Reactions of Aryl 5-substituted-2-Thiophenecarboxylates Promoted by 4-Z-$C_6H_4O^-$/4-Z-C_6H_4OH in 20 mol % DMSO(aq). Effect of Nucleophile on Acyl-Transfer Reaction

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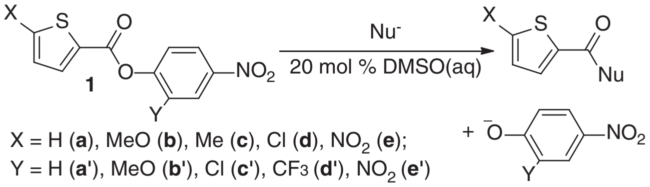
Nucleophilic substitution reactions of 5-$XC_4H_2(S)C(O)OC_6H_3$-2-Y-4-NO_2 (**1**) promoted by 4-Z-$C_6H_4O^-$/4-Z-C_6H_4OH in 20 mol % dimethyl sulfoxide (DMSO)(aq) have been studied kinetically. The reactions exhibited second-order kinetics with $\beta_{acyl} = -2.52$ to -2.83, $\rho(x) = 2.81-3.16$, $\beta_{nuc} = 0.88-0.04$ and $\beta_{lg} = -0.94$, respectively. The results have been interpreted with an addition–elimination mechanism in which the nucleophilic attack occurs in the rate-determining step. Comparison with existing data reveals that the rate-determining step changes from the second to the first step by the change in the nucleophile from R_2NH/$R_2NH_2^+$ to 4-Z-$C_6H_4O^-$/4-Z-C_6H_4OH.

Keywords: Nucleophilic substitution, Bronsted and Hammett plots, Concerted and stepwise mechanism

Introduction

Nucleophilic substitution reactions of $XC_6H_4C(O)OC_6H_4Y$ have been studied extensively under various conditions.[1–4] The results of the structure-reactivity studies have led to a qualitative understanding of the relationship between the reactant structure and the reaction mechanism. One of the most interesting results from these studies is the change in the rate-determining step (RDS) from the second to the first step by the change in the nucleophiles from amines to aryloxides. In contrast, much less is known about the corresponding acyl-transfer reactions involving heterocyclic aromatic compounds.

In an earlier paper, we reported the acyl-transfer reactions of 4′-nitrophenyl 5-substituted-2-thiophenecarboxylates [5-$XC_4H_2(S)C(O)OC_6H_4$-4-NO_2 (**1**)] promoted by secondary amines.[5] The reactions proceeded *via* an addition–elimination mechanism in which the break-down of the intermediate is the RDS. The electronic effects of the 5-thienyl substituent showed a much better correlation in the Yukawa–Tsuno plots than in the Hammett plots. Moreover, the ρ value increased but *r* value decreased as the nucleophile was changed to a better one. This outcome has been attributed to an increase in the electron density at the C═O bond and a decrease in the resonance demand. In this work, we have studied the acyl-transfer reactions of **1** promoted by 4-Z-$C_6H_4O^-$/4-Z-C_6H_4OH in 20 mol % dimethyl sulfoxide (DMSO)(aq) (Eq. (1)). We were interested in learning the effects of the change in the nucleophile from amines to aryloxides on the reactions of **1**.



X = H (**a**), MeO (**b**), Me (**c**), Cl (**d**), NO_2 (**e**);
Y = H (**a′**), MeO (**b′**), Cl (**c′**), CF_3 (**d′**), NO_2 (**e′**)
$Nu^- = ZC_6H_4O^-$; Z = H, MeO, Me, Cl, CN (1)

Results

Compounds **1aa′**-**ea′** were available from previous study.[5] The reaction of **1aa′** with $C_6H_5O^-$/C_6H_5OH in 20 mol % DMSO(aq) produced 4-nitrophenoxide as indicated by the gradual increase in the absorption at $\lambda_{max} = 410$ nm (4-$NO_2C_6H_4O^-$). For all reactions, the yields of aryloxides determined by comparing the infinity absorption of the samples from the kinetic studies with those of the authentic aryloxides were in the range of 97–99%.

