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Kinetics and Mechanism of the Pyridinolysis of Aryl Phenyl Chlorothiophosphates in Acetonitrile

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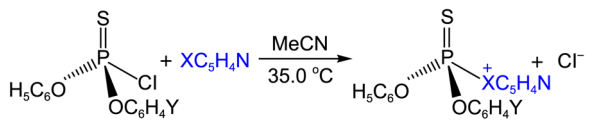
Kinetic studies for the reactions of Y-aryl phenyl chlorothiophosphates with X-pyridines have been carried out in acetonitrile at 35.0 ºC. The Hammett and Brönsted plots for substituent X variations in the nucleophiles are biphasic concave upwards with a break point at X = 3-Ph, while the Hammett plots for substituent Y variations in the substrates are biphasic concave downwards (and partially upwards) with a break point at Y = H. The signs and magnitudes of the cross-interaction constant (ρ_{XY}) are strongly dependent upon the nature of substituents, X and Y. The proposed mechanism is a stepwise process with a rate-limiting step change from bond breaking with the weaker electrophiles to bond formation with the stronger eletrophiles. The nonlinear free energy correlations of biphasic concave upward plots for substituent X variations in the nucleophiles are rationalized by a change in the attacking direction of the nucleophile from a backside with less basic pyridines to a frontside attack with more basic pyridines.

Key Words : Biphasic concave upward/downward free energy correlation, Phosphoryl transfer reaction, Pyridinolysis, Y-aryl phenyl chlorothiophosphates

Introduction

This lab reported various types (anilinolyses,[1] pyridinolyses,[2] and theoretical studies[3]) of phosphoryl and thiophosphoryl transfer reactions to clarify the mechanism and to gain the systematic information; the thio effects and steric effects of the two ligands (R_1 and R_2) on reactivity, electrophilicities of substrates, leaving group mobilities, substituent effects and deuterium kinetic isotope effects on mechanism. The authors' studies on the pyridinolyses are focused mainly on R_1R_2P(=O or S)Cl-type substrates involving the Cl leaving group in acetonitrile. Herein, the authors reported that the substituent effects of the nucleophiles (X) and/or substrates (Y) upon the pyridinolysis mechanism were more dramatic than those upon the anilinolysis mechanism.

Continuing the experimental studies on the phosphoryl transfer reactions, the kinetic studies of the reactions of Y-aryl phenyl chlorothiophosphates with X-pyridines in MeCN at 35.0 ± 0.1 ºC (Scheme 1) are reported to gain further information into the thiophosphoryl transfer reactions and the substituent effects of the nucleophiles and substrates on the reaction mechanism, as well as to compare with the reaction series of the pyridinolyses of R_1R_2P(=O or S)Cl-type substrates in MeCN.



X=4-MeO, 4-Me, H, 3-Ph, 3-Ac, 4-Ac
Y=4-MeO, 4-Me, H, 4-Cl, 3-Cl, 4-CN

Scheme 1. The studied reaction system.

Results and Discussion

The pseudo-first-order rate constants observed (k_{obsd}) for all reactions obey Eq. (1) with negligible k_0 (= 0) in MeCN. The second-order rate constants were determined with at least five pyridine concentrations [XC_5H_4N]. No third-order or higher-order terms were detected, and no complications were found in the determination of k_{obsd} or in the linear plot of Eq. (1). This suggests that there is no base-catalysis or noticeable side reactions, and the overall reaction follows the path given by Scheme 1.

