presented in Table 1.

All acylation processes afforded, after a simple separation procedure, the corresponding phenyl esters in excellent yields, even for greater acyl chlorides. The obtained results (e.g., formation of phenyl benzoate—entry 9, Table 1) are superior, in respect to yield and reaction time, to those previously reported for different PTC reactions.[5k,m]

The second step of our research was to switch the phenol **1** in the *O*-acetylation process with acetyl chloride, under PTC conditions, at 0 °C for 5 min. Table 2 summarizes these results.



Scheme 1. *O*-Acylation of *p*-phenols with various alkanoyl chlorides under PTC conditions.

Table 1. *O*-Acylation of phenol **1a** with various acyl chlorides under PTC conditions, at 0 °C for 5 min

	Acyl chloride		Reaction product	
Entry	Cpd	R-	Cpd	Yield (%)
1	**2a**	CH_3-	**3a**	92
2	**2b**	CH_3CH_2-	**3b**	88
3	**2c**	$CH_3CH_2CH_2$-	**3c**	89
4	**2d**	$CH_3(CH_2)_2CH_2$-	**3d**	84
5	**2e**	$(CH_3)_2CH$-	**3e**	96
6	**2f**	$(CH_3)_2CHCH_2$-	**3f**	100
7	**2g**	$(CH_3)_3C$-	**3g**	75
8	**2h**	*cyclo*-C_6H_{11}-	**3h**	89
9	**2i**	C_6H_5-	**3i**	100

O-Acetylation of *p*-substituted phenols gave the corresponding esters in fair to good yields. It is interesting to note that for hydrocarbon substituents, as the chain becomes longer, the yields decrease. However, substrates bearing branched substituents presented better results (entries 6 and 7, Table 2). At the same time, for heteroatom substituents, yields are greater for an electron-withdrawing substituent than for a donor one. At this point, we should also mention that compounds **3s** and **3q** could not be obtained by classical Schotten–Baumann procedures. Moreover, when a small substituent like the methyl group was shifted from *para*- position to *meta*- and *ortho*-, the yields of the esterification reaction product dropped, showing that steric hindrance plays a certain role in the process. We decided to see if the *O*-acylation of specially hindered substrates such as 2,6-disubstituted phenols **4** can occur using our reaction protocol. The obtained results are presented in Table 3.

With the exception of entry 7, when steric hindrance in both 2,6-disubstituted phenol and acyl chloride proved to be decisive in preventing the transformation, *O*-acylation with phenols bearing bulky groups is effective in only 5 min of stirring, at 0 °C. For comparison, the classical Schotten–Baumann reaction carried out

Table 2. *O*-Acetylation of *p*-substituted phenols under PTC conditions, at 0 °C for 5 min

	p-Substituted phenol		Reaction product	
Entry	Cpd	X-	Cpd	Yield (%)
1	**1a**	H	**3j**	92
2	**1b**	CH_3-	**3k**	95
3	**1c**	CH_3CH_2-	**3l**	70
4	**1d**	$CH_3CH_2CH_2$-	**3m**	63
5	**1e**	$CH_3CH_2(CH_3)CH$-	**3n**	62
6	**1f**	$(CH_3)_2CH$-	**3o**	91
7	**1g**	$(CH_3)_3C$-	**3p**	80
8	**1h**	CH_3O-	**3q**	51
9	**1i**	Cl-	**3r**	63
10	**1j**	NO_2-	**3s**	71
11	**1k**	*o*-CH_3-	**3t**	59
12	**1l**	*m*-CH_3-	**3u**	76

Table 3. *O*-Acylation of 2,6-disubstituted phenols with various alkanoyl chlorides under PTC conditions, at 0 °C for 5 min

	2,6-Disubstituted phenol		Acyl chloride		Reaction product	
Entry	Cpd	2,6-Substituent	Cpd	R-	Cpd	Yield (%)
1	**4a**	CH_3-	**2a**	CH_3-	**5a**	97
2	**4a**	CH_3-	**2g**	$(CH_3)_3C$-	**5b**	94
3	**4a**	CH_3-	**2i**	C_6H_5-	**5c**	86
4	**4b**	$(CH_3)_2CH$-	**2a**	CH_3-	**5d**	80
5	**4c**	$(CH_3)_3C$-	**2a**	CH_3-	**5e**	78
6	**4b**	$(CH_3)_2CH$-	**2g**	$(CH_3)_3C$-	**5f**	64
7	**4c**	$(CH_3)_3C$-	**2g**	$(CH_3)_3C$-	**5g**	0
8	**4d**	Cl-	**2a**	CH_3-	**5h**	54
9	**4e**	Br-	**2a**	CH_3-	**5i**	75
10	**4f**	CH_3O-	**2a**	CH_3-	**5j**	45