The rates of the reactions were determined by monitoring the increase in the absorption at the λ_{max} for the aryloxides in the range of 400–434 nm. Excellent pseudo first-order kinetics plots, which covered at least three half-lives were obtained. The rate constants are summarized in Tables S1–S6 in the Supporting Information. For all reactions, the plots of k_{obs} against base concentration were straight lines passing through the origin. This outcome indicates that the reactions are second-order, first-order to the substrate, and first-order to the nucleophile (Figures S1–S10). The second-order rate constants (k_N) were obtained either from the slopes of straight lines or by dividing the k_{obs} values by the nucleophile concentrations. The k_N values are summarized in Tables 1 and 2. The k_N value increased with increasing electron-withdrawing ability of the 5-thienyl substituents, the leaving group ability, and the basicity of the nucleophile.

The plots of log k_N values for **1aa′**-**1ea′** against the pK_a values of X-thiophenecarboxylic acid are depicted in Figure 1. The plots are linear with reasonable correlations. The β_{acyl} values obtained from the slopes of the plots are in the range of −2.52 to −2.83 (Table 3). In addition, the k_N values for phenolysis from **1aa′**-**1ea′** showed good correlation with the pK_a values of the promoting nucleophiles on the Brönsted plots (Figure 2). The β_{nuc} values are in the range of 0.88–1.04 (Table 4). Similarly, the plots of log k_N values for **1aa′**-**1ae′** vs. the pK_{lg} values of leaving groups correlated reasonably on the Brönsted plot (Figure 3). The slope of the plot is -0.94 ± 0.22.

The influence of substituents in the acyl moiety on the phenolysis rates gave excellent correlations with σ values on the Hammett plot (Figure 4 and Figures S11 and S12). The rate data correlated better with σ than with σ^- parameters. The Hammett ρ values are in the range of 2.81–2.93 (Figure S11).

Discussion

Mechanism of Acyl-Transfer Reactions of 1. The mechanism of the reaction between **1** and aryloxides has been assessed by the kinetic results. The reactions of **1** with 4-Z-$C_6H_4O^-$/4-Z-C_6H_4OH in 20 mol % DMSO(aq) are second-order, first-order to the substrate, and first-order to the nucleophile (Figure S1–S10). The k_N value increased with increasing electron-withdrawing ability of the 5-thienyl substituents, the leaving group ability, and the basicity of the nucleophile (Table 1).

The reaction mechanism and RDS have been elucidated by the Brönsted and Hammett plots. It is widely accepted that the β value can be regarded as a measure of the degree of charge transfer in the transition state, as long as the base is not involved in resonance effects of its own.[9] The Brönsted β_{acyl} value, which correlates the effect of substituent at the acyl moiety on the reaction rate, indicates the extent of the charge development and the hybridization change in going from

Table 2. Rate constants for the reactions of $C_4H_3(S)C(O)OC_6H_3$-2-Y-4-NO_2[a] promoted by 4-Z-$C_6H_4O^-$/4-Z-C_6H_4OH[b,c] in 20 mol % DMSO(aq) at 25.0 °C.

	k_N, M^{-1} $s^{-1d,e}$ When Y is			
Y	H (**1aa′**)	OCH_3 (**1ab′**)	Cl (**1ac′**)	CF_3 (**1ad′**), NO_2 (**1ae′**)
pK_a(Y-ArOH)[7]	7.14	7.05	5.43	5.28, 4.11
k_N	0.266	0.0290	0.719	5.75, 73.8

[a] [Substrate] = 5.0×10^{-5} M.
[b] [4-Z-$C_6H_4O^-$]/[4-Z-C_6H_4OH] = 1.
[c] [4-Z-$C_6H_4O^-$] = 6.0×10^{-4} – 0.1 M.
[d] Average of three or more rate constants.
[e] Estimated uncertainty, ±3%.

