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Nucleophilic Substitution Reactions of Aryl Dithioacetates with Pyridines in Acetonitrile

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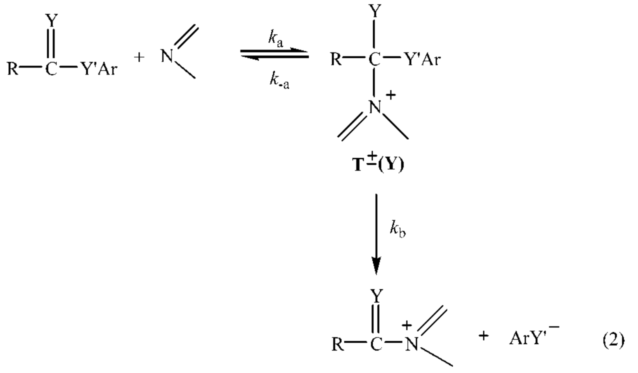
Kinetic studies of the pyridinolysis (XC_5H_4N) of aryl dithioacetates ($CH_3C(=S)SC_6H_4Z$) are carried out in acetonitrile at 60.0 °C. A biphasic Brönsted plot is obtained with a change in slope from a large value ($\beta_X \cong 0.9$) to a small value ($\beta_X \cong 0.4$) at $pK_a° = 5.2$, which is attributed to a change in the rate-limiting step from breakdown to formation of a zwitterionic tetrahedral intermediate, $T^{\pm}$, in the reaction path as the basicity of the pyridine nucleophile increases. A clear-cut change in the cross-interaction constants ρ_{XZ} from a large positive value ($\rho_{XZ} = +1.34$) to a small negative value ($\rho_{XZ} = -0.15$) supports the mechanistic change proposed.

Introduction

The aminolysis of carbonyl and thiocarbonyl esters has been a subject of considerable interest in mechanistic as well as synthetic organic chemistry.[1] In most of these reactions, involvement of a zwitterionic tetrahedral adduct has been postulated either as a transition state (TS) or as an intermediate, $T^{\pm}$.[1] Thiocarbonyl esters are more likely to react through a tetrahedral intermediate mainly because of the lower $\pi^*_{C=S}$ orbital than the $\pi^*_{C=O}$ level.[1c,2] For example, the $\pi^*_{C=S}$ level is lower by ca. 0.071 au (1.9 eV) than $\pi^*_{C=O}$ in $CH_3C(=Y)Cl$ at the RHF/6-31+G*//B3LYP/6-31+G* level.[2] The much lower $\pi^*_{C=S}$ level leads to a much more stabilized adduct ($T^{\pm}$) formation due to a greater charge transfer from the nucleophile (lone pair (*n*) of amine), as estimated by the second-order perturbation energy, $\Delta E^{(2)}{}_{n-\pi^*}$ in eq 1.[3]

$$\Delta E^{(2)}{}_{n-\pi^*} = -\frac{2F_{\pi^* n}}{\epsilon_{\pi^*} - \epsilon_n} \tag{1}$$

Experimentally, it has been pointed out time and again by Castro that substitution of Y = O by Y = S in $T^{\pm}(Y)$ (eq 2) decreases both k_{-a} and k_b with a greater decrease of k_{-a} than k_b for a given amine resulting in kinetic stability of $T^{\pm}(S)$.[1c,4] One of the consequences of this increased $T^{\pm}(S)$ stability with a greater decrease of k_{-a} than k_b is that the center of curvature at the $pK_a°$ (where $k_{-a} = k_b$) in the biphasic Brönsted-type plots occurs at a lower pK_a than that with Y = O.



