Anion Activation in the Synthesis of Ethers from Oxygen Anions and 1-Chloro-4-nitrobenzene

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Reactions of 1-chloro-4-nitrobenzene (1) with alkoxide ions in the parent alcohols do not afford satisfactory yields of the expected alkyl 4-nitroaryl ether except in the case of the short-chain primary alcohols. We report that in the model reaction of 1 with KOH in 2-propanol good yields of 1-isopropoxy-4-nitrobenzene (2) are obtained provided Bu_4NBr or alkali ion complexing agents such as 18-crown-6, Carbowax 20M, MPEG 5000, and Triton X-100 are present. Low molecular weight ethers, like glyme-5, are less effective, with ethylene glycol dimethyl ether having no effect at all. Work at temperatures below the solution boiling point is recommended to avoid competitive reduction of the NO_2 group. The preparative value of Bu_4NBr additions in analogous reactions of 1 to give $4\text{-}O_2NC_6H_4OR$ ethers (3) is also very significant when R is primary, secondary, and aryl (1-octyl, *sec*-butyl, phenyl). The reaction fails when R = *tert*-butyl and $4\text{-}O_2NC_6H_4$.

Rather surprisingly, 1-chloro-4-nitrobenzene is an unsuitable substrate for the preparation of alkyl 4-nitroaryl ethers by reaction with the appropriate alcohol in alkaline media, unless the alcohol is a short-chain primary one. In fact, standard procedures for the synthesis of alkyl aryl ethers involve alkylation of the aryl oxide ion according to one of the many modifications of the Williamson synthesis,[1] including, among others, use of phase-transfer catalysis,[2] tetraalkylammonium phenoxides[3] or fluoride,[4] and anion-exchange resins.[5] All these methods give high yields with primary, poorer yields with secondary, and fail with tertiary alkyl groups. A procedure involving reaction of alcohols (primary, secondary, and tertiary) with phenols in the presence of PPh_3 and diethyl azodicarboxylate has also been reported.[6]

Nitro-substituted alkyl aryl and diaryl ethers can be prepared from reaction of the corresponding fluoronitrobenzenes with alkoxide and aryl oxide ions.[1b,7] As mentioned earlier, use of the less expensive chloronitrobenzenes is generally precluded; this is so because of their low reactivity in nucleophilic aromatic substitution and of the relatively easy reduction of their nitro group in alkaline alcoholic solutions.[8,9] Thus, 1-chloro-4-nitrobenzene (1) can react with isopropoxide ion in 2-propanol according to two competing pathways, depending on reaction conditions: reduction of the nitro group and substitution of chlorine (see Scheme I).[9] Oxygen, for example, has a dramatic effect on the reaction course: while in carefully deoxygenated solutions reduction products form exclusively, under an atmosphere of oxygen these are completely suppressed, substrate consumption is much slower, and 2 is produced in 40% yield, along with ca. 10% of 4-nitrophenol.[9] The explanation offered for these results is that oxygen acts as a radical ion scavenger, quenching the reduction process, thought to proceed via the intermediate 1-chloro-4-nitrobenzene radical anion, and thus allowing the slower S_NAr pathway to compete.[9] The irreproducible results obtained in experiments conducted under an atmosphere of air were therefore related to the amount of oxygen dissolved in any given solution.[9]

A number of reduction "inhibiting" systems such as $(NH_2)_2CO$–air,[10] MnO_2,[8a,11] and $Cu(OH)_2$[12] have been employed to effect the desired substitutions. For reactions of 1 in 2-propanol, however, additions of K_2SO_3 or MnO_2 reportedly fail to give 2 in any appreciable yield.[11b] Mere inhibition of the reduction process by oxygen is unsatisfactory because production of 2 is slow and limited.

This paper reports on the effects of a number of reagents and reaction conditions on the reactivity of 1-chloro-4-nitrobenzene (1) in alkaline 2-propanol, chosen as a model system; recognized or potential complexing agents for alkali metal cations as well as tetraalkylammonium salts were used, with the intent of enhancing alkoxide nucleophilicity and thus promoting the substitution reaction. The investigation has been extended to include reactions of 1 with a few other representative alkoxide and aryl oxide ions.

