http://dx.doi.org/10.5012/bkcs.2013.34.6.1829

Kinetics and Mechanism of the Anilinolysis of Aryl Ethyl Isothiocyanophosphates in Acetonitrile

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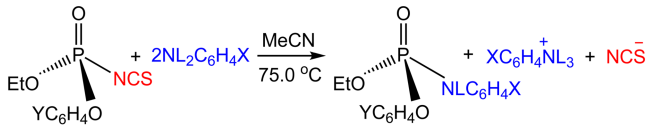
Received March 7, 2013, Accepted March 25, 2013

The nucleophilic substitution reactions of Y-aryl ethyl isothiocyanophosphates with substituted X-anilines and deuterated X-anilines were investigated kinetically in acetonitrile at 75.0 °C. The free energy relationships with X in the nucleophiles exhibited biphasic concave downwards with a break point at X = H. A stepwise mechanism with rate-limiting bond formation for strongly basic anilines and with rate-limiting bond breaking for weakly basic anilines is proposed based on the negative and positive ρ_{XY} values, respectively. The deuterium kinetic isotope effects (DKIEs; k_H/k_D) changed gradually from primary normal with strongly basic anilines, *via* primary normal and secondary inverse with aniline, to secondary inverse with weakly basic anilines. The primary normal and secondary inverse DKIEs were rationalized by frontside attack involving hydrogen bonded, four-center-type TSf and backside attack involving in-line-type TSb, respectively.

Key Words : Phosphoryl transfer reaction, Anilinolysis, Y-Aryl ethyl isothiocyanophosphate, Deuterium kinetic isotope effect, Cross-interaction constant

Introduction

To extend the kinetic studies on the phosphoryl transfer reactions, bimolecular nucleophilic substitution reactions of Y-aryl ethyl isothiocyanophosphates with substituted anilines ($XC_6H_4NH_2$) and deuterated anilines ($XC_6H_4ND_2$) have been investigated kinetically in acetonitrile (MeCN) at 75.0 ± 0.1 °C (Scheme 1). The kinetic results are discussed based on the selectivity parameters, cross-interaction constants (CICs)[1-3] and deuterium kinetic isotope effects (DKIEs; k_H/k_D).



L = H or D

X = 4-MeO, 4-Me, H, 4-Cl, 3-Cl; Y = 4-MeO, 4-Me, H, 3-MeO, 4-Cl

Scheme 1. Reactions of Y-aryl ethyl isothiocyanophosphates with $XC_6H_4NH_2(D_2)$ in MeCN at 75.0 °C.

Results and Discussion

The observed pseudo-first-order rate constants (k_{obsd}) followed Eq. (1) for all the reactions under pseudo-first-order conditions with a large excess of aniline nucleophile. The k_0 values were negligible ($k_0 \approx 0$) in MeCN. The second-order rate constants ($k_{H(D)}$) were determined for at least five concentrations of anilines. The linear plots of Eq. (1) suggest that no base-catalysis or noticeable side reactions occur, and that the overall reaction can be described by Scheme 1.

$$k_{obsd} = k_0 + k_{H(D)}[XC_6H_4NH_2(D_2)] \quad (1)$$

Tables 1-3 summarize the second-order rate constants (k_H and k_D), Hammett ($\rho_{X(H\text{ and }D)}$) and Brönsted ($\beta_{X(H\text{ and }D)}$) coefficients with X, and Hammett coefficients ($\rho_{Y(H\text{ and }D)}$) with Y, respectively. The pK_a values of the anilines in water were used to obtain the Brönsted β_X values in MeCN. This

Table 1. Second-order rate constants ($k_{H(D)} \times 10^4/M^{-1}\,s^{-1}$) of the reactions of Y-aryl ethyl isothiocyanophosphates with $XC_6H_4NH_2(D_2)$ in MeCN at 75.0 °C