In this work, we carried out kinetic studies of the pyridinolysis of aryl dithioacetates in acetonitrile, R = CH_3, Y = Y′= S, and amine = pyridine in eq 2, to elucidate the mechanism. We especially wanted to show that (i) the breakpoint, $pK_a°$, in biphasic Brönsted plots is at a much lower pK_a than that in the corresponding reactions of carbonyl (Y = O) esters and that (ii) there is a change in the sign and magnitude of the cross-interaction constant ρ_{XZ} in eqs 3a and 3b,[5] where X and Z represent substituents in the nucleophile and leaving group, respectively.

$$\log(k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z \tag{3a}$$

$$\rho_{XZ} = \partial\rho_X/\partial\sigma_Z = \partial\rho_Z/\partial\sigma_X \tag{3b}$$

Results and Discussion

The rate law obtained in the present reactions is given by eqs 4 and 5, where ArS^- is the leaving group, k_{obs} is the pseudo-first-order rate constant, k_0 and k_N are the rate constants for solvolysis and pyridinolysis of the

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[1] (a) Page, M. I.; Williams, A. *Organic and Bio-organic Mechanisms*; Longman: Harlow, 1997; Chapter 7. (b) Williams, A. *Concerted Organic and Bio-organic Mechanisms*; CRC Press: Boca Raton, 2000; Chapter 4. (c) Castro, E. A. *Chem. Rev.* **1999**, *99*, 3505.

[2] Lee, I.; Kim, C. K.; Li, H. G.; Sohn, C. K.; Kim, C. K.; Lee, H. W.; Lee, B.-S. *J. Am. Chem. Soc.* **2000**, *122*, 11162.

[3] (a) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899. (b) Epiotis, N. D.; Cherry, W. R.; Shaik, S.; Yates, R. L.; Bernardi, F. *Structural Theory of Organic Chemistry*; Springer-Verlag: Berlin, 1977; Chapter 4.

[4] (a) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 3501. (b) Castro, E. A.; Araneda, C. A.; Santos, J. G. *J. Org. Chem.* **1997**, *62*, 126. (c) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1999**, *64*, 6342.

[5] (a) Lee, I. *Chem. Soc. Rev.* **1990**, *19*, 317. (b) Lee, I. *Adv. Phys. Org. Chem.* **1992**, *27*, 57. (c) Lee, I.; Lee, H. W. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1529.

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Table 1. Second-Order Rate Constants, k_N ($\times 10^4$ M^{-1} s^{-1}), and Selectivity Parameters,[a] ρ_X, ρ_Z, ρ_{XZ}, and β_X, for the Reactions of Z-Phenyl Dithioacetates with X-Pyridines in Acetonitrile at 60.0 °C

		Z				
X	pK_a	4-CH_3	H	4-Cl	4-Br	ρ_Z[h]
4-CH_3O	6.47	44.9	158	375	495	2.37 ± 0.29
4-CH_3	6.00	36.6	118	291	387	2.34 ± 0.25
3-CH_3	5.68	25.3	91.5	205	291	2.37 ± 0.33
4-$C_6H_5CH_2$	5.59	21.5	79.3	192	238	2.40 ± 0.29
H	5.17	15.5	50.8	122	155	2.29 ± 0.25
3-C_6H_5	4.87	6.51	20.8	51.2	74.0	2.38 ± 0.29
3-CH_3CO	3.26	0.157	0.517	1.51	2.00	2.56 ± 0.22
3-Cl	2.84	0.0954	0.395	0.877	1.23	2.48 ± 0.38
4-CH_3CO	2.38	0.0331	0.114	0.398	0.633	2.93 ± 0.31
4-CN	1.90	0.0103	0.0425	0.161	0.269	3.22 ± 0.35
3-CN	1.45	0.00489	0.0209	0.0582	0.127	3.05 ± 0.53
ρ_X[b,c]		−1.71 ± 0.28	−1.72 ± 0.29	−1.75 ± 0.24	−1.78 ± 0.34	ρ_{XZ}[b,i] $= -0.15$
β_X[b,d]		0.37 ± 0.04	0.38 ± 0.03	0.38 ± 0.03	0.39 ± 0.05	
ρ_X[e,f]		−5.29 ± 0.47	−5.14 ± 0.47	−4.89 ± 0.55	−4.68 ± 0.49	ρ_{XZ}[e,j] $= +1.34$
β_X[e,g]		0.94 ± 0.02	0.91 ± 0.03	0.87 ± 0.02	0.83 ± 0.03	