simultaneously with our experiments for reactants in entries 4 and 5 showed no occurrence of any reaction product. It is interesting to note that Mukayama and coworkers obtained 2,6-dimethylphenyl 4-methoxybenzoate from the corresponding dimethylphenol, via phenoxydiphenylphosphines formed in situ from various *n*-BuLi-treated phenols and chlorodiphenylphosphine in only 23% yield, when the reaction was carried out for 6.0 h at 110 °C, and in 76% yield when the reaction was carried out for 2 h at 160 °C using a solvent such as p-xylene.[9] It is noteworthy that acid-catalyzed esterification of 2,6-disubstituted phenols is a process difficult to achieve, irrespective of the nature of the substituents,[10] and on more than one occasion a ring *C*-acylation product has been detected. However, some successes were recorded when using a polymer-supported PTC in solid–liquid PTC conditions[5e,h] or on when acetic anhydride was used as acylating reagent, either on 2,6-dimethylphenol in the presence of copper perchlorate[6n] or ruthenium chloride (after a 3-h treatment),[11] or on 2,6-di-*t*butyl-4-methylphenol in the presence of scandium triflate.[12] In the case of phenols substituted with heteroatoms, the yields we obtained after only 5 min are fair. However, better yields were achieved for 2,6-dichlorophenyl acetate, but working with acetic anhydride, in the presence of *o*-benzenedisulfonimide, for much longer reaction time: ~4 h.[13] Without any catalyst, 2,6-dimethoxyphenyl acetate was obtained in comparative yields after an even longer treatment: 24 h treatment at room temperature.[14]

Our system, which is much simpler because it is a liquid–liquid PTC reaction system, permitted the formation of only the *O*-acylation reaction product, remarkably free of other side-reaction products. Moreover, in our process, esterification of bulky phenols is completed in only 5 min instead of hours for other *O*-acylation processes.

Over the years, PTC gained its *lettre de noblesse* by overriding the difficulties of some classical chemical processes and permitting a large number of industrial applications.[15] One such potential application is the bis-esterification of dialkanoyl chlorides, aiming to synthesize oligomers and polymers with a predetermined number of units (such a practical application of polyesterification has been already tested[16]). We studied such a reaction between several dialkanoyl chlorides and phenol in PTC conditions at 0 °C and 5 min reaction time (Table 4).

Table 4. *O*-Acylation of phenol **1a** with various dicarboxylic acyl chlorides under PTC conditions, at 0 °C for 5 min

	Acyl dichlorides ClCO-$(CH_2)_n$-COCl		Reaction product	
Entry	Cpd	n	Cpd	Yield (%)
1	**6a**	2	**7a**	95
2	**6b**	3	**7b**	100
3	**6c**	4	**7c**	96

Straightforward isolation of pure reaction products is the main characteristic of this process. As a comparison, we performed a classic esterification, which afforded the corresponding diesters in 53%, 77%, and 71% yields.

Although optimum conditions for this PTC process have been established in our previous papers,[8] some considerations have to be made to outline the differences and advantages of our procedure over the existing ones.[5]

We targeted a simpler and shorter approach to the PTC process (most of the previous investigations[5] reported reaction times of several hours). We soon noticed the importance of NaOH concentration as well as of the speed of stirring. Our findings[8c] were later confirmed by the study of Yang and Huang[7] and by the present research. Thus, a violent shaking of the biphasic system will increase the surface of the interphase area, allowing a higher rate of mass transfer of the carrier PTC. On the other hand, a greater NaOH concentration than the 10% we used proved to be damaging for the process, because the hydroxide anion could compete with the phenoxide anion for the tetrabutylammonium cation. Nevertheless, compared with previous investigations,[5e,h,m] we used an excess of NaOH (0.015 mmol phenol–0.05 mmol NaOH, instead of equimolecular amounts), which favors the complete transformation of phenol in phenoxide in the aqueous phase.

Another advantage of our method is the use of dichloromethane instead of dichlorobenzene.[5e,h] Although there is a difference in polarity between the two chlorinated solvents, the mass transfer will be favored in the case of CH_2Cl_2 by the viscosity of the solvent: Dichloromethane is less viscous, thus allowing better passage through the interphase of the tetrabutylammonium chloride or tetrabutylammonium phenoxide, respectively. Yang and Huang obtained similar results when comparing the effectiveness of dichloromethane, dichlorobenzene, heptane, and hexane,[7a] and before them, Lee, Yeh, and Shih reported a similar pattern when comparing dichloromethane with dichlorobenzene, benzene, and toluene.[5m]

