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Aminolysis of Aryl Chlorothionoformates with Anilines in Acetonitrile: Effects of Amine Nature and Solvent on the Mechanism

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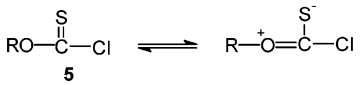
The aminolysis of aryl chlorothionoformates (**7**, $YC_6H_4OC(=S)Cl$) with anilines ($XC_6H_4NH_2$) in acetonitrile at 5.0 °C has been investigated. The rates are slower than those for the corresponding reactions of aryl chloroformates (**6**, $YC_6H_4OC(=O)Cl$). This rate sequence is a reverse of that for alkyl chloroformates (**1**−**4**) in water, for which rate-limiting formation of a tetrahedral intermediate, $T^{\pm}$, is predicted. On the basis of the large negative cross-interaction constant, $\rho_{XY} = -0.77$, failure of the reactivity−selectivity principle, normal k_H/k_D values involving deuterated nucleophiles ($XC_6H_4ND_2$), and low $\Delta H^{\neq}$ *with large negative* $\Delta S^{\neq}$ *values, a concerted mechanism with a four-membered hydrogen bonded cyclic transition state* (**11**) is proposed for the title reaction series. It has been shown that the solvent change from water to acetonitrile for the aminolysis of **6** and **7** causes a mechanistic change from stepwise to concerted.

Introduction

The aminolysis of carbonyl and thiocarbonyl derivatives has shown interesting mechanistic changes depending on the nonleaving acyl group and the solvent medium. For example, the rate sequence for the solvolysis of chloroformates (**1**−**4**) is reported to depend on the initial state stabilization of type **5**[1] (shown for the thiono analogue). The extent of delocalization of the lone pair

RO(CO)Cl **1** RS(CO)Cl **2** RO(CS)Cl **3** RS(CS)Cl **4**



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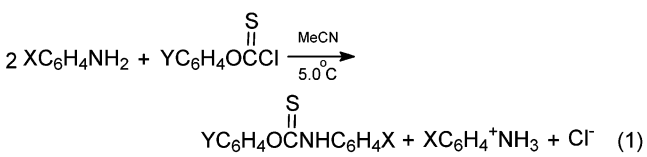
electrons (n) on RÖ (or RS) toward C=O (or C=S) has been shown to decrease in the order, **1** > **4** > **3** > **2**, and accordingly the solvolysis rates in water were found to increase in the reverse order (**1** < **4** < **3** < **2**), which was attributed to the initial state stabilization of the reactions.[1]

On the other hand, the aminolysis of methyl chloroformate[2] (**1** with R = Me) with pyridines in water was found to proceed by a stepwise mechanism with a change in the rate-determining step from breakdown to formation of a zwitterionic tetrahedral intermediate, $T^{\pm}$, with increasing basicity of the pyridines. In contrast, the aminolysis of phenyl chloroformate (**1** with R = Ph) with secondary alicyclic amines in water was reported to proceed by rate limiting formation of $T^{\pm}$.[3]

The aminolysis of aryl chlorothionoformates (**3** with R = YC_6H_4) with secondary alicyclic amines[4a] as well as with pyridines[4b] in water was also found to proceed by rate-limiting formation of $T^{\pm}$. This shows that the change of C=O to C=S in the aryl chloroformates does not cause a mechanistic change for the aminolysis in water. However, this is contrasted with a concerted process found for the aminolysis of aryl chloroformates (**6**; **1** with R = YC_6H_4) in acetonitrile.[5]

To shed more light on the mechanistic changes depending on the nonleaving RO group and on the reaction medium, we carried out kinetic studies on the aminolysis of aryl chlorothionoformates (**7**; **3** with R = YC_6H_4) with anilines in acetonitrile, eq 1.



$$2\,XC_6H_4NH_2 + YC_6H_4OCCl \xrightarrow[5.0\,^{\circ}C]{MeCN} YC_6H_4OCNHC_6H_4X + XC_6H_4{}^{+}NH_3 + Cl^{-} \quad (1)$$

In this work we varied substituents in the nucleophile (X) and in the nonleaving group (Y), and subjected the

