Aminolysis of Y-Substituted Phenyl 2-Thiophenecarboxylates and 2-Furoates: Effect of Modification of Nonleaving Group from 2-Furoyl to 2-Thiophenecarbonyl on Reactivity and Mechanism

Ik-Hwan Um* and Se-Won Min

Division of Nano Sciences and Department of Chemistry, Ewha Womans University, Seoul 120-750, Korea
**E-mail: ihum@ewha.ac.kr*
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Second-order rate constants (k_N) have been measured for reactions of Y-substituted phenyl 2-thiophenecarboxylates (**6a-h**) with morpholine and piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The Brønsted-type plot for the reactions of **6a-h** with morpholine is linear with β_{lg} = –1.29, indicating that the reactions proceed through a tetrahedral zwitterionic intermediate ($T^{\pm}$). On the other hand, the Brønsted-type plot for the reactions of **6a-h** with piperidine exhibits a downward curvature, implying that a change in the rate-determining step occurs on changing the substituent Y in the leaving group. Dissection of k_N into microscopic rate constants (*i.e.*, k_1 and k_2/k_{-1} ratio) has revealed that k_1 is smaller for the reactions of **6a-h** than for those of Y-substituted phenyl 2-furoates (**5a-h**), while the k_2/k_{-1} ratio is almost the same for the reactions of **5a-h** and **6a-h**. It is also reported that modification of the nonleaving group from the furoyl (**5a-h**) to the thiophenecarbonyl (**6a-h**) does not influence pK_a^o (defined as the pK_a at the center of the Brønsted curvature) as well as the k_2/k_{-1} ratio.

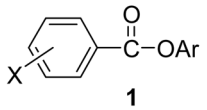
Key Words : Aminolysis, Brønsted-type plot, Intermediate, Stepwise mechanism, Rate-determining step

Introduction

Aminolysis of carboxylic esters with a good leaving group often resulted in a curved Brønsted-type plot, *i.e.*, β_{nuc} decreases from 0.9 ± 0.2 to 0.3 ± 0.1 as the basicity of the attacking amine increases. Such a curved Brønsted-type plot has been taken as evidence for a change in the rate-determining step (RDS).[1-7] The RDS has been suggested to change from breakdown of a tetrahedral zwitterionic intermediate ($T^{\pm}$) to its formation as the amine nucleophile becomes more basic than the leaving group by 4 to 5 pK_a units.[1-7]

Castro *et al.* have reported that the electronic nature of the nonleaving group influences pK_a^o, defined as the pK_a at the center of the Brønsted curvature where the RDS changes.[6] In pyridinolysis of 2,4-dinitrophenyl X-substituted benzoates (**1**, X = H, 4-Cl, and 4-NO_2) they found that the Brønsted-type plot is curved with pK_a^o = 9.5 for the reactions of unsubstituted benzoate but linear for the corresponding reactions of the 4-chloro and 4-nitro derivatives (pK_a^o > 9.5).[6] A similar result has been reported for reactions of 3,4-dinitrophenyl X-substituted phenyl carbonates (**2**) with quinuclidines.[7] Gresser and Jencks have proposed that an electron withdrawing substituent X in the nonleaving group favors amine expulsion from $T^{\pm}$ (*i.e.*, the k_{-1} process in Scheme 1) compared with ArO^- expulsion (the k_2 process in Scheme 1).[7] Thus, it has been concluded that a stronger electron-withdrawing substituent in the nonleaving group increases pK_a^o by decreasing the k_2/k_{-1} ratio.[6,7]

