http://dx.doi.org/10.5012/bkcs.2013.34.8.2455

Structure-Reactivity Correlations in Nucleophilic Displacement Reactions of Y-Substituted-Phenyl X-Substituted-Cinnamates with Z-Substituted-Phenoxides

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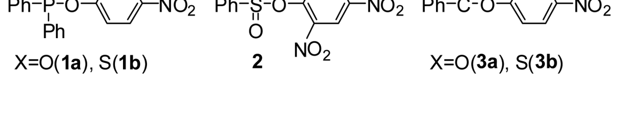
Received May 20, 2013, Accepted May 22, 2013

Second-order rate constants (k_N) have been measured spectrophotometrically for the nucleophilic displacement reactions of 4-nitrophenyl X-substituted-cinnamates (**4a-4e**) and Y-substituted-phenyl cinnamates (**5a-5e**) with Z-substituted-phenoxide anions in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The Hammett plot for the reactions of **4a-4e** with 4-chlorophenoxide (4-ClPhO$^-$) consists of two intersecting straight lines, which might be taken as a change in the rate-determining step (RDS). However, it has been concluded that the nonlinear Hammett plot is not due to a change in the RDS but is caused by stabilization of the ground state of substrates possessing an electron-withdrawing group in the cinnamoyl moiety through resonance interactions, since the Yukawa-Tsuno plot exhibits an excellent linear correlation with $\rho_X = 0.89$ and $r = 0.58$. The Brønsted-type plot for the reactions of 4-nitrophenyl cinnamate (**4c**) with Z-substituted-phenoxides is linear with $\beta_{nuc} = 0.76$. The Brønsted-type plot for the reactions of Y-substituted-phenyl cinnamates (**5a-5d**) with 4-chlorophenoxides (4-ClPhO$^-$) is also linear with $\beta_{lg} = -0.72$. The Hammett plot correlated with σ^- constants for the reactions of **5a-5d** results in a much better linear correlation than that correlated with σ^o constants, indicating that a partial negative charge develops on the O atom of the leaving aryloxide. Thus, the reactions have been concluded to proceed through a concerted mechanism.

Key Words : Brønsted-type plot, Hammett plot, Concerted mechanism, Stepwise mechanism, Phenyl cinnamate

Introduction

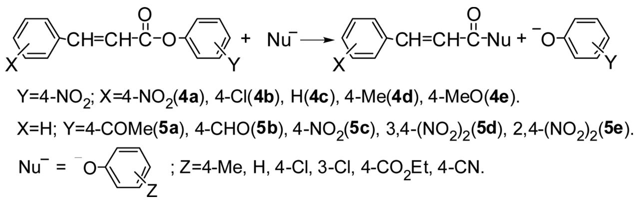
The mechanisms for nucleophilic substitution reactions of esters with amines are fairly well known, *e.g.*, a concerted mechanism or a stepwise pathway with one or two intermediates depending on the nature of the electrophilic center such as P=O, P=S, SO_2, C=O and C=S.[1-8] The linear Brønsted-type plots with $\beta_{nuc} = 0.5 \pm 0.1$ obtained from the reactions of 4-nitrophenyl diphenylphosphinate (**1a**) and diphenylphosphinothioate (**1b**) with amines have been taken as evidence for a concerted mechanism,[4] while a curved Brønsted-type plot reported for aminolysis of esters possessing a weakly basic leaving group, *e.g.*, 2,4-dinitrophenyl benzenesulfonate (**2**), has been interpreted as a change in the rate-determining step (RDS).[5g] Reactions of 4-nitrophenyl benzoate (**3a**) with a series of secondary amines have been reported to proceed through a stepwise mechanism with formation of a zwitterionic tetrahedral intermediate ($T^{\pm}$) being the RDS on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.81$.[5h] In contrast, the corresponding reactions of *O*-4-nitrophenyl thionobenzoate (**3b**) have been concluded to proceed through a stepwise mechanism with two intermediates (*i.e.*, $T^{\pm}$ and its deprotonated form T^-) since the plots of k_{obsd} *vs*. [amine] curved upward.[6]



X=O(**1a**), S(**1b**) **2** X=O(**3a**), S(**3b**)