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TABLE 1. The Second Order Rate Constants, k_2 ($\times 10$ M^{-1} s^{-1}) for the Reactions of Y-Phenyl Chlorothionoformates ($YC_6H_4OC(=S)Cl$) with X-Anilines ($XC_6H_4NH_2$) in Acetonitrile at 5.0°C

	Y				
X	*p*-OMe	*p*-Me	H	*p*-Cl	ρ_Y[a]
p-OMe	11.2[b]			86.8[b]	
	8.41	13.1	28.5	64.7	1.79 ± 0.08
	6.35[c]			48.0[c]	
p-Me	4.61	7.16	13.3	34.8	1.75 ± 0.04
H	1.63	2.46	4.38	10.3	1.60 ± 0.03
p-Cl	0.669[b]			3.61[b]	
	0.502	0.698	1.17	2.68	1.46 ± 0.04
	0.378[c]			1.98[c]	
m-Cl	0.181	0.231	0.391	0.780	1.29 ± 0.03
ρ_X[d]	−2.55 ± 0.06	−2.69 ± 0.07	−2.84 ± 0.07	−2.94 ± 0.09	ρ_{XY}[e] = −0.77
β_X[f]	0.90 ± 0.02	0.95 ± 0.02	1.00 ± 0.03	1.04 ± 0.02	

[a] The σ values were taken from ref 7. Correlation coefficients were better than 0.998 in all cases. [b] At 15 °C. [c] At −5 °C. [d] The σ values were taken from ref 7. Correlation coefficients were better than 0.999 in all cases. [e] Correlation coefficient was 0.999. [f] The pK_a values were taken from the following: Fischer, A.; Galloway, W. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3588. Correlation coefficients were better than 0.999 in all cases. X = *p*-CH_3O were excluded from the Brönsted plot for β_X(benzylamine) due to an unreliable pK_a value listed.

second-order rate constants, k_{XY}, to a multiple regression analysis to obtain the cross-interaction constant, ρ_{XY} in eq 2.[6] The sign and magnitude of ρ_{XY} provide mechanistic criteria for the nucleophilic substitution reactions.

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

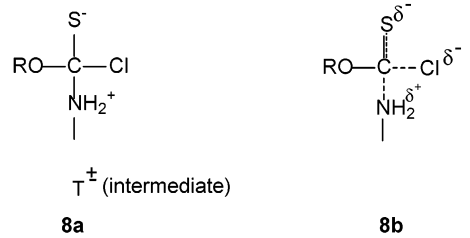
$$\rho_{XY} = \partial\rho_Y/\partial\sigma_X = \partial\rho_X/\partial\sigma_Y \quad (2b)$$

Results and Discussion

The second-order rate constants, k_2, are summarized in Table 1. These values were determined from the k_{obs}

$$k_{obs} = k_2[AN] \quad (3)$$

values of at least five aniline concentrations, [AN], under pseudo-first-order conditions, [AN] = 0.02−0.05 mol dm^{-3}, for [substrate] = 1×10^{-4} mol dm^{-3}. The aminolysis rates are found to follow good second-order kinetics and no complications by side reaction are found. The rates are ca. 10 times slower than those for the corresponding aminolysis of aryl chloroformate (**6**; R = YC_6H_4 in **1**) in acetonitrile.[5] For example, the k_2 values for **7** are 0.120 and 0.390 s^{-1} M^{-1} in MeCN at 25. 0°C (estimated by using activation parameters) for Y = *p*-OMe and *p*-Cl with X = *p*-Cl, respectively, and the corresponding values for **6** are 1.13 and 3.87 s^{-1} M^{-1}. Thus the aminolysis rate decreases by substitution of O (in **6**) by S (**7**). This is in contrast to the solvolysis rate increase observed for the same replacement of O by S, from methyl chloroformate (**1** with R = Me; $k = 0.674 \times 10^{-4}$ s^{-1}) to methyl chlorothionoformate (**3** with R = Me; $k = 1.73 \times 10^{-4}$ s^{-1}), in water at 4.62 and 4.96 °C, respectively.[1] As has been pointed out by the original authors[1] of the solvolysis studies, the initial state stabilization should be important in determining the rate sequence in water for chloroformates (**1**−**4**) with alkoxy nonleaving groups (R = Me, Et, and 2-Pr). In the rate-determining step, it is expected that, the greater the initial state (reactant) stabilization, the slower will become the bond formation. In contrast, the electron donor ability of the phenoxy group (σ_p = −0.03; σ_p^+ = −0.50)[7] is much lower than that of the methoxy group (σ_p = −0.27; σ_p^+ = −0.78),[7] and hence the effect of the initial state stabilization will be much weaker for PhO than for alkoxy group. Thus the solvolysis rate sequence for phenyl chloroformates (**1**−**4** with R = Ph) is no longer determined by the initial state stabilization, but is determined largely by the strength of push provided by the carbonyl (C=O or C=S) and nonleaving groups (RO− or RS−) to expel the leaving group, Cl^-, in the tetrahedral structure, which can be either an intermediate, **8a**, or a TS, **8b**. The change of S^- (in **3** and **4**)



