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Kinetics and Mechanism of the Benzylaminolysis of *O,O*-Diphenyl *S*-Aryl Phosphorothioates in Dimethyl Sulfoxide

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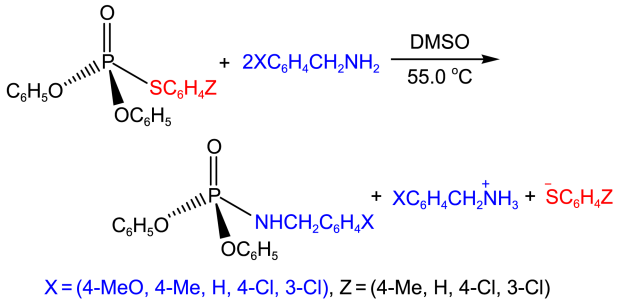
Kinetic studies of the reactions of *O,O*-diphenyl Z-*S*-aryl phosphorothioates with X-benzylamines have been carried out in dimethyl sulfoxide at 55.0 °C. The Hammett (log k_2 *vs* σ_X) and Brönsted [log k_2 *vs* pK_a(X)] plots for substituent X variations in the nucleophiles are biphasic concave downwards with a maximum point at X = H, and the unusual positive ρ_X and negative β_X values are obtained for the strongly basic benzylamines. The sign of the cross-interaction constant (ρ_{XZ}) is negative for both the strongly and weakly basic nucleophiles. Greater magnitude of ρ_{XZ} value is observed with the weakly basic nucleophiles ($\rho_{XZ} = -2.35$) compared to with the strongly basic nucleophiles ($\rho_{XZ} = -0.03$). The deuterium kinetic isotope effects (k_H/k_D) involving deuterated benzylamines [$XC_6H_4CH_2ND_2$] are primary normal ($k_H/k_D > 1$). The proposed mechanism is a concerted S_N2 involving a frontside nucleophilic attack with a hydrogen bonded, four-center-type transition state for both the strongly and weakly basic nucleophiles. The unusual positive ρ_X and negative β_X values with the strongly basic benzylamines are rationalized by through-space interaction between the π-clouds of the electron-rich phenyl ring of benzylamine and the phenyl ring of the leaving group thiophenoxide

Key Words : Phosphoryl transfer reaction, Benzylaminolysis, Deuterium kinetic isotope effect, Nonlinear bi-phasic free energy correlation

Introduction

In previous work, this lab reported the variety of phosphoryl and thiophosphoryl transfer reactions: anilinolyses,[1] pyridinolyses,[2] and theoretical studies.[3] The studied substrates were dominantly R_1R_2P(=O or S)Cl-type with the Cl leaving group in MeCN. Besides the Cl leaving group, the phenoxide (OC_6H_4Z; in MeCN and DMSO),[2b,1m] isothiocyanate (NCS; in MeCN),[2c] anilinide (NHC_6H_4Z; in DMSO),[2j] and thiophenoxide (SC_6H_4Z; in DMSO)[2e] leaving groups were employed to understand the leaving group mobility and leaving group effects on the reaction mechanism. The study on the benzylaminolysis for phosphoryl transfer reaction is the first time in this lab. The basicity of benzylamine [pK_a = 10.16 (DMSO), 16.76 (MeCN), 9.34 (H_2O)] is much greater (ΔpK_a = 4-7) than those of pyridine [pK_a = 3.45 (DMSO), 12.33 (MeCN), 5.17 (H_2O)] and aniline [pK_a = 3.82 (DMSO), 10.56 (MeCN), 4.58 (H_2O)].[4] The kinetic studies of the reactions of *O,O*-diphenyl Z-*S*-aryl phosphorothioates with X-benzylamines have been carried out in DMSO at 55.0 ± 0.1 °C (Scheme 1) to gain further information into the aminolysis mechanism and stereochemistry on the basis of the sign and magnitude of the cross-interaction constants (CICs) and deuterium kinetic isotope effects (DKIEs; k_H/k_D) involving deuterated benzylamines ($XC_6H_4CH_2ND_2$).



Scheme 1. The studied reaction system.