However, the mechanism for reactions with anionic nucleophiles remains controversial. Williams *et al*. have concluded that the reactions of 4-nitrophenyl acetate with a series of aryloxide anions proceed through a concerted mechanism.[9] The evidence provided was a linear Brønsted-type plot with $\beta_{nuc} = 0.75$.[9] The concerted mechanism has been supported by structure-reactivity correlations reported by Jencks,[10a] Rossi,[10b,c] and Castro,[10d] as well as kinetic isotope effect studies by Hengge,[11a] Marcus analysis by Guthrie,[11b] and theoretical calculations by Xie *et al.*[11c] On the contrary, Buncel *et al*. have reported that the reactions of aryl acetates with phenoxide anion proceed through a stepwise mechanism, in which the leaving-group departure occurs after the RDS, since σ^o constants results in a much better Hammett correlation than σ^- constants.[12] A similar conclusion has been drawn for alkaline ethanolyses of aryl diphenylphosphinates (*i.e.*, **1a** and its derivatives)[13a] and aryl benzenesulfonates (*i.e.*, **2** and its derivatives).[13b] However, we have recently reported that the reactions of **1a**, **1b**, **2** and **3a** with anionic nucleophiles (*e.g.*, OH^-, $CH_3CH_2O^-$ or aryloxides) proceed through a concerted mechanism on the basis of linear Yukawa-Tsuno plots with an *r* value of 0.4 ± 0.1.[14a-f]

Our study has now been extended to the nucleophilic substitution reactions of 4-nitrophenyl X-substituted-cinnamates (**4a-4e**) and Y-substituted-phenyl cinnamates (**5a-5e**) with a series of Z-substituted-phenoxide anions to investigate the reaction mechanism (Scheme 1). We have employed substituents X, Y and Z in the nonleaving group, the leaving groups, and in the incoming aryloxide, respectively, for a



Scheme 1

systematic study.

Results and Discussion

All of the reactions in this study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation ln $(A_\infty - A_t) = -k_{obsd}t + C$. The correlation coefficient for the linear regression was always higher than 0.9995. The plots of k_{obsd} *vs.* concentration of Z-substituted-phenoxide were linear. Thus, the second-order rate constants (k_{ZPhO^-}) were calculated from the slope of the linear plots. The uncertainty in k_{ZPhO^-} values is estimated to be less than ± 3 % from replicate runs. The $k_{4\text{-ClPhO}^-}$ values for the reactions of 4-nitrophenyl X-substituted-cinnamate (**4a-4e**) with 4-chlorophenoxide (4-ClPhO$^-$) are summarized in Table 1. The k_{ZPhO^-} values for the reactions of 4-nitrophenyl cinnamates (**4c**) with Z-substituted-phenoxide and the $k_{4\text{-ClPhO}^-}$ values for the reactions of Y-substituted-phenyl cinnamates (**5a-5e**) with 4-ClPhO$^-$ are summarized in Tables 2 and 3, respectively.

Effect of Nonleaving-Group Substituents on Reactivity and Reaction Mechanism. To investigate the effect of nonleaving-group substituent X on reactivity and reaction mechanism, the rate constants for the reactions of 4-nitrophenyl X-substituted-cinnamates (**4a-4e**) with 4-ClPhO$^-$ have been measured. As shown in Table 1, the $k_{4\text{-ClPhO}^-}$ value decreases as the substituent X changes from a strong EWG to a strong EDG, *e.g.*, it decreases from 0.844 $M^{-1}s^{-1}$ to 0.177 and 0.0614 $M^{-1}s^{-1}$ as the substituent X changes from 4-NO_2 to H and 4-MeO, in turn.

The effect of the substituent X on reactivity is illustrated in Figure 1. The Hammett plot consists of two intersecting straight lines. Traditionally, such nonlinear Hammett plot has been taken as evidence for a change in the RDS of a stepwise reaction. Thus, one might suggest that the reactions of **4a-4e** with 4-ClPhO$^-$ proceed through a stepwise mechanism with a change in the RDS upon changing the substituent X, *i.e.*, from breakdown of an intermediate to its formation as the substituent X changes form EWGs to EDGs.

