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Reactions of 4-Nitrophenyl 2-Thiophenecarboxylates with $R_2NH/R_2NH_2^+$ in 20 mol % DMSO (aq). Effects of 5-Thienyl Substituent and Base Strength

Sang Yong Pyun[*] and Bong Rae Cho[†,*]

Department of Chemistry, Pukyong National University, Pusan 608-737, Korea. [*]E-mail: sypyun@pknu.ac.kr
[†]Department of Chemistry, Korea University, Seoul 136-713, Korea. [*]E-mail: chobr@korea.ac.kr
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Reactions of 4-nitrophenyl 2-thiophenecarboxylate (**1a-e**) with $R_2NH/R_2NH_2^+$ in 20 mol % DMSO (aq) have been studied kinetically. The 2nd order kinetics, β_{nuc} = 0.88-0.98, and linear Hammett and Yukawa-Tsuno plots observed for these reactions indicate an addition-elimination mechanism in which the 2nd step is rate limiting. The β_{nuc} value increased with a stronger electron-withdrawing 5-thienyl substituent, the Hammett plots are linear except for X = MeO, and Yukawa-Tsuno plots are linear with ρ = 0.79-1.32 and r = 0.28-0.93, respectively. The ρ value increased and r value decreased with a stronger nucleophile, indicating an increase in the electron density at the C=O bond and a decrease in the resonance demand. These results have been interpreted with enhanced N-C bond formation in the transition state with the reactivity increase.

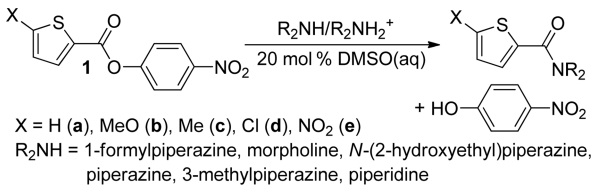
Key Words : Aminolysis, Brönsted-type plot, Hammett plot, Yukawa-Tsuno plot

Introduction

Extensive studies of the structure-reactivity relationships in the acyl transfer reactions from $XC_6H_4C(O)OC_6H_4Y$ have led to the qualitative understanding of the relationship between the reactant structure and mechanism.[1-3] The results of these studies have established two mechanistic pathways by which the aminolysis of esters proceeds.[4-13] The first is the concerted mechanism. The acyl-group transfer reactions of aryl phenyl carbonates with phenoxides and 4-nitrophenyl acetate with phenoxides have been concluded to be of this type.[7-9] The aminolysis can also proceed *via* a zwitterionic tetrahedral intermediate.[14-17] In contrast, much less is known about the corresponding acyl transfer reactions involving heterocyclic aromatic compounds.

Earlier, Um reported a mechanistic study on the aminolysis of 4-aryl 2-thiophene carboxylate.[18] The observation of the 2nd order kinetic as well as the large values of β_{nuc} and leaving group ρ^- suggested an addition-elimination mechanism in which the break-down of the intermediate is the rate determining step (RDS). It occurred to us that the effect of the electronic demand on the transition state can better be understood, if one measures the Hammett ρ values. However, there has been no study which employed different 5-thienyl substituents.

In order to provide a better insight into the aminolysis reaction, we have now investigated the reactions of 4-nitrophenyl 2-thiophenecarboxylates with $R_2NH/R_2NH_2^+$ in 20 mol % DMSO (aq) (eq. 1). We have employed different 5-thienyl substituents (**1a-e**) to study the electronic effect and $R_2NH/R_2NH_2^+$ as the nucleophile to keep the pH constant.



(1)

X = H (**a**), MeO (**b**), Me (**c**), Cl (**d**), NO_2 (**e**)
R_2NH = 1-formylpiperazine, morpholine, *N*-(2-hydroxyethyl)piperazine, piperazine, 3-methylpiperazine, piperidine

Results

4-Nitrophenyl 2-thiophenecarboxylates **1a-e** were prepared by reacting 5-substituted-2-thiophenecarboxylic acid chloride with 4-nitrophenol in the presence of Et_3N in CH_2Cl_2 as described previously.[19] For reactions of **1a-e** with $R_2NH/R_2NH_2^+$ in 20 mol % DMSO(aq), the yields of aryloxides determined by comparing the absorbance of the infinity samples from the kinetic studies with those of the authentic aryloxides are in the range of 96-98%.