On the contrary, we have shown that the nature of substituent X in the nonleaving group affects reactivity but does not influence reaction mechanism for aminolysis of 2,4-dinitrophenyl X-substituted benzoates (**1**),[5] benzenesulfonates (**3**)[8] and cinnamates (**4**),[9] and hydrolysis of **1** and its thiono analogues.[10] In all cases, the Hammett plots were nonlinear, *i.e.*, electron donating substituents in the nonleaving group (*e.g.*, 4-Me, 4-MeO, 4-NMe_2 etc.) exhibited negative deviations from the Hammett plots.[5,8-10] Traditionally, such nonlinear Hammett plots have been interpreted as a change in the RDS.[11] However, we have proposed another explanation for the nonlinear Hammett plots, *i.e.*, stabilization of the ground state (GS) of the substrates through resonance interaction between the electron-donating substituent X and the carbonyl, thiono carbonyl, and sulfonyl functionalities as illustrated in the resonance structures I and II.[5,8-10] This was because the Yukawa-Tsuno plots for the same reactions exhibited an excellent linearity. Furthermore, we have shown that pK_a^o and the k_2/k_{-1} ratio are not influenced by the electronic nature of the substituent X in the nonleaving group for the aminolysis of **1**.[12]



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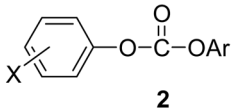

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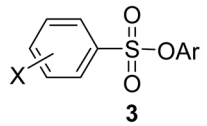

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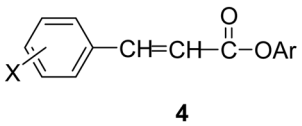

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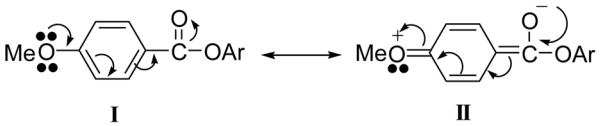

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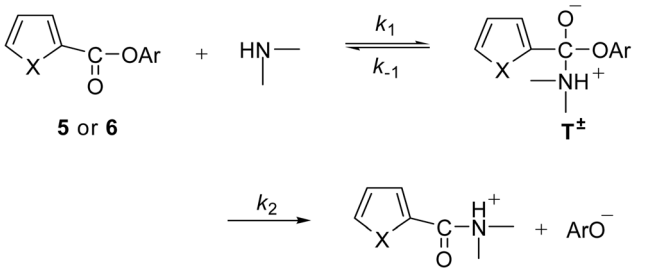

Scheme 1

We have extended our study to nucleophilic substitution reactions of Y-substituted phenyl 2-thiophenecarboxylates (**6a-h**) with morpholine and piperidine to investigate the effect of the leaving-group substituent Y on reactivity and reaction mechanism, as shown in Scheme 1. We have also studied the effect of modification of the nonleaving group from the furoyl to the thiophenecarbonyl by comparing the current kinetic data with those reported for the corresponding reactions of **5a-h**.[9b]

Results and Discussion

Reactions of **6a-h** with morpholine and piperidine proceeded with quantitative liberation of Y-substituted phenoxide and/or its conjugate acid. All reactions in this study obeyed pseudo-first-order kinetics under excess amine nucleophile. Pseudo-first-order rate constants (k_{obsd}) were determined from the equation $\ln(A_\infty - A_t) = -k_{obsd}t + c$. Correlation coefficients of the linear regressions were usually higher than 0.9995. The plots of k_{obsd} vs nucleophile concentrations were linear and passed through the origin, indicating that general base catalysis by the second amine molecule is absent and the contribution of H_2O and/or OH^- ion from hydrolysis of piperidine (or morpholine) to the k_{obsd} value is negligible. Thus, the rate equation can be expressed as eq. (1), in which [S] and [R_2NH] represent the concentration of substrate **6a-h** and amine nucleophile, respectively.

$$\text{Rate} = k_{obsd}[S], \text{ where } k_{obsd} = k_N[R_2NH] \quad (1)$$

Five different nucleophile concentrations were used to determine the second-order rate constant (k_N) from the slope of the linear plots. It is estimated from replicate runs that the uncertainty in rate constants is less than ± 3%. The k_N values determined in this way are summarized in Table 1 and graphically illustrated in Figure 1 as a function of the leaving group basicity.

