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Kinetics and Mechanism of Pyridinolyses of Aryl Methyl and Aryl Propyl Chlorothiophosphates in Acetonitrile

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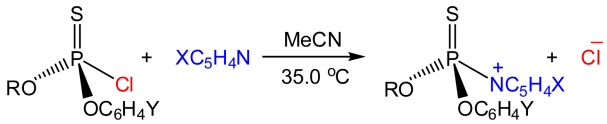
The nucleophilic substitution reactions of Y-aryl methyl (**8**) and Y-aryl propyl (**10**) chlorothiophosphates with X-pyridines are studied kinetically in acetonitrile at 35.0 ºC. The Hammett and Brönsted plots with X in the nucleophiles for both substrates exhibit biphasic concave upwards with a break region between X = 3-Me and H. The obtained values of the cross-interaction constants (ρ_{XY}) are negative with **8** while positive with **10** despite the same free energy correlations with X for both substrates. A stepwise mechanism with a rate-limiting bond formation is proposed with **8**, whereas a stepwise mechanism with a rate-limiting leaving group departure from the intermediate is proposed with **10** based on the sign of ρ_{XY}, negative and positive with **8** and **10**, respectively. A frontside nucleophilic attack is proposed with strongly basic pyridines based on the considerably great magnitudes of ρ_X and β_X values while a backside attack is proposed with weakly basic pyridines based on the relatively small magnitudes of ρ_X and β_X for both substrates.

Key Words : Biphasic free energy correlation, Thiophosphoryl transfer reaction, Pyridinolysis, Aryl methyl and propyl chlorothiophosphates

Introduction

It is generally known that the nonlinear free energy correlation of a concave upward plot is diagnostic of a change in the reaction mechanism, such as parallel reactions where the reaction path is changed depending on the substituents, while nonlinear free energy correlation of a 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.[1] The authors reported the pyridinolyses of the chlorothiophosphates [$(R_1O)(R_2O)P(=S)Cl$-type]: dimethyl [**1**: $R_1 = R_2 = Me$];[2a] methyl ethyl [**2**: $R_1 = Me$, $R_2 = Et$];[2b] diethyl [**3**: $R_1 = R_2 = Et$];[2a] ethyl propyl [**4**: $R_1 = Et$, $R_2 = Pr$];[2b] dipropyl [**5**: $R_1 = R_2 = Pr$];[2c] dibutyl [**6**: $R_1 = R_2 = Bu$];[2d] diisopropyl [**7**: $R_1 = R_2 = i$-Pr];[2e] Y-aryl ethyl [**9**: $R_1 = Et$, $R_2 = YC_6H_4$];[2f] and Y-aryl phenyl [**11**: $R_1 = Ph$, $R_2 = YC_6H_4$][2g] chlorothiophosphates. The biphasic concave upward free energy correlations for substituent X variations in the X-pyridines were observed for all the pyridinolyses of the chlorothiophosphates. These are rationalized by a change in the attacking direction of the nucleophiles from backside with weakly basic pyridines to frontside attack with strongly basic pyridines, based on the greater magnitudes of ρ_X and β_X values with strongly basic pyridines compared to those with weakly basic pyridines. To further our understanding of the thiophosphoryl transfer, as well as to obtain the information on the biphasic concave upward free energy correlations with X, here the nucleophilic substitution reactions of Y-aryl methyl (**8**) and Y-aryl propyl (**10**) chlorothiophosphates with X-pyridines have been carried out in acetonitrile (MeCN) at 35.0 ± 0.1 ºC (Scheme 1). The number of substrates follows the summation of the Taft steric constants of R_1 and R_2.[3]



R = Me (**8**), Pr (**10**)
X = 4-MeO, 4-Me, 3-Me, H, 3-Ph, 3-Ac, 4-Ac
Y = 4-MeO, 4-Me, H, 3-MeO, 4-Cl

Scheme 1. Pyridinolyses of Y-aryl methyl (**8**) and Y-aryl propyl (**10**) chlorothiophosphates in MeCN at 35.0 ºC.

Results and Discussion

Tables 1-3 list the second-order rate constants (k_2/M^{-1} s^{-1}), ρ_X and β_X with X, and ρ_Y with Y, respectively. The substituent X and Y effects in the nucleophiles and substrates, respectively, on the rates are in line with those for a typical nucleophilic substitution reaction with partial positive charge development at the nucleophilic N atom and with partial negative charge development at the reaction center P atom in the transition state (TS). The rates with **8** are somewhat faster than those with **10**. The Brönsted (Figs. 1 and 2 with **8** and **10**, respectively) and Hammett (Figs. S1 and S2 with **8** and **10**, respectively) plots for substituent X variations in the nucleophiles, however, exhibit discrete biphasic concave upwards with a break region between X = 3-Me and H for both substrates. The magnitudes of the ρ_X and β_X values with strongly basic pyridines (X = 4-MeO, 4-Me, 3-Me) are 2-3 times greater than those with weakly basic pyridines (X = H, 3-Ph, 3-Ac, 4-Ac) for both substrates. The Hammett plots (Figs. S3 and S4 with **8** and **10**, respectively) with Y in the substrates show linear. The magnitudes of the selectivity parameters (ρ_X, β_X and ρ_Y) of **8** are comparable with those

