Aminolyses of Y-substituted Phenyl 2-Furoates and Cinnamates: Effect of Nonleaving Group Substituent on Reactivity and Mechanism

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Received May 22, 2007

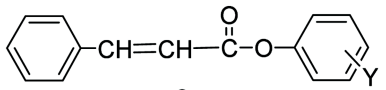
Second-order rate constants (k_N) have been determined spectrophotometrically for reactions of Y-substituted phenyl 2-furoates (**1a-h**) with piperidine and morpholine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The Brønsted-type plot exhibits a downward curvature for the reactions with strongly basic piperidine but is linear for the reactions with weakly basic morpholine. The slope of the curved Brønsted-type plot changes from –1.25 to –0.28 as the pK_a of the conjugate acid of the leaving aryloxides decreases. The pK_a at the center of the Brønsted curvature, defined as pK_a^o, was determined to be 6.4. The aminolysis of **1a-h** has been concluded to proceed through a stepwise mechanism on the basis of the curved Brønsted-type plot. The reactions of Y-substituted phenyl cinnamates (**2a-g**) with piperidine resulted in a curved Brønsted-type plot with a pK_a^o values of 6.4. However, the curved Brønsted-type plot has been suggested to be not due to a change in the RDS but due to a normal Hammond effect of a concerted mechanism, since the Brønsted-type plot for the corresponding reactions with morpholine results in also a curved Brønsted-type plot with a pK_a^o values of 6.1. The furoates with a basic leaving group (*i.e.*, **1b-g**) are less reactive than the corresponding cinnamates (*i.e.*, **2b-g**). The k_2/k_{-1} ratios for the reactions of **1b-h** are much smaller than unity, which has been suggested to be responsible for their low reactivity.

Key Words : Aminolysis, Brønsted-type plot, Rate-determining step, Concerted mechanism, Stepwise mechanism.

Introduction

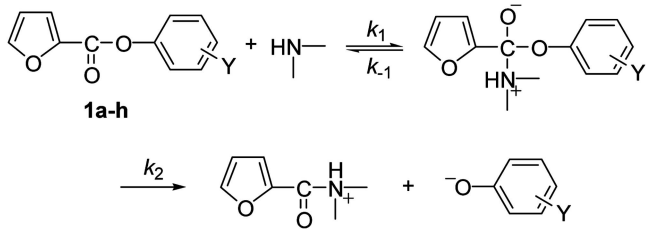
Reactions of esters with amines have generally been suggested to proceed through a stepwise mechanism.[1-11] Linear Free energy relationships such as Brønsted and Hammett equations have most commonly been used to determine reaction mechanisms. Aminolysis of esters with a good leaving group has often been reported to exhibit a curved Brønsted-type plot, *i.e.*, the slope changes from 0.9 ± 0.2 to 0.3 ± 0.1 as the basicity of the attacking amine increases.[1-11] Such a curved Brønsted-type plot has been suggested as evidence for a change in the rate-determining step (RDS) of a stepwise mechanism, *i.e.*, the RDS changes from breakdown of a tetrahedral zwitterionic intermediate to its formation as the attacking amine becomes more basic than the leaving group by 4 to 5 pK_a units.[6-11]

Castro *et al*. have found curved Brønsted-type plots for reactions of *S*-2,4-dinitrophenyl 4-substituted thiobenzoates with alicyclic secondary amines, *i.e.*, $\beta_1 = 0.1 – 0.44$ (at high pK_a) and $\beta_2 = 0.7$ (at low pK_a).[8a] Such curved Brønsted-type plots have also been obtained for aminolyses of bis(4-nitrophenyl) thionocarbonate[12] and 2,4-dinitrophenyl 4-methylphenyl carbonate.[13] Although the Brønsted-type plots for these reactions are curved, Castro *et al.* have concluded that the reactions proceed through a concerted mechanism and the curved Brønsted-type plots are not due to a change in the RDS but due to a normal Hammond effect.[8a,12,13] This is consistent with the conclusion drawn from reactions of benzoyl fluoride with a series of primary amines.[14] Song and Jencks have found a curved Brønsted-type plot with changing the slope from 0.67 to 0.23 for the aminolysis of benzoyl fluoride and attributed the curved Brønsted-type plot to a normal Hammond effect for a concerted mechanism, *i.e.*, an earlier transition-state structure for a more reactive nucleophile.[14] The main reason suggested for a concerted mechanism is that the difference in β_2 (0.67) and β_1 (0.23) values is much smaller than that obtained for stepwise reactions (*e.g.*, $\beta_2 – \beta_1 = 0.7 \pm 0.1$).[8a,12-15]