Results and Discussion

Reactions in the 2-Propanol/50% Aqueous KOH System. It appeared of interest to explore the reactivity of 1 in the heterogeneous system formed when 2-propanol is mixed with a 50% KOH aqueous solution; the concentration of base in the upper alcoholic layer, at 75 °C and under vigorous stirring, was determined titrimetrically to be 0.15 M.

A few indicative results are summarized in Table I and allow a comparison with the behavior in homogeneous 2-propanol solution. The reactivity of 1 under the two sets of conditions (entries 1 and 2) appears to be rather similar, possibly suggesting that in the two-phase system reaction also occurs in the bulk of the 2-propanol layer under homogeneous conditions.

An interesting observation emerges, however, from comparison of entries 1 and 2; after 45 h the starting material is totally consumed with only 40% of 2 formed in the homogeneous solution, whereas, in the heterogeneous mixture the same yield of 2 is obtained with 46% of 1 yet unreacted. It would thus appear as though con-

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Scheme I

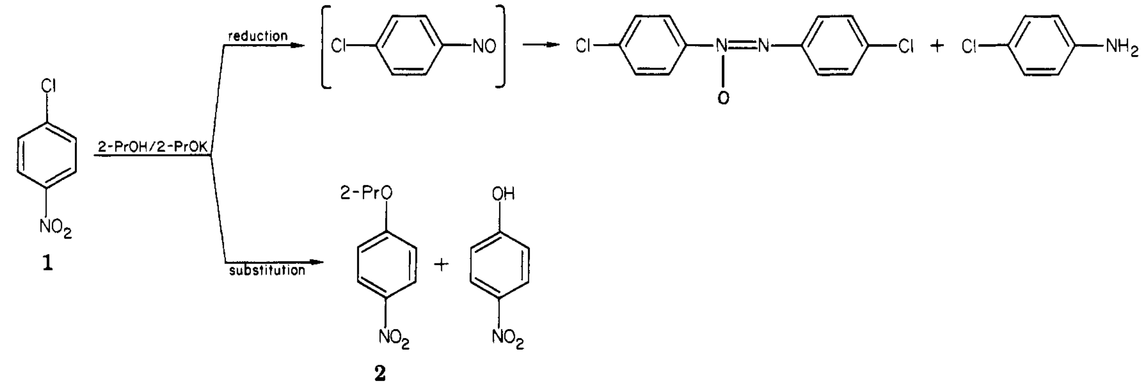

Table I. Reactions of 1-Chloro-4-nitrobenzene (1) with Isopropoxide Ion at 75 °C in Homogeneous 2-Propanol Solution and in the 50% Aqueous KOH/2-PrOH Two-Phase System

entry	reaction system	atmosphere	[1], M	added catalyst (concn, M)	reaction time, h	% yield[a] 1	% yield[a] 2
1[b]	2-PrOH/2-PrOK (0.24 M)	oxygen	0.03	none	45	0	40
2[c]	2-PrOH/50% KOH (aq)	oxygen	0.06	none	45.4	46	40
3[c]	2-PrOH/50% KOH (aq)	air	0.06	none	16.4	77	18
4[c]	2-PrOH/50% KOH (aq)	air	0.10	18-crown-6 (0.18[d])	21	5	59
5[c]	2-PrOH/50% KOH (aq)	air	0.10	Bu_4NHSO_4 (0.17[d])	21	1	63

[a] Determined by GLC analysis. [b] Reference 9. [c] Base concentration in the organic layer was 0.15 M. [d] Formal concentration in the organic phase under the assumption of nil partitioning into the aqueous phase.

current reactions with the $O_2^{-}\cdot$ species, responsible for the unaccounted for loss of material in the homogeneous solution,[9] are minimized in the two-phase system, possibly owing to superoxide ion extraction into the aqueous layer. Clarification of this phenomenon was not pursued experimentally.