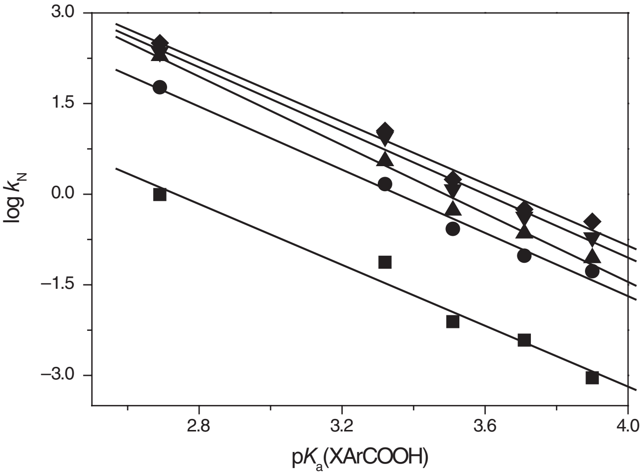


Figure 1. Brönsted plots of log k_N vs. pK_a (XArCOOH) values for the reactions of 5-$XC_4H_2(S)C(O)OC_6H_4$-4-NO_2 promoted by 4-Z-$C_6H_4O^-$/4-Z-C_6H_4OH in 20 mol % DMSO(aq) at 25.0 °C [Z = CN (■), Cl (●), H (▲), CH_3 (▼), OCH_3 (◆)].

Table 1. Rate constants for the reactions of 5-$XC_4H_2(S)C(O)OC_6H_4$-4-NO_2[a] promoted by 4-Z-$C_6H_4O^-$/4-Z-C_6H_4OH[b] in 20 mol % DMSO(aq) at 25.0 °C.

		k_N, $(M^{-1}\ s^{-1})^{e,f}$ When X is				
Z/X[c]	pK_a[d]	H (**1aa′**)	OCH_3 (**1ba′**)	CH_3 (**1ca′**)	Cl (**1da′**)	NO_2 (**1ea′**)
4-CN	7.95	0.00774	0.000837	0.00383	0.0749	0.983
4-Cl	9.38	0.266	0.0531	0.0960	1.47	59.0
H	9.95	0.540	0.0879	0.225	3.55	195
4-CH_3	10.19	1.20	0.192	0.420	8.88	225
4-OCH_3	10.20	1.75	0.352	0.562	11.1	317

[a] [Substrate] = 5.0×10^{-5} M.
[b] [4-Z-$C_6H_4O^-$]/[4-Z-C_6H_4OH] = 1.
[c] [4-Z-$C_6H_4O^-$] = 6.0×10^{-4}–0.1 M.
[d] pK_a data in 20 mol % DMSO(aq) taken from Refs. 4f and 6.
[e] Average of three or more rate constants.
[f] Estimated uncertainty, e rat.

Table 3. Brönsted β_{acyl} values for the reactions of 5-$XC_4H_2(S)C(O)OC_6H_4$-4-NO_2 promoted by 4-Z-$C_6H_4O^-$/4-Z-C_6H_4OH in 20 mol % DMSO(aq) at 25.0 °C.

Z	4-OCH_3	4-CH_3	H	4-Cl	4-CN
pK_a[a]	10.20	10.19	9.95	9.38	7.95
β_{acyl}	2.56 ± 0.26	−2.63 ± 0.15	−2.83 ± 0.15	−2.62 ± 0.18	−2.52 ± 0.18

[a] Ref. 7.

Table 4. Brönsted β values for the reactions of 5-$XC_4H_2(S)C(O)OC_6H_4$-4-NO_2 promoted by 4-Z-$C_6H_4O^-$/ 4-Z-C_6H_4OH in 20 mol% DMSO(aq) at 25.0 °C.

X	OCH_3	CH_3	H	Cl	NO_2
pK_a[a] (X—ArCOOH)	3.90	3.71	3.51	3.32	2.69
β_{nuc}	1.04 ± 0.08	0.89 ± 0.04	0.95 ± 0.05	0.88 ± 0.03	1.02 ± 0.08

[a] pK_a values of $XC_4H_2(S)COOH$. Ref. 8.

