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O-Methylation with Phenyltrimethylammonium chloride

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Alkyl and aryl ethers can be obtained by alkylation of the corresponding alcohols or phenols with, e.g., alkyl halides or sulfonates. These reactions usually proceed via S_N1- or S_N2-type mechanisms, often accompanied by the corresponding elimination reactions, (E1 or E2). Elimination and substitution reactions in general exist in competition, depending on the balance between nucleophilicity and base character of the reagents and the nature of the substrate. Strong bases and weak nucleophiles in non-ionizing solvents favor elimination, while weak bases that are also good nucleophiles, in non-ionizing solvents favor substitution. Increasing the polarity of the solvent favors S_N2 reactivity at the expense of E2 reactivity.

In the Hofmann degradation reaction quaternary alkylammonium salts with strong base give the corresponding elimination products. Competition between the elimination reaction and the substitution pathway has been reported.[1] However, the application of quaternary ammonium salts as alkylation reagents has found little synthetic use. A review dealing with *C*-alkylation with amines was presented in 1953.[2] Quaternary ammonium hydroxides were reported in some cases to form alcohols upon heating, while the corresponding phenoxides gave ethers of phenols.[3] In the literature is also a report of the alkylation of morphine to give codeine with phenyltrimethylammonium methoxide.[4] A more recent patent[5] described the same conversion using phenyltrimethylammonium chloride in the presence of potassium carbonate.

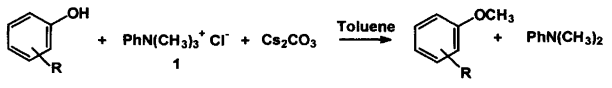
The potential of quaternary ammonium salts as useful and general reagents for *O*-alkylation reactions under mild reaction conditions, prompted us to initiate an investigation of the synthetic scope or the reaction. Here we report a study of the use of phenyltrimethylammonium chloride, **1**, for the alkylation of alcohols and phenols.

Results and discussion

Alkylations of a number of phenols and alcohols with **1** was carried out in refluxing toluene in the presence of a weak base, Scheme 1. The best results were obtained with solid Cs_2CO_3. Typically 10 mmol of substrate were alkylated with 15 mmol of **1** in the presence of a slight excess (6 mmol) of Cs_2CO_3 in 20–30 ml of refluxing toluene. Representative examples are shown in Table 1.

Reactivity. The reactivities of the substrates were estimated from the time required for 50 % conversion, Table 1. Phenols were readily converted into the corresponding methoxy compounds in essentially quantitative yields. Depending on the substitution, product formation was complete within 2–24 h. Phenols substituted with electron-withdrawing groups, e.g., NO_2, reacted slower than those substituted with electron-donating substituents, e.g., OCH_3. Alkyl, benzylic and allylic alcohols reacted somewhat slower than the phenols, often with incomplete conversion even after prolonged periods of time.

Selectivity. The observed differences in reactivity suggested that the reagent may exhibit some selectivity with respect to phenols. Indeed, upon alkylation of a series of molecules containing phenolic OH as well as alkyl OH groups, the phenol functions were in all cases methylated faster than the alcohol groups, resulting in selectivities of 95 % or better, Table 2. When a carboxylic acid group was also present in the substrate molecule, ester formation took place more readily than methylation of the phenolic OH groups. The selectivity appeared to parallel the relative acidities of the OH-nucleophiles in the molecules, and may thus be due to formation of the corresponding bases by reaction with the base present, (Cs_2CO_3). To ensure complete and ready alkylation of a phenol at least 0.5 mol equivalents of Cs_2CO_3 were required. Under the reaction conditions the ammonium salt **1** decomposed to *N*,*N*-dimethylaniline, suggesting



Scheme 1.

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Table 1. Alkylation of phenols and alcohols with **1**.

Entry	Substrate	*t*/h	Product	Half-life[a]	%Yield (isolated)[b]
1	4-Methoxyphenol	28	1,4-Dimethoxybenzene	30 min	97 (50)
2	3-*tert*-Butylphenol	27	3-*tert*-Butylanisole	6 h	99 (92)
3	3-Chlorophenol	6	3-Chloroanisole	10 min	98 (85)
4	4-Bromophenol	11	4-Bromoanisole	3 h	97 (56)
5	4-Fluorophenol	24	4-Fluoroanisole	2 h	95 (60)
6	4-Nitrophenol	48	4-Nitroanisole	23 h	87 (88)
7	1-Naphthol	21	1-Methoxynaphthalene	2.5 h	98 (87)
8	2-Naphthol	2	2-Methoxynaphthalene	10 min	99 (89)
9	1-Phenylethanol	42	1-Methoxy-1-phenylethane	46	
10	Cinnamyl alcohol	148	Cinnamyl methyl ether	24 h	98 (66)
11	4-*tert*-Butylcyclohexanol, *cis*+*trans*	102	Methoxy-4-*tert*-butyl-cyclohexane *cis*+*trans*	38	

[a] Approximate time for 50% conversion. [b] GLC yields.

Table 2. Selectivity on alkylation with **1**.

Entry	Substrate	*t*/h	Product	%Yield[a]
1	Salicyl alcohol	30	2-Methoxybenzyl alcohol	78
2	3-(2-Hydroxyphenyl)-2-propenoic acid	27	Methyl 3-(2-hydroxyphenyl)-2-propionate	92
3	1,5-Dihydroxy-1,2,3,4-tetrahydronaphthalene	8	1-Hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene	99
4	Mandelic acid	8	Methyl mandelate	94
5	2-Acetamidophenol	7	2-Methoxyacetanilide	99
6	2-Hydroxybenzoic acid	1	Methyl 2-hydroxybenzoate	87
7	2-Cyclohexyl-2-hydroxyacetic acid	29	Methyl 2-cyclohexyl-2-hydroxyacetate	99

[a] GLC yields.

the use of a larger excess of **1**. However, applying larger amounts of **1** or Cs_2CO_3 had only a marginal effect on the rates of reaction and the selectivities, presumably due to the heterogeneous nature of the reaction.

Experimental

General. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 NMR spectrometer using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. IR and GC–IR spectra were obtained on a Nicolet 20-SXC FT-IR instrument. Mass spectra were recorded on an AEI MS-902 spectrometer at 70 eV (IP). GLC measurements were made on a Varian 3700 gas chromatograph equipped with a CP-Sil19CB capillary column (25 m).

Alkylation with phenyltrimethylammonium chloride, 1. General procedure. To a mixture containing 2.57 g, 15 mmol, of phenyltrimethylammonium chloride, **1**, and 1.95 g, 6 mmol, of Cs_2CO_3 in 20 ml of toluene were added 10 mmol of the hydroxy compound. The resulting reaction mixture was heated at reflux for the time indicated in Tables 1 and 2. The reaction mixture was then washed first with a 1 M HCl solution, then water, and dried over anhydrous magnesium sulfate. Following evaporation of the solvent under reduced pressure, the crude product was subjected to recrystallization or bulb-to-bulb distillation. The spectroscopic and chromatographic properties of the products were in all cases in full agreement with those of authentic samples.

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