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Reactions of Aryl Halides with Phenoxides and Alkoxides by Phase Transfer Catalysis

Bong Rae Cho† **and Sung Dae Park**

Department of Chemistry, Korea University, 1–Anam Dong, Seoul 132, Korea (*Received January 30, 1984*)

The reaction of aryl halides with phenoxides and alkoxides were investigated under phase transfer catalytic conditions. 2, 4–Dinitro–and 4–nitrohalobenzenes reacted readily with phenoxides in NaOH(aq)–benzene in the presence of $Bu_4\overset{+}{N}Br$, affording the products quantitatively. Although the aryl halides did not react with alkoxides under the same condition, the reactions were completed within 2 hours at room temperature when conducted under solid–liquid phase transfer catalytic condition. The reactivity of aryl halides was in the order, Ar=2, 4–dinitrophenyl>4–nitrophenyl, and X=F>Cl, consistent with the S_NAr mechanism. The reactivity of oxyanions increased with the change of reaction condition from liquid–liquid to solid–liquid phase transfer catalysis. The results were explained with the concentration and the degree of hydration of the anion in benzene.

Introduction

Phase transfer catalysis (PTC) has been used in a variety of organic reactions[1,2]. In nucleophilic substitution reactions, this technique has been most successfully applied to the Williamson ether synthesis. The reactions of alkyl halides with alkoxides or phenoxides to give ethers show significant improvement in convenience, reaction rate, and yield when conducted under phase transfer catalytic conditions[1a,2a]. However, the synthesis of aryl ethers by phase transfer catalyzed nucleophilic aromatic substitution reaction has not been reported.

Recently, we studied the reactions of 2, 4–dinitrohalobenzenes with phenoxides in aqueous NaOH–benzene mixture as a model for the phase transfer polymerization[3]. The reactions proceeded readily at room temperature, affording the diaryl ethers quantitatively. As an an extension to this work, we have investigated the reactions of aryl halides with phenoxides and alkoxides under liquid–liquid (L–L) and solid–liquid (S–L) phase transfer catalytic (PTC) conditions (Eq. 1).

$$ArX+ROH \xrightarrow{PTC} ArOR \qquad (1)$$

Ar=2, 4-dinitrophenyl(**1**), 4-nitrophenyl(**2**)
X=F(**a**), Cl(**b**)
ROH=phenols, alcohols
PTC=NaOH(aq)/$Bu_4\overset{+}{N}\overset{-}{Br}/C_6H_6$,
NaH(s)/$Bu_4\overset{+}{N}\overset{-}{Br}/C_6H_6$

We have compared the reactivity of aryl halides, phenoxides, and alkoxides under various conditions. The concentration of oxyanions in benzene was also determined to provide an explanation for the relative reactivity of the anions.

Experimental

Melting points, uncorrected, were determined on a Electrothermal melting point apparatus. Proton nmr was recorded on a Varian Model EA–360A spectrometer and infrared spectra were obtained either with JASCO Model DS–710G or with Perkin–Elmer Model 710B spectrophotometer. For titration of the oxyanion concentration, Chemtrix

Type 60A potentiometer was used.

All starting materials were commercially available reagent grade and were used as received. Benzene and nitrobenzene were distilled from CaH_2 before use.

Reactions of aryl halides with phenoxides and alkoxides.

The reactions between various aryl halides and phenoxides or alkoxides were conducted by the following two procedures. The products were identified by comparision of their melting points and nmr and IR spectra with those of authentic samples.

Reactions under Liquid-Liquid Phase Transfer Catalytic Condition. Aryl halide (1.0 mmol), phenol or alcohol(3.0mmol), and $Bu_4\overset{+}{N}\overset{-}{Br}$ (9.6 mg, 0.03 mmol) were added to a mixture of aqueous NaOH solution (10 %, 10.0 m*l*) and benzene(5.0 m*l*). The mixture was stirred at room temperature and the reaction was followed by TLC. When the reaction was completed, the organic layer was separated, washed with 10 % NaOH(aq) solution and water, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The product was recrystallized when necessary.

Reactions Under Solid-Liquid Phase Transfer Catalytic Condition. Into a 25 m*l* round bottom flask equipped for inert atmosphere, NaH (0.12g 4.0 mmol, 80 % dispersion in oil) was added and washed several times with pentane to remove the mineral oil. Benzene (10.0 m*l*)was added to the NaH followed by phenol or alcohol (2.0 m mole), $Bu_4\overset{+}{N}\overset{-}{Br}$ (9.6mg, 0.03 mmol), and aryl halide (1.0 m*l*). The mixture was stirred at room temperature and the reaction was followed by TLC. The product was isolated as described above.