2a-g

We have recently performed reactions of Y-substituted phenyl cinnamates (**2a-g**) with piperidine and found that the Brønsted-type plot exhibits a downward curvature with pK_a^o = 6.4.[16] However, we have concluded that the reactions proceed through a concerted mechanism. This was because the reactions of **2a-g** with weakly basic morpholine have also resulted in a similarly curved Brønsted-type plot with pK_a^o = 6.1.[16] If the reactions with morpholine proceed through a stepwise mechanism with an intermediate, one might expect that the RDS changes from breakdown of the intermediate to its formation as the leaving aryloxide becomes less basic than the morpholine by 4 to 5 pK_a units, *i.e.*, the pK_a^o should be at the pK_a between 3.65 and 4.65 since the pK_a of the conjugate acid of morpholine in the current medium has been reported to be 8.65. The pK_a^o value



1 ; Y = 3, 4-$(NO_2)_2$ (**a**), 4-NO_2 (**b**), 4-CHO (**c**), 4-COMe (**d**), 4-CO_2Et (**e**), 3-Cl (**f**), 3-COMe (**g**), 4-Cl (**h**)

HN— = Piperidine and Morpholine

Scheme 1

of 6.1 found for the reactions **2a-g** with morpholine is only 2.5 pK_a units smaller than the pK_a of the conjugate acid of morpholine. Thus, it has been concluded that the curved Brønsted-type plots obtained for the reactions of **2a-g** with piperidine and morpholine is not due to a change in the RDS.[16]

To examine our previous conclusion, we have extended the kinetic study to reactions of Y-substituted phenyl 2-furoates (**1a-h**) with strongly basic piperidine and weakly basic morpholine. We have found that the Brønsted-type plot is curved for the reactions with piperidine but is linear for those with morpholine. We report the effect of modification of the nonleaving moiety from cinnamoyl to 2-furoyl on reactivity as well as on reaction mechanism.

Results and Discussion

All the reactions in the current study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were measured spectrophotometrically for the reactions of **1a-h** with piperidine and morpholine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The k_{obsd} values were determined from the linear plots of ln ($A_\infty - A_t$) *vs.* time. The plots of k_{obsd} *vs.* amine concentration were linear and passed through the origin, indicating that general base catalysis by a second amine molecule is absent and the contribution of H_2O and/or OH^- ion from solvolysis of amine to the k_{obsd} value is negligible. The apparent second-order rate constants (k_N) were determined from the slope of the linear plots of k_{obsd} *vs.* amine concentration. It is estimated from replicate runs that the uncertainty in the rate constants is less than ± 3%. The k_N values determined are summarized in Table 1 together with those for the corresponding reactions of Y-substituted phenyl cinnamates (**2a-g**) for comparison purpose.

Effect of Leaving Group Basicity on Reactivity and Mechanism. As shown in Table 1, the reactivity of the furoates decreases as the leaving aryloxide becomes more basic, *i.e.*, the k_N value for the reactions of Y-substituted phenyl 2-furoates (**1a-h**) with piperidine decreases from 382 $M^{-1}s^{-1}$ to 1.90 and 0.019 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the leaving aryloxide increases from 5.42 to 8.05 and 9.38, respectively. A similar result is shown for the reactions with morpholine.

Table 1. Summary of Second-Order Rate Constants for Reactions of Y-Substituted Phenyl 2-Furoates (**1a-h**) and Cinnamates (**2a-g**, in parentheses) with Piperidine and Morpholine in 80 mol % H_2O/ 20 mol % DMSO at 25.0 ± 0.1 °C[a]

Entry	Y-Phenol	pK_a	$k_N/M^{-1}s^{-1}$	
			piperidine	morpholine
a	Y = 3,4-$(NO_2)_2$	5.42	382	30.0
			(156)	(13.2)
b	Y = 4-NO_2	7.14	25.3	0.481
			(12.3)	(0.531)
c	Y = 4-CHO	7.66	4.79	0.0717
			(4.03)	(0.0970)
d	Y = 4-COMe	8.05	1.90	0.0199
			(1.71)	(0.0296)
e	Y = 4-CO_2Et	8.50	1.04	0.0122
			(1.24)	(0.0226)
f	Y = 3-Cl	9.02	0.157	0.00184
			(0.297)	(0.00394)
g	Y = 3-$COCH_3$	9.19	0.0843	0.00121
			(0.160)	(0.00160)
h	Y = 4-Cl	9.38	0.019	0.00049
			(–)	(–)

[a]The data in parenthesis are the second-order rate constants for the reactions of aryl cinnamates taken from ref. 16.