by O^- (in **1** and **2**) and that of RS− (in **2** and **4**) by RO− (in **1** and **3**) are known to increase the nucleofugality of the leaving group,[8] Cl^-, the effect of the former being greater. This could be the reason for the solvolysis rate sequence for the R = Ph series, **1** > **2** > **3** > **4**, being quite different from the rate sequence for the R = alkyl series as noted in the Introduction.

The aminolysis of both aryl chloroformates,[3,9] **6**, and aryl chlorothionoformates,[4a] **7**, with secondary alicyclic amines in water is reported to proceed by rate-limiting formation of $T^{\pm}$. Since the expulsion rates of amines from $T^{\pm}$ increases in the order pyridines < anilines < secondary alicyclic amines < quinuclidines < benzylamines,[10] it is reasonable to expect that the same mechanism, i.e., rate-limiting formation of $T^{\pm}$, applies to the aminolysis of both **6** and **7** with anilines in water. This is because,

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as the expulsion rate from $T^{\pm}$ decreases, the intermediate, $T^{\pm}$, becomes more stable (stability of $T^{\pm}$ with anilines is reported to be greater than that with secondary alicyclic amines)[11] and the possibility of a stepwise mechanism increases, i.e., the aminolysis with anilines is more likely to proceed by the stepwise mechanism than with the secondary alicyclic amines under the same reaction conditions.[10] For example, the aminolyses of *O*-ethyl *S*-(2,4-dinitrophenyl)- (**9a**: EtO−C(=O)·SC_6H_3·2,4-$(NO_2)_2$) and *O*-ethyl *S*-(2,4,6-trinitrophenyl)carbonates (**9b**: EtO−C(=O)·SC_6H_2·2,4,6-$(NO_2)_3$) have been studied in water at 25 °C with amines of the increasing order of expulsion rate from $T^{\pm}$, pyridines[12] < anilines[11] < secondary alicyclic amines[13] < quinuclidines[10a] < (benzylamines).[14] A gradual shift of mechanism was observed from stepwise to concerted as the expulsion rate of amine from $T^{\pm}$ increased: For the aminolyses with pyridines both **9a** and **9b** were found to react by a stepwise mechanism,[11] whereas those with secondary alicyclic amines[13] and quinuclidines[10a] proceed by a concerted mechanism. Quite interestingly, the aminolysis with anilines[12] is stepwise with **9a** but is concerted with **9b**, which should form a less stable intermediate than **9a** due to the stronger nucleofugality of the trinitrothiophenolate in **9b** than the dinitrothiophenolate leaving group in **9a**. The aminolysis with benzylamines[14] is also concerted (in acetonitrile). Similarly, the aminolysis of aryl dithioacetates, **10**, in acetonitrile is stepwise with pyridines[15] (with a change of the rate-limiting step from breakdown, $\beta_X = 0.9$, to formation, $\beta_X = 0.4$, of $T^{\pm}$) and anilines[16] (with rate-limiting breakdown of $T^{\pm}$, $\beta_X = 0.84$), but is concerted with benzylamines[16] ($\beta_X = 0.55$). The aminolysis of **10** with secondary alicyclic amines[17] was found to proceed by rate-limiting formation of $T^{\pm}$ in water. Another interesting case is the aminolysis of aryl dithiobenzoates ($YC_6H_4C(=S)\cdot SC_6H_4Z$) in acetonitrile.[18−20] The intermediates, $T^{\pm}$, are so stable that the reactions are stepwise all the way from pyridines through anilines to benzylamines in the increasing order of nucleofugality of amines from $T^{\pm}$. However, there is a subtle shift of the rate-limiting step from biphasic plots with a change of the rate-determining step from breakdown ($\beta_X = 0.8$) to formation ($\beta_X = 0.2$) of $T^{\pm}$ with pyridines,[18] to the simple rate limiting breakdown of $T^{\pm}$ with anilines ($\beta_X = 0.8$),[19] and to the rate-limiting formation of T± with benzylamines ($\beta_X = 0.24$).[20] Thus, the shift of aminolysis mechanism from stepwise with rate-limiting breakdown of $T^{\pm}$ (to formation of $T^{\pm}$) to concerted with increasing nucleofugality of the amines from $T^{\pm}$ is generally followed, and an inversion of the sequence has rarely been observed.