Determination of the concentration of phenoxide and akoxide in benzene. Under Liquid-Liquid Phase Transfer Catalytic Condition. A mixture of methanol or phenol (3.1 mmol), $Bu_4\overset{+}{N}\overset{-}{Br}$ (0.30 g, 0.9 mmol), benzene (10.0 m*l*), and aqueous NaOH solution (10 %, 25.0 m*l*) was stirred at room temperature. After 1.0 hour, 3.0 m*l* of the benzene layer was separated and mixed with 15.0 m*l* of methanol. The total base concentration in the mixed solvent was determined by potentiometric titration against a standardized HCl solution. For a blank test, the same procedure was repeated without methanol or phenol. The oxyanion concentration in benzene was obtained by substracting the base concentration in the blank solution from the total base concentration.

Under Solid-Liquid Phase Transfer Catalytic Condition. Into a 25 m*l* flask, NaH (0.185 g, 6.2 mmol, 80 % dispersion in oil) was added and washed several times with pentane under nitrogen. A solution of methanol or phenol (3.1 mmol) in benzene (10.0 m*l*) was added to the NaH followed by $Bu_4\overset{+}{N}\overset{-}{Br}$ (0.30 g, 0.93 mmol). The mixture was strirred for 1.0 hour at room temperature under nitrogen. The oxyanion concentration in benzene was determined as described above.

Results and Discussion

Reactions of Aryl Halides with Phenoxides and Alkoxides by Liquid-Liquid phase Transfer Catalysis. We have previously reported the results for the reactions of **1a** and **1b** with phenoxides under liquid-liquid phase transfer catalytic condition.[3] In this work, we have reinvestigated some of our earlier results and studied the reactions of **2a** and **2b** with phenoxide and of **1b** with alkoxides. Table 1 shows the results for the reactions of aryl halides with phenoxides in aqueous NaOH-benzene with and without $Bu_4\overset{+}{N}\overset{-}{Br}$.

TABLE 1: Reactions of Aryl Halides with Phenoxides by Liquid-Liquid Phase Transfer Catalysis($ArX + YC_6H_4OH \xrightarrow{L\text{-}L\ PTC} ArOC_6H_4Y$)

Entry[a]	ArX	Y	Temp.	Time(h)	Yield(%)	mp(°C) (*lit*.mp)
1	**1a**	H	*RT*	0.5	88,8	71–73(70)[4]
2[b]	**1a**	H	*Reflux*	2.0	63.2	71–73
3	**1a**	*p*-OCH_3	*RT*	2.5	95.9	111–113(110)[5]
4	**1a**	*p*-Cl	*RT*	2.5	95.2	120–123(123)[4]
5	**1a**	*p*-NO_2	*RT*	2.5	49.0	115–118(116)[4]
6[c]	**1a**	*p*-NO_2	*RT*	0.5	81.5	116–117
7	**1b**	H	*RT*	4.0	88.8	71–73
8[b]	**1b**	H	Reflux	12.0	64.0	71–73
9	**1b**	*p*-OCH_3	*RT*	4.0	97.9	111–113
10	**1b**	*p*-Cl	*RT*	4.0	98.0	121–123
11	**1b**	*p*-NO_2	*RT*	7.0	0.0	
12[c]	**1b**	*p*-NO_2	R*T*	2.0	87.3	115–117
13	**2a**	H	Reflux	4.0	97.0	57–59(56–57)[6a]
14[b,d]	**2a**	H	Reflux	12.0	0.0	
15[d]	**2b**	H	Reflux	12.0	0.0	

[a] Except for entries 2, 8, 13, 14, and 15, the data are from ref. 3; [b] Without $Bu_4\overset{+}{N}\overset{-}{Br}$; [c] Nitrobenzene was used as organic solvent; [d] 95 % of starting material was recovered.

When the reactions between aryl halides and phenoxides were conducted in the absence of the catalyst, the products were obtained in low yields after refluxing for 2 to 12 hours entries 2, 8, and 14). However, the rates were greatly accelerated by the addition of a small amount of the catalyst (entries 1,7, and 13). Thus, all of the aryl halides, except for **2b**, reacted completely with phenoxides within 4 hours (Table 1).

The results are not unexpected in view of the roles of the catalyst[1b,2b]. Much evidence in the literature indicates that the catalyst transport the anion to the organic phase and the transfered anion exhibits remarkably high reactivity[1b,1c,2b]. An experimental support for the former under the present reaction condition is in Table 4. The concentration of phenoxide is increased about 10 times in benzene by the addition of the catalyst.