Table 1. Summary of Second-Order Rate Constants ($k_{4\text{-ClPhO}^-}$) for the Reactions of 4-Nitrophenyl X-Substituted-Cinnamates (**4a-4e**) with 4-Chlorophenoxide in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C

	X	$k_{4\text{-ClPhO}^-}/M^{-1}s^{-1}$
4a	4-NO_2	0.844
4b	4-Cl	0.224
4c	H	0.177
4d	4-Me	0.0958
4e	4-MeO	0.0614

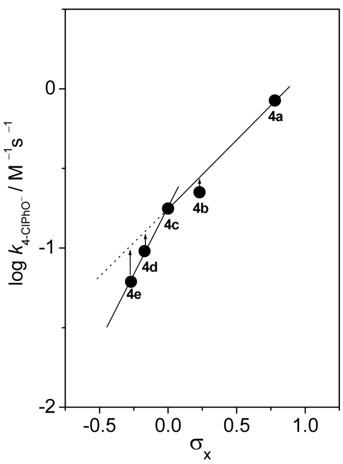
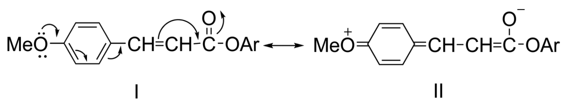


Figure 1. Hammett correlation of $k_{4\text{-ClPhO}^-}$ for the reactions of 4-nitrophenyl X-substituted-cinnamates (**4a-4e**) with 4-chlorophenoxide (4-ClPhO$^-$) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

However, we propose that the nonlinear Hammett plot is not due to a change in the RDS but is caused by stabilization of the ground-state (GS) of substrates possessing an EDG in the cinnamoyl moiety (*e.g.*, **4b**, **4d** and **4e**) as modeled by the resonance structures I and II. This is because the presence of such resonance structures would stabilize the GS of the substrate, which would cause a decrease in the reactivity. This idea is supported by the fact that **4b**, **4d** and **4e** exhibit negative deviation from the linear Hammett plot composed of **4a** and **4c**. Furthermore, the negative deviation is more significant for the substrate possessing a stronger EDG (*e.g.*, **4e**).



To examine the above argument, the Yukawa-Tsuno Eq. (1) has been employed. Eq. (1) was originally derived to account for the kinetic data obtained from solvolysis of benzylic systems, in which a partial positive charge develops on the reaction center.[15] We have shown that Eq. (1) is highly effective to clarify ambiguities in reaction mechanisms for various nucleophilic displacement reactions, *e.g.*, alkaline hydrolysis of Y-substituted-phenyl diphenylphosphinates,[14d] 2,4-dinitrophenyl X-substituted-benzoates[14f] and *O*-aryl thionobenzoates,[14c] alkaline ethanolysis of aryl benzenesulfonates,[14a] and Michael-type reactions of 1-aryl-2-propin-1-ones with amines.[16]

$$\log k^X/k^H = \rho_X [\sigma_X^o + r(\sigma_X^- - \sigma_X^o)] \quad (1)$$

Thus, a Yukawa-Tsuno plot has been constructed for the reactions of **4a-4e** with 4-ClPhO$^-$. As shown in Figure 2, the

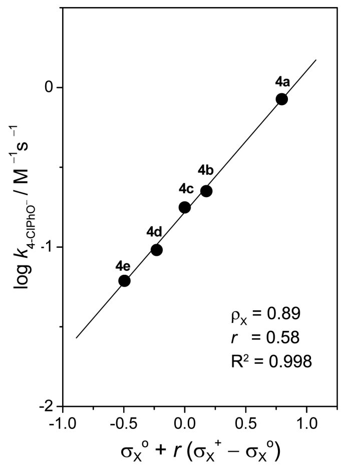


Figure 2. Yukawa-Tsuno plot for the reactions of 4-nitrophenyl X-substituted cinnamates (**4a-4e**) with 4-ClPhO$^-$ in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

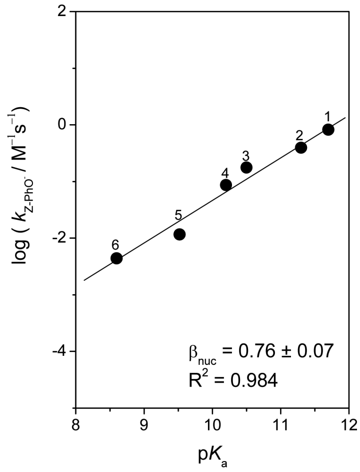


Figure 3. Brønsted-type plot for the reactions of 4-nitrophenyl cinnamate (**4c**) with Z-substituted-phenoxide ions in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

Yukawa-Tsuno plot exhibits an excellent linear correlation with $\rho_X = 0.89$ and $r = 0.58$. Such linear Yukawa-Tsuno plot clearly supports our preceding proposal that the nonlinear Hammett plot shown in Figure 1 is not due to a change in the RDS but is caused by the GS-stabilization through resonance interactions.