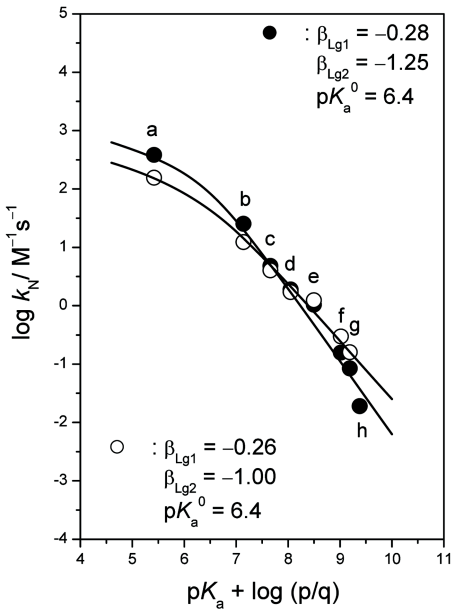


Figure 1. Brønsted-type plots for reactions of **1a-h** (●) and **2a-g** (○) with piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

The effect of the leaving group basicity on reactivity is illustrated in Figure 1. The Brønsted-type plots for reactions of **1a-h** and **2a-g** with piperidine are curved. Such curved Brønsted-type plots have often been reported for aminolysis of esters with a good leaving group and suggested as evidence for a change in the RDS of a stepwise mechanism.[1-11] Thus, one might attribute the curved Brønsted-type plots shown in Figure 1 to a change in the RDS of a stepwise mechanism.

The nonlinear Brønsted-type plots shown in Figure 1 have

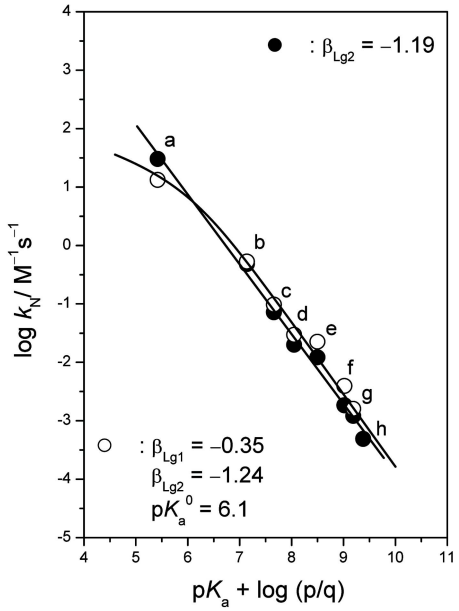


Figure 2. Brønsted-type plots for reactions of **1a-h** (●) and **2a-g** (○) with morpholine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

been analyzed using a semiempirical equation (eq. 1) on the basis of a stepwise mechanism. In eq. 1, β_{Lg1} and β_{Lg2} represent the slope of the Brønsted-type plots for the weakly basic and strongly basic leaving groups, respectively, while k_N^o refers to the k_N value at pK_a^o. The results are as follows: $\beta_{Lg2} = -1.25$ and $\beta_{Lg1} = -0.28$ for the reactions of **1a-h**, and $\beta_{Lg2} = -1.00$ and $\beta_{Lg1} = -0.26$ for the reactions of **2a-g**, and $pK_a^o = 6.4$ for both reaction systems.

$$\log (k_N/k_N^o) = \beta_{Lg1}(pK_a - pK_a^o) - \log [(1 + \alpha)/2],$$
$$\text{where } \log \alpha = (\beta_{Lg1} - \beta_{Lg2})(pK_a - pK_a^o) \quad (1)$$

It has generally been understood that a change in the RDS occurs as the attacking amine becomes more basic than the leaving group or the leaving group becomes less basic than the attacking amine by 4 to 5 pK_a units.[6-11] The pK_a^o value determined in the reactions of **1a-h** and **2a-g** with piperidine is 6.4, which is *ca*. 4.6 pK_a units smaller than the pK_a of the conjugate acid of piperidine ($pK_a = 11.02$ in 20 mol % DMSO). Accordingly, the curved Brønsted-type plots with the pK_a^o value of 6.4 appear to be consistent with a change in the RDS of a stepwise mechanism.