[a] σ values were taken from Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. β_X values were determined using pK_a values in H_2O. Justification for this procedure is provided in the following references: (a) Lee, I.; Kim, C. K.; Han, I. S.; Lee, H. W.; Kim, W. K.; Kim, Y. B. *J. Phys. Chem. B* **1999**, *103*, 7302. (b) Coetzee, J. F. *Prog. Phys. Org. Chem.* **1965**, *4*, 45. (c) Spillane, W. J.; Hogan, G.; McGrath, P.; King, J.; Brack, C. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2099. (d) Foroughifar, N.; Leffek, K. T.; Lee, Y. G. *Can. J. Chem.* **1992**, *70*, 2856. (e) Ritchie, C. D. *Solute−Solvent Interactions*; Marcel-Dekker: New York, 1969; p 228. pK_a values of pyridines in water at 25 °C were taken from: (a) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*, 3rd ed.; Chapman and Hall: New York, 1984; pp 154−155. (b) Dean, J. A. *Handbook of Organic Chemistry*; McGraw-Hill: New York, 1987; Chapter 8. (c) Fischer, A.; Galloway, J. A.; Vaughan, J. *J. Chem. Soc.* **1964**, 3591. (d) pK_a values where X = 3-C_6H_5 and X = 4-CH_3CO were taken from ref 18. [b] For X = 4-CH_3O, 4-CH_3, 3-CH_3, 4-$C_6H_5CH_2$, and H. [c] Correlation coefficients are better than 0.948 in all cases. [d] Correlation coefficients are better than 0.980 in all cases. [e] For X = H, 3-C_6H_5, 3-CH_3CO, 3-Cl, 4-CH_3CO, 4-CN, and 3-CN. [f] Correlation coefficients are better than 0.970 in all cases. [g] Correlation coefficients are better than 0.996 in all cases. [h] Correlation coefficients are better than 0.971 in all cases. [i] Correlation coefficient is 0.965. [j] Correlation coefficient is 0.958.

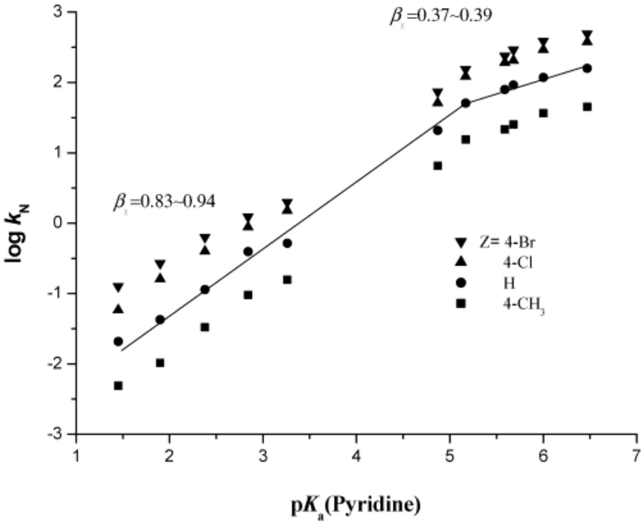

Figure 1. Brönsted plots (β_X) for the reactions of Z-phenyl dithioacetates with X-pyridines in acetonitrile at 60.0 °C.

substrate, respectively, and [Py] and [S] represent the pyridine and substrate concentrations, respectively. The value of k_0 was negligible in acetonitrile, $k_0 \cong 0$.

$$d[ArS^-]/dt = k_{obs}[S] \tag{4}$$

$$k_{obs} = k_0 + k_N[Py] \tag{5}$$

The second-order rate constants for pyridinolysis (k_N) were obtained as the slopes of plots of eq 5. These values, together with those of the pK_a of the conjugate acids of the pyridines, are summarized in the Table 1.