Additions of 18-crown-6 or Bu_4NHSO_4, in ca. equimolar amounts with the base present in the organic phase, accelerate substrate consumption, leading, in both cases, to final yields of ca. 60% of **2** in 21 h (entries 3–5, Table I).

These testing experiments indicate that, as in other nucleophilic aromatic substitutions,[13] use of two-phase conditions is not particularly advantageous; they also point, however, to significant advantages in performing the reaction in the presence of quaternary ammonium salts and alkali ion complexing agents.

Reactions in 2-Propanol. The general procedure involves mixing a concentrated (0.6 M) 2-propanol/KOH solution with a 2-propanol solution of **1**, a hydrocarbon standard for GLC analysis, and the selected potential "catalyst".[14] Reactions were usually conducted in a thermostated bath at 75 °C rather than at reflux (82 °C); this point turned out to be of crucial importance and is discussed below. Catalysts used in this investigation are 18-crown-6, Bu_4NBr, Triton X-100, Carbowax 20M, MPEG 5000, diethylene glycol dimethyl ether, and tetraethylene glycol dimethyl ether (glyme-5). Relevant data and results are summarized in Table II, with entry 1 referring to a blank run.

Some of the effects are rather remarkable. 18-Crown-6 and Bu_4NBr behave almost identically, affording **2** in 3 h in 80% yield. Polyethylene glycols are also very effective: Carbowax 20M ($M_r \simeq 20000$) and MPEG 5000 (polyethylene glycol monomethyl ether, M_r = ca. 5000) give **2** in 79% and 64% yields, respectively, in 5 h. A longer reaction time, 8 h, is required to obtain a final yield of 71% of **2** in the presence of Triton X-100; the peculiar course followed by this reaction is discussed at the end of this section.

Table II. Reactions of 1-Chloro-4-nitrobenzene (1) (0.03 M) with KOH (0.29 M) in 2-Propanol at 75 °C under Air in the Presence of Added Catalysts

entry	added catalyst (concn, M)	reaction time, h	% yield[a] 1	% yield[a] 2
1	none	21	36	41.5
		46	12	59
2	18-crown-6 (0.24)	3	2	80
3	Bu_4NBr (0.28)	3	2	79
4	Triton X-100 (ca. 0.3)	3	5	50
		5.2	<1	64
		8	0	71
5	Carbowax 20M (ca. 4 × 10^{-3})	5	3	79
6	MPEG 5000 (ca. 2 × 10^{-2})	5	2	64
7[b]	glyme-5 (0.6)	5	24.5	58
		22	<1	75
8[c]	glyme-5 (0.6)	5	41	39
		22	2	61
9	$CH_3OCH_2CH_2OCH_3$ (1.7)	24	28	56

[a] Determined by GLC analysis. [b] KOH 0.33 M. [c] NaOH 0.26 M.

Less efficient appear to be the low molecular weight linear chain polyethers, diethylene glycol dimethyl ether, and glyme-5: the former has virtually no effect whereas with the latter a good yield of **2** is obtained (75%), but a longer reaction time is required (22 h) than with the long-chain polyethers. Substitution of Na^+ for K^+ as counterion is rather inconsequential (entries 7 and 8).

Catalyst concentration is found to affect the percent yield of **2** which increases from 21% to 52% and 68% when the Bu_4NBr concentration changes from 0.09 to 0.25 and 0.53 M, respectively, in reactions of 1-chloro-4-nitrobenzene (0.036 M) with KOH (0.29 M) in refluxing 2-propanol. The

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[14] The term catalyst is used here indiscriminately to indicate any added reagent.