Results and Discussion

The pseudo-first-order rate constants observed (k_{obsd}) for all reactions obeyed eq. (1) with negligible k_0 (≈ 0) in DMSO. The clean second-order rate constants (k_2) obtained as the slope of the plot of k_{obsd} against at least five concentrations of benzylamine are summarized in Tables 1 together with selectivity parameters (ρ_X, β_X, ρ_Z, and ρ_{XZ}). The linear plots of eq. (1) suggest that there is no base-catalysis or noticeable side reactions and that the overall reaction is described by Scheme 1.

$$k_{obsd} = k_0 + k_2[XC_6H_4CH_2NH_2] \quad (1)$$

The Brönsted β_X values are obtained by correlating log k_2(DMSO) with pK_a(H_2O). The β_X values listed in Table 1 seem to be less reliable since the pK_a values used are not those determined in DMSO, but rather in water. Using the pK_a values for the anilinium ions determined in DMSO, an approximate straight line is obtained when they are plotted against those determined in water.[5] Spillane and coworkers reported that the β_X value for the reactions of *N*-phenyl sulfamoyl chloride ($PhNHSO_2Cl$) with X-anilines in DMSO is similar when determined using the pK_a values of anilines

Table 1. Second-Order Rate Constants ($k_2 \times 10^4$/$M^{-1}s^{-1}$) and Selectivity Parameters[a] of the Reactions of *O,O*-Diphenyl Z-*S*-Aryl Phosphorothioates with X-Benzylamines in DMSO at 55.0 °C

X \ Z	4-Me	H	4-Cl	3-Cl	ρ_Z[h]
4-MeO	1.40	2.03	5.22	8.03	1.46 ± 0.05
4-Me	1.46	2.08	5.61	8.51	1.49 ± 0.05
H	1.59	2.30	6.16	8.92	1.46 ± 0.05
4-Cl	0.494	0.734	1.30	1.74	1.02 ± 0.01
3-Cl	0.313	0.404	0.546	0.636	0.57 ± 0.01
$-\rho_X$[b,d]	–0.21 ± 0.01	–0.21 ± 0.01	–0.26 ± 0.01	–0.16 ± 0.01	ρ_{XZ}[b,i] =
β_X[b,e]	–0.36 ± 0.02	–0.34 ± 0.02	–0.49 ± 0.02	–0.33 ± 0.01	–0.03 ± 0.04
$-\rho_X$[c,f]	1.94 ± 0.06	2.05 ± 0.02	2.85 ± 0.02	3.10 ± 0.01	ρ_{XZ}[c,j] =
β_X[c,g]	1.93 ± 0.04	2.04 ± 0.01	2.84 ± 0.01	3.08 ± 0.03	–2.35 ± 0.03

[a]The σ values were taken from Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. The pK_a values of the X-benzylammonium ions in water were taken from Blackwell, L. F.; Fischer, A. Miller, I. J.; Topsom, R. D.; Vaughan, J. *J. Chem. Soc.* **1964**, 3588. [b]X = (4-MeO, 4-Me, H). [c]X = (H, 4-Cl, 3-Cl). [d]Correlation coefficients (r) are better than 0.978. [e]$r \geq 0.802$. [f]$r \geq 0.994$. [g]$r \geq 0.997$. [h]$r \geq 0.992$. [i]$r = 0.986$. [j]$r = 0.996$.

measured in water (β_X = 0.69) and DMSO (β_X = 0.62).[6] Accordingly, it may be inferred that the β_X values in Table 1 are considered to indicate the trends of changes with substituents, but not far from real values.