Table 1. Second-Order Rate Constants ($k_2 \times 10^4/M^{-1}\ s^{-1}$) of the Reactions of Y-Aryl Methyl (**8**) and Y-Aryl Propyl (**10**) Chlorothiophosphates with X-Pyridines in MeCN at 35.0 ºC

substrate	X \ Y	4-MeO	4-Me	H	3-MeO	4-Cl
8	4-MeO	311 ± 1	354 ± 1	410 ± 1	460 ± 1	625 ± 1
	4-Me	121 ± 1	148 ± 2	163 ± 1	189 ± 1	250 ± 1
	3-Me	50.9 ± 0.3	55.3 ± 0.2	62.6 ± 0.1	67.1 ± 0.4	85.6 ± 0.3
	H	6.65 ± 0.02	7.12 ± 0.01	8.35 ± 0.01	10.7 ± 0.1	14.4 ± 0.1
	3-Ph	5.52 ± 0.01	5.84 ± 0.02	6.78 ± 0.01	8.37 ± 0.02	12.2 ± 0.1
	3-Ac	1.68 ± 0.01	1.83 ± 0.02	1.98 ± 0.01	2.32 ± 0.01	3.14 ± 0.03
	4-Ac	1.14 ± 0.01	1.19 ± 0.03	1.39 ± 0.01	1.59 ± 0.03	2.09 ± 0.01
10	4-MeO	202 ± 1	245 ± 1	300 ± 1	321 ± 1	419 ± 1
	4-Me	76.6 ± 0.2	95.2 ± 0.3	123 ± 1	139 ± 1	193 ± 2
	3-Me	30.7 ± 0.2	40.9 ± 0.1	52.8 ± 0.1	63.1 ± 0.4	94.5 ± 0.2
	H	4.24 ± 0.01	5.48 ± 0.02	7.81 ± 0.01	8.86 ± 0.1	11.5 ± 0.1
	3-Ph	3.06 ± 0.01	3.95 ± 0.02	5.93 ± 0.02	7.26 ± 0.03	9.32 ± 0.1
	3-Ac	0.619 ± 0.002	0.958 ± 0.001	1.55 ± 0.01	1.95 ± 0.02	2.81 ± 0.01
	4-Ac	0.386 ± 0.001	0.534 ± 0.003	0.914 ± 0.001	1.25 ± 0.01	1.78 ± 0.01

of **10**. The magnitudes of the ρ_X values invariably decrease (*i.e.*, more negative value) as substituent Y in the substrates becomes more electron-withdrawing with **8**, whereas those invariably increase (*i.e.*, less negative value) as substituent Y becomes more electron-withdrawing with **10**. Meanwhile, the magnitudes of the ρ_Y values invariably decrease as the pyridine becomes less basic for both strongly (ρ_Y = 0.55 with X = 4-MeO to 0.41 with 3-Me) and weakly basic pyridines (ρ_Y = 0.65 with X = H to 0.50 with 4-Ac) with **8**, whereas those invariably increase for both strongly (ρ_Y = 0.58 with X = 4-MeO to 0.89 with 3-Me) and weakly basic pyridines (ρ_Y = 0.84 with X = H to 1.32 with 4-Ac) as the pyridine becomes less basic with **10**. It is worthy of note that the variation trends of ρ_X and ρ_Y values with **8** are opposite to those with **10** in spite of the same tendency of biphasic concave upward free energy correlations for both substrates (*vide infra*).

The cross-interaction constant (CIC; ρ_{XY}) is defined as Eqs. (1) and (2), where X and Y represent the substituents in the nucleophiles and substrates, respectively.[4] The ρ_{XY} has a negative value in a stepwise mechanism with a rate-limiting bond formation (and a concerted S_N2). In contrast, it has a positive value for a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate. The magnitude of ρ_{XY} is inversely proportional to the distance between X and Y through the reaction center.

$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \quad (1)$$

$$\rho_{XY} = \rho_X/\sigma_Y = \rho_Y/\sigma_X \quad (2)$$

The two ρ_{XY} values are obtained because the Hammett plots with X are biphasic for both substrates. Figs. 3 and 4