X \ Y		4-MeO	4-Me	H	3-MeO	4-Cl
4-MeO	k_H	29.7 ± 0.1	35.7 ± 0.4	39.2 ± 0.2	49.2 ± 0.2	56.6 ± 0.5
	k_D	25.9 ± 0.1	–	32.6 ± 0.2	–	43.5 ± 0.2
4-Me	k_H	25.0 ± 0.1	29.6 ± 0.2	33.2 ± 0.1	41.4 ± 0.1	46.9 ± 0.1
	k_D	23.5 ± 0.2	–	29.4 ± 0.1	–	38.3 ± 0.1
H	k_H	18.9 ± 0.1	22.3 ± 0.2	24.5 ± 0.1	30.4 ± 0.1	34.4 ± 0.2
	k_D	19.4 ± 0.1	–	23.8 ± 0.1	–	31.1 ± 0.1
4-Cl	k_H	2.26 ± 0.01	3.33 ± 0.01	4.54 ± 0.05	7.09 ± 0.01	11.3 ± 0.1
	k_D	2.48 ± 0.01	–	4.79 ± 0.02	–	11.5 ± 0.1
3-Cl	k_H	0.563 ± 0.002	1.07 ± 0.01	1.65 ± 0.01	2.43 ± 0.01	5.43 ± 0.02
	k_D	0.673 ± 0.001	–	1.83 ± 0.01	–	5.88 ± 0.03

Table 2. Hammett ($\rho_{X(H \text{ and } D)}$)[a] and Brönsted ($\beta_{X(H \text{ and } D)}$)[b] coefficients with X for the reactions of Y-aryl ethyl isothiocyanophosphates with $XC_6H_4NH_2(D_2)$ in MeCN at 75.0 °C[c]

X \ Y	4-MeO	4-Me	H	3-MeO	4-Cl
4-MeO, 4-Me, H $-\rho_{X(H)}$	0.73 ± 0.01	0.75 ± 0.01	0.76 ± 0.01	0.78 ± 0.01	0.80 ± 0.01
$-\rho_{X(D)}$	0.47 ± 0.01	-	0.51 ± 0.01	-	0.54 ± 0.01
$\beta_{X(H)}$	0.26 ± 0.01	0.27 ± 0.01	0.27 ± 0.01	0.28 ± 0.01	0.29 ± 0.01
$\beta_{X(D)}$	0.17 ± 0.01	-	0.18 ± 0.01	-	0.20 ± 0.01
H, 4-Cl, 3-Cl $-\rho_{X(H)}$	4.11 ± 0.02	3.57 ± 0.01	3.17 ± 0.01	2.94 ± 0.01	2.16 ± 0.01
$-\rho_{X(D)}$	3.94 ± 0.01	-	3.02 ± 0.01	-	1.95 ± 0.01
$\beta_{X(H)}$	1.42 ± 0.04	1.23 ± 0.06	1.09 ± 0.05	1.02 ± 0.01	0.75 ± 0.02
$\beta_{X(H)}$	1.36 ± 0.05	-	1.04 ± 0.05	-	0.67 ± 0.01

[a]The σ values were taken from ref. 8. [b]The pK_a values of X-anilines in water were taken from ref. 9. [c]Correlation coefficients (r) of ρ_X and β_X values are better than 0.997.

Table 3. Hammett coefficients ($\rho_{Y(H \text{ and } D)}$) with Y for the reactions of Y-aryl ethyl isothiocyanophosphates with $XC_6H_4NH_2(D_2)$ in MeCN at 75.0 °C[c]

X	$\rho_{Y(H)}$[a]	$\rho_{Y(D)}$[b]
4-MeO	0.54 ± 0.02	0.45 ± 0.02
4-Me	0.53 ± 0.02	0.42 ± 0.01
H	0.50 ± 0.02	0.41 ± 0.02
4-Cl	1.33 ± 0.04	1.33 ± 0.06
3-Cl	1.78 ± 0.08	1.88 ± 0.06

[a]Y = (4-MeO, 4-Me, H, 3-MeO, 4-Cl). [b]Y = (4-MeO, H, 4-Cl). [c]Correlation coefficients (r) of ρ_Y values are better than 0.982.

procedure was justified experimentally and theoretically.[4-7] Herein, the $\Delta pK_a = pK_a(MeCN) - pK_a(H_2O)$ values for structurally similar amines were almost constant. Therefore, the determination of β_X by plotting log k_H(MeCN) against p$K_a(H_2O)$ is probably justified.