However, we have recently suggested that the curved Brønsted-type plot for the reactions of **2a-g** with piperidine is not due to a change in the RDS but due to a normal Hammond effect.[16] This was because the reactions of **2a-g** with weakly basic morpholine also resulted in a curved Brønsted-type plot as shown in Figure 2, *i.e*., the slope changes from –1.24 to –0.35 and the $pK_a^o = 6.1$. The pK_a of the conjugate acid of morpholine has been reported to be 8.65 in the current reaction medium.[16] Thus, the pK_a^o for the reactions of **2a-g** with morpholine should have been determined at pK_a between 3.65 and 4.65, if the reactions proceeded through a stepwise mechanism with a change in the RDS. However, as shown in Figure 2, the pK_a^o for the reactions of **2a-g** with morpholine is 6.1, which is only *ca*. 2.5 pK_a units smaller than the pK_a of the conjugate acid of morpholine. Accordingly, the reactions of **2a-g** have been concluded to proceed through a concerted mechanism, and the curved Brønsted-type plots for the reactions with piperidine as well as with morpholine have been attributed to a normal Hammond effect, *i.e*., an earlier transition state structure for a more reactive substrate.[16]

The above argument can be further supported by the fact that the Brønsted-type plot is linear for the corresponding reactions of **1a-h** with weakly basic morpholine (Figure 2), but is curved for the reactions with strongly basic piperidine with a pK_a^o value of 6.4 (Figure 1). Thus, one can suggest that the reactions of **1a-h** proceed through a stepwise mechanism without changing the RDS for the reactions with morpholine but with changing the RDS for the corresponding reactions with piperidine on the basis of the linear and curved Brønsted-type plots for the reactions with morpholine and with piperidine, respectively.

Effect of Nonleaving Group on Reactivity. As shown in Table 1, the furoates with a weakly basic leaving group are more reactive than the corresponding cinnamates but the reverse is true for esters with a strongly basic leaving group, i.e., for reactions with piperidine, the furoates **1a-d** are more reactive than the cinnamates **2a-d**, but the furoates **1e-g** are less reactive than the cinnamates **2e-g**. For the reactions with morpholine, only the furoate **1a** is more reactive than the cinnamate **2a**, while the other furoates (*e.g*., **1b-g**) are less reactive than the corresponding cinnamates (*e.g*., **2b-g**).

We have recently shown that reactivities of esters is significantly influenced by the electronic nature of the substituent X in the nonleaving group of aryl X-substituted benzoates, thionobenzoates, benzenesulfonates, and cinnamates, *i.e*., the reactivity increases with increasing the acid-strengthening ability of the substituent X in the nonleaving group.[9-11,16] The pK_a of 2-furoic acid is 3.16,[17a] while that of cinnamic acid is 4.44.[17b] Thus, one might expect that the furoates **1a-g** are more reactive than the cinnamates **2a-g**. However, as mentioned above, the reactivity order is not as expected on the basis of the acidity of 2-furoic acid and cinnamic acid. One might attribute the unexpected reactivity order to the difference in their reaction mechanisms, *i.e*., a stepwise mechanism for the reactions of **1a-h** *vs*. a concerted one for the reactions of **2a-g**.

Determination of Microscopic Rate Constants. To examine the above argument, the microscopic rate constants (*i.e*., k_2/k_{-1} ratio and k_1) associated with the reactions of **1a-h** with piperidine have been calculated. The apparent second-order rate constant k_N can be expressed as eqs 2 and 3 by applying the steady-state condition to the intermediate on the basis of the proposed mechanism in Scheme 1.

$$\text{Rate} = k_1k_2\,[\text{substrate}][\text{piperidine}] / (k_{-1} + k_2) \quad (2)$$

$$k_N = k_1k_2 / (k_{-1} + k_2) \quad (3)$$

Equation 3 can be simplified to eqs 4 and 5. Then, β_{Lg1}

Table 2. Summary of Microscopic Rate Constants k_1 and k_2/k_{-1} Ratios for the Reactions of **1a-h** with Piperidine in 80 mol % H_2O/ 20 mol % DMSO at 25.0 ± 0.1 °C