Reaction Mechanism. As shown in Table 1, the second-order rate constant (k_N) for the reactions with morpholine decreases rapidly as the basicity of the leaving aryloxides increases, e.g., it decreases from 10.1 $M^{-1}s^{-1}$ to 3.20 × 10^{-3} and 1.44 × 10^{-4} $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of leaving aryloxides increases from 5.42 to 8.05 and 9.19, respectively. A similar result is shown for the corresponding reactions with piperidine, although piperidine exhibits much larger k_N values than morpholine.

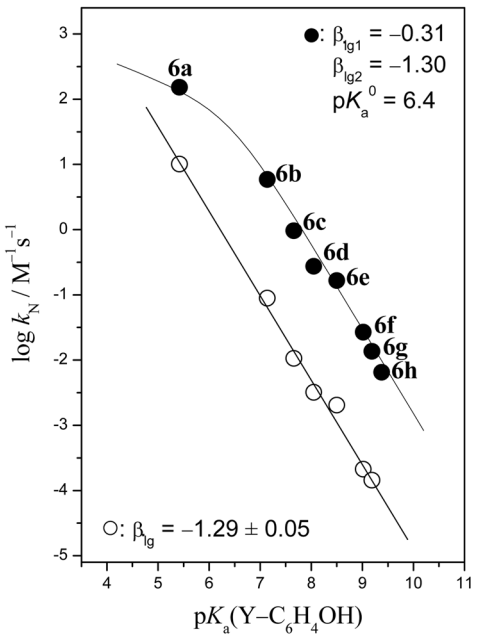

Figure 1. Brønsted-type plots for reactions of **6a-h** with morpholine (○) and piperidine (●) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

Table 1. Summary of Second-order Rate Constants for Reactions of Y–Substituted Phenyl 2-Thiophenecarboxylates (**6a-h**) with Morpholine and Piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C

Entry	Y	pK_a (Y-PhOH)	k_N/M^{-1} s^{-1}	
			morpholine	piperidine
6a	3,4-$(NO_2)_2$	5.42	10.1	152
6b	4-NO_2	7.14	8.91×10^{-2}	5.89
6c	4-CHO	7.66	1.06×10^{-2}	9.60×10^{-1}
6d	4-COMe	8.05	3.20×10^{-3}	2.74×10^{-1}
6e	4-CO_2Et	8.50	2.03×10^{-3}	1.65×10^{-1}
6f	3-Cl	9.02	2.12×10^{-4}	2.67×10^{-2}
6g	3-COMe	9.19	1.44×10^{-4}	1.36×10^{-2}
6h	4-Cl	9.38	[a]	6.50×10^{-3}

[a]Too slow to measure k_N.

The effect of leaving group basicity on reactivity is illustrated in Figure 1. The Brønsted-type plot for the reactions of **6a-h** with morpholine is linear with $\beta_{lg} = -1.29$, indicating that the reactions proceed through a zwitterionic tetrahedral intermediate $T^{\pm}$ without changing the RDS. On the other hand, the Brønsted-type plot for the reactions of **6a-h** with piperidine exhibits a downward curvature, implying that the RDS changes as the leaving group basicity changes.

The RDS of aminolysis of carboxylic esters has generally been understood to change from breakdown of $T^{\pm}$ to

formation of $T^{\pm}$ as the amine becomes more basic than the leaving aryloxide (or the leaving group is less basic than the attacking amine) by 4 to 5 pK_a units.[1-7] Since the pK_a of the conjugate acid of morpholine was reported to be 8.65 in 20 mol % DMSO at 25.0 ± 0.1°C,[5a] one can expect that a change in the RDS for the reactions with morpholine would occur at pK_a between 3.65 and 4.65, which is beyond the pK_a of 3,4-dinitrophenol (*i.e.*, 5.42), the conjugate acid of the least basic leaving group in this study.

The above argument can be supported by the curved Brønsted-type plot obtained for the reactions with the more basic piperidine. Since the pK_a of the conjugate acid of piperidine in 20 mol % DMSO at 25.0 ± 0.1°C was reported to be 11.02,[5a] one can expect that a change in the RDS for the reactions with piperidine would occur at pK_a between 6.0 and 7.0. In fact, the center of the Brønsted curvature is determined to be at pK_a = 6.4. Thus, the curved Brønsted-type plot for reactions of **6a-h** with piperidine can be taken as evidence for a change in the RDS.

