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### Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: <u>http://www.tandfonline.com/loi/lsyc20</u>

# QUATERNARY AMMONIUM SALT-ASSISTED ORGANIC REACTIONS IN WATER: ALKYLATION OF PHENOLS

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Available online: 09 Nov 2006

To cite this article: Jean Jacques Vanden Eynde & Isabelle Mailleux (2001): QUATERNARY AMMONIUM SALT-ASSISTED ORGANIC REACTIONS IN WATER: ALKYLATION OF PHENOLS, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:1, 1-7

To link to this article: http://dx.doi.org/10.1081/SCC-100000172

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#### SYNTHETIC COMMUNICATIONS, 31(1), 1-7 (2001)

### QUATERNARY AMMONIUM SALT-ASSISTED ORGANIC REACTIONS IN WATER: ALKYLATION OF PHENOLS

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#### ABSTRACT

A series of quaternary ammonium salts has been tested as phase transfer agents to promote reactions between phenols and alkyl halides in an aqueous solution of sodium hydroxide in the absence of organic solvent. Methyltrioctylammonium chloride emerges as the most effective catalyst.

Nowadays, there is an increasing awareness of the urgent necessity to limit, as far as possible, any source of pollution. Consequently and in response to the public pressure, the environmental legislation is becoming ever more severe. Facing up to those facts, chemists have to dedicate numerous efforts to the development of clean technologies.

That new challenge has led recently to a growing interest in the displacement of organic reactions to aqueous media (1-3), which has been achieved successfully in the Ruhr Chemie Rhône-Poulenc hydroformylation process (4).

Water is an abundant, cheap, nontoxic, and nondangerous solvent. Obviously, it does not dissolve most of the organic reactants, but that fact has been recognized

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as a benefit on rates and selectivities of several transformations (1-3). Moreover, the addition of a phase transfer agent, generally a quaternary ammonium salt, enables to improve an intimate contact with an organic layer (3-11).

2

The aim of this paper is to disclose suitable experimental conditions to promote alkylation of phenols in an aqueous solution of sodium hydroxide and in the absence of any organic solvent. That reaction yields aryl ethers, a functionality that is a key constituent in the structures of many pharmaceutically important chemicals.

#### RESULTS

The reaction between phenols and alkyl halides in an aqueous solution of sodium hydroxide requires the contact between two nonmiscible phases and yields a water-insoluble product. Therefore, its course can be monitored readily by UV spectroscopy on samples of the aqueous phase, as the phenolates are the sole species that absorb in that wavelength region. That method was used to select the most attractive phase transfer catalyst from a kinetic point of view in a model reaction involving 1,2-dihydroxybenzene (**1a**-Fig. 1;  $\epsilon = 2870 \text{ 1 mol}^{-1} \text{ cm}^{-1}$ ;  $\lambda \max = 275 \text{ nm}$ ) and iodomethane. By that way, we observed that **1a** reacts slowly with an excess (3 eq) of iodomethane in an aqueous solution of sodium hydroxide (5M) at 50°C.

After 1 h, only 5% of the starting material **1a** is consumed. Addition of a quaternary ammonium salt (10% mol relative to **1a**) accelerates the process as indicated by inspection of the results collected in Table 1. Among the transfer agents we tested, methyltrioctylammonium chloride (Aliquat<sup>®</sup> 336) emerges as the most effective catalyst. Interestingly, in contrast with conclusions (12) dealing with other phase transfer catalysis experiments, no synergistic effect of a crown ether-quaternary ion salt pair takes place.

To evaluate the synthetic potential of the method, we performed the same experiments in a boiling solution of sodium hydroxide, extending the reaction time arbitrarily to 1 h. After cooling, the mixture was extracted with dichloromethane. Before evaporation of the solvent, the organic layer was filtered through a cake of alumina to retain the ammonium salt. Yields in 1,2-dimethoxybenzene, determined by <sup>1</sup>H NMR, are collected in Table 1. The data parallel the results of the



Figure 1.

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Table 1. Influence of the Catalyst on the Alkylation of 1a with Methyl Iodide

	[1a] (mol/l) <sup>a</sup> after		Isolated Yield <sup>b</sup> ,
Catalyst (10% mol relative to 1a)	30 mn	60 mn	%
None	0.78	0.76	25
Benzyltriethylammonium chloride	0.68	0.56	40
Tetrabutylammonium hydrogenosulfate (TBA)	0.44	0.38	65
TBA/15-crown-5	0.54	0.51	60
Cetyltrimethylammonium bromide	0.45	0.35	80
Methyltrioctylammonium chloride	0.45	0.33	90

 ${}^{a}C_{0}$  (1a) = 0.8 mol l<sup>-1</sup>; C<sub>0</sub> (CH<sub>3</sub>I) = 2.4 mol l<sup>-1</sup>; T = 50°C.