The rates of aminolysis were determined by monitoring the increase in the absorption at the λ_{max} for the 4-nitrophenoxide at 400 nm. Excellent pseudo-first order kinetics plots, which covered at least three half-lives were obtained. The rate constants are summarized in Tables S1-6 in the Supporting Information. The plots of k_{obs} *vs* base concentration are straight lines passing through the origin, indicating that the reactions are second-order, first order to the ester and first order to the amine (Figure Sl-15). The slopes are the overall second-order rate constants k_N. The k_N values for the reactions of **1a-e** are summarized in Table 1. The rate increased with the increase in the electron-withdrawing ability of the 5-thienyl substituent and the pK_a value of the amine.

Brönsted plots for the aminolysis from **1a-e** are depicted in Figure 1. Excellent correlations were obtained between $\log(k_N/q)$ and pK_{a+} $\log(p/q)$ values, where p and q represent the number of equivalent protons in the acid HA and the number of equivalent basic sites in the conjugated base A^-, respectively.[20] The β_{nuc} values are in the range of 0.88-0.98 (Table 2). Figure 2 shows the plots of $\log(k_N/q)$ *vs* σ values

Table 1. Rate constants for the aminolysis of 5-$XC_4H_2(S)C(O)OC_6H_4$-4-NO_2[a] promoted by $R_2NH/R_2NH_2^+$ [b] in 20 mol % DMSO(aq) at 25.0 °C

Amine[c]	pK_a[d]	K_N, M^{-1} s^{-1}[e,f] When X is				
		H (**1a**)	OCH_3 (**1b**)	CH_3 (**1c**)	Cl (**1d**)	NO_2 (**1e**)
1-formylpiperazine	7.98	0.00593	0.00220	0.00489	0.00907	0.0366
morpholine	8.65	0.055	0.0184	0.0494	0.122	0.421
N-(2-hydroxylethyl)piperazine	9.38	0.15	0.0251	0.0823	0.205	0.84
piperazine	9.85	0.53	0.172	0.409	0.890	4.94
3-methylpiperidine	10.8	2.16	0.930	2.15	7.50	22.7
piperidine	11.02	3.70	1.38	3.10	8.07	56.3

[a][Substrate] = 5.0 × 10^{-5} M. [b][R_2NH]/[$R_2NH_2^+$] = 1.0. [c][R_2N] = (8.0 × 10^{-4} – 0.18) M. [d]pK_a data in 20 mol % DMSO (aq) taken from refs 3f and16. [e]Average of three or more rate constants. [f]Estimated uncertainty, ± 3%.

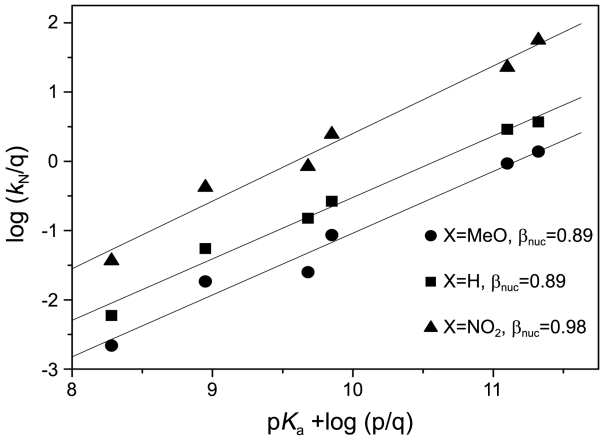


Figure 1. Brönsted plots for the aminolyses of 5-$XC_4H_2(S)C(O)$-OC_6H_4-4-NO_2 promoted by $R_2NH/R_2NH_2^+$ in 20 mol % DMSO (aq) at 25.0 °C [X = H (**1a**, ■), OCH_3 (**1b**, ●), NO_2 (**1d**, ▲)].