The ρ_X value of 0.89 obtained in this study is much smaller than that reported previously for the reactions of 2,4-dinitrophenyl X-substituted-benzoates with three representative anions OH^- ($\rho_X = 1.93$), CN^- ($\rho_X = 1.72$)and N_3^- ($\rho_X = 1.75$).[14f] The small ρ_X value found in this study is consistent with the report that insertion of one –CH_2– or –CH=CH– group between the reaction site and the substituent causes a decrease in ρ_X by a half.[17] However, one cannot get any conclusive information on the reaction mechanism from the linear Yukawa-Tsuno plot with $\rho_X = 0.89$ alone. To obtain more information on the reaction mechanism, the reactions of 4-nitrophenyl cinnamate (**4c**) with a series of Z-substituted-phenoxides have been carried out in the following section.

Effect of Amine Basicity on Reactivity and Reaction Mechanism. As shown in Table 2, the $k_{Z\text{-PhO}^-}$ value for the reactions of **4c** decreases as the basicity of the Z-substituted-phenoxide decreases, *e.g.*, it decreases from 0.820 $M^{-1}s^{-1}$ to 0.177 and 4.40 × 10^{-3} $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the incoming aryloxide decreases from 11.7 to 10.5 and 8.60, in turn.

The effect of basicity of Z-substituted-phenoxide on reactivity is illustrated in Figure 3. The Brønsted-type plot is linear with $\beta_{nuc} = 0.76 \pm 0.07$. The β_{nuc} value obtained in this study is almost identical to that reported previously for the corresponding reactions of 4-nitrophenyl benzoate (**3a**, $\beta_{nuc} = 0.72$)[18] and for those of 4-nitrophenyl acetate ($\beta_{nuc} = 0.75$).[9] Since the reactions of **3a** and 4-nitrophenyl acetate have been concluded to proceed through a concerted mechanism,[12,18] one might suggest that the reactions of **4c** proceed also through a concerted mechanism. However, a linear Brønsted-type plot with $\beta_{nuc} = 0.76$ is not sufficient to deduce the reaction mechanism conclusively.

Effect of Leaving-Group Basicity on Reactivity. To get more conclusive information on the reaction mechanism, the $k_{4\text{-ClPhO}^-}$ values for the reactions of Y-substituted-phenyl cinnamates (**5a-5e**) with 4-ClPhO$^-$ have been measured in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. As shown in Table 3, the $k_{4\text{-ClPhO}^-}$ value increases as the leaving-group basicity decreases, *e.g.*, it increases from 0.0188 $M^{-1}s^{-1}$ to 0.177 and 5.45 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the leaving aryloxide decreases from 8.94 to 7.79 and 3.94, in

Table 2. Summary of Second-Order Rate Constants ($k_{Z\text{-PhO}^-}$) for the Reactions of 4-Nitrophenyl Cinnamate (**4c**) with Z-Substituted-Phenoxides in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C

	Z	pK_a[a]	$k_{Z\text{-PhO}^-}$/$M^{-1}s^{-1}$
1	4-Me	11.7	0.820
2	H	11.3	0.395
3	4-Cl	10.5	0.177
4	3-Cl	10.2	0.0868
5	4-CO_2Et	9.52	0.0116
6	4-CN	8.60	0.00440

[a]The pK_a values in 80 mol % H_2O/20 mol % DMSO were taken from ref 18.

Table 3. Summary of Second-Order Rate Constants ($k_{4\text{-ClPhO}^-}$) for the Reactions of Y-Substituted-Phenyl Cinnamates (**5a-5e**) with 4-Chlorophenoxide (4-ClPhO$^-$) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C

	Y	pK_a[a]	$k_{4\text{-ClPhO}^-}$/$M^{-1}s^{-1}$
5a	4-COMe	8.94	0.0188
5b	4-CHO	8.45	0.0446
5c	4-NO_2	7.79	0.177
5d	3,4-$(NO_2)_2$	5.60	5.52
5e	2,4-$(NO_2)_2$	3.94	5.45

[a]The pK_a values in 80 mol % H_2O/20 mol % DMSO were taken from ref 18.