 ${}^{b}C_{0}$  (1a) = 0.8 mol l<sup>-1</sup>; C<sub>0</sub> (CH<sub>3</sub>I) = 1.6 mol l<sup>-1</sup>; T = reflux; time = 1 hour.

kinetic study. Indeed, the highest yield in isolated product was obtained by using methyltrioctylammonium chloride as the transfer agent. Cetyltrimethylammonium bromide is also efficient, but its tendancy to foam complicates the experimental procedure. The other salts give lower yields so we did not use them. Experimentally, we also noticed that the stoechiometric amount of iodomethane is sufficient to effect the dialkylation. In agreement with the mechanism of the reaction, which requires the formation of phenolate anions, a lower concentration of NaOH (0.5 M) or the use of sodium hydrogenocarbonate (5 M, 0.5 M) as the base (in the presence of 10% mol of methyltriocylammonium) dramatically decreases the yield in 1,2-dimethoxybenzene to 30, 20, or 5%, respectively. In that sense, too, sodium dodecylsulfate (10% mol), a popular anionic surfactant, exhibits a poor but positive activity (35%).

Having a simple procedure to methylate 1,2-dihydroxybenzene, we wished to estimate its range of applicability. Under our experimental conditions, compound



Figure 2.



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Product	Isolated Yield, %	Lit. Ref.
2a	90	21–24
2b	55	23-26
3a	60	23, 24, 27, 28
3b	65	14, 29
3c	75	14, 30
3d	95	14, 29
3e	50	23, 24, 31
<b>4</b> a	90	23, 24, 32, 33
4b	90	23, 24, 34, 35
4c	55	23, 24, 36, 37
4d	65	38
<b>4e</b>	95	39-41
4f	70	42–44

*Table 2.* Results for the Alkylation of **1a**, **1b**, and Various Phenols in the Presence of Methyltrioctylammonium Chloride

**1a** readily reacts with 1,2-dibromoethane, 1,3-dibromopropane, 1,4-dibromobutane, and even 1,5-dibromopentane. Yields vary from 50 to 95%. In particular, derivative **3c** has been obtained in 75% yield, whereas Ziegler (7) reports that its preparation requires two steps and that the yield of the second step does not exceed 40%. 3,4-Dihydroxybenzaldehyde (**1b**) and other phenols also can be alkylated under our experimental conditions, as indicated by the examples presented in Figure 2 (isolated yields are reported in Table 2). Mention should be made that in all cases the crude final products were isolated by decantation or filtration, thus limiting the use of an organic solvent to the purification by recrystallization when the expected compound is a solid.

#### CONCLUSION

Elegant protocols for the preparation of aryl ethers have recently been published. They recommend the use of polymer-supported bases (15) or irradiation of dry media with microwaves (16,17). This paper presents another simple experimental procedure (that could readily be scaled up) to alkylate phenols in an aqueous basic solution in the presence of a catalytic amount of methyltrioctylammonium and in the absence of any organic solvent. It is characterized by its wide range of applicability as it enables, e.g., the formation of 6- to 9-membered benzo fused systems, as well as the use of long chain alkyl halides. Our experimental conditions largely differ from those described by Bashall and Collins (18) as the



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#### ALKYLATION OF PHENOLS

ammonium salt does not play the role of a solvent. Let us also emphasize that we did not observe any poisoneous effect of the iodide ion when alkyl iodides were involved (18, 19), and that by-products from a Cannizzaro reaction (20) were not detected when starting from hydroxybenzaldehydes.

#### **EXPERIMENTAL SECTION**

All reagents, catalysts, and solvents are commercially available (Aldrich, Acros Organics). All products (**2**, **3**, **4**) have been described in the literaure and were fully characterized by their melting point (hot-stage microscope) or boiling point, and by their spectral data (NMR: Varian EM 360-L, Bruker AMX; IR: Perkin-Elmer 1760K).

#### **Quantitative Study**

A stirred mixture of 1,2-dihydroxybenzene (5.51 g; 50 mmol) and a catalyst (see Table 1; 5 mmol) in a 5 M aqueous solution (62.50 mL) of sodium hydroxide was held under thermostatic control at  $50^{\circ}$ C for two hours. Iodomethane (9.34 mL; 150 mmol) was added. A sample of the mixture was taken every 10 minutes, rapidly cooled down to  $0^{\circ}$ C, and diluted (2000 X) for UV analysis (Varian Cary 118).

#### General Procedure for the Alkylation

A mixture of the phenol (100 mmol), the alkyl halide (one or two equivalents), and methyltrioctylammonium chloride (10 mmol) in a 5 M aqueous solution (100 mL) of sodium hydroxide was stirred and heated under reflux for one hour. After cooling, the crude product was separated (decantation or filtration) and purified by distillation or recrystallization.

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