Scientific paper

Synthesis of Aryl Alkyl Ethers by Alkylation of Phenols with Quaternary Ammonium Salts

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Dedicated to the memory of the late Prof. Dr. Valentin Koloini

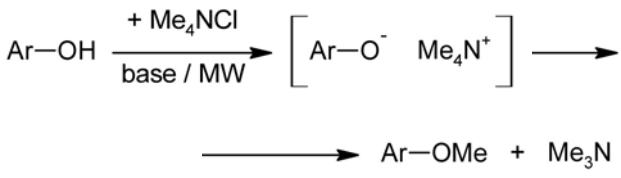
Abstract

Phenolic compounds can be efficiently *O*-methylated with tetramethylammonium chloride in diglyme or polyethyleneglycol (PEG) at temperatures of 150–160 °C and in the presence of either K_2CO_3 or NaOH. When applying benzyltrimethylammonium chloride as a reagent, the benzylation and methylation of phenols occurs, with the benzylation product always predominating. With allyl-substituted phenols as substrates and using NaOH as a base it was possible to achieve both the alkylation and the double-bond isomerization of the allyl group to obtain (*E*/*Z*)-propenyl-substituted methyl and benzyl aryl ethers in a single preparative step.

Keywords: Phenols, quaternary ammonium salts, alkylation, tetramethylammonium chloride

1. Introduction

In our recent investigation of phenolic derivatives,[1] we described the application of tetramethylammonium chloride (Me_4NCl) as a methylation reagent for phenols subjected to microwave heating at 145 °C and in the presence of K_2CO_3 or Cs_2CO_3 as the base (Scheme 1).[1a]

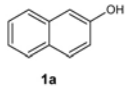
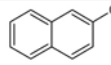
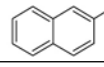
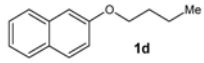
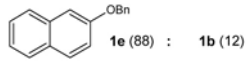
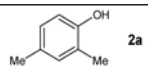
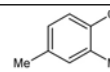
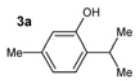
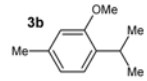
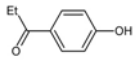
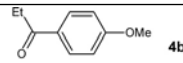
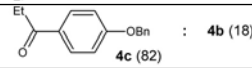
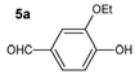
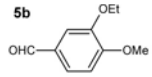
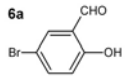
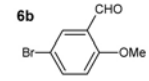
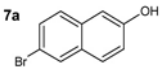
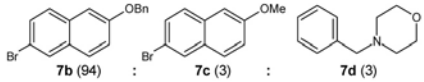
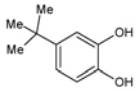
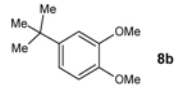
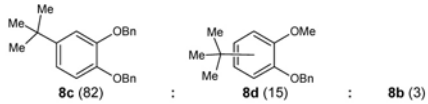
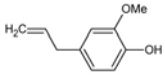
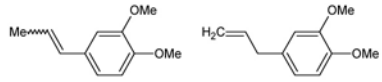
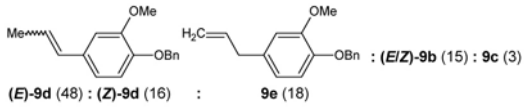
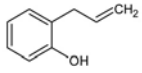
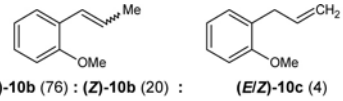
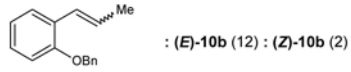


Scheme 1: Microwave-assisted methylation of phenols with Me_4NCl.

Quaternary ammonium salts (quats) are, in general, only rarely used as electrophilic reagents for the preparative alkylations of phenols or related nucleophiles. For example, the *O*-methylation of phenols with betaine (2-trimethylammonioacetate) was reported to occur under harsh conditions (200–230 °C and with CaO as a base).[2] Tetramethylammonium hydroxide (Me_4NOH) was reported to be a useful reagent for the *O*-methylation of estradiol and estriol.[3] The *N*-demethylation and *N*-debenzylation of quats by their reaction with thiophenol is a known method for preparing tertiary amines.[4] In fact, the S_N2 transition state in the reaction between the benzyldimethylphenylammonium and thiophenoxide ions has been thoroughly investigated by measuring the kinetic isotopic effects.[5] Ring-opening reactions, resulting from the nucleophilic attack on the quats derived from quinuclidine and some related azabicyclic systems, have been described.[6] The *O*-, *N*- and *S*-alkylation of some carboxylic acids, amines, anilines and thiophenol, with various quats at 160 °C in 1-methyl-2-pyrrolidinone (NMP) as a solvent, was also reported.[7] The oxidation of benzylammonium salts to benzaldehydes by heating in dimethyl sulfoxide has been attributed to a nucleophilic attack by the solvent, followed by the decomposition of the resulting benzyloxydimethylsulfonium ion.[8] Several other examples of nucleophilic substitution with quats can also be found in the literature[9] but for the preparative *O*-alkylations of phenols only the more reactive phenyltrimethylammonium salts have received further attention from organic chemists.[10]

Table 1: Reactions of phenols with quaternary ammonium chlorides.