The nature of the PTC catalyst is important: tetrabutylammonium chloride confirmed our expectations to be more suitable for this type of process than the previously used tetrabutylammonium bromide. Indeed, for the benzoylation of phenol with tetrabutylammonium chloride, in our reaction conditions we obtained a quantitative transformation (Table 1, entry 9) in only 5 min at 0 °C, while in an extensive study of the same process, Yang and Huang obtained only 67.4% after 1 h of treatment with tetrabutylammonium bromide at 35 °C.[7a] For their part, Lee, Yeh, and Shih reported 96% conversion for the same benzoylation process, after 2.5 h at 17 °C, using the same tetrabutylammonium bromide.[5m] However, we worked with a 10:1

ratio of phenol–PTC, while the previously mentioned authors used a 20:1 ratio. Increased content of PTC in the reaction mixture was confirmed to improve the yield of phenyl benzoate,[7a] as well as of all *O*-acylation products.[8] Moreover, the process can be successfully applied to other derivatives, such as the thioesters.[17]

Last but not least, an undoubtful advantage of this method over the "free-solvent" ones is the use of acyl chlorides instead of anhydrides, because only 1 equivalent of carboxylic acid is needed instead of 2 (one of them being completely lost in the process using anhydrides).

CONCLUSION

The PTC process for *O*-acylation of substituted phenols in the presence of 10% tetrabutylammonium chloride in a mixture of 10% aqueous NaOH and dichloromethane is rapid and extremely effective, superior to the previously described methods and unrivalled by other classic methods of esterification. Indeed, for a large number of mono- and disubstituted phenols, the reaction with mono- and dialkanoyl chlorides was almost quantitative at 0 °C after only 5 min.

EXPERIMENTAL

In all reactions, commercially available substituted phenols and alkanoyl chlorides were used after a prior purification step (generally, distillation or recrystallization). Analytical gas–liquid chromatograms (GLC) were carried out on a Yanagimoto G-180 F fitted with a FS-WCOT column (0.25 mm i.d., length 25 m) coated silicon OV-1701 or Yanagimoto G-80 packed column gas-chromatograph (Apiezon grease L, 10%, 1.5 m or silicone SE-30, 10%, 1 m). All reaction products were identified by comparison with GLC retention times of authentic samples, previously obtained through classic Schotten–Baumann or other suitable esterification procedures.

In a typical procedure, substituted phenol (15 mmol) was dissolved in 20 ml of 10% aqueous sodium hydroxide (50 mmol NAOH) solution in a 100-ml flask. Solutions of tetra-*n*-butylammonium chloride (1.5 mmol) in 5 mL of dichloromethane and acyl chloride (15 mmol) in 15 mL of dichloromethane were prepared. After cooling all solutions at 0 °C, they were mixed at once. The reaction mixture was kept under vigorous magnetic stirring (400 rpm) at 0 °C for 5 min and then poured over 50 mL of icy water. The organic layer was separated and the aqueous layer was extracted twice with 40 mL of diethyl ether. The combined organic extracts were washed with saturated NaCl solution. After drying on Na_2SO_4, the solvent was evaporated, and the residue was analyzed directly by gas chromatrography (GC), liquid chromatography (LC) and/or GC–mass spectrometry (MS). Quantitative determinations were carried out using the internal standard method. The product structures were also identified by infrared (IR), NMR spectra, and GC-mass analysis.

All NMR spectra were recorded on a Jeol JNM-LA 300, 300 MHz, for samples in $CDCl_3$ with Me_4Si as internal standard. Coupling constants (*J* values) are given in hertz (Hz). Identification of esters was made by GC (Shimadzu GC-17A GC instrument, carrier gas N_2, pressure 135 kgf/cm^2, flow 55 mL/min on a J&W Scientific DB-1 fused silica capillary column, length 30 m, i.d. 0.32 mm with film thickness

of 0.25 mm) and GC-MS (Hewlett-Packard HP6890 GC, carrier gas He, flow 1.5 mL/min, velocity 48 cm/s and pressure 10.3 psi, J&W Scientific DB-1 fused silica capillary column and Jeol Automass system II MS). Mass spectra and high-resolution mass spectra (HRMS) were recorded on a Jeol JMS-700 T, with 45 eV ionization energy and 600 μA current.

A certain number of esters are already known and have been previously described in the literature. Thus, the following compounds have been identified by comparison of their spectral data: phenyl acetate, **3a**,[6a] phenyl propionate, **3b**,[18] phenyl butyrate, **3c**,[19] phenyl pentanoate, **3d**,[9] phenyl isobutyrate (phenyl 2-methylpropanoate), **3e**,[20] phenyl isopentanoate (phenyl 3-methylbutyrate), **3f**,[20] phenyl pivalate (phenyl 2,2-dimethylpropanoate), **3 g**,[20,21] phenyl *cyclo*-hexanecarboxylate, **3 h**,[22] phenyl benzoate, **3i**,[23] *p*-tolyl acetate (4-methylphenyl acetate, *p*-cresyl acetate), **3j**,[24] *p-tert*butylphenyl acetate, **3o**,[25] *p*-methoxyphenyl acetate, **3p**,[6a,26] *p*-chlorophenyl acetate, **3q**,[24] *p*-nitrophenyl acetate, **3r**,[27] *o*-tolyl acetate (2-methylphenyl acetate, *o*-cresyl acetate), **3 s**,[28] *m*-tolyl acetate (3-methylphenyl acetate, *m*-cresyl acetate), **3 t**,[29] 2,6-dimethylphenyl acetate, **5a**,[13] 2,6-dichlorophenyl acetate, **5 h**,[30] 2,6-dimethoxyphenyl acetate, **5j**,[31] diphenyl succinate, **7a**,[32,33] diphenyl glutarate, **7b**,[33] diphenyl adipate, **7c**.[33]