The nonlinear Brønsted-type plot shown in Figure 1 can be analyzed using a semiempirical equation (eq. 2),[13] in which β_{lg1} and β_{lg2} represent the slope of the Brønsted-type plot at the low and the high pK_a region, respectively. The center of the Brønsted curvature has been defined as pK_a^o (*i.e.*, the pK_a where the RDS changes) and the k_N^o refers the k_N value at pK_a^o.

$$\log (k_N/k_N^o) = \beta_{lg1}(pK_a - pK_a^o) - \log [(1 + \alpha)/2],$$
$$\text{where } \log \alpha = (\beta_{lg1} - \beta_{lg2})(pK_a - pK_a^o) \quad (2)$$

The parameters determined from the fitting of eq. (2) to the experimental points are β_{lg1} = –0.31, β_{lg2} = –1.30, and pK_a^o = 6.4 for the reactions of **6a-h** with piperidine. A similar result has been reported for the reactions of Y-substituted phenyl 2-furoates (**5a-h**) with piperidine, *i.e.*, a curved Brønsted-type plot with β_{lg1} = –0.28, β_{lg2} = –1.25, and pK_a^o = 6.4. The pK_a^o value of 6.4 determined for the reactions of **6a-h** with piperidine is identical to that reported for the corresponding reactions of **5a-h**, indicating that the change in the electrophilic center from furoyl to thiophenecarbonyl does not influence the pK_a^o value.

Dissection of k_N into Microscopic Rate Constants, k_1 and k_2/k_{-1} Ratio. The microscopic rate constants (*i.e.*, k_1 and k_2/k_{-1} ratio) associated with the reactions of **6a-h** with piperidine have been calculated using the method reported by Castro *et al.*[13] on the assumption that the reactions proceed through a stepwise mechanism with a change in the RDS. The rate equation and the apparent second-order rate constant (k_N) for the current reactions can be expressed as eq. (3). Eq. (3) can be simplified to eq. (4) or (5). Then, β_{lg1} and β_{lg2} can be expressed as eqs. (6) and (7), respectively.

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

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

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

$$\beta_{lg1} = d(\log k_1)/d(pK_a) \quad (6)$$

Table 2. Summary of Microscopic Rate Constants, k_1 and k_2/k_{-1} Ratios, for Reactions of Y-Substituted Phenyl 2-Thiophenecarboxylates (**6a-h**) and 2-Furoates (**5a-h**, in parentheses) with Piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C[a]

Entry	Y	pK_a (Y-PhOH)	k_1 M^{-1} s^{-1}	10^3 k_2/k_{-1}
a	3,4-$(NO_2)_2$	5.42	168 (425)	9340 (8920)
b	4-NO_2	7.14	37.7 (157)	185 (192)
c	4-CHO	7.66	17.9 (84.7)	56.6 (60.0)
d	4-COMe	8.05	12.1 (77.6)	23.3 (25.1)
e	4-CO_2Et	8.50	20.0 (114)	8.34 (9.18)
f	3-Cl	9.02	10.5 (54.8)	2.55(2.87)
g	3-COMe	9.19	7.87 (43.0)	1.73 (1.97)
h	4-Cl	9.38	5.80 (14.8)	1.12 (1.29)

[a]The data in parentheses were taken from ref. 9b.

$$\beta_{lg2} = d(\log k_1k_2/k_{-1})/d(pK_a)$$
$$= \beta_{lg1} + d(\log k_2/k_{-1})/d(pK_a) \quad (7)$$

Eq. (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, the term $(\log k_2/k_{-1})_{pKa^o}$ is zero. Therefore, one can calculate the k_2/k_{-1} ratios for the reactions of **6a-h** from eq. (9) using pK_a^o = 6.4, β_{lg1} = –0.31 and β_{lg2} = –1.30.