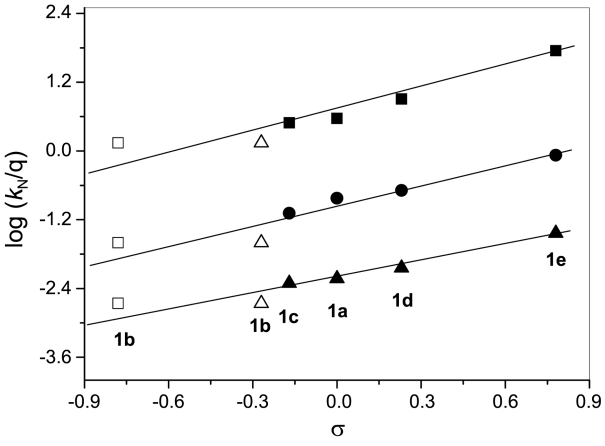


Figure 2. Hammett plots of log(k_N/q,q) *vs* σ values for the aminolysis of 5-$XC_4H_2(S)C(O)OC_6H_4$-4-NO_2 promoted by R_2NH/$R_2NH_2^+$ in 20 mol % DMSO (aq) at 25.0 °C. [R_2N = piperidine (■), *N*-(2-hydoxylethyl)piperazine (●), 1-formylpiperazine (▲)]. (△ and □ are points for log(k_N/q) *vs* σ and σ$^+$, respectively).

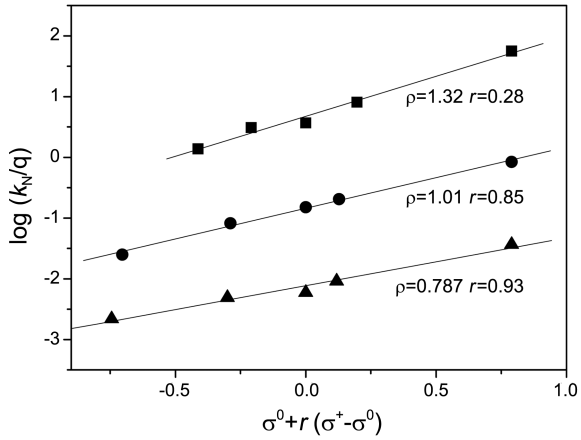


Figure 3. Yukawa-Tsuno plots of the aminolyses of 5-$XC_4H_2(S)$-$C(O)OC_6H_4$-4-NO_2 promoted by $R_2NH/R_2NH_2^+$ in 20 mol % DMSO (aq) at 25.0 °C [R_2N = piperidine (■), *N*-(2-hydoxylethyl)piperazine (●), 1-formylpiperazine (▲)].

Table 2. Brönsted β values for the aminolyses of 5-$XC_4H_2(S)C(O)$-OC_6H_4-4-NO_2 promoted by $R_2NH/R_2NH_2^+$ in 20 mol % DMSO (aq) at 25.0 °C

X	OCH_3	CH_3	H	X = Cl	X=NO_2
σ[a]	-0.27	-0.17	0	0.23	0.78
β_{nuc}	0.89 ± 0.7	0.88 ± 0.7	0.89 ± 0.05	0.94 ± 0.07	0.98 ± 0.07

[a]Reference 21.

Table 3. The ρ and r values for the aminolysis of 5-$XC_4H_2(S)C(O)$-OC_6H_4-4-NO_2 promoted by $R_2NH/R_2NH_2^+$ in 20 mol % DMSO (aq) at 25.0 °C

	Amine	pK_a[a]	ρ	r
1	piperidine	11.02	1.32 ± 0.07	0.28
2	3-methyl piperidine	10.80	1.06 ± 0.1	0.50
3	piperazine	9.85	1.02 ± 0.07	0.68
4	1-(2-hydroxyethyl)piperazine	9.38	1.01 ± 0.04	0.85
5	morpholine	8.65	0.89 ± 0.09	0.90
6	1-formylpiperazine	7.98	0.79 ± 0.07	0.93

[a]pK_a data in 20 mol % DMSO (aq) taken from refs 3f and16.

