Kinetics and Mechanism of the Pyridinolysis of Aryl Furan-2-carbodithioates in Acetonitrile

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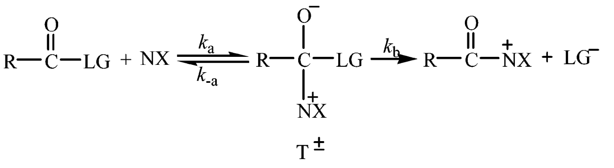
Kinetic studies on the pyridinolysis of aryl furan-2-carbodithioates **1** are carried out at 60.0 °C in acetonitrile. The biphasic rate dependence on the pyridine basicity with a breakpoint at $\mathrm{p}K_a^\circ = 5.2$ is interpreted to indicate a change of the rate-limiting step from breakdown ($\beta_X = 0.7-0.8$) to formation ($\beta_X = 0.2$) of the tetrahedral intermediate, $T^\pm$, at the breakpoint as the basicity of the pyridine nucleophile is increased. Observation of the breakpoint is possible with pyridines since the expulsion rate of the pyridine (k_{-a}) from $T^\pm$ is sufficiently low, with the low k_{-a}/k_b ratio leading to a low breakpoint, $\mathrm{p}K_a^\circ$. The clear-cut change in the cross-interaction constants, ρ_{XZ}, from a positive ($\rho_{XZ} = +0.86$) to a small negative ($\rho_{XZ} = -0.11$) value at the breakpoint supports the mechanistic change proposed. The magnitudes of ρ_Z and activation parameters are also consistent with the proposed mechanism.

Introduction

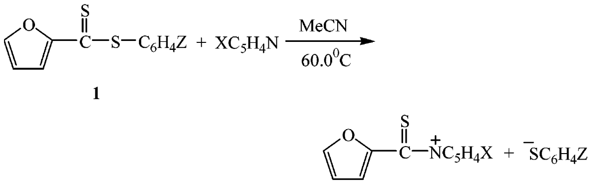
Structure−reactivity relationships in acyl-transfer reactions provide an important means of elucidating the mechanism of the reactions.[1] In the aminolysis of esters, a break at $\mathrm{p}K_a^\circ$ from a large ($\beta_{nuc} = \beta_X \geq 0.8$) to a small ($\beta_X \cong 0.2$) dependence of the rate (k_N) on the basicity of the attacking amine (XN) is often observed.[1] The break at $\mathrm{p}K_a^\circ$ has been interpreted as a consequence of a change in the rate-limiting step from leaving group (LG^-) expulsion (k_b) from a tetrahedral intermediate, $T^\pm$, with less basic amines to nucleophilic attack (k_a) with more basic amines, eq 1, where $k_N = (k_a/k_{-a})k_b = Kk_b$.



(1)

The breakpoint, $\mathrm{p}K_a^\circ$, has been shown to depend on various factors which influence the relative rates of expulsion of the nucleophile, amine, (k_{-a}), and leaving group (k_b) from a tetrahedral intermediate,[1,2] k_{-a}/k_b in eq 1. Keeping other conditions constant, the breakpoint, $\mathrm{p}K_a^\circ$, occurs at a lower $\mathrm{p}K_a$ value due to a decrease in k_{-a}/k_b: (i) as the leaving ability of LG^- increases,[3] (ii) as the nonleaving R becomes a stronger electron-donating group[2a,4] (larger k_b), (iii) as the amine nature changes successively from primary (e.g., benzylamine) → secondary (alicyclic) → aniline → pyridine[5] (successive decrease in k_{-a}/k_b), (iv) by substitution of S^- for O^- in $T^\pm$, i.e., for thiono rather than carbonyl esters,[2c,d,6] (decrease in k_{-a} more than k_b), (v) in an aqueous rather than aprotic solvent[2a,7](decrease in k_{-a}).