Table 2. ρ_X and β_X Values of the Reactions of Y-Aryl Methyl (**8**) and Y-Aryl Propyl (**10**) Chlorothiophosphates with X-Pyridines in MeCN at 35.0 ºC[a]

substrate	X	ρ_X, β_X\Y	4-MeO	4-Me	H	3-MeO	4-Cl
8	4-MeO~3-Me	$-\rho_X$	3.93 ± 0.01	4.03 ± 0.02	4.08 ± 0.01	4.18 ± 0.03	4.32 ± 0.03
		β_X	0.89 ± 0.01	0.92 ± 0.02	0.93 ± 0.01	0.95 ± 0.03	0.98 ± 0.03
	H~4-Ac	$-\rho_X$	1.55 ± 0.01	1.56 ± 0.01	1.59 ± 0.02	1.68 ± 0.02	1.73 ± 0.02
		β_X	0.29 ± 0.01	0.29 ± 0.01	0.29 ± 0.01	0.31 ± 0.01	0.32 ± 0.02
10	4-MeO~3-Me	$-\rho_X$	4.09 ± 0.01	3.89 ± 0.02	3.77 ± 0.01	3.53 ± 0.01	3.23 ± 0.01
		β_X	0.93 ± 0.01	0.88 ± 0.02	0.86 ± 0.01	0.80 ± 0.01	0.74 ± 0.01
	H~4-Ac	$-\rho_X$	2.10 ± 0.03	1.98 ± 0.02	1.85 ± 0.01	1.73 ± 0.01	1.62 ± 0.01
		β_X	0.39 ± 0.01	0.36 ± 0.02	0.34 ± 0.01	0.32 ± 0.01	0.30 ± 0.01

[a]Correlation coefficients (r) are better than 0.999 for both ρ_X and β_X.

Table 3. ρ_Y Values of the Reactions of Y-Aryl Methyl (**8**) and Y-Aryl Propyl (**10**) Chlorothiophosphates with X-Pyridines in MeCN at 35.0 ºC[a]

substrate	ρ_Y\X	4-MeO	4-Me	3-Me	H	3-Ph	3-Ac	4-Ac
8	ρ_Y	0.55 ± 0.03	0.56 ± 0.03	0.41 ± 0.03	0.65 ± 0.04	0.65 ± 0.05	0.49 ± 0.04	0.50 ± 0.03
10	ρ_Y	0.58 ± 0.02	0.75 ± 0.03	0.89 ± 0.04	0.84 ± 0.02	0.97 ± 0.01	1.26 ± 0.03	1.32 ± 0.01

[a]r ≥ 0.960 for ρ_Y.

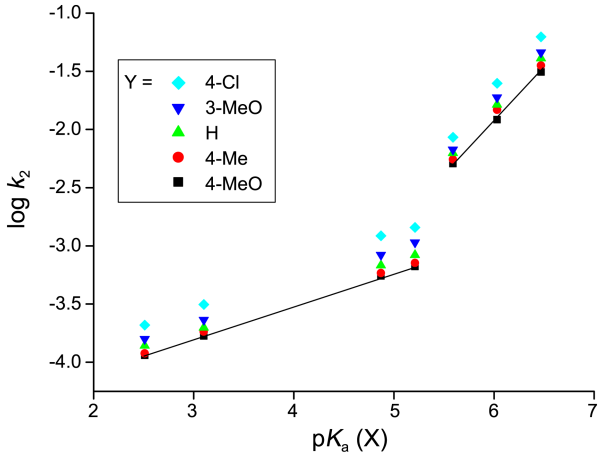


Figure 1. Brönsted plots with X of the reactions of Y-aryl methyl chlorothiophosphates (**8**) with X-pyridines in MeCN at 35.0 °C.

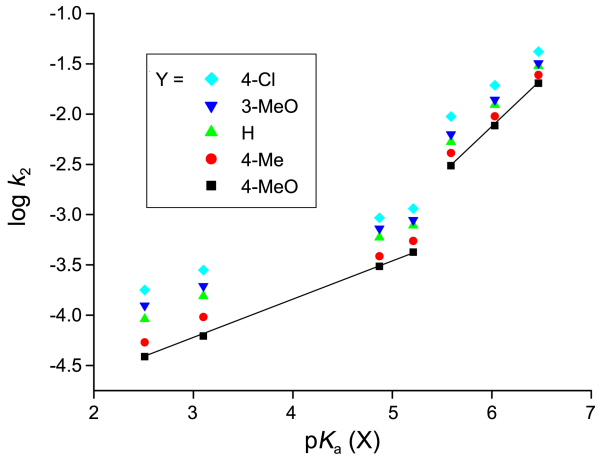


Figure 2. Brönsted plots with X of the reactions of Y-aryl propyl chlorothiophosphates (**10**) with X-pyridines in MeCN at 35.0 °C.