$$k_{obsd} = k_0 + k_2[XC_5H_4N] \quad (1)$$

The second-order rate constants [k_2 (M^{-1} s^{-1})] are summarized in Table 1, together with selectivity parameters, ρ_X, β_X, ρ_Y, and ρ_{XY}. The β_X values were determined using pK_a values in water; the slopes from the plots of log k_2(MeCN) against pK_a(H_2O). Justification of this procedure has been experimentally and theoretically provided.[4] The substituent effects in the nucleophiles and substrates on the rates are in accord with those for a typical nucleophilic substitution reaction with positive charge development at the nucleophilic N atom ($\rho_X < 0$ and $\beta_X > 0$) and negative charge development at the reaction center P atom ($\rho_Y > 0$) in the transition state (TS). However, the Hammett (log k_2 *vs* σ_X) and Brönsted [log k_2 *vs* pK_a(X)] plots for substituent X variations in the nucleophiles are biphasic concave upwards with a break point at X = 3-Ph (Fig. 1), while the Hammett plots (log k_2 *vs* σ_Y) for substituent Y variations in the substrates are predominantly biphasic downwards with a break point at Y = H but slightly biphasic upwards for X = 4-MeO with a break point at Y = H (Fig. 2).

The magnitudes of ρ_X (= –6.62 to –7.31) and β_X (= 1.36-

Table 1. Second-Order Rate Constants ($k_2 \times 10^4$/M^{-1} s^{-1}) and Selectivity Parameters[a] of the Reactions of Y-Aryl Phenyl Chlorothiophosphates with X-Pyridines in MeCN at 35.0 °C

X \ Y	4-MeO	4-Me	H	4-Cl	3-Cl	4-CN	ρ_Y[b]	ρ_Y[c]
4-MeO	204	207	267	445	517	779	0.46 ± 0.03	0.69 ± 0.03
4-Me	25.0	27.2	37.0	42.9	44.0	51.0	0.65 ± 0.02	0.21 ± 0.01
H	1.65	1.66	3.33	4.24	4.31	5.05	1.20 ± 0.09	0.26 ± 0.02
3-Ph	0.832	0.847	1.66	1.77	1.87	2.46	1.18 ± 0.08	0.26 ± 0.03
3-Ac	0.0921	0.264	0.822	0.874	0.930	1.26	3.45 ± 0.09	0.28 ± 0.03
4-Ac	0.0570	0.161	0.440	0.456	0.460	0.627	3.21 ± 0.10	0.23 ± 0.04
$-\rho_X$[d,e]	7.23 ± 0.12	7.26 ± 0.11	6.62 ± 0.11	7.04 ± 0.16	7.15 ± 0.19	7.31 ± 0.24	ρ_{XY}[b,d,j] =	ρ_{XY}[c,d,k] =
β_X[d,f]	1.49 ± 0.13	1.50 ± 0.12	1.36 ± 0.12	1.45 ± 0.17	1.47 ± 0.20	1.50 ± 0.25	2.42 ± 0.11	–1.02 ± 0.15
$-\rho_X$[g,h]	2.72 ± 0.09	1.63 ± 0.01	1.24 ± 0.09	1.26 ± 0.10	1.29 ± 0.11	1.26 ± 0.11	ρ_{XY}[b,g,l] =	ρ_{XY}[c,g,m] =
β_X[g,i]	0.48 ± 0.16	0.29 ± 0.03	0.23 ± 0.06	0.23 ± 0.06	0.24 ± 0.07	0.23 ± 0.08	5.14 ± 0.09	–0.04 ± 0.08

[a]The σ values were taken from Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. The pK_a values were taken from (i) Fischer, A.; Galloway, W. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3591; (ii) Dean, J. A. *Handbook of Organic Chemistry*; McGraw-Hill: New York, 1987; Chapter 8. [b]Y = (4-MeO, 4-Me, H). Correlation coefficients, *r*, are better than 0.933. [c]Y = (H, 4-Cl, 3-Cl, 4-CN). $r \geq 0.891$. [d]X = (4-MeO, 4-Me, H, 3-Ph). [e]$r \geq 0.985$. [f]$r \geq 0.983$. [g]X = (3-Ph, 3-Ac, 4-Ac). [h]$r \geq 0.964$. [i]$r \geq 0.983$. [j]$r = 0.991$. [k]$r = 0.981$. [l]$r = 0.980$. [m]$r = 0.935$.