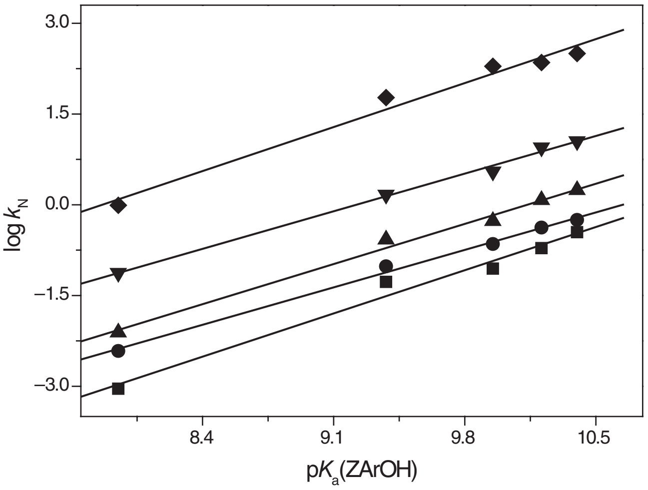


Figure 2. Brönsted plots of log k_N vs. pK_a(ZArOH) values for the reactions of 5-X-$C_4H_2(S)C(O)OC_6H_4$-4-NO_2 promoted by 4-Z-$C_6H_4O^-$/4-Z-C_6H_4OH in 20 mol % DMSO(aq) at 25.0 °C [X = OCH_3 (■), CH_3 (●), H (▲), Cl (▼), NO_2 (◆)].

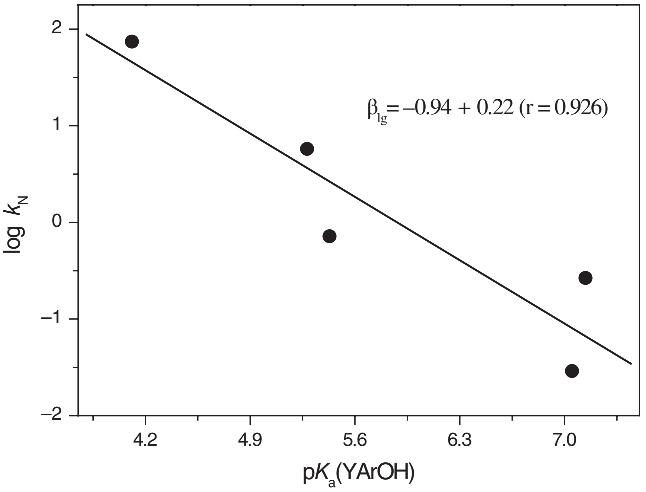


Figure 3. Brönsted plots of log k_N vs. pK_a(Y-ArOH) values for reactions of $C_4H_3(S)C(O)OC_6H_3$-2-Y-4-NO_2 promoted by 4-Cl-$C_6H_4O^-$/4-Cl-C_6H_4OH in 20mol% DMSO(aq) at 25.0 °C.

the reactant to the transition state.[3,10] If the nucleophile attacks the carbonyl group in the RDS, the β_{acyl} value should be a large negative value. If, on the other hand, the leaving group departure is involved in the RDS, a small negative or positive β_{acyl} value is predicted. Thus, the observed values of $\beta_{acyl} = -2.52\sim -2.83$ for ArO^- promoted reactions from **1** is consistent with the nucleophilic attack by aryloxides being the RDS. Moreover, β_{acyl} values are much larger than $|\beta_{lg}| = 0.94$, which is usually taken as the extent of the leaving group cleavage in the transition state. Further, the Brönsted plots for β_{acyl} showed much better correlation than the $|\beta_{lg}|$ plot (Figures 1 and 3). These results indicate a greater extent of C—O bond formation than the C_α—OAr bond cleavage in the transition state.