$$ArOH + R^1R^2R^3R^4NCl \rightarrow ArOR^{(1-4)}$$

Entry	Substrate	Ammonium salt	Product(s) (their approximate molar ratios)[a]	Reaction time [h]	Method[b]	Product isolated; yield
1	 **1a**	Me_4NCl	 **1b**	6	A	**1b**; 95%
2				6	B	**1b**; 95%
3		Et_4NCl	 **1c**	6	B	**1c**; 7%
4		Bu_4NCl	 **1d**	6	B	**1d**; 27%
5		$BnMe_3NCl$	 **1e** (88) : **1b** (12)	6	A	**1e**; 73%
6		$BnEt_3NCl$	**1e** (97) : **1c** (3)	6	A	**1e**; 47%
7	 **2a**	Me_4NCl	 **2b**	2	A	**2b**; 36%
8				6	C	**2b**; 83%
9	 **3a**	Me_4NCl	 **3b**	2	A	**3b**; 50%
10				12	A	**3b**; 95%
11		$PhMe_3NCl$		0.5	A	**3b**; 86%
12	 **4a**	Me_4NCl	 **4b**	4	B	**4b**; 81%
13		$BnMe_3NCl$	 **4b** (18) **4c** (82)	4	B	**4c**; 75%
14	 **5a**	Me_4NCl	 **5b**	6	B	**5b**; 75%
15	 **6a**	Me_4NCl	 **6b**	4	B	**6b**; 16%
16	 **7a**		 **7b** (94) : **7c** (3) : **7d** (3)	2	B	**7b**; 72% **7d**; 3%[c]
17	 **8a**	Me_4NCl	 **8b**	10	B	**8b**; 90%
18		$BnMe_3NCl$	 **8c** (82) : **8d** (15) : **8b** (3)	8	B	**8c**; 56%
19	 **9a**	Me_4NCl	 (*E*)-**9b** (72) : (*Z*)-**9b** (18) : **9c** (10)	4	C	78%[d]
20		$BnMe_3NCl$	 (*E*)-**9d** (48) : (*Z*)-**9d** (16) : **9e** (18) : (*E*/*Z*)-**9b** (15) : **9c** (3)	4	C	(*E*/*Z*)-**9d**; 42%
21	 **10a**	Me_4NCl	 (*E*)-**10b** (76) : (*Z*)-**10b** (20) : (*E*/*Z*)-**10c** (4)	4	C	75%[d]
22		$BnMe_3NCl$	 (*E*)-**10d** (74) : (*Z*)-**10d** (12) : (*E*)-**10b** (12) : (*Z*)-**10b** (2)	4	C	(*E*/*Z*)-**10d**; 67%

In our study,[1a] the aprotic solvents of low polarity (for example: 1,2-dimethoxyethane, ethyl acetate, and toluene) that are less efficient at solvating the ammonium electrophile and the phenoxide nucleophile were found to be optimal for the methylation of phenols with Me_4NCl. Such a microwave-assisted reaction in a closed vessel is advantageous on a millimolar scale, but for scaling up the reaction, an alternative employment of conventional heating could prove just as useful. This idea prompted us to investigate the scope and limitations of the modified reaction, applying conventional heating in an open flask as well as the behavior of other quaternary ammonium salts in this peculiar type of nucleophilic substitution. The 1,2-dimethoxyethane (glyme) proved to be a particularly efficient solvent for the microwave-assisted reaction in the closed vessel. We therefore decided to use the higher boiling diglyme or polyethyleneglycol (PEG) as related solvents that would allow us to conduct the reaction at atmospheric pressure.

2. Results and Discussion

The alkylations, as presented in the Table 1, were performed at 150–160 °C under three types of reaction conditions: applying K_2CO_3 as a base in either diglyme during reflux (method A) or PEG (method B), while NaOH in PEG was used for the reactions where the presence of a strong base was desirable (method C). A 25% molar excess of the quats was generally used. The reaction mixtures were diluted with 1M NaOH solution and worked up by either extraction (entries 1–6, 12–16, 18–20, and 22) or by steam distillation in the cases of more volatile products (entries 7–11, 17, and 21). The crude products were first analyzed by ^{1}H NMR spectroscopy to determine the products formed and their approximate molar ratio. In cases where several products were formed, the major one was isolated and subsequently characterized.

Using either method A or B in the methylation of 2-naphthol with Me_4NCl gave the same results (entries 1 and 2). We found that the use of method B was preferable, because it avoided the application of reflux conditions. The slurry of the substrate, the quat and the base in the minimal amount of PEG was stirred in an oil bath. For most substrates the methylation required at least four hours of heating. For example, 2,4-dimethylphenol (**2a**) and thymol (**3a**) gave only 36% and 50% yields, respectively, when using method A with a 2 h reaction time (entries 7 and 9). Yet when prolonging the reaction time to 12 h, the thymol gave a nearly quantitative yield of **3b** (entry 10). The reactivity of Me_4NCl was thus expectedly lower than that of phenyltrimethylammonium chloride ($PhMe_3NCl$), which gave an 86% yield under the same conditions within 30 minutes of reaction time (entry 11).

The alkylation of 2-naphthol (**1a**) with tetraethylammonium chloride (Et_4NCl) and tetrabutylammonium chloride (Bu_4NCl) resulted mainly in the formation of tarry side products. Only poor yields of the ethylated and butylated products (**1c** and **1d**, respectively) could be isolated from these complex mixtures (7% and 27% of isolated yields; entries 3 and 4). Most likely the competing Hofmann elimination, a side reaction to which such quats are prone,[9a] is at least partially responsible for the low yields of **1c** and **1d**, but the formation of tarry products might also indicate that other side reactions play an important role.