Using the k_N and pK_a values in Table 1, the Brönsted plots for the reactions under study were obtained as shown in Figure 1. The slopes ($\beta_X = \beta_{nuc}$) are shown in Table 1, where the Hammett coefficients, ρ_X (= ρ_{nuc}) and ρ_Z (= ρ_{lg}), and the cross-interaction constant, ρ_{XZ}, are also presented. We note that the Brönsted plots are biphasic with a change in the slope. For Z = H, the slope changes from $\beta_X = 0.91$ to 0.38 at pK_a° = 5.2 as the basicity of pyridine increases (see Figure 1). This breakpoint agrees with that calculated by means of a semiempirical equation derived by Castro et al.[4b,6] The values of β_X are in accord with the corresponding values found in other similar aminolysis reactions: the aminolysis of aryl dithioacetates with anilines and with *N*,*N*-dimethylanilines at 50 °C in acetonitrile gave $\beta_X = 0.84$ and 0.85 (for Z = H), respectively.[7] The β_X values at low pK_a values for the pyridinolysis of 2,4-dinitrophenyl and 2,4,6-trinitrophenyl *O*-ethyl thiolcarbonates in water were 0.9 and 0.8 with pK_a° = 8.6 and 7.3, respectively,[6] and that for *O*-ethyl 4-nitrophenyl thiolcarbonate in the whole pK_a range (pK_a = 3.43−9.87) was $\beta_X = 0.8$.[6] Similarly, for the pyridinolysis of 2,4-dinitrophenyl and 2,4,6-trinitrophenyl thiolacetates in water, the β_X values were 0.85 and 0.80 with pK_a° = 6.6 and 4.9, respectively, at 25 °C.[8]

On the basis of the biphasic Brönsted plots and the rate law obtained in the present work, we propose the reaction scheme shown in eq 2, where R = CH_3, Y = Y′= S, and amine = pyridine, as the most probable mechanism for the present reactions.

In this mechanism for pyridines of high pK_a values, $k_{-a} \ll k_b$ so that the k_a step is the rate-determining step, i.e., $k_N = k_a$, with a smaller Brönsted slope β_X (0.37−0.39). On the other hand, at low pK_a values where $k_{-a} \gg k_b$ and $k_N = (k_a/k_{-a})k_b = Kk_b$, the k_b step should be rate limiting with a steeper Brönsted slope β_X (0.83−0.94). At the center of the Brönsted curvature, $k_{-a} = k_b$, a pyridine with pK_a = pK_a° (5.2) has the same leaving ability from

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(6) Castro, E. A.; Pizarro, M. I.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 5982.

(7) Oh, H. K.; Woo, S. Y.; Shin, C. H.; Park, Y. S.; Lee, I. *J. Org. Chem.* **1997**, *62*, 5780.

(8) Castro, E. A.; Ureta, C. *J. Chem. Soc., Perkin Trans. 2* **1991**, 63.

the tetrahedral intermediate, T$^{\pm}$, as that of the leaving group ArS^{-}.

The low pK_a° ($\sim$5.2) obtained in this work for the dithio compound (Y = Y′ = S) is in contrast to the much higher pK_a° value (>9.6) observed for the corresponding thiol series (Y = O, Y′ = S),[9] for which the rate-limiting expulsion of ArS^{-} from the tetrahedral intermediate, T$^{\pm}$, (with $\beta_X = 1.3-1.6$) can be predicted even at a higher pK_a range (p$K_a \cong 9.1-9.6$). This may be due to the greater nucleofugality of benzylamines relative to pyridines and also partly due to the change of Y = S to Y = O. Similarly, the depression of pK_a° has been reported for Y = S relative to the corresponding Y = O series: for the aminolysis of *S*-phenyl thioacetate, the estimated pK_a° was 12.2, which is larger than that calculated for the same aminolysis of phenyl dithioacetate, pK_a° ≅ 10.[10] For the aminolysis of *O*-ethyl 4-nitrophenyl dithiocarbonate and *O*-ethyl *S*-(4-nitrophenyl) thiocarbonate, the pK_a° values are 9.6 and 10.7, respectively.[11] Again, for the aminolysis of 4-nitrophenyl benzoate and the corresponding thionobenzoate, the reported values were pK_a° > 11 and 9.2, respectively.[12] These examples of lower pK_a° values with Y = S than with Y = O clearly support the contention that the tetrahedral intermediate with Y = S, T$^{\pm}$(S), is more stable or that k_{-a} and k_b are smaller than those with Y = O, T$^{\pm}$(O). The decrease in k_{-a} is, however, greater than that in k_b.