The β_{nuc} value can be used to assess the extent of the bond formation between the nucleophile and the substrate in the rate-limiting transition state.[11] Earlier, Um *et al.* reported that the β_{nuc} values for the reactions of 4-nitrophenyl phenylcarbonate and 4-nitrophenyl benzoate with aryloxides in 20 mol %

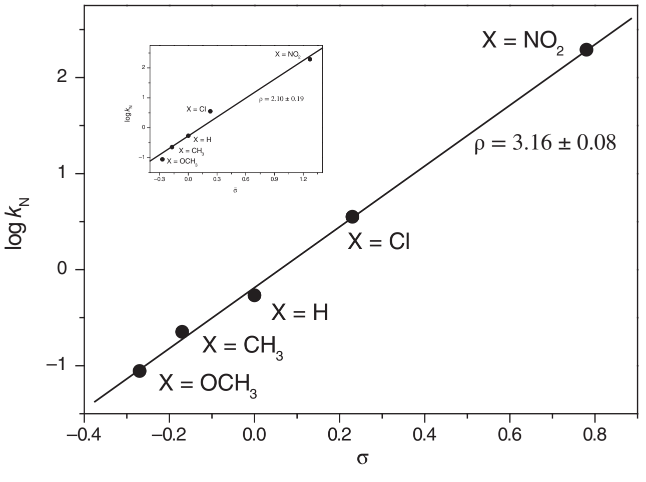
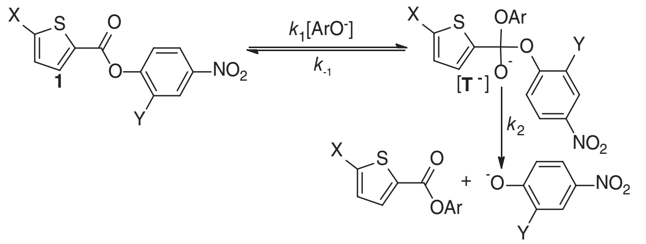


Figure 4. Hammett plot of log k_N vs. σ values for the reactions of 5-$XC_4H_2(S)C(O)OC_6H_4$-4-NO_2 promoted by $C_6H_5O^-$/C_6H_5OH in 20 mol % DMSO(aq) at 25.0 °C. Inset: Plot of log k_N vs. σ^- for the same reaction.



Scheme 1.

DMSO(aq) were 0.54 and 0.72, respectively.[12] This outcome has been interpreted with the concerted mechanism. On the other hand, the $\beta_{nuc} = 0.90$ determined for reactions of substituted phenyl acetate with *p*-chlorophenoxide has been attributed to the addition–elimination mechanism in which the formation of the tetrahedral intermediate is the RDS.[13] Therefore, the observed $\beta_{nuc} = 0.88–1.04$ for **1** is consistent with the addition–elimination mechanism with the first step being the RDS.

The Hammett $\rho(x)$ value is a measure of the extent of negative charge development in the transition state.[11a,14] For ArO^- promoted reactions from **1**, $\rho(x) = 3.16$ was determined (Figure 4). The large $\rho(x)$ value indicates significant extent of the C═O bond rehybridization in the transition state.[4a,16]

The combined results reveal that the aryloxide-promoted acyl-transfer reactions from **1** proceed by an addition–elimination mechanism in which the first step is RDS (Scheme 1). The transition state structure is more skewed toward the formation of C—O bond than the cleavage of C_α—OAr bond, with a greater extent of C—O bond formation than the C_α—OAr bond cleavage and more negative charge development at the α-carbon.

Effect of Nucleophile on the Acyl-Transfer Reactions. Comparison of the transition state parameters presented in Table 5 reveals that the transition state structure changes significantly by the variation of the nucleophile from $R_2NH/R_2NH_2^+$ to $Z\text{-}C_6H_4O^-/4\text{-}Z\text{-}C_6H_4OH$. As the nucleophile is changed from R_2NH to ArO^-, the Hammett $\rho(x)$ value increases by three-fold, indicating a large increase in the rehybridization at the carbonyl carbon in the transition state. The large positive Hammett $\rho(x)$ value observed for the reactions of **1** with ArO^- as the nucleophile is in good agreement with the large negative β_{acyl} value for the same reactions; in both case, the reaction rates are highly sensitive to the electronic effects of the substituent X in the acyl moiety.