Table III. Effect of Bu_4NBr on the Reaction of 1-Chloro-4-nitrobenzene (1) (0.03 M) with Potassium Alkoxides and Aryl Oxides

entry	solvent	[base], M	temp, °C	$[Bu_4NBr]$, M	reaction time, h	% yield[a] 1	% yield[a] 3
1	1-octanol	0.30	100		0.75	0	3[b]
2	1-octanol	0.30	100	0.28	0.28	1	96
3	2-butanol	0.30	90		22.4	8	33
4	2-butanol	0.30	90	0.28	1.7	1	81
5	2-butanol	0.29	95	0.25	0.6	3	62
6	2-butanol	0.29	reflux		0.6	0	2
7	2-butanol	0.29	reflux	0.25	0.5	2	57
8	*tert*-butyl alcohol	0.29	reflux		4	96	0
9	*tert*-butyl alcohol	0.29	reflux	0.28	4	49	0
10	PhCl	0.30 (PhOK)	reflux		5	93	1
11	PhCl	0.30 (PhOK)	reflux	0.28	5	0	93
12[c]	PhCl	0.25 ($4\text{-}O_2NC_6H_4OK$)	reflux	0.39	48	68	16

[a] Determined by GLC analysis unless otherwise specified. [b] 4,4-Dichloroazoxybenzene and 4-chloroaniline formed in 22% and 31% yields, respectively. [c] Isolated yields. 1-Butoxy-4-nitrobenzene formed in 66% yield based on 4-nitrophenoxide.

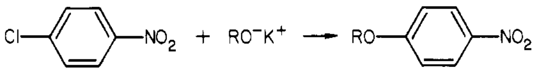
effect is here emphasized because of the effective competition by the reduction process in refluxing solutions (vide infra).

Attention is drawn to the necessity of avoiding reflux conditions which lead invariably to lower yields of the substitution product. An example is provided by comparison of entry 3 of Table II with a reaction run under the same conditions but in refluxing 2-propanol: the yield of **2** drops from 76% (at 75 °C) to 52% (at reflux, 82–83 °C). A more drastic effect is found with glyme-5: when the experiment described in Table II (entry 7) was repeated at reflux, substrate consumption was complete after 1.5 h with less than 5% of **2** being produced. The same trend is observed for the analogous reaction of **1** in 2-butanol (vide infra); higher yields are obtained as the temperature is lowered (cf. Table III).

These results suggest that, superimposed upon kinetic temperature effects, an additional factor, connected to the condition of refluxing, must be operative in determining the course of the reaction; this is likely related to the fast reduction process ensuing upon release of dissolved oxygen from the boiling solution. The S_NAr path is apparently fast enough to favorably compete with the reduction process at reflux in the presence of enough Bu_4NBr, but this is not so in the presence of the poorer "catalyst" glyme-5.

The behavior of solutions containing Triton X-100 deserves a note of comment. Substrate consumption proceeds at a rate comparable to that found in the presence of 18-crown-6 and Bu_4NBr, but production of **2** is slower, continuing after complete substrate disappearance (see Table II, entry 4). A possible explanation for these results is that Triton X-100, a primary alcohol, may compete with the isopropoxide ion in nucleophilically displacing the chloride ion; the ether product of this reaction subsequently undergoes substitution of the long-chain primary alkoxy group by the isopropoxide ion to give **2**. Transetherification of alkyl 2,4-dinitrophenyl ethers with various alcohols in the C_1–C_4 range under basic conditions has been reported by Ogata and Okano;[15] longer chain alcohols were found to be unreactive.[15] For the 4-NO_2 phenyl analogues, of interest in the present discussion, data are scarce and limited to primary alcohols.[8b] Qualitative support for this interpretation of the results obtained with Triton X-100 was sought by studying the effect of additions of methanol to the usual reaction system. Experiments conducted at 75 °C in 2-propanol containing various amounts of methanol indicate that substrate consumption is accelerated due to attack by methoxide to give 4-nitroanisole; the latter is subsequently converted to **2**. Thus, in the presence of 2.5 M MeOH, only 1% of **1** is still present after 7.7 h, along with 82% of 4-nitroanisole and 13% of **2**. After 72 h the yields of 4-nitroanisole and of **2** become 64 and 14%, respectively. Additional data are reported in the Experimental Section.

Reactions of 1 with Selected Alkoxide and Aryl Oxide Ions. The results obtained in 2-propanol indicate Bu_4NBr to be the most attractive catalyst on a cost-effective basis; the effects of additions of Bu_4NBr on the reaction of **1** with a few other representative alkoxide and aryl oxide ions have also been studied. These were the anions of 1-octanol, 2-butanol, *tert*-butyl alcohol, phenol, and 4-nitrophenol. Relevant data for reaction 1 are collected in Table III.