The stepwise mechanism predicted for **6** and **7** with anilines in water is, however, in contrast to the concerted mechanism found for the aminolysis of **6** with anilines in acetonitrile.[5] The solvent change from water to a less polar solvent, MeCN, thus causes a mechanistic change for **6** from stepwise in water to concerted in MeCN. The change of solvent from water to acetonitrile destabilizes the zwitterionic intermediate resulting in an increase in the rate of expulsion of amines from $T^{\pm}$. The lower stability of $T^{\pm}$ leading to the higher expulsion rate of a given amine from $T^{\pm}$ in a less polar solvent compared to a more polar one is due to the zwitterionic nature of $T^{\pm}$. Mechanistic changes from stepwise to concerted incurred by a solvent change from water to acetonitrile are often observed. An example is the aminolysis of *O*-ethyl aryl dithiocarbonate (EtO−C(=S)·SAr), which proceeds by a stepwise mechanism with pyridines[8] and secondary alicyclic amines[21] in water but concertedly with anilines[14] and benzylamines[22] in acetonitrile. As noted above, anilines should also react by the stepwise mechanism in water since the expulsion rate of aniline is less than that of the secondary alicyclic amines. Similarly, the aminolysis of *O*-ethyl 2,4,6-trinitrophenyl dithiocarbonate is stepwise with a biphasic plot in water, but is concerted ($\beta_X = 0.53$) in a less polar solvent (44 wt % EtOH−H_2O).[23] This was attributed to the enhanced expulsion rate of the amine from $T^{\pm}$ in the less polar solvent while the nucleofugality of the leaving group remains practically unaffected by the solvent nature resulting in the more destabilized $T^{\pm}$ kinetically in the less polar solvent.[23]

It is therefore highly likely that the aminolysis of **7** with anilines in acetonitrile also proceeds by a concerted mechanism.

We propose a concerted mechanism for the aminolysis of aryl chlorothionoformate, **7**, in acetonitrile on the following grounds: (i) The rate sequence for the phenoxy series, k_2 (**6** with C=O) > k_2 (**7** with C=S) in acetonitrile, is a reverse of that for the alkoxy series, k_2 (**1** with C=O) < k_2 (**3** with C=S) in water, reflecting a mechanistic change from a rate-limiting formation of $T^{\pm}$ for the alkoxy series in water to a concerted mechanism for the phenoxy series in acetonitrile. A change of C=O to C=S leads to a decrease in push provided to expel the leaving group, Cl^-, in the tetrahedral TS (**8b**), and this will result in a decrease in the rate of the concerted process for **7** relative to **6**.[4,8] Of course, the same rate decrease may be expected from the intermediate, $T^{\pm}$ (**8a**), in a rate-limiting *breakdown* of $T^{\pm}$. However, the stepwise mechanism with rate-limiting breakdown of $T^{\pm}$ has never been found, either for **6** or for **7** in water or in acetonitrile with any type of amines. The stepwise mechanism with rate-limiting formation of $T^{\pm}$ has been reported for **7** with pyridines in water.[4b] Pyridines are known to have a stronger ability to stabilize the intermediate, $T^{\pm}$, than anilines,[11] and

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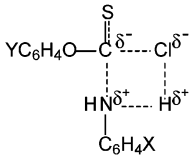
TABLE 2. The Secondary Kinetic Isotope Effects for the Reactions of Y-Phenyl Chlorothionoformates with Deuterated X-Anilines ($XC_6H_4ND_2$) in Acetonitrile at 5.0 °C