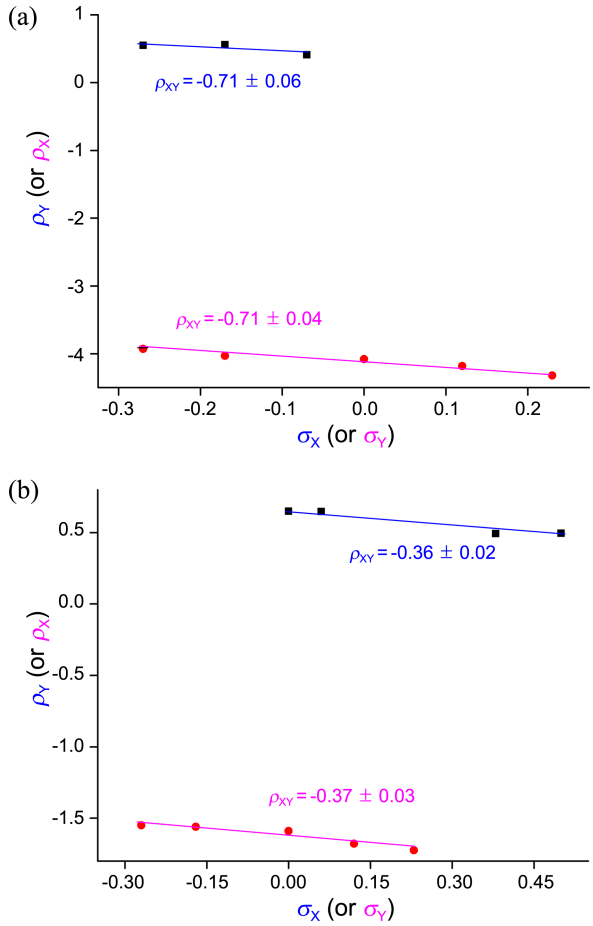


Figure 3. Plots of ρ_X *vs* σ_Y and ρ_Y *vs* σ_X of the reactions of Y-aryl methyl chlorothiophosphates (**8**) with X-pyridines in MeCN at 35.0 °C. The obtained ρ_{XY} values by multiple regression are: (a) ρ_{XY} = –0.71 ± 0.03 (r = 0.995) with strongly basic pyridines (X = 4-MeO, 4-Me, 3-Me); (b) ρ_{XY} = –0.36 ± 0.04 (r = 0.991) with weakly basic pyridines (X = H, 3-Ph, 3-Ac, 4-Ac).

show the plots of ρ_X *vs* σ_Y and ρ_Y *vs* σ_X to determine the ρ_{XY} values, according to Eq. (2). The signs of ρ_{XY} are negative with **8**, while positive with **10** for both strongly and weakly basic pyridines (*vide supra*). Accordingly, the authors propose the reaction mechanism as follows: (i) In **8**, a stepwise process with a rate-limiting bond formation (or a concerted process) for both strongly and weakly basic pyridines based on the negative signs of ρ_{XY}; (ii) In **10**, a stepwise process with a rate-limiting leaving group departure from the intermediate for both strongly and weakly basic pyridines based on the positive signs of ρ_{XY}. These indicate that: (i) the nonlinear free energy correlation of a concave upward plot is not always diagnostic of a change in the reaction mechanism; (ii) it is sometimes dangerous to clarify the mechanism based on the type of the free energy correlation; (iii) it is sometimes dangerous to suggest the mechanism based on the magnitudes of the selectivity parameters;[5] and finally (iv) the CIC is one of the strong tools to substantiate the reaction mechanism.

The magnitudes of the CICs with strongly basic pyridines (ρ_{XY} = –0.71 and 1.59 with **8** and **10**, respectively) are greater than those with weakly basic pyridines (ρ_{XY} = –0.36 and 0.94 with **8** and **10**, respectively) for both substrates, indicating that the interaction between X and Y with strongly basic pyridines is larger than that with weakly basic pyridines in the TS for both substrates. The magnitudes of the CICs with **10** are larger than those with **8** for both strongly and weakly basic pyridines, indicating that the interaction between X an Y in **10** is greater than that with **8** in the TS. These suggest that the distance between X and Y in **10** is shorter than that in **8**. In other words, the distance between the reaction center P atom and Y in **10** is shorter than that in **8**, taking into account the comparable magnitudes of β_X values for both **8** and **10**.[6] Regarding the greater magnitudes of the CICs and β_X values with strongly basic pyridines than those with weakly basic pyridines are substantiated by a frontside (equatorial) attack TSf and backside (apical) attack TSb, respectively (Scheme 2). It is well known that a weakly basic group has a greater apicophilicity so that apical approach is favored for such nucleophiles.[7] The apical nucleophilic attack should lead to a looser P–N bond in the TBP-5C structure because the apical bonds are longer than the equatorial bonds, and hence a smaller magnitude of ρ_{XY} as