turn. It is noted that 2,4-dinitrophenyl cinnamate (**5e**) is slightly less reactive than 3,4-dinitrophenyl cinnamate (**5d**), although the former possesses a less basic leaving group than the latter. However, this is consistent with the reports that esters possessing a 2,4-dinitrophenoxy group as a leaving group are less reactive than the corresponding esters bearing a 3,4-dinitrophenoxy group.[19] Gresser *et al.* have suggested that the steric hindrance exerted by the 2-nitro group in the leaving group is responsible for the decreased reactivity shown by esters possessing a 2,4-dinitrophenoxy group.[19]

The effect of the leaving-group basicity on reactivity is demonstrated in Figure 4. The Brønsted-type plot is linear with β_{lg} = –0.74 ± 0.03 when **5e** is excluded from the correlation. The β_{lg} value of –0.74 obtained from the current reactions is much larger than the β_{lg} value of –0.34 ± 0.05 reported for the reactions of *O*-Y-substituted-phenyl thionobenzoates (**3b** and its derivatives) with OH^-, CN^- and N_3^-, which were suggested to proceed through a stepwise mechanism with formation of an intermediate being the RDS.[14c] Alkaline ethanolysis of phenyl Y-substituted-phenyl carbonates has also been reported to proceed through a stepwise mechanism, in which leaving-group departure occurs after the RDS on the basis of a linear Brønsted-type plot with β_{lg} = –0.42.[8d]

It is noted that 4-ClPhO⁻ is more basic and a poorer nucleofuge than the leaving Y-substituted-phenoxide employed in this study. Accordingly, if the current reactions proceed through a stepwise mechanism, leaving-group departure would occur after the RDS. In this case, a small β_{lg} value is expected. In fact, we have shown that β_{lg} is small for stepwise reactions with leaving-group departure occurring after the RDS, *e.g.*, β_{lg} = –0.34 ± 0.05 for the reactions of *O*-Y-substituted-phenyl thionobenzoates with OH^-, CN^- and N_3^- [14c] and β_{lg} = –0.42 alkaline ethanolysis of phenyl Y-substituted-phenyl carbonates.[8d] Since the β_{lg} value of –0.74 is too large for reactions in which leaving-group departure occurs after the RDS, one can suggest that the reactions proceed through a concerted mechanism. This idea is consistent with the preceding proposal that the reactions of **4c** with a series of Z-substituted-phenoxide ions proceed through a concerted mechanism on the basis of the β_{nuc} value of 0.76.

To examine the above argument, Hammett plots have been constructed using σ_Y^o and σ_Y^- constants in Figure 5. If the reaction proceeds through a concerted mechanism, a partial negative charge would develop on the O atom of the leaving aryloxide in the transition state (TS). Since such negative charge can be delocalized to the substituent Y through resonance interactions, σ_Y^- constants should result in a better Hammett correlation than σ_Y^o constants. In contrast, if the reaction proceeds through a stepwise mechanism, leaving-group departure would occur after the RDS. Then, one might expect that σ_Y^o constants exhibit a better Hammett correlation than σ_Y^- constants. This is because no negative charge would develop on the O atom of the leaving aryloxide in the TS, if leaving-group departure occurs after the RDS. In fact, Figure 5 shows that σ_Y^- constants result in a much better Hammett correlation than σ_Y^o constants. This indicates clearly that a partial negative charge develops on the O atom of the leaving aryloxide, which can be delocalized to the substituent Y in the leaving group. Thus, one can conclude that the reactions in this study proceed through a concerted mechanism.

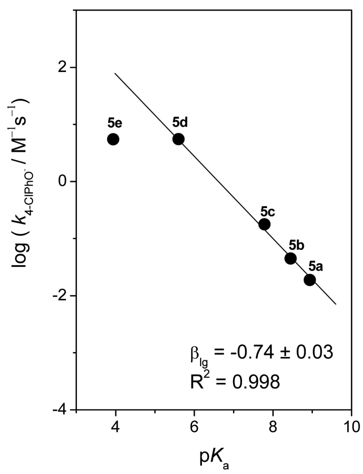


Figure 4. Brønsted-type plot for the reactions of Y-substituted-phenyl cinnamates (**5a-5e**) with 4-chlorophenoxide in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