The ρ_Z values are large (ca. 2.4 and 3.0 for the more basic and weakly basic pyridines, respectively). In terms of β_Z (β_{lg}), these correspond to $\beta_Z(CH_3CN) \cong -0.6$ and -0.8, respectively, ($\beta_Z(H_2O) \cong -1.0$ and -1.3 calculated by pK_a values of thiophenols in water for the more basic and weakly basic pyridines, respectively)[13] which are relatively large negative values. The sensitivity of k_N to the leaving group basicities ($\beta_Z \cong -0.8$) with weakly basic pyridines is in agreement with those obtained in the aminolysis of aryl esters and diaryl carbonates when expulsion of the leaving group from the intermediate is the rate-limiting step.[14] For rate-limiting formation of the tetrahedral intermediate, β_Z values of between 0 and -0.5 were obtained for the aminolysis of the aryl esters and carbonates and ethyl *S*-aryl dithiocarbonates.[14,15] On the other hand, for the concerted aminolysis reactions of *O*-ethyl *S*-aryl thiocarbonates, the β_Z value of -0.2 is reported in water.[16]

Table 2. Activation Parameters[a] for the Reactions of Z-Phenyl Dithioacetates with X-Pyridines in Acetonitrile

X	Z	t (°C)	k_N ($\times 10^4$ M^{-1} s^{-1})	$\Delta H^{\ddagger}$ (kcal/mol)	$-\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})
4-CH$_3$	4-CH$_3$	60.0	36.6	8.3	45
		50.0	23.8		
		40.0	15.3		
4-CH$_3$	4-Br	60.0	387	8.1	41
		50.0	256		
		40.0	167		
3-Cl	4-CH$_3$	60.0	0.0954	8.5	56
		50.0	0.0613		
		40.0	0.0394		
3-Cl	4-Br	60.0	1.23	8.3	52
		50.0	0.799		
		40.0	0.518		

[a] Calculated by the Eyring equation. Maximum errors calculated (by the method of Wiberg, K. B. *Physical Organic Chemistry*; Wiley: New York, 1964; p 378) are ±0.6 kcal/mol and ±2 cal mol^{-1} K^{-1} for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, respectively.

There is a clear-cut change in the ρ_{XZ} value (Table 1) from a large positive value ($\rho_{XZ} = +1.34$) for the rate-limiting expulsion of the ArS^{-} group from the intermediate, T$^{\pm}$, with the weakly basic pyridines (X = H−3-CN) to a small negative value ($\rho_{XZ} = -0.15$) for the rate-limiting formation of T$^{\pm}$ with the more basic pyridines (X = 4-CH$_3$O−H). Thus, on the basis of the cross-interaction constants, ρ_{XZ}, the mechanistic change is more clearly defined.[5c,17] Similar changes in the cross-interaction constants accompanying mechanistic changes have been observed within a series of nucleophiles used, especially pyridines[18] since a biphasic dependence of the rate upon the basicity of pyridines is often obtained.

The activation parameters determined with the rate constants at three temperatures are shown in Table 2. The activation enthalpies are low ($\Delta H^{\ddagger} \cong 8$ kcal/mol), and activation entropies have large negative values ($\Delta S^{\ddagger} = -41$ to -56 cal mol^{-1} K^{-1}). The large negative $\Delta S^{\ddagger}$ values (from -52 to -56 cal mol^{-1} K^{-1}) for the weakly basic pyridine (X = 3-Cl) are in accord with the rate-limiting expulsion of the leaving group since the soft ArS^{-} groups formed in the TS are solvated by the soft aprotic solvent (MeCN) molecules.