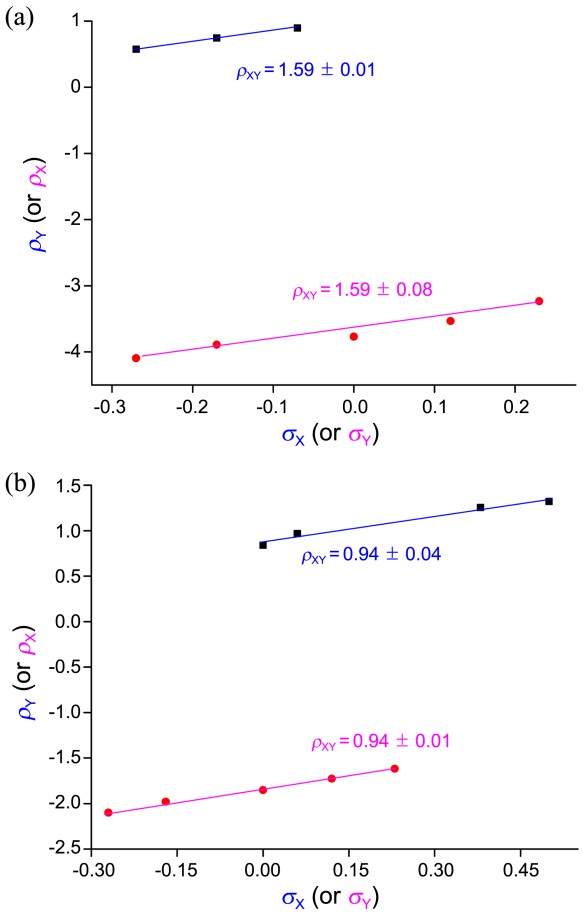
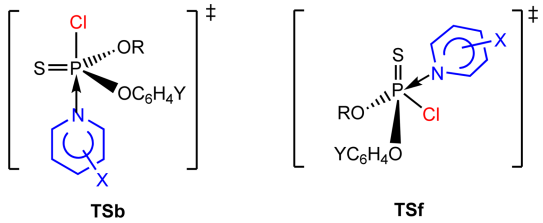


Figure 4. Plots of ρ_X *vs* σ_Y and ρ_Y *vs* σ_X of the reactions of Y-aryl propyl chlorothiophosphates (**10**) with X-pyridines in MeCN at 35.0 °C. The obtained ρ_{XY} values by multiple regression are: (a) ρ_{XY} = 1.59 ± 0.03 (r = 0.995) with strongly basic pyridines (X = 4-MeO, 4-Me, 3-Me); (b) ρ_{XY} = 0.94 ± 0.02 (r = 0.998) with weakly basic pyridines (X = H, 3-Ph, 3-Ac, 4-Ac).

well as β_X is obtained.

Table 4 summarizes the second-order rate constants with unsubstituted pyridine at 35.0 °C, natural bond order (NBO) charges at the reaction center P atom in the gas phase [B3LYP/6-311+G(d,p) level of theory],[9] summations of the steric constants [$\Sigma E_S = E_S(R_1) + E_S(R_2)$] of the two ligands,[3,10] β_X and ρ_{XY} for the pyridinolyses of **1-11** in MeCN. The substituent effects of X and Y on the pyridinolyses of chlorothiophosphates are really significant. As reported earlier, the pyridinolysis rates of the chlorothiophophates do not have linear correlations with NBO charges at the reaction center P atom in the substrates (or inductive effects of the two ligands) and also with the summations of steric constants (or the steric effects) of the two ligands.[11]



Scheme 2. Backside attack TSb and frontside attack TSf (R = MeO or PrO).[8]

Activation parameters, enthalpies and entropies of activation, for the pyridinolyses (with C_5H_5N) of **8** and **10** are summarized in Table 5. The enthalpies of activation are relatively small (7-8 kcal mol^{-1}) and entropies of activation are relatively large negative values (–45 to –49 cal mol^{-1} K^{-1}). The small value of activation enthalpy and large negative value of activation entropy are typical for the aminolyses (pyridinolyses or anilinolyses) of P=S (and P=O) systems regardless of the mechanism, concerted, stepwise with a rate-limiting bond making or stepwise with a rate-limiting bond breaking. Activation parameters for the pyridinolyses (with C_5H_5N) of **1-11** are summarized in Table R1.[12]

Experimental Section

Materials. Y-aryl methyl and propyl chlorothiophosphates (Y = 4-MeO, 4-Me, H, 3-MeO, 4-Cl) were prepared by the following two steps. In step 1, Y-aryl dichlorothiophosphates were prepared by reacting thiophosphoryl chloride with substituted phenol for 3 hr in the presence of triethylamine in methylene chloride on cooling bath at –10.0 °C with con-

Table 4. Summary of the Second-Order Rate Constants ($k_2 \times 10^3$/M^{-1} s^{-1}) at 35.0 °C, NBO Charges at the Reaction Center P Atom, Summations of the Steric Constants and Selectivity Parameters (β_X and ρ_{XY}) for the Reactions of **1-11** with X-Pyridines in MeCN

no	R_1O	R_2O	$k_2 \times 10^3$[a]	charge at P	$-\Sigma E_S$	β_X[e]	ρ_{XY}
1	MeO	MeO	1.54[c]	1.687	0	1.09/0.20	–
2	MeO	EtO	0.620	1.693	0.07	1.50/0.43	–
3	EtO	EtO	1.19[c]	1.701	0.14	1.02/0.29	–
4	EtO	PrO	0.609	1.700	0.43	1.44/0.36	–
5	PrO	PrO	1.16	1.702	0.72	1.08/0.31	–
6	BuO	BuO	1.01	1.703	0.78	1.26/0.31	–
7	*i*-PrO	*i*-PrO	0.460	1.723	0.94	0.99/0.15	–
8	MeO	YC_6H_4O	0.835[b]	1.686	2.48	0.89-0.98/0.29-0.32	–0.71/–0.36[e]
9	EtO	YC_6H_4O	0.137[b,d]	1.687	2.55	2.31-2.33/0.45-0.47	0/0/0/0[f]
10	PrO	YC_6H_4O	0.781[b]	1.687	2.84	0.74-0.93/0.30-0.39	1.59/0.94[e]
11	PhO	YC_6H_4O	0.333[b]	1.661	4.96	1.36-1.50/ 0.23-0.48	2.42/5.14/–1.02/–0.04[f]