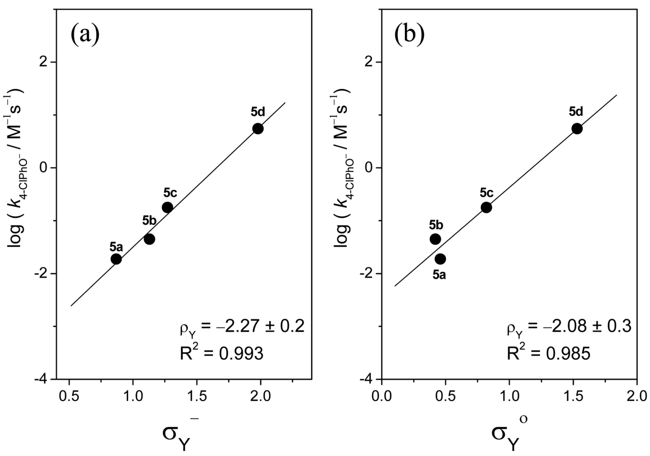


Figure 5. Hammett plots correlated with σ_Y (a) and σ_Y^o (b) constants for the reactions of Y-substituted-phenyl cinnamates (**5a-5d**) with 4-chlorophenoxide (4-ClPhO⁻) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

Conclusions

The current study has allowed us to conclude the following: (1) The Hammett plot for the reactions of **4a-4e** with 4-ClPhO⁻ consists of two straight lines, while the Yukawa-Tsuno plot exhibits an excellent linear correlation with ρ_X = 0.89 and r = 0.58. Thus, the nonlinear Hammett plot is not due to a change in the RDS but is caused by stabilization of the GS through resonance interactions. (2) The Brønsted-type plot is linear with β_{nuc} = 0.76 for the reactions of **4c** with Z-substituted phenoxides. (3) The Brønsted-type plot for the reactions of **5a-5d** with 4-ClPhO$^-$ is also linear with β_{lg} = –0.74. (4) The Hammett plot correlated with σ_Y^- constants results in a much better linear correlation than that correlated with σ_Y^o constants, indicating that a partial negative charge develops on the O atom of the leaving group in TS. (5) Since 4-ClPhO$^-$ is more basic and a poorer nucleofuge than the Y-substituted phenoxides in this study, a stepwise mechanism with leaving-group departure being the RDS is not possible. Thus, the reactions have been concluded to proceed through a concerted mechanism.

Experimental Section

Materials. 4-Nitrophenyl X-substituted-cinnamates (**4a-4e**) and Y-substituted-phenyl cinnamates (**5a-5e**) were readily prepared from the reaction of the respective cinnamoyl chloride with phenol in anhydrous ether under the presence of triethylamine as reported previously.[17] The crude products were purified by column chromatography and their purity was checked by their melting points and spectral data such as ^{1}H and ^{13}C NMR spectra. DMSO and other chemicals were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use. Due to low solubility of the substrates in pure water, aqueous DMSO (80 mol % H_2O/20 ml % DMSO) was used as the reaction medium.

Kinetics. The kinetic study was performed using a UV-Vis spectrophotometer equipped with a constant temperature circulating bath to maintain the reaction mixture at 25.0 ± 0.1 °C. The reactions were followed by monitoring the appearance of Y-substituted phenoxide ion. All reactions were carried out under pseudo-first-order conditions, in which the concentration of the nucleophile was kept in much excess over that of the substrate.

Typically, the reaction was initiated by adding 5 μL of a 0.02 M solution of the substrate in acetonitrile to a 10-mm quartz UV cell containing 2.50 mL of the thermostated reaction mixture made up of solvent and aliquot of Z-substituted phenoxide stock solution, which was prepared by adding 2 equiv. of Z-substituted phenol and 1 equiv. of standardized NaOH solution to make a self-buffered solution. All solutions were transferred by gas-tight syringes. Generally, the phenoxide concentration in the reaction mixtures was varied over the range (2–50) × 10^{-3} M, while the substrate concentration was *ca.* 4 × 10^{-5} M. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, ln ($A_\infty - A_t$) = $-k_{obsd}t + C$. The plots of ln ($A_\infty - A_t$) *vs.* time were linear over 90 % of the total reaction. Usually, five different phenoxide concentrations were employed and replicate values of k_{obsd} were determined to obtain the second-order rate constants ($k_{Z\text{-PhO}^-}$) from the slope of linear plots of k_{obsd} *vs.* aryloxide concentrations.

Products Analysis. Y-Substituted-phenoxide ion was liberated quantitatively and identified as one of the products by comparison of the UV-vis spectrum after completion of the reaction with that of authentic sample under the same reaction condition.

Acknowledgments. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (KRF-2012-001637). E. H. Kim and J. S. Kang are also grateful for the BK 21 Scholarship.

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