The second-order rate constant of the studied substrate with pyridine (C_5H_5N) was 1.10×10^{-2} in MeCN at 35.0 °C,[2e] while that with benzylamine ($C_6H_5CH_2NH_2$) is 2.30×10^{-4} $M^{-1}s^{-1}$ in DMSO at 55.0 °C. Taking into account (i) the greater basicity of benzylamine compared to pyridine (ΔpK_a = 4-7),[4] (ii) the greater polarity of DMSO compared to MeCN [$\Delta\varepsilon_r$(dielectric constant) = 46.45(DMSO) – 35.94 (MeCN) = 10.51], and (iii) the higher reaction temperature of benzylaminolysis compared to pyridinolysis (Δt = 20.0 °C), the benzylaminolysis rate should be much faster than the pyridinolysis rate. However, the obtained pyridinolysis rate is much faster than benzylaminolysis rate, completely contrary to the expectation. This means that another factor plays an important role to determine the reactivity of the aminolysis rate. The approach of the benzylamine nucleophile to the P reaction center should cause extensive steric hindrance when the attacking and leaving groups occupy apical positions in a trigonal bipyramidal pentacoordinate transition state (TBP-5C TS) of a backside attack, because of not only a relatively large size of the benzylamine nucleophile, but also the orientation restriction of the attacking benzylamine. The lone pair of the amino nitrogen is sp^3-type, thus the angle of C(α-carbon)-N(amino nitrogen)-P(reaction center of substrate) would be > 109.5° in the TS. The degree of steric hindrance would thus be greater as the ligands of R_1 and R_2 become bulkier in the TS. In contrast, the pyridine ring, located more or less parallel to the attacking axis in the TBP-5C TS, would experience much less steric congestion compared to the phenyl ring of the benzylamine. These statements also rationalize that the predominant factor to determine the anilinolysis rates of $R_1R_2P(=O)Cl$ in MeCN is the degree of steric hindrance of the two ligands over the electrophilicity of the P reaction center,[1d-m] while the steric effects of the two ligands are not major factor to determine the pyridinolysis rate.[2d,f-i,k,l] The degree of steric hindrance would thus be much greater as the ligands of R_1 and R_2 become bulkier for benzylaminolysis. Consequently, in the studied reaction system, much slower rate of benzylaminolysis compared to pyridinolysis is attributed to the steric effects of the two large phenoxy ligands, $(C_6H_5O)_2$. To avoid the great steric effects of the two large ligands, a frontside attack could compete with a backside attack and/or be an alternative reaction path instead of a backside attack as observed in the anilinolyses.[1c-f,h,k]

The Hammett (Fig. 1; log k_2 *vs* σ_X) and Brönsted [Fig. 2; log k_2 *vs* pK_a(X)] plots for substituent X variations in the nucleophiles are biphasic concave downwards with a maximum point at X = H. Thus, the unusual positive ρ_X and negative β_X values are obtained for the strongly basic benzylamines. These results suggest an atypical nucleophilic substitution reaction with negative charge development at the nucleophilic nitrogen atom in the TS. The Hammett (Fig. 3; log k_2 *vs* σ_Z) plots for substituent Z variations in the leaving groups show linear free energy correlations. The rate increases with a more electron-withdrawing substituent Z in the leaving groups, which is consistent with a typical nucleophilic substitution reaction with negative charge develop-

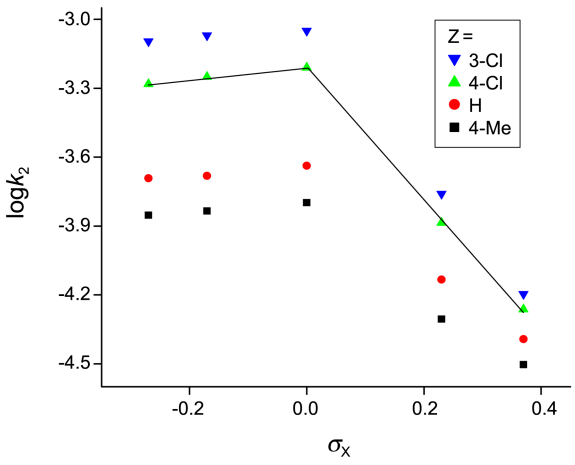


Figure 1. The Hammett (log k_2 *vs* σ_X) plots of the reactions of *O,O*-diphenyl Z-*S*-aryl phosphorothioates with X-benzylamines in DMSO at 55.0 °C.