1 **3** (1)

RO = $CH_3(CH_2)_6CH_2O$, $CH_3CH_2CH(CH_3)O$, $(CH_3)_3CO$, C_6H_5O, $4\text{-}O_2NC_6H_4O$

1-Octanol was chosen as a model to test the potential preparative value of reaction 1 with long-chain primary alkoxides. Comparison of entries 1 and 2 of Table III shows the dramatic effect produced by the addition of Bu_4NBr to the reaction mixture: the yield of 1-(octyloxy)-4-nitrobenzene changes from a mere 3% to almost quantitative. Interestingly, we find that reduction of the nitro group prevails in the absence of the ammonium salt catalyst, as indicated by the formation of 4,4′-dichloroazoxybenzene (22% yield) and 4-chloroaniline (31% yield).

Similar remarkable effects are observed in 2-butanol. At 90 °C 1-(*sec*-butoxy)-4-nitrobenzene is obtained in 81% yield in less than 2 h in the presence of Bu_4NBr; the yield drops to 33% after 22 h, in the absence of catalyst (entries 3 and 4). Experiments performed at three different temperatures show that, as is the case in 2-PrOH/2-PrOK solutions, the substitution product yield increases when the temperature is reduced: 57% at reflux (98 °C), 62% at 95 °C, and 81% at 90 °C (entries 4, 6, and 8). The rate of substrate consumption in refluxing solutions is not appreciably affected by the addition of catalyst (entries 7 and 8), suggesting that reduction has become competitive, in accord with the findings in 2-propanol solutions. Interestingly, however, we detected only less than 1% of 4,4′-dichloroazoxybenzene, the primary stable product of the

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reduction of 1 in 2-PrOH,[9] accompanied by a small amount (11%) of 4-chloroaniline.

Reaction 1 fails in *tert*-butyl alcohol: addition of Bu_4NBr is found to accelerate substrate consumption, but no 1-*tert*-butoxy-4 nitrobenzene could be detected in the reaction mixture (entries 9 and 10). This further illustrates the complex behavior of nitro aromatics in the *t*-BuOK/*t*-BuOH system.[16]

Many nitro-substituted diaryl ethers are of interest for their herbicidal and fungicidal activity. To test for possible advantages in using Bu_4NBr in the preparation of this type of compounds, we examined the reactions of 1 with phenoxide and 4-nitrophenoxide ions. We found that treatment of 1 with equimolar amounts of PhOK and Bu_4NBr in refluxing PhCl gave, in 5 h, an excellent yield of 4-nitrophenyl phenyl ether; only 1% of the product was formed in the absence of catalyst after the same reaction time. The effect of the catalyst is, in this case, probably related to its ability to bring the phenoxide ion into solution as, in its absence, the phenoxide salt appears largely undissolved.

An attempt to carry out the same reaction under two-phase conditions proved unsuccessful; when a chlorobenzene solution of 1 (0.033 M) was stirred at reflux with a 2.95 M aqueous solution of PhOK containing 0.28 M Bu_4NBr, 86% of the starting material was found unreacted after 5 h, accompanied by 4% of 4-nitrophenyl phenyl ether.

Traditional methods for the preparation of 4-nitrophenyl phenyl ether from 1 involve reaction with an aqueous solution of PhOK at 150 °C for 6 h (66% yield) or at 130–160 °C in the presence of Cu.[1b] Recent patents describe the use of hexadecyltrimethylammonium chloride[17a] and glymes[17b] in aqueous media and of $N[(CH_2CH_2O)_2Et]_3$ in PhCl.[17c] The method here described appears as a very attractive and convenient alternative.