Entry	Y-Phenol	pK_a	k_1/M^{-1}s^{-1}	$10^2k_2/k_{-1}$
1a	Y = 3,4-$(NO_2)_2$	5.42	425	892
1b	Y = 4-NO_2	7.14	157	19.2
1c	Y = 4-CHO	7.66	84.7	6.00
1d	Y = 4-COMe	8.05	77.6	2.51
1e	Y = 4-CO_2Et	8.50	114	0.918
1f	Y = 3-Cl	9.02	54.8	0.287
1g	Y = 3-$COCH_3$	9.19	43.0	0.197
1h	Y = 4-Cl	9.38	14.8	0.129

and β_{Lg2} can be expressed as eqs 6 and 7, respectively.

$$k_N = k_1k_2/k_{-1}, \text{ when } k_2 \ll k_{-1} \quad (4)$$

$$k_N = k_1, \text{ when } k_2 \gg k_{-1} \quad (5)$$

$$\beta_{Lg1} = d(\log k_1) / d(pK_a) \quad (6)$$

$$\beta_{Lg2} = d(\log k_1k_2/k_{-1}) / d(pK_a) = \beta_{Lg1} + d(\log k_2/k_{-1}) / d(pK_a) \quad (7)$$

Equation 7 can be rearranged as eq 8. Integral of eq 8 from pK_a^o results in eq 9. Since $k_2 = k_{-1}$ at pK_a^o by definition, the term $(\log k_2/k_{-1})_{pKa}{}^o$ is zero. Therefore, the k_2/k_{-1} ratios have been calculated from eq 9 using the β_{Lg1}, β_{Lg2}, and pK_a^o values, and summarized in Table 2. Using the k_N values in Table 1 and the k_2/k_{-1} ratios in Table 2, the k_1 values have been calculated from eq 3, and summarized in Table 2.

$$\beta_{Lg2} - \beta_{Lg1} = d(\log k_2/k_{-1}) / d(pK_a) \quad (8)$$

$$(\log k_2/k_{-1})_{pKa} = (\beta_{Lg2} - \beta_{Lg1})(pK_a - pK_a^o) \quad (9)$$

As shown in Table 2, the k_1 value and the k_2/k_{-1} ratio decrease as the basicity of the leaving group increases as expected. It is also noted that $k_2/k_{-1} \ll 1$ when pK_a 7.14. The effect of leaving group basicity on these microscopic rate constants is illustrated in Figures 3 and 4. The plot of log k_1 *vs.* pK_a is linear with a slope of –0.29, while that of log k_2/k_{-1} *vs.* pK_a results in a much larger slope (*i.e.*, –0.97). This result indicates that the reactivity of **1a-h** toward piperidine is more strongly influenced by the k_2/k_{-1} ratios than by the k_1 values.

Figure 4 shows that log $k_2/k_{-1} = 0$ at pK_a = 6.4. The k_2/k_{-1} ratio becomes smaller than unity as the pK_a of the conjugate acid of the leaving aryloxide becomes larger than 6.4. The fact that $k_2/k_{-1} < 1$ for the furoate esters with basic leaving aryloxides (*e.g.*, **1b-h**) can explain why they are less reactive than the corresponding cinnamate esters (*e.g.*, **2b-g**) toward morpholine, although 2-furoic acid is a stronger acid than cinnamic acid. This is because the k_2/k_{-1} term is included in the apparent second-order rate constants (k_N) for the reactions of the furoate esters (see eq. 4). In fact, the k_1 values for the reactions of **1a-g** with piperidine (Table 2) are much larger than the k_N values for the corresponding reactions of **2a-g** (Table 1). Thus, one can suggest that the difference in the reaction mechanism between the furoate and the cinnamate systems is responsible for the unexpected reactivity order as mentioned in the preceding section.