The relative reactivity of the aryl halides can be estimated by the time required for complete reaction. The order of reactivity of the aryl halide is **1a**>**1b**>**2a**>**2b** under liquid-liquid phase transfer catalytic condition (entries, 1, 7, 13 and 15). The results indicate that the dependence of reactivity on aryl substituents and leaving group for the series of aryl halides is similiar to that observed in classical nucleophilic substitution[7].

The reactions of **1a** and **1b** with other phenoxides were also briefly examined. *p*-Methoxy-and *p*-chlorophenoxides reacted at rates similiar to that of phenoxide. Although the reactions with *p*-nitrophenoxide proceeded much more slowly, the rates were increased when nitrobenzene was used

TABLE 2: Reactions of Aryl Halides with Phenoxides by Solid-Liquid Phase Transfer Catalysis ($ArX + YC_6H_4OH \xrightarrow{\text{S-L PTC}} ArOC_6H_4Y$)

Entry	ArX	Y	Temp.	Time	Yield(%)	mp(°C)
1	**1a**	H	*RT*	10 min	93.5	72–73
2[a]	**1a**	H	*RT*	10 min	87.8	71–73
3	**1a**	*p*-OCH_3	*RT*	10 min	89.5	111–113
4	**1a**	*p*-Cl	*RT*	10 min	92.9	120–123
5	**1a**	*p*-NO_2	Reflux	1.0 h	66.7	115–118
6[b]	**1a**	*p*-NO_2	*RT*	30 min	82.4	115–117
7	**1b**	H	*RT*	10 min	90.0	71–73
8[a]	**1b**	H	Reflux	1.0 h	91.0	71–73
9	**1b**	*p*-OCH_3	*RT*	10 min	89.3	112–114
10	**1b**	*p*-Cl	*RT*	1.0 h	87.7	121–123
11	**1b**	*p*-NO_2	Reflux	3.0 h	87.4	115–117
12[b]	**1b**	*p*-NO_2	Reflux	30 min	80.2	115–117
13	**2a**	H	Reflux	30 min	97.0	57–59
14[a,c]	**2a**	H	Reflux	12 h	0.0	
15	**2b**	H	Reflux	3.5 h	92.0	58–60
16[a,c]	**2b**	H	Reflux	12 h	0.0	

[a] Without $Bu_4\overset{+}{N}\overset{-}{Br}$; [b] Nitrobenzene was used as organic solvent; [c] 95 % of starting material was recovered.

TABLE 3: Reactions of Aryl Halides with Alkoxides by Solid-Liquid Phase Transfer Catalysis ($ArX + ROH \xrightarrow{\text{S-L PTC}} ArOR$)

Entry	ArX	R	Temp.	Time	Yield(%)	mp(°C) (*lit*.mp)
1	**1b**	Me	*RT*	10 min	92.2	91–93(94–95)[6a]
2[a]	**1b**	Me	*RT*	6.0 h	89.9	92–94
3	**1b**	Et	*RT*	10 min	82.2	86–87(86)[6b]
4	**1b**	*n*-Pr	*RT*	10 min	91.4	b[13]
5	**1b**	*i*-Pr	*RT*	30 min	80.0	51–53(53)[12]
6	**1b**	*t*-Bu	*RT*	30 min	Trace	
7	**2a**	Me	*RT*	1.0 h	95.4	52–54(54)[6d]
8[a]	**2a**	Me	Reflux	12 h	Trace	
9	**2a**	Et	*RT*	1.0 h	97.5	57–58(57–58)[6e]
10	**2a**	*n*-Pr	*RT*	1.0 h	94.5	b[12]
11	**2a**	*t*-Bu	*RT*	12 h	Trace	
12	**2b**	Me	*RT*	2,0 h	97.0	52–54
13	**2b**	Me	Reflux	12 h	Trace	

[a] Without $Bu_4\overset{+}{N}\overset{-}{Br}$; [b] Oil, identified by nmr and IR.

as organic solvent to improve the solubility of *p*-nitrophenoxide anion (entries 5, 6, 11 and 12)[8]. Therefore, the slower reaction of *p*-nitrophenoxide may be attributed to the low nucleophilicity and the poor solubility of the anion in benzene[9].

In contrast to the reactions of alkoxides with alkyl halides[2a] and of phenoxides with aryl halides (Table 1), **1b** did not react with alkoxides under liquid-liquid phase transfer catalytic condition (Eq. 2).

$$\mathbf{1b} + ROH \xrightarrow[\text{reflux, 12 hour}]{NaOH(aq)/Bu_4\overset{+}{N}\overset{-}{Br}/C_6H_6} \text{no reaction} \quad (2)$$

$$ROH = MeOH,\ n\text{-}BuOH,\ C_6H_5CH_2OH,\ HOCH_2CH_2OH$$

We studied several alcohols with different solubility in water and benzene, because some alcohols may cause poor phase separation between the two layer and reduce the reactivity of the alkoxide. However, the results were the same regardless of the structure of the alcohols (Eq. 2). Thus, it appears that even highly activated aryl halide (**1b**) is less reactive than the primary alkyl halides in nucleophilic substitution[2a].