[a]Value with X = H at 35.0 °C. [b]Value with Y = H. [c]Extrapolated value. [d]Empirical kinetic data. [e]Strongly/weakly basic pyridines. [f]Strong nucleophiles and weak electrophiles/weak nucleophiles and weak electrophiles/strong nucleophiles and strong electrophiles/weak nucleophiles and strong electrophiles.

Table 5. Activation parameters for the reactions of Y-aryl methyl (**8**) and Y-aryl propyl (**10**) chlorothiophosphates with C_5H_5N in MeCN

substrate	Y	t/°C	$k_2 \times 10^4$/M^{-1} s^{-1}	$\Delta H^{\ddagger}$/kcal mol^{-1}	$-\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
8	4-MeO	35.0	6.65 ± 0.02	8.0 ± 0.3	47 ± 1
		45.0	10.6 ± 0.1		
		55.0	15.7 ± 0.1		
	4-Me	35.0	7.12 ± 0.01	8.2 ± 0.4	46 ± 1
		45.0	11.6 ± 0.1		
		55.0	17.1 ± 0.1		
	H	35.0	8.35 ± 0.01	8.3 ± 0.1	46 ± 1
		45.0	13.3 ± 0.1		
		55.0	20.4 ± 0.1		
	3-MeO	35.0	10.7 ± 0.1	8.3 ± 0.1	45 ± 1
		45.0	16.8 ± 0.2		
		55.0	26.0 ± 0.3		
	4-Cl	35.0	14.4 ± 0.1	8.0 ± 0.1	46 ± 1
		45.0	22.3 ± 0.1		
		55.0	34.1 ± 0.1		
10	4-MeO	35.0	4.24 ± 0.01	7.9 ± 0.4	48 ± 1
		45.0	6.80 ± 0.01		
		55.0	9.91 ± 0.02		
	4-Me	35.0	5.48 ± 0.02	7.8 ± 0.2	48 ± 1
		45.0	8.62 ± 0.01		
		55.0	12.7 ± 0.3		
	H	35.0	7.81 ± 0.01	7.8 ± 0.3	47 ± 1
		45.0	12.4 ± 0.1		
		55.0	18.1 ± 0.1		
	3-MeO	35.0	8.86 ± 0.01	7.5 ± 0.1	48 ± 1
		45.0	13.4 ± 0.1		
		55.0	19.8 ± 0.1		
	4-Cl	35.0	11.5 ± 0.1	7.1 ± 0.4	49 ± 1
		45.0	16.7 ± 0.3		
		55.0	24.8 ± 0.2		

stant stirring. Triethylamine hydrochloride was separated by filtration. The filtrate was treated with water-$NaHCO_3$ and ether for work up after removal of solvent under reduced pressure. Ether extracted organic part was dried over anhydrous $MgSO_4$ for 6-8 h. The product mixture was isolated by filtration and finally separated through column chromatography (silica gel, ethyl acetate/*n*-hexane) and dried under reduced pressure using oil diffusion pump. In step 2, Y-aryl methyl and propyl chlorothiophophates were synthesized by reacting Y-aryl dichlorothiophosphates with methanol and propanol, respectively, for 3-4 h on cooling bath at –10.0 °C with constant stirring. The substrates were isolated in the similar way described in step 1 and were identified by TLC, ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR and GC-MS. The physical constants after column chromatography (silicagel/ethylacetate + *n*-hexane) were as follows (see Supporting Information):

(4-$CH_3OC_6H_4O$)(CH_3O)P(=S)Cl. Liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ and TMS) δ 3.80 (aliphatic, 3H, s), 3.97-4.02 (aliphatic, 3H, s), 6.87-6.90 (aromatic, 2H, d), 7.17-7.19 (aromatic, 2H, d); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 22.11, 55.60-56.02, 114.65-157.62; ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ 72.26 (PS, 1P, d, J = 16.4Hz); GC-MS (EI, m/z) 252 (M^+).

(4-$CH_3C_6H_4O$)(CH_3O)P(=S)Cl. Liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ and TMS) δ 2.35-2.36 (aliphatic, 3H, s), 3.98-4.02 (aliphatic, 3H, s), 7.15-7.19 (aromatic, 4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 20.83-56.00, 120.81-162.76; ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ 71.73 (PS, 1P, d, J = 15.2Hz); GC-MS (EI, m/z) 236(M^+).