The analogous reaction with 4-nitrophenoxide ion proved, however, unsatisfactory; only 16% of bis(4-nitrophenyl) ether formed after 48 h, accompanied by 1-butoxy-4-nitrobenzene in 66% yield (based on the amount of 4-nitrophenoxide initially used) and 68% of unreacted 1 (all isolated yields). 1-Butoxy-4-nitrobenzene must derive from attack of 4-nitrophenoxide on Bu_4NBr; this is supported by the finding of Bu_3N in the reaction mixture. Decomposition of tetraalkylammonium salts in basic solutions at elevated temperatures is well documented.[18,19] Poor performance of this particular system can therefore be ascribed partly to catalyst and nucleophile destruction becoming competitive with the slower S_NAr reaction of the weakly nucleophilic 4-nitrophenoxide ion. Preparation of bis(nitrophenyl) ethers from reaction of chloronitrobenzenes with nitrophenoxides requires use of high temperatures and of solvents such as Me_2SO and DMF.[1b,20]

In contrast to the erratic behavior typical of reactions of 1 in 2-PrOK/2PrOH under an atmosphere of air,[9] good reproducibility is observed for the "catalyzed" reactions here reported. Thus, the final yield of ether product in the presence of 0.25–0.28 M Bu_4NBr in duplicate experiments was 78% and 81% in 2-butanol at 90 °C and 98% and 98% in 1-octanol at 100 °C, respectively. Further evidence for the well-behaved nature of "catalyzed" reactions is provided by the predictable changes in rate and product yield observed when the Bu_4NBr and KOH concentration is varied slightly. Thus, for reactions in 2-propanol at 75 °C, the final yield of 2 was 85% (0.55 M Bu_4NBr, 0.20 M KOH), 79% (Table II, entry 3), and 75% (0.12 M Bu_4NBr, 0.12 M KOH), respectively.

Conclusions

Production of alkyl 4-nitroaryl ethers via reaction of 1-chloro-4-nitrobenzene with RO^- in ROH (R = primary and secondary) becomes very efficient provided an appropriate catalyst is used. Results obtained with 2-PrOK/2-PrOH, chosen as model, show ammonium salts and polyethylene glycols to be catalysts which are as effective (or nearly so) as crown ethers, with the advantage of much lower costs; Bu_4NBr appears particularly attractive for reasons of efficient, low cost, and easy recovery and regeneration.[21] Use of this catalyst provides also an excellent route for the preparation of 4-nitrophenyl phenyl ether. Interestingly, the "catalyst" efficiency pattern found in this study of an S_NAr process in homogeneous solution matches rather strictly the one observed by Bradshaw and co-workers for an aliphatic nucleophilic substitution process under PTC conditions.[22]

Experimental Section

Materials and Solvents. Alcohols were commercial products distilled according to literature procedures,[23] except for 1-octanol (Merck) which was used as received. Chlorobenzene was fractionally distilled. 1-Chloro-4-nitrobenzene (Carlo Erba) was recrystallized from ethanol. Carbowax 20M (Varian Aereograph), Triton X-100 (Fluka), MPEG 5000 (Hoechst), glyme-5 (Fluka), and diethylene glycol dimethyl ether (Carlo Erba) were used as received. Bu_4NHSO_4 and Bu_4NBr were the products of Bofors Chemicals and Fluka. The bromide salt was vacuum dried at 78 °C for 1 h before use. 18-Crown-6 was prepared according to literature procedures.[24] Linear chain hydrocarbons (C_{12}–C_{22}; GLC standards by Carlo Erba) were used in GLC analysis.

Reactions in 2-PrOH/50% Aqueous KOH. A solution of 1 (0.06–0.1 M) and a GLC hydrocarbon standard (0.03 M) in 2-propanol (15 mL) was added, with the desired amount of catalyst, to a 50% aqueous KOH solution (20 mL) in a three-necked 100-mL flask equipped with a reflux condenser and mechanical stirrer and kept in a constant temperature bath. Aliquots (ca. 1 mL) of the organic upper layer were withdrawn at desired times, neutralized by addition of a tiny chunk of dry ice, diluted with Et_2O, and, when water-soluble catalysts were used, shaken with H_2O before GLC analysis.