X	Y	k_H ($\times 10\ M^{-1}s^{-1}$)	k_D ($\times 10\ M^{-1}s^{-1}$)	k_H/k_D
p-OMe	*p*-OMe	8.41 (±0.07)	5.68 (±0.05)	1.48 ± 0.02[a]
p-OMe	*p*-Me	13.1 (±0.1)	8.45 (±0.07)	1.55 ± 0.02
p-OMe	H	28.5 (±0.3)	17.7 (±0.2)	1.61 ± 0.03
p-OMe	*p*-Cl	64.7 (±0.1)	38.3 (±0.5)	1.69 ± 0.03
p-Cl	*p*-OMe	0.502 (±0.005)	0.332 (±0.002)	1.51 ± 0.02
p-Cl	*p*-Me	0.698 (±0.007)	0.442 (±0.005)	1.58 ± 0.02
p-Cl	H	1.17 (±0.02)	0.791 (±0.006)	1.67 ± 0.02
p-Cl	*p*-Cl	2.68 (±0.06)	1.57 (±0.02)	1.71 ± 0.04

[a] Standard deviations.

many of the aminolyses of esters and carbonates (but not phenyl chloroformates) with pyridines are reported to be the stepwise mechanism with rate-limiting breakdown of $T^{\pm}$ **10b**. (ii) The sign of ρ_{XY} for **7** is negative ($\rho_{XY} = -0.77$), which is a necessary condition for the concerted reactions[10b,24] as it was found for the concerted reaction with **6** ($\rho_{XY} = -0.04$).[5] A further increase of push provided to expel Cl^- by the nonleaving acyl group with $PhN(CH_3)$ ($\sigma_p = -0.56$, $\sigma_p^+ = -1.40$ for PhNH)[7] in $PhN(CH_3)C(=O)Cl$ [25] also leads to a concerted process in acetonitrile with $\rho_{XY} = -0.14$. (iii) The rate (k_2) and selectivity data (ρ_X, β_X, and ρ_Y) show that a faster rate is accompanied by a stronger selectivity, i.e., the reactivity−selectivity principle (RSP) does not hold.[10b,24] This type of anti-RSP is considered as another criterion for the concerted mechanism.[10b,24] (iv) The kinetic isotope effects (KIEs), k_H/k_D, involving deuterated nucleophiles[26] ($XC_6H_4ND_2$) are normal, i.e., $k_H/k_D > 1.0$ in Table 2. This is not consistent with the rate-limiting bond formation in a stepwise mechanism, since in such cases inverse KIEs are expected due to the increased N−H(D) vibrational frequencies in the more crowded TS.[26] Such inverse KIEs were indeed found for **6** in acetonitrile.[5] For the thiono analogue (**7**; C=S) the push provided to expel the leaving group (Cl^-) is weaker than that for the carbonyl compounds (**6**; C=O), and hence the hydrogen bonding by the N−H(D) proton toward the Cl^- ion to assist the leaving group expulsion may be needed. We therefore propose a four-membered cyclic TS structure in a concerted process for the present reaction series, **11**. The TS proposed is



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supported by larger magnitudes of ρ_X (−2.55 to −2.94), β_X (0.90 to 1.04), ρ_Y (1.29 to 1.79), and ρ_{XY} (−0.77) for **7** (Table 1) than the corresponding values for **6**, ρ_X (−2.27 to −2.30), β_X (0.79 to 0.80), ρ_Y (1.20 to 1.26), and ρ_{XY} (−0.04), indicating that the TS with **7** (**11**) has a much tighter structure than that with **6** (**8b**); the thiono series (**7**) has a greater degree of bond formation (larger magnitude of ρ_X and β_X) with a lower degree of leaving group expulsion (larger ρ_Y) so that overall the TS is tighter (larger magnitude of ρ_{XY})[6] than the carbonyl series, **6**. (v) The activation parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ in Table 3, are consistent with the proposed mechanism. The $\Delta H^{\neq}$ values are small due to the assistance in the C−Cl bond cleavage by the hydrogen bonding in **11**, and the $\Delta S^{\neq}$ values are large negatives due to the strained hydrogen bonded cyclic TS structure.