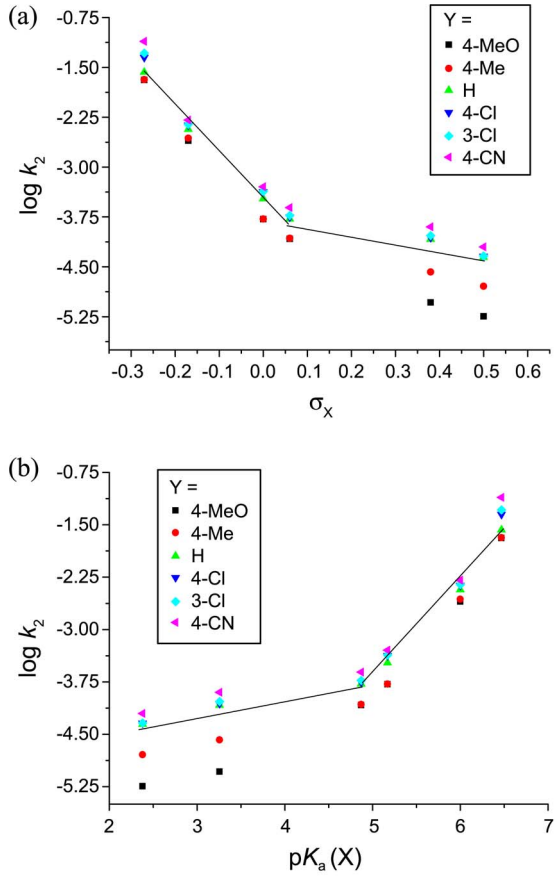


Figure 1. (a) The Hammett (log k_2 *vs* σ_X) and (b) Brönsted plots [log k_2 *vs* pK_a(X)] of the reactions of Y-aryl phenyl chlorothiophosphates with X-pyridines in MeCN at 35.0 °C.

1.50) values with more basic pyridines (X = 4-MeO, 4-Me, H, 3-Ph) are considerably greater than those (ρ_X = –1.24 to –2.72 and β_X = 0.23-0.48) with less basic pyridines (X = 3-Ph, 3-Ac, 4-Ac), indicating much greater degree of bond formation (or much greater positive charge development on the nucleophilic N atom) for more basic pyridines than for less basic pyridines (*vide infra*). The ρ_Y values for the

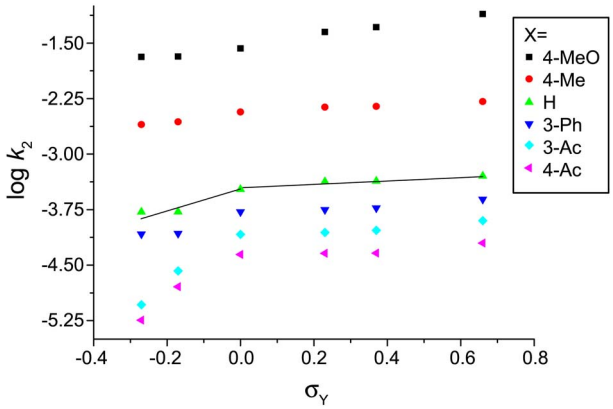


Figure 2. The Hammett plots (log k_2 *vs* σ_Y) of the reactions of Y-aryl phenyl chlorothiophosphates with X-pyridines in MeCN at 35.0 °C.

weaker electrophiles with electron-donating substituents Y (= 4-MeO, 4-Me, H) are significantly greater than those for the stronger electrophiles with electron-withdrawing substituents Y (= H, 4-Cl, 3-Cl, 4-CN) except X = 4-MeO, indicating the greater negative charge development on the P reaction center with the weaker electrophiles than with the stronger electrophiles.