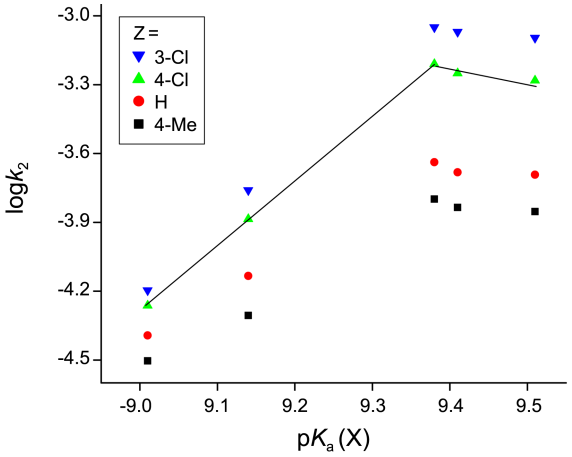


Figure 2. The Brönsted plots [log k_2 *vs* pK_a(X)] of the reactions of *O,O*-diphenyl Z-*S*-aryl phosphorothioates with X-benzylamines in DMSO at 55.0 °C.

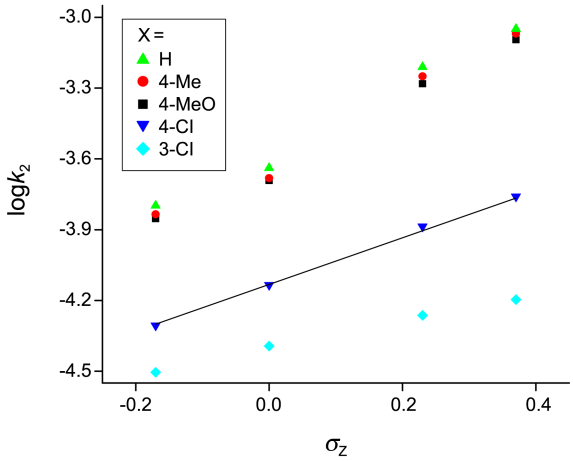


Figure 3. The Hammett plots (log k_2 *vs* σ_Z) of the reactions of *O,O*-diphenyl Z-*S*-aryl phosphorothioates with X-benzylamines in DMSO at 55.0 °C.

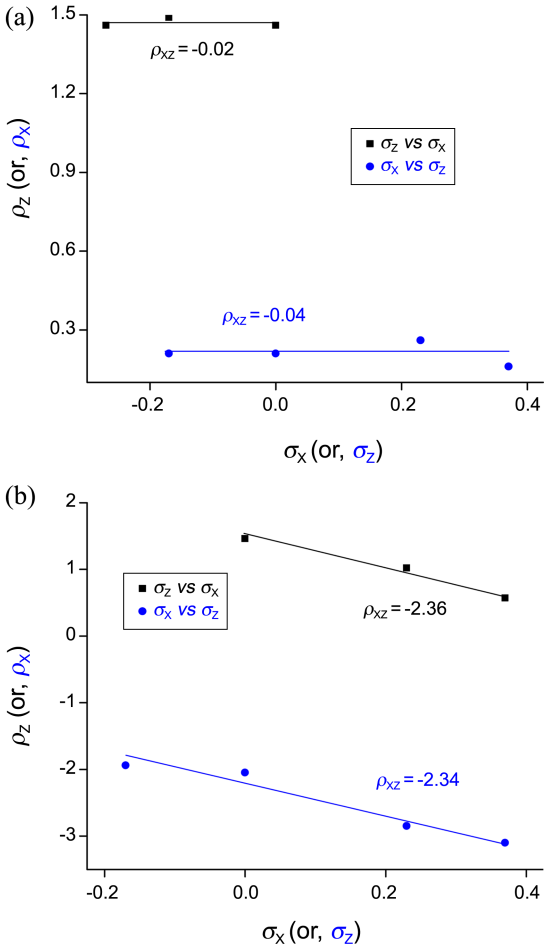


Figure 4. Determination of ρ_{XZ} (= $\partial\rho_X/\partial\sigma_Z = \partial\rho_Z/\partial\sigma_X$) by plotting ρ_Z (or ρ_X) against σ_X (or σ_Z) for the reactions of *O,O*-diphenyl Z-*S*-aryl phosphorothioates with X-benzylamines in DMSO at 55.0 °C. The obtained ρ_{XZ} values by multiple regressions are: (a) ρ_{XZ} = –0.03 ± 0.04 (r = 0.986) for the strongly basic benzylamines (X = 4-MeO, 4-Me, H) and (b) ρ_{XZ} = –2.35 ± 0.03 (r = 0.996) for the weakly basic benzylamines (X = H, 4-Cl, 3-Cl).

ment at the thiophenoxy sulfur atom in the TS.