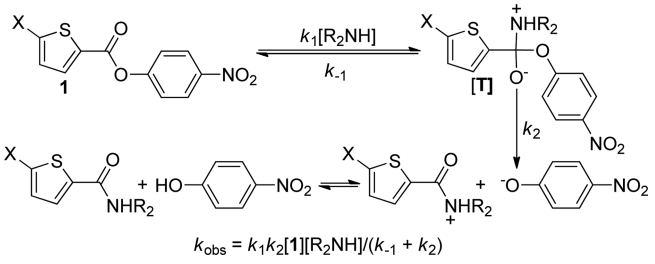
for the R_2NH-promoted aminolysis of **1a-e**. The influence of the 5-thienyl substituents on the aminolysis rates correlated well with the Hammett σ values except for **1b** (X = OCH_3), which showed negative deviation from the straight line defined by other substituents and positive deviation when plotted against σ$^+$ (Figure 2). In contrast, the rate data showed excellent correlations with the Yukawa-Tsuno plots using σ + r(σ$^+$ – σ) (Figure 3). The ρ and r values are listed in

Table 3. The reactions exhibit ρ = 0.79-1.42 and r = 0.28-0.93. The ρ value increased and r value decreased with a stronger base.

Discussion

Mechanism of Aminolysis of 1. The mechanism of aminolysis of **1** was assessed by using the kinetic parameters. The reaction is overall 2nd order, 1st order to **1** and 1st order to the nucleophile. However, it is not possible to determine the RDS with the rate equation alone because the addition-elimination mechanism should be 2nd order, regardless of whether the 1st ($k_2 >> k_{-1}$) or 2nd step ($k_2 << k_{-1}$) is RDS (Scheme 1). We, therefore, have utilized the Brönsted β_{nuc} and Hammett ρ values. Brönsted β_{nuc} value is an approximate measure of the degree of charge transfer at the transition state.[17,22] Curved Brönsted plots have been suggested as evidence for a change in the RDS of a stepwise mechanism.[14b,23] The acyl transfer reactions of 2,4-dinitrophenyl benzonates with pyridine in aqueous ethanol[27] and of 2,4-dinitrophenyl aryl carbonates with quinuclidines[14b] have been concluded to be of this type. On the other hand, a linear Brönsted plot was reported for the reactions of *p*-nitrophenyl acetate and its sulfonate and phosphinate analogues with various phenoxides.[7-9] For aminolysis of **1a-e**, the plots of $\log(k_N/q)$ *vs* $pK_a + \log(p/q)$ of the amine nucleophiles are straight lines with β_{nuc} = 0.88-0.98 (Table 2). The large β_{nuc} values are consistent with transition states which resembles the intermediate (T) with extensive N-C bond formation. This interpretation is supported by the slight increase in the β_{nuc} values with a stronger electron-withdrawing 5-thienyl substituent. It was expected that a stronger electron-withdrawing group would increase the reactivity of the C=O bond, facilitate the N-C bond formation, and increase the positive charge on the nitrogen atom, as observed (Table 3). Moreover, the β_{nuc} values are very similar to that reported for the reaction of **1a** with R_2NH in 20 mol % DMSO (aq). Since the reaction mechanism is not expected to change by the minor variation of the nucleophile from R_2NH to $R_2NH/R_2NH_2^+$, it seems reasonable to assume that the aminolysis of **1a-e** should proceed by the addition-elimination mechanism with the 2nd step as the RDS (Scheme 1).

Effect of 5-Thienyl Substituent. The rate of reaction increased as the electron-withdrawing ability of the 5-thienyl substituent increased. The Hammett plots of log k_N *vs* σ are linear except for X = MeO, which showed negative deviation from the straight lines, and positive deviation when plotted against σ^+ value (Figure 2). The OMe group seems to donate the electron density to the C=O bond more than expected from the σ value, thereby causing the negative deviation. The additional electrons might be donated by the through-resonance (**I**, **II**) between the MeO and C=O groups (Scheme 2). However, the positive deviation in the plot *vs* σ^+ value requires that such effect should not be as effective as in cumyl cation (**III**, **IV**), a model compound that was used to define the σ^+ value.[25] Hence, the rate data for **1b** should correlate with the Hammett equation when plotted against a substituent constant which is in between those of σ and σ^+ values (Figure 2).