The much slower rates of reactions between **1b** and alkoxide (Eq. 2) than those between **1b** and phenoxides (Table 1) may be ascribed to the low concentration of the alkoxide in benzene. According to Table 4, the concentration of methoxide in benzene is nearly zero under the experimental condition.

Reactions of Aryl Halides with Phenoxides and Alkoxides by Solid-Liquid Phase Transfer Catalysis. The reactions of aryl halides with phenoxides and alkoxides were also investigated under solid-liquid phase transfer catalytic condition. The phenoxides or alkoxides, generated *in situ* from NaH and phenols or alcohols, were reacted with aryl halides in benzene using $Bu_4\overset{+}{N}\overset{-}{Br}$ as a catalyst.

Table 2 includes the results of reactions of aryl halides with phenoxides under this condition.

The reactions were greatly faciliated by changing the reaction condition from liquid-liquid to solid-liquid phase transfer catalysis. Except for the reactions of **1a** and **1b** with *p*-nitrophenoxide (entries 5 and 11) and of **2a** and **2b** with phenoxide (entries 13 and 15), all of the reactions were completed within 1 hour at room temperature. The reactions proceeded even in the absence of the catalyst (entries 2 and 8) at rates comparable to those of liquid-liquid phase transfer catalyzed reactions (entries 1 and 7 in Table 1). The relative reactivity of aryl halides and phenoxides under this condition was the same as that observed under liquid-liquid phase transfer catalytic condition.

The results of the reactions between aryl halides and alkoxides under solid-liquid phase transfer catalytic condition are summarized in Table 3. The extent of increase in rate with the change of the reaction condition is even greater in this case. Although **1b** did not react with alkoxides in aqueous NaOH-benzene system (Eq. 2), the reactions of **1b**, **2a** and **2b** with alkoxides were completed within 2 hours at room temperature when conducted under solid-liquid phase transfer catalytic condition (Table 3). The order of reactivity of the alkoxides, 1°>2°>3°, may be due to their steric effect. The relative reactivity of aryl halides in this reaction was also the same as that in Table 1.

The enhanced rates of reactions under solid-liquid phase transfer catalytic condition can be attributed to the increased concentration and nucleophilicity of the oxyanions in benzene. A distribution study has revealed that the concentration of both phenoxide and methoxide in benzene is higher under this condition than that under liquid-liquid phase transfer catalytic condition (Table 4). Moreover, the reactivity of the oxyanions under this anhydrous condition should also be greater than that in aqueous-organic system, where the anion in organic phase is hydrated to the extent of a few molecules per ion[1d,2c].

Concentration of Oxyanions in Benzene.

In order to provide an explanation for the reactivity of each oxyanions, the concentration of the anions in benzene

TABLE 4: Concentration of Oxyanions in Benzene under Various Coniditions

Reaction Condition	ROH	$[RO^-]$ in benzene[a]	
		With PTC	Without PTC
L-L PTC	PhOH	0.75±0.12	0.071±0.006
	MeOH	0.010±0.005	0.011±0.003
S-L PTC	PhOH	1.2±0.1	0.19±0.04
	MeOH	1.4±0.1	0.15±0.01

[a] Data presented are mole % of oxyanions dissolved in benzene. The amount of oxyanion in benzene was divided by moles of the catalyst initially added.

was determined under various conditions (Table 4). The oxyanion concentration in the organic layer was only in the range of 0–1.4 % of the total catalyst. However, the relative concentration of the anions agrees well with the order of reactivity (*vide supra*).

The anion concentration in benzene is always higher in the presence than that in the absence of the catalyst. The concentration is increased by changing the reaction condition from liquid–liquid to solid-liquid phase transfer catalysis.

The near zero concentration of methoxide in benzene under liquid–liquid phase transfer catalytic condition may be due to the low acidity of methanol. The pK_a's of phenol and methanol are 10 and 16, respectively[14]. Therefore, the methoxide concentration in aqueous sodium hydroxide would be about 1,000 times lower than that of phenoxide. If similiar phase transferriability is assumed for both ions, the concentration of methoxide in benzene should also be about 1/1,000 of phenoxide. When all of the methanol was converted to sodium methoxide under the solid–liquid phase transfer catalytic condition, the concentration of methoxide in benzene became similiar to that of phenoxide.

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