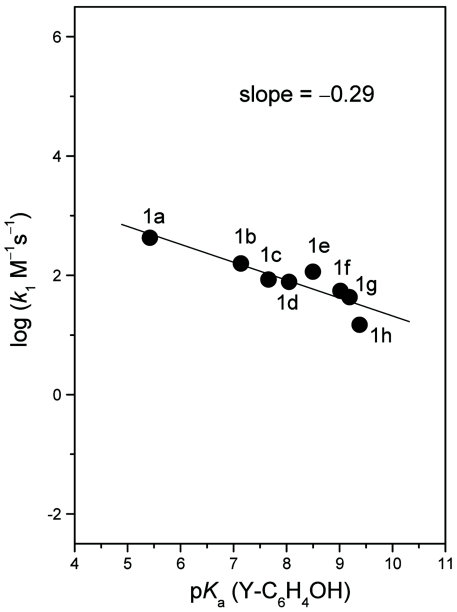


Figure 3. Plot of log k_1 *vs.* pK_a of the conjugate acids of the leaving aryloxides for reactions of **1a-h** with piperidine in 80 mol % H_2O/ 20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

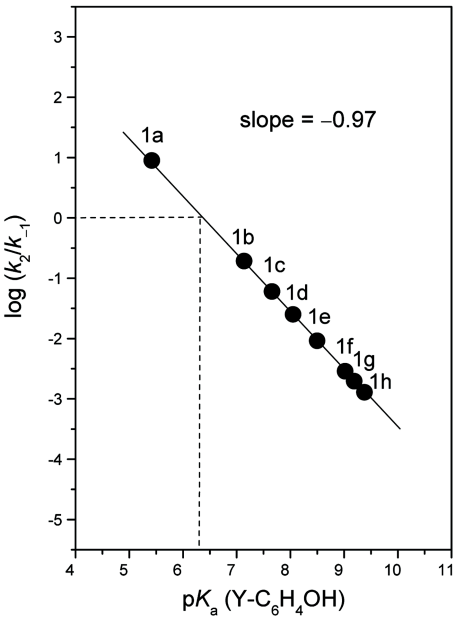


Figure 4. Plot of log k_2/k_{-1} *vs.* pK_a of the conjugate acids of the leaving aryloxides for reactions of **1a-h** with piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

Conclusions

The present study has allowed us to conclude the following: (1) The Brønsted-type plot exhibits a downward curvature for the reactions of **1a-h** with strongly basic piperidine but is linear for the corresponding reactions with weakly basic morpholine. (2) The curved Brønsted-type plot has been interpreted to indicate a change in the RDS of a

stepwise mechanism. (3) The furoate esters with basic leaving group (*e.g.*, **1b-g**) are less reactive than the corresponding cinnamates (*e.g.*, **2b-g**), although 2-furoic acid is a stronger acid than cinnamic acid. (4) The k_1 values for the reactions of **1a-g** with piperidine are larger than the k_N values for the corresponding reactions of **2a-g**. (5) The fact that the k_2/k_{-1} ratio < 1 for the reactions of **1b-h** is responsible for the result that **1b-g** are less reactive than **2b-g**.

Experimental Section

Materials. The furoates **1a-h** were readily prepared from the reaction of Y-substituted phenol and 2-furoyl chloride in the presence of triethylamine in anhydrous ether. The purity was confirmed by its melting point and ^{1}H NMR spectrum. Amines and other chemicals were of the highest quality available. Due to the low solubility of **1a-h** in pure H_2O, aqueous DMSO was used as the reaction medium (*i.e.*, 20 mol % DMSO/80 mol % H_2O). Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. The kinetic studies were performed at 25.0 ± 0.1 ^{o}C with a UV-Vis spectrophotometer equipped with a constant temperature circulating bath for slow reactions (*e.g.*, $t_{1/2}$ > 10 s) or with a stopped-flow spectrophotometer for fast reactions (*e.g.*, $t_{1/2}$ < 10 s). The reactions were followed by monitoring the appearance of Y-substituted phenoxide ion (or its conjugate acid). All the reactions were carried out under pseudo-first-order conditions in which the amine concentration was at least 20 times greater than that of the substrate.

Typically, reaction was initiated by adding 5 μL of 0.02 M of a substrate solution in MeCN by a 10 μL syringe into a 10 mm UV cell containing 2.50 mL of the reaction medium and the amine. The amine stock solution of *ca.* 0.2 M was prepared in a 25.0 mL volumetric flask under nitrogen by adding 2 equiv of amine to 1 equiv of standardized HCl solution in order to obtain a self-buffered solution. All the transfers of reaction solutions were carried out by means of gas-tight syringes.

Acknowledgment. This work was supported by a grant from KOSEF of Korea (R01-2004-000-10279-0). K. Akhtar is also grateful to Ewha Womans University for International Exchange Scholarship.

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