Figure 1 presents the Brönsted plots with X in the nucleophiles [log k_H vs pK_a(X)]. The Hammett [Figs. S1 (log k_H *vs* σ_X) and S2 (log k_D *vs* σ_X)] and Brönsted [Fig. S3: log k_D *vs* pK_a(X)] plots with X in the nucleophiles, and the Hammett plots [Figs. S4 (log k_H *vs* σ_Y) and S5 (log k_D *vs* σ_Y)] with Y in the substrates are shown in the supporting information. The substituent effects of X on the reaction rates are compatible with a typical nucleophilic substitution reaction. The rate increases as the aniline becomes more basic. The free energy relationships with X, however, exhibit biphasic concave downwards with a break point at X = H. The magnitudes of the selectivity parameters of ρ_X and β_X with strongly basic anilines (X = 4-MeO, 4-Me, H) are much smaller than those with weakly basic anilines (X = H, 4-Cl, 3-Cl). The substituent effects of Y on the reaction rates are consistent with a typical nucleophilic substitution reaction, and the rate increases with a more electron-withdrawing substituent. The magnitudes of the ρ_X, β_X and ρ_Y values with the anilines are somewhat greater than those with the deuterated anilines. This suggests that these values are more sensitive to the substituent effects of anilines on the rate compared to those of deuterated anilines.

The CIC can be one of the strong tools to clarify the mechanism based on the substituent effects of the nucleophiles, substrates and/or leaving groups on the reaction rates.[1-3] The

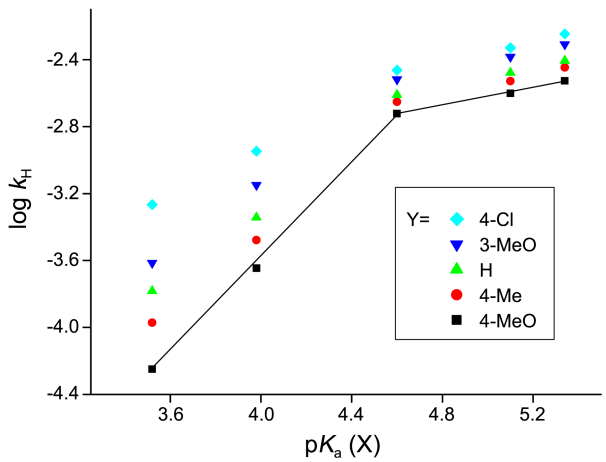


Figure 1. Brönsted plots with X [log k_H *vs* pK_a(X)] of the reactions of Y-aryl ethyl isothiocyanophosphates with $XC_6H_4NH_2$ in MeCN at 75.0 °C.

sign of the CIC has made it possible to correctly interpret the reaction mechanism. The sign of the CIC [ρ_{XY}, Eqs. (2)] is negative in a stepwise reaction with rate-limiting bond formation (or in a normal S_N2 reaction), and positive in a stepwise reaction with rate-limiting leaving group expulsion from the intermediate.

$$\log (k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \quad (2a)$$

$$\rho_{XY} = \partial^2 \log (k_{XY}/k_{HH})/\partial\sigma_X\partial\sigma_Y = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X \quad (2b)$$

The two ρ_{XY} values were obtained because the Hammett plots with X are biphasic. Figure 2 shows the plots of $\rho_{X(H)}$ *vs* σ_Y and $\rho_{Y(H)}$ *vs* σ_X to determine the $\rho_{XY(H)}$ values for strongly and weakly basic anilines, respectively, according to Eq. (2b).[10] The signs of ρ_{XY} are negative ($\rho_{XY(H)} = -0.13$) with strongly basic anilines (X = 4-MeO, 4-Me, H) but positive ($\rho_{XY(H)} = 3.46$) with weakly basic anilines (X = H, 4-Cl, 3-Cl).