When using benzyltrimethylammonium chloride ($BnMe_3NCl$) the reaction gave both the benzylation and methylation products (**1b** and **1e**) in a ratio of 88 : 12 (entry 5); the predominant benzylation product **1e** was isolated in a 73% yield. In fact, the yield of such a reaction when using $BnMe_3NCl$ is quite acceptable for preparative purposes. This is also a much more comfortable method when comparing this reagent to the use of the lachrymatory benzyl bromide or chloride, which are most commonly used for the benzylation of phenols. Benzylation with $BnMe_3NCl$ is a useful alternative for simple substrates that are not sensitive to the higher temperature required, particularly when considering this reagent is both commercially available and inexpensive. On the other hand, when using benzyltriethylammonium chloride ($BnEt_3NCl$) the reaction gave a relatively poor yield of **1e**, regardless of the fact that it exhibited a higher selectivity toward benzylation (entry 6).

The methylation of *p*-hydroxypropiophenone (**4a**) and 3-ethoxy-4-hydroxybenzaldehyde (**5a**) with Me_4NCl gave good yields (entries 12 and 14). In contrast, 5-bromo-2-hydroxybenzaldehyde (**6a**) only gave a low yield (16%) of 5-bromo-2-methoxybenzaldehyde (**6b**) (entry 15).

To study the chemical behavior of a quat incorporating the ammonium nitrogen in a heterocyclic ring, we alkylated 6-bromo-2-naphthol (**7a**) with *N*-benzyl-*N*-methylmorpholinium chloride (entry 16). The main product was again the benzylated one, **7b**. The methylation product **7c** could only be detected in a low ratio (the benzylation/methylation selectivity was about 30 to 1). Still, the ease of the methyl-group transfer seems comparable to that in $BnMe_3NCl$ when the statistical difference of one *vs*. three transferable methyl groups is taken into account. In order to catch the eventual products arising from the nucleophilic attack on the two electrophilic endocyclic methylene groups, we also isolated the water-

[a] The crude product from the reaction-mixture extraction was analyzed by ^{1}H NMR. Only the major products that could be positively identified from the spectroscopic data are taken into account: their sum is normalized to 100% and the approximate molar ratio is given.
[b] A: K_2CO_3, diglyme, reflux (approx. 155 °C); B: K_2CO_3, PEG, 150–160 °C; C: NaOH, PEG, 150–160 °C.
[c] In this case the water-insoluble amine fraction was also isolated in order to check if any ring-opening reactions occurred.
[d] The mixture could not be separated chromatographically or otherwise. Therefore, the yield given is for the sum of products.

insoluble basic fraction of the amine products. Their chromatographic separation yielded mainly *N*-benzylmorpholine (**7d**), whereas the other side products were present in amounts too small for a proper characterization. *N*-Benzylmorpholine (**7d**) is the leaving group during the methylation pathway yielding **7c** and thus it is not surprising that it was present in the reaction mixture in an equimolar amount. The ring-opening pathway of the morpholinium ring could therefore not be demonstrated.

The catechol (**8a**) was efficiently dimethylated with twice the regular amount of Me_4NCl (entry 17). Its reaction with $BnMe_3NCl$ gave a mixture of all the possible benzylation and methylation products, of which the dibenzylated product **8c** strongly predominated (entry 18). The two possible mixed methylation/benzylation products **8d** formed to an extent of about 15%, as shown by the ^{1}H NMR spectroscopy (the phenolic monoalkylated products were mainly lost during the extraction and are thus not included in the given ratio). Regardless of the mixture's complexity, the dibenzylated product **8c** was easily isolated in a 56% yield by a recrystallization from methanol.

Exploiting the high reaction temperature to provide a synthetic advantage we applied NaOH as a base on allyl-substituted phenols, hoping that it would promote not just the *O*-alkylation but also the isomerization of the double bond to the thermodynamically more favorable propenylbenzenes. Such an isomerization can be either base or transition-metal catalyzed.[11] The base-catalyzed version is most commonly achieved by the application of KOH in high boiling alcohols or other solvents. Efficient modifications using hydroxides with quaternary ammonium salts as the phase-transfer catalysts were also described.[12] However, K_2CO_3 as a base was found to be too weak for eugenol (**9a**) as a substrate in our microwave-assisted methylation[1a] and we could not detect any double-bond isomerization after 25 min at 145 °C. Thus, for the isomerization to occur, we performed the alkylations of eugenol (**9a**) and 2-allylphenol (**10a**) with Me_4NCl and $BnMe_3NCl$, applying NaOH in PEG (method C). The main products were indeed the *O*-alkylated propenyl derivatives, as mixtures of (*E*)- and (*Z*)-isomers (entries 19 to 22). In the crude product mixtures some non-isomerized allyl intermediates could always be detected (these varied from 4% to 18%, as estimated from the ^{1}H NMR spectroscopic data). The *E*/*Z* ratio varied from 3 : 1 to 6 : 1, thus always in favor of the (*E*)-isomer. Due to the similar physical properties and the chromatographic mobility of all these isomers we could not separate them if they were liquid at room temperature. In some cases, however, this can be done by fractionation through very efficient distillation columns, but this is not a feasible option on such a small scale. In fact, all our attempts to achieve the separation of the diastereoisomers and allylic intermediates on TLC or by radial chromatography failed. With the analytical HPLC reverse phase column, partial separation could be achieved at long retention times. Only the solid (*E*)-*O*-benzylisoeugenol ((***E***)**-9d**) could easily be isolated by the recrystallization of **(*E*/*Z*)-9d** from ethanol.