The CICs (ρ_{XZ}) are determined, where X and Z represent the substituents in the nucleophile and leaving group, respectively (eqs. 2).[7] According to eq. (2b), the ρ_{XZ} values can be obtained from the slopes of the plots of ρ_X *vs* σ_Z and ρ_Z *vs* σ_X for the strongly (Fig. 4(a); X = 4-MeO, 4-Me, H) and weakly basic nucleophiles (Fig. 4(b); X = H, 4-Cl, 3-Cl), respectively. 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_{XZ} has a negative value (or sometimes a small positive value) in a concerted S_N2 and a stepwise mechanism with a rate-limiting bond formation. However, it has a positive value for a stepwise mechanism with a rate-limiting leaving group departure from the intermediate. The magnitude of ρ_{XZ} is inversely proportional to the distance between the nucleophile and leaving group in the TS.[7]

$$\log (k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z \quad (2a)$$

$$\rho_{XZ} = \rho_X/\sigma_Z = \rho_Z/\sigma_X \quad (2b)$$

The negative sign of ρ_{XZ} values suggests that the reaction proceeds through S_N2 mechanism, regardless of the nature of the substituents, electron-donating or -withdrawing. At a glance, the interaction between X and Z seems to be much greater with the weakly basic nucleophiles (X = H, 4-Cl, 3-Cl) compared to with the strongly basic nucleophiles (X = 4-MeO, 4-Me, H) considering the magnitude of ρ_{XZ} = –2.35 for the weakly basic nucleophiles and ρ_{XZ} = –0.03 for the strongly basic nucleophiles. On the contrary, however, the interaction between X and Z for the strongly basic benzylamines is really much greater than for the weakly basic benzylamines since the unusual positive ρ_X values are ascribed to the strong interaction between X and Z (*vide infra*). The large magnitudes of ρ_{XZ} (= –2.35) and positive ρ_X values imply that the nucleophile and leaving group are in close enough proximity to interact strongly. This is in agreement with the TS involving a frontside nucleophilic attack. The large magnitudes of the ρ_{XZ} values ($|\rho_{XZ}| \geq 0.5$)[8a] were obtained due to the frontside nucleophilic attack as follows: (i) the reactions of aryl bis(4-methoxyphenyl)

phosphates with the weakly basic pyridines in MeCN (ρ_{XZ} = –1.98);[2b] (ii) the anilinolysis of anilino thioethers in MeOH (ρ_{XZ} = –1.70);[8a] (iii) the pyridinolysis of *Z*-*N*-aryl-*P,P*-diphenyl phosphinic amides in DMSO with poor leaving groups (ρ_{XZ} = –1.54);[2j] (iv) the benzylaminolysis of *Z*-aryl cyclopropane carboxylates in MeCN (ρ_{XZ} = +1.06);[8b] (v) the benzylaminolysis of *Z*-aryl 2-furoates in MeCN (ρ_{XZ} = +1.19);[8c] (vi) the benzylaminolysis of *Z*-thiophenyl acetates in MeCN (ρ_{XZ} = +0.90).[8d] (vii) the anilinolysis of cumyl arenesulfonates in MeCN (ρ_{XZ} = –0.75);[8e] (viii) the anilinolysis of 1-phenylethyl arenesulfonates in MeOH (ρ_{XZ} = –0.56);[8f] (iv) the anilinolysis of 2-phenylethyl arenesulfonates in MeOH (ρ_{XZ} = –0.45).[8g]