Scheme 1

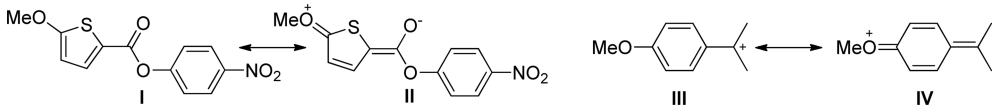
The extra resonance stabilization by the π-donor substituents can better be expressed by the Yukawa-Tsuno equation (eq. 2).[26]

$$\log(k/k_0) = \rho\{\sigma + r(\sigma^+ - \sigma)\} \quad (2)$$

In this equation, the ρ value is a measure of the extent of negative charge development at the reaction site, $(\sigma^+ - \sigma)$ is the resonance substituent constant measuring the π-delocalization capability of the donor group, and r is a parameter characteristic of the given reaction, measuring the extent of resonance demand, *i.e.*, the degree of resonance interaction between the aryl group and the reaction site in the rate-determining transition state.[26] When r = 0, the equation is identical to the Hammett equation, while it becomes the Brown equation, $\log(k/k_0) = \rho^+\sigma^+$, when r = 1. For the aminolysis of **1**, the Yukawa-Tsuno plots of $\log(k_N/q)$ *vs* $\sigma + r(\sigma^+ - \sigma)$ are straight lines with ρ = 0.79-1.32, and r = 0.28-0.93, respectively (Figure 3). The ρ value increased and r value decreased with a stronger base (Table 3). A similar result was reported.[3g] This indicates an increase in the electron density at the carbonyl carbon and a decrease in the resonance demand. A stronger nucleophile should facilitate the N-C bond formation, increase the electron density at the carbonyl carbon, and decrease the resonance demand.

Conclusions

The reactions of **1a-e** with $R_2NH/R_2NH_2^+$ in 20 mol % DMSO (aq) proceed by the addition-elimination mechanism in which the 2nd step is the RDS. The reaction rate increased and the N-C bond formation was facilitated by a stronger electron-withdrawing 5-thienyl substituent. When the nucleo-



Scheme 2

phile was changed to a stronger one, the ρ value increased and r value decreased, indicating an increase in the electron density at the C=O bond and a decrease in the resonance demand. An increase in N-C bond formation in the transition state with a stronger nucleophile is clearly indicated. Noteworthy is the much better correlation of the electronic effect of the 5-thienyl substituent with the Yukawa-Tsuno than with the Hammett equation.

Experimental Section

Materials. All of the 4-nitrophenyl 5-substituted-2-thiophenecarboxylates **1** were prepared by the reactions of 4-nitrophenol with 5-substituted-2-thiophenecarboxyl chloride in the presence of Et_3N in methylene chloride.[19] The spectral and analytical data of the compounds were consistent with the proposed structures. The yield (%), IR (KBr, C=O, cm^{-1}), ^1H NMR (400 MHz, $CDCl_3$, *J* values are in Hz), and ^{13}C NMR (100 MHz), and mass spectral data for the new compounds are as follows.

$C_4H_3(S)C(O)OC_6H_4$-4-NO_2 (1a): Yield 86%; IR 1710 cm^{-1}; ^1H NMR δ 7.22 (dd, 1H, *J* = 3.76, 4.8), 7.43 (d, 2H, *J* = 9.2), 7.73 (dd, 1H, *J* = 1.4, 5.12), 8.02 (dd, 1H, *J* = 1.4, 3.76), 8.32 (d, 2H, *J* = 9.2); ^{13}C NMR δ 122.5, 125.3, 128.5, 131.7, 134.3, 135.5, 145.5, 155.3, 159.5; LRMS (EI); *m/z* 249 [M^+] (5), 112 (23), 111 (100), 83 (16).