3. Conclusion

We demonstrated that tetramethylammonium chloride (Me_4NCl) and benzyltrimethylammonium chloride ($BnMe_3NCl$) can be used as methylation and benzylation reagents for phenols. The other quaternary ammonium salts that we tried were generally less efficient for the alkylation of the above substrates. The methylation and benzylation of allyl-substituted phenols, such as eugenol or 2-allylphenol, with the use of a strong base like NaOH, led to the concurrent double-bond isomerization.

4. Experimental

4. 1. General

NMR spectra were recorded on a Bruker Avance DPX 300-MHz spectrometer in $CDCl_3$ (unless where D_2O is specified) with tetramethylsilane (TMS) as the internal standard (or DSS in D_2O) at 29 °C. Melting points are uncorrected and were measured on a Kofler micro hot stage. Reactions were monitored with TLC or HPLC (Nucleosil C-18 column using an acetonitrile/water mobile phase and a UV detector at 254 nm). Mass spectra were recorded with a VG-Analytical AutoSpec Q instrument. Elemental analyses (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. All reagents used were commercially available, with the exception of the *N*-benzyl-*N*-methylmorpholinium chloride, the synthesis of which is given below. The potassium carbonate was finely ground and dried at 150 °C for 12 hours. Polyethyleneglycol (PEG) with an average molecular mass of 400 was used (PEG400).

***N*-Benzyl-*N*-methylmorpholinium chloride.** A solution of *N*-methylmorpholine (13.8 mL, 125 mmol) and benzyl chloride (11.5 mL, 100 mmol) in methanol (120 mL) was heated during reflux for 3 h and then evaporated *in vacuo*. The residue was triturated in acetone (100 mL), the crystalline solid filtered, washed with acetone (3 × 30 mL) and dried in vacuum to give *N*-benzyl-*N*-methylmorpholinium chloride (21.85 g, 96% yield): mp = 243–245 °C dec. (lit.[13] 236 °C dec.); ^{1}H NMR (D_2O, sodium 3-(trimethylsilyl)-1-propanesulfonate, DSS, as an internal standard) δ 3.09 (s, 3H, Me), 3.32–3.42 (m, 2H), 3.53–3.66 (m, 2H), 3.96–4.15 (m, 4H) (4 × morpholine CH_2), 4.60 (s, 2H, CH_2), 7.55 (m, 5H, Ph); ^{13}C NMR (D_2O, DSS as an internal standard) δ 46.2, 59.5, 60.9, 69.9, 126.5, 129.7, 131.4, 133.6; IR (KBr) ν 1489, 1454, 1439, 1402, 1119 cm^{-1}.

4. 2. Alkylations by the Method A

Typical Procedure. 2-Methoxy-4-methyl-1-isopropylbenzene (3b).[1,14] The slurry of thymol (**3a**, 4.50 g; 30 mmol), tetramethylammonium chloride (4.25 g, 37.5 mmol), K_2CO_3 (5.17 g, 37.5 mmol) and diglyme (12 mL) was stirred during reflux for 12 h (reaction-mixture temperature 150–155 °C) (Table 1, Entry 10). Upon cooling, water was added (80 mL) and the reflux condenser changed with a distillation setup. The product was then steam–distilled, adding more water when necessary, finishing only when no more colorless oil came over with the steam. The distillate was extracted with petroleum ether (30 mL), washed with 1-M aqueous NaOH (2 × 30 mL), water (30 mL), dried over Na_2SO_4 and evaporated *in vacuo* to give **3b** as a colorless oil (4.67 g, 95% yield); ^{1}H NMR δ 1.19 (d, *J* 6.9 Hz, 6H, 2 × Me), 2.32 (s, 3H, Me), 3.27 (sept., *J* 6.9 Hz, 1H, CH), 3.81 (s, 3H, OMe), 6.67 (s, 1H, ArH), 6.74 (d, *J* 7.8 Hz, 1H, ArH), 7.09 (d, *J* 7.8 Hz, 1H, ArH); IR (NaCl) *ν* 1612, 1580, 1504, 1460 cm^{-1}.

The reaction of **3a** with phenyltrimethylammonium chloride ($PhMe_3NCl$) was performed as above with a 30-min reaction time (Table 1, Entry 11). The petroleum ether extract was additionally washed twice with 1-M aqueous HCl in order to remove the *N*,*N*-dimethylaniline originating from the $PhMe_3NCl$. Yield of **3b**: 4.21 g (86%).

2-Methoxynaphthalene (1b).[1,15] After a 6-h reaction time (Table 1, Entry 1), the reaction mixture was diluted with water (80 mL), extracted with ethyl acetate (60 mL), washed twice with 1-M aqueous NaOH (30 mL), water (30 mL), dried over Na_2SO_4 and evaporated *in vacuo* to give a brownish residue ,which after a short-path vacuum distillation gave an colorless oil, which immediately solidified on cooling (4.51 g, 95% yield); mp = 70–71 °C (lit.[15] 71–72 °C); ^{1}H NMR δ 3.92 (s, 3H), 7.10–7.18 (m, 2H, OMe), 7.33 (m, 1H, ArH), 7.43 (m, 1H, ArH), 7.75 (m, 3H, ArH); IR (KBr) *ν* 1632, 1597, 1506, 1476, 1462 cm^{-1}.