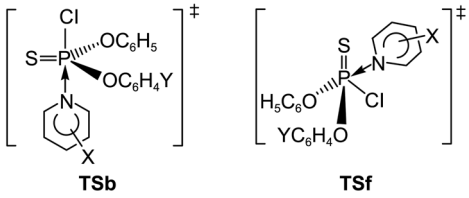
The cross-interaction constants (CICs; ρ_{XY}), Eqs. (2), are determined, where X and Y represent the substituents in the nucleophile and substrate, respectively.[5] The sign and magnitude of the CICs have made it possible to correctly interpret the reaction mechanism and degree of tightness of the TS, respectively. In general, 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.[5]

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

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

Since both Hammett plots for substituent X and Y variations are biphasic with a break point, four different values of ρ_{XY} are available: (i) ρ_{XY} = +2.42 (r = 0.991) for the stronger nucleophiles and weaker electrophiles; (ii) ρ_{XY} = +5.14 (r = 0.980) for the weaker nucleophiles and electrophiles; (iii) ρ_{XY} = –1.02 (r = 0.981) for the stronger nucleophiles and electrophiles; (iv) ρ_{XY} = –0.04 (r = 0.935) for the weaker nucleophiles and stronger electrophiles. All the ρ_{XY} values are calculated with twelve second-order rate constants,[6] and the correlation coefficients, r ($\leq$ 0.98), for (ii), (iii), and (iv) are not tolerable. However, the sign of ρ_{XY} values can be acceptable. In other words, the smaller magnitude of ρ_{XY} is expected for less basic pyridines than for more basic pyridines since the distance between X and Y for less basic pyridines is greater than that for more basic pyridines (*vide supra*). However, the obtained magnitudes of ρ_{XY} for the weaker electrophiles are not consistent with expectation from the β_X values [ρ_{XY} = 2.42 (more basic pyridines) < 5.14 (less basic pyridines)], while those for the stronger electrophiles are in line with expectation from the β_X values [ρ_{XY} = |–1.02| (more basic pyridines) > |–0.04| (less basic pyridines)].

The authors propose mechanism for the studied reaction system, divided into four blocks, on the basis of the sign of ρ_{XY} and magnitudes of ρ_X and β_X values as follows: (i) a stepwise mechanism with a rate-limiting leaving group departure from the intermediate involving a frontside attack TSf (Scheme 2) for more basic pyridines (X = 4-MeO, 4-Me, H, 3-Ph) and weaker electrophiles (Y = 4-MeO, 4-Me, H) based on the positive sign of ρ_{XY} and great magnitudes of ρ_{XY}, ρ_X, and β_X values; (ii) a stepwise mechanism with a rate-limiting leaving group departure from the intermediate involving a backside attack TSb (Scheme 2) for less basic pyridines (X = 3-Ph, 3-Ac, 4-Ac) and weaker electrophiles (Y = 4-MeO, 4-Me, H) based on the positive sign of ρ_{XY} small magnitude of ρ_X and β_X; (iii) a stepwise mechanism with a rate-limiting bond formation involving a frontside attack TSf for more basic pyridines (X = 4-MeO, 4-Me, H, 3-Ph) and stronger electrophiles (Y = H, 4-Cl, 3-Cl, 4-CN) based on the negative sign of ρ_{XY} and great magnitudes of ρ_X and β_X values; (iv) a stepwise mechanism with a rate-limiting bond formation involving a backside attack TSb for less basic pyridines (X = 3-Ph, 3-Ac, 4-Ac) and stronger electrophiles (Y = H, 4-Cl, 3-Cl, 4-CN) based on the negative sign of ρ_{XY} and small magnitudes of ρ_X and β_X values.



Scheme 2. Backside attack TSb and frontside attack TSf.

In the present work, the three atypical results are indicated regarding (i) the ρ_X (and β_X), (ii) ρ_Y values, and (iii) Cl leaving group. Firstly, the overall magnitudes of ρ_X and β_X values are predominantly dependent upon the attacking direction of the pyridine nucleophile, a backside or frontside, over the rate-determining step, bond formation or breaking. When the pyridine nucleophile attacks backside towards the Cl leaving group in the trigonal bipyramidal pentacoordinate (TBP-5C) TSb (Scheme 2), the nucleophile occupies the apical position. On the other hand, when the pyridine attacks frontside towards the Cl leaving group, the pyridine occupies the equatorial position in the TBP-5C TSf.[7] The apical bond length is greater than the equatorial one. As a result, the greater and smaller values of β_X for a frontside and backside attack are observed, respectively. Secondly, the relatively great values of ρ_Y with the weaker electrophiles suggest the tight TS; the great extent of the degree of bond formation and the small extent of the degree of bond breaking. In contrast, the relatively small values of ρ_Y with the stronger