$$\beta_{lg2} - \beta_{lg1} = d(\log k_2/k_{-1})/d(pK_a) \quad (8)$$

$$(\log k_2/k_{-1})_{pKa} = (\beta_{lg2} - \beta_{lg1})(pK_a - pK_a^o) \quad (9)$$

The k_1 values have been determined from eq. (10) using the k_N values in Table 1 and the k_2/k_{-1} ratios calculated above. The k_1 and k_2/k_{-1} ratios obtained in this way are summarized in Table 2 together with those reported for the reactions of **5a-h** with piperidine for comparison purpose.

$$k_N = k_1k_2/(k_{-1} + k_2) = k_1/(k_{-1}/k_2 + 1) \quad (10)$$

Effect of Modification of Nonleaving Group on Reactivity and Mechanism. Aryl 2-thiophenecarboxylates were reported to be less reactive than aryl 2-furoates toward amines.[14] Table 2 shows that the k_1 value is smaller for the reactions of **6a-h** than for those of **5a-h**. On the other hand, the k_2/k_{-1} ratio is almost the same for the reactions of **6a-h** and **5a-h**. Thus, k_1 is fully responsible for the difference in the reactivity between the furoates **5a-h** and the thiophenecarboxylates **6a-h**.

The effect of leaving group basicity on k_1 and k_2/k_{-1} ratios is illustrated in Figures 2 and 3, respectively. Reactions of **6a-h** exhibit better correlation than those of **5a-h** in the plots of log k_1 *vs* pK_a (Figure 2). The slopes determined are –0.29 and –0.34 for the reactions of **5a-h** and **6a-h**, respectively, which are small but typical for aminolyses proceeding through rate-determining formation of $T^{\pm}$. It is also noted that k_1 is smaller for the reactions of **6a-h** than for those of **5a-h** regardless of the leaving group basicity.

The plots of log k_2/k_{-1} *vs* pK_a exhibit excellent linear correlations. The slope of the linear plots and the magnitude of the k_2/k_{-1} ratios are almost identical for the reactions of **5a-h** and **6a-h**, which is quite contrasting to the reports by Gresser *et al.* and by Castro *et al.* that the k_2/k_{-1} ratio is

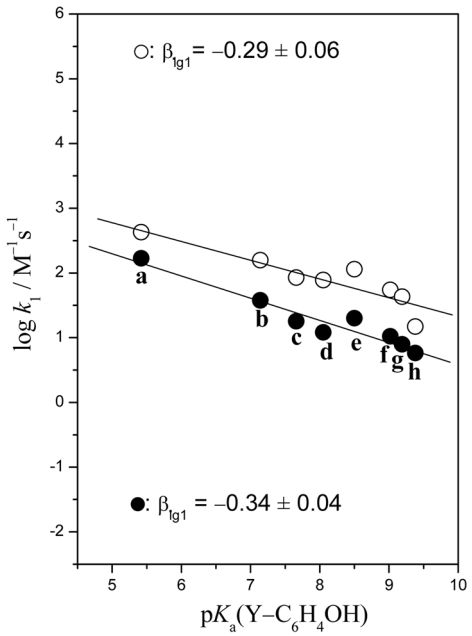

Figure 2. Plots of log k_1 *vs* pK_a of the conjugate acids of the leaving aryloxides for reactions of **5a-h** (○) and **6a-h** (●) with piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

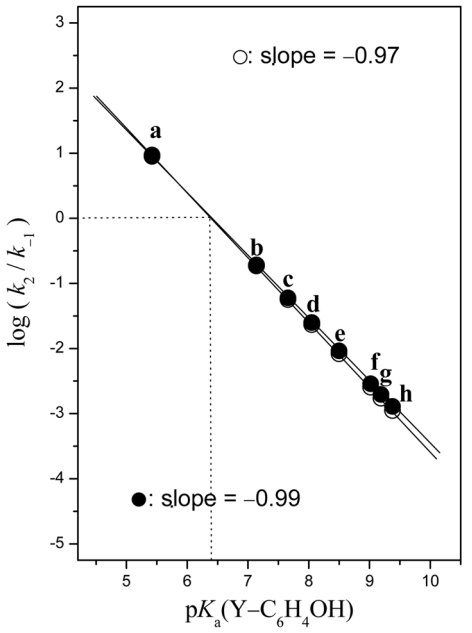

Figure 3. Plots of log k_2/k_{-1} *vs* pK_a of the conjugate acids of the leaving aryloxides for reactions of **5a-h** (○) and **6a-h** (●) with piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