2-Benzyloxynaphthalene (1e).[5] The reaction of 2-naphthol (**1a**) with benzyltrimethylammonium chloride ($BnMe_3NCl$) (Table 1, Entry 5) and the extraction were performed with the same protocol as for **1b**. The crude product, which contained **1e** and **1b** in a ratio 88 : 12 (based on ^{1}H NMR spectroscopic data), was recrystallized from methanol to give **1e** as crystalline powder (5.08 g, 73% yield); mp = 97–98 °C (lit.[8] 97–99 °C); ^{1}H NMR δ 5.18 (s, 2H, CH_2), 7.23 (m, 2H, ArH), 7.30–7.52 (m, 7H, ArH), 7.69–7.79 (m, 3H, ArH); IR (KBr) *ν* 1624, 1593, 1506, 1451, 1388 cm^{-1}.

The reaction with benzyltriethylammonium chloride ($BnEt_3NCl$) (Table 1, Entry 6) was done as above, to give **1e** after recrystallization (3.30 g, 47% yield).

1-Methoxy-2,4-dimethylbenzene (2b).[16] Methylation of 2,4-dimethylphenol as for **3b**, with a 2-h reaction time (Table 1, Entry 7), gave a colorless oil (1.47 g, 36% yield); ^{1}H NMR δ 2.19 (s, 3H, Me), 2.25 (s, 3H, Me), 3.79 (s, 3H, OMe), 6.71 (m, 1H, ArH), 6.94 (m, 2H, ArH); IR (KBr) *ν* 1615, 1507, 1464, 1442, 1378, 1305 cm^{-1}.

4. 3. Alkylations by the Method B

Typical procedure. 1-(4-Methoxyphenyl)propan-1-one (4b).[1,17] The slurry of *p*-hydroxypropiophenone (4.50 g; 30 mmol), tetramethylammonium chloride (4.25 g, 37.5 mmol), K_2CO_3 (5.17 g, 37.5 mmol) and PEG (12 mL) was stirred for 4 h in an oil bath at 150–160 °C (temperature of the reaction mixture) (Table 1, Entry 12). Upon cooling, water was added (80 mL), the mixture was extracted with diethyl ether (50 mL), the etheral extract was washed with 1-M aqueous NaOH (2 × 30 mL), water (30 mL), dried over Na_2SO_4 and evaporated *in vacuo* to give an oil, which after a short-path vacuum distillation gave a colorless oil that slowly crystallized in the refrigerator (4.00 g, 81% yield); mp = 25–27 °C (from petroleum ether) (lit.[17] 27 °C); ^{1}H NMR δ 1.21 (t, *J* 7.2 Hz, 3H, Me), 2.95 (q, *J* 7.2 Hz, 2H, CH_2), 3.87 (s, 3H, OMe), 6.93 (AA'XX', *J* 9.0 Hz, 2H, ArH), 7.95 (AA'XX', *J* 9.0 Hz, 2H, ArH); IR (KBr) *ν* 1679, 1602, 1510, 1460, 1418 cm^{-1}.

2-Ethoxynaphthalene (1c).[18] The reaction of **1a** with tetraethylammonium chloride (Et_4NCl) (Table 1, Entry 3) and the extraction were performed on a 15 mmol scale under the same protocol as for **4b**. The product **1c** (180 mg, 7% yield) was isolated using radial chromatography with petroleum ether as the eluent; mp = 35–37 °C (lit.[4] 37–38 °C); ^{1}H NMR δ 1.49 (t, *J* 7.0 Hz, 3H, Me), 4.16 (q, *J* 7.0 Hz, 2H, CH_2), 7.15 (m, 2H, ArH), 7.33 (m, 1H, ArH), 7.44 (m, 1H, ArH), 7.74 (m, 3H, ArH); IR (KBr) *ν* 1624, 1595, 1508, 1462, 1388 cm^{-1}.

2-*n*-Butoxynaphthalene (1d).[19] The reaction of **1a** with tetrabutylammonium chloride (Bu_4NCl) (Table 1, Entry 4) was performed on a 10-mmol scale, as for **1c**. The recrystallization from a minimal amount of methanol gave **1d** (0.54 g, 27% yield); mp = 31.5–32 °C (lit.[4] 31–35 °C); ^{1}H NMR δ 1.00 (t, *J* 7.4 Hz, 3H, Me), 1.54 (m, 2H, CH_2), 1.83 (m, 2H, CH_2), 4.08 (t, *J* 6.5 Hz, 2H, OCH_2), 7.14 (m, 2H, ArH), 7.31 (m, 1H, ArH), 7.42 (m, 1H, ArH), 7.73 (m, 3H, ArH); IR (KBr) *ν* 1628, 1595, 1508, 1462, 1389 cm^{-1}.