5-$MeOC_4H_2(S)C(O)OC_6H_4$-4-NO_2 (1b): Yield 78%; IR 1716 cm^{-1}; ^1H NMR δ 4.01 (s, 3H), 6.34 (d, 1H, *J* = 4.28), 7.41 (d, *J* = 9.24, 1H), 7.77 (d, 1H, *J* = 4.28), 8.31 (d, *J* = 9.24, 1H); ^{13}C NMR δ 60.6, 106.3, 116.4, 122.5, 125.2, 135.8, 145.2, 155.6, 159.6, 174.3; LRMS (EI); *m/z* 279 [M^+] (5), 141 (100), 126 (8), 98 (15).

5-$MeC_4H_2(S)C(O)OC_6H_4$-4-NO_2 (1c): Yield 85%; IR 1715 cm^{-1}; ^1H NMR δ 2.59 (s, 3H), 6.88 (d, *J* = 3.76, 1H), 7.41(d, *J* = 9.24, 2H), 7.83 (d, *J* = 3.76, 1H), 8.31 (d, *J* = 9.24, 2H); ^{13}C NMR δ 15.9, 122.5, 125.2, 127.0, 128.9, 136.1, 145.3, 150.6, 155.5, 159.4; LRMS (EI); *m/z* 263 [M^+] (5), 126 (49), 125 (100), 97 (14), 53 (34), 63 (6), 53 (46), 50 (5).

5-$ClC_4H_2(S)C(O)OC_6H_4$-4-NO_2 (1d): Yield 79%; IR 1715 cm^{-1}; ^1H NMR δ 7.05 (d, *J* = 4.10, 1H), 7.41 (d, *J* = 9.24, 2H), 7.80 (d, *J* = 4.10, 1H), 8.32 (d, *J* = 9.24, 2H); ^{13}C NMR δ 122.4, 125.3, 127.9, 129.7, 135.2, 139.8, 145.5, 155.0, 158.5; LRMS (EI); *m/z* 283 [M^+] (10), 146 (14), 145 (100), 117 (19), 73 (33).

5-$NO_2C_4H_2(S)C(O)OC_6H_4$-4-NO_2 (1e): Yield 69%; IR 1710 cm^{-1}; ^1H NMR δ 7.45 (d, *J* = 9.24, 2H), 7.93 (d, *J* = 4.08, 1H), 7.96 (d, *J* = 4.08, 1H), 8.35 (d, *J* = 9.24, 1H); ^{13}C NMR δ 122.3, 125.5, 128.1, 133.6, 136.2, 145.9, 154.5, 156.7, 158.2; LRMS (EI); *m/z* 294 [M^+] (3), 156 (100), 110 (22), 98 (9), 82 (9).

Reagent grade methylene chloride and secondary were fractionally distilled from CaH_2. The solutions of R_2N/R_2NH^+ in 20 mol % DMSO(aq) were prepared by dissolving equivalent amount of R_2NH and R_2NH^+ in 20 mol % DMSO (aq).

Kinetic Studies. All of the reactions were followed using a UV-vis spectrophotometer with thermostated cuvette holders. Reactions were followed by monitoring the increase in the absorbance of the aryloxides at 400-434 nm under pseudo-first-order conditions employing at least a 10-fold excess of nucleophiles as described before. In almost every case, plots of $\ln(A_\mu - A_t)$ *vs* time were linear over at least 2 half-lives. The slope was the pseudo-first-order rate constants. Freshly prepared buffer solutions were used in all kinetic runs.

Product Studies. The products were identified by periodically monitoring the UV absorption of the reactions mixtures under the reaction condition. The yields of aryloxides determined by comparing the UV absorptions of the infinity samples with those for the authentic aryloxides were in the range of 96-98%.

Control Experiments. The stabilities of **1** were determined by periodical scanning of the solution with the UV spectrophotometer. The solutions of **1** in MeCN were stable for at least two weeks when stored in the refrigerator.

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Support Information Available. Observed rate constants for elimination from **1a-e** promoted by R_2N/R_2NH^+ in 20 mol % DMSO (aq), plots of k_{obs} *vs* base concentration, and NMR spectra for all compounds are available on request from the correspondence author (21 pages). e-mail:sypyun @pknu.ac.kr.

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