All other compounds presented in their IR spectra a characteristic absorbtion of the ester moiety around 1750 cm^{-1} and were fully described by their ^1H NMR and MS spectra.

Selected Data

***p*-Ethylphenyl acetate, 3l.** ^1H NMR (δ, *J*, Hz, $CDCl_3$): 1.21 (t, 3H), 2.23 (s, 3H), 2.61 (q, 2H), 6.97 (d, 2H), 7.16 (d, 2H); MS (*m/z*): 164 (MP), 122, 107 (BP), 77, 43.

***p-sec*-Butylphenyl acetate, 3n.** ^1H NMR (δ, *J*, Hz, $CDCl_3$): 0.81 (t, 3H), 1.21 (d, 3H), (dt, 2H), 2.24 (s, 3H), 2.58 (m, 1H), 6.99 (d, 2H), 7.16 (d, 2H); MS (*m/z*): 192 (MP), 150, 121 (BP), 91, 77, 43.

***p*-Isopropylphenyl acetate, 3o.** ^1H NMR (δ, *J*, Hz, $CDCl_3$): 1.22 (d, 6H), 2.23 (s, 3H), 2.88 (q, 1H), 6.98 (d, 2H), 7.20 (d, 2H); MS (*m/z*): 178 (MP), 136, 121 (BP), 91, 43.

2,6-Dimethylphenyl pivalate, 5b. ^1H NMR (δ, *J*, Hz, $CDCl_3$): 1.40 (s, 9H), 2.12 (s, 6H), 7.03 (m, 3H); MS (*m/z*): 206 (MP), 153, 136, 122 (BP), 107, 84, 77.

2,6-Dimethylphenyl benzoate, 5c. ^1H NMR (δ, *J*, Hz, $CDCl_3$): 2.19 (s, 6H), 7.09 (m, 3H), 7.52 (m, 2H), 7.65 (m, 1H), 8.23 (m, 2H); MS (*m/z*): 226 (MP), 153, 136, 121, 105 (BP), 81, 77.

2,6-Diisopropylphenyl acetate, 5d. ^1H NMR (δ, *J*, Hz, $CDCl_3$): 1.21 (d, *13.4*, 12H), 2.35 (s, 3H), 2.91 (hp, *13.4*, 2H), 6.96 (m, 1H), 7.25 (m, 2H); MS (*m/z*): 220 (MP), 178, 163 (BP), 91.

2,6-Ditertbutylphenyl acetate, 5e. ^1H NMR (δ, *J*, Hz, $CDCl_3$): 1.34 (s, 18H), 2.33 (s, 3H), 7.14 (m, 1H), 7.32 (m, 2H); MS (*m/z*): 248 (MP), 205, 191 (BP), 163, 131, 115, 91, 77, 57.

2,6-Diisopropylphenyl pivalate, 5g. ^{1}H NMR (δ, *J*, Hz, $CDCl_3$): 1.19 (d, *6.9*, 12H), 1.41 (s, 9H), 2.88 (hp, *6.9*, 2H), 7,16 (m, 3H); MS (*m*/*z*): 262 (MP), 178, 163, 85, 57 (BP).

2,6-Dichlorophenyl acetate, 5h. ^{1}H NMR (δ, *J*, Hz, $CDCl_3$): 2.39 (s, 3H), 7.13 (m, 1H), 7.34 (m, 2H); MS (*m*/*z*): 204/06/08 (MP), 162/64/66 (BP), 126/28, 84.

2,6-Dibromophenyl acetate, 5i. ^{1}H NMR (δ, *J*, Hz, $CDCl_3$): 2.37 (s, 3H), 7.03 (m, 1H), 7.26 (m, 2H); MS (*m*/*z*): 292/94/96 (MP), 250/52/54, 170/72, 91, 63, 47.

2,6-Dimethoxyphenyl acetate, 5j. ^{1}H NMR (δ, *J*, Hz, $CDCl_3$): 2.34 (s, 3H), 3.81 (s, 6H), 6.61 (d, 2H), 7.12 (t, 1H); MS (*m*/*z*): 196 (MP), 154 (BP), 139, 107, 89, 77.

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