1-(4-Benzyloxyphenyl)propan-1-one (4c).[20] The reaction of **4a** with benzyltrimethylammonium chloride ($BnMe_3NCl$) (Table 1, Entry 13) and the extraction were performed under the same protocol as for **4b**. The crude product, which contained **4c** and **4b** in a 82 : 18 ratio (^{1}H NMR spectroscopic data), was recrystallized from heptane/ethyl acetate (~ 10 : 1) to give **4c** as a fluffy crystalline product (5.43 g, 75% yield): mp = 100–102 °C (lit.[20] 102–103 °C); ^{1}H NMR δ 1.21 (t, *J* 7.3 Hz, 3H, CH_2CH_3), 2.94 (q, *J* 7.3 Hz, 2H, CH_2CH_3), 5.13 (s, 2H, OCH_2), 7.00

(AA'XX', *J* 9.0 Hz, 2H, ArH), 7.30–7.46 (m, 5H, Ph), 7.94 (AA'XX', *J* 9.0 Hz, 2H, ArH); IR (KBr) *ν* 1680, 1597, 1508, 1456 cm^{-1}.

3-Ethoxy-4-methoxybenzaldehyde (5b).[1,21] The same protocol was used as for **4b,** with a 6-h reaction time (Table 1, Entry 14). After evaporating the extract an oil was obtained, which crystallized upon standing to give **5b** (4.05 g, 75% yield); mp = 47–49 °C (lit.[21] 49.5–50.5 °C); ^{1}H NMR δ 1.49 (t, *J* 7.0 Hz, 3H, Me), 3.96 (s, 3H, OMe), 4.17 (q, *J* 7.0 Hz, 2H, CH_2), 6.98 (d, *J* 8.2 Hz, 1H, ArH), 7.43 (dt, *J* 8.2, 1.9 Hz, 2H, ArH), 9.85 (s, 1H, CHO); IR (KBr) *ν* 1691, 1677, 1599, 1511, 1440 cm^{-1}.

5-Bromo-2-methoxybenzaldehyde (6b).[22] The same protocol with 4 h reaction time was used as for **4b** (Table 1, Entry 15). After evaporating the extract a brown solid was obtained which was recrystallized from ethanol/water to give **6b** as off-white crystals (1.05 g, 16% yield); mp = 111–114 °C (lit.[6] 113–114.5 °C); ^{1}H NMR δ 3.93 (s, 3H, Me), 6.90 (d, *J* 8.9 Hz, 1H, ArH), 7.63 (dd, *J* 8.9, 2.6 Hz, 1H, ArH), 7.92 (d, *J* 2.6 Hz, 1H, ArH), 10.39 (s, 1H, CHO); IR (KBr) *ν* 1673, 1591, 1478, 1391, 1267 cm^{-1}.

2-(Benzyloxy)-6-bromonaphthalene (7b).[23] 6-Bromo-2-naphthol (**7a**) was alkylated with *N*-benzyl-*N*-methylmorpholinium chloride with a 2-h reaction time and a 12-mmol reaction scale (Table 1, Entry 16). The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (50 mL), the extract was washed with 1-M aqueous NaOH (2 × 30 mL) and water (30 mL). The ethyl acetate solution was extracted with 1-M aqueous HCl (30 mL); this aqueous extract was made basic with 2-M NaOH, back extracted with diethyl ether (25 mL) and evaporated *in vacuo* to give the amine fraction of products as a colorless oil (160 mg). The ethyl acetate solution was evaporated *in vacuo* to give a yellowish powder, which upon recrystallization from methanol yielded **7b** as shiny scales (2.70 g, 72% yield); mp = 109–111 °C (lit.[6] 110 °C); ^{1}H NMR δ 5.17 (s, 2H, CH_2), 7.15–7.27 (m, 2H), 7.31–7.53 (m, 6H), 7.55–7.69 (m, 2H), 7.92 (d, *J* 1.8 Hz, 1H) (all aryl protons); IR (KBr) *ν* 1625, 1585, 1497, 1454, 1383 cm^{-1}. The amine fraction was separated by employing radial chromatography with petroleum ether : ethyl acetate (1 : 1) as the eluent, yielding *N*-benzylmorpholine (**7d**)[24] as an oily product (60 mg, 3% yield); ^{1}H NMR δ 2.44 (m, 4H, 2 × CH_2), 3.49 (s, 2H, PhCH_2), 3.70 (m, 4H, 2 × CH_2), 7.21–7.35 (m, 5H, Ph); IR (NaCl) *ν* 1493, 1450, 1393, 1351, 1286 cm^{-1}.

4-*tert*-Butyl-1,2-dimethoxybenzene (8b).[25] The same reaction protocol was used as for **4b**, but starting from **8a** (5.0 g, 30 mmol), tetramethylammonium chloride (8.5 g, 75 mmol), K_2CO_3 (10.34 g, 75 mmol) and PEG (24 mL) with a 10-h reaction time (Table 1, Entry 17). The product was isolated using steam distillation to give a colorless oil, which crystallized upon standing to give **8b** (5.25 g, 90% yield); mp = 32–34 °C (lit.[25] 34–35.5°C); ^{1}H NMR δ 1.31 (s, 9H, *t*-Bu), 3.86 (s, 3H, OMe), 3.89 (s, 3H, OMe), 6.80 (m, 1H, ArH), 6.88–6.94 (m, 2H, ArH); IR (KBr) *ν* 1606, 1591, 1523, 1471, 1449 cm^{-1}.