In the present work, we report the result of kinetic studies on the pyridinolysis of aryl furan-2-carbodithioates **1** in acetonitrile at 60.0 °C, eq 2. The aim is to



(2)

X = 4-CH_3O, 4-CH_3, 3-CH_3, 4-$C_6H_5CH_2$, H, 3-C_6H_5, 3-CH_3CO, 3-Cl, 4-CH_3CO, 4-CN, and 3-CN

Z = 4-CH_3, H, 4-Cl, and 4-Br

complete the previous studies[8] on the aminolysis mech-

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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-Aryl Furan-2-carbodithioates with X-Pyridines in Acetonitrile at 60.0 °C

		Z				
X	pK_a	4-CH_3	H	4-Cl	4-Br	$\rho_Z{}^h$
4-CH_3O	6.47	9.88	14.4	21.0	30.5	1.03 ± 0.23
4-CH_3	6.00	8.40	12.0	17.4	24.6	0.99 ± 0.22
3-CH_3	5.68	7.47	10.8	15.7	23.0	1.03 ± 0.24
4-$C_6H_5CH_2$	5.59	6.76	10.0	14.7	21.3	1.05 ± 0.23
H	5.17	6.31	8.96	12.8	18.1	0.97 ± 0.22
3-C_6H_5	4.87	2.75	3.97	6.44	8.83	1.12 ± 0.20
3-CH_3CO	3.26	0.191	0.312	0.593	0.855	1.45 ± 0.23
3-Cl	2.84	0.0933	0.186	0.327	0.438	1.50 ± 0.19
4-CH_3CO	2.38	0.0365	0.0747	0.111	0.185	1.45 ± 0.33
4-CN	1.90	0.0132	0.0240	0.0425	0.0692	1.54 ± 0.30
3-CN	1.45	0.00494	0.00884	0.0159	0.0285	1.60 ± 0.37
$\rho_X{}^{b,c}$		-0.70 ± 0.06	-0.73 ± 0.08	-0.75 ± 0.10	-0.77 ± 0.14	$\rho_{XZ}{}^{b,i} = -0.11$
$\beta_X{}^{b,d}$		0.16 ± 0.02	0.16 ± 0.01	0.17 ± 0.01	0.17 ± 0.01	
$\rho_X{}^{e,f}$		-4.09 ± 0.25	-3.88 ± 0.19	-3.79 ± 0.19	-3.68 ± 0.21	$\rho_{XZ}{}^{e,j} = +0.86$
$\beta_X{}^{e,g}$		0.81 ± 0.02	0.77 ± 0.03	0.75 ± 0.03	0.73 ± 0.02	

[a] The σ values were taken from Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. The pK_a values of pyridines in water at 25 °C were taken from the following: (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. The pK_a values of X = 3-C_6H_5 and X = 4-CH_3CO were taken from Koh, H. J.; Han, K. L.; Lee, H. W.; Lee, I. *J. Org. Chem.* **1998**, *63*, 9834 and ref 13, respectively. [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] The correlation coefficient is 0.956. [j] The correlation coefficient is 0.992.

anism of **1** and to further clarify the influence of the amine nature on the $pK_a°$ value. As an additional criterion for the elucidation of the mechanism, we determined the cross-interaction constants,[9] ρ_{XZ}, in eqs 3, where X and Z denote substituents in the pyridine nucleophile and the leaving group, respectively.