Therefore, the authors propose the following reaction mechanism: (i) a stepwise process with rate-limiting bond formation with strongly basic anilines based on the negative sign of ρ_{XY}; (ii) a stepwise process with rate-limiting leaving group departure from the intermediate with weakly basic anilines based on the positive sign of ρ_{XY}. These are in line

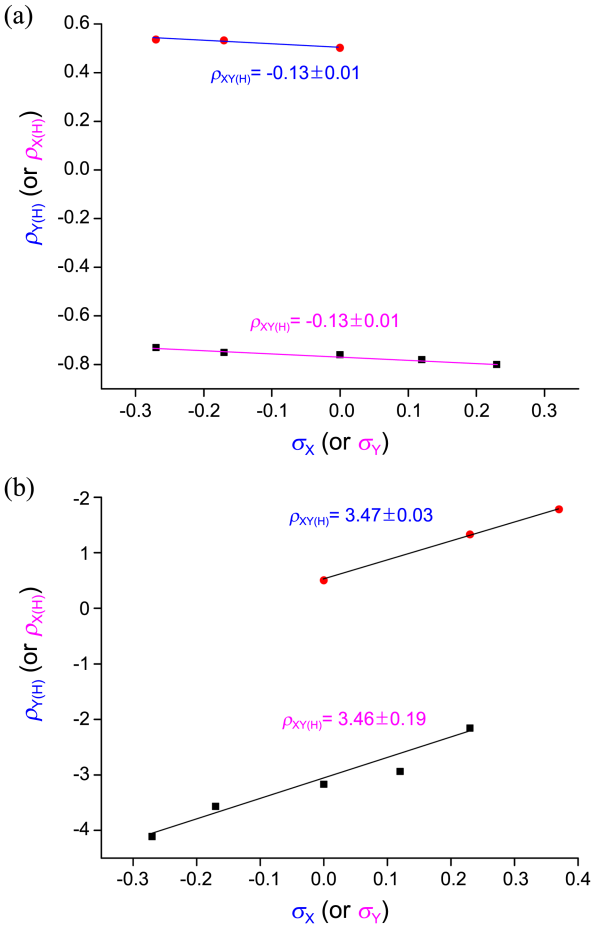


Figure 2. Plots of $\rho_{X(H)}$ *vs* σ_Y and $\rho_{Y(H)}$ *vs* σ_X of the reactions of Y-aryl ethyl isothiocyanophosphates with $XC_6H_4NH_2$ in MeCN at 75.0 °C. The obtained $\rho_{XY(H)}$ values by multiple regression are: (a) $\rho_{XY(H)}$ = –0.13 ± 0.02 (r = 0.986) with strongly basic anilines (X = 4-MeO, 4-Me, H); (b) $\rho_{XY(H)}$ = 3.46 ± 0.05 (r = 0.994) with weakly basic anilines (X = H, 4-Cl, 3-Cl).

with the conventional criteria, where nonlinear free energy correlation of the concave downward plot is diagnostic of a rate-limiting step change from bond breaking with weakly basic nucleophiles to bond formation with strongly basic nucleophiles.[11-20] In this mechanism for anilines with high pK_a values, $k_{-a} << k_b$, meaning that the k_a step is the rate-determining step, *i.e.*, $k_{H(D)} = k_a$ with smaller Brönsted coefficients β_X in Eq. (3). On the other hand, at low pK_a values where $k_{-a} >> k_b$ and $k_{H(D)} = (k_a/k_{-a})k_b = Kk_b$, the k_b step should be the rate-limiting step with steeper Brönsted slopes of β_X. At the breakpoint of the Brönsted plot, $k_{-a} = k_b$, aniline with pK_a = pK_a^o has the same leaving ability from the intermediate as that of the leaving group of NCS^-.

$$\text{Substrate + Nucleophile} \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \text{Intermediate} \xrightarrow{k_b} \text{Products} \quad (3)$$