4-*tert*-Butyl-1,2-dibenzyloxybenzene (8c). The reaction of **8a** (5.0 g, 30 mmol) with benzyltrimethylammonium chloride (14.0 g, 75 mmol) (Table 1, Entry 18) was performed as above for **8b**, with the exception that the extraction with ethyl acetate was used to isolate the product mixture, which was recrystallized from methanol to give pure **8c** as colorless crystals (5.85 g, 56% yield); mp = 61–62 °C; ^{1}H NMR δ 1.24 (s, 9H, *t*-Bu), 5.11 (s, 2H, CH_2), 5.15 (s, 2H, CH_2), 6.87 (m, 2H, ArH), 6.98 (d, *J* 1.5 Hz, 1H, ArH), 7.23–7.37 (m, 6H, ArH), 7.40–7.47 (m, 4H, ArH); ^{13}C NMR δ 31.4, 34.3, 71.4, 71.8, 113.9, 114.6, 118.3, 127.3, 127.5, 127.6, 127.7, 128.36, 128.39, 137.60, 137.61, 144.7, 147.1, 148.3; IR (KBr) *ν* 1634, 1601, 1589, 1519, 1455 cm^{-1}; MS (ESI) *m/z*: 369 (MNa^+); HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{26}O_2Na$, 369.1831; found, 369.1820. Anal. Calcd for $C_{24}H_{26}O_2$: C 83.20, H 7.56. Found: C 83.32, H 7.76.

4. 4. Alkylations by the Method C

O*-Methylisoeugenol ((*E*/*Z*)-9b).** The slurry of eugenol (**9a**, 8.29 g, 50 mmol), tetramethylammonium chloride (7.1 g, 62.5 mmol) and NaOH (2.6 g, 62.5 mmol) in PEG (20 mL) was stirred for 4 h in an oil bath at 150–160 °C (temperature of the reaction mixture) (Table 1, Entry 19). Upon cooling, water was added (100 mL), the mixture extracted with diethyl ether (60 mL), washed with 1-M aqueous NaOH (2 × 30 mL), water (30 mL), dried over Na_2SO_4 and evaporated *in vacuo* to give a slightly orange oil, which after short-path vacuum distillation gave a colorless oil (6.91 g, 78% yield). NMR spectroscopic analysis of the product revealed the *E* : *Z* diastereomeric ratio to be 4 : 1 (the coupling constants for the C*H*=C*H* protons were 15.7 Hz and 11.6 Hz, respectively) and also showed the presence of approximately 10% of *O*-methyleugenol (**9c**). MS (EI) *m/z* (relative intensity): 178 (M^+, 100), 163 (40), 147 (14), 107 (26), 103 (15), 91 (25); HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{11}H_{14}O_2$, 178.0994; found 178.0992; IR (NaCl) *ν* 1599, 1583, 1514, 1460, 1416 cm^{-1}. The ^{1}H NMR spectrum of the major component (E*)-9b**[26] is given as follows: δ 1.86 (dd, *J* 6.6, 1.6 Hz, 2H, Me), 3.87 (s, 3H, OMe), 3.89 (s, 3H, OMe), 6.10 (dq, *J* 15.7, 6.6 Hz, 1H, CH=C*H*-Me), 6.34 (dq, *J* 15.7, 1.6 Hz, 1H, C*H*=CH-Me), 6.79 (d, *J* 8.2 Hz, 1H, ArH), 6.85 (dd, *J* 8.2, 1.8 Hz, 1H, ArH), 6.89 (d, *J* 1.8 Hz, 1H, ArH). The presence of **(*E*)-9b** was additionally confirmed by adding an authentic commercial sample to the above mixture.

***O*-Benzylisoeugenol ((*E*/*Z*)-9d).** The slurry of eugenol (**9a**, 5.0 g, 30 mmol), benzyltrimethylammonium chlo-

ride (7.18 g, 37.5 mmol) and NaOH (1.6 g, 37.5 mmol) in PEG (12 mL) was stirred for 4 h in an oil bath at 150–160 °C (temperature of the reaction mixture) (Table 1, Entry 20). Upon cooling, water was added (80 mL), the mixture was extracted with diethyl ether (60 mL), washed with 1-M aqueous NaOH (2 × 30 mL), water (30 mL), dried over Na_2SO_4 and evaporated *in vacuo* to give a brown oil, which was diluted with methanol/water (8:1, 50 mL). The solid precipitated after standing at cold was filtered off to give **(*E*/*Z*)-9d** as long needles (3.20 g, 42%). NMR spectroscopic analysis showed the *E* : *Z* diastereomeric ratio to be approximately 7 : 1 (the coupling constants for the C*H*=C*H* protons were 15.7 Hz and 11.6 Hz, respectively). MS (EI) *m/z* (relative intensity): 254 (M^+, 39), 163 (71), 91 (100); HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{17}H_{18}O_2$, 254.1307; found, 254.1310. Anal. Calcd for $C_{17}H_{18}O_2$: C 80.28, H 7.13. Found: C 80.42, H 6.98. A sample of (*E*/*Z*)-mixture was recrystallized from ethanol to give (*E*)-*O*-benzylisoeugenol **((*E*)-9d)**: mp 51–52 °C (lit.[27] 53–54 °C); ^{1}H NMR δ 1.84 (dd, *J* 6.5, 1.3 Hz, 3H, Me), 3.87 (s, 3H, OMe), 5.11 (s, 2H, OCH_2), 6.08 (dq, *J* 15.7, 6.5 Hz, 1H, CH=C*H*Me), 6.31 (dq, *J* 15.7, 1.3 Hz, 1H, C*H*=CHMe), 6.78 (m, 2H, ArH), 6.89 (s, 1H, ArH), 7.20–7.47 (m, 5H, Ph); ^{13}C NMR δ.18.3, 55.9, 71.1, 109.1, 114.2, 118.5, 123.9, 127.2, 127.7, 128.4, 130.6, 131.7, 137.2, 147.3, 149.7; IR (KBr) *ν* 1598, 1582, 1512, 1456, 1414, 1381 cm^{-1}.