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

$$\rho_{XZ} = \partial\rho_Z/\partial\sigma_X = \partial\rho_X/\partial\sigma_Z \quad (3b)$$

Results and Discussion

The reactions obeyed the simple kinetic law given by eqs 4 and 5, where ArS^- is thiophenoxide ion and Py is pyridine. Plots of k_{obsd} vs [Py] were linear,

$$d[ArS^-]/dt = k_{obsd}[\text{substrate}] \quad (4)$$

$$k_{obsd} = k_N[\text{Py}] \quad (5)$$

and the k_N values were obtained from the slopes of these plots. The second-order rate constants, k_N, are summarized in Table 1. The rates of pyridine nucleophiles (e.g., $k_N = 8.96 \times 10^{-4}$ M^{-1} s^{-1} at 60.0 °C, Z = H) are slower than those of benzylamine ($k_N = 3.40 \times 10^{-2}$ M^{-1} s^{-1} at 15.0 °C, Z = H)[8] and aniline ($k_N = 4.35 \times 10^{-3}$ M^{-1} s^{-1} at 40.0 °C, Z = H).[8] Figure 1 shows the Brönsted plots (β_X) by using the k_N and pK_a values. The β_X values are collected in Table 1 together with the Hammett coefficients, ρ_X (=ρ_{nuc}) and ρ_Z (=ρ_{lg}), and the cross-interaction constant, ρ_{XZ}. Although the β_X values are based on the plots of log k_N(MeCN) vs $pK_a(H_2O)$, they can provide reasonable guides since a near constant ΔpK_a (=pK_a(MeCN) − $pK_a(H_2O)$ ≅ 7.5) was experimentally[10] as well as theoretically[11] found, and the slopes will remain practically the same irrespective of whether $pK_a(H_2O)$ or pK_a(MeCN) is used in the Brönsted correlation. We note that the Brönsted plots in Figure 1 are biphasic with a change in the slope at the breakpoint $pK_a° = 5.2$ as the basicity of pyridine increases; e.g., for Z =H, the slope changes from $\beta_X = 0.77$ to $\beta_X = 0.16$ at the breakpoint $pK_a° = 5.2$. The magnitude of β_X is somewhat smaller than those ($\beta_X \geq 0.8$)[1,2] normally obtained but is well

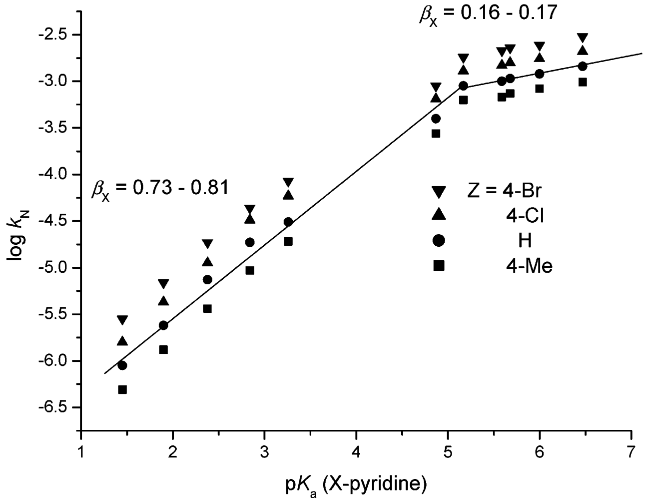

FIGURE 1. Brönsted plots (β_X) for the reactions of Z-aryl furan-2-carbodithioates with X-pyridines in acetonitrile at 60.0 °C.

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within the range ($\beta_X \geq 0.7-0.8$ in water[12] and 0.6−0.7 in acetonitrile[13]) of the corresponding values for the stepwise reactions with rate-limiting expulsion of the leaving group. For example, in the aminolysis of ethyl *S*-aryl thiolcarbonates, $C_2H_5OC(=O)SC_6H_4Z$, with secondary alicyclic amines in water, the slopes were $\beta_X = 0.7-0.8$,[12] and in the pyridinolysis of *S*-phenyl 4-nitrobenzoates, $4\text{-}NO_2C_6H_4C(=O)SC_6H_4Z$, in acetonitrile, the slopes were $\beta_X = 0.6-0.7$,[13] both of which were consistent with a stepwise mechanism where the breakdown of a zwitterionic tetrahedral intermediate, $T^{\pm}$, is rate-determining. The $\beta_X = 0.16$ obtained for more basic pyridines in Table 1 is also consistent with a stepwise mechanism in which the formation of $T^{\pm}$ is rate-limiting.[2a] In the pyridinolysis of aryl dithioacetates, $CH_3C(=S)SC_6H_4Z$, a biphasic plot with a change of slope from $\beta_X \cong 0.9$ to a small value of $\beta_X \cong 0.4$ was observed with a breakpoint at $pK_a° = 5.2$.[14]