(C_6H_5O)(CH_3O)P(=S)Cl. Liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ and TMS) δ 3.99-4.03 (aliphatic, 3H, s), 7.25-7.27 (aromatic, 3H, m), 7.37-7.39(aromatic, 2H, d); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 56.00, 121.12-150.24; ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ 71.19 (PS, 1P, d, J = 16.5Hz); GC-MS (EI, m/z) 222(M^+).

(3-$CH_3OC_6H_4O$)(CH_3O)P(=S)Cl. Liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ and TMS) δ 3.81 (aliphatic, 3H, s), 3.98-4.02 (aliphatic, 3H, s), 6.80-6.87 (aromatic, 3H, m), 7.25-7.27 (aromatic, 1H, t); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 55.74-56.27, 107.54-160.82; ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ 70.91 (PS, 1P, d, J = 15.9Hz); GC-MS (EI, m/z) 252 (M^+).

(4-ClC_6H_4O)(CH_3O)P(=S)Cl. Liquid; ^{1}H-NMR (400 MHz, MeCN-d_3) δ 4.00-4.01 (aliphatic, 3H, s), 7.28-7.30 (aromatic, 2H, d), 7.44-7.46 (aromatic, 2H, d); ^{13}C-NMR (100 MHz, MeCN-d_3) δ 55.80, 118.38-149.87; ^{31}P-NMR (162 MHz, MeCN-d_3) δ 76.74 (PS, 1P, d, J = 15.9 Hz); GC-MS (EI, m/z) 256(M^+).

(4-$CH_3OC_6H_4O$)(C_3H_7O)P(=S)Cl. Liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ and TMS) δ 1.01-1.05 (aliphatic, 3H, t), 1.81-1.84 (aliphatic, 2H, m), 3.80 (aliphatic, 3H, s), 4.21-4.29 (aliphatic, 2H, t), 6.87-6.89 (aromatic, 2H, d), 7.17-7.20 (aromatic, 2H, d); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 10.1, 23.2, 55.6, 72.2, 114.6, 122.1, 143.8, 157.5; ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ 70.7 (1P, PS); GC-MS (EI, m/z) 280 (M^+).

(4-$CH_3C_6H_4O$)(C_3H_7O)P(=S)Cl. Liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ and TMS) δ 0.98-1.05 (aliphatic, 3H, t), 1.81-1.85 (aliphatic, 2H, m), 2.35 (aliphatic, 3H, s), 4.26-4.32 (aliphatic, 2H, t), 7.15-7.17 (aromatic, 4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 10.0, 20.8, 23.2, 72.1, 120.8, 130.1, 135.9, 148.1; ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ 69.9 (1P, PS); GC-MS (EI, m/z) 264 (M^+).

(C_6H_5O)(C_3H_7O)P(=S)Cl. Liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ and TMS) δ 1.01-1.05 (aliphatic, 3H, t), 1.82-1.84 (aliphatic, 3H, m), 4.26-4.35 (aliphatic, 3H, t), 7.25-7.28 (aromatic, 2H, d), 7.36-7.39 (aromatic, 2H, d); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 10.2, 23.4, 72.4, 121.5, 126.4, 129.9, 157.0; ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ 69.4 (1P, PS); GC-MS (EI, m/z) 250 (M^+).

(3-$CH_3OC_6H_4O$)(C_3H_7O)P(=S)Cl. Liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ and TMS) δ 0.98-1.05 (aliphatic, 3H, t), 1.80-1.84 (aliphatic, 2H, m), 3.79-3.81 (aliphatic, 3H, s), 4.27-4.32 (aliphatic, 2H, t), 6.80-6.88 (aromatic, 3H, m), 7.25-7.28 (aromatic, 1H, t); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 10.3, 23.4, 55.7, 72.5, 107.6, 112.2, 113.5, 130.2, 148.8, 174.6; ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ 69.1 (1P, PS); GC-MS (EI, m/z) 280 (M^+).

(4-ClC$_6$H$_4$O)(C$_3$H$_7$O)P(=S)Cl. Liquid; ^{1}H-NMR (400 MHz, $CDCl_3$ and TMS) δ 1.01-1.05 (aliphatic, 3H, t), 1.81-1.85 (aliphatic, 2H, m), 4.28-4.32 (aliphatic, 2H, t), 7.20-7.23 (aromatic, 2H, d), 7.34-7.37 (aromatic, 2H, d); ^{13}C-NMR (100 MHz, $CDCl_3$ and TMS) δ 10.0, 23.2, 72.4, 122.7, 129.8, 131.8, 148.7; ^{31}P-NMR (162 MHz, $CDCl_3$ and TMS) δ 69.4 (1P, PS); GC-MS (EI, *m/z*) 285 (M^+).

Kinetic Procedure. The second-order rate constants and selectivity parameters were obtained as previously described.[1] Initial concentrations were as follows; [substrate] = 5×10^{-3} M and [XC_5H_4N] = (0.10-0.30) M for both substrates.