dependent on the electronic nature of the substituent in the nonleaving group.[6,7] Gresser and Jencks found that the pK_a^o value of quinuclidinolysis of 3,4-dinitrophenyl X-substituted phenyl carbonates increases as the substituent X in the nonleaving group of the carbonates becomes stronger electron-withdrawing.[7] This was attributed to greater stabilization of the transition state (TS) for expulsion of 3,4-dinitrophenoxide ion relative to that for amine expulsion from $T^{\pm}$.[7] A similar conclusion has been drawn by Castro *et al*. for pyridinolysis of 2,4-dinitrophenyl X-substituted benzoates.[6] It has been argued that an electron withdrawing substituent X decreases k_2 but increases k_{-1}, which results in a decrease in the k_2/k_{-1} ratio.[6,7]

However, we have proposed that the k_2/k_{-1} ratio is independent of the electronic nature of the substituent X in the nonleaving group.[5,12] This is because both the amine and leaving aryloxide leave with the bonding electrons from the zwitterionic intermediate $T^{\pm}$. Accordingly, an electron donating substituent X would increase both k_2 and k_{-1} while an electron withdrawing X would decrease both k_2 and k_{-1}. In fact, we have shown that the electronic nature of the substituent X does not influence the k_2/k_{-1} ratio in reactions of 2,4-dinitrophenyl X-substituted benzoates with a series of secondary amines.[12] The same result has been obtained in this study. As shown in Figure 3, *i.e.*, the k_2/k_{-1} ratio is almost identical for the reactions of **5a-h** and **6a-h**, although 2-furoic acid (pK_a = 3.16) is a stronger acid than 2-thiophenecarboxylic acid (pK_a = 3.53).[15]

Conclusions

The current study has allowed us to conclude the following: (1) The Brønsted-type plot for the reactions of **6a-h** with morpholine is linear with β_{lg} = –1.29, indicating that the reactions proceed through $T^{\pm}$. (2) The corresponding reactions with piperidine resulted in a curved Brønsted-type plot, implying that a change in the RDS occurs. (3) The pK_a^o has been found to be the same for the reactions of **6a-h** and **5a-h**, which confirms our previous proposal that pK_a^o is not influenced by the electronic nature of the substituent X in the nonleaving group. (4) The k_1 value is smaller for the reactions of **6a-h** than for those of **5a-h**, while the k_2/k_{-1} ratio is almost identical for the reactions of **5a-h** and **6a-h**. (5) The smaller k_1 value for the reactions **6a-h** is mainly responsible for their lower reactivity.

Experimental Section

Materials. Y-Substituted phenyl 2-thiophenecarboxylates (**6a-h**) were readily prepared from the reaction of Y-substituted phenol and 2-thiophenecarbonyl chloride in the presence of triethylamine in anhydrous ether. Their purity was confirmed by their melting points and ^{1}H NMR spectra. Morpholine, piperidine, and other chemicals were of the highest quality available. Due to the low solubility of **6a-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 °C with a Scinco S-3100 UV-Vis spectrophotometer equipped with a constant temperature circulating bath for slow reactions (*e.g.*, $t_{1/2}$ 10 s) or with an Applied Photophysics MV-17 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 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 Hamilton gas-tight syringes.

Products Analysis. Y-Substituted phenoxides (and/or the conjugate acids) were liberated quantitatively and identified as one of the reaction products by comparison of the UV-vis spectra after the completion of the reactions with those of the authentic sample under the same reaction conditions.

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