In addition to the CICs, the DKIEs (k_H/k_D) are also one of the strong tools to clarify the reaction mechanism. When partial deprotonation of the aniline occurs in rate-limiting step by hydrogen bonding, the DKIEs are primary normal ($k_H/k_D > 1.0$).[21-27] In contrast, the DKIEs can only be secondary inverse ($k_H/k_D < 1.0$) in a stepwise process (or a normal S_N2 reaction) because the N–H(D) vibrational frequencies invariably increase upon going to the TS because of an increase in the steric congestion.[28-30] In this respect, DKIEs have provided a useful means to determine the TS structures in the nucleophilic substitution reactions, as well as how the reactants alter the TS structures, particularly through changes in the substituents. The incorporation of deuterium in the nucleophile has an advantage in that the α-DKIEs reflect only the degree of bond formation, particularly for the secondary inverse DKIEs. Therefore, the steric congestion increases with increasing extent of bond formation, resulting in a smaller k_H/k_D value.

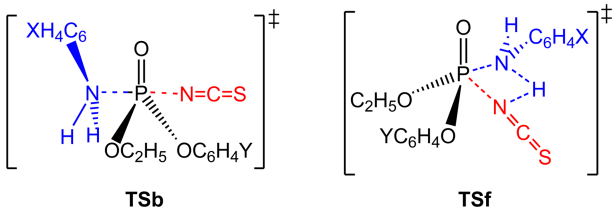
In this study, the DKIEs change from primary normal with X = 4-MeO and 4-Me, *via* primary normal and secondary inverse with X = H, to secondary inverse with X = 4-Cl and 3-Cl, as shown in Table 4. The magnitudes of the k_H/k_D values invariably increase with more basic aniline and with more electron-withdrawing Y. The maximum value of k_H/k_D = 1.30 with X = 4-MeO and Y = 4-Cl indicates extensive hydrogen bonding, whereas the minimum value of k_H/k_D = 0.84 with X = 3-Cl and Y = 4-MeO indicates severe steric congestion in the TS, suggesting great extent of bond formation in the TS. The secondary inverse and primary normal DKIEs are substantiated by backside attack involving in-line-type TSb and frontside attack involving four-center-type hydrogen bond TSf, respectively (Scheme 2).

The TSb-H could be another plausible TS structure, in which hydrogen bonding of an amine hydrogen atom occurs on the P=O oxygen atom (Scheme 3). In the present work, three possible TS(s) could substantiate the primary normal DKIEs: (i) TSf, (ii) TSb-H or (iii) both TSb-H and TSf. The anilinolyses of tetracoordinate phosphorus with the Cl^- leaving group have been studied extensively in this laboratory, and the data obtained for primary normal DKIEs involving

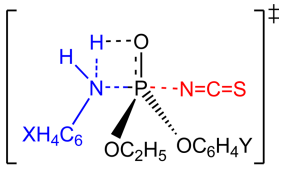
Table 4. DKIEs (k_H/k_D) of the reactions of Y-aryl ethyl isothiocyanophosphates with $XC_6H_4NH_2(D_2)$ in MeCN at 75.0 °C

X \ Y	4-MeO	H	4-Cl
4-MeO	1.15 ± 0.01[a]	1.20 ± 0.01	1.30 ± 0.01
4-Me	1.06 ± 0.01	1.13 ± 0.01	1.22 ± 0.01
H	0.974 ± 0.007	1.03 ± 0.01	1.11 ± 0.01
4-Cl	0.911 ± 0.005	0.948 ± 0.011	0.983 ± 0.012
3-Cl	0.837 ± 0.003	0.902 ± 0.007	0.924 ± 0.006

[a]Standard error $\{= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}\}$ from ref. 31.



Scheme 2. Backside attack involving in-line-type TSb and frontside attack involving a hydrogen bonded, four-center-type TSf.