Reactions in Homogeneous Alcohol Solutions. A solution of 1 (0.06 M) and of a GLC standard (0.02 M) in 10 mL of the selected alcohol was added at room temperature to a two-necked 50-mL flask containing 10 mL of a 0.6 M KOH solution in the same alcohol. Addition of Bu_4NBr to the final solution caused a white precipitate to form. 18-Crown-6 and polyether catalysts were added to the basic solution, which was stirred for a few minutes before the 1-chloro-4-nitrobenzene solution was added. After the mixture was swirled, the flask, fitted with a reflux condenser, was immersed in a constant-temperature bath or heated to reflux with a heating mantle. Aliquots were treated as described above.

Reactions of 1 in 2-Propanol Containing Small Amounts of Methanol. Three experiments (0.010 M 1 and 0.5 M KOH)

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were conducted at 75 °C in 2-propanol containing 0.2, 0.6, and 2.5 M MeOH, respectively. The procedures and analysis were as described above. Relevant data are as follows (reaction time (h), % yield of **1**, % yield of **2**, % yield of 4-nitroanisole). For 0.2 M MeOH: 7.7, 21, 30, 40; 22.5, 1, 53, 27; 72, 0, 68, 2. For 0.6 M MeOH: 17, 0, 34, 60; 40.5, 0, 55, 34; 66, 0, 68, 19. For 2.5 M MeOH: 7.7, 1, 13, 82; 28, 0, 38, 53; 72, 0, 64, 14.

Reactions of 1 with Aryl Oxide Ions. Equimolar amounts of KOH and ArOH were dissolved in H_2O, and the solvent was removed under reduced pressure; the residue was warmed in a hot water bath and dried under vacuum. A solution of **1** (0.03 M) and of a GLC standard (0.01 M) in PhCl was added with Bu_4NBr, and the mixture was stirred with a mechanical stirrer and brough to reflux. In the absence of a catalyst the ArOK remained largely undissolved. Some precipitate was evident also in the presence of the ammonium salt. Aliquots were treated as described above.

Analytical Methods and Compounds. GLC analyses were performed on a Varian 3700 instrument with glass columns packed with 3% XE-60 on Chromosorb W AW DMCS and 10% UCW982 on Chromosorb W AW DMCS. NMR spectra were recorded on a Varian EM360A spectrometer. Mass spectra were recorded on a VG MM16F spectrometer.

Ether products, $ROC_6H_4NO_2$, used to calculate GLC molar responses, were prepared according to reaction 1 and characterized by their spectral properties (NMR, MS) and melting points. **1-(*sec*-Butoxy)-4-nitrobenzene:** oil [lit.[25] bp 106–108 °C (0.8 mmHg)]; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.0 (t, 3 H) 1.3 (d, 3 H), 1.7 (quintet, 2 H), 4.4 (sextet, 1 H), 6.8–8.2 (AA'BB', 4 H); mass spectrum (70 eV), *m*/*e* (relative intensity) 195(M), 140 (100), 139, 123, 109, 93. **1-(Octyloxy)-4-nitrobenzene:** mp 24 °C (lit. 24,[26] 26 °C[27]); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.8–1.9 (m, unresolved, 15 H), 4.0 (t, 2 H), 6.8–8.2 (AA'BB', 4 H); mass spectrum (70 eV), *m*/*e* (relative intensity) 251(M), 139, 123, 112, 109, 71, 57, 43 (100). **4-Nitrophenyl phenyl ether:** mp 58–59 °C (lit. 59–59.3,[28] 56–58 °C[29]); ^1H NMR ($CDCl_3$, Me_4Si) matches literature data;[30] mass spectrum (70 eV), *m*/*e* (relative intensity) 215 (M, 100), 199, 185, 168, 141, 129, 115, 77. **Bis(4-nitrophenyl) ether:** mp 145–146 °C (lit. 145,[31] 147–148 °C[32]); ^1H NMR ($CDCl_3$, Me_4Si) 7.1–8.3 (AA'BB', 2 H + 2 H); mass spectrum (70 eV), *m*/*e* (relative intensity) 260 (M, 100), 244, 230, 214, 184, 168, 139, 128.

A typical preparative reaction is described below. For reactions in 1-octanol the solvent was removed by distillation of the azeotrope with water.