Summary

We have confirmed that the aminolysis of aryl dithioacetates in acetonitrile proceeds by a stepwise mechanism through a zwitterionic tetrahedral intermediate, T$^{\pm}$, with rate-limiting expulsion of the thiophenoxide (ArS^{-}) group by observing the breakpoint at pK_a° = 5.2 due to change in the rate-limiting step associated with the intermediate, T$^{\pm}$. The relatively low pK_a° value is ascribed to the stability of the tetrahedral intermediate where the decrease in k_{-a} is greater than that in k_b with Y = S relative to that with Y = O. The mechanistic change from rate-limiting expulsion of the leaving group from T$^{\pm}$ to formation of the intermediate is well defined by a change in the cross-interaction constants ρ_{XZ} from a large positive value (+1.34) to a small negative value (−0.15).

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(9) Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc.* **1999**, *20*, 1418.

(10) (a) Castro, E. A.; Ibanez, F.; Santos, J. G.; Ureta, C. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1919. (b) Castro, E. A.; Ureta, C. *J. Org. Chem.* **1989**, *54*, 2153.

(11) (a) Cabrera, M.; Castro, E. A.; Salas, M.; Santos, J. G.; Sepulveda, P. *J. Org. Chem.* **1991**, *56*, 5324. (b) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1994**, *59*, 3572.

(12) (a) Camphell, P.; Lapinskas, B. A. *J. Am. Chem. Soc.* **1977**, *99*, 5378. (b) Um, I.-H.; Kwon, H.-J.; Kwon, D.-S.; Park, J.-Y. *J. Chem. Res., Synop.* **1995**, 301.

(13) These values of β_Z in CH$_3$CN were estimated as follows: the pK_a(H$_2$O) vs σ^- plots for phenols and thiophenols have similar slopes, $\rho^- \cong 2.0$ (ref 1a, p 259). The β_Z values for phenoxide leaving groups had a ratio of β_Z (by pK_a in MeCN):β_Z (by pK_a in H$_2$O) ≅ 0.62 (Lee, H. W.; Guha, A. K.; Kim, C. K.; Lee, I. *J. Org. Chem.* **2002**, *67*, 2215) so that this factor of 0.62 was applied to β_Z(H$_2$O) values obtained for thiophenoxide leaving groups in the present work.

(14) (a) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018. (b) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963, 6970.

(15) Castro, E. A.; Cubillos, M.; Ibanez, F.; Moraga, I.; Santos, J. G. *J. Org. Chem.* **1993**, *58*, 5400.

(16) Castro, E. A.; Salas, M.; Santos, J. G. *J. Org. Chem.* **1994**, *59*, 30.

(17) Lee, I. *Bull. Korean Chem. Soc.* **1994**, *15*, 985.

(18) (a) Koh, H. J.; Han, K. L.; Lee, I. *J. Org. Chem.* **1999**, *64*, 4783. (b) Koh, H. J.; Han, K. L.; Lee, H. W.; Lee, I. *J. Org. Chem.* **1998**, *63*, 9834.

Experimental Section

Materials. Commercially purchased acetonitrile was used after three distillations. The pyridine nucleophiles were purchased commercially and used without further purification.

Substrates. Preparations and analytical data are reported elsewhere.[7]

Kinetic Measurement. Rates were measured conductometrically in acetonitrile. The conductivity bridge used in this work was a homemade computer-automatic A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obs}, were determined with a large excess of pyridine, [Py]. Second-order rate constants, k_N, were obtained from the slopes of plots of k_{obs} vs [Py] with more than five concentrations of pyridine and were reproducible to within ±3%.

Product Analysis. 4-Bromophenyl dithioacetate (0.05 M) was reacted with an excess of pyridine (0.5 M) with stirring for more than 15 half-lives at 60.0 °C in acetonitrile. The salt was filtered, and the solvent was removed from the precipitate. Analysis of the product gave the following results.

$CH_3C(=S)N^+C_5H_5{}^-SC_6H_4$-4-Br: mp 65−67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 2.78 (3H, s, CH_3), 7.61−7.98 (4H, m, C_6H_4S), 8.55−8.89 (5H, m, C_5H_5N); ^{13}C NMR (100.4 MHz, $CDCl_3$) 232.7 (C=S), 139.8, 125.7, 122.1, 121.5, 121.4, 113.6, 109.9, 25.5 (CH_3).

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