(*E*/*Z*)-1-methoxy-2-(prop-1-en-1-yl)benzene ((*E*/*Z*)-10b). The slurry of 2-allylphenol (**10a**, 6.94 g, 50 mmol), tetramethylammonium chloride (7.1 g, 62.5 mmol) and NaOH (2.6 g, 62.5 mmol) in PEG (20 mL) was stirred for 4 h in an oil bath at 150–160 °C (temperature of the reaction mixture) (Table 1, Entry 21). Upon cooling, water was added (100 mL) and the products steam–distilled, as described for **3b**. The distillate was extracted with petroleum ether (30 mL), washed with 1-M aqueous NaOH (2 × 30 mL), water (30 mL), dried over Na_2SO_4 and evaporated *in vacuo* to give **(*E*/*Z*)-10b** as a colorless oil (5.55 g, 75% yield). NMR spectroscopic analysis revealed the *E* : *Z* diastereomeric ratio to be 3.7 : 1 (the coupling constants for the C*H*=C*H* protons were 15.9 Hz and 11.6 Hz, respectively) and also showed the presence of approximately 4% 2-allylanisole (**10c**). MS (EI) *m/z* (relative intensity): 148 (M^+, 100), 133 (24), 119 (36), 117 (23), 115 (27), 105 (34), 91 (49); HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{10}H_{12}O$, 148.0888; found, 148.0889; IR (NaCl) *ν* 1598, 1489, 1460, 1437, 1243 cm^{-1}. The ^{1}H NMR spectrum of the major component **(*E*)-10b**[28] as determined from the mixture of products: δ 1.90 (dd, *J* 6.6, 1.7 Hz, 2H, Me), 3.84 (s, 3H, OMe), 6.22 (dq, *J* 15.9, 6.6 Hz, 1H, CH=C*H*-Me), 6.71 (dq, *J* 15.9, 1.7 Hz, 1H, C*H*=CH-Me), 6.88 (m, 2H, ArH), 7.17 (m, 1H, ArH), 7.38 (dd, *J* 7.6, 1.6 Hz, 1H, ArH).

(*E*/*Z*)-1-(Benzyloxy)-2-(prop-1-en-1-yl)benzene ((*E*/*Z*)-10d). The slurry of 2-allylphenol (**10a**, 4.10 g; 30 mmol), benzytrimethylammonium chloride (7.18 g, 37.5 mmol) and NaOH (1.6 g, 37.5 mmol) in PEG (12 mL) was stirred for 4 h in an oil bath at 150–160 °C (temperature of the reaction mixture) (Table 1, Entry 22). Upon cooling, water was added (100 mL), the mixture was extracted with diethyl ether (80 mL), washed with 1-M aqueous NaOH (2 × 30 mL), water (30 mL), dried over Na_2SO_4 and evaporated *in vacuo* to give a brown oil. The benzylated and methylated products had very similar chromatographic mobility on TLC. Thus, the mixture was first purified from polar impurities by filtering its petroleum ether solution through a plug of silica to give a colorless oil (5.48 g), from which the methylated products were removed by steam distillation, leaving behind pure **(*E*/*Z*)-10d** (4.5 g, 67% yield). ^{1}H NMR spectroscopic analysis revealed the *E* : *Z* diastereomeric ratio to be 6.3 : 1 (the coupling constants for the C*H*=C*H* protons were 15.9 Hz and 11.6 Hz, respectively). MS (EI) *m/z* (relative intensity): 224 (M^+, 8), 105 (8), 91 (100); HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{16}H_{16}O$, 224.1201; found 224.1206; IR (NaCl) *ν* 1597, 1578, 1488, 1449, 1378 cm^{-1}. The ^{1}H NMR spectrum of the major component **(*E*)-10d**[28] is given: δ 1.89 (dd, *J* 6.6, 1.7 Hz, 2H, Me), 5.09 (s, 2H, CH_2), 6.24 (dq, *J* 15.9, 6.6 Hz, 1H, CH=C*H*-Me), 6.79 (dq, *J* 15.9, 1.7 Hz, 1H, C*H*=CH-Me), 6.91 (m, 2H, ArH), 7.14 (m, 1H, ArH), 7.27–7.47 (m, 6H, ArH).

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Povzetek

Fenolne spojine se da učinkovito *O*-metilirati s tetrametilamonijevim kloridom v diglimu ali polietilen glikolu (PEG) pri temperaturah 150–160 °C in v prisotnosti K_2CO_3 ali NaOH. Z uporabo benziltrimetilamonijevega klorida kot reagenta potečeta tako benziliranje kot tudi metiliranje fenolov, pri čemer je vedno prednosten produkt benziliranja. Pri uporabi alil-substituiranih fenolov kot substratov in NaOH kot baze je mogoče izvesti tako alkiliranje kakor tudi izomerizacijo dvojne vezi alilne skupine, pri čemer nastanejo (*E*/*Z*)-propenil-substituirani metil in benzil aril etri v eni sami preparativni stopnji.