1-Isopropoxy-4-nitrobenzene (2). KOH in pellets (1.76 g) was dissolved in warm 2-propanol (100 mL) in a two-necked 250-mL flask fitted with a reflux condenser. Bu_4NBr (15 g) and **1** (2.0 g) were then added, and the flask was immersed in a 75 °C bath. The progress of the reaction was followed by TLC analysis (eluent toluene). The mixture was filtered, and the solvent was removed from the filtrate at reduced pressure. The oily residue was taken up with ether, washed with H_2O, dilute HCl, and H_2O, dried with $CaCl_2$, and evaporated to dryness. The crude product (2.3 g, 79%) was purified by column chromatography at low pressure (petroleum ether/toluene) and recrystallization from pentane: yield 1.7 g (72%); mp 32–33 °C (lit. 33,[32] 32–33 °C[9]); ^1H NMR ($CDCl_3$, Me_4Si) 1.4 (d, 6 H), 4.6 (septet, 1 H), 6.75–8.2 (AA'BB', 4 H); mass spectrum (70 eV), *m*/*e* (relative intensity) 181 (M), 139 (100), 123, 109, 93, 81, 65.

Registry No. 1, 100-00-5; 2, 26455-31-2; Bu_4NHSO_4, 32503-27-8; Bu_4NBr, 32503-27-8; $CH_3OCH_2CH_2OCH_3$, 110-71-4; isopropoxide, 15520-32-8; 18-crown-6, 17455-13-9; Triton, 9002-93-1; Carbowax 20M, 56592-21-3; MPEG 5000, 54386-07-1; glyme-5, 143-24-8; 1-octanol, 111-87-5; 2-butanol, 78-92-2; *tert*-butyl alcohol, 75-65-0; chlorobenzene, 108-90-7; 1-*sec*-butoxy-4-nitrobenzene, 63929-88-4; 1-(octyloxy)-4-nitrobenzene, 78723-40-7; 4-nitrophenyl phenyl ether, 620-88-2; bis(*p*-nitrophenyl) ether, 101-63-3.

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Kinetic Study of the Acid-Catalyzed Rearrangement of 4-Acetyl-3,3-dimethyl-5-hydroxy-2-morpholino-2,3-dihydrobenzo[*b*]furan

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A kinetic study of the acid-catalyzed rearrangement of the title compound (**6**) to form 5,8-dihydroxy-4,4-dimethyl-1(4*H*)-naphthalenone (**4**) in dioxane–water, ethanol–water, and ethanol–dioxane is reported. In water mixtures the presence of 4-acetyl-2,5-dihydroxy-3,3-dimethyl-2,3-dihydrobenzo[*b*]furan (**7**) is detected, and it slowly leads to the rearrangement product **4**. The rate constant of the transformation **6** → **4** is more than 100-fold faster than **7** → **4**, and the kinetic data were evaluated as parallel first-order reactions **4** ← **6** → **7**. The hydrolysis and rearrangement rate constants behavior in different media is explained with a reaction scheme involving the participation of imonium and ethyl acetal intermediates more reactive than **7**.

In previous papers[1,2] we have described the acid-catalyzed rearrangement of some 4-acetyl-5-hydroxy-2,3-dihydrobenzo[*b*]furans containing a cyclic *O*,*N*-acetal group. This transformation involves the formation of a new carbocyclic ring, leading to 1(4*H*)-naphthalenone or 1,4-naphthoquinone systems, depending on the degree of substitution of the substrate at C-3 position. Scheme I shows the above reactions and the preparation of the corresponding heterocyclic substrates **2** and **3** from 2-acetyl-1,4-benzoquinones (**1**) and enamines.

The participation of hemiacetal intermediates has been established[2] when the rearrangement **3** → **5** is carried out in aqueous media. It is interesting to notice that the treatment of the cyclic *O*,*N*-acetal **2** in ethanol–hydrochloric acid solution leads to the rearrangement product 5,8-dihydroxy-4,4-dimethyl-1(4*H*)-naphthalenone (**4**) in

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