On the other hand, in the reactions of **1** the β_X values were 1.2−1.5 and 0.8−0.9 with benzylamines (at 15.0 °C) and anilines (at 40.0 °C), respectively,[8] and no breakpoints were observed. This means that the breakpoints are at $pK_a° \geq 9.7$ ($pK_a° = 9.7$ of 4-methoxybenzylamine; the upper limit of the pK_a employed in the previous study[8]) and $pK_a° \geq 5.4$ ($pK_a° = 5.4$ of 4-methoxyaniline; the upper limit of the pK_a employed in the previous study[8]) for the reactions with benzylamines and anilines, respectively. The decreasing $pK_a°$ value, which is related to the decrease in the k_{-a}/k_b ratio in the order benzylamine (≥9.7) > aniline (≥5.4) > pyridine (=5.2), is consistent with the general sequence of the rate of amine expulsion (k_{-a}) from the tetrahedral intermediate, primary amines > secondary alicyclic amines > anilines > pyridines.[5] For the aminolysis of **1** the breakpoint, $pK_a°$ (=5.2), can be experimentally observed only in the reactions with pyridines since in the reactions with benzylamines and anilines the corresponding $pK_a°$ values are higher than the pK_a values of the more basic benzylamine and aniline used. This is why a biphasic plot with a clear-cut breakpoint, $pK_a°$, is often observed in the aminolysis with pyridine nucleophiles, as in the pyridinolysis of aryl dithioacetates[14] and **1** in this work, both at $pK_a° = 5.2$. There are other reasons for the relatively low $pK_a°$ value (=5.2) for the two pyridinolyses of the dithio series: (i) The thiono (S^-) rather than carbonyl (O^-) series leads to a lower $pK_a°$ due to a decrease in the k_{-a}/k_b ratio, since the lower proclivity of S^- than O^- in $T^{\pm}$ to form a double bond and expel a leaving group leads to a slower amine expulsion from $T^{\pm}$ (smaller k_{-a}) relative to ArS^- leaving (k_b).[2c,6] For example, the reactions of benzylamines with *S*-phenyl acetates,[15] $CH_3C(=O)SC_6H_4Z$, in acetonitrile proceed by a stepwise mechanism with rate-limiting expulsion of the $ZC_6H_4S^-$ leaving group ($pK_a° \geq 9.7$) from $T^{\pm}$, but those with aryl dithioacetates proceed by rate-limiting formation of $T^{\pm}$ [16] ($pK_a° \leq 9.14$; the lower limit of the pK_a employed, 4-chlorobenzylamine). (ii) The thiophenoxide leaving groups ($ZC_6H_4S^-$) used have lower basicities than phenoxide leaving groups ($ZC_6H_4O^-$) for the same Z, and hence, k_b should be greater (decrease in k_{-a}/k_b), leading to a lower $pK_a°$ than the corresponding esters with a phenoxide leaving group.[3]