TSb-H

Scheme 3. Backside attack involving a hydrogen bonded, four-center-type TSb-H.

deuterated anilines were rationalized by TSf-type, in which hydrogen bonding of an amine hydrogen atom occurs to the departing chloride.[32-38] The authors also suggested TSf-type in which hydrogen bonding of an amine hydrogen atom occurs to the departing phenoxy oxygen atom for the anilinolyses of aryl dimethyl, methyl and diphenyl phosphinates.[39] Therefore, at this point, the authors are in favor of TSf in the present work.

In summary, the authors propose the following reaction mechanism: (i) for weakly basic anilines (X = 3-Cl, 4-Cl), a stepwise process with rate limiting leaving group departure from the intermediate, involving predominant backside attack TSb based on the positive ρ_{XY} ($\rho_{XY(H)}$ = 3.46 and $\rho_{XY(D)}$ = 3.97) and secondary inverse DKIEs (k_H/k_D = 0.84-0.98); (ii) for aniline (X = H), $k_{-a} = k_b$ with $pK_a = pK_a^o$, the nucleophile of aniline and leaving group of NCS^- have the same leaving ability from the intermediate, and the attacking direction of the nucleophile changes gradually from backside to frontside as Y becomes more electron-withdrawing (k_H/k_D = 0.97 with Y = 4-MeO, 1.03 with Y = H, and 1.11 with Y = 4-Cl); and (iii) for stronly basic anilines (X = 4-Me, 4-MeO), a stepwise process with rate-limiting bond formation, involving predominant frontside attack, hydrogen bonded, four-center-type TSf based on the negative ρ_{XY} ($\rho_{XY(H)}$ = –0.13 and $\rho_{XY(D)}$ = –0.14) and primary normal DKIEs (k_H/k_D = 1.06-1.30).

Table 5 lists the activation parameters, enthalpies and entropies of activation, for the reactions of Y-aryl ethyl isothiocyanophosphates with unsubstituted aniline. The enthalpies of activation are relatively low values and entropies of activation are relatively large negative values regardless of the rate-limiting step, bond formation or breaking.

Table 5. Activation parameters for the reactions of Y-aryl ethyl isothiocyanophosphates with $C_6H_5NH_2$ in MeCN

Y	t/°C	$k_H \times 10^3$/ $M^{-1}\,s^{-1}$	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$-\Delta S^{\ddagger}$/ cal $mol^{-1}\,K^{-1}$
4-Me	55.0	1.21 ± 0.03		
	65.0	1.66 ± 0.02	6.3 ± 0.1	53 ± 1
	75.0	2.23 ± 0.02		
H	55.0	1.37 ± 0.01		
	65.0	1.81 ± 0.01	5.9 ± 0.3	54 ± 1
	75.0	2.45 ± 0.01		
3-MeO	55.0	1.67 ± 0.01		
	65.0	2.22 ± 0.02	6.1 ± 0.3	53 ± 1
	75.0	3.04 ± 0.01		

Experimental Section

Materials. HPLC grade MeCN (water content is less than 0.005%) was used without further purification. The anilines were redistilled or recrystallized prior to use. Deuterated anilines were synthesized by heating anilines and deuterium oxide (99.9 atom % D) and one drop of HCl as catalyst at 85 °C for 72 h. After numerous attempts, the anilines were deuterated at more than 98%, as confirmed by ^{1}H NMR. Y-Aryl ethyl isothiocyanophosphates were prepared in the following two steps. In step 1, Y-aryl ethyl chlorophosphates were prepared by reacting ethyl dichlorophosphate with substituted phenols for 3 h in the presence of triethylamine in acetonitrile in a cooling bath at –30.0 °C with constant stirring. Triethylamine hydrochloride was separated by filtration. The filtrate was treated with water-$NaHCO_3$ and ether for work up after solvent removal under reduced pressure. The ether extracted organic part was dried over anhydrous $MgSO_4$ for 6-8 h. The product mixture was isolated by filtration, separated by column chromatography (silica gel, ethyl acetate/*n*-hexane) and dried under reduced pressure using an oil diffusion pump. In step 2, Y-aryl ethyl isothiocyanophosphates were synthesized by reacting Y-aryl ethyl chlorophosphate with potassium thiocyanate for 3-4 h in acetonitrile in a cooling bath at –30.0 °C with constant stirring. The substrates were isolated in the similar way described in step 1 and were identified by TLC, IR, ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR and GC-MS (supporting information). The physical constants after column chromatography (silicagel/ethylacetate + *n*-hexane) were as follows:

(4-$CH_3OC_6H_4O$)(C_2H_5O)P(=O)NCS: Pink colored oily liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ and TMS) δ 1.91 (aliphatic, 3H, t, J = 7.2 Hz), 4.28 (aliphatic, 3H, s), 4.81 (aliphatic, 2H, q, J = 7.2 Hz), 7.37 (aromatic 2H, d, J = 9.2 Hz), 7.63 (aromatic, 2H, d, J = 8.8 Hz.); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 15.95, 55.63, 66.11, 114.92-157.48, 149.74; ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ –17.07 (1P, s); ν_{max} (Thin film), 2990-2838 cm^{-1} (C-H, str. aliphatic), 1973 cm^{-1} (NCS, broad str. region), 1518 cm^{-1} (P=O str.), 1312, 1257, 1046 cm^{-1} (P-O-Alph str.); GC-MS for $C_{10}H_{12}NO_4PS$ (EI, *m/z*) 273 (M^+).

(4-$CH_3C_6H_4O$)(C_2H_5O)P(=O)NCS: Pink colored oily liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ and TMS) δ 1.43 (aliphatic, 3H, t, J = 7.2 Hz), 2.34 (aliphatic, 3H, s), 4.32 (aliphatic, 2H, q, J = 7.2 Hz), 7.06-7.19 (aromatic, 4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 15.93, 20.73, 66.23, 94.38-148.29, 135.96; ν_{max} (neat), 3040 (C–H, str. aromatic), 2988 (C–H str. aliphatic), 1977 (N=C=S, str.), 1504, 1300, 1163, 1030, 820 (P–O–Ph and P=O str.); ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ –17.52(P=O, 1P, s); GC-MS for $C_{10}H_{12}NO_3PS$ (EI, *m/z*) 257 (M^+).

(C_6H_5O)(C_2H_5O)P(=O)NCS: Red-brown oily liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ and TMS) δ 1.42 (aliphatic, 3H, t, J = 7.2 Hz), 4.31-4.36 (aliphatic, 2H, q, J = 7.2 Hz), 7.21-7.39 (aromatic, 5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 15.96, 66.05, 120.21-130.06, 149.67; ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ –17.81 (P=O, 1P, s); ν_{max} (Thin film),

2986 cm^{-1} (C-H, str. aliphatic), 1994 cm^{-1} (NCS, broad str. region), 1489 cm^{-1} (P=O str.), 1299, 1198, 1035 cm^{-1} (P-O-Alph str.); GC-MS for $C_9H_{10}NO_3PS$ (EI, *m/z*) 243 (M^+).

(3-$CH_3OC_6H_4O$)(C_2H_5O)P(=O)NCS: Light pink colored oily liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ and TMS) δ 1.43 (aliphatic, 3H, t, *J* = 7.2 Hz), 3.78 (aliphatic, 3H, s), 4.33 (aliphatic, 2H, q, *J* = 7.2 Hz), 6.74-6.82 (aromatic, 4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 15.79, 55.41, 66.37, 105.97-160.76, 150.18; ν_{max} (Thin film), 2990-2838 cm^{-1} (C-H, str. aliphatic), 1976 cm^{-1} (NCS, broad str. region), 1607 cm^{-1} (P=O str.), 1491, 1138, 1028, 769 cm^{-1} (P-O-Alph str.); ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ 17.97 (P=O, 1P, s); GC-MS for $C_{10}H_{12}NO_4PS$ (EI, *m/z*) 273 (M^+).