Product Analysis. Phenyl methyl and 4-methoxyphenyl propyl chlorothiophosphates were reacted with excess pyridine, respectively, for more than 15 half-lives in MeCN at 35.0 ºC. Solvent was removed under reduced pressure. The product was isolated by adding ether and insoluble fraction was collected. The product was purified to remove excess pyridine by washing several times with ether and MeCN. The product was isolated through column chromatography (30% ethyl acetate/n-hexane) and then dried under reduced pressure. Analytical and spectroscopic data of the products gave the following results (see Supporting Information):

[(MeO)(PhO)P(=S)NC$_5$H$_5$]$^+$Cl$^-$. White gummy solid; ^{1}H-NMR (400 MHz, MeCN-d_3) δ 4.36 (aliphatic, 3H, s), 7.81-7.85 (aromatic, 2H, t), 7.97-8.05 (aromatic, 2H, t), 8.32-8.38 (aromatic, 1H, t), 8.42-8.46 (aromatic, 1H, t), 8.71-8.73 (aromatic, 2H, d), 8.83-8.85 (aromatic, 2H, d); ^{13}C-NMR (100 MHz, MeCN-d_3) δ 49.3, 121.6, 121.7, 122.3, 122.4, 124.6, 127.6, 129.0, 130.0, 143.8, 146.3, 146.6; ^{31}P-NMR (162 MHz, MeCN-d_3) δ 51.1 (1P, s, P=S); LC-MS for $C_{12}H_{13}ClNO_2PS$ (EI, *m/z*), 301 (M^+).

[(4-CH$_3$OC$_6$H$_4$O, PrO)P(=S)NC$_5$H$_5$]$^+$Cl$^-$. Colorless liquid; ^{1}H-NMR (400 MHz, MeCN-d_3) δ 0.90-0.94 (aliphatic, 3H, t), 1.10-1.13 (aliphatic, 2H, m), 3.7-0-3.74 (aliphatic, 3H, s), 4.53-4.57 (aliphatic, 2H, t), 6.63-7.14 (aromatic, 2H, t), 7.61-7.71 (aromatic, 2H, t), 8.01-8.10 (aromatic, 1H, t), 8.15-8.20 (aromatic, 2H, t); ^{13}C-NMR (100 MHz, MeCN-d_3) δ 10.7, 25.5, 56.2, 64.0, 115.1, 115.5, 116.9, 118.4, 122.6, 123.3, 126.9, 129.4, 143.1, 145.6, 147.0; ^{31}P-NMR (162 MHz, MeCN-d_3) δ 5.49 (1P, s, P=S); LC-MS for $C_{15}H_{19}ClNO_3PS$ (EI, *m/z*), 359 (M^+).

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References and Notes

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5. Note that the magnitudes of the selectivity parameters (ρ_X, β_X and ρ_Y) of **8** are comparable with those of **10**.
6. The β_X value is dependent upon the degree of bond formation, *i.e.*, the distance between X and reaction center, while the ρ_{XY} value is dependent upon the distance between X, *via* reaction center and Y.
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8. The charge distributions between **8** and **10** in the TS should be different because a rate-limiting step is bond formation with **8** while bond breaking with **10**. The attacking direction of the nucleophile is only shown in the Scheme 2.
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10. '$\Sigma E_S = E_S(R_1) + E_S(R_2)$' is employed instead of '$\Sigma E_S = E_S(R_1O) + E_S(R_2O)$' because the data of $E_S(R_iO)$ is not available [$E_S(R)$ = 0(Me); –0.07(Et); –0.36(Pr); –0.39(Bu); –0.47(*i*-Pr); –2.48(Ph)].
11. Detailed discussion is described in ref. 2b.
12. **Table R1.** Activation Parameters for the Reactions of **1-11** with C_5H_5N in MeCN

substrate	$\Delta H^{\ddagger}$/kcal mol^{-1}	$-\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}	ref.
1: $(MeO)_2P(=S)Cl$	7.1	48	2a
2: (MeO)(EtO)P(=S)Cl	7.8	48	2b
3: $(EtO)_2P(=S)Cl$	6.0	53	2a
4: (EtO)(PrO)P(=S)Cl	5.9	54	2b
5: $(PrO)_2P(=S)Cl$	4.7	57	2c
6: $(BuO)_2P(=S)Cl$[b]	9.3	42	2d
7: $(i\text{-}PrO)_2P(=S)Cl$	15.2	25	2e
8: $(MeO)(YC_6H_4O)P(=S)Cl$	8.3[a]	46[a]	this work
9: $(EtO)(YC_6H_4O)P(=S)Cl$	5.9[a]	57[a]	2f
10: $(PrO)(YC_6H_4O)P(=S)Cl$	7.8[a]	47[a]	this work
11: $(PhO)(YC_6H_4O)P(=S)Cl$	6.4[a]	53[a]	2g

[a]Value with Y = H. [b]See ref. 2b; the enthalpy of activation is relatively large and entropy of activation is relatively small negative value.