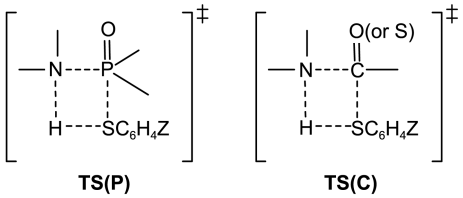
The DKIEs can be only secondary inverse ($k_H/k_D < 1$) in a normal S_N2 reaction, since the NH(D) vibrational frequencies invariably increase upon going to the TS, given the increase in steric hindrance in the bond formation step; the greater the bond formation, the greater the steric congestion occurs, and the smaller the k_H/k_D value becomes.[9] In contrast, when partial deprotonation of the benzylamine occurs in a rate-limiting step by hydrogen bonding, the DKIEs are primary normal ($k_H/k_D > 1$); the greater the extent of the hydrogen bond that occurs, the greater the k_H/k_D value becomes.[10] The DKIEs, k_H/k_D, involving deuterated benzylamines are summarized in Table 2. In the present work, the obtained primary normal DKIEs (k_H/k_D = 1.02-2.28 > 1) imply the partial deprotonation of the benzylamine, i.e., hydrogen bonding, in the TS. The real primary normal DKIE due to the hydrogen bond should be greater than the observed value, since the other hydrogen (deuterium) atom in the N-H(D) moiety, not involved in the hydrogen bond, yields the secondary inverse DKIE ($k_H/k_D < 1$) due to the steric congestion.

The authors herein propose the reaction mechanism for both the strongly and weakly basic benzylamines: (i) a concerted S_N2 mechanism on the basis of the negative sign of ρ_{XZ}; (ii) involving a frontside nucleophilic attack on the basis of the positive sign of ρ_X with the strongly basic benzylamines and great magnitude of ρ_{XZ} with the weakly basic benzylamines; (iii) with a hydrogen bonded, four-center-type TS(P) on the basis of the primary normal DKIEs. A hydrogen bonded, four-center-type TS(C) was reported for the benzylaminolyses[11] and anilinolyses[12] of various substrates containing carbonyl (and thiocarbonyl) carbon reaction center on the basis of the primary normal DKIEs.

Table 2. Deuterium Kinetic Isotope Effects (k_H/k_D) of the Reactions of *O,O*-Diphenyl *Z*-*S*-Aryl Phosphorothioates with X-Benzylamines in DMSO at 55.0 °C

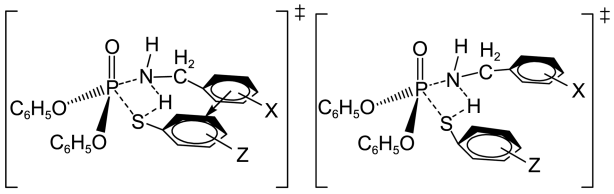
X	Z	$k_H \times 10^4/M^{-1}\ s^{-1}$	$k_D \times 10^4/M^{-1}\ s^{-1}$	k_H/k_D
4-MeO	H	2.03 ± 0.01	1.44 ± 0.01	1.41 ± 0.01[a]
H	H	2.30 ± 0.01	1.01 ± 0.01	2.28 ± 0.01
4-Cl	H	0.734 ± 0.012	0.719 ± 0.009	1.02 ± 0.02

[a]Standard error {= $1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}$} from Crumpler, T. B.; Yoh, J. H. *Chemical Computations and Errors*; John Wiley: New York, 1940; p 178.



Hydrogen bonded, four-center-type TS

As discussed, the studied reaction proceeds through a concerted process involving a frontside attack with hydrogen bonded four-center-type TS(P) for both the strongly and weakly basic benzylamines. However, the ρ_X values are unusual positive with the strongly basic benzylamines while normal negative with the weakly basic benzylamines. In the case of the strongly basic benzylamines (X = 4-MeO, 4-Me, H), the π-cloud of the phenyl ring of the 'electron-rich' benzylamine interacts strongly with the π-cloud of the phenyl ring of the leaving group thiophenoxide in the adjacent position by through-space interaction in the TS I (*vide supra*). As a result, the nucleophilic N atom of benzylamine becomes more positive in the TS than in the ground state due to the π-electron transfer from the nucleophile to the leaving group by strong through-space interaction, and the positive ρ_X and negative β_X values are obtained. In the case of the weakly basic benzylamines (X = H, 4-Cl, 3-Cl), TS II is proposed in which the through-space interaction between the two phenyl rings is little since the substituent X is electron-withdrawing, and normal negative ρ_X and positive β_X values are obtained.