Table 2. Summary of Summations of Inductive Effects of the Two Ligands ($\Sigma\sigma_I$), NBO Charges on the P Reaction Center, Second-Order Rate Constants ($k_2 \times 10^3$/M^{-1} s^{-1}) at 35.0 °C, and Selectivity Parameters for the Reactions of $R_1R_2P(=L)Cl$-type Substrates with X-pyridines in MeCN

L	R_1	R_2	$\Sigma\sigma_I$	charge on P	$k_2 \times 10^3$[a]	β_X	ρ_{XY}	ref.
S	Ph	YC_6H_4O	0.52	1.462	11.2[b]	0.87-0.95	–0.46	2f
S	Ph	Ph	0.24	1.236	1.83	1.53/0.38[d]	–	2d
S	MeO	MeO	0.60	1.687	1.54[c]	1.09/0.20[d]	–	2g
S	EtO	EtO	0.56	1.701	1.19[c]	1.02/0.29[d]	–	2g
S	Me	Me	–0.02	1.180	0.744	0.97/0.27[d]	–	2h
S	PhO	YC_6H_4O	0.80	1.661	0.333[b]	1.36-1.50/0.23-0.48[d]	+2.42/–1.02/+5.14/–0.04[e]	this work
O	Me	Me	–0.02	1.793	102,000[c]	0.17/–0.03[d]	–	2h
O	PhO	YC_6H_4O	0.80	2.230	266[b,c]	0.16-0.18	–0.15	2a
O	Et	Et	–0.02	1.817	127	0.45	–	2j
O	MeO	MeO	0.60	2.226	64.7	0.63	–	2g
O	Ph	Ph	0.24	1.844	54.6	0.68	–	2d
O	EtO	EtO	0.56	2.236	52.8	0.73	–	2g

[a]For the reactions with unsubstituted pyridine (X = H) at 35.0 °C. [b]For the reactions of unsubstituted substrate (Y = H). [c]Extrapolated values from the Arrhenius plots. [d]For more/less basic pyridines. [e]See the footnote in Table 1.

electrophiles suggest the late TS; the great extent of the degree of bond formation and breaking. Thirdly, the Cl leaving group is known as one of the good leaving groups, and the stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate is rare especially for phosphoryl transfer reactions.[8]

In general, the nonlinear free energy correlation of a concave upward plot is diagnostic of a change in the reaction mechanism where the reaction path is changed depending on the substituents, while nonlinear free energy correlation of the concave downward plot is diagnostic of a rate-limiting step change from bond breaking with the weakly basic nucleophiles to bond formation with the strongly basic nucleophiles.[9] In the present work, the nonlinear free energy correlations of biphasic concave downward plots for substituent Y variations in the substrates are ascribed to a rate-determining step change from bond breaking with the weaker electrophiles to bond formation with the stronger elctrophiles, and the nonlinear free energy correlations of biphasic concave upward plots for substituent X variations in the nucleophiles are ascribed to a change in the attacking direction of the nucleophile from a frontside attack (TSf) with more basic pyridines to a backside (TSb) with less basic pyridines.