In contrast there are also other factors in favor of a higher $pK_a°$ for the present reaction series: (i) An aprotic solvent, acetonitrile, favors amine expulsion (larger k_{-a}) to form ester compared to aqueous solution by stabilizing the TS for the breakdown of $T^{\pm}$ to form uncharged products relative to that for the formation of an anionic leaving group and a cationic amide.[2a,7] This will raise the k_{-a}/k_b ratio and hence lead to a higher $pK_a°$ value. (ii) An electron-withdrawing group, R in an acyl moiety, results in a rate increase[17] in the stepwise reactions where leaving group expulsion is rate-determining, but favors the expulsion of amine relative to thiophenoxide ion, i.e., a k_{-a}/k_b increase.[2a,4] In the reactions of aryl dithio series, $RC(=S)SC_6H_4Z$, with anilines, R = $2\text{-}C_4H_3O$ (2-furyl group) renders a greater rate ($k_N = 4.35 \times 10^{-3}$ M^{-1} s^{-1} at 40.0 °C, Z = H) relative to R = CH_3 ($k_N = 9.46 \times 10^{-4}$ M^{-1} s^{-1} at 50.0 °C, Z = H) and R = C_6H_5 ($k_N = 2.85 \times 10^{-3}$ M^{-1} s^{-1} at 55.0 °C, Z = H).[8,18] This means that the 2-furyl group is a stronger electron acceptor than either CH_3 or C_6H_5, and hence, the k_{-a}/k_b ratio should be greater with a higher $pK_a°$ value than that for the aryl dithio series with R = CH_3 and C_6H_5. This is indeed evidenced by the mechanistic change from rate-limiting breakdown of $T^{\pm}$ with anilines to a stepwise mechanism with rate-limiting formation of $T^{\pm}$ (i.e., $pK_a°$ is at lower values) in the aminolysis of the two dithio compounds (R = CH_3[16] and C_6H_5[19]) with benzylamines in contrast to no mechanistic change, i.e., the stepwise mechanism with rate-limiting breakdown of $T^{\pm}$, for the aminolysis of the 2-furyl[8] series with anilines and benzylamines. The $pK_a°$ observed (=5.2) is then the consequence of balance between these two opposing effects on the k_{-a}/k_b ratio.

The size of ρ_Z in Table 1 also reflects the mechanistic change. The magnitudes of ρ_Z change from larger values, $\rho_Z = 1.5-1.6$, for less basic pyridines to smaller values, $\rho_Z \cong 1.0$ for more basic pyridines, which is in agreement with the decrease in bond cleavage as the rate-determining step switches from breakdown to formation of the intermediate. Such a decrease in the magnitude of the ρ_Z values from large ($\rho_Z \cong 3.0$) to small ($\rho_Z \cong 2.3$) with the mechanistic change is also reported in the pyridinolysis of aryl dithioacetates.[14] A rough estimate[20] of the β_Z ($=\beta_{lg}$) values shows a decrease from $\beta_Z \cong -0.5$ to $\beta_Z \cong -0.3$ at the breakpoint in agreement with the change in the rate-determining step.

Another important result that supports a mechanistic change at $pK_a° = 5.2$ from breakdown to formation of $T^{\pm}$ as the basicity of pyridine is increased is a clear-cut

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[20] These values of β_Z in CH_3CN were estimated as follows: The $pK_a(H_2O)$ 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 the ratio β_Z (by pK_a in MeCN)/β_Z (by pK_a in H_2O) ≅ 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 $\beta_Z(H_2O)$ values obtained for thiophenoxide leaving groups in the present work.

TABLE 2. Activation Parameters[a] for the Reactions of Z-Aryl Furan-2-carbodithioates with X-Pyridines in Acetonitrile

X	Z	t (°C)	k_N ($\times 10^4$ M^{-1} s^{-1})	$\Delta H^\ddagger$ (kcal mol^{-1})	$-\Delta S^\ddagger$ (cal mol^{-1} K^{-1})
4-CH_3	4-CH_3	60.0	9.88	5.0	57
		50.0	7.57		
		40.0	5.77		
4-CH_3	4-Br	60.0	30.5	5.5	54
		50.0	22.5		
		40.0	16.8		
3-Cl	4-CH_3	60.0	0.0933	5.9	64
		50.0	0.0675		
		40.0	0.0494		
3-Cl	4-Br	60.0	0.438	6.0	61
		50.0	0.321		
		40.0	0.231		