The β_{nuc} value increased only slightly by the same variation of the nucleophile, indicating a small increase in the C—O bond formation. The smaller $|\beta_{lg}|$ value observed for ArO^- indicates a smaller degree of C_α—OAr bond rupture in the transition state. Taken together, these results can most reasonably be explained in terms of the change in the RDS from second to first step by the nucleophile variation from $R_2NH/R_2NH_2^+$ to $4\text{-}Z\text{-}C_6H_4O^-/4\text{-}Z\text{-}C_6H_4OH$. The RDS of the addition–elimination reaction depends on the relative rates of the k_{-1} and k_2 steps. Since ArO^- is a better leaving group than R_2NH, it is more likely for the first step being the RDS for the ArO^--promoted substitution reactions. Exactly the opposite result is expected for the R_2NH-promoted reactions. It is interesting to note that the change in the RDS occurs for both $XC_6H_4C(O)OC_6H_4Y$ and **1** by the same variation of the nucleophile. It appears that it is the nature of the nucleophile, not the α-aryl group, that is important for determining the RDS.

Table 5. Effect of the nucleophiles variation on the acyl-transfer reactions from $5\text{-}XC_4H_2(S)C(O)OC_6H_3\text{-}2\text{-}Y\text{-}4\text{-}NO_2$ in 20 mol % DMSO(aq) at 25.0 °C.

Nucleophiles	R_2NH[a]	$C_6H_5O^-$
pK_a[b]	9.85	9.95
Relative rate	1	1
β_{acyl}	—	-2.83 ± 0.15
β_{nuc}[c]	0.89 ± 0.05	0.95 ± 0.05
$\lvert\beta_{lg}\rvert$[c]	1.29 ± 0.05[d,e]	0.94 ± 0.22
$\rho(x)$[f]	1.02 ± 0.07	3.16 ± 0.08

[a] R_2NH = piperazine.
[b] Ref. 7.
[c] X = H.
[d] Ref. 15.
[e] R_2NH = morpholine.
[f] Y = H.

Conclusions

The acyl-transfer reactions of **1** with $4\text{-}Z\text{-}C_6H_4O^-/4\text{-}Z\text{-}C_6H_4OH$ in 20 mol % DMSO(aq) proceed by the addition–elimination mechanism in which the first step is RDS. As the nucleophile was changed from R_2NH to ArO^-, the extent of rehybridization at the carbonyl carbon and the extent of C_α–O bond formation increased, and the degree of C_α–OAr bond cleavage decreased. This outcome indicates that the nucleophilic attack is more advanced than the leaving group departure in the rate-limiting transition state. The most interesting result from this study is the change of the RDS from second to first step by the change of the nucleophile from $R_2NH/R_2NH_2^+$ to $4\text{-}Z\text{-}C_6H_4O^-/4\text{-}Z\text{-}C_6H_4OH$.

Experimental

Materials. Aryl 5-substituted-2-thiophenecarboxylates **1** were available from previous investigations.[5] DMSO was distilled under reduced pressure from CaH_2. The *p*-chlorophenol and *p*-cresol were recrystallized from *n*-hexane. Other phenols were used without further purification. The buffer solutions of $Z\text{-}C_6H_4O^-/4\text{-}Z\text{-}C_6H_4OH$ in 20 mol % DMSO(aq) were prepared by adding appropriate amount of the conjugate acid to 5 N NaOH solutions.

Kinetic Studies. Reactions of **1** with $Z\text{-}C_6H_4O^-/4\text{-}Z\text{-}C_6H_4OH$ in 20 mol % DMSO(aq) were followed by monitoring the increase in the absorbance of the aryloxides in the range of 400–434 nm with a UV–Vis spectrophometer as described before.[5]

Product Studies. The products of Z-$C_6H_4O^-$ promoted reactions from **1** were identified by UV spectrophotometer. When the reaction mixture was scanned periodically by monitoring the UV absorption, the absorbance due to the aryl oxide increased. The yields of aryloxides determined by comparing the UV absorptions of the infinity samples with those for the authentic aryloxides are in the range of 97–99%.

Control Experiments. The stability of **1** was determined as reported earlier.[5] The solutions of **1** in MeCN were stable for at least 2 weeks when stored in the refrigerator.

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Supporting Information. Additional supporting information is available in the online version of this article.

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