Experimental Section

Materials. The substrates were prepared as described previously.[2e] GR grade dimethyl sulfoxide was dried over 4 Å molecular sieve and then used after three distillations under reduced pressure. The X-benzylamine nucleophiles, GR grade, were used after recrystallization (4-methylbenzylamine; mp 12-13 °C, recrystallized in ice bath) or distillation. For preparation of deuterated benzylamine, X-benzylamines (2 g) were taken with 15 mL ethyl ether and 10 mL of D_2O. The mixture was stirring for 24 hrs at room temperature. The deuterated benzylamines were isolated with ether and dried over anhydrous $MgSO_4$. Finally, X-benzylamines were isolated by solvent evaporation under reduced pressure and identified by ^{1}H-NMR.

Kinetic Procedure. Rates were measured conductometrically at 55.0 °C using a computer controlled conductivity bridge constructed in this lab. Pseudo-first-order rate constants, k_{obsd}, were measured by using curve-fitting method in

ORIGIN program. Pseudo-first-order rate constants were determined with large excess of benzylamine; [Substrate] = 5×10^{-3} M and [X-BnA] = 0.10-0.25 M. Pseudo-first-order rate constants were reproducible within ± 3%.

Product Analysis. Diphenyl 3-chloro-*S*-phenyl and 4-methyl-*S*-phenyl phosphorothioate (0.05 M) were reacted with 4-methoxybenzylamine and 4-chlorobenzylamine (0.5 M), respectively, in DMSO at 55.0 °C. After more than 15 half-lives, product was isolated by solvent extraction process using ethylacetate (50 mL) and water (5 mL) mixture. Product and other reactants were isolated from ethylacetate fraction. Finally the product was isolated by column chromatography using 20% ethylacetate/*n*-hexane. Analytical data of the products gave the following results:

$(C_6H_5O)_2P(=O)NHCH_2C_6H_4(4\text{-}OCH_3)$: Brown solid (silica gel, 20% ethylacetate/*n*-hexane); mp 58-60 °C.; Anal. Found: C, 75.8; H, 7.2; N, 11.2. Calcd. for $C_{16}H_{18}N_2O$; C, 75.56; H, 7.13; N, 11.02. ^{1}H NMR (200 MHz, $CDCl_3$), δ 3.2 (s, 1H), 3.786 (s, 3H), 4.173-4.253 (q, 2H), 6.790-7.378 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 113.948-159.045 (C=C, aromatic, 18C, s/m), 55.274 (CH_2, 1C, m), 45.222 (OCH_3, 1C, m); ^{31}P NMR (162 MHz, $CDCl_3$), δ 3.892 (1P, s); ν_{max} (nujol mull), 3267 (N-H, str. amide), 3067 (C-H, str. aromatic [along with aliphatic region merged with nujol transmittance]), 1510, 1470, 1203 (P-O-Ph), 1247 (P=O str.); *m/z* 369 (M^+).

$(C_6H_5O)_2P(=O)NHCH_2C_6H_4(4\text{-}Cl)$: Brown jelly (silica gel, 20% ethylacetate/*n*-hexane); Anal. Found: C, 58.4; H, 5.1; N, 5.4. Calcd. for $C_{19}H_{17}NPO_3Cl$; C, 61.1; H, 4.6; N, 3.8. ^{1}H NMR (200 MHz, $CDCl_3$), δ 3.4 (s, 1H), 3.839 (s, 2H) 7.224-7.301 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 113.848-169.039 (C=C, aromatic, 18C, s/m), 45.651 (CH_2, 1C, m); ^{31}P NMR (162 MHz, $CDCl_3$), δ 3.845 (1P, s); ν_{max} (nujol mull), 3277 (N-H, str. amide), 3180 (C-H, str. aromatic), 1495, 1200 (P-O-Ph), 1251 (P=O str.).

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