Table 2 shows summations of inductive effects of the two ligands [$\Sigma\sigma_I = \sigma_I(R_1) + \sigma_I(R_2)$],[10] the natural bond order (NBO) charges [calculated at the B3LYP/6-311+G(d,p) level][11] on the reaction center P, second-order rate constants with unsubstituted pyridine at 35.0 °C, and selectivity parameters (β_X and ρ_{XY}) for the pyridinolyses of $R_1R_2P(=L)Cl$-type substrates in MeCN. The sequence of the row is the order of the second-order rate constant for the P=S and P=O systems, respectively. The authors proposed a normal S_N2 process for the pyridinolyses of $R_1R_2P(=L)Cl$-type substrates in MeCN except the present work, and the biphasic concave upward free energy correlations for substituent X variations are rationalized by the attacking direction change from a frontside with the strongly basic pyridines to a backside with the weakly basic pyridines. In general, the substituent X effects of P=S systems are more dramatic than those of P=O systems on reaction mechanism. In the P=S systems, only the pyridinolyses of *O*-aryl phenyl phosphonochloridothioate exhibit linear free energy correlation for substituent X variations. In contrast, only the pyridinolysis of dimethyl phosphinic chloride exhibit biphasic free energy correlation for substituent X variations in the P=O systems. The P=O systems are more reactive than their P=S counterparts for several reasons, the so-called 'thio effect' which is mainly the electronegativity difference between O and S that favors O over S.[12] The NBO charges on the P atom of P=O systems are greater (ca. 0.5-0.6) than those of their P=S counterparts, implying the electronegativity difference between O and S. The anilinolysis rate is predominantly dependent upon the steric effects of the two ligands, R_1 and R_2, i.e., the greater the size of the two ligands, the rate consistently becomes slower.[1] However, the pyridinolysis rate has no consistency with the steric effects of the two ligands, R_1 and R_2. Furthermore, the pyridinolysis rate has no consistency with the NBO charge on the reaction center P or $\Sigma\sigma_I$. The authors tentatively suggest that the pyridinolyses of $R_1R_2P(=L)Cl$-type substrates are not charge-controlled but orbital-controlled reactions, and further theoretical and experimental works are required to substantiate the major factor to play an important role in the pyridinolysis rates of $R_1R_2P(=L)Cl$-type substrates.

In summary, the reactions of Y-aryl phenyl chlorothiophosphates with X-pyridines are studied kinetically in MeCN at 35.0 °C. The Hammett and Brönsted plots for substituent X variations in the nucleophiles are biphasic concave upwards with a break point at X = 3-Ph, while the Hammett plots for substituent Y variations in the substrates are biphasic concave downwards with a break point at Y = H. The stepwise mechanism is proposed with a rate-limiting step change from bond breaking for the weaker electrophiles to bond formation for the stronger eletrophiles. Biphasic concave upward Hammett and Brönsted plots for substituent X variations in the nucleophiles are rationalized by a change in the nucleophilic attacking direction from frontside for the strongly basic pyridines to backside for the weakly basic pyridines.

Experimental Section

Materials. Aryl phenyl chlorothiophosphates were prepared as described previously.[1c] GR grade pyridines were used without further purification and all other materials were as reported previously.[1c,2]

Kinetic Procedure. Rates were measured conductometrically at 35.0 °C. The conductivity bridge used in this work 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 origin program with a large excess of pyridines, [Substrates] = 3×10^{-3} M and [Pyridine] = 0.10-0.22 M. Second-order rate constants, k_2, were obtained from the slope of a plot of k_{obsd} *vs.* [X-Pyridine] with at least five concentrations of pyridine. The k_2 values are the averages of more than three runs.

Product Analysis. Diphenyl chlorothiophosphate was reacted with excess 4-methoxypyridine, for more than 15 half-lives at 35.0 °C in MeCN. Acetonitrile 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. Analytical data of the products are as follows:

$(C_6H_5O)_2P(=S)N^+C_5H_4$-4-$CH_3OCl^-$: Yellowish solid; mp 92-94 °C; IR (nujol mull) 3173 (C-H, aromatic), 1643, 1619, 1592 (P-O-C_6H_4), 722 (P=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 7.2 Hz, 2H, pyridinium), 7.52 (t, J = 11.2 Hz, 4H, phenyl), 7.45 (t, J = 7.8 Hz, 4H, phenyl), 7.30 (d, J = 7.2 Hz, 2H, pyridinium), 7.25 (t, J = 7.2 Hz, 2H, phenyl), 4.17 (s, 3H, CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.85, 152.60, 143.40, 129.20, 123.70, 121.20, 111.95, 57.12 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 56.20 (s, 1P, P=S); Anal. Calcd. for $C_{18}H_{17}NO_3PSCl$: C, 54.90; H, 4.35; N, 3.56; S, 8.14.

Found: C, 55.15; H, 4.58; N, 3.60; S, 7.89.

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