TABLE 3. Activation Parameters[a] for the Reactions of Y-Phenyl Chlorothionoformates with X-Anilines in Acetonitrile

X	Y	$\Delta H^{\neq}$/kcal mol^{-1}	$-\Delta S^{\neq}$/cal mol^{-1} K^{-1}
p-OMe	*p*-OMe	3.9	45
p-OMe	*p*-Cl	4.1	47
p-Cl	*p*-OMe	3.8	50
p-Cl	*p*-Cl	4.0	47

[a] Calculated by the Eyring equation. The maximum errors calculated (by the method of Wiberg: Wiberg, K. B. *Physical Organic Chemistry*; Wiley, New York, 1964; p 378) are ±0.9 kcal mol^{-1} and ±3 eu for $\Delta H^{\neq}$ and $\Delta S^{\neq}$, respectively.

Reference to Table 1 reveals that the β_X values are 0.9−1.0, which are rather larger compared to the values normally expected for the concerted aminolysis reactions, $\beta_X = 0.4-0.7$.[10a] However, β_X values smaller than 0.4[27] and larger than 0.7[28] have also been reported for the concerted aminolysis reactions. Especially in solvents less polar than water, larger β_X values (1.3−1.6) are often observed for the concerted processes.[29] Therefore the large β_X values obtained in the present work may well be due to the less polar solvent used, MeCN. The relatively large β_X values are, however, consistent with the rather tight TS structure predicted with a tighter bond formation.

We conclude that the aminolysis of aryl chlorothionoformates, **7**, with anilines in acetonitrile proceeds by a concerted mechanism with a four-membered hydrogen bonded cyclic TS structure. The mechanism is the same as that of the carbonyl analogue, **6**, but the thiono series, **7**, lacks a strong push to expel the leaving group in the TS, unlike with **6**, and the TS structure differs between the two series, **8b** for **6**, but **11** for **7**. It is noteworthy that while the aminolyses of both **6** and **7** with secondary alicyclic amines (and also with anilines) in water are stepwise, those of **6** and **7** with anilines are concerted in acetonitrile.

Experimental Section

Materials. GR grade acetonitrile was used after three distillations. GR grade aniline nucleophiles were used after recrystallization.

Preparation of Phenyl Chlorothionoformates. Phenyl chlorothionoformates were prepared by the literature method of Hill, Thea, and Williams.[30] A solution of phenol (67 mmol) in 5% NaOH (60 mL) was added to a solution of thiophosgene (67 mmol) in chloroform (40 mL). The reaction was stirred for 1 h at 0−5 °C and the chloroform layer washed with dilute

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HCl and water. Solvent was removed under reduced pressure and product was separated by column chromatography (silica gel, 10% ethyl acetate−*n*-hexane) (yield >85%). IR (Nicolet 5BX FT-IR) and ^{1}H and ^{13}C NMR (JEOL 400 MHz) data were found to agree well with the literature value.[30]

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 by the Guggenheim method with a large excess of aniline. Second-order rate constants, k_N, were obtained from the slope of a plot of k_{obs} vs [AN] with more than five concentrations of aniline. The k_N values in Table 1 are the averages of more than three runs and were reproducible within ±3%.

Product Analysis. The substrate *p*-methoxyphenyl chlorothionoformate (0.05 mol) was reacted with excess aniline (0.5 mole) with stirring for more than 15 half-lives at 5.0 °C in acetonitrile and the products were isolated by evaporating the solvent under reduced pressure. The product mixture was subjected to column chromatography (silica gel, 20% ethyl acetate−*n*-hexene). Analysis of the product gave the following results.

***p*-MeO-C$_6$H$_4$OC(=S)NHC$_6$H$_5$:** liquid; ^{1}H NMR(400 MHz, $CDCl_3$) δ 3.80 (3H, s, CH_3), 6.51 (1H, s, NH), 7.05−7.54 (9H, m, C_6H_4, C_6H_5); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 192.1, 157.7, 147.3, 143.3, 129.5, 127.9, 122.4, 114.5, 114.2, 55.6; ν_{max}(KBr) 3255 (NH), 3056 (CH, aromatic), 2836 (CH, CH_3), 1598 (C=C, aromatic), 1382 (C−N), 1241 (C=S), 1130 (C−O); MS *m*/z 259 (M^+). Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.8; H, 5.11. Found; C, 64.6; H, 5.12.

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