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

change in the cross-interaction constant from a relatively large *positive* value ($\rho_{XZ} = +0.86$) to a small *negative* value ($\rho_{XZ} = -0.11$) at the breakpoint. Similar changes of the ρ_{XZ} values have been reported for the pyridinolysis of *S*-phenyl 4-nitrobenzoates[13] and aryl dithioacetates.[14] In the former the ρ_{XZ} values change from +1.41 to −0.32 at p$K_a° \cong 4.2$ and in the latter from +1.34 to −0.15 at p$K_a° = 5.2$ as the basicity of pyridine is increased. These are of course interpreted to indicate mechanistic changes from breakdown to formation of $T^{\pm}$. These changes in the ρ_{XZ} values with changes in the rate-determining step provide further credence to the cross-interaction constant as a useful mechanistic criterion.

The activation parameters, $\Delta H^\ddagger$ and $-\Delta S^\ddagger$, for the pyridinolysis of **1** are shown in Table 2. Both the $\Delta H^\ddagger$ and $-\Delta S^\ddagger$ values are rather smaller for a more basic pyridine (X = 4-CH_3O) than a less basic pyridine (X = 3-Cl), albeit the differences are small but significant enough to be over the error limits. These trends are in accord with the breakdown step (for X = 3-Cl) requiring larger energy and lower (more negative) entropy in the TS due to bond cleavage to the two ionic products, eq 2.

Last, examination of the trends of changes in k_N, ρ_X (β_X), and ρ_Z in Table 1 shows that the faster rate ($\partial k_N > 0$) is invariably accompanied by a smaller magnitude of the selectivity parameter, $\partial\beta_X < 0$, $\partial\rho_Z < 0$, and $\partial|\rho_X| < 0$; i.e., the reactivity−selectivity principle (RSP)[21] holds. The adherence of the rate data to the RSP constitutes another mechanistic criterion for the stepwise mechanism with rate-limiting breakdown of the intermediate,[19,22] $T^{\pm}$, and provides additional support for our proposed mechanism.

Experimental Section

Materials. The GR grade acetonitrile was used after three distillations. The pyridine nucleophiles, GR grade, were used without further purification. The preparations and analytical data of the substrates are reported elsewhere.[8]

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_{obsd}, were determined with a large excess of pyridine (Py); [substrate] = 2.0×10^{-4} M, and [Py] = 5×10^{-2} to 8×10^{-1} M. Second-order rate constants, k_N, were obtained from the slope of a plot of k_{obsd} vs [Py] with more than five concentrations of pyridine and were reproducible to within ±3%.

Product Analysis. The substrate 4-bromophenyl furan-2-carbodithioate (0.05 M) was reacted with excess 4-methylpyridine (0.5 M) with stirring for more than 15 half-lives at 60 °C in acetonitrile. The salt was filtered, and solvent was removed from the precipitate. Analysis of the product gave the following results.

Data for $(C_4H_3OC({=}S)NC_5H_4\text{-}4\text{-}CH_3)^+(4\text{-}BrC_6H_4S)^-$: semisolid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (3H, s, CH_3), 6.44−7.32 (3H, m, furan), 7.33 (2H, dd, phenyl), 7.42 (2H, d, pyridine), 7.62 (2H, dd, phenyl), 8.52 (2H, d, pyridine); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 230.7 (C=S), 146.9, 137.3, 136.9, 133.1, 132.5, 131.0, 129.8, 120.3, 113.7, 25.6 (CH_3); ν_{max} (KBr), 3375 (furan, C−H), 1554, 1452 (C=C, phenyl), 1072 (C=S), 812 (C−H, pyridine), 804 (C−H, phenyl); MS *m/z* 405 (M^+). Anal. Calcd for $C_{18}H_{15}BrNOS_2$: C, 53.3; H, 3.69. Found: C, 53.5; H, 3.68.

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