(4-ClC_6H_4O)(C_2H_5O)P(=O)NCS: Pink-yellow colored oily liquid; ^{1}H-NMR (400MHz, $CDCl_3$ and TMS) δ 1.40 (aliphatic, 3H, t, *J* = 7.2 Hz), 4.29 (aliphatic, 2H, q, *J* = 7.2 Hz), 6.71-7.33 (aromatic, 4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 15.96, 66.32, 116.65-130.09, 149.25; ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ −17.79 (P = O, 1P, s); ν_{max} (Thin film), 2988-27.75 cm^{-1} (C-H, str. aliphatic), 1989 cm^{-1} (NCS, broad str. region), 1485 cm^{-1} (P=O str.), 1296, 1202, 1034 cm^{-1} (P-O-Alph str.); GC-MS for $C_9H_9ClNO_3PS$ (EI, *m/z*) 277 (M^+).

Kinetics Measurement. The rates were measured conductometrically at 75.0 °C. The conductivity bridge used in this study was a self-made computer-automated A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obsd} were measured by curve fitting analysis in the Origin program with a large excess of anilines, [Substrate] = 5×10^{-3} M and [X-Aniline] = (0.10-0.30) M. The second-order rate constants, $k_{H(D)}$, were obtained from the slope of a plot of k_{obsd} *vs*. [X-Aniline] with five concentrations of anilines. The k_{obsd} values were the average of at least three runs, which were reproducible within ± 3%.

Product Analysis. Ethyl phenyl isothiocyanophosphate was reacted with excess aniline for more than 15 half-lives at 75.0 °C in MeCN. Acetonitrile was evaporated under reduced pressure. The product mixture was treated with ether using a work-up process with dilute HCl and dried over anhydrous $MgSO_4$. After filtration, the product was isolated by evaporating the solvent under reduced pressure. The analytical and spectroscopic data of the product gave the following results (supporting information):

(C_6H_5O)(C_2H_5O)P(=O)NHC_6H_5: Light brown liquid; ^{1}H-NMR (400 MHz, MeCN-d_3) δ 1.26 (aliphatic, 3H, t, *J* = 7.2 Hz), 4.19 (aliphatic, 2H, q, *J* = 7.2 Hz), 5.32 (aliphatic, 1H, m), 6.94-7.48 (aromatic, 10H, m); ^{13}C-NMR (100 MHz, MeCN-d_3) δ 18.58, 64.57, 104.67-131.20; ^{31}P-NMR (162 MHz, MeCN-d_3) δ 8.24 (P=O, 1P); GC-MS for $C_{14}H_{16}NO_3PS$ (EI, *m/z*) 277(M^+).

Acknowledgments. This work was supported by Inha University Research Fund.

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10. The CICs of $\rho_{XY(H)}$ and $\rho_{XY(D)}$ with strongly (X = 4-MeO, 4-Me, H) and weakly (X = H, 4-Cl, 3-Cl) basic anilines are summarized in Table R1. The values of $\rho_{XY(H)}$ and $\rho_{XY(D)}$ are similar. The plots of $\rho_{X(D)}$ *vs* σ_Y and $\rho_{Y(D)}$ *vs* σ_X to determine the $\rho_{XY(D)}$ values are shown in Fig. S6 (supporting information).

Table R1. CICs ($\rho_{XY(H\ and\ D)}$) for the reactions of Y-aryl ethyl isothiocyanophosphates with $XC_6H_4NH_2(D_2)$ in MeCN at 75.0 °C

X	$\rho_{XY(H)}$[a]	$\rho_{XY(D)}$[b]
4-MeO, 4-Me, H	−0.13 ± 0.02 (r = 0.986)[c] with 15 k_H values	−0.14 ± 0.01 (r = 0.991) with 9 k_D values
H, 4-Cl, 3-Cl	3.46 ± 0.05 (r = 0.994) with 15 k_H values	3.97 ± 0.04 (r = 0.997) with 9 k_D values

[a]Y = (4-MeO, 4-Me, H, 3-MeO, 4-Cl). [b]Y = (4-MeO, H, 4-Cl). [c]Correlation coefficient (r).

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